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Demikian surat tugas ini dibuat, untuk dilaksanakan dengan baik, terima kasih.

Jakarta, 17 Juni 2022

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Enni Juliani, M.Kep
Wakil Ketua I



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Acknowledgements:

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Example references Journals:

Standard Journal Article

Rampal L and Liew BS. Coronavirus disease (COVID-19) pandemic. Med J Malaysia 2020; 75(2): 95-7.

Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.

NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

Books and Other Monographs:

Personal Author(s)

Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

Chapter in Book

McFarland D, Holland JC. Distress, adjustments, and anxiety disorders. In: Watson M, Kissane D, Editors. Management of clinical depression and anxiety. Oxford University Press; 2017: 1-22.

Corporate Author

World Health Organization, Geneva. 2019. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. WHO Technical Report Series, No. 1015.

NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 2019; 569: 260-64.

World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 85, April 14, 2020. [cited April 2020] Accessed from: <https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200414-sitrep-85-covid-19>.

Online articles

Webpage: Webpage are referenced with their URL and access date, and as much other information as is available. Cited date is important as webpage can be updated and URLs change. The "cited" should contain the month and year accessed.

Ministry of Health Malaysia. Press Release: Status of preparedness and response by the ministry of health in and event of outbreak of Ebola in Malaysia 2014 [cited Dec 2014]. Available from: http://www.moh.gov.my/english.php/database_stores/store_view_page/21/437.

Other Articles:

Newspaper Article

Panirchellvum V. 'No outdoor activities if weather too hot'. the Sun. 2016; March 18: 9(col. 1-3).

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Rampal L. World No Tobacco Day 2021 -Tobacco Control in Malaysia. Berita MMA. 2021; May: 21-22.

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Acute leukemia and lymphoma in pregnancy, a retrospective study from a tertiary center in Malaysia

Rui Jeat Fann, MD^{1,2}, Emily Christine d'silva, MBBS³, Tanusha Kunju, MD², Teng Kang Wong, MD², Bee Sun Lee, MD¹, Jameela Sathar, MD², Soon Keng Cheong, MBBS¹

¹Faculty of Medicine and Health Sciences, University Tunku Abdul Rahman, ²Department of Hematology, Ampang General Hospital, Selangor, ³Department of Obstetrics and Gynaecology, Ampang General Hospital, Selangor

ABSTRACT

Introduction: Most evidence about the management of cancer and hematological malignancy in pregnancy are derived from retrospective observational studies with a small sample size. Availability of sufficiently large data has enabled evidence-based decision-making in this clinical dilemma.

Materials and Methods: Retrospective study looking into patients diagnosed with acute leukemia or lymphoma in pregnancy from 1st January 2014 to 1st January 2020 in Ampang General Hospital including newly or previously diagnosed and relapsed disease

Results: 37 cases of acute leukemia or lymphoma in pregnancy occurred in 34 patients. Majority of acute leukemia or lymphoma in pregnancy diagnosed in 1st trimester or in the setting of previously established or relapsed disease was therapeutically terminated. Thirteen pregnancies treated with antenatal chemotherapy resulted in livebirths except one stillbirth. More adverse obstetric outcomes are observed in pregnancies that did not receive antenatal chemotherapy, but association did not reach statistical significance. There was no significant difference in fetal outcome between cohort with and without antenatal chemotherapy. No treatment related mortality was observed in pregnancies with antenatal chemotherapy. Overall survival for newly diagnosed acute leukemia in pregnancy is significantly better with antenatal chemotherapy versus no antenatal chemotherapy.

Conclusion: Treatment with chemotherapy in 2nd trimester of pregnancy onwards appears to have tolerable risks with favorable obstetric and fetal outcome. Deferment of treatment for acute leukemia in pregnancy to after delivery may cause increased risk of maternal and fetal adverse outcome.

KEYWORDS:

Leukemia, lymphoma, pregnancy, antenatal chemotherapy

INTRODUCTION

Oversea registries show that cancer in pregnancy is rare, estimated to be 1 in 1000 pregnancies and is the second most common cause of maternal death after gestation-related vascular complications.^{1,2} Solid tumours (breast and cervix)

accounted for the majority of cancer in pregnancy followed by lymphoma and leukemia.³

Historically, most evidences about the management of cancer and hematological malignancy in pregnancy are derived from retrospective observational studies with a small sample size. For the past decade, we have witnessed increasing publications from multinational multicenter studies. International Network of Cancer, Infertility and Pregnancy (INCIP) is the largest known registry with contributions from 67 centers from 28 countries that combines both oncological and obstetric data of women with a cancer diagnosis during pregnancy. Lymphomas and leukemias were listed as the second and fourth most common malignancies in pregnancy respectively in the registry.^{4,5}

Availability of sufficiently large data has enabled evidence-based recommendations to be made to guide health care workers and patients in decision-making in this clinical dilemma. Recent recommendations concur with management guidelines from the International consensus meeting of Prenatal Hematologic Malignancies in 2014.⁵⁻⁷ Recognizing the challenges balancing the welfare of both mother and fetus-in-utero, treatment of hematological malignancies in pregnancy should not differ from non-pregnant in principle. A host of factors such as subtype of malignancy, gestational age, aggressiveness of disease and tumor burden, maternal wellbeing during diagnosis in addition to psycho-social aspect and future fertility prospect need to be addressed during the formulation of treatment.

There is no local registry about the incidence of hematological malignancies in pregnancy. Local publication of guidelines, case series and case reports about managing solid tumour in pregnancy (breast, cervix and lung) are available but not hematological malignancies. A significant knowledge gap still exists regarding incidence of hematological malignancy and outcome for both pregnant mother and pregnancy in our local setting.

Department of Hematology of Ampang Hospital is Malaysia's national referral center for hematology diseases. This is a pilot study in Ampang Hospital with the objective to contribute more data and knowledge regarding hematological malignancies namely leukemias and lymphomas in pregnancy in our local population.

This article was accepted: 17 May 2023

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MATERIALS AND METHODS

Study Type and Design

This is a retrospective study looking into patients diagnosed with acute leukemia or lymphoma in pregnancy from 1st January 2014 to 1st January 2020 in Ampang General Hospital. Acute leukemia and lymphoma are as per definition by WHO Classification of Tumours of Hematopoietic and lymphoid Tissues revised 4th edition 2017. Patients were identified from the registry of delivery, termination of pregnancy and chemotherapy in Ampang General Hospital. Patients diagnosed with acute leukemia or lymphoma during pregnancy, including newly diagnosed, previously diagnosed active or relapsed disease from 1st January 2014 to 1st January 2020 in Ampang General Hospital were recruited.

Important variables that were collected included age, parity, gestational age during diagnosis, types of leukemia or lymphoma, types of treatment offered, pregnancy and fetal outcome and long-term outcome of the patients.

This study was registered with the National Medical Research Register Malaysia, and ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-19-3980-51915)

Statistical Analysis

The data analyses were carried out using the SPSS version 22. Descriptive data were expressed as mean $\pm$ standard deviation (SD) unless otherwise stated. Kruskal-Wallis ANOVA was used for non-normally distributed data. Categorical data were analyzed using Chi-square or Fisher's exact test. A value of $p < 0.05$ is considered statistically significant.

The Kaplan-Meier method was used to estimate median survival times, and the log-rank test at a 5% significance level was used to test the equality of survival between groups. All p -values were 2-sided and values ≤ 0.05 were considered statistically significant.

RESULTS

Sociodemographic and Antenatal Characteristic

A total 37 cases of acute leukemia or lymphoma in pregnancy occurred in 34 patients during the study period in Ampang General Hospital. Three patients had two consecutive pregnancies complicated with acute leukemia or lymphoma. Most of the patients were Malay (83.8%) with a median age of 26 years upon diagnosis. Pregnancy complicated with lymphoma is more common than that of acute leukemia. A significant number of patients (27%) had either established diagnosis of the disease before the current pregnancy, refractory or relapsed disease. Sociodemographic and antenatal characteristics of the study population are summarised in Table I.

Antenatal Management

Diagnosis of acute leukemia or lymphoma or pregnancy was made predominantly during 1st (32.4%) and 2nd trimester of gestation (35.1%). Four diagnosis of lymphoma were made postpartum as the diagnostic procedure was deferred but the

mothers had symptoms during pregnancy. The majority of acute leukemia or lymphoma in pregnancy (75%) diagnosed in 1st trimester were therapeutically terminated (Figure 1). The commonest indication is to facilitate treatment for patients that had acute leukemia or lymphoma in early pregnancy. One therapeutic termination of pregnancy was indicated for serious fetal anomalies due to unintended chemotherapy exposure. Termination of pregnancy in the setting of previously established or relapsed disease was 77.8%.

13 (35.1%) pregnancies began antenatal chemotherapy while 15 (40.5%) had treatment or diagnostic investigation deferred. None had received any surgery or radiotherapy. Two pregnancies that were diagnosed with lymphoma in 1st trimester of gestation had treatment delayed to 2nd trimester.

Three patients (one acute myeloid leukemia and two lymphomas) had consecutive pregnancies with poor obstetrics outcome. One had consecutive termination of pregnancy (TOP), another had a TOP with subsequent pregnancy ended with both maternal and fetal demise. The third patient had preterm delivery at 33rd weeks of gestation complicated with neonatal death at day 18 of birth.

OBSTETRIC AND FETAL OUTCOME

For the processing of obstetric outcomes, pregnancies that were terminated were excluded from the analysis (Table II). Among the twenty-eight remaining pregnancies, thirteen (46.4%) received antenatal chemotherapy. These pregnancies resulted in livebirths except one stillbirth. This stillbirth was seen in a pregnancy that had unplanned pregnancy during treatment for Hodgkin lymphoma resulting in 1st trimester exposure to chemotherapy.

Among twenty-eight pregnancies that continued, more adverse obstetric outcomes are observed in pregnancies that did not receive antenatal chemotherapy including two miscarriages and four maternal demises, but the association was not statistically significant ($p = 0.08$). One missed marriage in 2nd trimester of therapy-related AML in pregnancy without antenatal chemotherapy had fetus with congenital anomalies (diaphragmatic hernia, ventricular septal defect and cyclopia). The majority of maternal deaths were related to disease related complications (one spontaneous tumor lysis in Burkitt lymphoma and two venous thromboembolisms in acute myeloid leukemia and diffuse large B cell lymphoma respectively). These patients deteriorated shortly after diagnosis while awaiting decision for treatment. One maternal death occurred in a pregnancy complicated with relapsed AML and the patient opted for palliative care.

76.2% livebirths were born prematurely and there was no significance difference between pregnancies that receive antenatal chemotherapy and those did not ($p = 1.00$). This finding corresponds to similarly high rate of iatrogenic delivery either by elective Caesarean section or induction of labour.

28.5% of livebirths were small for gestational age defined by weight below 10th centile in growth chart with 33.3% in the

Table I: Sociodemographic and antenatal characteristics of 37 pregnancies complicated with acute leukemia or lymphoma

	All patients, n = 37, %	Acute Leukemia, n=15, %	Lymphoma, n=22, %	p value
Median age	26 (23.5-27.5)	27 (24-32)	26 (23-28)	0.683
Ethnicity				
Malay	31 (83.8)	11 (73.3)	20 (90.9)	NA
Chinese	2 (5.4)	1 (6.7)	1 (4.5)	
Indian	2 (5.4)	1 (6.7)	1 (4.5)	
East Malaysian	1 (2.7)	1 (6.7)	0 (0)	
Other nationality	1 (2.7)	1 (6.7)	0 (0)	
Disease subtype				
Ph+ ALL		1 (6.7)		NA
Ph- ALL		1 (6.7)		
T- ALL		1 (6.7)		
AML with t(15:17)		2 (13.2)		
AML with inv (16)		3 (20.0)		
AML, NOS		5 (33.3)		
MDS transformed AML		1 (6.7)		
Therapy related AML		1 (6.7)		
Hodgkin lymphoma			13 (59.1)	
Burkitt's lymphoma			1 (4.5)	
DLBCL			6 (27.3)	
PMBL			2 (9.1%)	
Primigravida	14 (37.8)	4 (26.7)	10 (44.5)	0.47
Newly diagnosed				
Yes	27 (73.0)	11 (73.3)	16 (72.7)	1.00
No				
Known disease	6 (16.2)	2 (13.3)	4 (18.1)	
Relapsed disease	3 (8.1)	2 (13.3)	1 (4.5)	
Refractory	1 (2.7)	0 (0)	1 (4.5)	
Diagnosis of pregnancy or disease				
1st trimester	12 (32.4)	5 (33.3)	7 (31.8)	NA
2nd trimester	13 (35.1)	8 (53.3)	5 (22.7)	
3rd trimester	8 (21.6)	2 (13.3)	6 (27.3)	
Postpartum	4 (10.8)	0 (0)	4 (18.2)	
Antenatal Management				
Chemotherapy	13 (35.1)	6 (40.0)	7 (31.8)	0.70
No chemotherapy	15 (40.5)	5 (33.3)	10 (45.5)	
Termination of pregnancy (TOP)	9 (24.3)	4 (26.7)	5 (22.7)	

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; inv, inversion; NOS, non-otherwise specified; APML, acute promyelocytic leukemia; HL, Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; Ph, Philadelphia chromosome; PMBL, primary mediastinal B cell lymphoma; TOP, termination of pregnancy

Table II: Obstetric and fetal outcome of 28 pregnancies that did not have therapeutic termination

	Chemotherapy (n=13), %	No chemotherapy (n=15), %	p value
Leukemia	6 (46.2)	5 (33.3)	0.70
Lymphoma	7 (53.8)	10 (66.7)	
Median gestational week at diagnosis	23	24*	
		(4 diagnosed postpartum)	
Outcome			0.08
No livebirth			
Miscarriages	0 (0)	2 (13.3)	
Maternal demise	0 (0)	4 (26.7)	
Stillbirth	1 (7.7)	0 (0)	
Live birth	12 (92.3)	9 (60)	
	Chemotherapy with livebirths (n=12)	No chemotherapy with livebirths (n=9)	
Median gestational week at delivery	34	34	1.00
Delivery			
32-37 week	9 (75.0)	8 (88.9)	1.00
>37 week	3 (25.0)	1 (11.1)	
LSCS	6 (50)	8 (88.9)	
Vaginal delivery	6 (50)	1 (11.1)	0.16
Iatrogenic delivery	9 (75)	9 (100)	0.23
Mean Birthweight (kg)	2.02	2.07	0.67
Small for gestational age	4 (33.3)	2 (22.2)	1.00
Median Apgar score at 5 minute	9	10	0.02
NICU admission	10 (83.3)	7 (77.8)	0.57
28 days neonatal death	1 (8.3)	0 (0)	1.00
Congenital anomalies	1 (8.3)	1 (11.1)	1.00

LCSC, lower segment Caesarean section; NICU, neonatal intensive care unit

Table III: Detailed description of 14 pregnancies that were exposed to chemotherapy

	Diagnosis	Disease status	GW diagnosis	GW Chemotherapy	Treatment	GW of Last Treatment	GW Delivery	Delivery Method	Maternal Adverse events	Fetal Adverse events
1	AML inv (16)	New	19	20	DA 3+7, 2 HIDAC	31	37	Induced, vaginal	Neutropenic sepsis	None
2	MDS transformed AML	New	25	28	DA 3+7	28	34	Induced, vaginal	Neutropenic sepsis	Presumed sepsis, prematurity
3	AML (NOS)	On treatment	11	1st trimester	decitabine	1st trimester	19	TOP	None	Fetal anomalies
4	AML (NOS)	New	22	24	DA 3+7, HIDAC	31	33	EMLSCS for fetal distress	Neutropenic sepsis leading to preterm labour	Fetal neutropenia, congenital heart disease neonatal death
5	AML (NOS)	New	24	24	DA 3+7	24	34	Induced, vaginal	Neutropenic sepsis	TTN, prematurity
6	APML	New	25	25	ATRA + idarubicin	25	34	Induced, vaginal	Neutropenic sepsis	None
7	APML	New	36	3rd trimester	ATRA	36	36	EMLCSC	Wound breakdown	Prematurity
8	HL	New	10	15	4 ABVD	31	37	Induced, EMLSCS	Bleomycin lung toxicity	Pneumonia
9	HL	New	27	30	1 ABVD	32	34	ELLSCS	None	Prematurity
10	DLBCL	New	21	21	6 RCHOP	21	34	ELLSCS	None	Prematurity, respiratory distress syndrome
11	DLBCL	New	23	24	2 RCHOP	33	37	EMLSCS vaginal	None	None
12	DLBCL	New	8	24	3 RCHOP	30	33		Neutropenic sepsis leading to preterm delivery	Prematurity, respiratory distress syndrome
13	PMBL	New	31	31	1 CHOP	31	34	Induced, vaginal	None	Pneumonia
14	Grey zone lymphoma	On treatment	1st trimester	1st trimester	6 AVD	29	29	vaginal	Pre-eclampsia	IUGR and stillbirth

AML, acute myeloid leukemia; inv, inversion; NOS, non-otherwise specified; APML, acute promyelocytic leukemia; HL, Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; PMBL, primary mediastinal B cell lymphoma; GW, gestational week; DA 3+7, daunorubicin and arabinoside; HIDAC, high dose cytarabine. ATRA, all-trans retinoic acid; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; AVD, Adriamycin, vinblastine, dacarbazine; RCHOP, rituximab, cyclophosphamide, vincristine, prednisolone; TOP, termination of pregnancy; EMLSCS, emergency lower segment Caesarean section; ELLSCS, elective lower segment Caesarean section; TTN, transient tachypnea of newborn; IUGR, intrauterine growth restriction

cohort of antenatal chemotherapy and 22.2% in the cohort without antenatal chemotherapy. Birthweight, median week of delivery, modality of delivery, frequency of small for gestational age and neonatal intensive care admission do not differ significantly between these two cohorts. Median Apgar score at 5 minutes was significantly higher in livebirths that did not receive antenatal chemotherapy (10) than livebirths that receive antenatal chemotherapy (9) ($p=0.02$). One neonatal death with congenital heart disease complicated with neutropenic sepsis was seen in pregnancy that received antenatal chemotherapy for Hodgkin lymphoma. Another livebirth without antenatal chemotherapy had complex cyanotic heart disease.

PREGNANCIES EXPOSED TO CHEMOTHERAPY

Table III details fourteen pregnancies (seven leukemias and seven lymphomas) that were exposed to antenatal chemotherapy. No treatment-related maternal mortality was seen. Unintended chemotherapy exposures in 1st trimester occurred in two unplanned pregnancies (case number 3 and 14) during treatment of acute myeloid leukemia and grey zone lymphoma respectively. Case number 3 is a case of FLT3 positive AML in remission who had unintended decitabine maintenance administration in 1st trimester. The pregnancy was therapeutically terminated due to serious fetal

anomalies detected during the antenatal scan. After delivery, the fetus was found to have physical abnormalities that include holoprosencephaly, cleft lip and palate, mid facial deformity and polydactyly(8). Case number 14 with grey zone lymphoma who had unplanned pregnancy diagnosed during the course of treatment was unintentionally exposed to adriamycin, vinblastine and dacarbazine in 1st trimester. The pregnancy was however complicated with intrauterine growth restriction secondary to preeclampsia leading to stillbirth at 29th weeks of pregnancy.

The remaining twelve pregnancies had planned chemotherapy from 2nd trimester onwards with all resulted in live births. The chemotherapeutic agents exposed are myriad and seven pregnancies have received more than one cycle of chemotherapy before delivery. Three received monoclonal antibody rituximab and two received ATRA. All received combination chemotherapy except one who received single-agent ATRA. The commonest maternal adverse events were neutropenic sepsis which occurred in less than half (42.8%) of the pregnancies.

The most common neonatal adverse events were related to complications of prematurity, more commonly due to iatrogenic premature delivery. However, an event of

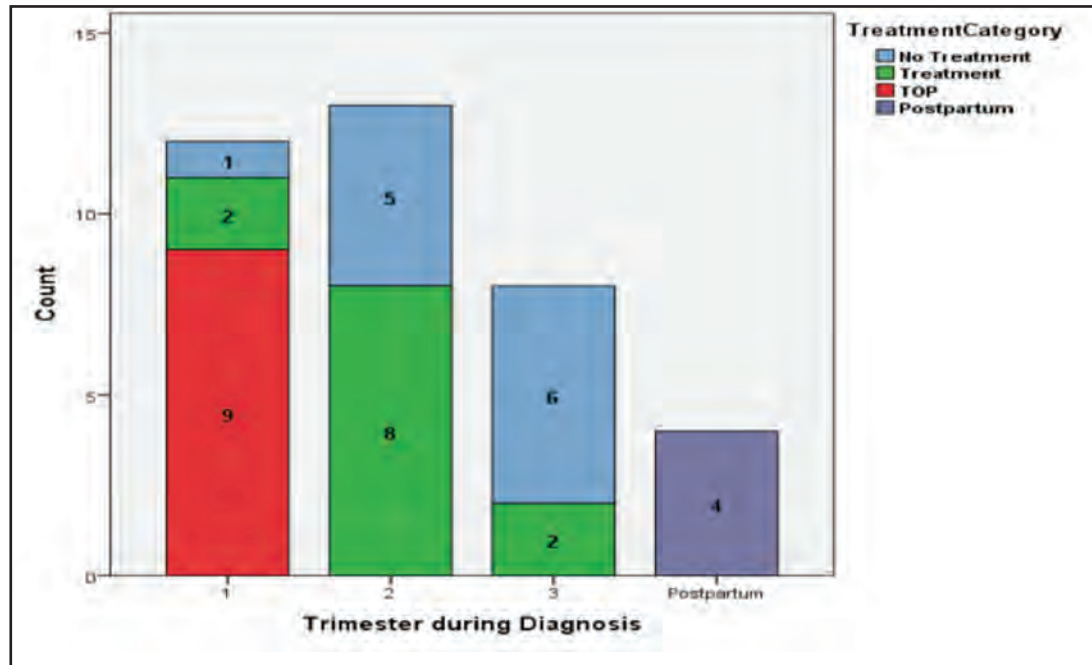


Fig. 1: Trimester when the diagnosis was made and antenatal management of 37 pregnancies complicated with acute leukemia or lymphoma

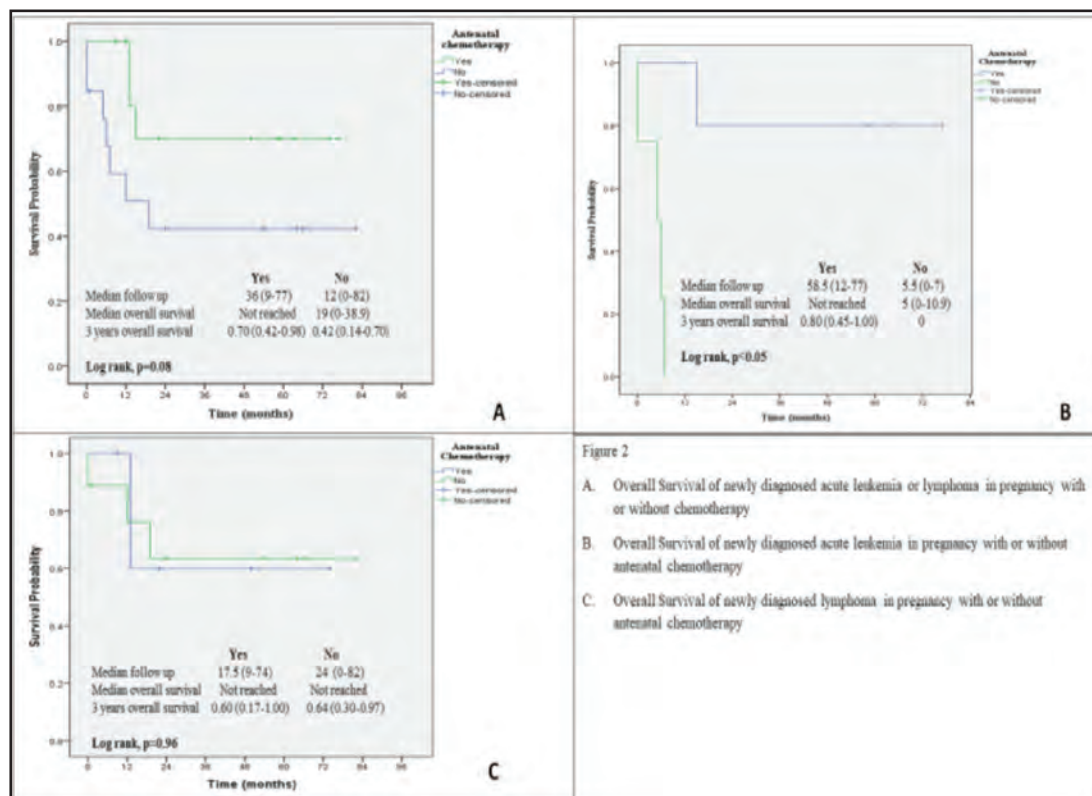


Fig. 2: Overall survival of newly diagnosed acute leukemia or lymphoma in pregnancy with or without chemotherapy

maternal neutropenic sepsis has resulted in preterm births leading to neonatal death at day 18 of life contributed by prematurity, neutropenic sepsis and congenital heart disease.

Maternal Long-term Outcome

Pregnancies with newly diagnosed acute leukemia or lymphoma that were not therapeutically terminated were selected for survival analysis. With median follow up of 19 months (0-82 months) of twenty-five pregnancies (Figure 2), antenatal chemotherapy has longer median survival (not reached) than cohort without antenatal chemotherapy, 19 months (95% CI, 0-38.9) but the difference is not significant (χ^2 (1), $p=0.08$). However, subgroup analysis of newly diagnosed acute leukemia in pregnancy shows that median survival is significantly better with antenatal chemotherapy versus no antenatal chemotherapy (χ^2 (1), $p<0.05$), not reached as compared to 5 months. While subgroup analysis with newly diagnosed lymphoma in pregnancy does not demonstrate significant a difference of median survival with antenatal chemotherapy.

DISCUSSION

We observe significant premature livebirths due to iatrogenic delivery either by induction of labour or elective caesarean section in our study. The frequency is significantly higher compared to the frequency that occurred in the general population⁹. This finding is similar to many cohort studies and case series of cancers in pregnancy but the association between antenatal chemotherapy and preterm birth is controversial.^{4,6,9-11} The frequency of preterm birth has no significant association with antenatal chemotherapy in our study. The decision for iatrogenic preterm birth may be multifactorial namely maternal deterioration, fetal distress, limitation of fetal exposure to chemotherapy, initiation of treatment, expedite diagnostic process or preference for planned controlled delivery. The question of whether iatrogenic preterm delivery should be a standard practice is controversial. Managing team needs to be aware that preterm delivery is known to have adverse effects on perinatal outcome and neurodevelopment later and Lu et al. have stated that preterm birth explained 89% of neonatal mortality in mother with cancers.¹² The effect of preterm births is also reflected in the increased incidence of neonatal intensive care admission of 81% of all livebirths.

Cytotoxic drugs used to treat acute leukemia and lymphoma such as cyclophosphamide, anthracyclines, cytarabine, vinca alkaloids are known to cross the placenta but probably with reduced fetal concentration with the placenta acting as barrier.⁷ Administration of cytotoxic drugs during 1st trimester of pregnancy has been associated with embryo death, spontaneous abortion and teratogenicity with the estimated risk of 25% if combination chemotherapy.^{6,13-14} Two pregnancies which had chemotherapy in 1st trimester had unfavorable outcome. Our cohort reported a likely association of unintended decitabine exposure in 1st trimester of pregnancy with serious fetal anomalies and was therapeutically aborted⁸. The other pregnancy was complicated with pre-eclampsia and stillbirth. The international consensus panel made the recommendations that termination of pregnancy may be contemplated if treatment cannot be delayed beyond 1st trimester due to

maternal deteriorating condition or aggressiveness of disease.⁶ At the time of writing, only one study has reported favorable outcome (no fetal anomaly, low rate of prematurity and favorable long term outcome) for pregnancy complicated with hematological malignancy that received chemotherapy in 1st trimester.¹⁵ However, the majority of literatures have not reported similar finding.¹⁶⁻¹⁷

Antenatal chemotherapy from the 2nd trimester onwards is not associated with increased risk of congenital anomalies but with intrauterine growth restriction (IUGR), prematurity, lower birth weight, small for gestational age and a higher rate of stillbirth.^{4,10,17-18} Our study reported no significant difference in frequency of congenital anomalies, small for gestational age and median birthweight between the cohort that received antenatal chemotherapy and the cohort that did not. Furthermore, 7 pregnancies in our cohort were treated with more than 1 cycle of chemotherapy with some receiving intensive chemotherapy such as high dose cytarabine with a favorable outcome. A study of breast cancer in pregnancy by Cardonick et al. shows that birthweight and rate of small for gestational age were not significantly affected by antenatal chemotherapy.¹⁹ A retrospective study by Garofalo et al. from Italy also demonstrated that birthweight and rate of small for gestational age did not differ between the group that received chemotherapy and the group that did not.²⁰ The lack of difference may suggest that malignancy itself has adverse effects on fetal growth. Hematological malignancies probably has stronger association with small for gestational age compared with other solid tumors, while leukemia has a more profound effect than lymphoma.^{10,12} The underlying mechanisms that have been proposed include having an impaired placental supply of oxygen and nutrient, maternal malnutrition, chronic inflammation, anemia and thrombosis.²⁰⁻²¹

Transient neonatal myelosuppression (TNM), defined as leukopenia and/or neutropenia combined with anemia and/or thrombocytopenia during the 1st week of life in newborns exposed to maternal chemotherapy during pregnancy has been reported in case reports and reviews. Neonates with TNM may be at risk of infection but the outcome was favorable with one death among fifteen cases of TNM from the review by Udink et al.²¹ This complication is probably rare but the interval between antenatal chemotherapy to delivery probably is the most significant risk factor corresponding to maternal myelosuppression nadir.²¹ In a case series of fifty neonates exposed to antenatal chemotherapy for acute leukemia in the last month of pregnancy, 33% were cytopenic at birth with one neonatal death at day 21 and additional mortality at day 90. We observed a neonatal death with antenatal exposure of high dose cytarabine consolidation two weeks before birth due to neutropenic sepsis complicated with multiple organ dysfunction and the absolute neutrophil count was 0 at birth coinciding with maternal neutropenic sepsis. Four neonates with antenatal chemotherapy (two had RCHOP, an ABVD and an ATRA) within three weeks of delivery did not suffer from such complication. Different regimes of chemotherapy with variable intensity leading to variable duration of myelosuppression may explain this observation. Therefore, it is recommended to avoid delivery during maternal myelosuppression nadir and antenatal chemotherapy should

not be administered beyond 35th weeks of gestation or within three weeks of anticipated delivery.^{18,22}

Though antenatal chemotherapy poses significant risks to fetus and neonate, the neonatal outcome is generally favorable. As acute leukemia and certain lymphoma are generally aggressive diseases and patients may present with life threatening presentation, maternal well-being should take precedence and treatment should not be delayed and pregnant patient should be treated similarly as non-pregnant patient if possible. Delay in treatment due to concern for fetal risk may jeopardize maternal safety leading to maternal death during pregnancy. The largest registry of cancer in pregnancy did not report any chemotherapy-related mortality of all cancer types.⁴ A multicenter retrospective study on lymphoma occurring in pregnancy did not observe any chemotherapy-related death but a retrospective study of 37 cases of acute leukemia in pregnancy reported an induction death.²³⁻²⁴ Our data demonstrated the tolerability of antenatal chemotherapy for mothers with no treatment related mortality and the commonest toxicity being neutropenic sepsis which was manageable with good supportive treatment. The four early maternal deaths during pregnancy in our cohort without antenatal chemotherapy stresses that deferment of treatment for aggressive hematological malignancy to after delivery due to concern for fetal wellbeing may subject both mother and fetus to unacceptable risk of mortality and morbidity.

Our finding shows delay in treatment for acute leukemia in pregnancy may result in inferior overall survival probably due to early mortality. Lack of significant difference of overall survival of lymphoma in pregnancy based on receipt of antenatal chemotherapy indicates selected patients with indolent course, low tumor burden, diagnosis at advanced pregnancy may have treatment deferred to after delivery after careful assessment without affecting the long term outcome.^{7,24-25}

We observe significant pregnancies in our cohort which were complicated with non-newly diagnosed leukemia or lymphoma have a higher incidence of therapeutic pregnancy termination and poorer obstetric outcome. Furthermore, 3 mothers had 2 consecutive pregnancies complicated with active hematological malignancies implies a lack of integration of fertility planning and contraceptive counselling into the management of female patients with hematological malignancies in reproductive age. Female cancer patients within reproductive age may remain fertile with normal menstruation after chemotherapy or radiotherapy and 45% participants of one cross-sectional study would terminate the pregnancy if they became pregnant during treatment. In addition to that, a majority of participants did not practice effective contraception method during cancer treatment.²⁶ Pregnancy should be avoided within 2-3 years of remission of hematological malignancies due to probability of recurrence during this period.¹ Unplanned pregnancy during or shortly after cancer treatment may result in unintended chemotherapy administration which is demonstrated in two cases in our cohort resulting in poor obstetric and neonatal outcome.

Most of the retrospective and observational studies are derived from European countries and our study offers a perspective from Malaysia, a developing country in South East Asia. It offers an insight into our treatment strategy and challenges faced in managing pregnancy associated with acute leukemia or lymphoma in comparison with other countries.

One significant limitation is the small sample size from a single center and with retrospective research design. Multicenter involvement with the establishment of a national registry for hematological malignancy in pregnancy in the future would allow collaboration with the international registry to improve clinical knowledge and recommend evidence-based practice. In addition to that, a larger sample size may allow analysis into specific hematological malignancy to enable disease-specific management recommendations.

CONCLUSION

Management of acute leukemia or lymphoma in pregnancy is challenging. Treatment with chemotherapy in 2nd trimester of pregnancy onwards appears to have tolerable risks with favorable obstetric and fetal outcome. Deferment of treatment for acute leukemia in pregnancy to after delivery may cause increased risk of maternal and fetal adverse outcome but may be considered in certain subsets of lymphoma in pregnancy.

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DECLARATIONS

This study was approved by the medical research and ethics committee, Ministry of Health Malaysia NMRR-19-3980-51915.

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Breaking through the steroid stigma: a single-centre study on topical corticosteroid perception and adherence in dermatology patients and caregivers

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ABSTRACT

Introduction: Topical corticosteroid phobia is a common phenomenon that can result in poor treatment adherence and therapeutic failure. **Objectives:** This study aims to evaluate the prevalence and degree of topical corticosteroid phobia and its impact on treatment adherence in various dermatological conditions. Additionally, we explored the sources of information regarding topical corticosteroids.

Materials and Methods: A cross-sectional study was conducted among 300 participants with topical corticosteroid usage experience. Topical corticosteroid phobia was assessed with the topical corticosteroid phobia (TOPICOP) scale, and treatment adherence was measured with the Elaboration d'un outil d'évaluation de l'observance des traitements médicamenteux (ECOB) score. Information sources regarding topical corticosteroids were identified, and their level of trust was assessed. The data were collected via questionnaires in three languages, namely English, Malay and Mandarin.

Results: The study found that topical corticosteroid phobia was prevalent, with 98% of participants expressing a certain degree of phobia. The mean global TOPICOP score was $32.7 \pm 6.7\%$. The mean score of each domain was $27.1 \pm 17.2\%$ for knowledge and belief, $35.7 \pm 23.8\%$ for fears and $40.8 \pm 25.8\%$ for behaviour. Patients/caregivers who have eczema, highly educated, severe disease, low tolerability to symptoms, previous adverse effects with topical corticosteroids and tend to traditional/non-steroidal alternative therapy usage had a significant association with topical corticosteroid phobia ($p < 0.05$). Dermatologists were the most common and trusted source of information on topical corticosteroids.

Conclusions: This study highlights the widespread topical corticosteroid phobia in dermatological practice. Dermatologists should take the lead in combating steroid phobia and provide patients with public awareness regarding topical corticosteroids to improve treatment adherence and therapeutic outcomes.

KEYWORDS:

Topical corticosteroids, steroid phobia, TOPICOP, treatment adherence

INTRODUCTION

Topical corticosteroids have been a cornerstone of dermatological practice for over 70 years, effectively treating a wide range of skin conditions from inflammatory diseases to autoimmune disorders.¹⁻³ Although the adverse effects of topical corticosteroids have been well documented, their efficacy and safety, if used appropriately, are equally well recognised.¹⁻² Nevertheless, topical corticosteroid phobia remains a prevalent issue encountered in everyday clinical practice, where patients or caregivers experience excessive fear and anxiety about using topical corticosteroids.⁴⁻⁸ Systematic reviews from 2017 to 2021 reported that the prevalence of topical corticosteroid phobia ranged from 21.0% to 95.7%.⁹⁻¹⁰

Topical corticosteroid phobia posed a significant obstacle to therapy adherence, resulting in poor treatment outcomes and reduced quality of life.^{5,7,10-15} Kojima et al. found a higher non-adherence rate of 57.7% among patients with topical corticosteroid phobia than patients without topical corticosteroid phobia who reported non-adherence (25.0%).¹² Factors contributing to topical corticosteroid phobia may include misinformation from various sources, such as the internet, friends, relatives and even healthcare professionals.^{3,6,8,10,12-13,16-19}

As a diverse and multi-ethnic nation, Malaysia is home to various disease backgrounds. Despite the prevalence of steroid phobia, there has been a lack of studies on this issue in our country, until now.^{14,25} Previous studies also often used the term "phobia" empirically without properly quantifying the studied parameters.^{5,7,9,12} Our primary objective is to assess the prevalence and define the degree of topical corticosteroid phobia in the local setting. The secondary objectives are to study the correlation of topical corticosteroid phobia with treatment adherence and identify the sources of topical corticosteroid-related information. This study aims to provide a better understanding of the phenomenon of topical corticosteroid phobia and inform future educational and counselling efforts to improve adherence to topical corticosteroid therapy.

MATERIALS AND METHODS

The present cross-sectional study was carried out at the

dermatology clinic of Hospital Sultanah Bahiyah, Alor Setar, Kedah between July 2021 and February 2022. Participants with a history of topical corticosteroid usage, including patients or caregivers, were invited to participate in the survey irrespective of their primary dermatological conditions. In the case of participants under the age of 18, their parents or guardians assisted with the questionnaire.

Data were collected through a comprehensive questionnaire that was divided into four parts. The first part gathered information on participant demographics, skin conditions, and past experiences with topical corticosteroids. The second part involved the use of the validated Elaboration d'un outil d'évaluation de l'observance des traitements médicamenteux (ECOB) topical treatment mini questionnaire consisting of four questions to assess treatment compliance.²¹ The third part evaluated the level of topical corticosteroid phobia using the validated Topical Corticosteroid Phobia Scale (TOPICOP), which measured 12 items across three domains of topical corticosteroid phobia (knowledge and beliefs, fears and behaviour) in atopic dermatitis. The responses were scored on a four-point Likert scale (score range 0–3: 0=never, 1=sometimes, 2=often and 3=always; or 0= totally disagree, 1=do not really agree, 2=almost agree and 3=totally agree) to a maximum of 36 points. The higher the score, the higher the degree of steroid phobia.⁵ Additional questions were included to assess traditional/herbal medicine usage and willingness to use a non-steroidal agent. The last part of the questionnaire investigated the sources of information on topical corticosteroids and assessed the level of trust in each of these sources. Permission to use the questionnaires and translate them into other languages was obtained from the authors.

The questionnaire was translated into Malay and Mandarin languages using forward and backward translations. A pilot study involving 15 participants for each language was conducted to assess the test-retest and intra-rater reliabilities using Cohen's unweighted kappa statistic for nominal scale (ECOB) and intraclass correlation coefficient (ICC) for interval scale (TOPICOP).^{20,22} The k values for questions ECOB1 and ECOB4 in Malay and Mandarin questionnaires ranged from 0.71 to 0.74 ($p < 0.05$) and 0.76 to 1.00 ($p < 0.05$), indicating a substantial to almost perfect strength of agreement between the test and retest. However, Cohen's kappa was inconclusive for questions EOB2 and EOB3 in the Malay questionnaire because three out of four subcategorical values were ≤ 1 . Nevertheless, both EOB2 and EOB3 showed high concordance pairs during comparison with EOB2 having 13/15 concordance pairs and EOB3 having 14/15. The ICC revealed moderate to almost perfect reliability in Malay (0.54–0.88, $p < 0.05$) and Mandarin (0.54–0.94, $p < 0.05$) questionnaires.

The calculated sample size was 279 including an additional 10% potential dropout from the survey.²³ Descriptive statistics were used to analyse the final responses, which were presented as frequencies and percentages for categorical variables. Independent t -test was used to identify binary variables, while one-way ANOVA was used to assess variables with multiple groups associated with greater TOPICOP scores. Fisher's exact test and Pearson Chi-square

test were applied to determine the association between categorical variables. Statistical significance was set at p -value < 0.05 . The data analysis was performed using SPSS statistics for Windows, version 26.

This study was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia, and was registered with the National Medical Research Registry (NMRR-21-1312-5999). All ethical considerations were taken into account to ensure the confidentiality of the participants' data.

RESULTS

This study recruited a sizable cohort of 300 participants, and their socio-demographic and clinical characteristics were summarised in Table I. Of these participants, 41.7% were male and 58.3% were female, with a median age of 46 years. The most prevalent skin conditions reported were eczema (61.5%), psoriasis (31.3%), vitiligo (3.2%), connective tissue disease (3.2%) and seborrheic dermatitis (1.1%). Notably, non-drug adherence (54%) slightly outstripped the adherence group (46%).

The responses of participants to the TOPICOP scale were analysed based on the various domains assessed, as depicted in Table II. 98% ($n=294$) of the participants indicated some level of steroid phobia in the present study. The mean global TOPICOP score was $32.7 \pm 16.7\%$. Further, the mean score of each domain was $27.1 \pm 17.2\%$ for knowledge and belief, $35.7 \pm 23.8\%$ for fears and $40.8 \pm 25.8\%$ for behaviour.

Our research findings highlight the fact that patients with eczema are more prone to steroid phobia compared to those without this condition. This disparity was significant in the behaviour domain ($t=2.12$, $p=0.03$). Our results also revealed that patients who showed non-adherence tendencies scored higher on the TOPICOP scale. This relationship was statistically significant in the behaviour domain ($t=2.15$, $p=0.03$).

The results of the study indicate a statistically significant relationship between education levels and mean scores in the TOPICOP domains of global ($F(2, 297)=7.5$, $p=0.00$), knowledge and belief ($F(2, 297)=3.5$, $p=0.03$) and fear ($F(2, 297)=12.1$, $p=0.00$). Specifically, the mean scores were significantly higher in participants with university-level education compared to those with secondary or non-formal education-primary education levels in all three domains. In the global domain, the mean scores for the university group were $36 \pm 16.6\%$, significantly higher than the scores for the secondary education group ($30.8 \pm 15.6\%$, $p=0.03$) and the non-formal education-primary education group ($24.2 \pm 19.0\%$, $p=0.00$). In the knowledge and belief domain, the university group had a mean score of $29 \pm 16.2\%$, which was significantly higher than the score for the non-formal education-primary education group ($19.5 \pm 20.7\%$, $p=0.03$). In the fear domain, the university group had a mean score of $41.6 \pm 23.9\%$, which was significantly higher than the score for the secondary education group ($32.2 \pm 21.4\%$, $p=0.00$) and the non-formal education-primary education group ($20.6 \pm 25.4\%$, $p=0.00$) (Table III). Furthermore, the data revealed a significant association between non-adherence

Table I: Socio-demographic and clinical characteristics of participants

Variable	No. (%)
Gender (n=300)	
Male	125 (41.7)
Female	175 (58.3)
Age range (years; n=300)	
≤ 20	12 (4)
21–30	61 (20.3)
31–40	62 (20.7)
41–50	59 (19.7)
51–60	43 (14.3)
≥ 61	63 (21)
Ethnicity (n=300)	
Malay	221 (73.7)
Chinese	62 (20.7)
Indian	10 (3.3)
Other	7 (2.3)
Education level (n=300)	
Non-formal education	3 (1)
Primary school	24 (8)
Secondary school	129 (43)
Pre-university education	88 (29.3)
Undergraduate degree	50 (16.7)
Master's degree/Doctorate	6 (2)
Top five reported skin conditions (n=283)	
Eczema	174 (61.5)
Psoriasis	88 (31.1)
Vitiligo	9 (3.2)
Connective tissue diseases	9 (3.2)
Seborrheic dermatitis	3 (1.1)
Duration of skin condition (n=300)	
< 6 weeks	2 (0.7)
6 weeks–3 months	15 (5)
3 months–1 year	32 (10.7)
1 year–2 years	41 (13.7)
> 2 years	210 (70)
Perceived severity of skin condition (n=300)	
Lowest severity	37 (12.3)
Low severity	82 (27.3)
Moderate severity	137 (45.7)
High severity	44 (14.7)
Perceived tolerance to skin condition (n=300)	
Lowest tolerance	14 (4.7)
Low tolerance	48 (16)
Moderate tolerance	183 (61)
High tolerance	55 (18.3)
Period of steroid use (n=300)	
< 2 weeks	8 (2.7)
2 weeks–3 months	42 (14)
3 months–1 year	38 (12.7)
> 1 year–2 years	37 (12.3)
> 2 years	175 (58.3)
Adherence with topical steroids *ECOB score (n=300)	
Adherence	138 (46)
Non-adherence	162 (54)

and non-formal education-primary education levels, with 81.5% of non-adherence participants belonging to this group (Table IV).

The present study investigates the relationship between disease severity, tolerability of skin symptoms, and fear of using topical corticosteroids in the management of skin conditions. The results revealed that participants who perceived high disease severity had significantly higher knowledge and belief domain scores than those who

perceived low disease severity ($F(3, 296)=2.9, p=0.04$; post hoc analysis: high severity, $33\pm22.2\%$ vs low severity, $23.6\pm16.9\%$, $p=0.02$). The study also found that participants with high tolerability to skin symptoms had lower fear domain scores than those with moderate tolerability ($F(3, 296)=1.7, p=0.02$; post hoc analysis: high tolerability, $27.7\pm24.5\%$ vs moderate tolerability, $37.7\pm23.4\%$, $p=0.04$). There was no significant difference observed between the high tolerability group and the other groups (Table III).

Table II: Degree of steroid phobia based on TOPICOP scale with additional questions

Dimension	Domain subscore Mean $\pm$ SD (%)	Question	%			
			Totally disagree/ never	Not really agree/ sometimes	Almost agree/ often	Totally agree/ always
Knowledge and belief	27.1 $\pm$ 17.2%	Topical corticosteroids pass into the bloodstream	15.3	43.0	38.0	3.7
		Topical corticosteroids can lead to infections	41.3	50.7	6.7	1.3
		Topical corticosteroids make you fat	54.0	37.3	6.7	2.0
		Topical corticosteroids damage your skin	35.7	43.3	17.0	4.0
		Topical corticosteroids will affect my future health	33.0	47.7	16.7	2.7
Fears	35.7 $\pm$ 23.8%	Topical corticosteroids can lead to asthma	50.0	45.3	3.7	1.0
		I am afraid of putting cream (topical corticosteroids) on certain zones like the eyelids where the skin is thinner	32.3	33.0	18.7	16.0
		I don't know of any side effects but I'm still afraid of topical corticosteroids	28.0	36.0	28.0	8.0
		I am afraid of applying too much cream (topical corticosteroids)	34.0	50.3	10.7	5.0
		I wait as long as I can before treating myself with topical corticosteroids	41.7	35.3	19.0	4.0
Behaviour	40.8 $\pm$ 25.8%	I stop treatment as soon as I can	41.0	32.3	20.3	6.3
		I need reassurance about topical corticosteroids	15.7	17.7	27.7	39
		I would rather try TCMs/herbal medications before using topical corticosteroids	66.7	23.0	7.3	3.0
Global TOPICOP score Additional questions	32.7 $\pm$ 16.7%	I would rather use something that does not contain steroids	43	31.7	16	9.3
		I have benefited from topical corticosteroid use	4	11.7	66	18.3
		I have experienced side effects from topical corticosteroid use	37.3	44	16.3	2.3

SD: standard deviation; TCM: traditional Chinese medicine; TOPICOP: topical corticosteroid phobia

According to the findings presented in the study, there is a significant relationship between higher TOPICOP scores and the likelihood of trying traditional medicine ($p=0.00$) and non-steroidal alternatives ($p=0.00$), respectively (Table III). Moreover, the results indicate that a considerable proportion of participants who portrayed a preference for traditional medicine ($p=0.01$) and non-steroidal alternatives ($p=0.04$) did not comply with topical corticosteroids (Table IV).

The study results demonstrated a significant difference in TOPICOP scores between participants who experienced a positive outcome from topical corticosteroid therapy and those who did not. Participants who benefited from topical corticosteroid therapy showed a lower TOPICOP score ($p=0.00$), whereas those who suffered from adverse effects of topical corticosteroids had a higher TOPICOP score ($p=0.00$) (Table III). The findings also suggest that poor adherence to treatment was associated with participants who did not benefit from topical corticosteroid therapy ($p=0.01$) and experienced negative effects ($p=0.09$) (Table IV).

Our study results indicated that various socio-demographic variables, such as gender, age, ethnicity, marital status, income, duration of skin conditions and steroid usage did not

show any significant association with the global TOPICOP score and other domains.

A substantial proportion of the study participants obtained knowledge about topical corticosteroids from multiple sources, including dermatologists (76.3%), other doctors (28.3%), the internet and media (26.6%) and friends and family (16%). Of these, the majority of participants (99.3%) trusted the expertise of dermatologists, while 82.3% had confidence in other doctors' knowledge. The internet and media were a source of information for just over half of the participants (54.3%), with 46.7% expressing trust in friends and family as a source of information (Table V).

DISCUSSION

The debilitating condition of atopic dermatitis affects many individuals, but the presence of steroid phobia has made effective management of symptoms a challenging task.^{3,9,10,11,13} The emergence of TOPICOP has facilitated the assessment and comparison of steroid phobia, making treatment more accessible. With its demonstrated efficacy in evaluating patients with a range of dermatological conditions, TOPICOP has proven to be an indispensable tool.^{16,24} Our study is the

Table III: Comparison of TOPICOP means scores across participant characteristics

	Knowledge and Belief		Fears		Behaviour		Global	
Education level	Mean±SD (%)							
Non-formal education-primary education	19.5±20.7 ^a		20.6±25.4 ^a		37.0±22.0		24.2±19.0 ^a	
Secondary education	26.7±17.2		32.2±21.4 ^b		37.5±25.7		30.8±15.6 ^b	
University	29.0±16.2 ^a		41.6±23.9 ^{a, b}		44.5±26.2		36.0±16.6 ^{a, b}	
F p	3.5	0.03	12.1	0.00	2.9	0.06	7.5	0.00
Disease severity								
Lowest	27.1±16.8		30.9±22.7		40.8±28.7		31.5±17.9	
Low	23.6±16.9 ^a		33.7±23.4		40.2±24.4		30.3±16.9	
Moderate	27.4±15.3		35.9±23.7		41.1±25.2		32.9±15.4	
High	33.0±22.2 ^a		42.4±25.2		40.9±28.5		37.3±19.0	
F p	2.9	0.04	1.7	0.14	0.0	1.00	1.7	0.16
Disease tolerability								
Lowest	26.6±19.3		29.4±26.0		29.4±29.1		28.0±19.5	
Low	27.4±16.1		38.9±22.2		44.7±28.8		34.6±16.5	
Moderate	28.5±16.8		37.7±23.4 ^a		40.9±24.9		33.9±15.7	
High	22.5±18.8		27.7±24.5 ^a		40.0±24.9		28.2±19.0	
F p	1.7	0.16	3.2	0.02	1.3	0.27	2.3	0.08
Traditional medicine								
Never	23.5±16.2 ^{a, b, c}		31.1±23.1 ^{a, b, c}		36.1±24.6 ^{a, b, c}		28.5±15.4 ^{a, b, c}	
Sometimes	31.7±15.5 ^a		40.6±22.5 ^{a, d}		45.9±23.8 ^a		37.5±14.8 ^{a, d, e}	
Often	40.9±16.0 ^b		48.5±17.0 ^b		60.1±29.4 ^b		47.6±15.6 ^{b, d}	
Always	40.1±24.8 ^c		67.9±23.9 ^{c, d}		60.5±23.0 ^c		52.2±20.0 ^{c, e}	
F p	12.3	0.00	12.3	0.00	9.8	0.00	18.7	0.00
Non-steroidal alternatives								
Never	20.6±16.9 ^{a, b, c}		25.8±21.7 ^{a, b, c}		30.4±23.3 ^{a, b, c}		24.4±15.2 ^{a, b, c}	
Sometimes	30.3±14.3 ^a		40.8±17.5 ^a		44.1±20.6 ^{a, d}		36.4±12.7 ^{a, d}	
Often	34.4±17.1 ^b		42.8±24.4 ^b		49.1±27.1 ^b		40.2±16.0 ^b	
Always	34.1±18.5 ^c		51.6±32.2 ^c		63.5±29.0 ^{c, d}		45.8±18.7 ^{c, d}	
F p	12.9	0.00	16.7	0.00	19.4	0.00	26.5	0.00
Benefited from topical corticosteroids								
Totally disagree	25.0±17.8		33.3±21.7		43.5±34.0		31.7±18.3	
Not really agree	31.7±14.4 ^a		44.4±24.4 ^a		47.6±24.0 ^a		38.9±14.6 ^a	
Almost agree	29.9±16.1 ^b		38.4±22.4		42.4±25.2 ^b		35.1±15.7	
Totally agree	14.7±17.5 ^{a, b}		20.8±23.1 ^a		30.3±24.8 ^{a, b}		20.2±15.5 ^a	
F p	13.6	0.00	10.5	0.00	4.3	0.01	15.2	0.00
Adverse effects from topical corticosteroids								
Totally disagree	16.7±15.3		22.4±23.2		28.5±24.1		21.1± 14.5	
Not really agree	31.0±13.7 ^a		39.1±18.2 ^a		44.8±23.2 ^a		36.5± 12.3 ^a	
Almost agree	40.6±17.5 ^b		53.1±22.1 ^b		53.7±22.0 ^b		47.0± 10.4 ^b	
Totally agree	27.0±12.2 ^{a, b}		61.9±20.1 ^{a, b}		73.0±32.0 ^{a, b}		47.2± 14.4 ^{a, b}	
F p	34.5	0.00	31.3	0.00	20.8	0.00	50.8	0.00

a-e: groups with significant differences in post hoc analysis
SD: standard deviation

first to explore the phenomenon of steroid phobia in the local population and its impact on atopic dermatitis, as well as other dermatological conditions.

Our study results revealed that an overwhelming majority of participants (98%, n=294) experienced a sense of fear when it came to using topical corticosteroids. Interestingly, previous studies reported a relatively lower percentage of individuals (39-59.6%) expressing similar concerns about topical corticosteroid usage in atopic dermatitis.^{14,25} Our study also showed that our mean global TOPICOP score was 32.7%, falling below the average range reported in other countries (20.7–58.4%).^{3,16,26} This disparity in scores reflects the significant cultural diversity between different regions worldwide. Additionally, our study population consisted of patients with varying dermatological conditions, making it challenging to compare the results directly with existing literature.

Steroid phobia originated from confusion and

misunderstanding about topical corticosteroids.^{6,10,12-13,16-18} In our study, nearly half (41.7%) of the participants believed that topical corticosteroids could pass into their bloodstream, but the truth is that systemic absorption is minimal when used correctly.^{2,8,28} Surprisingly, over a third of the cohort (36%) did not know of any side effects associated with topical corticosteroids, and two-thirds (66.7%) needed reassurance about steroid therapy. It is clear that a lack of knowledge and conflicting information only perpetuates fear and anxiety among steroid users.^{6,11} That is why it is crucial to empower patients and caregivers with accurate information, so they can feel confident in the safety of steroid therapy and have guidance in recognising the varying potency of topical corticosteroid formulations.^{10,11,13}

Our study has uncovered an interesting correlation that participants with eczema expressed a higher degree of steroid phobia than those without the condition, particularly in the behaviour domain (p=0.03). This may be because eczema is more common among the young population and patients or caregivers worry about prolonged steroid usage.²⁴

Table IV: The association of treatment adherence with sociodemographic and clinical characteristics of participants

		Treatment adherence No (%)		<i>p</i>
		Adherence	Non-adherence	
Education level	Non-formal education-primary education	5 (18.5%)	22 (81.5%)	0.01 ^a
	Secondary education	62 (48.1%)	67 (51.9%)	
	University	71 (49.3%)	73 (50.7%)	
Duration of skin condition	<1 year	16 (32.7%)	33 (67.3%)	0.04 ^a
	>1 year	122 (48.6%)	129 (51.4%)	
Traditional medicine use	Never	94 (47%)	106 (53%)	0.01 ^b
	Sometimes	38 (55.1%)	31 (44.9%)	
	Often	4 (18.2%)	18 (81.8%)	
	Always	2 (22.2%)	7 (77.8%)	
Non-steroidal alternative treatment use	Never	69 (53.5%)	60 (46.5%)	0.04 ^a
	Sometimes	44 (46.3%)	51 (53.7%)	
	Often	15 (31.3%)	33 (68.8%)	
	Always	10 (35.7%)	18 (64.3%)	
Benefited from topical corticosteroids	Totally disagree	4 (33.3%)	8 (66.7%)	0.01 ^a
	Not really agree	7 (20%)	28 (80%)	
	Almost agree	100 (50.5%)	98 (49.5%)	
	Totally agree	27 (49.1%)	28 (50.9%)	
Experienced adverse effects from topical corticosteroids	Totally disagree	57 (41.3%)	55 (34%)	0.09 ^b
	Not really agree	63 (47.7%)	69 (52.3%)	
	Almost agree	17 (34.7%)	32 (65.3%)	
	Totally agree	1 (14.3%)	6 (85.7%)	

^a: Pearson Chi-square; ^b: Fisher's exact test

Table V: Sources of information regarding topical steroids and level of trust

%				
1. Where do you get information on topical corticosteroids?				
	Never	Sometimes	Often	Always
Dermatologists	0.3	23.3	23.0	53.3
Other doctors	37.0	34.7	18.3	10.0
Friends and family	50.0	34.0	8.3	7.7
Internet and the media	37	36.3	14.3	12.3
2. How much do you trust the following sources for information on topical corticosteroids?				
	Always distrust	Sometimes distrust	Sometimes trust	Always trust
Dermatologists	0.0	0.7	16.3	83.0
Other doctors	10.7	7.0	37.0	45.3
Friends and family	27.7	25.7	35.7	11.0
Internet and the media	24.0	21.7	41.0	13.3

Sadly, the greater the fear of topical corticosteroids, the less likely patients are to comply with their prescribed therapy, leading to treatment failure.¹³ This issue has been emphasised by many parties and supported by previous studies, including our own.^{9-12,15} In fact, we found that the non-adherence cohort scored higher on the TOPICOP scale, reinforcing the critical role of addressing steroid phobia in improving patient outcomes.

According to Noorlaili et al., there is a strong link between education level and steroid phobia, with those who have attained higher education levels being more prone to this fear ($p=0.01$).¹⁴ Similarly, in the same study, individuals with advanced education also had significantly higher scores on the TOPICOP scale ($p<0.05$), indicating a greater knowledge of steroids and their potential effects. This suggests that individuals with higher education levels are more likely to seek information from various sources, such as doctors, the internet and the media, and as a result, have a more in-depth understanding of steroid usage and side effects. Although this correlation between education and steroid phobia is not

commonly reported in other literature, it sheds light on the various factors that may contribute to this phenomenon.¹⁶

A recent systemic review of 37 studies revealed that caretakers of patients with severe atopic dermatitis were more likely to exhibit steroid phobia.¹⁰ Our study also found a significant correlation between high disease severity and a greater knowledge and belief domain score ($p=0.04$), while participants who had a higher tolerance for their skin symptoms demonstrated less fear of topical corticosteroids. ($p=0.02$). This suggests that the presumed cause-and-effect relationship between disease severity and tolerability with steroid phobia may be reversed. In other words, steroid phobia may be responsible for the improper use of topical corticosteroids, leading to uncontrolled disease and low tolerance levels. However, it should be noted that some studies have found no connection between steroid phobia and the severity of illness or tolerance.¹²⁻¹³

This study offers a fascinating insight into the potential link between a fear of using topical corticosteroids and a preference for traditional medicine and non-steroidal

alternatives. We found that participants with higher TOPICOP scores were more inclined to try traditional medicine ($p=0.00$) and non-steroidal alternatives ($p=0.00$) and demonstrated low adherence to steroid therapy ($p<0.05$). While traditional and alternative therapies remain unproven in efficacy, they are highly acceptable in many Asian cities and gaining popularity in the Western world.^{3,7,13,16,20} In fact, parents in an Australian focus-group study expressed a preference for “natural” therapies they believed to be safer than medical treatment with topical steroids.¹⁸ Similarly, approximately 50% of participants in a study by Choi et al. would opt for a non-steroidal agent, even if it were more expensive.¹⁶ Ironically, some of these alternative treatments may contain potent corticosteroids, which can be inadvertently used by steroid-phobic patients.²⁰ To address this issue, steroid-sparing agents such as calcineurin inhibitors and phosphodiesterase inhibitors may provide a viable alternative for patients and caregivers who are wary of using topical steroids.

It comes as no surprise that individuals who do not experience the desired effects of topical corticosteroids or suffer from adverse reactions are more prone to steroid phobia ($p<0.05$). Such fear may result in unfavourable clinical outcomes, such as early discontinuation of therapy and limited use of topical corticosteroids. Consequently, this may lead to inadequate anti-inflammatory action, resulting in a chronic disease course and frequent relapses.^{8,10} Therefore, it is essential for treating physicians to closely monitor treatment response and disease progression. Encouraging patients and their caretakers to share their experiences can facilitate the establishment of a quality patient-physician relationship. This connection offers an opportunity for early intervention, promotes patients' adherence to therapy, and ultimately leads to better disease control.

The findings of this survey highlighted the critical role of dermatologists as primary sources of information on corticosteroids, as they are the most trusted by patients and caregivers.^{3,6,16} However, conflicting and incorrect messages may still permeate the public sphere, making it crucial for dermatologists to educate their patients on the proper use of topical steroids, including the concept of a fingertip unit.^{3,10} Such education may help alleviate fears of overapplication and improve adherence to therapy. In fact, a study demonstrated that a short educational session led by a dermatologist resulted in a significant improvement in the phobia index score.¹⁹ As such, there is a need to further enhance the role of dermatologists as content providers, with potential avenues for improvement including educational videos targeted towards specific fear and behaviour components.²⁹ Future studies should focus on optimising such approaches to maximise their impact on reducing steroid phobia.

Despite the crucial role of healthcare providers in educating patients about corticosteroid use, recent studies have revealed concerning inaccuracies in the information provided by general practitioners and pharmacists.^{6,8,10,17} Such misinformation can lead to confusion and undermine patient trust in the treatment. It is imperative for healthcare

providers to stay up-to-date with accurate knowledge and information, to ensure patients receive correct messages and promote treatment adherence.

While our study provides valuable insights, it is important to acknowledge its limitations. One such limitation is that it was a single-centre, hospital-based study, which may restrict the generalisability of our findings to the broader population. Moreover, our use of a self-administered questionnaire is subject to certain inherent limitations, such as missing data and potential misinterpretation of questions by participants. Additionally, we were unable to objectively assess the severity of the participants' skin conditions and their tolerance levels. Future studies could investigate the relationship between corticosteroid formulations, potency and the degree of steroid phobia. These studies would be invaluable in identifying effective interventions to overcome steroid phobia and enhance treatment outcomes.

CONCLUSION

The pervasive phenomenon of topical corticosteroid phobia has taken hold in diverse dermatological ailments. Alarming apprehensions were significantly found to be associated with patients/caregivers afflicted with eczema, those with a high level of education, those burdened with severe symptoms, those with low tolerance towards symptoms, those who experienced adverse effects with topical corticosteroids previously, and those who exhibit a tendency towards traditional/alternative therapy usage. Understanding the widespread prevalence of topical corticosteroid phobia provides a comprehensive framework to conduct well-controlled studies that would assess interventions aimed at mitigating the fears and improving treatment outcomes. In this regard, dermatologists are urged to take a proactive stance in overcoming steroid phobia and actively providing their patients with public awareness and education regarding the efficacy and safety of topical corticosteroids.

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Assessment of adherence to antithrombotic therapy in patients with atrial fibrillation during the COVID-19 pandemic

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ABSTRACT

Introduction: Despite epidemiological evidence linking COVID-19 with cardiovascular diseases, little is known about whether and how coronavirus infection (CVI) influences atrial fibrillation (AF), the most prevalent arrhythmia in clinical practice.

Materials and Methods: We examined 621 patients with AF using the Morisky-Green scale (MMAS-4) criteria to assess adherence to antithrombotic therapy. They received inpatient treatment during the COVID-19 pandemic.

Results: A total of 118 patients out of 621 underwent CVI. Most patients had mild (33.9%) and moderate (49.15%) CVI. We managed to confirm the data of studies by foreign authors, according to which treatment with anticoagulants for at least 1 month reduces the severity of coronavirus infection, as well as protects against thrombotic complications.

Conclusion: It is necessary to improve the management of AF, especially if someone was infected with COVID-19. The susceptibility to AF is increased in the acute phase of COVID-19 infection. Personal electrocardiogram devices as well as remote monitoring (teleconsultations) could optimise the care of such patients.

KEYWORDS:

Atrial fibrillation, Morisky-Green scale, COVID-19, antithrombotic therapy

INTRODUCTION

COVID-19 has a diverse clinical picture. Uncontrolled diabetes, hypertension, obesity, old age, as well as male gender are considered to be risk factors, predisposing to severe COVID-19 and cardiovascular diseases as well.¹ Atrial fibrillation (AF) is one of the most important medical and socially significant problems, associated with increased mortality, stroke, left ventricular (LV) dysfunction and other thromboembolic complications. The mortality rate in patients with AF doubles regardless of the presence of other known risk factors. Only antithrombotic therapy is known to reduce AF-related mortality.²⁻⁴

AF is one of the most common cardiac arrhythmias and occurs in the general population in 1 to 2% of cases, and the frequency of AF increases with age. Multicentre studies have revealed that the prevalence of this pathology among people at the age below 60 years is ~ 0.5%; at the age of 60 years-5%, > 75 years - >10%. It has also been shown that AF is more common in men than in women. Paroxysms of AF account for >1/3 of hospital admissions due to cardiac arrhythmias, including in connection with an increase in the life expectancy of the population, there is an increase in the prevalence of AF by an average of 13% over the past 20 years.⁵

COVID-19 has become a rapidly growing epidemiological problem worldwide. The clinical manifestations of the disease are quite diverse and depend, mainly, on the patient's age and concomitant diseases. Patients with arrhythmias, coronary heart disease, heart failure, and CV risk factors (male gender, elderly age, diabetes mellitus [DM], arterial hypertension [AH], obesity and cerebrovascular diseases) have a higher risk of death in the course of this disease. The COVID-19 pandemic dictates the need to create new conditions for providing specialised care to patients with cardiac arrhythmias and conduction disorders.^{6,7}

PURPOSE OF THE STUDY

To assess the adherence to antithrombotic therapy in patients with AF during the COVID-19 pandemic. Determine the relationship between oral anticoagulants and the severity of coronavirus infection in patients with fibrillation.

MATERIALS AND METHODS

The study included 621 patients with AF who received inpatient treatment. The mean age of the patients was 68.73 (range from 25 to 93 years). Among the patients, there were 259 men (41.71%), mean age 66.38 ± 2.05 years, 362 women (58.29%), mean age 70.42 ± 1.5 years. Adherence to antithrombotic therapy was assessed on the basis of the Morisky-Green scale (MMAS-4) criteria.⁸ The MMAS-4 questionnaire consists of four questions (Table I).

The MMAS-4 is often used in scientific research as the main tool and as a reference for comparison in the development of

Table I: Morisky-Green (self-reporting Medication-taking) scale

Questions	Risk level depending on patient response	
	Patient answered "Yes"	Risk level
1. Do you ever forget to take your medicine?	0 times	High
2. Are you careless at times about taking your medicine?	1 time	Medium
3. When you feel better do you sometimes stop taking your medicine?	2 times	Low
4. Sometimes if you feel worse when you take the medicine, do you stop taking it?	3 times	
	4 times	

Table II: Patients' adherence to medication (antiarrhythmic drugs and anticoagulants)

Commitment assessment	Number of patients (n/%)		
	Men	Women	Total
1 Not committed to therapy (1 to 2 points)	69 (11.11%)	75 (12.08%)	144 (23.19%)
2 Not committed enough (3 points)	58 (9.34%)	72 (11.59%)	130 (20.93%)
3 Committed to therapy (4 points)	132 (21.26%)	215 (34.62%)	347 (55.88%)
p value	≤ 0.05	≤ 0.05	≤ 0.05

Table III: Severity of coronavirus infection in patients with atrial fibrillation

No	Degree of severity	Total (%)
1	Asymptomatic form	4.2%
2	Mild	33.9%
3	Moderate	49.1%
4	Severe	12.8%
	p value	≤ 0.05

new, more detailed, and specialised scales. The MMAS-4 questionnaire was developed in 1985 and published in 1986. The MMAS-4 is a reliable and effective method of identifying patients at risk of non-compliance with the treatment regimen. And it can still be used in a doctor's daily medical practice to support treatment adherence in patients with atrial fibrillation.

The MMAS-4 questionnaire consists of four questions. To determine whether the patient skips taking medications, if he feels good or bad, whether he forgets to take medications, and whether he is attentive to the recommended time for taking medications. The MMAS-4 is used in the standard examination of patients with various chronic diseases to identify potentially non-adherent patients.^{9,10} Each question was asked to choose a positive or negative answer (yes/no). Each negative answer was rated at 1 point. Patients who score 4 points, are considered to be committed to therapy, 1 to 2 points-not committed, and 3 points-insufficiently committed, with the risk of moving to the group of those who are not committed to treatment. There was a weak direct correlation between oral anticoagulant use and the severity of CVI. 118 out of 621 patients with AF had CVI. They were asymptomatic (4.2%), mild (33.9%) and moderate (49.1%) severity in severity. The share of patients with severe illnesses was 12.8%.

The statistical analysis was carried out according to the Mann-Whitney criteria.

The relevance of the problem of studying AF, is related to the fact that this violation of the heart rhythm is one of the

causes of heart failure, increased mortality, stroke, and other thromboembolic complications, hospitalisations, deterioration of the quality of life and reduced exercise tolerance. Mortality in this group of patients is doubled regardless of the presence of other known risk factors. Since patients have been receiving antithrombotic therapy for a long time, we decided to evaluate their adherence to therapy and the severity of their COVID-19 history against the background of chronic therapeutic anticoagulation.^{11,12}

RESULTS

We found that 23.19% of patients are not committed to therapy, 20.93% are insufficiently committed and only 55.88% of patients are committed to therapy.

The MMAS-4 rating scale for adherence to therapy, depending on gender, is presented in Table II. 144 patients did not adhere to therapy. Looking at the sex distribution, more women were non-adherent to therapy (12.08% against 11.11% of men). Insufficient adherence was found in 130 patients, where the proportion of women also prevailed over men (11.59% vs. 9.34%, respectively).

Consequently, in 55.88% of patient's adherence to therapy was established, and in women, the percentage of adherence also prevailed in comparison with males (34.62% vs. 21.26%).

The majority of patients taking long-term antithrombotic therapy had mild (33.9%) and moderate (49.15%) CVI. The proportion of patients with severity was only 12.71%. A weak

direct correlation was determined between the intake of oral anticoagulants and the severity of CVI (Table III). This confirms the data of studies by foreign authors [5,6,7], according to which treatment with anticoagulants for at least 1 month reduces mortality, the severity of the transferred coronavirus infection and can protect against thrombotic complications.

DISCUSSION

Patient adherence assessment is a large sample of patients, which allows us to evaluate the psychometric properties of the MMAS-4 questionnaire. Thus, this analysis can help us understand the MMAS-4 as a measure of medication adherence. The advantage of this questionnaire is that it is a brief measure of medication adherence. It is used in both research and medical practice more frequently.^{16,17}

Studies have shown that 87.9% of patients required mandatory anticoagulant therapy, but only 69.2% of patients out of the total number of patients with AF take it. The indicators obtained in our work on the adherence of patients with AF to therapy, also confirm the data of foreign studies. They published the problem of insufficient patient adherence to treatment. This leads to a decrease in the therapeutic effect, significantly increases the development of complications of the underlying disease, and also leads to a decrease in the patient's quality of life and an increase in government costs for treatment.¹⁸

It is necessary to take measures to improve the management of this pathology: actively conduct sanitary-and educational work (thereby reducing risk factors for the development of the disease, such as alcohol consumption, control and treatment of major diseases); explain what complications can lead to insufficient adherence to the prescribed therapy.¹⁹

As in the acute phase of COVID-19 infection, the susceptibility to AF is increased and a worsening of existing AF likely, utilisation of personal electrocardiogram devices as well as remote monitoring (teleconsultations) could optimise care of patients with AF and those with a high risk for developing AF.²⁰

LIMITATIONS

Although our study helped answer our research question, it has some limitations. The main limit is that the study is retrospective. The difficulty was that we were not allowed to determine adherence to antithrombotic therapy during the immediate hospital stay. In addition, we could not assess other properties of the measure, such as group validity and sensitivity to changes in medication adherence over time. This limitation is also evident in some studies.^{13,14}

Another limitation was that all patients considered received therapy at the same hospital. Accordingly, the full range of medication adherence that is theoretically possible with this study method was not obtained. There is a difficulty regarding the extent to which the climate of different medical facilities affects adherence in patients with atrial fibrillation. Researchers in China, who used a similar methodology, came up against a similar limitation.¹⁵

We would also like to note that the translation of the article into English was performed not by a professional translator or a native speaker, but by a person with a high level of English.

The results we obtained are nevertheless valid for answering our research question since the data on adherence to therapy and the correlation between anticoagulant intake and disease severity were statistically significant.

We hope the limitations mentioned above will serve as recommendations for how the next study on a similar topic should be conducted.

CONCLUSION

Even a mild degree of infection caused by COVID-19 can cause thrombotic complications, especially in patients suffering from atrial fibrillation (AF). So, according to the results of our study, the Morisky-Green scale (MMAS-4) questionnaire can be recommended as a screening of adherence to therapy in patients with AF to identify potentially unaffected patients in everyday clinical practice due to its statistical significance. Thus, this method will reduce the risk of thrombotic complications in patients with COVID-19. We would like to note that the appointment of anticoagulants can reduce the severity of the coronavirus infection and protect these patients from thrombotic complications.

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Benefits and challenges of teleconsultation service for non-communicable disease follow-up in public healthcare clinics in Malaysia: a qualitative study

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ABSTRACT

Introduction: Teleconsultation gained popularity to provide safe medical care during the pandemic. However, literature on the sustainability of teleconsultation service at primary care beyond pandemic situations is scarce. This study aimed to determine the use of teleconsultation services for non-communicable disease (NCD) follow-up and explore the benefits and challenges of the service implementation during and beyond COVID-19 pandemic in Malaysia.

Materials and Methods: An exploratory qualitative study was conducted using videoconferencing. Fourteen medical officers working in public primary healthcare clinics from various regions of Malaysia were chosen using purposive sampling process, and participants underwent a total of seven paired in-depth interview (IDI) sessions. IDIs were video recorded, transcribed and subjected to interpretive thematic analysis.

Results: The two main themes which emerged were the benefits and challenges of NCD teleconsultation service. Various categories relating to benefits of teleconsultation for NCD care are as follows: (1) Improved efficiency for patient care delivery (improved effectiveness, convenient, improved safety, better disease monitoring, patient empowerment) and (2) Benefits for Health Care Providers (improved healthcare and service delivery). Main challenges identified were as follows: (1) Challenges for Delivery of Care (Patients' adaptation in using teleconsultation service, Patients abusing the system, Poor digital literacy, No proper disease monitoring record), (2) Challenges for Health Care Providers (Lack of dedicated team and training, Higher workload and time-consuming) and (3) Challenges for Health Care System (Institutional policy, legal and regulatory weakness, Medical record documentation and prescription updates).

Conclusion: Optimisation of NCD patient healthcare delivery via teleconsultation is beneficial during and after pandemic. Targeted improvements to address current challenges are crucial to optimise its use beyond the pandemic period in the Malaysian public healthcare system.

KEYWORDS:

Teleconsultation, public primary healthcare clinic, non-communicable disease (NCD), coronavirus disease 2019 (COVID-19)

INTRODUCTION

In late December 2019, a continuous outbreak of mysterious pneumonia was reported in Seafood Wholesale Market, in Wuhan, Hubei, China.¹ Within a short period of time following its initial occurrence, the disease spread to other nations worldwide. The World Health Organization (WHO) then declared the illness a global pandemic on March 11, 2020,² and thereafter known as Coronavirus Disease 2019 (COVID-19). The COVID-19 pandemic is considered the greatest global economic and health challenge of this century.³

Malaysia is one of many nations impacted by the pandemic. On March 18, 2020, Malaysian government enforced the Movement Control Order (MCO) to limit the disease spread and fatalities.⁴ MCO prohibited mass movement and gatherings at all places nationwide.⁵ Its adoption, which only permits one driver per vehicle and travel restriction confined to a 10-km radius around one's residence, resulted in a substantial impact on the accessibility and provision of healthcare services to non-COVID-19 patients.⁶ Many patients skipped or delayed their routine surveillance follow-up for chronic diseases due to the MCO. These measures could potentially increase their risk of developing complications or worsen the course of their illness.² Thus, one of the most important method for enabling people to continue receiving medical care while remaining safe at home is the use of teleconsultation.⁷

Teleconsultation is defined as synchronous or asynchronous consultation using information and communication technology to omit geographical and functional distance.⁸ In Malaysia, teleconsultation via Virtual Clinic (VC) services at public healthcare clinics has been outlined under the National Health Reform Agenda initiative in 2019 and also included in the 12th Malaysia Plan. The service was

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Table I: Socio-demographic and practice characteristics of participants (n = 14)

Participant ID	Age (years)	Gender	Ethnicity	Duration of service (years)	Location of Healthcare clinic (region)
P1	35	Female	Malay	10	Central
P2	32	Male	Malay	5	Sabah
P3	35	Male	Malay	9	Central
P4	32	Male	Chinese	6	Sarawak
P5	30	Female	Indian	3	Northern
P6	34	Female	Malay	7	Sarawak
P7	35	Male	Malay	8	Eastern
P8	29	Male	Malay	2	Eastern
P9	36	Female	Malay	10	Southern
P10	34	Male	Malay	8	Northern
P11	36	Female	Others	9	Central
P12	32	Female	Malay	4	Northern
P13	36	Male	Malay	10	Northern
P14	30	Female	Indian	2	Southern

Two of the main themes which emerged from the interviews were the (1) Benefits and (2) Challenges of teleconsultation services.

implemented as a Proof of Concept (PoC) in August 2019 at a few chosen public healthcare clinics for a year, and the service was expanded from 5 to 40 public healthcare clinics during the COVID-19 pandemic in 2020.

Recognising that teleconsultations is currently seen as a vital adjunctive tool for ensuring access to healthcare services; this study was proposed to investigate the benefits and limitations of teleconsultation adoption for NCD follow-up during the COVID-19 pandemic among Medical Officers. Given that healthcare professionals who conducted these consultations were responsible for the quality of this modality, it is crucial to understand how they felt about this service. By identifying the limitations of teleconsultation service that was implemented in the current healthcare system, improvements can be made before expanding teleconsultation for other healthcare services such as home visits for patients who may be physically (i.e., bedridden) or geographically challenged to attend on-site follow-up at public primary healthcare clinics.

MATERIALS AND METHODS

Study Design and Study Setting

This was an exploratory qualitative study among 14 Medical Officers working in 13 Public Primary Healthcare Clinics across Malaysia between June and September 2022. Clinics which provided teleconsultation services were identified and categorised based on state and region, representing both Peninsular and East Malaysia.

Participants

The participants were purposively selected from different states in Malaysia. The included participants shared some key characteristics i.e.: (1) Medical Officer (MO) who is fully registered with Malaysian Medical Council (i.e. grades UD43 and above), (2) working in public primary healthcare clinics and (3) had experience conducting teleconsultation service. Medical Officers who had no experience providing teleconsultation service or pre-registration house officers were excluded. The participants were divided into smaller groups of two people, based on participants' request and to overcome scheduling problems for the IDIs. The grouping of participants was done using a simple random sampling method.

Data Collection

The semi-structured interviews were conducted based on a topic guide that had been designed. The questions for the interview had been vetted by the research team and had undergone pilot testing on two medical officers prior to the study commencement. The questions required very minimal changes before finalisation. Training sessions were conducted prior to the study commencement, and experts gave feedback and guidance to the researcher. One researcher conducted all the interviews. A total of 7 IDIs were conducted using Zoom videoconferencing application to record video interviews, with the participants' prior consent. The recordings were then transcribed verbatim for analysis. The researcher then checked all transcripts against the video recordings to ensure accuracy. For the purpose of reporting, all the excerpts in Malay were translated into English. The translations were done by the researcher who is a native Malay language user with good English proficiency and checked for accuracy by two other researchers with bilingual professional proficiency (in Malay and English). Transcripts were made available to all researchers.

Data Analysis

The transcripts were analysed using thematic analysis method. Codes were identified from the transcribed data using NVIVO Plus 12 Software. The coded data were grouped based on potential themes and classified into main themes and sub-themes. A thematic map was formed once the themes have been reviewed. As the themes evolved, the study was considered to have attained data saturation when no more new themes emerged from the interviews. This was achieved by the fifth IDI (involving total of 10 participants) and confirmed by two more additional IDIs (with 4 participants). All research members³ convened to discuss and finalise the themes and subthemes before consensus was achieved.

Ethical Approval and Consent to Participate

Ethical approvals were obtained from the Research and Ethics Committee National University of Malaysia [JEP-2021-581] & Ministry of Health Medical Research and Ethics Committee (MREC). The study was also registered with the National Medical Research Registry (NMRR) [NMRR-21-1895-60059 (IIR)]. All the participants were briefed about the study, and those who agreed to participate gave verbal permission and

Table II: Themes for benefits of teleconsultation service

Themes	Transcripts
1.1 Improved efficiency of Care Delivery	
1.1.1 Improve effectiveness	<i>"I think that our teleconsultation system is very good to reduce the crowd in our clinic, the congestion in our clinic because NCD patients alone, let's say, our diabetic patient, morning alone, can reach (up) to 90 patients per day" (P1)</i> <i>"For our NCD, what we will do is, our NCD patient we monitor SMBG patients who don't need to be seen urgently, BP monitoring or post ACE inhibitor renal profile reviewing results – situations that don't need the patients to be physically (present) in the clinic" (P11)</i> <i>"One more thing is about compliance issue, patient give reasons of not coming to see doctor because – a lot of people, afraid of COVID infection, afraid to mix with other people, hard to find parking, tired. At least with teleconsultation, there is no excuses to skip appointment. We only need to call and ask, "Are you free now?", most of the patient will answer the call and this can reduce number of defaulter" (P10)</i>
1.1.2 Convenient	<i>"As far as I have been doing the teleconsultation, patients they like it, most of them they like this service because they can do consultation over the phone at the comfort of their own homes" (P1)</i> <i>"...some of the patients prefer to do the teleconsultation instead of come to the clinic to wait for long hours, queue for hours just to see the doctor for 5 minutes and collect medication then go back to their house" (P6)</i> <i>"They do not need to come and wait for a few hours to see doctors and wait for prescriptions. All these can cut down on their waiting time and logistic costs, so patients like it because of those reasons" (P1)</i> <i>"In my opinion, this service is convenient to patient and important for accessibility – especially for client that cannot come for frequent appointments for example those who is (are) working outstation" (P13)</i>
1.1.3 Improve safety	<i>"Specifically, during this COVID-19 pandemic time, benefit is - reduce the crowds, patients have less contact with those high risk patients of COVID" (P1)</i> <i>"Initially, the intention for virtual clinic during pandemic is to reduce the risk of infection and transmission" (P12)</i>
1.1.4 Better disease monitoring and patient empowerment	<i>"The benefits for NCD monitoring is that we can monitor patient closely especially in uncontrolled DM patients. We can review SMBG frequently and when optimized only we discharged from virtual clinic" (P13)</i> <i>"So those who are interested to participate in teleconsultation, they will try their best to really...you know to be part of the criteria and then they will try to monitor themselves so things like that it empowers them to...for better...for their own health improvement." (P6)</i>
1.2 Benefits for Health Care Providers	
1.2.1 Improve healthcare service delivery	<i>"With this kind of system, it is really based on appointment based so we are able to control. I give a more quality service and better consultation as well" (P4)</i> <i>"Not all but probably 30% of the patients have their children involved, so they are more likely cooperative to help. Some of the patients will feel that it is more of a personalized care through this service" (P11)</i>

signed the written consent form. The participants' identities were coded to maintain anonymity.

RESULTS

A total of seven IDIs were carried out among individuals of different demographic backgrounds as shown in Table I. The mean age of the participants was 33.3 (SD 2.4) years, and average number of years served as medical officer at a public primary healthcare centre was 6.6 (SD 3.0) years.

BENEFITS

Benefits of teleconsultation for NCD monitoring were clustered around two main themes: (1.1) Improved efficiency of care delivery and (1.2) Benefits for health care providers.

Improved Efficiency of Care Delivery

Altogether four sub-themes were identified, first was improved effectiveness in the implementation of teleconsultation services would aid in reducing congestion and overcrowding in the clinic. Clinical assessments, such as reviewing laboratory blood results and reviewing home blood pressure monitoring (HBPM) and self-monitoring of blood

Table III: Themes for challenges of teleconsultation service

Themes	Transcript
2.1 Challenges for Delivery of Care	
2.1.1 Patients' adaptation in using teleconsultation service	"... most of the time when we ask them why you didn't pick up the phone is because they are afraid of 'scam'" (P4) "It takes time. Sometimes call was not answered, need to call other patient then try to call the previous patient again. Sometimes need to call multiple times" (P12) "Somehow the satisfaction of seeing someone physically is better and have contact with someone. To convince patients to use teleconsultation is a challenge for me because they feel that everything is back to normal as compared to MCO period" (P14)
2.1.2 Patient abusing the system	"Because we are using our own phones, of course some patients abuse the system. They WhatsApp me and my colleagues also, sometimes at night, during the weekends, middle of the night. "I'm having chest pain doctor, what should I do?"...and some of them abuse the system requesting to change their appointment due to inevitable reason also" (P1)
2.1.3 Poor digital literacy	"Some of them don't know how to operate XX (3rd party platform) and we must teach them step-by-step. Worst case scenario, end up we must call them also and explain step-by-step which is very time-consuming explaining to them, how to go about the thing" (P3) "The cons are – most of our NCD patients are old and elderly, so we can't expect them to be IT savvy and they might have some trouble. Eventually, we call them 5 minutes before and say, "I'm calling you in 5 minutes, can you turn on your XX (3rd party platform)?" and it won't happen so we will opted for telephone call instead" (P14)
2.1.4 No proper disease monitoring record	".....because we ask patient to monitor their HBPM and SMBG...so...sometimes patient not properly did it" (P6) "...So, the entire...the picture of the SMBG wasn't really reflected when I do calls with them" (P4)
2.2 Challenges for Health Care Providers	
2.2.1 Lack of dedicated team and training	"As we are moving towards a digitalised environment, we would need to have cooperation and assistance from everyone to run this service smoothly. Because our clinic is manual, no staff to give next appointment (date), all documentation was done by that one medical officer (MO). So in (the) long run, we need more staff in the future to help run this service" (P14) "...need to have a leader and specific team for virtual clinic. If we (medical officer) request any of the staff to help us for virtual clinic, number of staff for other work is also not enough. In the end, we need to do all the work ourselves - trace card, trace results, book appointment" (P7) "When you are talking about healthcare clinics' staffs, not everyone is familiar with this. So, I think we do need multiple training. For now, we do have training but only for the medical officer who are involved in this because this thing works as one unit and not one person" (P14)
2.2.2 Higher workload and time consuming	"Also, because our clinic is still using the manual system, not the Tele-Primary Care (TPC) that is when all the headache comes, as we have to trace the cards, manual documentation, and also virtual documentation. The work burden is a bit more" (P5) "...it will take time to take consent and convinced patient, sometimes to go through this lengthy path of work – it is difficult to commit" (P11)
2.3 Challenges for Health Care System	
2.3.1 Institutional policy, legal and regulatory weakness	"What is the guideline and act that we need to apply when they received our consultation – do they need to pay? If there are paying, then we need to give them receipt" (P9) "If patient come for DOTs at Pusat Rawatan 1 (PR1), usually only Community Nurse will attend to them, but there is no black and white in paper that mentioned that they can do virtual clinic. Supporting staffs expecting instructions from superiors to do virtual clinic, then only they will do it" (P7)
2.3.2 Medical record documentation and prescription updates	"However, when doing teleconsultation, patient did not come, so when we need to explain on which medication is modified, when to come to collect medication and so on – it is a challenge" (P9) "...we don't have a proper system. In clinic we use Tele-Primary Care – Oral Health Clinical Information System (TPC-OHCIS) but we need to transfer the documentation, it takes time. So sometimes we tend to forgot to document – only in their book that we write" (P9)

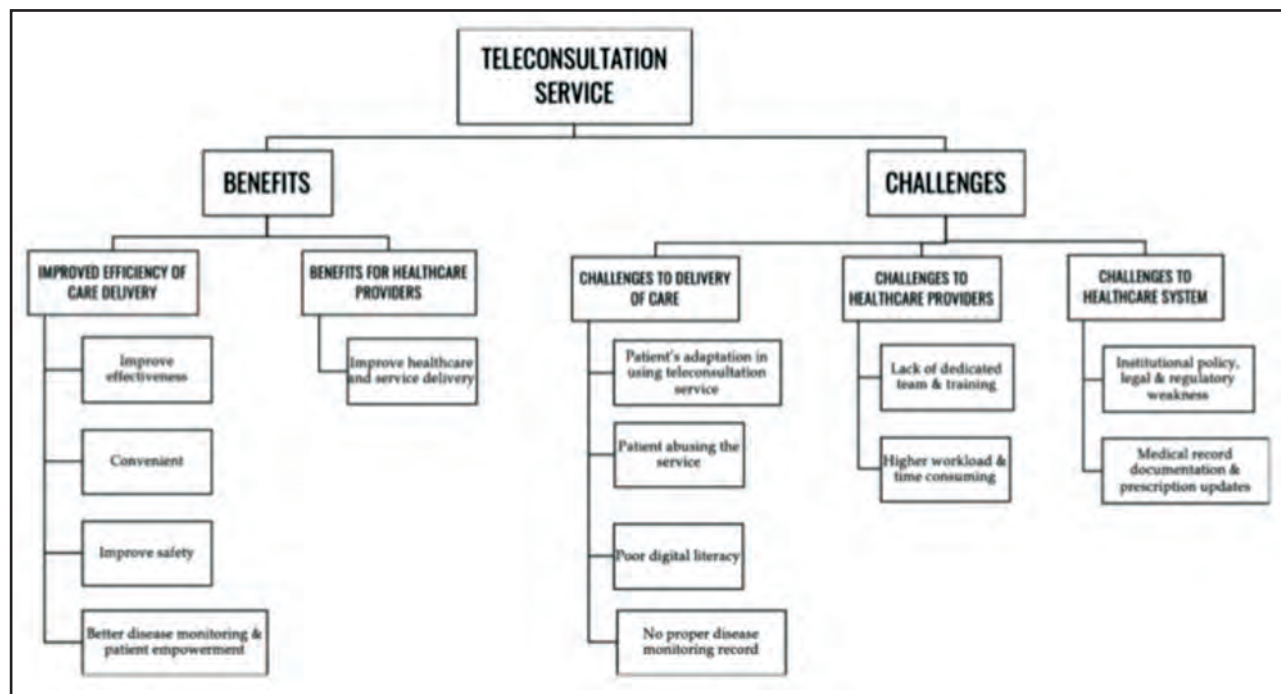


Fig. 1: Themes and subthemes identified

glucose (SMBG), may not require the patient to be physically present in the clinic and this can be achieved via teleconsultation. Second, teleconsultation service is convenient for patients as one of the participants (P10) mentioned that the number of people who missed appointments due to work-related obligations may be reduced because this service can be accessed anytime and from any location at patients' convenience.

The fact that this service aids patients to avoid lengthy waiting time at clinics and saves money on transportation are two of the most frequently mentioned topics of conversation among participants. Not only is it more convenient for the patient but it also greatly lowers the costs from both the patient and healthcare providers' perspectives (i.e., the total cost of healthcare), which is an important consideration during an economic downturn. Thirdly, teleconsultation service improves patients' safety by reducing exposure and risk of contracting COVID-19 infection in crowded clinics. Fourthly, participants also believed that patients felt more empowered to take care of themselves as improved disease monitoring is supported through frequent teleconsultation follow-up sessions. Some participants emphasised that teaching the elderly new skills, i.e., using an email system or operating a third-party internet platform for teleconsultation services, would be a part of cognitive stimulation which would be beneficial for them as well.

Benefits for Healthcare Providers

Teleconsultation services provide an avenue for improving healthcare and service delivery. For instance, according to P11, patients feel as though they are receiving more individualised care from the doctor than they would receive during a regular in-person visit to the clinic. The appointment-based teleconsultation service also aids in limiting the number of patients seen each day, resulting in

improved service and consultation. A few participants (P4, P8, P9) remarked that the use of teleconsultation services ensures continuity of care as well because the same doctor overseeing the virtual clinic would see the same patient, which is occasionally not possible during on site clinic appointments.

CHALLENGES

Challenges were summarised into three themes: (2.1) Challenges for Delivery of Care, (2.2) Challenges for Healthcare Providers and (2.3) Challenges for Healthcare Systems.

Challenges for Delivery of Care

Total of four sub-themes were identified. Firstly, and which is the most difficult challenge in providing service via teleconsultation, is the patients' adaptability to use the service. P4 mentioned that some patients did not respond to calls or emails when contacted because they are afraid of 'scam' calls. Second subtheme identified was that some patients abused the teleconsultation service. According to P1, some patients took advantage of the 'contact' with health care services by requesting assistance in changing clinic appointments due to unavoidable circumstances, enquiring about acute complaints and using the contact number as a personal direct access, both during and after office hours or when the public health center is closed. The researchers noted that the device used for official teleconsultations ranged from using a device provided by the district health office to personal mobile telephones belonging to the participants themselves. A few participants (P11, P14) also brought up the fact that some patients genuinely prefer in-person clinic visits over virtual consultations and frequently missed the teleconsultation appointments (P11, P13).

Thirdly, one of the difficulties that healthcare professionals face while offering teleconsultation services is the low level of digital literacy among the patients. Some patients were not familiar with how to use a particular platform. P2 reported that he found it challenging to perform teleconsultation because the patient could not even use a phone or email. Fourthly, a small number of participants (P4, P6, P7) stated that some patients receiving follow-up via teleconsultation lacked sufficient disease surveillance monitoring, i.e., SMBG and HBPM records. Teleconsultation would be difficult since clinical decisions required justification e.g., to substantiate modification of the patients' medication regime.

Challenges for Health Care Providers

There were two sub-themes identified under challenges for health care providers. First, there was a lack of a trained dedicated team to support the teleconsultation service. Most participants thought that a committed team and adequate staff training were essential for the successful implementation of the teleconsultation service. According to P7, there was no assistance from other staffs at his clinic since he was the only one conducting the service. Since there were numerous tasks that had to be completed to ensure the service functioned smoothly, this became a huge challenge. A small number of participants (P8, P11, P14) also complained that the staff did not receive sufficient prior training to deliver this service. Some of the staff became hesitant and refused to participate in teleconsultations since they were unfamiliar with the technology used.

Second subtheme was teleconsultation service added heavier workload to the healthcare staff and was time consuming to conduct. One participant (P5) felt that having a teleconsultation service added to their daily workload. Pre-teleconsultation session for new patients required several steps (i.e., tracing the medical records plus scheduling the appointments), and these became an additional burden for the MO who had to cope with the lack of supporting staff during pandemic. The participants claimed that one of the obstacles they faced in providing this service was getting the patients' consent and explaining the teleconsultation service to them. They found organising teleconsultations to be more labour-intensive and time-consuming to perform, which was often burdened by the increased administrative tasks.

Challenges for Health Care System

There were two sub-themes identified under challenges for health care system. One of the difficulties in offering teleconsultation services was dealing with legal, ethical and regulatory constraints. P7 reported that some staff were reluctant to undertake teleconsultations since there were no official guidelines or policies stating that supporting staff were permitted to provide teleconsultation services. In addition, one participant (P9) brought up the subject of payment, pointing out that while teleconsultation patients were not charged, those who physically visited the clinic were expected to pay for the services. Therefore, it was necessary to address these issues and problems if teleconsultation services would be maintained as a regular service.

Second subtheme was related to the medical record and prescription updates. The fact that medical professionals

frequently failed to update the documentation in the clinic information system e.g., patients' current clinical status and prescription changes after each session was another drawback in offering teleconsultation services. This raised a potential medico-legal issue which was not adequately addressed or clarified in some health centres. Difficulties arise when the patient receives teleconsultation from a different MO who may not be aware of the updated management plans undertaken by the prior MO. Additionally, one participant (P9) experienced difficulties with medication readjustment during the teleconsultation service. Compared to in-person consultations, it was more difficult to adjust and change patients' medication when using a teleconsultation service. Undocumented consultations harbour potential medico-legal consequences for both the healthcare providers and patients.

DISCUSSION

Before the COVID-19 pandemic, teleconsultation was not commonly practiced, and neither patients nor healthcare professionals thought the idea of obtaining healthcare services over a virtual platform was feasible.⁹ The quick rise in COVID-19 cases and the widespread lockdowns had impacted patient care delivery, hence it was recommended that teleconsultation services be adopted as a substitute for in-person visits to reduce the risk of disease transmission. Teleconsultations have been extensively expanded in recent years since it has been proven to be the right solution during the COVID-19 pandemic.

Participants in this study acknowledged a variety of advantages of providing teleconsultation services. The reduction of COVID-19 transmission and improved safety during pandemics were clear benefits of teleconsultations emphasised by healthcare professionals in this study. Numerous other advantages for patients and healthcare providers were also recognised, including improved patient convenience and time savings, reduction in defaulters and subsequently increased efficacy, similarly supported and mentioned in earlier studies.^{10,11}

Numerous participants in this study felt that conducting teleconsultations can improve healthcare and service delivery. They believed that the service would help them build better relationships and rapport with patients as well as increase patients' trust in healthcare professionals. However, the results differ from earlier studies. Conversely, those studies found that the loss of personal connection prevented patients from discussing personal matters during telemedicine appointments.¹² Additionally, it was noted in several studies that both patients and healthcare professionals were concerned about the development and maintenance of rapport. Patients can feel that video consultations put them at a distance from their healthcare practitioners and risk developing a distrustful connection.^{11,13} According to a study by Wilson et al., the length of the typical doctor-patient consultation appears to be closely related to how satisfied the patient is with their care.¹⁴ Click or tap here to enter text. More protected time that healthcare providers devote to each patient during teleconsultations as compared to physical visit may play a role in the personalisation of

care; however, further studies are required to confirm this. In addition to the benefits of teleconsultation service, although it was mentioned in the literature that teleconsultations expedited the healthcare system,¹⁵ none of the participants went into further details. They only mentioned their own experiences learning new systems, which had changed their job description. Although they might have had trouble picking up new skills, it nonetheless aided in their advancement.

The challenges of implementation of teleconsultation identified by our participants were consistent with other earlier studies.^{11,16,17} The patients' acclimatisation to the system is the most frequent challenge experienced by healthcare professionals when providing teleconsultation services. Some of them did not answer telephone calls when contacted. Patients' fears and reluctance to answer the phone during teleconsultation services are legitimately attributed to the high number of scam calls in Malaysia. The Commercial Crimes Investigation Department (CCID) of the Royal Malaysian Police (PDRM) reports that between 2020 to March 2021, a total of 13 120 scam calls worth more than RM580 million in damages were reported, a dramatic increase in Malaysia during the COVID-19 outbreak.¹⁸ As Malaysia has a high rate of scam calls, patients' anxiety about answering calls from unknown numbers is understandable. Pre-session prompting utilising introductory messages or posters delivered text messaging before a planned virtual consultation might help reassure patients that the number or email address is legitimate.

Few interviewees mentioned that patients preferred in-person visits to clinics over teleconsultation services, and this has turned into one of the obstacles to the adoption of teleconsultation service. The idea of being able to physically speak with one another and consulting face-to-face is also a part of the therapeutic process between a doctor and a patient. This is corroborated by Lampraki, who concluded that social isolation during the COVID-19 epidemic, particularly during the MCO, may be reduced by regular interaction and meetings.¹⁹ During MCO, patients who had follow-ups and needed medical attention were allowed to leave their homes to go to clinic or hospital.²⁰ The patients benefited from being able to leave the house while under lockdown, and unconsciously benefited as part of a therapeutic process to finally meet someone, leading to a preference for physical visits as compared to teleconsultations.

Technological difficulties and patients' poor digital literacy were issues voiced among healthcare professionals. This has been reported in multiple studies discussing similar issues.^{21,22} Therefore, to prevent problems with technological difficulties, careful patient selection is essential. Identification of the suitable profile for NCD patients who would benefit from teleconsultation is necessary. There may be some patients who are qualified for teleconsultation service but have certain digital proficiency limitations; this should not be a reason for complete exclusion from this service. Options like the presence of a responsible main caregiver who would be able to assist and be actively involved during the consultation can be taken into consideration. This assertion

is reinforced by a study conducted by Sophy et al., which found that caregivers' own technology and digital literacy can have an impact on patients' ability to receive and benefit from successful teleconsultation service.²³

The interviewees also emphasised how crucial it is to have a committed team while providing teleconsultation services. One research concluded that for teleconsultation services to achieve its potential, a well-structured team was required.²⁴ A proper team approach is needed to ensure that workload is distributed to prevent burnout. Some participants indicated that there is a need for a designated staff to manage technical support to ensure the teleconsultation service runs well. By defining the key person, positions and functions, task distribution can be ensured. In addition, to manage this rapidly changing system, healthcare personnel must also possess the necessary training.²⁵ To ensure that the staff is comfortable with the system and the tools, training on the usage of teleconsultations is essential.²⁶ It is important to have standardised orientation and training process for staff so that they can manage teleconsultations as part of the clinic's services. Additionally, the training materials must be based on current, up-to-date national guidelines as well as regional primary care regulations and governance.

Teleconsultation involves the circulation of very personal data i.e., the patients' health information. Therefore, when establishing teleconsultation services, the perspective of data protection should be considered. The Personal Data Protection Act (PDPA) limits access to the data and assures confidentiality to protect patients' personal information and health information.²⁷ Although teleconsultation services appear handy because patients can participate in consultations from their own offices or homes, confidentiality issues still prevail and must be appropriately addressed. Some studies concluded that the major barrier to teleconsultations was the lack of privacy and confidentiality during consultations.^{28,29} One of the participants (P11) highlighted the fact that some Retroviral Disease (RVD) patients preferred telephone calls without any video or photos. They felt that discussions conducted virtually lacked confidentiality, and the likelihood that the patient's co-workers or friends would be aware of their health status if the consultation was held in a public space, raising medicolegal implications. To allay patient concerns about confidentiality, proper guidelines and instructions on how teleconsultations should be conducted should be emphasised, such as the necessity to be in a single room or cubicle and the use of headphones to ensure privacy. Hence, proper official advanced scheduling for teleconsultations must be allocated in the clinic schedule to ensure adequate privacy is accorded during sessions. During the interview, one participant suggests using a standard or universal platform rather than the current platform- which requires an email address, to conduct teleconsultations. However, confidentiality issues should be raised as some platforms would not be secure for medical data due to the possibility of data leakage.

Few participants also suggested the promotion of teleconsultation services to the community with the purpose to increase their awareness regarding this service. Some advocates for the extension of services in the allied health

field are recommended, including services from dieticians and physiotherapists. However, detailed work processes and guidelines are required before information is disseminated and service scope is expanded, as mentioned in a study by Intan Sabrina and Defi. Ensuring uniformity of teleconsultation services requires the development of a comprehensive and universally adaptable telemedicine guidelines that can be tailored to the local context of each country.³⁰ This can also guarantee that the adoption of the teleconsultation service benefits both patients and healthcare providers.

STRENGTH AND LIMITATIONS

To the best of our knowledge, this is the first qualitative study to examine the advantages and difficulties of teleconsultation following its extensive use in Malaysia during the COVID-19 pandemic. The qualitative approach of the study allowed for a deeper understanding of how the participants handled the current existing service and the difficulties they faced during implementation.

It is important to understand the findings of this study in consideration of its constraints. Only Medical Officers were involved in this study; hence, subsequent research should emphasise on incorporating other healthcare personnel's opinion, including allied health groups. It would also be advisable to study the barriers perceived by patients related to the implementation of video consultations to improve the quality of service delivered.

CONCLUSION

To successfully integrate teleconsultation as a method of service within a health system, it is critical to understand how healthcare professionals perceive them. Optimisation of NCD patient healthcare delivery via teleconsultation is beneficial in providing tailored patient consultations which promote empowerment for self-care. Challenges to healthcare providers require better organisation of the teleconsultation session and workflow algorithms, technical support, medico-legal and policy issues. Targeted improvements should be made to address challenges to optimise its use beyond the pandemic period in the Malaysian public healthcare system. Concerted efforts to improve the current system will assist in ensuring its operability, effectiveness and acceptance of the service.

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Risk factors of necrotising enterocolitis among 28-34 weeks preterm neonates at a Tertiary Care Hospital, East Java, Indonesia

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ABSTRACT

Introduction: Necrotising enterocolitis (NEC) is a serious health problem primarily affects preterm and very low birthweight (VLBW) infants. However, the pathomechanism of NEC remains elusive. This study aimed to analyse the risk factors for NEC among preterm neonates in East Java, Indonesia.

Materials and Methods: A single-centre, prospective, case-control study involving 32 subjects of preterm neonates was conducted at a tertiary care hospital in Malang, East Java, Indonesia between January to June 2022. A total of 15 preterm neonates with NEC and 17 preterm neonates without NEC were enrolled in this study. Data on demographic, clinical and laboratory findings were collected. Multiple logistic regression test was performed to analyse the risk factors for NEC development. Further profiling within 15 subjects with NEC, i.e., NEC grade $\geq$ II, were conducted to collect systemic, abdominal, laboratory, abdominal x-ray (AXR) and blood culture findings.

Results: The risk factors related to NEC development in preterm infants were multi-morbidity (adjusted OR = 11.96; 95% CI 1.85 168.38; $p = 0.046$), antibiotic exposure (OR = 15.95; 95% CI 1.54 165.08; $p = 0.020$) and requiring advanced neonatal resuscitation at birth (OR = 10.04; 95% CI 1.09 92.11; $p = 0.041$). Further profiling within NEC cohorts highlighted respiratory distress (86.7%), (oro)gastric retention (80.0%), thrombocytopenia (53.3%), gastrointestinal dilatation in AXR (53.3%), and positive blood culture *Klebsiella pneumoniae* (40.0%) were most common findings.

Conclusion: Preterm neonates with multimorbidity, prolonged antibiotic exposure, and requiring advanced resuscitation at birth were more likely to develop NEC. Early detection of the risk factors and determinant factors for survival may help to improve the clinical outcome.

KEYWORDS:

Clinical characteristics, necrotising enterocolitis, prematurity, risk factors

INTRODUCTION

Necrotising enterocolitis (NEC) is an acute inflammatory, multifactorial disease of intestinal injury and necrosis which primarily affect preterm infants and is a leading cause of morbidity and mortality.¹ The global incidence of NEC is reported to vary from 7 to 13% in preterm and very low birthweight (VLBW) infants, i.e., birthweight < 1500 gm.^{2,3} In Indonesia, the incidence was 8.6% among preterm infants born in single-centre tertiary hospital, yet the data were sparse and limited.⁴ Of all NEC cases primarily in VLBW infants, 27 to 52% was reported to require further surgical intervention, including laparotomy and bowel resection.⁵ Despite modern advances in intensive neonatal care, NEC mortality rate remains frequent, with rates reported between 18% and 63%.⁶⁻⁸

Although the aetiology of NEC remains elusive, multiple risk factors, including prematurity, low birth weight, hypoxia, abnormal microbiota colonisation in the intestinal tract, microcirculatory disorders, formula feeding and patent ductus arteriosus, were highlighted to involve in the development of NEC.⁹ Recent studies showed sepsis, as a severe infectious disease, is considered a contributing factor for NEC. The incidence of NEC in sepsis patients ranges from 34% to 57%.^{10,11} However, these risk factors findings might be widely varied based on advancements of neonatal intensive care that might differ between developed and developing country, leading to a varying degree of neonatal risk factors in NEC development. In all regards, NEC becomes one of the most devastating conditions in preterm and VLBW infants.

Diagnosis of NEC is established by Modified Bell's criteria, which comprises of systemic signs, abdominal and radiologic findings.¹² Due to the multifactorial nature of NEC, clinical

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manifestations were non-specific and overlapping with other disease of gastrointestinal origins; clinicians thus depend on plain abdominal x-ray (AXR) to find the telltale sign of NEC, i.e. pneumatosis intestinalis, where it was not always present and approximately found in 39.4% of all NEC cases.¹³⁻¹⁵ Therefore, identifying specific risk factors for NEC in preterm infants would be helpful to optimise strategies to reduce morbidity and mortality, as well as to provide directions for clinical treatment strategies. This present study was aimed to describe the incidence, characteristics, and determine the correlation between risk factors of NEC for preterm neonates in a tertiary hospital in Malang, East Java province of Indonesia. Further profiling of abdominal signs, AXR and laboratory findings within our NEC cohorts might contribute to a description that may differ in other country.

MATERIALS AND METHODS

Study design and patients

This case-control study, involving subjects of preterm neonates born at a gestational age (GA) < 35 weeks, was conducted at a single-centre tertiary hospital perinatology unit of Saiful Anwar General Hospital (SAGH), East Java, Indonesia, between January to June 2022. The subjects were followed-up and further divided into two groups, i.e., preterm neonates with NEC and preterm neonates without NEC. Subjects were followed-up until reaching clinical outcomes or age of 28 days. All subjects included in this study were received exclusive or predominant breastfeeding and none of them received probiotics. This study was approved by Research Ethics Committee of Saiful Anwar General Hospital and registered to clinicaltrials.gov (NCT05335577) as part of more comprehensive study. Informed consents were obtained from all parents.

Extensive data on GA, birthweight, sex, singleton, Ballard score of maturity, Lubchenco intrauterine growth criteria, Downes score (DS) of respiratory distress, APGAR score, and extent of neonatal resuscitation was obtained. Additional clinical data included surfactant administration, antenatal corticosteroid, history of packed red cells (PRC) transfusion, clinical pathologies, antibiotic exposure and laboratory findings were also collected. Maternal profiles of comorbidities, body mass index, mode of delivery and passive smoker status were collected. These data were then analysed to be included in risk factor analysis.

Among NEC cohorts detected in this study, further profiling was conducted on systemic signs, abdominal, laboratory and AXR findings based on Modified Bell's criteria. In NEC cohorts developing sepsis, blood culture results were also collected. Data collection was ceased in case of death, transfer to another hospital or parents willing to drop out of study. Preterm infants were excluded in case of severe congenital anomalies, surgery within study period, death before the diagnosis of NEC established or parents' refusal upon informed consent.

Definitions

NEC cases were defined as infants diagnosed with NEC grade 2 or higher based on Modified Bells' criteria. NEC cases were established by two independent neonatologists. AXR features

of cohorts were reviewed independently by one senior radiologist blinded to the study. Blood samples and laboratory features were analysed independently by central clinical pathology unit of SAGH.

Neonatal resuscitation was, based on Indonesian Pediatric Association national protocol, adopted from Neonatal Resuscitation Program 8th edition.^{16,17} There were four main steps of neonatal resuscitation based on severity, i.e., initial steps (warm, dry, stimulate and position airway), followed by positive-pressure ventilation (PPV), cardiac compression and intubation and epinephrine administration at birth. Advanced resuscitation was defined as neonates requiring PPV or higher intervention of resuscitation, i.e., cardiac compression and intubation, or epinephrine administration at birth.

Surfactant administration was defined as exogenous surfactant replacement therapy protocol given within 24-h of life. Antenatal corticosteroid administration was defined as intravenous corticosteroid given within 24 to 48-h before birth in part of lung maturation induction. History of PRC transfusion was defined as red blood cells transfusion within 48-h prior to NEC development or within 14 days of life. Exposure to antibiotics were defined as antibiotic administration within first week of life or minimum $\geq$ 48-h prior to NEC diagnosis. The type of antibiotics administered were also noted.

Clinical multimorbidity was defined as diagnoses established by the attending neonatologist in response to patients' conditions. Multiple morbidities were defined as subjects suffered from > 2 co-occurring clinical diagnoses. Sepsis was defined as positive blood culture confirming bacteraemia or procalcitonin level > 2.0 ng/ml with corresponding clinical pictures of temperature instability and bradycardia. Severe congenital anomalies were defined as confirmed congenital abnormalities that lead to hemodynamic instability, i.e., hypoperfusion or shock. Surgery exclusion criteria was defined as any surgery within study period at indication other than NEC grade 3.

Statistical analysis

This present study performed multistep analysis on the cohort. During the study period, the demographic, clinical and laboratory parameters of all preterm infants with NEC were compared with those preterm infants without NEC. A descriptive analysis was conducted to obtain central tendencies of the cohorts; numeric variables was expressed in mean $\pm$ SD or median and interquartile range (IQR), while categorical variables expressed in frequency and percentages. Predictive factors with p values of $\leq$ 0.25 were included in the multiple logistic regression analysis using backward stepwise selection method.

RESULTS

Overall cohort

A total of 35 subjects were recruited, however three subjects from preterm non-NEC dropped out due to guardian's refusal to participate in this study. Among them, 15 (10.07%, 15/149 subjects) preterm infants developed NEC and 17 preterm non-

Table I: Demographic and clinical characteristics of subjects at birth

Characteristics	Value
Neonatal factors	
Gestational age (weeks, median, IQR)	31.5 (30.5 34.0)
Birthweight (grams, mean $\pm$ SD)	1562.81 $\pm$ 330.23
Sex (n, %)	
Male	11 (34.4)
Female	21 (65.6)
APGAR score at 1' (median, IQR)	6 (3-6)
APGAR score at 5' (median, IQR)	8 (5-8)
Lubchenco intrauterine growth criteria (n, %)	
Small for gestational age (SGA)	6 (18.8)
Appropriate for gestational age (AGA)	26 (81.3)
Downes score at birth (median, IQR)	3 (0-4)
Antenatal corticosteroid (n, %)	
No	23 (71.9)
Yes	9 (28.1)
Nutritional type (n, %)	
Breastmilk	25 (78.1)
Predominant breastmilk	7 (21.9)
Laboratory aspects at birth (mean $\pm$ SD)	
Haemoglobin (g/dl)	15.78 $\pm$ 2.28
Leukocyte count (cell/mm ³)	11 963 $\pm$ 5 934
Platelets count (cell/mm ³)	235 927 $\pm$ 70 491
Haematocrit (%)	45.85 $\pm$ 7.05
Absolute neutrophil count (cell/mm ³)	6 213 $\pm$ 4 456
Immature/total neutrophil ratio	0.19 $\pm$ 0.51
C-reactive protein (mg/l)	0.207 $\pm$ 0.44
Random blood glucose (mg/dl)	75.16 $\pm$ 22.70
Maternal factors	
Singleton vs twin pregnancy (n, %)	
Singleton	25 (78.1)
Gemelli (twin)	7 (21.9)
Mode of delivery (n, %)	
Pervaginam	8 (25.0)
Caesarian section	24 (75.0)
Body Mass Index (BMI) (n, %)	
18-25 kg/m ²	30 (93.8)
< 18 kg/m ² or > 25 kg/m ²	2 (6.2)

APGAR score = Appearance, pulse, grimace, activity, respiratory score; IQR = Interquartile range (25th – 75th quartile); SD = Standard deviation.

NEC were eligible to participate in this study. During the study period, all preterms with NEC participated. Subjects with NEC (n = 15) were comprised of five males (33.3%), while preterm without NEC were consisted of six males (35.3%) with no significant difference was found between the two groups (p = 0.907, OR 0.92 95% CI 0.21 3.96). The overview of demographic, clinical, and laboratory features is summarized in Table I.

Case (NEC) and control cohorts

Univariate analysis showed the risk factors for NEC development including GA < 32 weeks (OR = 13.00; 95% CI 2.40 70.46; p = 0.001), birthweight < 1500 grams (OR = 8.94; 95% CI 1.80 44.34; p = 0.005), DS of neonatal respiratory distress $\geq$ 4 (OR = 20.63; 95% CI 3.19 133.4; p < 0.001), requirements of advanced neonatal resuscitation upon birth (OR = 1 8.00; 95%CI 2.76 117.6; p = 0.001), and history of PRC transfusion (OR = 2.70; 95% CI 1.65 4.42; p = 0.010), multiple morbidities (OR = 45.5; 95% CI 4.48 461.9; p < 0.001), and history of antibiotic exposure (OR = 48.75; 95% CI 5.99 396.5; p < 0.001). Several factors contributed statistically significant in the odds of preterm neonates developing NEC was depicted in Table II. Furthermore, outcome of adjusted odds ratio through multivariate analysis were summarized in Table III.

Preterm with NEC cohort

Preterm neonates with NEC were developed in 15 subjects (47%) with incidence of 10.07%. This cohort was analysed further and described based on Modified Bell's criteria parameters. Signs of shock were defined as decrease of tissue perfusion characterised by cold clammy extremities, capillary refill time (CRT) > 2 s, or hypotension requiring inotropes or vasopressor. Neonates that developed sepsis clinically were confirmed by positive blood culture. Early onset NEC were defined as onset of NEC less than or equal to 7 days of life.¹⁸ In this study, 66.7% of cases were early-onset, with a median age of diagnosis of 5 days. The most prominent aetiology found in blood culture was *Klebsiella pneumoniae*. Table IV summarised the clinical finding on preterm neonate subjects with NEC.

Subjects with NEC were 14 (93.3%) had multiple clinical pathologies with the most prominent were neonatal pneumonia (12 subject, 80%) that developed respiratory failure (11 subject, 73.3%) and hyaline membrane disease (9 subject, 60%). The clinical pathologies other than NEC was depicted in Table V. Transfusion of PRC was found significantly higher in NEC cohort with the average dose of 27.32 ml/kg. Antibiotic exposure was correlated with higher

Table II: Contributing risk factors related to NEC development between subjects

Parameters	Preterm with NEC	Preterm without NEC (Control)	p-value	OR (95% CI)
Total n = 32 (100%)	15 (47%)	17 (53%)		
NEONATAL FACTORS				
Gestational age (%)				
< 32 weeks	12 (80)	4 (23.5)	0.001^{*,a}	13.00 (2.40 70.46)
≥ 32 weeks	3 (20)	13 (76.5)		
Birthweight (%)				
< 1500 gram	11 (73.3)	4 (23.5)	0.005^{*,a}	8.94 (1.80 44.34)
≥ 1500 gram	4 (26.7)	13 (76.5)		
Downes score criteria				
≥ 4	11 (73.3)	2 (11.8)	< 0.001^{*,a}	20.63 (3.19 133.4)
< 4	4 (26.7)	15 (88.2)		
APGAR score at 1' criteria				
0-3	5 (33.3)	4 (23.5)	0.538 ^a	1.63 (0.34 7.67)
4-6	10 (66.7)	13 (76.5)		
APGAR score 5'				
0-6	6 (40.0)	4 (23.5)	0.316 ^a	2.17 (0.47 9.95)
7-10	9 (60.0)	13 (76.5)		
Extent of neonatal resuscitation (%)				
Positive-pressure ventilation	12 (80.0)	4 (23.5)		Reference
Cardiac compression and intubation	1 (6.7)	1 (5.9)	0.457	3.00 (0.15 25.9)
No indication of resuscitation	2 (13.3)	12 (70.6)	0.001^{*,a}	18.00 (2.76 117.6)
Lubchenco criteria (n, %)				
Small for gestational age (SGA)	1 (6.67)	6 (35.8)	0.011^{*,a}	2.36 (1.51 3.70)
Appropriate for gestational age (AGA)	14 (93.3)	11 (64.7)		
Surfactant administration (%)				
No	13 (86.7)	17 (100.0)	0.120 ^a	0.43 (0.29 0.65)
Yes	2 (13.3)	0		
History of PRC transfusion (%)				
Yes	5 (33.3)	0	0.010^{*,a}	2.70 (1.65 4.42)
No	10 (66.7)	17 (100.0)		
Sepsis				
Yes	11 (78.6)	1 (5.9)	< 0.001^{*,a}	88.0 (7.08 139.9)
No	3 (21.4)	16 (94.1)		
Multimorbidity (%)				
Yes	14 (93.3)	4 (23.5)	< 0.001^{*,a}	45.5 (4.48 461.9)
No	1 (6.7)	13 (76.5)		
Antibiotic exposure (%)				
Yes	13 (86.7)	2 (11.8)	< 0.001^{*,a}	48.75 (5.99 396.5)
No	2 (13.3)	15 (88.2)		
Clinical outcome (%)				
Death	12 (80.0)	1 (5.9)	< 0.001^{*,a}	64.0 (5.90 694.1)
Discharged	3 (20.0)	16 (94.1)		
Length of stay (days)	15 (11-22)	8 (5-10.5)	0.001^{*,b}	
Maternal factor				
Maternal comorbidities (%)				
Any comorbidity	14 (93.3)	14 (82.4)	0.087 ^a	2.07 (1.42 3.02)
No comorbidity	1 (6.7)	3 (17.6)		
Maternal comorbidities (%)				
No comorbidity	0 (0)	2 (11.8)		Reference
PPROM, PROM	8 (53.3)	7 (41.2)	0.156	2.14 (1.35-3.68)
Pre-eclampsia/eclampsia	2 (13.3)	3 (17.6)	0.290	1.67(0.82-3.41)
Antepartum bleeding	1 (6.7)	2 (11.8)	0.361	1.50(0.67-3.34)
Others	5 (26.7)	3 (17.6)	0.151	2.33 (0.99-5.49)
Amniotic fluid index criteria (%)				
Oligohydramnios	3 (23.1)	3 (20.0)	0.843 ^a	1.20 (0.20-7.31)
Normal AFI	10 (76.9)	12 (80.0)		
Pre-partum antibiotic (%)				
No	1 (6.7)	5 (29.4)	0.100 ^a	0.171 (0.02-1.68)
Yes	14 (93.3)	12 (70.6)		
Passive smoker status (%)				
No	9 (60.0)	6 (35.3)	0.210 ^a	0.640 (0.31-1.32)
Yes	6 (40.0)	10 (63.5)		

^aAnalysis with Chi-square test; ^bAnalysis with independent t-test; *p-value < 0.05 was considered statistically significant. APGAR score = Appearance, Pulse, Grimace, Activity, Respiratory score. CI = confidence interval. NEC = necrotising enterocolitis. OR = odds ratio, crude. PPRM = Premature prelabour rupture of the membrane. PROM = Prelabour rupture of the membrane. PRC = Packed red blood cells.

Table III: Multivariate analysis of risk factors related to NEC

Parameters	Preterm with NEC	Preterm without NEC (Control)	p-value	Adjusted OR (95% CI)
Total n = 32 (100%)	15 (47%)	17 (53%)		
Multimorbidity (%)				
Yes	14 (93.3)	4 (23.5)	0.046*	11.95 (1.85 168.38)
No	1 (6.7)	13 (76.5)		
Antibiotic exposure (%)				
Yes	13 (86.7)	2 (11.8)	0.020*	15.95 (1.54 165.08)
No	2 (13.3)	15 (88.2)		
Extent of neonatal resuscitation (%)				
Requiring advanced resuscitation	13 (86.7)	5 (29.4)	0.041*	10.04 (1.09 92.11)
No indication of resuscitation	2 (13.3)	12 (70.6)		

CI = Confidence interval. OR = odds ratio. NEC = Necrotising enterocolitis.

Table IV: Clinical presentations upon NEC diagnosis

Systemic clinical signs	N (%)
Respiratory distress	13 (86.7)
Signs of shock	8 (53.5)
Temperature instability	7 (47.6)
Apnea	3 (20.0)
Bradycardia	1 (6.7)
Abdominal clinical signs	N (%)
Gastric retention	12 (80.0)
Gastrointestinal bleeding	9 (60.0)
Abdominal distension	8 (53.3)
Decreased bowel sound	1 (6.7)
Heme-positive stool	1 (6.7)
Laboratory findings	N (%)
Thrombocytopenia	8 (53.3)
Metabolic acidosis	7 (46.7)
Disseminated intravascular coagulopathy	3 (20.0)
Plain abdominal radiologic features	N (%)
Gastric and/or intestinal dilatation	8 (53.3)
Intestinal wall thickening	1 (6.7)
Pneumatosis intestinalis	3 (20.0)
Pneumoperitoneum	1 (6.7)
Blood culture results	N (%)
Klebsiella pneumoniae	6 (40.0)
Pseudomonas aeruginosa	1 (6.67)
Enterococcus faecium	1 (6.67)
Aeromonas salmonicida	1 (6.67)
No colony growth was found	6 (40.0)
Modified Bell's criteria	N (%)
NEC grade II	13 (86.7)
NEC grade III	2 (13.3)
Age of NEC diagnosis (days) (median, IQR)	5 (3-9)
Onset of NEC	N (%)
Early-onset	10 (66.7)
Late-onset	5 (33.3)

IQR = Interquartile range (25th – 75th quartile); NEC = Necrotising enterocolitis.

odds of developing NEC. In this study, the most frequently administered antibiotics prior to NEC diagnosis were ampicillin-sulbactam and gentamycin (n = 13, 86.7%) and followed by amikacin (n = 3, 20%) and meropenem (n = 2, 13.3%).

DISCUSSION

NEC is an acute, multifactorial inflammatory disease of intestinal injury which primarily affect preterm infants. The exact aetiology and pathophysiology of NEC remained elusive because of its multifactorial nature. Various risk

factors involvements had been proposed, including both neonatal and maternal-related factors.^{2,9} However, the most consistent risk factors remained prematurity and birthweight, the increasing prematurity and the lesser birthweight increased the odds of the infants to develop NEC.^{2,11} This study confirmed, once again, that prematurity and lower birthweight were consistent risk factors of NEC.

The incidence rate of NEC among preterm infants in this study was 10.07%. This finding was higher than those from other countries. Zozaya et al (2022) highlighted 8.8% NEC incidence in Spain preterm cohorts.¹⁹ Considering ethnicity

Table V: Clinical pathologies other than necrotising enterocolitis

Clinical pathologies	N (%)
Neonatal pneumonia	12 (80.0)
Respiratory failure	11 (73.3)
Hyaline membrane disease	9 (60.0)
Septic shock	9 (60.0)
Indirect hyperbilirubinemia	8 (53.5)
Early onset sepsis	7 (46.7)
Late onset sepsis	5 (33.3)
Vitamin D deficiency	3 (20.0)
Acyanotic congenital heart disease	2 (13.3)
Vitamin K deficiency related bleeding	2 (13.3)

factors, the incidence of NEC was 9 to 10% according to Malaysian National Neonatal Registry (MNNR) 2004 to 2005 where this study involved VLBW infants, where most preterm infants manifested.²⁰ This study also showed a higher incidence compared to similar single-centre study in Jakarta, Indonesia, where the incidence was 8.6% among preterm infants.⁴ The varying incidence of NEC might be attributable to different degree of clinical comorbidities experienced by subjects. The advances in neonatal intensive care were correlated with longer survival of severely distressed neonates and this might contribute to increasing diagnosis of NEC in our cohorts.

Contributing risk factors in the diagnosis of NEC within preterm infants in this study were GA, birthweight, DS of respiratory distress, requirement of advanced neonatal resuscitation, history of PRC transfusion within 48-h prior to diagnosis, multiple clinical pathologies, and antibiotics exposure. This study confirmed prematurity and VLBW were consistent risk factors attributable to NEC regardless of ethnicity or difference in country income status.^{2,19,21}

More recent pathogenesis showed that prematurity exposed infants to a higher odd of NEC was thought to be gut dysbiosis. Previous studies noted that there was significant difference in intestinal microbiota between full-term and preterm neonates. The GA was proposed as the pivotal driver of the premature gut microbiota establishment, as prematurity is believed to be attributable to a delay in the transition to an established adult-type signature microbiota. This notion supported that there is a significant reduction in the incidence of NEC within full-term neonates, as their gut microbiota were more likely to be similar to adult-type.²²⁻²⁴ In preterm infants, there is increased relative abundance of Proteobacteria, with some of its members were Enterobacteriaceae, *Klebsiella* spp and *E. coli*, followed by a decrease in Firmicutes (*Lactobacillus* spp) and Bacteroidetes (*Bacteroidetes* spp and *Prevotella* spp).^{22,23} Previous study conducted by Corebima et al (2019) also exhibited the role of increasing *Klebsiella pneumoniae* in preterm infant microbiome was correlated with a higher degree of human β -defensin 2 levels where it posed significant higher inflammatory response within gut mucosal microenvironment.²⁵ These previous findings showed preterm infants exhibited delayed establishment of commensal anaerobic microbes compared to their full-term counterparts and might explain some possible routes why, in this study, the isolated blood-borne bacteria was *Klebsiella pneumoniae* in our cohorts. However, further investigation is encouraged to

confirm gut dysbiosis and NEC, especially in Indonesia population.

In this study, no probiotics were given in both of our cohorts. The role of probiotics was debatable, but the proposed mechanism was modulating gut microbiota. However, the role of probiotics was still limited as most strains were under investigation in small experimental population. A retrospective cohort study by Que et al (2021) showed no significant difference in the incidence and severity of NEC within 310 subjects receiving *Bifidobacterium* and *Lactobacillus* probiotics vs 355 that did not, i.e. (4% vs 5%, $p = 0.10$).²⁶ A phase 3 trial involving 1314 preterm infants showed evidence of benefit for probiotics intervention for both NEC or late-onset sepsis finding; thus routine administration of probiotics was not recommended.²⁷ However, a number of clinical trials were conducted to confirm debatable findings of probiotics in preventing NEC.

The need of advanced neonatal resuscitation at birth, i.e., requirement of PPV or higher, at birth was correlated with higher odds of developing NEC and further strengthen its impact after conduction of multivariate analysis. Advanced resuscitation was significantly found in NEC, most commonly positive-pressure ventilation, in contrast with its non-NEC counterpart where resuscitation was not indicated or only needed initial steps of resuscitation. This finding was correlated with the degree of hypoxemia and respiratory distress found in this study, i.e., D). DS was assessed by following parameters, i.e., respiratory rate, cyanosis, retraction, grunting and respiratory sound, to clinically evaluate the degree of respiratory distress in infants, where $DS < 4$ meant mild respiratory distress and ≥ 4 were moderate-to-severe distress.²⁸ The subjects' DS was assessed within 30 to 60' postnatal.

Both advanced neonatal resuscitation and degree of respiratory distress were correlated with systemic hypoxia/ischaemia, where it was further validated with the source of hypoxic insult due to hyaline membrane disease and/or neonatal pneumonia in our study. The other signs of hypoxia were noted by lower APGAR score at 1' and 5', although did not reach statistical significance, it showed overall lower APGAR score in NEC cohort. Systemic hypoxic/ischemic insult was attributable to NEC development. In a recent study by der Heide et al (2020), hypoxic/ischemic event was correlated with higher risk of developing NEC as this hypoxic event might cause splanchnic hypoperfusion leading to gut mucosal ischemia and mucosal integrity disruption.^{29,30}

PRC transfusion was correlated with higher odds of developing NEC. This is an interesting finding since it is a relatively recent discovery associated with the transfusion-associated NEC (TANEC). Limited studies were found to correlate PRC transfusion with the risk of NEC. TANEC has been described as NEC that arises within 48 hours following blood transfusion.³¹ A review by Gephart (2012) showed PRC transfusion was related to NEC, the hypothesised mechanisms were the result of an abnormal response of the mesenteric blood flow velocity (MBFV) in the post-transfusion state such that low perfusion state interacted with the mechanism of feeding and contribute to intestinal injury. In that sense, two other studies showed practice to hold feeding before and during transfusion was correlated with the decreased of TANEC incidence in preterm infants.^{31–33} However, another finding from a prospective, multicentre cohort exhibited exposure to RBC transfusion was not correlated with increased risk of NEC, but the hypoxic insults did, i.e., anaemia as the underlying condition that contribute to NEC.³⁴ Another proposed pathophysiology of transfusion and NEC was iron overload, confirmed by serum ferritin assay. However, the exact cutoff between transfusion and higher risk of NEC was limited. As there were limited subjects of NEC with transfusion in our study period, an investigation to analyse the correlation between PRC transfusion dosage and NEC is needed.

In multivariable analysis, multiple clinical pathologies and antibiotic exposure were attributed to the higher risk of NEC in this study. Clinical pathologies were associated with systemic hypoxic/ischemic hits and therefore increase the risk of NEC. In a longitudinal multicentre cohorts of preterm infants showed that comorbidities were attributed to higher risk of NEC, where the more severe pathologies was correlated to a higher degree of ischemic insults in GI mucosal integrity leading to inflammation and necrosis.^{19,29}

Among multiple factors associated with pathogenesis of NEC, the widespread administration of antibiotics in NICU might play role in the development of NEC in preterm infants. Although the use of antibiotics was targeted to combat systemic infection, an adverse effects of antibiotic use in infants' immature GI tract was hypothesised. This finding was in concordance with other studies. As gut microbiome in preterm infants differed from their full-term counterparts, antibiotic exposure, especially prolonged administration, were correlated with a higher degree of reducing infants gut microbiota diversity and promoting overgrowth of pathogenic microbes over commensal species, such as Enterobacteriaceae and Clostridia.^{22,35} As the commencement of antibiotics is within neonatologist jurisdiction, a more strict risk-to-benefit ratio is required and the need of consensus establishment of evidence-based duration of antibiotic for neonatal sepsis is essential.

This study was conducted in a prospective manner, allowing multiple risk factors to be evaluated simultaneously to get outcome of interest longitudinally in an exact timestamp. Any confounding was mitigated with strict inclusion criteria, stratification, and multivariate analysis. However, there was some limitation of this study due to its limited number of subjects and single-centre setting. Further investigation is encouraged to validate these findings in a larger, multi-centre inter-hospital cohort and randomised trials.

CONCLUSION

This prospective, case-control study confirmed that lower gestational age, VLBW, degree of respiratory distress and neonatal resuscitation at birth were correlated with higher risk of developing NEC in preterm neonates. Other factors contribute to higher odds of NEC was administration of PRC transfusion within 48-h prior to diagnosis of NEC. From multivariate analysis, multimorbidity, prolonged antibiotic exposure, and the extent of neonatal resuscitation were independently correlated with higher risk of NEC development. Further researches are required to validate these findings with larger, multicentre study.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL APPROVAL

The study had been registered with the local ethics committee under Saiful Anwar General Hospital, Health Research Ethics Commission no. 400/011/K.3/302/2022. Informed consents were obtained from all parents.

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AUTHORS CONTRIBUTIONS

BIRVC: Conceptualisation, methodology, investigation, data curation, writing – original draft. KH: Validation, formal analysis, resources, writing – review and editing. WB: Funding acquisition, project administration, visualisation, writing – original draft. DS: Validation, writing – review and editing, data curation. RR: Supervision, validation, methodology. ES: Data curation, investigation, formal analysis. WW: Formal analysis, investigation, resources. IN: Validation, data curation, visualisation.

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Bacteriological study of antibiotic sensitivity test in chronic rhinosinusitis before and during COVID-19

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ABSTRACT

Introduction: Chronic rhinosinusitis (CRS) is an inflammation of the nasal mucosa and paranasal sinuses for more than 3 months that affects 5 to 12% of the quality of life. Antibiotics are the first line of management for CRS. Increased antibiotic resistance causes ineffective treatment of CRS. This study aims to determine the bacterial pattern that causes CRS before and during the COVID-19 pandemic. Culture sensitivity tests in rhinosinusitis patients were conducted to see changes in the bacterial resistance patterns to antibiotics before and during the COVID-19 pandemic and to determine the appropriate use of antibiotics and prevent an increase in antibiotic resistance in the ENT-HNS outward department of RSUP Dr. M. Djamil Padang.

Materials and Methods: The type of research was a retrospective study with a total sample of 174 CRS patients who had undergone culture and sensitivity tests. The study population was all CRS patients who were treated at the ENT-HNS outward department at RSUP DR. M. Djamil Padang from 2016 to 2021, underwent surgery and received antibiotic treatment at secondary health services. Antibiotic sensitivity cultures are required for surgery and to determine antibiotics use after surgery. This research was conducted from February to May at the Tertiary Hospital of Dr. M. Djamil Padang. The data collection technique used a total sampling technique. The sample in this study was taken from the medical records of patients at the ENT-HNS outward department of RSUP Dr. M. Djamil Hospital, Padang.

Results: The results showed that the prevalence of CRS with polyps before COVID-19 was 63.8% of cases. After COVID-19, the prevalence of CRS with polyps was found to be 60% of cases. Before the COVID-19 pandemic, CRS was most common among those aged ≥ 41 to 50 years (27%) and the most common bacteria causing CRS with or without polyps was *Staphylococcus aureus* (39%; 44%). The bacteria causing CRS with or without polyps after COVID-19 were mostly *Staphylococcus epidermidis* (50% of cases). Before the COVID-19 pandemic, amoxicillin-clavulanic acid had a high resistance of 75 to 100%, however, after COVID-19 there was a change in antibiotic resistance patterns and an increase in ciprofloxacin resistance of 56 to 100% was obtained.

Conclusion: This change in antibiotic resistance pattern needs attention to prevent drug resistance, especially after COVID-19.

KEYWORDS:

Chronic rhinosinusitis, polyps, nonpolyps, bacterial patterns, culture, sensitivity, pandemic COVID-19

INTRODUCTION

According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020), rhinosinusitis is an inflammation of the nasal and paranasal sinuses characterised by two or more symptoms. One of which must be nasal obstruction or a runny nose, and other symptoms such as facial pain, olfactory disturbances, signs on endoscopic examination (nasal polyps and/or mucopurulent discharge and/or oedema of the nasal mucosa), and/or changes in computed tomography (CT) of the sinuses and/or COM that last at least 12 weeks.¹

Chronic rhinosinusitis (CRS) is a common health problem and affects 5 to 12% of the world's population.¹ It has two phenotypes, namely chronic rhinosinusitis with polyps (CRSwNP) and without polyps (CRSSNP).² In Dr. Mohammad Hoesin Palembang hospital, 13.7% of cases of CRS with polyps and 61% of cases with CRS without polyps were found.^{3,4}

At the University of Silesia in Katowice in Poland, the most common bacteria causing CRS with polyps were gram-negative intestinal bacilli (40.4%). Whereas in CRS without polyps, other bacteria caused *Staphylococcus epidermidis* (33.8%).⁵

Research in Medan found that the most common causes of gram-positive bacteria were *Staphylococcus aureus* (13%) and *Staphylococcus epidermidis* (4.3%), while the gram-negative bacteria that caused polyp and non-polyp chronic rhinosinusitis were *Klebsiella oxytoca* 21.7%.⁶ Studies at RSUP Dr. M.Djamil, Padang, found the bacteria that caused CRS with the most polyps, namely *Staphylococcus aureus* (35%), *Staphylococcus epidermidis* (6%), *Klebsiella sp* (13%), while the bacteria that caused CRS without polyps were *Staphylococcus aureus* (22%), *Staphylococcus epidermidis* (7%) and *Klebsiella sp* (4%).⁴

Antibiotics have an important role in the treatment of CRS.^{1,7} Antibiotics can be given for 7 to 10 days. The role of macrolides in the management of CRS is more related to their immunomodulatory properties than their antibacterial properties. Macrolides reduce proinflammatory cytokines, neutrophil infiltration and oxidative damage to mucosal tissues. Doxycycline is effective in CRS with nasal polyposis

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due to its ability to inhibit matrix metalloproteinase activity. However, macrolides can increase the risk of side effects on the heart. In some literature, it is suggested to pay attention to the patient's medication and cardiac risk factors before starting therapy because there will be a risk of arrhythmia and abnormalities in the cardiac muscle. The increasing use of antibiotics has led to the emergence of antimicrobial resistance (AMR) which is a major health challenge. One strategy to prevent antibiotic resistance is to optimise the use of antibiotics, paying attention to the right dose, duration and use.⁸ It is estimated that by 2050, the increase in antibiotic resistance will cause the deaths of up to 10 million people and cost as much as US\$100 million.⁹

At RSUP Dr. M.Djamil Padang found a pattern of resistance for bacteria that cause CRS, namely *Staphylococcus aureus* resistant to ampicillin, ciprofloxacin and ceftriaxone.⁴ Diponegoro University found 20% of bacteria were resistant to tetracycline, 4.0% to trimethoprim-sulfamethoxazole, 12% to erythromycin and 3.0% to gentamicin. A total of 10 studies using culture media found a 300-fold increase in the MIC of amoxicillin (0.25 g/ml to 75 g/ml).¹⁰

Langford et al. reported that 14.3% of COVID-19 patients had a secondary infection and more than 70% of patients received broad-spectrum antibiotics such as fluoroquinolones and third generation cephalosporins. In influenza sufferers, there is damage to the epithelial cells by the virus resulting in mucociliary dysfunction which results in easy passage of bacteria through their cell surfaces to bind to the nasopharynx area. As a result, a bacterial infection occurs which causes continued damage and inhibits the repair and regeneration of epithelial cells.¹¹

There was a change in the pattern of bacteria before and after the pandemic. Putri et al. in the 2016 to 2017 period, the most bacteria recorded in polyp and non-polyp patients was *Staphylococcus aureus*, while the research conducted in the 2018 to 2020 period recorded the most bacteria was *Staphylococcus epidermidis*. Ortega-Pena et al. found that *Staphylococcus epidermidis* plays an important role in inhibiting the development of COVID-19 because it induces the production of type I and III interferons and reduces the expression of the SARS-COV-2 receptor in nasal epithelial cells.¹²

The pattern of bacterial resistance has changed from time to time. Mahmoudi et al. showed that *Enterobacteriaceae* isolates from COVID-19 patients had the highest resistance to co-trimoxazole (74%), piperacillin (67.5%), ceftazidime (47.5%), and cefepime (42.5%). All isolates were sensitive to amikacin (100%). *S. aureus* isolates were sensitive to vancomycin (100%) and had a resistance level of more than oxacillin, erythromycin and clindamycin (90%). *P. aeruginosa* is susceptible (90%) to imipenem. In the study conducted for the 2018-2020 period, the percentage of sensitivity to gentamicin was 80% and 95%, while the resistance to the antibiotic ampicillin with a sensitivity percentage of 5%, amoxicillin clavulanate (5 to 10%).¹³

The pattern of bacterial resistance changes from time to time, so research is needed to determine the patterns of change that

happened. Changes in the pattern of bacterial resistance make treatment more difficult, worsening the patient's condition and causing high costs.¹⁴ The high incidence of CRS and antibiotic resistance that occurred mainly in the city of Padang made researchers interested in knowing the pattern of bacteria and culture sensitivity in CRS patients in RSUP Dr. M. Djamil, Padang, between 2016 to 2021 before the COVID-19 pandemic and during the COVID-19 pandemic.

MATERIALS AND METHODS

This study is a descriptive study with a retrospective method. The sample size in this study was 174 samples. The sampling technique used was the total sampling technique. The samples in this study were taken from patient medical records at the ENT-HNS outward department of RSUP Dr. M. Djamil Hospital, Padang for the period 2016 to 2021. This study compared bacterial patterns and culture sensitivity of CRS patients before and during the COVID-19 pandemic. The variables studied were nasal polyps, age, gender, bacterial patterns, and bacterial culture sensitivity. The study population was all CRS patients who sought treatment at the ENT-HNS outward department of RSUP Dr. M. Djamil Hospital, Padang from 2016 to 2021 and received antibiotic treatment in a secondary hospital. Antibiotic sensitivity tests were carried out as a condition for surgery and for the use of antibiotics after surgery. culture and antibiotic sensitivity tests were carried out at the Microbiology Laboratory of the Faculty of Medicine, Andalas University. Data analysis was performed using SPSS to determine the distribution and percentage of bacterial patterns and culture sensitivity in CRS patients.

RESULTS

Characteristics of respondents

This study was conducted on 174 chronic rhinosinusitis patients with or without polyps in RSUP Dr. M. Djamil, Padang and Microbiology Laboratory, Faculty of Medicine, Andalas University, which met the inclusion and exclusion criteria. The characteristics of the respondents were grouped by year, presence or absence of nasal polyps, age, and gender.

The pattern of bacteria causing chronic rhinosinusitis

The results of the study found patterns of bacteria that cause CRS in RSUP Dr. M. Djamil, Hospital, Padang from 2016 to 2021. There were 20 species of bacteria that cause CRS with or without polyps. In Table II bacterial patterns are grouped by year and CRS phenotype.

Table II. Bacterial patterns of CRS patients with and without polyps at RSUP Dr. M. Djamil Hospital, Padang from 2016 to 2019 before COVID-19 and from 2020 to 2021, during COVID-19

The bacteria that caused rhinosinusitis before COVID-19 were caused by *Staphylococcus aureus* (39%; 44%), followed by *Klebsiella sp* (21%), while after COVID-19 the most common bacteria that caused CRS were *Staphylococcus epidermidis* (50%).

Table I: Characteristics of respondents

Variable	Frequency		%	
	2016 to 2019	2020 to 2021	2016 to 2019	2020 to 2021
Pattern of polyp and non-polyp				
CRS wNP	111	18	63.8	60
CRS sNP	63	12	36.2	40
Amount	174	30	100	100
Age (Years)				
<20	8	1	4.6	3.3
21-30	22	7	12.6	23.3
31-40	36	7	20.7	23.3
41-50	47	7	27	23.3
51-60	40	1	23	3.3
>60	21	7	12.1	23.3
Amount	174	30	100	100
Gender				
Male	81	14	46.5	46.7
Female	93	16	53.5	53.3
Amount	174	30	100	100

Table II: Bacterial patterns of CRS patients with and without polyps at RSUP Dr. M. Djamil Hospital, Padang from 2016 to 2019 before COVID-19 and from 2020 to 2021, during COVID-19

No Bacterial species	CRS wNP				CRS sNP			
	2016 to 2019	F	2020 to 2021	F	2016 to 2019	F	2020 to 2021	F
1. Staphylococcus aureus	43	39%	3	17%	28	44%	1	8%
2. Staphylococcus epidermidis	22	20%	9	50%	16	25%	6	50%
3. Klebsiella sp.	23	21%	3	17%	5	8%	1	8%
4. Coagulase-Negative Staphylococcus	8	7%	0	0%	1	2%	0	0%
5. Streptococcus sp.	5	5%	1	6%	2	3%	0	0%
6. Acinetobacter baumannii	2	2%	0	0%	0	0%	0	0%
7. Acinetobacter lwoffii	1	1%	0	0%	0	0%	0	0%
8. Citrobacter koseri	1	1%	0	0%	0	0%	0	0%
9. Pseudomonas aeruginosa	3	3%	0	0%	5	8%	1	8%
10. Burkholderia sp.	0	0%	0	0%	1	2%	0	0%
11. Proteus mirabilis	0	0%	0	0%	0	0%	1	8%
12. Raoultella ornithinolytica	0	0%	0	0%	1	2%	0	0%
13. Sphingomonas paucimobilis	0	0%	0	0%	0	0%	1	8%
14. Staphylococcus equorum	0	0%	0	0%	1	2%	0	0%
15. Staphylococcus pseudintermedius	0	0%	0	0%	0	0%	1	8%
16. Staphylococcus sp.	0	0%	0	0%	1	2%	0	0%
17. Pantoea sp.	0	0%	1	6%	0	0%	0	0%
18. Mycobacterium lacunata	0	0%	1	6%	0	0%	0	0%
19. Serratia marcescens	0	0%	0	0%	2	3%	0	0%
20. MRSA	3	3%	0	0%	0	0%	0	0%
Amount	111		18		63		12	

Bacterial sensitivity culture

Based on Table II data, a culture test for bacterial sensitivity to antibiotics was carried out. After data analysis, a pattern of bacterial resistance to the use of antibiotics was found. The use of the antibiotics, ampicillin, gentamicin, ciprofloxacin, ceftriaxone, meropenem, and cefoperazone has high resistance to the bacteria that cause CRS.

Before COVID-19, amoxicillin had a high level of resistance, whereas after COVID-19, there was an increase in resistance to the fluoroquinolone group.

DISCUSSION

Characteristics of respondents

Based on data analysis, the prevalence of CRS with polyps at RSUP Dr. M. Djamil was 63.8%, which was higher than the prevalence of CRS without polyps, 36.2%. The Department of

Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, University of Colorado, University of Utah, University of Virginia, Oregon Health Sciences University found that CRS incidence with polyps was 59.7% and without polyps 40.3%.¹⁵ The Global Allergy and Asthma European Network (GALEN) found that 445 people had CRS with polyps and 237 people without polyps.¹⁶

Based on the analysis of the data, it was found that there is no difference in the incidence of CRS with or without polyps before and after COVID-19. There were 60% of CRS cases with polyps in 2020 until 2021. Study by Sbeih et al. found that 5.22% of COVID-19 cases were accompanied by CRS.¹⁷ Another study by Wang et al. showed that 6.1% of COVID-19 cases were accompanied by CRS. These results are higher than studies conducted in China and Europe, with 0 to 3% of cases.¹⁸

Table III: Patterns of bacterial sensitivity to antibiotics in patients of CRS with and without polyps at RSUP Dr. M. Djamil Hospital, Padang from 2016 to 2019, before COVID-19, and 2020 to 2021 during COVID-19

No CRSwNP	2016 to 2019					2020 to 2021				
	AMC f	GM f	CIP f	CRO f	MEM f	CFZ f	AMC f	GM f	CIP f	CRO f
1 <i>S. aureus</i>	89	19	54	65	22	14			33	
2 <i>Klebsiella</i> spp	75	26	43	48	17	9	100			
3 <i>S. epidermidis</i>	88	14	33	67	20	33			56	
4 <i>Streptococcus</i> sp.	100	20							100	
No CRSsNP	f	f	f	f	f	f	f	f	f	f
1 <i>Klebsiella</i> spp	100			40			100		100	100
2 <i>S. epidermidis</i>	75	7	50	60	18	29			67	
3 <i>P. aeruginosa</i>	100		33	100				100		
4 <i>Proteus mirabilis</i>									100	100

AMC = Amoxicillin clavulanic acid, GM = Gentamicin, CIP = Ciprofloxacin, CRO = Ceftriaxonr, MEM = Meropenem

Based on age data, the prevalence of CRS from 2016 to 2019 at RSUP Dr. M. Djamil 27% of cases are under 50 years old, and 23% of cases are over 50 years old with and without polyps. In a Canadian study, cases of CRS increased with age.¹⁹ Nasal polyps rarely occur in children unless accompanied by comorbidities such as cystic fibrosis, which is produced by the cystic fibrosis transmembrane conductance regulator (CFTR), which is closely related to CRS and allergic fungal rhinosinusitis. In children, cellularity and lymphocytic infiltration are more prominent, whereas in adults there is a stronger eosinophilic infiltration and a glandular hyperplastic process.²⁰ Elderly CRS patients have characteristic inflammatory signs associated with a neutrophilic proinflammatory response.²¹ Patients aged 60 years and older have higher levels of IL-1b, IL-6, IL-8, and TNF-a compared to younger patients.²²

There is no significant difference found between age and the incidence of CRS from 2020 to 2021 after the COVID-19 pandemic. Up to 23.3% of CRS cases occurred between the ages of 21 and 50. A decrease in the incidence of chronic rhinosinusitis (3.3%) was observed at the age of 51-60. Sbeih et al. and Tunjai et al. found that there was no significant age difference between COVID-19 patients with CRS and COVID-19 patients without CRS.^{16,22}

In this study, it was found that CRS is more common in women. From 2016 to 2019, 53.5 cases of CRS were found in women. The same results were also obtained between 2020 to 2021, with more women than men experiencing the CRS (53.3%). Hirsch et al. found that the prevalence of CRS was higher in women (66.7%)²³, another study conducted NHIS in the United States found fewer male sufferers than male sufferers (39.7%: 60.3%).²⁴ Sbeih et al. also found that 52% of chronic rhinosinusitis cases occurred in women with COVID-19.¹⁷ Women are two times more likely to experience CRS than men. The high prevalence of CRS is associated among women with a higher level of concern for women to get services. The smaller size of the sinus ostia in women makes them more susceptible to further obstruction and infection.^{16,25}

Bacteria cause Chronic Rhinosinusitis

Before COVID-19, ten species of bacteria caused CRS with polyps, and after COVID-19, seven species of bacteria that caused CRS with polyps were found in RSUP Dr. M. Djamil Padang. There were differences in the distribution patterns of the bacteria that cause CRS with polyps and without polyps

in 2016 to 2019 before the COVID-19 pandemic and in 2020 to 2021 during the COVID-19 pandemic. In 2016 to 2019 before COVID-19, most CRS with polyps were caused by *Staphylococcus aureus* (39%), *Klebsiella* sp. (21%), and *Staphylococcus epidermidis* (20%) whereas, CRS without polyps was caused by *Staphylococcus aureus* (44%), *Staphylococcus epidermidis* (25%) and *Klebsiella* sp. (8%). In Medan, *Staphylococcus aureus* was found to be the cause of CRS with the most polyps.⁶ In the Beijing Tongren Hospital, it was found that the most dominant cause of CRS in polyps was *coagulase-negative Staphylococcus* (24.3%), *Corynebacterium* (19.9%) and *Staphylococcus epidermidis* (19.1%). In non-polyp CRS caused by *S. Epidermidis* (21.2%), *Corynebacterium* (21.2%), *Coagulase-negative staphylococci* (18.2%) and *Staphylococcus aureus* (13.6%). In this study, the causative bacteria varied between polyps and non-polyps.²⁶

In 2020 to 2021 different results were obtained, namely the most common causes of CRS with or without polyps were *Staphylococcus epidermidis* (50%; 50%), *Staphylococcus aureus* and *Klebsiella* sp. (17%; 8%). In China it was found that *S. Epidermidis* was the most common bacterium that causes, followed by *Pseudo diphtheria*, *Staphylococcus aureus*, *Haemophilus influenza* mole and *Haemella influenzaemola*.²⁷ In 2021, a study was carried out in Poland to isolate the cause of CRS. The data analysis found that *coagulase-negative staphylococcus* and *S. Epidermidis* were the most common causes.¹² Salman et al. of the 20 studies studied, found that 40% of cases of co-infection with COVID-19 were caused by *S. Aureus*. Salman et al. suggested that there were 5.62% of cases of bacterial co-infection in COVID-19 patients.²⁸ The cause of secondary infection is not known with certainty, another hypothesis states that immune system dysregulation and lymphopenia are the factors which influence the incidence of secondary infection in COVID-19. Khuruna et al. found that the gram-negative bacteria *A. Baumannii* was the dominant cause of secondary infection in COVID-19 (24.3%). From the results of blood isolation it was found that 6% of *Acinetobacter* sp. was resistant to carbapenems.²⁹

The research is consistent with other research conducted by various countries throughout the pandemic. The high number of *S. Epidermidis* bacteria that cause CRS in this study is related to the COVID-19 pandemic. This is supported by research conducted in 2022 which states that *S. Epidermidis* is more abundant in the anterior part of the nares than in the inside.

Bacterial Sensitivity Culture

The results of bacterial antibiogram examination in polyp and non-polyp CRS patients between 2016 to 2019, before the COVID-19 pandemic, it can be concluded that most are resistant to ampicillin and amoxicillin-clavulanic acid (75 to 100%). There are differences in the pattern of antibiotic resistance before and during the COVID-19 pandemic in CRS. During the COVID-19 pandemic, antibiotic resistance was found against the fluroquinolone class, namely ciprofloxacin. This difference in the pattern of antibiotic resistance is also related to the difference in the distribution of the bacteria that cause CRS before and during the COVID-19 pandemic (56 to 100%). Aldhwihi et al. compared antibiotic resistance before and during COVID-19. Aldhwihi et al. found a bacterial resistance level for ciprofloxacin at 84.2%.³⁰

In South Korea found that patients with CRS were at increased risk for COVID-19 infection. In CRS, there is immune dysfunction, such as damage to the epithelial barrier and deficiency of specific antibodies. Viral infections can also cause CRS. Lee et al. found that CRS was caused by a viral infection which was 2.9 times higher, and 21.6% of cases were caused by a *Coronavirus* infection.³¹ Sbeih and Jorge found that CRS patients using intranasal corticosteroids increased the risk of COVID-19 treatment. There is a potential difference in the density of ACE2 and TMPRSS2 affecting viral shedding in CRS. The Expression of non-eosinophilic CRS, ACE2 and TMPRSS2 was found to be higher than that of eosinophilic CRS. The increase in ACE2 and TMPRSS2 increases the risk of exposure to COVID-19 because ACE2 is the main receptor in COVID-19 infection.¹⁷

According to WHO, the percentage of antibiotic use during the treatment of COVID-19 reaches 94 to 100%, this percentage is higher than the reported incidence of secondary infections, which is 10 to 15%. Of the 7 to 8% of cases requiring hospitalisation and 14% of ICU admissions and 72% of patients received antibiotic treatment. This has led to an increase in antibiotic resistance or AMR. The increasing use of antibiotics causes the loss of effectiveness of antibiotics such as carbapenems which are used to treat severe bacterial infections. In addition, AMR can increase the costs and impact patient or caregiver productivity due to length of hospital stay.³²

CONCLUSION

1. There is no difference in the prevalence of chronic rhinosinusitis (CRS) with or without polyps before and during the COVID-19 pandemic in 2020 to 2021. The prevalence of CRS with polyps at RSUP Dr. M.Djamil at 63.8%, this figure is higher than the prevalence of CRS without polyps, which is 36.2%.
2. There were differences in the distribution patterns of the bacteria that cause CRS with polyps and without polyps in 2016 to 2019 before the COVID-19 pandemic and in 2020 to 2021 during the COVID-19 pandemic. In 2016 to 2019 before COVID-19, most chronic rhinosinusitis with polyps were caused by *Staphylococcus aureus* (39%), *Klebsiella* sp. (21%), and *Staphylococcus epidermidis* (20%). CRS without polyps was caused by *Staphylococcus*

aureus (44%), *Staphylococcus epidermidis* (25%) and *Klebsiella* sp. (8%). In 2020 to 2021 different results were obtained, e.g., the most common causes of CRS with or without polyps were *Staphylococcus epidermidis* (50%;50%), *Staphylococcus aureus* and *Klebsiella* sp (17%; 8%).

3. There are differences in the pattern of antibiotic resistance before and during the COVID-19 pandemic in chronic rhinosinusitis. Before the COVID-19 pandemic were resistant to Amoxicillin-Clavulanic Acid, (75 to 100%) while during the COVID-19 pandemic there was an increase in resistance to Ciprofloxacin (56-100%).

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Telemedicine therapy among chronic pain patients during the COVID-19 pandemic

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ABSTRACT

Introduction: Patients with chronic pain have been one of the most difficult patients to manage during the COVID-19 pandemic. As pain physicians navigate through this pandemic in order to maintain contact with their patients, telemedicine emerged as a very useful tool. It helped patients to access care despite being in distant areas, or during the lockdown period. The objective of this research is to assess the perception of chronic pain patients who received telemedicine therapy. Self-efficacy and coping level of pain among these chronic pain patients were also assessed.

Materials and Methods: This is a cross-sectional study involving patients who are under follow-up at the Chronic Pain Clinic, Hospital Pulau Pinang for more than a year and received telemedicine during this pandemic. Participants had to fill out a self-administered questionnaire. Once respondents completed the questionnaires, the answered questionnaires were collected for analysis.

Results: A total of 154 patients between 22 and 88 years old were included in this study. Most of the participants had a history of pain for more than 3 years (44.2%). The majority of our patients are still working (55.8%). From the patients who were working, 7.8% of them lost their jobs during the pandemic. 31.2% of patients reported that the pain condition had worsened while the rest did not experience any difference in their pain condition. More than half (59%) of the patients' reported telemedicine was beneficial for their pain management, while only 41% felt that their telemedicine was helpless for their pain management during the pandemic.

Conclusion: Telemedicine is beneficial for patients with chronic pain. Telemedicine can be used post-pandemic and may produce a good outcome with patients.

KEYWORDS:

Telemedicine, COVID-19, chronic pain, pandemic

INTRODUCTION

Patients with chronic pain have been one of the most difficult patients to manage during the COVID-19 pandemic. The pandemic left many patients burdened with their chronic pain due to delayed treatment. The pandemic had caused face-to-face access of patients to pain physicians limited.¹

As pain physicians navigate through this pandemic in order to maintain contact with their patients, telemedicine emerged as a very useful tool. It helped patients get care despite being in distant areas, or during the lockdown period.

Due to the current pandemic period, other sources of stressors were amplified, which caused worsening chronic pain. Physical therapy (PT) programs, which is an integral part of multimodal chronic pain management, were stopped during the COVID-19 pandemic. This also affected other multimodal pain treatment strategies, including visits to the psychiatrist, psychologist and pain counsellors. This caused the active guidance of cognitive behaviour therapy (CBT), coping skills and stress management to be affected. Due to social distancing policies, all new appointments were deferred, and ongoing treatments for existing pain patients were further postponed.²

Psychosocial issues may also lead to heightened pain perception. Therefore, it is not surprising that this pandemic has caused chronic pain symptoms to worsen as a result of stress. These stressors include financial loss, personal loss and anxiety.³ During this period, pain practitioners had very few treatment options. These included prescribing more opioids to ensure patients stay away from the already overburdened emergency departments.⁴

The Chronic Pain Clinic in Hospital Pulau Pinang (HPP) started in 2010. Currently, the clinic serves patients from all over Pulau Pinang. Usually, patients will be reviewed regularly face-to-face at 3 to 6 month intervals, depending on their pain condition and medication. During the COVID-19 pandemic and the Movement Control Order (MCO), patients found it difficult and frightening to visit the clinic. Telemedicine was used to overcome this problem. Telemedicine or phone consultation is very new to our pain clinic services. Self-efficacy beliefs in chronic pain patients have been assessed either by reference to confidence in their ability to perform specific tasks or their confidence in performing more generalised constructs like coping with pain.⁵ This research will help us understand how far telemedicine had been helpful in supporting patients to develop coping skills. There are few studies published regarding self-efficacy and coping skills among chronic pain patients, especially during the pandemic period.

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The objective of this research is to assess if telemedicine is beneficial for chronic pain patients. Self-efficacy and catastrophising of pain among these chronic pain patients were also assessed.

MATERIALS AND METHODS

This was a prospective cross-sectional study, done in the Chronic Pain Clinic, HPP. These patients were recruited using convenience sampling and needed to answer the survey only once. The samples recruited for the study were patients who had visited the pain clinic of HPP more than 1 year prior to the MCO. Due to COVID-19, patients were not able to visit our pain clinic. As an alternative, patients were managed or consulted via phone conversation. The estimated duration of this study was 6 months. The Medical Research and Ethics Committee (MREC) approval was obtained prior to the research (NMRR-21-241-58474 S1R2).

Our criteria for inclusion applied to patients over 18, and with a history of chronic pain. Only patients who have attended a minimum of three sessions of telemedicine were recruited. Chronic pain was defined as persistent or recurrent pain which lasts longer than 3 months.⁶ Our exclusion criteria were those that did not meet the criteria for chronic pain. Details of the research were explained clearly to the participants. They were given sufficient time to read through the information sheet for their participation in the study. Any queries were answered by the investigator before the consent-taking process. Clinic nurses assisted in delivering and collecting back the survey. The rights and treatment of the patients will not be affected if they refuse to participate in the study. They can withdraw consent at any time without providing a reason. The study results will not be revealed to them.

A consecutive sampling method was used, whereby all the potential participants who fulfilled all the criteria were approached for participation in the study. A special phone number will be assigned to the participant and documented on the screening log to maintain confidentiality.

Participants had to fill out a self-administered questionnaire, which was provided to them when they return to the clinic for face-to-face consultation. Once respondents complete the questionnaires, the answered questionnaires were collected for analysis.

Based on a sample size calculation for a study of a finite population (Creative Research Systems, 2012), with approximately 220 patients at the chronic pain clinic of HPP, a minimum sample size of 140 patients were calculated to represent a cross-section of the population.⁷ This will allow the study to determine self-efficacy and coping skills with a margin of error of +/- 5%. An additional 10% was included in the calculated sample size to compensate for dropouts, for a final sample size of 154 patients.

The questionnaire consists of three parts:

Part A: Demographic data: Age of respondent, gender, education status, diagnosis, pain score and effects of the pandemic.

Part B: Pain self-efficacy questionnaire (PSEQ)

This is a 10-item scale, where patients were asked to rate how confident they were to do a range of activities or functions at present, despite their pain, by selecting a number on a 7-point scale, where 0="not at all confident" and 6="completely confident". Examples of items include the following: 'I can do most of the household chores (e. g., tidying-up, washing dishes, etc.), despite the pain'. Scores on the PSEQ range from 0 to 60, with higher scores indicating stronger self-efficacy beliefs. The test-retest reliability and internal consistency of the PSEQ in different studies with chronic pain patients were reported as 0.79 and 0.92, respectively.⁵ A Malay-validated PSEQ was used (Cronbach alpha was 0.95).⁸

Part C: Pain-related self-statements (PRSS)

This 18-item measure has two sub-scales (active coping and catastrophising). Items include statements such as "I cannot stand this pain any longer". When using a 0–5 scale, where 0=almost never and 5=almost always, patients rate how often they have the specified thoughts when their pain is more severe. The subscale score is the mean of the items scored, yielding a possible score out of 5. This instrument is valid and reliable in assessing cognitive patterns relevant to persons suffering from chronic pain.³ We used a Malay version questionnaire which was validated (Cronbach alpha was 0.88).⁸ For this study purpose only sub-scale catastrophising was analysed, a mean score > 3.2 is considered significant.

The collected data were analysed with the SPSS version 23.

RESULTS

In total, 154 patients aged 22 to 88 were included in the study. Most of the participants had a history of pain for over 3 years (44.2%). Most of our patients are still working (55.8%). From the patients who were working, 7.8% of them lost their job during the pandemic. 31.2% of patients reported worsening pain conditions while the rest did not experience any difference in their pain condition. (Table I).

In total, 154 patients aged 22 to 88 were included in the study. Most of the participants had a history of pain for over 3 years (44.2%). Most of our patients are still working (55.8%). From the patients who were working, 7.8% of them lost their job during the pandemic. 31.2% of patients reported worsening pain conditions while the rest did not experience any difference in their pain condition. (Table I).

PSEQ score showed that almost 67% of patients had scored less than 40, which indicates that the patients tend to have poor coping skills (Table III). Another 33% of patients showed to have good coping skills and had gained more benefit from the telemedicine compared to the poor coping skills group, $X^2(2)=4.17$; $p=0.04$. Pearson correlation was performed to look for a relationship between the PSEQ score and the average pain score. It showed patients with good coping reported having lower pain scores ($r=-0.48$, $p=0.01$).

Based on the pain-related self-statements (PRSS) psychometric tool, 48.7% of our patients showed catastrophising pain behaviour.

Table I: Demographic data of patients

Variables	N (%)
Gender	
Male	73 (47)
Female	81 (53)
Education level	
Primary	41 (26.6)
Secondary	64 (41.6)
Higher secondary	30 (19.5)
University	19 (12.3)
Employment status	
Working	86 (55.8)
Not working	68 (44.2)
Pain duration	
1 year	16 (10.4)
1-2 years	34 (22.1)
2-3 years	36 (23.4)
> 3 years	68 (44.2)
During pandemic	
Worsening pain condition	48 (31.2)
Lost job	12 (7.8)

Table II: Perception of patient towards telemedicine

Question	N (%)
Telemedicine was beneficial in pain management	
Yes	91 (59)
No	63 (41)
Satisfaction towards telemedicine experience	
Satisfied	72 (46.7)
Neutral	48 (31.2)
Not satisfied	34 (22.1)
Will choose telemedicine in the future	
Agree	64 (41.5)
Neutral	48 (31.2)
Don't Agree	42 (27.3)

Table III: Psychometric properties of patients

Psychometric tool	N (%)
Patient self-efficacy questionnaire (PSEQ)	
≥ 40	51 (33.0)
<40	103 (67.0)
Pain related self-statement (PRSS)	
Pain catastrophising behaviour (> 3.2)	75 (48.7)

DISCUSSION

Our study showed that almost half of the participants were satisfied with the use of telemedicine in managing chronic pain. These results echoed several research done recently.⁹⁻¹¹ Most of them are also keen to continue the use of telemedicine for their future management. The study also showed that patients with good self-efficacy skills tend to benefit more from telemedicine, with a lower pain score. This study has shown that telemedicine is a good method of treatment for our patients.

Telemedicine has a huge potential in revolutionising the health industry.¹² Telemedicine is the practice of medicine using audio, video and data communications.¹³ Malaysia had started the initiative to implement e-health since the establishment of Malaysia's Telemedicine Blueprint in July 1997.¹⁴ The objectives of telehealth was to strengthen

healthcare delivery via the use of telecommunications, information and multimedia technologies. Soon after that, more hospitals have been installed with applications of telehealth components.¹⁵

Telemedicine has several advantages.^{16,17} These include easy access to remote areas, reducing the time and cost of patient transfer, home care monitoring, second opinion for complex interpretations, disease surveillance, and standardisation in provision of healthcare.

However, there are some barriers to telemedicine.^{18,19} These barriers include lack of telecommunication technology, uncommitted management, lack of budget, unavailability of efficient staff and resistance to practice telemedicine among doctors.

Telemedicine in Malaysia has led to cost savings, efficient allocation of resources, enhanced diagnostic options and better health outcomes.²⁰ With these benefits, the use of telemedicine for chronic pain patients should be further explored.

The main limitation in this study is that convenience sampling was used for sample collection. The response rate was likely higher in individuals who are more comfortable with technology. Thus, the results may not be generalised to individuals who are less comfortable with or do not have access to this technology. A possible solution to overcome this limitation is to provide a telemedicine station at a nearby health centre, which could be shared among the patients within the vicinity.

CONCLUSION

This study found that telemedicine is beneficial to patients suffering from chronic pain during the COVID-19 pandemic. Telemedicine also has a positive impact on the self-efficacy and catastrophising of pain among these patients. However, more studies need to be done to justify the importance of the need for telemedicine among chronic pain patients.

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CONFLICT OF INTEREST

None declared.

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Chlorogenic acid may improve memory function and decrease inflammation of frontal lobe in diabetic rat

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ABSTRACT

Introduction: Diabetes Mellitus (DM) is a chronic disease with many complications, one of which is diabetic encephalopathy which is characterised by memory dysfunction. Hyperglycaemia that occurs in DM will activate inflammatory pathways in neurons, including NF- κ B pathway. Activation of this pathway produce proinflammatory agents such as MCP-1 and IL-6, which activate glial cells. Activation of glial cells is characterised by Glial Fibrillary Acid Protein (GFAP). Chlorogenic acid (CGA) has been reported to have anti-inflammatory effects and can improve memory function. This research aimed to determine the effect of CGA as anti-inflammation, its effect on memory function, mRNA expression of NF- κ B, MCP-1, IL-6, and GFAP of frontal lobe.

Materials and Methods: A total of 24 male rats were randomly divided into six groups: control, DM 1.5 month (DM1.5), DM 2 months (DM2) and the group with three different doses of CGA 12.5 (CGA1), 25 (CGA2), and 50 (CGA3) mg/KgBW. Frontal lobe tissue is taken for analysis of mRNA expression for NF- κ B, MCP-1, IL-6, and GFAP using Reverse Transcriptase PCR (RT-PCR). Samples were also taken for histopathology preparation and stained by immunohistochemistry method using anti-GFAP antibodies to observe glial cell activation in frontal lobe tissue.

Results: The group that was given CGA at all doses have statistically significant better memory function, i.e. DM2 versus CGA1 ($p = 0.036$), CGA2 ($p = 0.040$), and CGA3 ($p = 0.021$). The result of mRNA expression in NF- κ B was lower in the group given CGA, i.e. DM2 compared to CGA2 ($p = 0.007$). mRNA expression of MCP-1 was significantly lower in all CGA treatment groups compared to the non-CGA group ($p = 0.000$). IL-6 mRNA expression was lower than the group not given CGA, DM compared to CGA2 ($p = 0.028$). GFAP mRNA expression was lower than the group given CGA in DM, DM2 group compared to CGA1 ($p = 0.04$) and CGA3 ($p = 0.004$).

Conclusion: Administration of CGA can improve memory function at all doses given, and can reduce brain inflammatory activity, especially in the CGA2 group.

KEYWORDS:

Chlorogenic acid, Diabetes Mellitus, Memory, Inflammation, frontal lobe

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder caused by the inability of insulin production by the pancreas or resistance by end organ tissues and results in high blood glucose levels (hyperglycaemias) and can be followed by a progressive decrease in pancreatic beta cell function.^{1,2} DM is a chronic disease that can develop into many complications in various organs. One of the most dangerous complications of chronic hyperglycaemia is diabetic encephalopathy which is characterised by decreased cognitive function and motor dysfunction.³

Hyperglycaemia that occurs in DM will activate inflammatory pathways in neurons, then neurons will release inflammatory agents and activate glial cells. Inflammation in neurons involves several pathways, one of which is the PKC pathway. The activated PKC pathway will activate NF- κ B in the nucleus then will express proinflammatory agents such as MCP-1 and IL-6.⁴ Metabolic dysfunction and oxidative stress will also cause changes that occur rapidly and activate glial cells. The main indicator of this response is Glial Fibrillary Acid Protein (GFAP). Abnormal GFAP expression is mostly concentrated in the cortex and hippocampus.⁵ Inflammation that occurs due to hyperglycaemia will then cause damage to the cerebrum called diabetic encephalopathy. Diabetic encephalopathy shows symptoms of decreased cognitive function, including memory.⁶ The brain regions most susceptible to damage due to DM are the hippocampus and frontal cortex.⁷

One of the functions of the frontal cortex is to play a role in working memory. Lesions in the frontal lobe will result in memory dysfunction including spatial memory and working memory.¹⁰ Several studies, one of which is by inhibiting GSK-3 β , have shown that this inhibition prevents cognitive dysfunction in DM rats using the Morris water maze assay, and shows lower expression of proinflammatory agents in the brain.¹¹ Administration of antioxidants in the form of crocin compounds also has a beneficial effect in improving memory dysfunction, and reducing hyperglycaemia and oxidative stress in DM rats by streptozotocin induction.¹⁰ Administration of chlorogenic acid (CGA) in rats with cognitive dysfunction induced with intracerebroventricular streptozotocin demonstrates prevention of cognitive dysfunction.¹¹ CGA is also known to inhibit memory deficits and hippocampal cell death in mice with a transient global ischemia model.¹²

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CGA is one of the polyphenol compounds in coffee that has the highest antioxidant content, which is $\pm 200\ 550$ mg/cup of coffee with 26% activity compared to beta carotene (0.1%), alpha tocopherol (0.3%) and vitamin C (8.5%).¹³ CGA is the most widely consumed polyphenol compound and reported to have antioxidant and anti-inflammatory effects. CGA has been reported to inhibit mRNA expression and levels of the cytokine interleukin-8 (IL-8).¹⁴ The study also reported the neuroprotective effect of CGA on scopolamine-induced memory and learning impairment in mice and found that decaffeinated CGA-rich instant coffee was able to protect against learning and memory disorders through cholinergic and antioxidant mechanisms.¹⁵ Several pre-clinical studies conducted to determine the effects of CGA on cognitive function in rodents have also shown that CGA has the potential to improve spatial learning and memory, reduce memory impairment, reduce anxiety, improve motor function and protect against ischemia-induced neuronal damage.¹⁶

Inflammation of neurons that occurs due to hyperglycaemia in DM is a serious problem and can interfere with cognitive function and memory and one of the vulnerable parts of the brain is the hippocampus and frontal cortex.^{17,18} There is no study that clarifies the effect of CGA on memory dysfunction and frontal lobe inflammation caused by DM. Therefore, further research is needed regarding the effect of CGA on memory dysfunction and frontal cortex inflammation by studying the frontal lobe mRNA expression of GFAP, MCP-1, NF- κ B and IL-6 in diabetic rats.

MATERIALS AND METHODS

Design

This research is a quasi-experimental study with a post-test only controlled group design used 2-month-old male *Rattus norvegicus* Wistar strain with a body weight (BW) of 150 200 grams obtained from the University of Muhammadiyah Yogyakarta. Rats ($n=24$) are divided into six groups: control; DM1.5 (DM for 1.5 months); DM2 (DM for 2 months); and three groups with several dosages of CGA as treatment groups. This research has been approved by the ethics committee of the Faculty of Medicine, Universitas Gadjah Mada with number KE/FK/1117/EC/2020.

Diabetic Induction

DM model was prepared by injection of streptozotocin (60 mg/kg) dissolved in 0.1 M citric acid pH 4.5). DM is defined by measuring glucose levels that are more than 250 mg/dL by checking blood sugar from the tail vein.

CGA Administration

CGA was dissolved using PBS was administered by intraperitoneal (IP) injection with a total volume of 1 ml/kgBW. Three variation of CGA dosage: 12.5 mg/kgBW (CGA1), 25 mg/kgBW (CGA2) and 50 mg/kgBW (CGA3). CGA was administered to CGA1, CGA2, CGA3 groups for 14 consecutive days.

Probe Test

All six groups were assessed with probe test before termination using Morris water maze to assess memory dysfunction. Rats were being trained to search probe in 5 days before undergo probe test.

Termination

Termination was carried out on day 60. In accordance with the AVMA guidelines for euthanasia for animals: 2013 Edition, the termination of the experimental animals was carried out using ketamine at a dose of 100 mg/kgBW which was injected intraperitoneally. Frontal lobe tissue was taken and immediately stored in a 1.5 ml tube filled with RNA preservation solution at -20°C in the anatomy laboratory.

Reverse Transcriptase PCR (RT-PCR)

Frontal lobe tissue used for RNA extraction and RNA will then be used for the production of cDNA. cDNA was used for RT-PCR and followed by electrophoresis procedure. The mRNA expression test for NF- κ B (fCACTCTCTTTTGGAGGT; rTGGATATAAGGCTTTACG), MCP-1 (f C A G G T C T C T G T C A C G C T T C T ; rAGTATTTCATGGAAGGAATAG, IL-6 (f T T G G A T G G T C T T G G T C C T T A G C C ; rTCCTACCCCAACTTCCAATGCTC), and GFAP (f C G A A C G A G T C C T T G G A G A G G ; rTACAGGAATGGTGATGCGGT) was performed by densitometric analysis after electrophoresis and β -actin used as a house keeping gene.

Immunohistochemical (IHC) Staining

IHC staining was performed at the same time for each tissue group using Abcam Rabbit Anti-GFAP antibody and Biotin mouse/rabbit probe HRP labelling kit with DAB brown. Observation of the results of IHC staining was carried out under a light microscope in the entire field of view of the frontal lobe cortex tissue, with a magnification of 400 times. The assessment was carried out by observing the brown colour of the coronal section of the frontal lobe histology.

Data Analysis

The data obtained were tested with the Shapiro Wilk test to determine data distribution. One way ANOVA test and post hoc Least Significant Difference (LSD) test used for normal data distribution and Kruskal Wallis test and Mann Whitney post-hoc test for non-normal data distribution. The value of $p < 0.05$ was used as the significance criteria.

RESULTS

Blood Glucose Level

Blood glucose levels are divided into two types in each group: GDS1 taken before CGA administration (0.9% NaCl administration in the DM group) and data after CGA administration (Figure 1). Previously all data were tested for normality using the Saphiro-Wilk test with blood glucose results in the control group, DM1.5; DM2, CGA1, and CGA3 showed normal distribution results ($p \geq 0.05$) so a paired t-test statistical test was used. Meanwhile, the CGA2 group showed an abnormal distribution ($p = 0.007$) so the Wilcoxon statistical test was used.

Probe Test

The results of the probe test for the six groups are presented in Table I. The control group had the longest time in the correct quadrant (Q4), while the time in the DM1.5 and DM2 groups gradually decreased. In the three groups that were given CGA, the time in quadrant 4 was longer than in the DM2 group.

Table I: Mean, SD, and SEM of probe test result (in Q4)

Groups	Mean $\pm$ SD (seconds)	SEM (seconds)
Control	64.466 $\pm$ 6.431	2.876
DM1.5	52.306 $\pm$ 13.152	5.882
DM2	33.05 $\pm$ 6.159	2.754
CGA1	48.106 $\pm$ 10.264	4.590
CGA2	47.782 $\pm$ 5.795	2.591
CGA3	49.065 $\pm$ 12.530	5.115

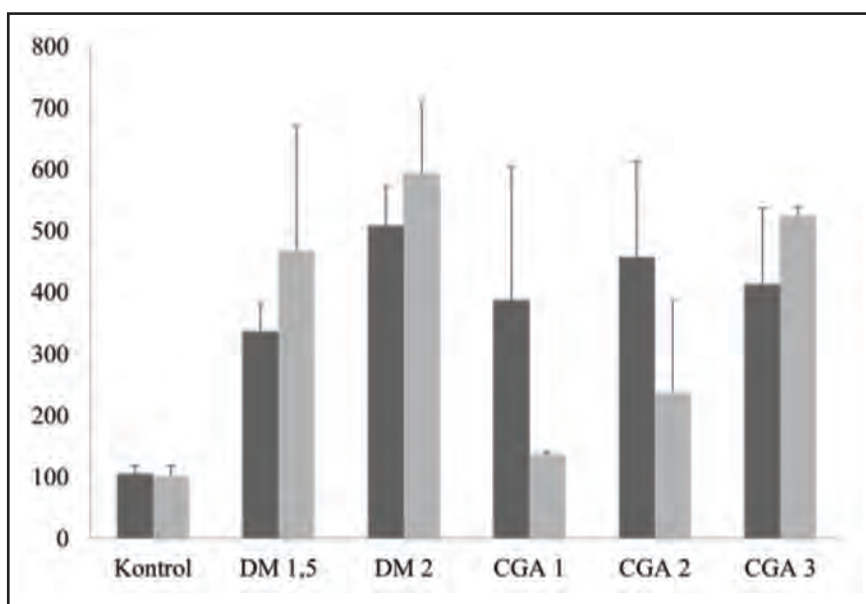


Fig. 1: Blood glucose level

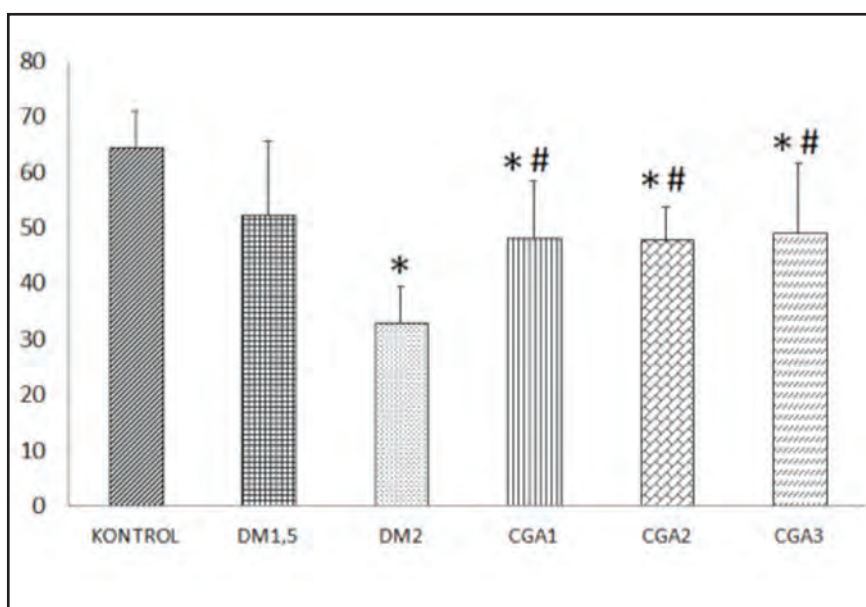


Fig. 2: Graph of the length of time the rat is in the right quadrant. There was a significant difference between the control group and DM2 ($p = 0.000$); control group with CGA1 ($p = 0.022$); control group with CGA2 ($p = 0.024$); and the control group with CGA3 ($p = 0.026$). There was also a significant difference in the DM2 group with CGA2 (0.040).

*: Significantly different to control; #: Significantly different to DM2

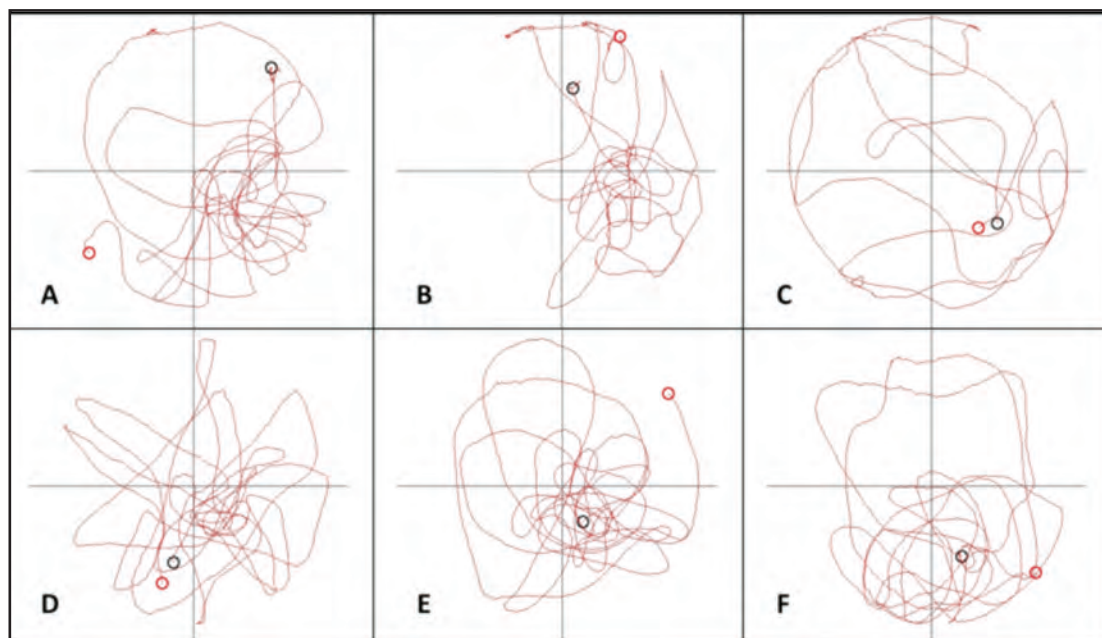


Fig. 3: Rats's trajectory in probe test A: control, B: DM1.5, C: DM2, D: CGA1, E: CGA2, F: CGA3

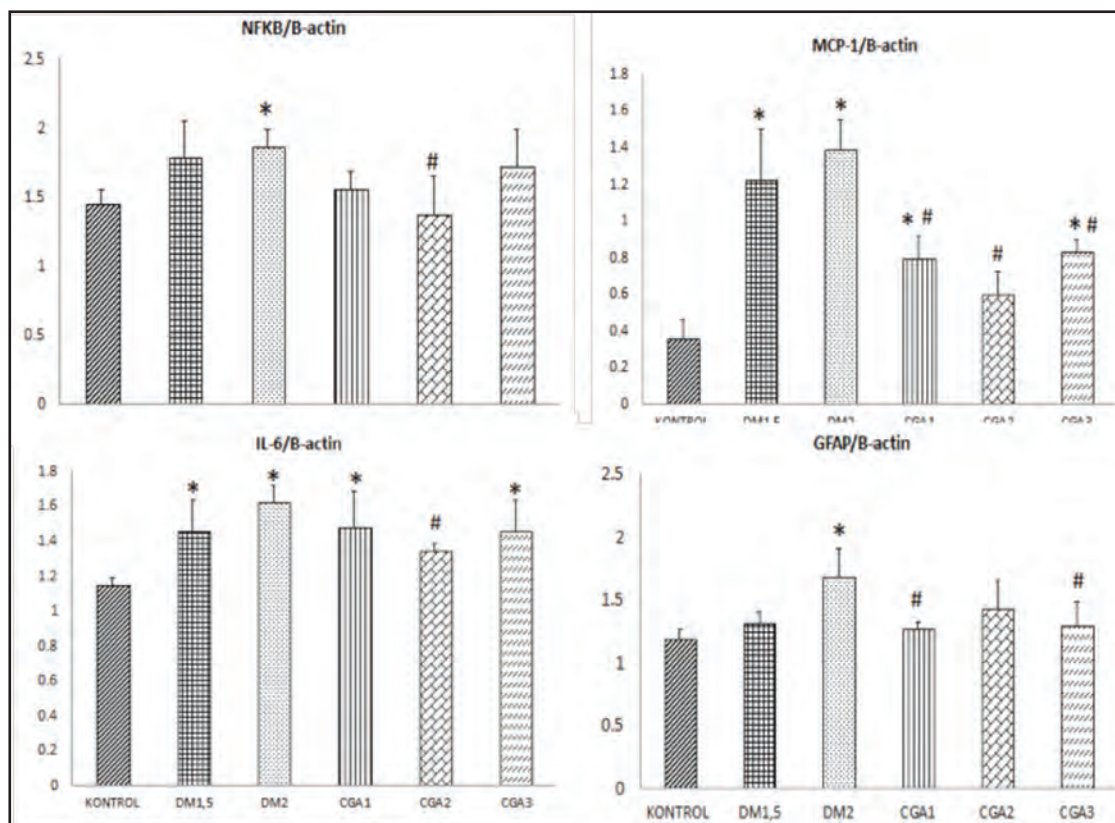


Fig. 4: NFKB, IL-6, MCP-1 and GFAP mRNA expression. DM2 has significantly higher mRNA expression in to control in all inflammatory marker and glial activation marker. There was a significant difference between the control group and DM2 in all mRNA expressions of inflammatory agent genes and glial activation marker genes. CGA2 has significantly lower mRNA expression of inflammatory agent to DM2. There is inconsistent result of GFAP mRNA expression in CGA groups. *: Significantly different from the control; #: Significantly different from DM2

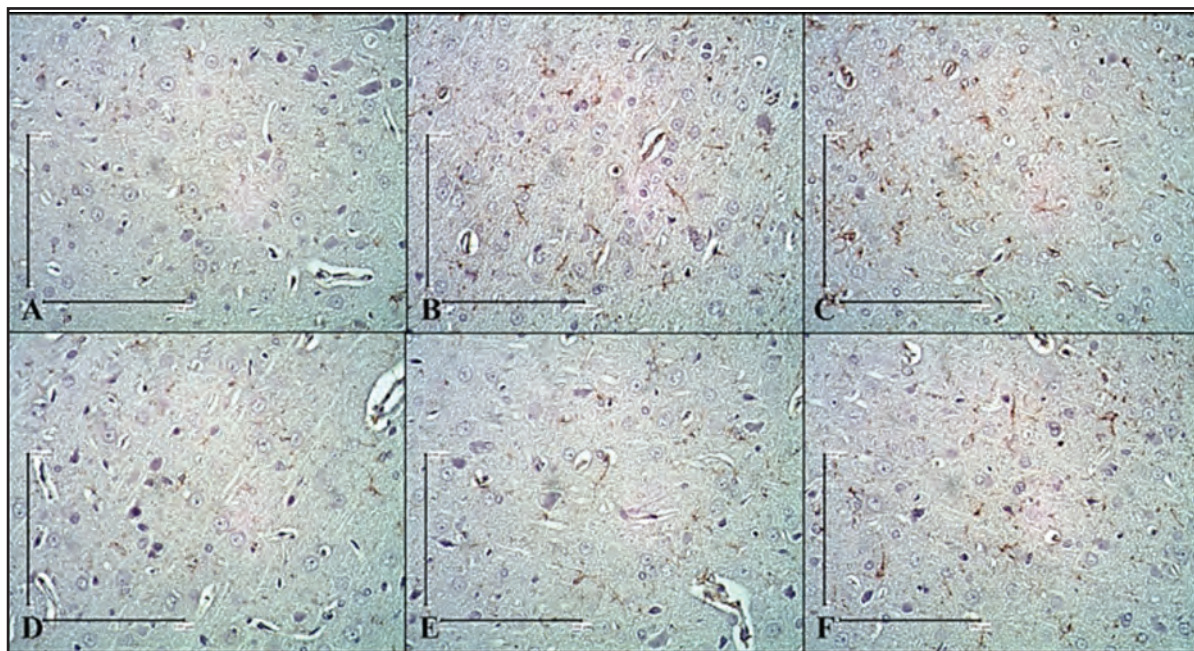


Fig. 5: Anti-GFAP IHC antibody staining; A: Control; B: DM1.5; C: DM2; D: CGA1; E: CGA2; F: CGA3

The results of the probe test from the six groups were tested for normality using the Saphiro-Wilk test with the results of all groups being normally distributed ($p \geq 0.05$), then the data was tested for one-way ANOVA with post-hoc LSD. The test results showed a significant level of $p = 0.005$ indicating a statistically significant difference in at least one group with each other.

After further testing with post-hoc LSD, the control group time was not significantly different from the DM1.5 group, but significantly different from the DM2 group; this indicates that the memory function in the DM2 group was lower than the control group. The three groups given CGA had a higher and statistically significant difference with time in the DM2 group, whereas between the three groups given CGA there was no statistical difference.

Probe Test Trajectory

In addition to looking at the length of time in the right quadrant (Q4-bottom right), the researchers also observed the trajectory that the rats took. In the control group, the rat focused more on looking at Q4, while in the DM1.5 and DM2 groups, the rat also circled a lot of other quadrants, and it was very visible in the DM2 group trajectory, the rat searched did not focus on the correct quadrant but almost the entire quadrant was surrounded by rat. In addition, in the DM2 group trajectory images, rat do not appear to have a search focus on Q4 (Figure 3).

Frontal Lobe mRNA NFKB Expression

The results of the NFKB densitometry data were first tested for normality with the Saphiro-Wilk test with the results that all groups were normally distributed ($p \geq 0.05$). Then, a one-way ANOVA test was carried out with post-hoc LSD with a significant result of 0.04 so that it can be concluded that there is a statistically significant difference in at least 1 group with other groups.

Frontal Lobe mRNA MCP-1 Expression

Data was tested by one-way ANOVA test with $p=0.000$. After the post-hoc LSD test, the control group was statistically significant with the DM1.5 group ($p=0.000$) and the DM2 group ($p=0.000$), indicating that both DM models had higher MCP-1 mRNA expression than the control group. Meanwhile in the CGA group, the three groups, namely CGA1, CGA2, and CGA3 had lower MCP-1 mRNA expression than the DM1.5 and DM2 groups, and were statistically significant in the three groups. Meanwhile, between the three groups that were given CGA, there was no statistical difference in the expression of MCP-1 mRNA.

Frontal Lobe mRNA IL-6 Expression

One-way ANOVA test was carried out with the results of $p=0.013$; Then from the post-hoc test there was a significant difference between the DM1.5 group; DM2; CGA1, and CGA3 with the control group, the results of the CGA 1 group had lower and statistically significant IL-6 mRNA expression compared to the DM2 group, and not significantly different from control.¹⁹

Frontal Lobe mRNA GFAP Expression

One-way ANOVA test was performed with $p=0.04$ and after the post-hoc LSD test, the control group was not significantly different from the DM1.5 group ($p=0.056$) but the DM1.5 group showed higher GFAP expression but not statistically significant. Then the control group was significantly different from the DM2 group ($p=0.04$), indicating that the DM2 group had a higher significant GFAP expression than the control group. In the three groups given CGA, all three had lower GFAP expression than the DM2 group, but it was only significant in the CGA1 and CGA 3 groups. Meanwhile, in the three groups given CGA, there was no statistically significant difference with each other.

IHC anti-GFAP Antibody

On IHC-anti-GFAP staining of the frontal lobe, positive IHC is indicated by the presence of a brown colour. In the DM group, both DM1.5 and DM2, the brown colour which indicated the GFAP protein was more abundant and thicker than in the control group. In the group given CGA, the brown colour appeared less than in the DM group.¹⁹

DISCUSSION

In this study, we wanted to find out the effect of CGA administration on memory function (probe test), mRNA expression of pro inflammatory factors (NF- κ B, MCP-1, and IL-6), as well as protein expression of glial activation markers as GFAP, in DM-induced rat using streptozotocin. We also observed the appearance of anti-GFAP IHC staining as well as the trajectories taken by rat in the probe test of Morris water maze. In the results of the blood glucose test, the average blood glucose was higher in both DM groups, and in the three CGA groups, this showed that the creation of DM models in rat was successful. In the group that obtained CGA at doses of 12.5 mg/kgBW (CGA1) and 25 mg/kgBW (CGA2) showed decrease in blood glucose levels after 2 weeks of CGA administration but did not differ significantly. In the CGA3 group, the average glucose increased but was also not significant, it is likely that this happened because CGA doses of 50 mg/kgBW or higher doses had genotoxic effects on the bone marrow and stress on vital organ.¹⁸ This is inconsistent with previous studies, a clinical trial that showed significant reductions in fasting glucose in humans with impaired glucose tolerance (IGT) after capsule administration containing CGA 400 mg three times a day for 12 weeks.²⁰ In addition, in clinical trials of metabolic syndrome patients who were given green coffee extract 400 mg twice a day for 8 weeks also lowered the average fasting blood sugar.²¹ Whereas in another study in DM rats with streptozotocin induction as well, CGA at doses of 100 mg/kgBW and 150 mg/kgBW orally for 28 days rats significantly lowered the blood glucose levels of rats, in this study doses of 100 mg/kgBW rats had better blood glucose reduction results.²²

The antidiabetic effect on CGA comes from various mechanisms, especially CGA has the effect of inhibiting glucose absorption in the small intestine by inhibiting glucose-6-phosphate translocase as well as inhibiting glucose-6-phosphatase in liver. In addition, CGA will inhibit the uptake of glucose from the intestines by inhibiting the α -glucosidase by reducing the synergistic transportation of glucose so that blood glucose will decrease.¹⁴ In this study, CGA was injected intraperitoneally so that it might reduce the effect of CGA as an anti-glycaemic, thus causing an insignificant decrease in blood glucose levels in all CGA groups.

In the probe test, researchers looked at how long the rat would look for platforms in the right quadrant for 120 seconds and observed the trajectory that the rat passed. Previously, for 5 days, rats were trained to swim in search of platforms. This test showed memory ability in rat, in this study it was found that DM-induced rat, for both 1.5 months and 2 months had worse memory than control group, but only the DM2 group differed significantly. This data indicates that there has been memory impairment due to DM in rat

progressively and in DM2 months the rat's memory is significant, this is also supported by a picture of the trajectory that rat passed with DM, rats appeared to rotate around the entire quadrant in both DM2 groups. The results of the probe test Morris water maze showed that the resulting DM model experienced the progressivity of memory worsening from the DM1.5 group to the DM2 group. Other studies on rat also showed that the group of rat that had higher glucose levels showed worse spatial memory test results on Morris water maze.²³

In the entire CGA group, the results of rat travel time in Q4 were higher, indicating better memory than in the 2-month DM group, but not yet equivalent to the control group. Meanwhile, in the three groups given by CGA, there were no statistical differences between them. This suggests that administering CGA at all three doses can improve the effect of improving memory function caused by DM, although there is no dose-dependent sign of CGA administration yet. On the trajectory passed by the rats, it was also seen that the trajectory passed by the CGA group had more focus on Q4 compared to the DM group. This is in accordance with other studies on the effect of CGA in improving scopolamine-induced memory function decline, namely at doses of 6 mg/kgBW and 9 mg/kgBW showing improvements in probe test results.¹⁵ Administration of CGA also showed improvement in decreased memory impairment due to transient ischemia at doses of 2.5 mg/kgBW, 5 mg/kgBW and 10 mg/kgBW.¹² This study is in accordance with the results of previous studies, with the administration of CGA 50 mg/kgBW can improve memory in rats which experienced a decrease in memory function by inducing intraventricular streptozotocin.¹¹

Better memory function in groups with CGA administration may occur because CGA has anti-inflammatory effects. This is in accordance with studies using the administration of GSK-3 β inhibitors (SB216763) which are one of the inhibitors of inflammatory processes in DM model, and also showed memory improvement and decreased levels of IL-6, TNF- α , and NF- κ B protein expression.⁹ Increased inflammatory markers in neural tissue (neuroinflammation) that occur in DM along with BBB damage are socialized with memory dysfunction.²³ In accordance with the theory of CGA has an anti-inflammatory effect so that memory function is better in the group with CGA administration.

Inflammation in neurons involves several pathways, one of which is the CCP pathway. The activated PKC pathway will activate NF- κ B on cytosol, NF- κ B which is a transcription factor then goes to the nucleus thus initiating transcription from proinflammatory factors such as MCP-1 and IL-6.⁴ Inflammation in neurons will activate glia cells.^{24,25} Metabolic dysfunction and oxidative stress will also cause rapid changes and activate glia cells. The main indicator of this response is glial fibrillary acid protein (GFAP). Abnormal GFAP expression is mostly concentrated in the cortex and hippocampus.⁵ Other research results (Datusalia dan Sharma, 2014) also states that GSK-3 β inhibitors can reduce inflammation and improve memory function in DM models, this is in accordance with the properties of CGA, one of which has molecular docking in AKT and can reduce the activity of GSK-3 β .²⁶

In this study, the group with CGA dose administration of 25 mg/kgBW had significantly lower expression of NF- κ B mRNA of the frontal lobe than in the DM2 group. This shows that at these doses CGA can reduce inflammatory activity that occurs in the CCP pathway. ChCGA can bind to PH domain of AKT, a protein kinase, making AKT phosphorylated into p-AKT. The active AKT then causes Glycogen synthase kinase-3 (GSK-3) inactivation²⁷. GSK-3 is a protein kinase that is widely found in the brain, GSK-3 β contributes to abnormal phosphorylation of microtubule-bound proteins associated with the incidence of Alzheimer's disease.^{27,28} GSK-3 has two isoforms namely GSK-3 α and GSK-3 β . GSK-3 α is found mainly in the hippocampus, cortex, striatum, and cerebellum. While GSK-3 β is found in all parts of the brain.²⁷ GSK-3 β regulates inflammation in neurons by means of NF- κ B maintaining the integrity of TLR, NEMO, as well as inhibiting the accumulation of CREB.²⁹ Decreased activity on GSK-3 β because of CGA will further decrease the activity of NF- κ B. This is in accordance with the results of this study, namely in DM, especially DM 2 months, mRNA expression of the frontal lobe from NF- κ B increased compared to controls, while in the group given CGA decreased compared to the DM2 group, in this study, especially in the CGA2 group.

Hyperglycaemia activates the CCP pathway where NF- κ B experiences increased activity. NF- κ B which is a transcription factor will then enter the nucleus and bind to the DNA. NF- κ B bonding with DNA will induce transcription from proinflammatory agents such as IL-6, TNF- α , IL-1.⁴ In accordance with the theory, the expression of mRNA IL-6 frontal lobes in the CGA2 group was lower and statistically more in the group with CGA administration than not, corresponding to the expression of NF- κ B mRNA which also decreased in the CGA2 group.

In the results of mRNA expression NF- κ B and IL-6 frontal lobe decreased significantly only in the CGA2 group. This can occur because there is a possibility that the dose of CGA1 is too small, while the dose of CGA3 or higher has a genotoxic effect on the bone marrow and stress on the organs of vital.¹⁸ Meanwhile, in MCP-1 mRNA expression, the frontal lobe showed lower and statistically significant expression in all groups. This may be because CGA also has antioxidant effects, where increased expression of MCP-1 can also occur at high levels of ROS, and CGA also has antioxidant effects so that increased expression of MCP-1 is involved only in inflammatory pathways but also apoptosis pathways involving oxidative stress. The presence of oxidative stress induces activation of the JNK pathway, which mediates the c-JUN component uniting with the c-FOS component into a heterodimer AP-1. AP-1 heterodimer is a transcription factor that will then enter the nucleus, inducing transcription of proinflammatory factors, one of which is MCP-1. In accordance with the theory, the mRNA expression of MCP-1 frontal lobes in all three CGA groups was lower and statistically more in the group with CGA administration than in not. This is in accordance with several previous studies that show that CGA administration can decrease the expression of MCP-1 in the kidneys and liver.^{30,31}

Metabolic dysfunction and oxidative stress will also cause rapid changes and activate glia cells. The main indicator of

this response is GFAP. Abnormal GFAP expression is mostly concentrated in the cortex and hippocampus.³ In this study, GFAP mRNA expression was also significantly higher in the DM2 group than the control group, and lower in the CGA group than DM2, especially those with significant differences in the CGA1 and CGA3 groups. This is also consistent with previous studies that looked at GFAP expression on the retina with dm models.³² The existence of a trend that does not correspond to this increase in doses may be due to the regulation of GFAP production itself occurring not only at the transcription level, but also the post-translational level.²⁴ However, in the staining of the anti-GFAP IHC on the frontal lobe, it was seen that the DM group expressed many positive signs and decreased in all three groups given CGA.

Given this result of the study, we hope that the use of CGA in memory dysfunction can be considered. This study has various limitations, including: this study did not examine other factors such as apoptosis of neuron cells, this study did not count the number of cells and synapses that affect memory.

CONCLUSION

The group given CGA at all doses have statistically significant better memory function than DM2 group in probe test Morris water maze. The result of mRNA expression in NF- κ B and IL6 was lower in the group given CGA2 than DM2. mRNA expression of MCP-1 was significantly lower in all CGA treatment groups compared to the non-CGA groups (DM1.5; DM2); while in GFAP mRNA expression was lower in CGA1 and CGA3 groups than DM2. Treatment with chlorogenic acid (CGA) may improve memory function at all doses given, and can reduce brain inflammatory activity, especially in the CGA2 group.

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Comparison of the antiseptic effectiveness of octenidine dihydrochloride with povidone-iodine for *Acinetobacter baumannii* contaminated wounds in Wistar rat

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ABSTRACT

Introduction: Effective antiseptic use is essential in healthcare settings to prevent the spread of diseases, especially in areas with high patient traffic and exposure to various pathogens. One essential pathogenic germ is *Acinetobacter baumannii*. Octenidine and povidone-iodine have been demonstrated to be effective against *A. baumannii* in vitro. This study will compare octenidine dihydrochloride and povidone-iodine as wound-cleansing solutions for wounds contaminated with *A. baumannii* in vivo.

Materials and Methods: Twenty-four rats were divided into three groups: normal saline, octenidine dihydrochloride and povidone-iodine. Wounds were made on the rats' backs, and *A. baumannii* germs were inoculated into the wounds. After 3 hours, the wound was irrigated with wound cleansing solution according to the group for 30 seconds. Each wound was taken swab culture before and after wound irrigation and tissue culture 5 hours after wound irrigation.

Results: All specimens showed bacterial colony growth with a median value of 1.22×10^5 CFU before irrigation. Wound irrigation with normal saline did not reduce colony counts, while there was a 3-log reduction to 5-log reduction in the octenidine and povidone-iodine groups. Statistically, there was no significant difference in the mean number of colonies between the octenidine and povidone-iodine groups after irrigation ($p = 0.535$). However, 3 hours after irrigation, all specimens that experienced 3-log reduction showed regrowth to more than 1×10^5 CFU. In contrast, specimens subjected to 5-log reduction did not exhibit any regrowth.

Conclusion: The antiseptic effectiveness of octenidine dihydrochloride is equivalent to povidone-iodine in eradicating *A. baumannii* colonies in wounds in vivo.

KEYWORDS:

Antiseptic, octenidine dihydrochloride, povidone-iodine, *A. baumannii*

INTRODUCTION

Infection wound care is a global problem that requires innovative strategies to fight microorganisms and biofilms.

Antiseptic irrigation is expected to reduce germ colonies and help eradicate infection. One essential pathogenic germ is *Acinetobacter baumannii*. This opportunistic pathogen can cause nosocomial infections, especially in operating rooms and intensive care units.^{1,2} Based on data from the Clinical Microbiology Unit of Dr. Soetomo General Hospital Surabaya in January–December 2019, it was reported that *A. baumannii* bacteria were the most commonly found bacteria in the burn unit, surgical ward, high care unit and intensive observation room, besides that these bacteria were resistant to 7 of 11 antibiotics including gentamycin, amoxicillin-clavulanate, ceftazidime, piperacillin-tazobactam, levofloxacin and chloramphenicol.

Infection by these bacteria leads to impaired wound healing. It can also spread to the circulatory system resulting in sepsis, with a high mortality rate if patients are not adequately treated.³ *A. baumannii* has a faster rate of biofilm development than other species.⁴ The biofilm matrix surrounding the bacteria allows the germs to survive in extreme circumstances and become antibiotic-resistant. As a result, drugs now available to treat *A. baumannii* biofilm-related infections have become ineffective.⁵ Given that any injury carries a high risk of infection, effective management of bacterial biobload is a crucial component of wound care.

A crucial step in preventing further infectious incidences is using antiseptics to fight colonisation and infection directly at the portal of entry. Many experiments have been undertaken in the previous few decades to produce novel antiseptic agents like chlorhexidine, iodine or iodophores to attain the best circumstances in killing or inhibiting bacteria.⁶ Denysko et al.⁷ found that among the tested antiseptics, decamethoxin and octenidine showed the greatest activity against clinical strains of *A. baumannii*, followed by povidone-iodine, polyhexanide, chlorhexidine and miramistine.⁷ Commercially available products containing decamethoxin and miramistine are not available in Indonesia. Chlorhexidine-cetrimide and povidone-iodine are the recommended antiseptics for wound care at Dr. Soetomo General Hospital Surabaya. In addition, Pradnyana's⁸ comparative analysis revealed that povidone-iodine exhibited superior efficacy in reducing bacterial colony counts in *A. baumannii*-infected wounds compared to chlorhexidine-cetrimide. Povidone-iodine is an antiseptic solution commonly used in healthcare settings to prevent

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and treat infections. It is effective against a broad range of bacteria, viruses, fungi and protozoa, making it a versatile antiseptic agent used in various healthcare settings. However, povidone-iodine carries the risk of affecting thyroid function.⁹ Considering these factors, exploring alternative antiseptics to replace previously used ones is crucial. Currently, octenidine is offered as an alternative antiseptic in Indonesia. Octenidine dihydrochloride is a novel cationic antiseptic that belongs to the bispyridine class.¹⁰ It disrupts the microbial cell envelopes and eukaryotic cell membranes through strong adherence to lipid components and binding to negatively charge microbial surfaces. Preliminary results imply a particularly strong adherence to lipid bacterial cell membrane components explaining the high antimicrobial efficacy without adversely affecting human epithelial or wound tissue.¹¹⁻¹³ Comparison of its biocompatibility with other disinfectants, such as povidone-iodine or chlorhexidine, showed that octenidine is an antiseptic with low cytotoxicity and high microbicidal effect.^{14,15} Octenidine was found to have the most potent efficacy against biofilms of multidrug-resistant clinical microorganisms, including *A. baumannii* in vitro.⁷

However, no data have been reported for the effectiveness of octenidine and povidone-iodine as an antiseptic solution against *A. baumannii* in vivo. This study aims to determine the antiseptic effectiveness of octenidine dihydrochloride 0.1% and povidone-iodine 10% as antiseptic by comparing the bacterial colony reduction on wounds contaminated with *A. baumannii*.

MATERIALS AND METHODS

Animal Preparation

Animals Male Wistar Rat (200–300g, 7–10 weeks of age) were obtained from Animal Lab of Pharmacy Department Universitas Airlangga and maintained under a 12-hour light/dark cycle. Food and water were available ad libitum. The rats were divided into three groups (Group 1 was the control group; Group 2 was octenidine dihydrochloride group; and Group 3 was the povidone iodine group). Sample size was eight rats per group using the resource equation method.¹⁶

$E = \text{Total number of animals} - \text{Total number of groups}$

According to this method, a value “E” is measured, which is nothing but the degree of freedom of analysis of variance (ANOVA). The value of E should lie between 10 and 20. If E is less than 10 then adding more animals will increase the chance of getting more significant result, but if it is more than 20 then adding more animals will not increase the chance of getting significant results. Any sample size that keeps E between 10 and 20 should be considered as an adequate. The sample size of eight rats per group in this study is considered adequate for the purposes of statistical analysis.

Wound Creation

Animal handling was performed under anaesthesia induced by ketamine (20 mg/kg; Ketamine HCl, Bernofarm Pharmaceutical Company, Indonesia). The rat's back was shaved then a 2 × 2 cm deep full-thickness wound was made on the skin using a scalpel. At the end of the experiments, the animals were killed with an overdose of pentobarbital.

Wound Contamination and Bacterial Counts

A. baumannii strains tested were obtained from the Institute of Tropical Disease Airlangga University, a positive culture isolate of patients at Dr. Soetomo General Hospital Surabaya. *A. baumannii* were inoculated into the wounds at the dose of 1.5×10^8 CFU/mL (0.5 mL McFarland), and the wound was covered with a transparent dressing. After 3 hours, the wound was irrigated with wound cleansing solution according to the group using a 20 cc syringe with constant pressure for 30 seconds. The first group was designated as the control group. This group was only applied normal saline 0.9% (Ecosol NaCl®, B-Braun Medical Ltd., Indonesia); the second group was applied octenidine dihydrochloride 0.1% (Octadin®, Infion Ltd., Indonesia) and the third group was applied povidone iodine 10% (Betadine®, Mahakam Beta Farma Ltd., Indonesia).

The wounds were swabbed with sterile cotton-tipped applicators before and after wound irrigation. In addition, tissue cultures were taken at 3 hours after irrigation. The samples were plated onto Mueller-Hinton agar (Oxoid CM0337, UK) to quantify the number of viable bacteria and incubated at 37°C overnight. Specimens were ground and plated immediately, and colony-forming units (CFUs) were read 24 hours after plating using biological microscopes (Olympus CX23, Japan).

Statistical Analysis

Data analysis was performed using a statistical software package (Statistical Package for Social Sciences 15 for Windows). The significance level was considered to be $P < 0.05$.

Ethical Clearance

All experimental protocols described in the present study were approved by the Health Research Ethics Committee Faculty of Dentistry Universitas Airlangga (151/HRECC.FODM/II/2023).

RESULTS

All specimens showed bacterial colony growth with a median value of 1.22×10^5 CFU (range 1.02×10^5 – 1.43×10^5). As shown in Table I, wound irrigation with normal saline did not reduce colony counts. At the same time, there was a 3-log reduction to 5-log reduction in colony counts in the octenidine and povidone-iodine groups. However, 3 hours after irrigation, all specimens that experienced 3-log reduction showed regrowth to more than 1×10^5 CFU, whereas specimens subjected to 5-log reduction did not exhibit any regrowth (Table II). Statistically, there was no significant difference in the mean reduction of colonies between the octenidine and Povidone-iodine groups after irrigation ($p=0.535$), as shown in Table III.

DISCUSSION

A. baumannii multidrug-resistant strains tend to evolve quickly, which is concerning. In intensive care units, it makes up between 2 and 10% of all gram-negative hospital-acquired infections.¹⁷ The use of antiseptics as the primary active ingredient and potentiator of antibiotics is crucial for treating patients with infected burns, post-traumatic wounds

Table I: Frequency of bacterial reduction post irrigation on *A. baumannii*-contaminated wounds

Group	No Reduction	Log-3 Reduction	Log-5 Reduction
Normal Saline	8 (100%)	-	-
Octenidine	-	6 (75%)	2 (25%)
Povidone-Iodine	-	7 (87.5%)	1 (12.5%)

Table II: Frequency of bacterial growth 3-hour post irrigation on *A. baumannii*-contaminated wounds

Group	No growth	>10 ⁵ CFU
Octenidine	2 (25%)	6 (75%)
Povidone-iodine	1 (12.5%)	7 (87.5%)

Table III: Mean reduction and mean growth of CFU on antiseptic applications

	Octenidine (%)	Povidone-iodine (%)	p-value*
Mean reduction post irrigation	99.25	99.13	0.535
Mean growth 3 hours post irrigation	99.00	99.00	0.535

* Mann-Whitney U test.

and surgical wounds in the context of the global rise in antibiotic resistance.^{18,19}

This study compared the effectiveness of octenidine antiseptic with povidone-iodine for wounds contaminated with *A. baumannii* in Wistar rat. This was the first in vivo study in this field to compare the efficacies of two antiseptics for treating *A. baumannii* contamination wounds in an experimental model.

The use of octenidine and povidone-iodine resulted in a significant bacterial count reduction. However, our findings indicate no significant difference between the effectiveness of povidone-iodine and octenidine antiseptics in reducing *A. baumannii* colonies in vivo. We found the mean CFU reduction after the application of the antiseptics were as follows: octenidine 99.25% and povidone-iodine 99.13% ($p=0.535$). Denysko et al. (2022) found that both octenidine and povidone-iodine had bactericidal action against *A. baumannii* in an in vitro study. Among the tested antiseptics, decamethoxin and octenidine showed the greatest activity against clinical strains of *A. baumannii*, followed by povidone-iodine, polyhexanide, chlorhexidine and miramistine.⁷ In an in vitro study, Koburger et al. described the most effective antiseptics. Prioritising the agent of choice should be octenidine = povidone-iodine >> polyhexanide > chlorhexidine > triclosan when an immediate effect is needed. If a longer contact time is necessary (as in wound antiseptics and mucosal infection therapy), polyhexanide = octenidine > chlorhexidine > triclosan > povidone-iodine should be prioritised.²⁰

The difference in antiseptic effectiveness against *A. baumannii* observed in the previous study and the absence of significant differences in the in vivo study may be due to several factors. In vitro studies are conducted under controlled laboratory conditions and may not fully reflect the human body's complexities and the in vivo environment. In vivo studies, on the other hand, are conducted in living organisms and may involve factors such as immune response, wound healing and tissue damage that can affect the effectiveness of antiseptics.

This study also examined the number of colonies three hours after irrigation using tissue culture to determine whether the antiseptic effect was still in effect. Specimens that underwent a 3-log reduction demonstrated regrowth to levels exceeding 1×10^5 CFU, whereas specimens that underwent a 5-log reduction did not exhibit any regrowth. While complete eradication of bacteria is ideal, it is often not achievable in clinical settings, particularly in the presence of biofilm or other factors that may promote bacterial growth. Therefore, a reduction to log 3 CFU can still be considered a good outcome, especially since it was achieved after a single 30 seconds irrigation treatment in this study. However, further research is needed to determine if repeated irrigation or prolonged treatment could completely eradicate the bacteria in this wound model.

CONCLUSIONS

In this study, it can be concluded that octenidine dihydrochloride and povidone-iodine irrigation effectively reduce the number of colonies of *A. baumannii* colonies. The antiseptic effectiveness of octenidine dihydrochloride is equivalent to povidone-iodine in eradicating colonies of *A. baumannii* bacteria in vivo.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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Potency antiinflammatory of ethanol extract gel of Kepok banana peel (*Musa balbisiana*)

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ABSTRACT

Introduction: Inflammation is the body's defense response to foreign invasion, tissue damage or both. Flavonoid compounds have anti-inflammatory activity. One of the traditional medicines is Kepok banana peel (*Musa balbisiana*) contains flavonoids, saponins and triterpenoids. This study aims to determine the effective dose of ethanol extract of kepok banana peel as an anti-inflammatory.

Materials and Methods: Kepok banana peel was macerated using 70% ethanol. The extract is made in the form of a gel formulation because it has a high water content so it can moisturise the skin and spread easily when applied. This research was conducted with 25 male rats in 5 treatment groups. The gel was given 30 minutes after the rats were induced with 0.1 ml of 1% carrageenan. The rat anti-inflammatory test was observed through oedema volume data and the percentage of anti-inflammatory activity. Data analysis used the ANOVA test ($p < 0.05$).

Results: The treatment group had an anti-inflammatory effect which was marked by a significant difference from the negative control group.

Conclusion: The effective dose of ethanol extract gel of kepok banana peel as an anti-inflammatory is 8%.

KEYWORDS:

ethanol extract gel of kepok banana peel; *Musa balbisiana*; antiinflammatory; medicine

INTRODUCTION

Inflammation is a vascular tissue response to infection and tissue damage by bringing cells and molecules of the body's defenses from the blood circulation to the location needed to eliminate disturbing causes. The mechanism of inflammation is the local reaction of tissues or cells to a stimulus or injury.¹ The many side effects that may be caused by steroid and non-steroidal anti-inflammatory drugs make people tend to turn to traditional medicine using plants that are thought to have antiinflammatory properties.² There are several plants that are trusted by the public or empirically can treat inflammation, one of which is kepok banana peel (*Musa balbisiana*).^{2,3} Kepok banana peels contain flavonoids, saponins and triterpenoid compounds. The choice of banana

peel as a natural ingredient in this study was due to the presence of flavonoid compounds which have potential as antioxidants. In other studies reported that banana peels contain substances that play a role in wound healing, namely saponins and flavonoids.³ Gels are semisolid systems, which are interpenetrated by a liquid. The advantages of gel preparations are cosmetic features that are attractive to patients, non-sticky, easy to apply and wash off. Besides that, flavonoids have low solubility in water with a short filling time in the small intestine, so gel preparations are made to increase their bioavailability.⁴ So that, the researchers wanted to conduct research on the potency antiinflammatory of the ethanol extract gel of kepok banana peel (*Musa balbisiana*).

MATERIALS AND METHODS

Preparation of Kepok Banana Peel Ethanol Extract Gel Formula

The sample used was kepok banana peel (*Musa balbisiana*) obtained from Batu City, East Java, Indonesia. Kepok banana peels that have been dried are blended into a blender until fine powder is formed then the powder is weighed 500 g then a maceration process is carried out with 70% ethanol solvent then evaporation is carried out until a thick extract of kepok banana peel is obtained. Then, it was prepared in a gel formula. The gel preparation formula was made with various concentrations of the ethanol extract of kepok banana peel (*Musa balbisiana*), namely 2%, 4%, and 8%. The negative control is gel base/carbopol. The positive control was anti-inflammatory drugs (diclofenac sodium gel). This research has been approved by the Health Research Ethics Commission, Faculty of Medicine, Universitas Brawijaya.

Anti-inflammatory Test

1% carrageenan was prepared as an induction inflammation.⁵ The gel was administered topically. The test was carried out with the rat's right leg inserted into the plethysmometer containing liquid mercury that had been prepared until the liquid rises to the upper limit line, a number is recorded on the tool as the initial volume (V_0), namely the volume of the leg before being given the drug and induced with carrageenan solution. Each paw of the rat was injected with 0.1 ml of 1% carrageenan solution and 30 minutes later, each rat was given a suspension of the test material topically according to the group. Measurements were taken by dipping the right leg of the rat into a plethysmometer liquid containing liquid mercury until the

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Table I: Gel dosage formula

Composition	Negative Control (K -)	Positive Control (K +)	Extract dose 1	Extract dose 2	Extract dose 3
Ethanol extract Kepok banana peel	-	Gel Na diclofenac	2%	4%	8%
Carbopol 940	1%		1%	1%	1%
TEA (Triethanolamine)	3%		3%	3%	3%
Glycerin	10%		10%	10%	10%
Propylene glycol	15%		15%	15%	15%
Aquades	Ad 30 ml		Ad 30 ml	Ad 30 ml	Ad 30 ml

Table II: Antiinflammation percentage

Group	% Antiinflammation
Negative control (n=5)	0
Positive control (n=5)	61.3
Extract dose 2% (n=5)	28.3
Extract dose 4% (n=5)	42.9
Extract dose 8% (n=5)	50.0

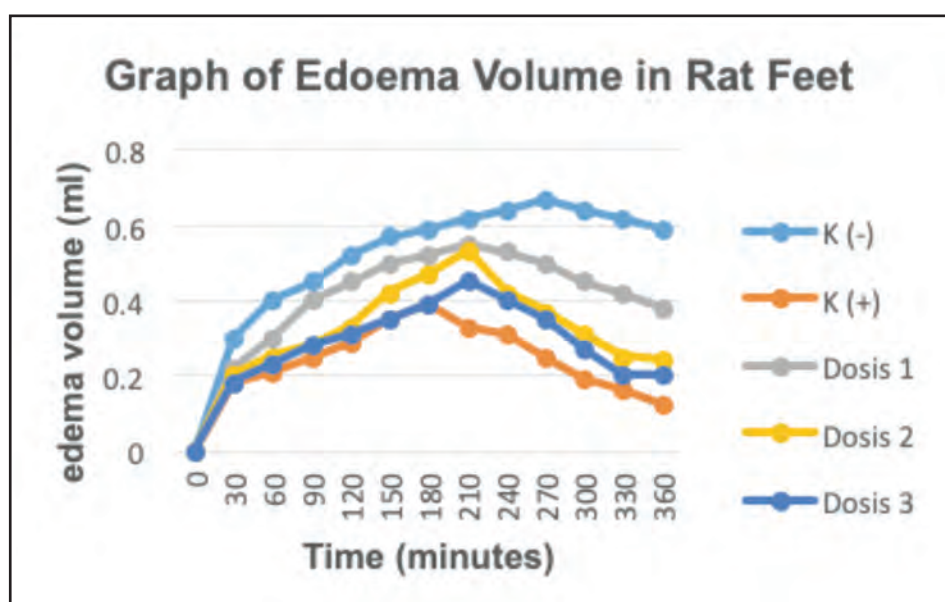


Fig. 1: Graph of Oedema volume in rat feet

solution reached the upper limit of the rat's right leg and recorded the numbers obtained.⁶ Changes in the inflammatory volume of the rat feet per unit time to administration of banana peel gel were calculated as the percentage of inflammation with the following equation:

$$\% \text{ Anti Inflammation} = \frac{V_t - V_0}{V_0} \times 100\%$$

V_t = Inflammatory volume of rat foot per unit time

V_0 = Initial Leg Volume of rat

RESULTS

500 g of kepok banana peel simplicia was macerated using 70% ethanol solvent and the results of the viscous extract were 17.5 g and the percent extract yield was 3.48%. The viscous extract obtained was subjected to antiinflammatory

testing which was carried out using rats and then divided into five groups with the number of male rats in each group amounting to five rats (Table I). The method that was used as an antiinflammatory activity test is plethysmometer filled with mercury.⁷ The oedema values that have been obtained were carried out statistical tests to find out the data that differed significantly between groups. The results of the statistical analysis of each group through normality and homogeneity tests were $p > 0.05$, meaning that the data was normally distributed and homogeneous. Then, proceed with the One Way ANOVA test. The results showed that the three dose groups differed significantly from the negative control ($p < 0.05$), so that the three dose groups had anti-inflammatory effects. The 2% and 4% doses were not significantly different from the positive control ($p > 0.05$) while the 8% dose was significantly different from the positive control group ($p < 0.05$).

DISCUSSION

Based on Figure 1, it shows that the volume of oedema in the negative control is the largest volume compared to the positive control group, dose 1, dose 2 and dose 3. The graph above shows that there was a continuous increase in oedema volume from the 30 minutes to the 210 minutes in the positive group, dose 1, dose 2 and dose 3. In the negative control group, the oedema volume still showed the greatest volume until minute 270. Its caused by the release of inflammatory mediators such as prostaglandins, histamine, bradykinin and serotonin in the tissue after being induced by carrageenan. The decrease in the positive control group occurred in the 210 minutes. Dose 1, dose 2, and dose 3 occurred at 240 to 360 minutes. There was inhibition of prostaglandin synthesis into the tissues. So that, the group that can provide an anti-inflammatory effect is the positive control group, dose 1, dose 2, and dose 3, especially at 240 to 360 minutes, whereas the negative control group does not give this effect.

The highest percent antiinflammatory value was the positive control group, which was 61.3%, followed by the 3rd dose group of 50%, and the 2nd dose group of 42.9%, and the 1st dose group of 28.3% percent (Table II). The antiinflammatory closest to the positive control was the dose 3 group that had the most effective potential to inhibit inflammation. The anti-inflammatory effect of the ethanol extract of kepok banana peel is thought to be due to the presence of flavonoid compounds. Flavonoids have anti-inflammatory activity by inhibiting the production of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α insilico.⁷ Flavonoid compounds also have activity in inhibiting NO production. Nitric oxide (NO) is a gaseous free radical produced by phagocytes, which are equipped with inducible nitric oxide synthase (iNOS), activated by interferon-gamma (IFN- γ) or tumour necrosis factor (TNF). Transforming growth factor-beta (TGF- β) as a strong inhibitor and interleukin-4 (IL-4), IL-10 as a weak inhibitor of iNOS. NO will cause blood vasodilation and inflammation.^{5,6,7}

CONCLUSION

Kepok banana peel (*Musa balbisiana*) ethanol extract gel has anti-inflammatory activity. Kepok banana peel (*Musa balbisiana*) ethanol extract gel concentration of 8% has anti-inflammatory power by 50%. This research requires further research because it still uses experimental animals as research subjects, so clinical trials are needed in humans to determine the dosage and effectiveness of kepok banana peel as an anti-inflammatory.

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Local wisdom in wound treatment practice in Tengger tribe farmers

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ABSTRACT

Introduction: Farmers have a high risk of injury either due to the use of agricultural tools, or chemicals, or the geographical conditions of the agricultural area. This study aimed to describe the use of local wisdom in the practice of wound treatment among Tengger tribal farmers in Indonesia.

Materials and Methods: This qualitative study used accidental sampling, conducted in the agricultural land of Ngadisari Village, Sukapura District, Probolinggo Regency, East Java for 3 weeks in November 2020. This study involved all farmers who were working on the land at the time of the study (n=30). The questionnaires consist of demographic, wound characteristics and wound treatment processes.

Results: The practice of wound treatment for the Tengger Tribe farmers is divided into two stages, namely the initial wound stage (stopping bleeding) using gums of medical plants and the wound healing stage, which is divided into treatment for the outer body using mashed leaf herbs and for the inner body using herbs that function to increase body stamina.

Conclusion: The local wisdom Tengger ethnic-based wound treatment uses whatever is in nature to stop the bleeding and increase the wound healing process.

KEYWORDS:

Wound treatment, complementary therapy, Tengger tribe, Agnoring

INTRODUCTION

Agriculture has traditionally been one of the most dangerous jobs for workers.^{1,2} Farming has a mortality rate five times higher than all other professions combined. This increased risk of death is accompanied by a progressively more severe degree of injury. Globally, at least 170,000 agricultural workers are seriously injured each year. Non-fatal injuries occur in approximately 33% of the farming population in the United States, with 3% of accidents resulting in permanent disability.^{3,4} In Indonesia, the incidence of injuries nationally has increased, and the prevalence of injuries that occur to farmers or farm workers is 8.2%.⁵ Most of the injuries (89%) occurred during agricultural work.⁶

Wounds that commonly occur in farmers are cuts (79.7%), stab wounds (11.3%) and lacerations (7.5%). Mostly caused

by hand tools followed by slipping at work, sharp instruments, animals and falls from heights.² The Tengger people live on the slopes of Mount Bromo and Semeru⁷ with the livelihoods of most of the people farming. Agricultural fields are on mountain slopes and hilly peaks. This condition places Tengger farmers at risk of injury. The traumatic injury required emergency medical attention, something that took a long time to reach the agricultural area that sits on a mountainside. This causes farmers to do anything to deal with injuries or wounds that occur in agricultural areas. The Tengger tribe is one of the tribes in Indonesia that still adhere to its customs and culture, including local knowledge regarding treatment using medicinal plants.⁸ Previous research has succeeded in identifying the types of plants used in medicine by the Tengger people, but there has been no research on plants or other materials that are specifically used by the community, especially Tengger tribal farmers when an injury occurs.

MATERIALS AND METHODS

This study used a qualitative design to describe the use of local wisdom in wound treatment practice among Tengger ethnic farmers. Data collection methods through in-depth interviews were then described in narrative form. The population in this study is the farmers in Ngadisari Village. The research was conducted on the agricultural land of Ngadisari Village, for 3 weeks in November 2020, and involved all farmers who were working on the land at the time of the study, using accidental sampling. This research information is taken from farming communities who have experienced injuries and their healing using natural materials. The total number of participants was 30 people. The questionnaires consist of demographic data, wound characteristics and wound treatment processes from the initial to the recovery phase. The characteristics of the participants, characteristics of the wound and wound management were described in descriptive analysis using percentages and frequency.

RESULTS

The majority of participants were female (60%). The location of the almost injuries (76,7%) was on the hands (on the fingers), 63,4% has cuts with a length of 0.5-2 cm and a depth of about 0.5 cm. Most of the injuries (93,4%) were caused by sharp objects, and the majority of the participants (80,2%) used traditional therapy (Table I). Figure 1 shows that the wound treatment practice used by the participants

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Table I: Demographic, characteristics of the wound and wound management among farmers (n=30)

Variables	n	%
Gender		
Male	12	40
Female	18	60
Cause of wound		
Sharp objects (agricultural tools such as sickles and hoes)	28	93.4
Accidents on the way to and from work	2	6.6
Wound location		
Hand (on the fingers)	23	76.7
Foot	6	20
Head	1	3.3
Wound length and depth (cm)		
0,5-2 and 0,5	19	63.4
>3 and 0,5-1	11	36.6
Wound management		
Traditional therapy	24	80.2
Combined medical and traditional therapy	6	19.8

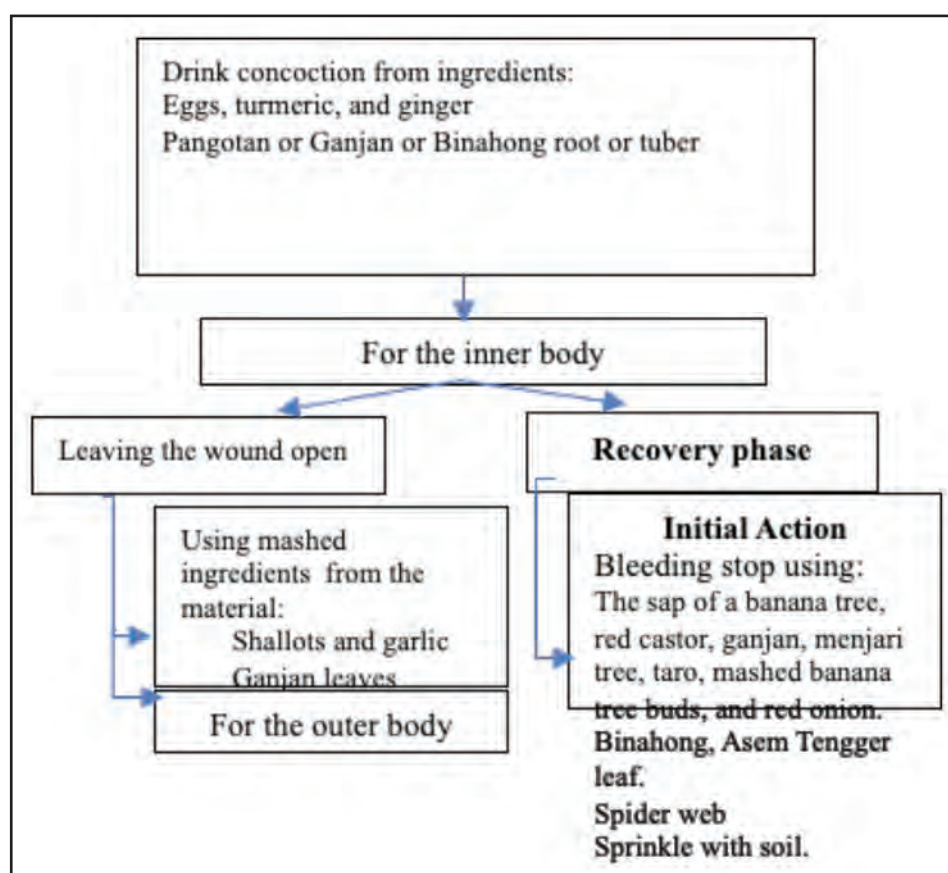


Fig. 1: Wound treatment Practice by Farmer in the Tengger Tribe

consists of two phases. The initial action is to stop bleeding and the second phase is the recovery phase using therapy for the inner and outer body.

When an injury occurs in the fields, participants immediately look for banana leaf sap, red castor leaf sap, ganjan leaf sap, taro stem sap or menjari tree sap, as well as banana tree buds, then pound them and apply them to the injured area. Participants also use binahong leaves, but they said that this

treatment did not originate from their ancestors. They will take bihanong leaves (usually an odd number of 3,5,7) then pound them and apply them to the wound area. Several participants wrapped their wounds with Asem Tengger leaves, and cobwebs found around the fields. A few participants sprinkled the wounds with the soil or doused them with their urine. Another action taken is to suppress the bleeding area with a cloth, especially on wounds with massive bleeding. After arriving home, they clean the

wounds and then soak them in warm water. During the recovery phase, the participants were drinking concoctions made from free-range chicken eggs, mixed with turmeric and ginger (turmeric 2 fingers, ginger 1 finger, washed, cut into pieces, boiled with a cup of water, until the water is reduced. The cold boiled water is then mixed with 1 free-range chicken egg); or drinking boiled herbs roots/tubers by taking about one handful of tubers or roots and then boiling it with enough water, consumed coldly twice a day. While therapy for the outer body by using a mashed ingredient, the wound is left open.

DISCUSSION

Most farmers tend to choose traditional therapy because it works fast and is practical. The location of the fields which are quite far from health facilities (about 3-5 km) makes the community think that the fastest way to deal with wounds is to take advantage of materials available around the fields. One participant uses a combination of medical and traditional therapy, because the wound occurred in the head area and was quite wide, so medical action was needed to suture the wound to stop the bleeding and close the wound. Then proceed with traditional therapy during the healing process.

At the beginning of the injury, most participants stated that they use traditional therapies that have been passed down from generation to generation without knowing the scientific reasons. However, several studies can provide scientific reasons for this. The previous studies identified that banana, red castor, ganjan leaf sap, taro stem sap or menjari tree sap contain materials that help wound healing, namely flavonoids, saponins, tannins and alkaloids. Flavonoids shorten the time of inflammation and activate macrophages. Saponins increase the formation of new blood vessels in wounds, the process of fibroblast proliferation and the synthesis of other extracellular matrix collagen.⁹ Tannins and alkaloids function as antioxidants to reduce free radicals by transferring hydrogen atoms to the wound area and increasing wound closure.¹⁰ Lectin in taro plays a role in immune function and cell growth.¹¹ Polyphenolic compounds and essential oils in menjari tree (*Sonchus Asper Hill*) sap have anti-inflammatory properties. Ganjan (*Artemisia vulgaris L.*) also contains antibacterial agents such as sesquiterpenes and terpenoids.¹² Asem Tengger (*Radicula Armoracia Robinson*) leaves contain kaempferol and quercetin which plays a role as an antiseptic.¹³ When using these ingredients, there is no specific dosage for each ingredient. The amount of material used follows the adequacy of the material to cover the wound.

Spider webs are believed by participants to heal wounds quickly and stop bleeding. Scientifically, spider webs can reduce wound closure and re-epithelialisation time, also rich in vitamin K.¹⁴ Participants sprinkling the wound with soil is related to the Tengger people's belief in fire, water, air and earth as the main elements.¹⁵ Soaking the wound in warm water is done because warm water has a cleansing effect and reduces pain. Participants doused the wound with urine because previous generations believed it could stop bleeding and speed-up wound healing.

In the recovery phase, curcumin compounds in turmeric have antimicrobial and antioxidant properties. Oral treatment of curcumin is found to be more potent than topical treatment for angiogenesis at wound sites.¹⁶ A complete essential amino acid in chicken eggs is the main ingredient in the formation of damaged tissue cells.¹⁷ Ginger (*Zingiber officinale Roscoe*) can increase the density of collagen fibres⁹ and the number of fibroblast cells.¹⁸ The use of shallot and garlic "lanang" mash because hereditary traditions are believed to speed up the wound-drying process. The garlic "lanang" contain saltivine, scordinin, Gurwitch rays which can accelerate cell growth and sulphur in garlic, which is volatile when exposed to air and can speed up the wound-drying process.¹⁹ The action of the wound is left open because, according to participants drying of the wound will occur faster if the wound is left in an open condition. If it is wrapped, the wound will be damp and will not dry out quickly. According to the participants, the wound care method used resulted in good wound healing without any complications. The time needed for wound healing depends on the extent and depth of the wound. Participants say that wounds with an area of 1-3 cm can heal within 3-7 days, and one participant with deep wounds (> 0.5 cm) to the muscle and more than 10 cm has completely healed to normal function within one year.

CONCLUSION

Tengger culture-based wound treatment uses whatever it is in nature to stop the bleeding in the initial phase and increase the wound healing process in the recovery phase.

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The relationship between physical activity level and dysmenorrhoea in young women

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ABSTRACT

Introduction: Menstrual disorders that often occur are menstrual pain (dysmenorrhoea), especially in adolescence. The average incidence of dysmenorrhoea in young women is between 16.8 and 81% worldwide. Physical activity is one of the relaxation techniques that can be used to reduce dysmenorrhoea. The purpose of this study was to find out the relationship between Physical Activity level and the incidence of dysmenorrhea in young women at SMP Negeri 16 Padang.

Materials and Methods: This research used observational analytic methods with cross-sectional design. The sample in this study was young women (9th class students), totaling 39 people. This study used the IPAQ Questionnaire Sheet and pain scale rate to confirm dysmenorrhoea. Analysis of this study used chi square.

Results: We found that most respondents (61.5%) had dysmenorrhoea, and more than half of respondents (61.5%) rarely did Physical Activity. Bivariate test results found that there is a relationship between Physical Activity level and dysmenorrhoea (p value = 0.044, α = 0.05, df = 3). From the analysis results, the value of OR = 4.500 was also obtained, meaning that respondents who did not exercise regularly had a 4.5 times chance of experiencing dysmenorrhea compared to respondents who did regular exercise.

Conclusion: Respondents who rarely do physical activity often experience dysmenorrhoea. Therefore, good education is needed for young women, which is one of the things that can be done to prevent and reduce the event of dysmenorrhoea is to exercise regularly.

KEYWORDS:

Physical Activity Level, Dysmenorrhoea, Young Women

INTRODUCTION

Adolescence is a transition period from children to adulthood. In young women, one sign of the maturity of the reproductive organs is marked by the arrival of menstruation or menarche. Based on data from the National Health and Nutrition Examination Survey (NHANES), the average age of menarche in Indonesia is 12.5 years with a range of 9–14 years.¹

Menstrual disorders that often occur are menstrual pain (dysmenorrhoea). The pain takes place in the days before or early menstruation.² Pain is usually felt in the lower or middle abdomen and sometimes even extends to the hips, thighs and back.⁴ Abdominal pain during menstruation or dysmenorrhea that is felt by every woman is different, some are slightly disturbed but some are so disturbed that they cannot carry out activities.² If this pain cannot be handled properly, it will interfere with daily activities and learning outcomes.

According to the World Health Organization (WHO), the incidence of dysmenorrhoea is quite high throughout the world. The average incidence of dysmenorrhoea in young women is between 16.8 and 81%. Dysmenorrhoea incidence in Indonesia is 54.89% primary dysmenorrhoea.³ Abnormalities occur in 60–70% of women in Indonesia, with 15% of them complaining that their activities are limited due to dysmenorrhoea.¹

Painful menses or dysmenorrhea affects 40–90% of women. Despite its high prevalence, understanding of its pathophysiology and its relation to other pain syndromes in women is still limited. Dysmenorrhea has been historically categorized into two distinct types: primary and secondary. Primary dysmenorrhea is menstrual pain without pelvic pathology, with onset typically just after menarche. Pain in primary dysmenorrhea occurs during menses and lasts 2–3 days. Secondary dysmenorrhea describes menstrual pain when underlying pathology is identified (such as uterine or ovarian lesions); its onset may be years after menarche. Pain may start 1–2 weeks before menses and persist beyond, lasting several days.⁴

Dysmenorrhoea felt by every woman is different. Some are disturbed so they cannot do activities. One effective way to prevent dysmenorrhoea is by doing physical activity. From a preventive perspective, risk factors for dysmenorrhea should be identified. Previous studies have shown that lifestyle factors, including physical activity and diet, are related to the condition in adolescents.⁵ Some physical exercises can increase blood supply to the reproductive organs thereby facilitating blood circulation.

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Table I: Characteristics of the respondents (N=39)

Respondent characteristics	Mean (SD)	Median	p value (t-test)
Age	14.54 years (0.600)	14 years	0.967
Menarche age	12.51 years (0.854)	13 years	0.311
Body weight	49.6 kg (13.00)	46 kg	0.920
Height	152.4 cm (7.77)	153 cm	0.163
Body Mass Index	21.2 (19.48)	20	0.611

Table II: Relationship of Physical Activity level with dysmenorrhoea (N = 39)

Physical Activity level	Dysmenorrhoea						p value
	Yes		No		Total		
	f	%	f	%	f	%	
Seldom (<3 times a week)	18	75	6	25	24	100	0.0234 (α = 0,05, df = 3)
Often (≥3 times a week)	6	40	9	60	15	100	
Total	24	61.5	15	38.5	39	100	

Women who do regular exercise at least 30–60 minutes every 3–5 times per week can prevent dysmenorrhoea. If women regularly exercise, women can provide oxygen for almost 2 times per minute so that oxygen is conveyed to vasoconstriction blood vessels. Women can take a leisurely walk, light jogging, swimming, gymnastics or cycling according to their respective conditions.⁶

On the other hands, exercising three days before the beginning of menstruation increases the flow of pelvic blood, disrupting the accumulation of prostags in this part of the body and thus delay the emergence of pain. Exercise during menstrual pain also leads to the transfer of excess substances and prostaglandins which are faster than the uterus, which is the main factor responsible for menstrual pain, and thus reduce the duration of pain during menstruation.⁷

MATERIALS AND METHODS

This type of research used observational analytic methods with cross-sectional design to find out the relationship between Physical Activity level and the incidence of dysmenorrhea in young women at SMP Negeri 16 Padang. The research was conducted at SMP Negeri 16 Padang from July to September 2022. The population of this study was 116 peoples spread across 9 classes with varying numbers.

According to Arikunto in Rahmadi the sample is part of the number and characteristics possessed by the population. According to Arikunto in Rahmadi says that if the subject is less than 100, then the entire population becomes the research sample, but if the subject is more than 100 then you can take 10-15% or 15-25%. But, in this research, sampling was taken as much as 30% of the total population, because if researcher took 25% from population, the sample size was too small or less than 30, so that the researcher took 30% sample size from population and 10% added of sample for drop out. So, this research obtained as many as 39 people.⁸ The sampling technique used is Proportional Random Sampling, by dividing the number of students per class by the number of all students and then multiplying by the required number of samples. This study has received a letter of ethical

clearance with number 952/UN.16.2/KEP-FK/2022 from the Research Ethics Commission of Andalas University.

Information collected include physical activity, incidence of dysmenorrhoea and also characteristic of respondent such as age, menarche age, body weight, height, and body mass index. The incidence of dysmenorrhea is pain in the lower or middle abdomen, sometimes even up to the hips, thighs and back that is felt by young women during menstruation. Menstrual pain was measured using a visual pain scale. Interviews were conducted with respondents. Assessment of pain scale using the Visual Analog Scale. The researcher showed an analogy of the face when feeling pain. Respondents put a tick mark on the picture according to what the respondent felt when she felt dysmenorrhea. Expressed often if the pain score is more than 5, sometimes if the pain score is less than 5.

Physical activity level is stated as one of the relaxation techniques that can be used to reduce pain by doing sports. Researchers collect data by conducting interviews with respondents. Classified as seldom exercising if less than 3 times a week, often if exercising 3 or more times a week. Respondent Physical Activity are carried out using the IPAQ (The International Physical Activity Questionnaire) which is a standard questionnaire to assess one's Physical Activity. The amount of physical activity level performed can be measured using the International Physical Activity Questionnaire (IPAQ). The IPAQ questionnaire has been translated into Indonesian and tested for validity and reliability in 14 places and 12 countries. The validity and reliability values of this questionnaire are 0.30 and 0.80. So this questionnaire has been used internationally as an instrument to measure physical activity in adults between 15-49 years old. The advantage of the IPAQ questionnaire is that physical activity is described as not only exercising, such as physical activity at leisure, homework, physical activity related to work or physical activity related to movement/transport in the last seven days.^{9,10} The instrument's reliability and validity have been widely examined. The IPAQ Indonesian version has a high test-retest reliability of 0.884 and a validity correlation with

accelerometers of 0.00. The reliability tests validate the instruments' application in Indonesian adults.⁹

After that, all statistical research tests had carried out IBM SPSS statistics 26. Data analysis was performed using univariate and bivariate analysis. Bivariate analysis was performed using the chi square test with a 95% degree of confidence.

RESULTS

Based on the results of the research that has been carried out, the following results are obtained in table I. It was found that the average age of respondents was 14.54 years, experienced menarche at the age of 12.51 years, the average weight of 49.6 kg with an average height of 152.4 cm and with an average of IMT 21.2.

The relationship between physical activity level and dysmenorrhoea could be seen in Table II. The 24 respondents who rarely exercise, as many as 75% of respondents experienced dysmenorrhoea and of 15 people who exercise, 60% of respondents did not experience dysmenorrhoea with p value of 0.0234 $\alpha = 0.05$, $df = 3$. From the analysis results, the value of OR = 4.500 was also obtained, meaning that respondents who did not exercise regularly had a 4.5 times chance of experiencing dysmenorrhea compared to respondents who did regular exercise.

DISCUSSION

Based on table 1, it was found that the average age of the respondents was 14.54 years, the average age of menarche was 12.51 years, the average body weight was 49.6 kg, the average height was 152.4 cm and the average BMI was 21.2. The relationship between the characteristics above and the incidence of dysmenorrhea, none of the characteristic variables has a significant relationship with dysmenorrhea. Several studies have also found the same thing, that menarche age and nutritional status (BMI) have no relationship with dysmenorrhea.^{11,12} One of the reasons is differences in nutritional intake in adolescents that affect adolescent health. Hong Ju, Mark Jones in his research found that dysmenorrhea was inversely related to age, parity or number of live births, and use of oral contraceptives; and dysmenorrhea is positively associated with stress related to work and general life, as well as with a family history of dysmenorrhea.¹³ Based on the above research, it can be assumed that there is no relationship between the characteristic variables of age, age at menarche, weight, height and body mass index with dysmenorrhea.

The results of this study are in also same with the study from Taqiyah, et al which showed that out of 50 female students, 22 female students (22.0%) experienced mild dysmenorrhea where, 13 female students (90.9%) had adequate exercise habits while 9 female students (7.1%) had lack of exercise habits, while 19 female students (38.0%) experienced moderate dysmenorrhea where 16 female students (64.3%) had less exercise habits and 3 female students (4.5%) had moderate exercise habits sufficient, while the remaining 9

students (18.0%) experienced severe dysmenorrhea including 7 female students (28.6%) have less exercise habits and 2 female students (4.5%) have sufficient exercise habits. Based on the results of the analysis using the chi square statistical test, the value of $p: 0.000$ is obtained shows $p < \alpha (0.05)$, this means that there is a significant relationship between exercise habits less on the incidence of primary dysmenorrhea. There are several reasons people do not exercise regularly, two of them are the reasons for time and also costs. Costs are also often used as an excuse because of the assumption that serious sports require equipment that is not cheap. Though many sports do not require certain tools and places.^{14,15}

Most young women in SMP N 16 Padang City experience dysmenorrhoea. The results of this study are in line with the results of research from Fachruddin that most subjects experience primary dysmenorrhoea (69.1%), especially level 1 (49.5%), namely activities rarely disrupted, no systemic symptoms and rarely need analgesics.¹⁶

This increase results in uterine contractions and vasoconstriction of blood vessels, and the bloodstream that leads to the uterus decreases so that the uterus does not get an adequate oxygen supply, causing pain. So, young women should know how to decrease dysmenorrhoea.^{17,18} The results of this study are the same as being found in his research. There is an influence of exercise habits on the incidence of menstrual pain. This can be seen from the results of the statistical test which shows the p value = 0.000¹⁸

This study also had the same result from Tabrizi, et al that exercise is generally believed to relieve the symptoms of dysmenorrhea. One plausible explanation is that aerobic exercise is effective through shunting the blood flow away from the viscera, resulting in less blood con gestion in the pelvic area during the menstrual phase. Kazama et al. found that higher levels of sports activities were significantly related to a lower prevalence of severe dysmenorrhea (adjusted P for trend=0.045)⁵.

Women who do regular exercise at least 30–60 minutes every 3–5 times per week can prevent dysmenorrhoea. If women regularly exercise, women can provide oxygen for almost 2 times per minute so that oxygen is conveyed to vasoconstriction blood vessels. Women can take a leisurely walk, light jogging, swimming, gymnastics or cycling according to their respective conditions.⁶

Exercising 3 days before the beginning of menstruation increases the flow of pelvic blood, disrupting the accumulation of prostaglandin in this part of the body and thus delaying the emergence of pain. Exercise during menstrual pain also leads to the transfer of excess substances and prostaglandins which are faster than the uterus, which is the main factor responsible for menstrual pain and thus reduces the duration of pain during menstruation. Teenagers who rarely exercise have a chance of 1.2 times greater risk of having dysmenorrhoea than teenagers who often exercise. Endorphins are produced in the brain and spinal cord marrow.^{14,18,20}

A literature review from Rijanto, et al. that during adolescence there is a process of maturation of the reproductive organ system. So that the oxygen supply must also be met. Lack of physical activity will reduce the distribution of oxygen in the systemic circulation, thereby increasing a person's perception of pain, including dysmenorrhea. Adolescents with low levels of physical activity tend to be more at risk for more severe dysmenorrhea. On the other hand, adolescents who do regular physical activity can improve the working system of blood vessels so that they can reduce pain complaints and increase physical fitness. Based on this, it can be seen that the more routine a person does physical activity, the more likely it is to prevent or minimize the occurrence of dysmenorrhea. Exercise is a non-pharmacological management that is safer to use because it uses physiological processes.²¹

The present study has several limitations. First, the study used a cross-sectional design, which cannot determine causal relationships. In the context of this study, for example, the identified risk factors may have been caused by dysmenorrhea symptoms. A longitudinal study should be conducted to address this issue. Second, the participation rate was not sufficiently high, and thus generalization of our results should be made with caution. For example, it is possible that girls without dysmenorrhea may not have been interested in participating in the study. These methodological limitations should be addressed in future studies. Finally, we could not differentiate between primary and secondary dysmenorrhea, although secondary dysmenorrhea in adolescence is considered rare. This study requires further research related to other factors that can influence the events of dysmenorrhoea such as menstrual period, family history, nutritional status, sleep hours, and other factors.

CONCLUSION

From this study, it can be concluded that there is a significant relationship between physical activity level and dysmenorrhoea. Doing Sports is one of method to decrease or prevent dysmenorrhea especially in young women, because nowadays teenagers prefer to use gadget for long times and lack to do sports. So that, it make dysmenorrhea could be happened.

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CONFLICT OF INTEREST

Conflicts of interest have not been disclosed by any authors.

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The relationship between religious coping and academic resilience in nursing students

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ABSTRACT

Introduction: Religious coping is a way to overcome learning problems. Good religious coping has a positive impact on student educational processes and outcomes. However, until now, the relationship between religious coping and academic resilience has not been known. This study aimed to determine the relationship between religious coping and academic resilience.

Materials and Methods: This study used a cross-sectional approach with a stratified random sampling technique on 110 students from one university in Bandung, West Java, Indonesia. The inclusion criteria include actively registered nursing students from undergraduate and vocational programs. Religious coping was assessed using The Psychological Measure of Islamic Religiousness (PMIR) and the Academic Resilience Questionnaire was used to evaluate students' academic resilience level. The data were analyzed using descriptive and inferential analysis. The Spearman rank correlation test was used to determine the relationship between variables.

Results: The study's results revealed a significant relationship ($\rho = 0.415$; p value < 0.05) between religious coping and academic resilience. High religious coping is related to the amount of academic resilience in students.

Conclusion: Students are expected to be able to use a religious coping strategy to boost academic resilience and adapt to any situation. Thus, students with good religious coping skills and high resilience will be able to face and solve problems and adapt to current learning conditions.

KEYWORDS:

Academic resilience, learning process, religious coping, students

INTRODUCTION

Online learning is a modification of learning activities when it cannot be conducted face-to-face.^{1,2} Problems with online learning systems at universities, such as nursing schools, are more visible. Student problems are related to laboratory practicum learning activities which require activities to be carried out directly but cannot be facilitated through online learning.³⁻⁹ This condition causes academic stress that must be faced with proper coping by every student in online learning.

Several studies have found a positive relationship between academic resilience and academic achievement, so that if

students have low resilience, it will cause mental problems and cause academic stress.¹⁰⁻¹² Francis et al. said that symptoms of stress and anxiety can be overcome using religious coping and can improve mental health among medical students.¹³ Religious beliefs and practices can be used as resources in Islamic teachings to deal with difficult situations. Religion teaches its followers to be patient, pray, believe, and turn to God for guidance and assistance when needed. Individuals can learn from each existing situation; death, illness, and other losses have been planned, and it is God's will or God's love for his people, in general, when they face this highly stressful situation.¹⁴

However, the relationship between religious coping and academic resilience needs to be clarified. This study aims to determine the relationship between religious coping and academic resilience in students.

MATERIALS AND METHODS

This study used a cross-sectional design. A total of 110 students were involved in this study based on stratified random sampling. The students involved are from one university in Bandung, West Java, Indonesia. The inclusion criteria included active nursing students with undergraduate or vocational degrees. Students who were sick during the study were excluded. This study has received ethical approval from the Research Ethics Committee of Universitas 'Aisyiyah Bandung (137/KEP.01/UNISA-BANDUNG/VI/2022).

To measure religious coping used The Psychological Measure of Islamic Religiousness (PMIR), modified by Wida Ningsih and tested for validity with the item total correlation > 0.306 and the reliability index with Cronbach Alpha > 0.6 (0.895).^{12,15,16} The PMIR scale consists of 25 question items with a 5-point Likert scale. Meanwhile, academic resilience was measured using a research-based academic resilience scale. This scale has 23 items with a 4-point Likert scale. This scale was valid with an item-total correlation score > 0.344 and reliable with a Cronbach Alpha index of 0.904.

Data for the study was obtained in 2022 between June to July. To recruit respondents, the researchers informed eligible respondents about the purpose of the study and procedure and obtained their written consent. Respondents were assured that participating in the study was entirely voluntary, that their information would be kept secure and confidential. The survey took between 20 and 30 minutes to complete a digital questionnaire.

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Table I: Characteristics of respondent (n=110)

Characteristics	F	%	Correlation (p-value)		
			Religious Coping	Academic Resilience	
Age	18–21	32	29.1	0.776	0.640
	22–24	78	70.9		
Gender	Male	9	7.3	0.31	0.957
	Female	101	82.1		

Table II: Religious coping and academic resilience frequency distribution (n=110)

Variable		F	% (n = 110)	Mean ± SD
Religious coping	Very good	10	9.1	94.95 ± 5.029
	Good	100	90.9	
Academic resilience	High	87	79.1	77.16 ± 9.509
	Moderate	23	20.9	
	Low	0	0	

Table III: Correlation between religious coping and academic resilience

Religious coping	Academic Resilience			Coefficient Correlation (rho)	p value
	High	Moderate	Low		
Very good	10 (9.1%)	0	0	0.415	0.000
Good	82 (74.5%)	18 (16.4%)	0		

The data were analyzed using descriptive and inferential analysis. The demographic characteristics, religious coping, and academic resilience were displayed descriptive statistics. The Spearman rank correlation test was used to determine the relationship between variables. We used IBM SPSS version 24 software to process the data analysis.

RESULTS

Most respondents are aged 22-24 years, with a percentage of 70.9%. Based on gender, most female students with a rate of 82.1% (Table I). Meanwhile, almost all students (90.9%) have good religious coping, and the academic resilience possessed by most students (79.1%) is high (Table II). Table III shows that religious coping is significantly related ($\rho = 0.415$; p -value = 0.000) to academic resilience. This significant correlation also indicates that students with high religious coping have high academic resilience. The study results show that the students with good religious coping with high academic resilience 74.5%, as seen in Table III.

DISCUSSION

The study results show that religious coping is significantly related to academic resilience. High academic resilience will reduce stress on students. Religious coping can alleviate symptoms of depression and anxiety and improve mental health among medical students.^{13,17} In religious teachings, religious beliefs and practices are ways to deal with difficult situations and problems.

The study results show that high academic resilience is directly proportional to high academic resilience.^{10,18} Online learning during the COVID-19 pandemic is an alternative solution for organizing good education, but suitable religious

coping needs to be supported. Therefore, one must have high resilience to adapt to any situation.^{19–21} Academic resilience is used to prevent and overcome the adverse effects of difficult situations in an individual or group. Students are expected to be able to survive adversity.^{22–25}

The correlation between religious coping and academic resilience can be influenced by age. Adults will have a higher level of development and strengthen a person in solving problems so they can adapt to difficult situations²⁶. University students aged 18 to 25 are classified as growing-up individuals, so the older they are, the more they will have good religious coping skills and resilience.

Gender can affect religious coping with academic resilience, and women have better academic resilience than men.²⁷ When women face problems, they turn to the Creator. In addition, religious coping and academic resilience can be linked to educational programs. Students have academic resilience and positive religious coping to deal with existing academic problems.^{27,28}

Apart from age and gender, other factors influence religious coping and academic resilience, namely religious education and social support. Although in this study, we did not examine it. Someone with an excellent religious education will solve problems by getting closer to the Creator. Thus, the greater one's resilience, the better one's religious coping with a current issue. Social support includes the community and each culture showing a desire to rise above adversity. The ability to accept these adversity will also increase one's resilience.^{29,30} This study had limitations to the research, including the limited study sample and being recruited from a single centre, which was the most significant limitation.

CONCLUSIONS

There was a significant relationship between religious coping and academic resilience among students. This study result showed that the greater one's resilience, the better one's religious coping. Students are expected to be able to use a religious coping approach to strengthen academic resilience to adapt to any situation. Further study can examine the factors that influence religious coping and academic resilience.

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Indonesian and vietnamese information seeking behaviour related to COVID-19

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ABSTRACT

Introduction: Southeast Asia countries had been among the worst-hit countries by COVID-19. The misinformation was spread along with the increasing number of cases. This study aims to describe how Indonesians and Vietnamese behave in seeking information related to COVID-19.

Materials and Methods: The study used a cross-sectional design with purposive sampling technique (n=167). Targeted population was limited to 18 – 59 years of age. An online form was shared via WhatsApp, Facebook and Instagram of each contributor. Data collected includes sociodemographic data (age, gender, marital status, educational background, occupation, and residences), and data on information seeking behaviour. Data was analysed using SPSS V.20.

Results: Almost 95.70% of Indonesians and 89.20% of Vietnamese accessed the online information. A 75.68% Vietnamese and 46.24% Indonesians shared information with others, 59.14% of Indonesians and 20.3% of Vietnamese stated that they discussed the information with health workers.

Conclusion: Both countries have implemented proper online-based information. However, a good mass communication strategies were needed to protect people from the misinformation.

KEYWORDS:

Information seeking behaviour, COVID-19, Indonesian, Vietnamese

INTRODUCTION

Coronavirus diseases – 2019 (COVID-19) is a global issue to date. This pandemic had hit more than 200 countries.¹ As of September 23 2020, COVID-19 has caused up to 1 million deaths worldwide. WHO since March 2020 declared COVID-19 a global pandemic.² The data on cases and victims of COVID-19 distributed in various countries shows that COVID-19 has become a global issue and impacts international activities.³ This declaration is also based on the fact that this coronavirus is a new virus that can easily transmit among humans worldwide.⁴

Southeast Asian countries had been among the worst-hit countries. As of September 23rd 2020, there were 6.3 million confirmed cases in this region, ranks the 2nd highest in the world after the American Region with nearly 16 million confirmed cases.² In Indonesia, until September 22, 2020, there were 248,852 confirmed cases, with deaths rate hitting 4%². Stay at home, quarantine, increasing the capacity of health services and website www.covid19.go.id page are some steps in responding to the pandemic.⁴⁻⁶

The COVID-19 pandemic was first time confirmed in Vietnam on January 23rd, 2020. However, the Vietnamese Government's fast response had made Vietnam becoming one of the countries that have significantly reduced the spread of this virus. The combination of actions namely an early lockdown, the spread of the health information widely, encouragement in health declaration, regulating the use of masks in the wider community had been the effective ways to cope with this deadly virus in Vietnam. Previously, Vietnam was also the first country to be free from the spread of SARS in 2003.⁵

Steps to make health information "viral" in the community carried out by the Vietnamese Government including a video about preventing COVID-19 which resulted from a collaboration between the Vietnamese Ministry of Health and musicians, watched by more than 30 million people on YouTube. Songs with the theme of preventing COVID-19 were also broadcasted on local and international television. In addition, text messages via cell phones were also being carried out intensively.⁵ Vietnam had done mass testing and provided clear information to the public. These were effective to reduce the spread of COVID-19.^{7,8}

The study of Saud, Mashud, and Ida (2020) showed that online platforms such as social media were platforms for people to seek and collect information related to the coronavirus pandemic from various perspectives. This study revealed that the platform was easily accessible. In every crisis in a community and a pandemic, everyone tried to look for help, information, and stay informed about what was happening around them. Therefore, seeking health information were becoming more active in these times.^{6,7} However, the use of social media to seek information related

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Table I: Socio-demographic characteristics of respondent (N=167)

Category	IND (%) N=93	VIET (%) N=74	n (%) N=167
Age			
20–34	82 (88.17)	69 (93.24)	151 (90.4)
35–54	11 (11.83)	1 (1.35)	12 (7.2)
>55	0	4 (5.4)	4 (2.4)
Gender			
Female	73 (78.5)	52 (70.3)	125 (74.8)
Male	20 (21.5)	22 (29.7)	42 (25.2)
Educational Background			
Primary school	34 (36.6)	0	34 (20.4)
Secondary school	38 (40.90)	3 (4.1)	41 (24.6)
Degree/Diploma	5 (5.4)	69 (93.2)	74 (44.3)
Postgraduate	16 (17.2)	2 (2.7)	18 (10.77)
Occupation			
Medical	34 (36.6)	49 (66.2)	84 (50.3)
Non-medical	59 (63.4)	25 (33.8)	83 (49.7)
Residences			
Urban	68 (73.1)	49 (66.2)	117 (70.06)
Rural	25 (26.9)	25 (33.8)	50 (29.94)

Table II: Distribution frequency of information-seeking behaviour of Indonesian and Vietnamese

Classification	Indonesia (IND) n (%) N=93	Vietnam (VIET) n (%) N=74
Information accessibility		
Easy	80 (86.02)	68 (91.89)
Difficult	13 (13.98)	6 (8.11)
Internet Use		
Yes	89 (95.70)	66 (89.20)
No	4 (4.30)	8 (10.8)
Frequency of seeking information*		
Frequently	63 (67.74)	50 (70.42)
Moderately	13 (13.98)	15 (20.27)
Infrequently	17 (18.28)	9 (11.3)
Tendency to sharing information		
Yes	43 (46.24)	56 (75.68)
No	50 (53.76)	18 (24.32)
Discuss with the health workers about COVID-19		
Yes	55 (59.14)	15 (20.3)
No	38 (40.86)	59 (79.7)

*Based on the frequencies of seeking information daily, weekly, or monthly. Daily access refers to frequently, weekly access refers to moderate access, and monthly access refers to infrequently.

to Covid was also correlated to shallow capability to assess information cautiously.⁸ Thus, government roles in providing accurate information on social media was crucial, not only to solve information overload but also decrease the conflicts among levels of governments.⁹

During the pandemic, both in Indonesia and Vietnam, the governments decided to assert strict restrictions for citizens who hanging around outside their homes. Indonesia took large-scale social restriction policy even though the effectiveness of its implementation was questionable in some provinces.¹⁰ While Vietnam decided to implement a partial lockdown on April 1, 2020 that made the public dependent on online sources of health information.¹¹ Online platforms (i.e. government websites and social media such as Facebook, Instagram, and WhatsApp group) were mostly used to seek information related to the pandemic.^{9,10} Our study aims to

describe the behaviour of seeking information related to COVID-19 among Indonesian and Vietnamese in response to the pandemic.

MATERIALS AND METHODS

The study used a quantitative research approach with purposive sampling technique. Data was collected through an online survey. The research instruments were based on opened and closed-ended questions that were prepared to gather the responses. Furthermore, the form was transferred into google form document and the shareable link was spread out. The expected respondents were Indonesian and Vietnamese in age group between 18 – 59 years old. The respondents were targeted and approached through WhatsApp messenger and recruitment information was posted on Facebook and Instagram of each contributor.

The data was collected between May and July 2020. Data collected includes sociodemographic data (age, gender, marital status, educational background, occupation, and residences), and data on information seeking behaviour. The results were coded and first presented in Microsoft Excel and analyzed in SPSS V.20, presented with frequency distribution tables. There were 52 respondents from other countries and which were later on deleted. A total of 167 responses were tested and verified. Seventy-four (74) respondents were from Vietnam, and 93 were from Indonesia.

RESULTS

Table I describes the socio-demographic data. The age group of 20-34 years were dominated (90.4%), 74.8% were female, 44.3% were graduated the degree/diploma, 50.3% of respondents worked in the health sector and 70.06% of respondents lives in urban areas.

Table II explains the details about the information-seeking behaviour of both countries. The accessibility was mainly easy (86.02% IND, 91.89% VIET). Almost all of the respondents used online sources of information (95.7% IND, 89.20% VIET). Vietnamese tend to share to others, compare to Indonesians, but only 20% of them discuss the information with health workers.

DISCUSSION

This study revealed that most respondents access online information sources in terms of COVID-19. As many as 95.70% of respondents from Indonesia and 89.20% from Vietnam depended on online information sources during this pandemic, even more than half (67.74% IND, 70.42% VIET) of respondents stated that they accessed the internet almost every day to find information related to the COVID-19 pandemic. This finding was similar to a study in Taiwan that showed that most people used the internet as a primary source of information for COVID-19.¹²

The social situation that had changed significantly during the pandemic had made the use of online-based information crucial.¹²⁻¹⁴ Nasir, Baequni, and Nurmansyah (2020) revealed that the increase of COVID-19 cases was followed by an increase in misinformation in the community, especially about facts related to COVID-19, its transmission, and prevention. Therefore, providing precise and accurate information was a major responsibility of the Government to avoid misinformation in society that could spread fear and panic, resulting in adverse mental health and psychological well-being.¹³⁻¹⁵ It was evident that during COVID-19 pandemic, the high number of mental health problems related to constant exposure to social media.¹⁶

Lesson learned from the Vietnamese Government was the success of controlling the pandemic through a high level of preparedness and a host of coordinated efforts to provide accurate and credible information to the public about epidemic risks and ongoing infection control measures. Vietnam put a proactive communication strategy from the start of the pandemic through the use of online platforms (websites), simple text messages, easy-to-use applications for

the public, the use of influencers in society as an extension of information from the Government, and pandemic awareness campaigns.¹⁷

The results showed the response of the Indonesian and Vietnamese of online platform based information. More than half (53.76%) of respondents from Indonesia stated that they would not share the information they got from the internet directly to others, on the contrary, most Vietnamese people would share that information (75.68%). Possible reasons for this are that the Indonesian people were becoming more critical and wanted to analyze the information they got and afterwards share it with others. The second reason is that people tended to be careful about hoaxes that might be contained in the information, so they chose not to share this information with others before knowing the authenticity of the information. The information overload could lead to unverified information sharing.¹⁸ On the other side, Vietnamese people have official information resources on websites. Therefore, in order to spread outstanding issues about COVID-19, people tended to share this information.

Misinformation from COVID-19 occurred on social media massively. Government has taken steps to handle this hoax quickly, by forming a special team to eradicate hoaxes. However, this misinformation continued to spread in the community.¹⁴ A study by Apoke and Omar found that predictors of false information sharing related to COVID-19 were passing the time, socialization, information seeking, and information sharing.¹⁹ Besides, the avoidant behavior of news could also lead to misleading information.²⁰ A study conducted in Italy suggested that health institutes could manage misinformation circulation by using Google Trends because they could observe the most searched information and thus predicting human behavior and misinformation.²¹ Moreover, a study suggested that health promotion using social media might result in larger traction compare to using confronting approach that commonly used in mass media promotion.²²

Nasir, Baequni, and Nurmansyah (2020) found out there were 11 misinformation topics that were relevant to the context of Indonesian society, such as this virus could not live in the Indonesian climate, the virus was a biological weapon, this virus spread through the air, turmeric made the body susceptible, unable to hold your breath for 10 seconds if you infected with this virus and some other information related to the prevention of COVID-19. From the data of this study, it is revealed that there were groups who still had a misunderstanding about COVID-19 and its prevention in Indonesian society.¹⁴

Even though these two countries respondents' state the ease of access to information related to COVID-19, several things needed the public's attention after reading information online. Practising in filtering relevant and reliable information before it was distributed, was an important education for each individual during a pandemic.

Some things that became the focus of the Vietnamese people when searching for information related to COVID-19 were updated news on the pandemic (76.0%), information about

disease symptoms (63.9%) and updated news on the outbreak (61.0%).¹⁴ From the information obtained, only about 60% of Indonesians chose to discuss this information with health workers, while the rest chose the opposite. In contrast, only 20% of the Vietnamese people chose to have discussions with health workers. The reason for this issue most likely was that Vietnamese people only talk to healthcare workers when there are signs of suspicion of COVID-19 infections. In addition, to the reputable websites that had been made available to the public, the Vietnamese Government also provided hotline numbers if anyone suspects that they were infected with COVID-19. Therefore, people discuss mainly through hotlines if they had problems related to COVID-19. This consumption of information related to COVID-19 online could be beneficial to reduce worry and improve preventive behaviours.²³

Health workers have an important role in the community as the frontline of human resources who face a high-risk contact with infected patients during a pandemic. Health workers are public references who can be accessed and asked about the validity of information from mass media since people tend to access mass media more than the sources provided by organizations or associations to seek information about COVID-19.²⁴ Therefore, health workers must be equipped with the right knowledge about this pandemic to build public trust in health workers' capabilities. This study implies the importance of proper, progressive and constructive mass communication. Good mass communication is a step to convey accurate and reliable information to the public. As revealed by our respondents in this study, it appears that in general, the governments of the two countries already have special formulations for mass communication. Open communication ensured public understanding of and support the government response, facilitating government-citizen cooperation. Even after the pandemic has ended, it is imperative that people guarantee reliable information.

There were several limitations of this research. The vital shortcoming was the sample size that most likely to happen in an online survey. People tend to ignore the announcement about an online survey and not interested to fill the form. Also, the design of this study was a descriptive study. It was an urge to do different approach to gather the optimal sample size in the future study and modify the design to get better result to date. However, our study offers unique data about information seeking behaviour between two groups namely Indonesian and Vietnamese. Since the COVID-19 was an emerging disease in the early 2020, so there had not been much research in this issue at that moment, and our study offers the update of this issue in both countries as a lesson learned for further action to control the pandemic through an online-based information.

CONCLUSION

This research shows that in general, both countries had practised good strategies in delivering online-based information, due to the greater dependence of the community during the movement restriction and partial lockdown. Access to information is also wide open in society. Websites related to COVID-19 had also been provided by the

governments and can be accessed at any time. However, effective mass communication measures need to pay attention to the Government in conveying information so that the public is protected from the misinformation and unreliable news during a pandemic.

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CONFLICT OF INTEREST

Conflicts of interest have not been disclosed by any authors.

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Swiss ball exercise post-stroke with hemiparesis to improve mobility: a randomised controlled trial

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ABSTRACT

Introduction: This research was done to find out how well post-stroke therapy works in reducing side effects and improving patient mobility.

Materials and Methods: This study used a randomised control trial design involving 42 post-stroke patients (mean 40 days after onset) with hemiparesis from January to October 2022, who were separated into two groups and randomly allocated to either the experimental group (n=21) or the control group (n=21). The intervention group received 24 times Swiss Ball Exercise (SBE), and the control group received 24 times conventional therapy.

Results: We found for the intervention group using SBE on TUG ($p<0.001$), TIS ($p<0.001$), FTBS ($p=0.011$), DGI ($p=0.005$) and RMAB ($p<0.001$).

Conclusion: After a stroke, patients with hemiparesis who exercise on a Swiss ball experience improved body function and movement.

KEYWORDS:

Hemiparesis, mobility, stroke, Swiss ball exercise

INTRODUCTION

Non-communicable diseases are now more common than they were 3 years ago. In 2018, there were an anticipated 2.1 million more stroke cases or a rise of 10.9%.¹ Balance issues, such as muscle weakness, decreased soft tissue flexibility and sensory-motor control, can be caused by sensorimotor disorders, which can also cause sensory disturbances, abnormal muscle tone and sensory disturbances.² Physical, emotional, psychological, cognitive and social factors are all present in these conditions.³ Long-term physical restrictions in patients make them dependent on their families for assistance with daily activities.⁴ Stroke survivors have a high rate of long-term disability, and neuro-rehabilitation remains an important component of post-stroke care. Clear standards of care have been created in numerous nations to improve the delivery of both inpatient and outpatient stroke services. Research demonstrates that functional recovery is predictable in the initial days following stroke, despite the fact that recovery differs among stroke patients. Swiss ball exercise (SBE) is one of the approved treatments. SBE is exercises using a ball aimed at reducing back pain, by

increasing the strength of the abdominal muscles, gluteal muscles, and back extensor muscles. The study's findings demonstrate that SBE is the most efficient technique for enhancing post-stroke patients' balance and mobility.⁵ This study's objective was to show how SBE improved post-stroke patients' levels of mobility and balance.

MATERIALS AND METHODS

In this study, post-stroke patients were the participants of a randomised control trial design with a control group that performed tests before and after the study. The sample for this study was collected using the consecutive sampling method, and the inclusion criteria were acute post-stroke patients who had hemiparesis of the upper and lower limbs for a period of 1–3 months, were aged 40–60, both male and female, and have sensory and motor abnormalities. Patients with cognitive deficits, mental illnesses, a history of spinal surgery, spinal deformity or haemorrhagic stroke were excluded from the study. Forty-two people were divided into two groups which became the research sample, as can be seen in Figure 1.

The first group engaged in SBE for 35 to 40 minutes 1 time, the exercises were done 6 times a week for 4 weeks. The physiotherapist is in charge of all treatment sessions. SBE consists of 1) Reducing the frequency of assistance, 2) Increasing arm ability, 3) Advancing the balance limit 4) Increasing Hold time. The Times Up and Go Test (TUG) and the Trunk Impairment Scale (TIS) were used to assess truncal function after 3 months. To clarify the results of the key end measures, tests such as the Berg Balance Scale, Four Test Balance Scale (FTBS), Dynamic Gait Index (DGI) and Rivermead Motor Assessment Battery (RMAB) were conducted to find out the increase in mobility. This research has also passed an ethical test through the health research ethics committee with number 099.6/II.3.AU/F/KEPK/V/2022.

The pre-and post-treatment results were reported as the "time" variable among the participants, whilst the experimental and control groups were regarded as the "condition" factor between people using a t-test analysis. If the Time Conditions indicated a significant interaction, there was a significant difference between the pretreatment and post-treatment evaluations for the two groups. For the TIS and its subscales, the Bonferroni correction was applied to probability scores. For the key outcome measures listed in

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Table I: Characteristics of respondents (N=42)

	Intervention		Control	
	f	%	f	%
Age				
31–40 years old	3	14.2	5	23.8
41–50 years old	6	28.6	6	28.6
51–60 years old	8	38.1	8	38.1
> 60 years old	4	19.1	2	9.5
Gender				
Man	13	61.9	11	52.4
Woman	8	38.1	10	47.6
Long suffering stroke				
< 1 year	6	28.6	4	19.1
1–2 years	12	57.2	11	52.4
2–3 years	3	14.2	6	28.5
Paretic side				
Right	12	57.2	11	52.4
Left	9	28.6	10	47.6
Type of stroke				
Ischaemic	14	66.7	11	52.4
haemorrhagic	7	33.3	10	47.6

Table II: Outcome measures of the respondents (N=42)

	Pretreatment		Post-treatment		p-value	
	Intervention	Control	Intervention	Control	Time	Time • Condition
TIS						
Static sitting balance	5.42 (1.69)	4.92 (2.14)	7.05 (0.01)	6.38 (2.32)	<0.001	1.000
Dynamic sitting balance	3.78 (1.77)	3.98 (1.83)	8.55 (2.31)	5.11 (1.87)	<0.001	<0.001
Coordination	0.76 (0.71)	0.72 (0.58)	3.61 (1.52)	1.45 (0.93)	<0.001	<0.001
Total	9.96 (4.17)	9.62 (4.55)	19.21 (3.84)	12.94 (5.12)	<0.001	<0.001
Romberg						
Eyes open	18.57 (14.75)	14.96 (14.68)	24.82 (10.12)	20.12 (12.32)	0.002	0.746
Eyes Closed	14.01 (13.14)	9.98 (14.62)	23.30 (12.49)	13.25 (13.21)	<0.001	0.356
FTBS	1.59 (1.46)	1.52 (1.86)	4.25 (1.43)	2.65 (2.01)	<0.001	0.011
DGI	4.72 (7.51)	4.06 (7.54)	13.71 (10.62)	6.13 (8.52)	<0.001	0.005
RMAB						
Gross function	4.76 (4.22)	4.26 (4.32)	9.91 (2.82)	6.18 (3.98)	<0.001	0.001
Leg and trunk	3.16 (2.76)	3.12 (2.47)	9.21 (1.44)	4.78 (3.54)	<0.001	<0.001
Arm	3.12 (4.31)	3.08 (4.01)	6.09 (5.37)	5.11 (5.32)	<0.001	0.412
Total	11.04 (11.29)	10.46 (10.8)	25.21 (9.63)	16.07 (12.84)	<0.001	<0.001
TUG	2.54 (2.48)	2.14 (2.01)	4.33 (4.28)	3.01 (2.97)	<0.001	<0.001

TIS: Trunk Impairment Scale, FTBS: Four Test Balance Scale, DGI: Dynamic Gait Index, RMAB: Rivermead Motor Assessment Battery

Table II, the significance level was established at $p=0.007$ at a level of significance of $p=0.05$. For some experiments, secondary outcome measures were not adjusted.

RESULTS

Each of the treatments and control groups received 21 stroke patients. In both the intervention and control groups, all patients underwent 24 treatments. The characteristics of the two groups can be seen in Table I. When comparing the two groups' demographic characteristics and stroke-related data, we did not find any differences. Both groups experienced significant improvement for 4 weeks after therapy can be seen in Table II.

DISCUSSION

We found that 24 additional treatments over 4 weeks with an average duration of 35 minutes improved truncal function

and mobility in post-stroke patients. This therapy also improves postural control while the patient is standing.⁶ This shows that SBE is important for the rehabilitation of stroke patients.⁷ This is also the same as other studies, which explain that therapy to stimulate truncal function is very important and requires regular exercise. Higher truncal levels were obtained because of longer exercise.⁸

SBE also improves balance and sitting and standing exercises as can be seen in table II. These results are the same as research conducted by Lee in 2022, exercises carried out as soon as possible will increase mobility.^{8,9} The motor methods stimulated by this exercise are effective and efficient. All patients are subjected to the exercises by the therapists engaged in direct activities.¹⁰ Truncal stability is an important point of exercise because it maintains function stability and coordinated use of the extremities.¹¹ This exercise also stimulates the reduction of weakness experienced by the

patient. This therapy also improves coordination between joints in the bones of the extremities.¹² SBE can be an alternative therapy to increase the mobility of post-stroke patients at a low cost. further research is needed with a larger sample by combining several therapies to see more impact. during observation, patients who were younger or with an average age of less than 41 years experienced a better increase in mobility, and that occurred in men. patients who were more enthusiastic about doing the swiss ball exercise and seemed to have a higher motivation to recover also experienced a drastic increase. this becomes the basis for further research related to the motivation of each post-stroke patient in undergoing treatment. This study has weaknesses, namely in analyzing data on the characteristics of respondents still using categories and the intervention was only carried out for 4 weeks, better research results might be obtained.

CONCLUSION

SBE increases truncal function. This exercise also influences balance and increases mobility from a sitting and standing position. Further development is needed for other, more specific interventions.

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Effectiveness of virgin coconut oil and regular repositioning in preventing pressure ulcers in children

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ABSTRACT

Introduction: Pressure ulcers have adverse effects on health. Thus, early detection of damage to skin integrity is important for preventing the occurrence of pressure sores. Virgin Coconut Oil (VCO) is a nonpharmacological therapy that can be applied to overcome the problem of damage to skin integrity. Virgin coconut oil contains antioxidants and is rich in vitamin E. Meanwhile, two-hourly repositioning is a nursing intervention performed to prevent pressure ulcers.

Materials and Methods: This study aimed to evaluate the implementation of Virgin Coconut Oil and regular repositioning for preventing pressure sores. The designs used quasi experiment pretest and posttest nonequivalent control group; 86 participants were selected through a nonprobability sampling technique by consecutive sampling.

Results: The fundings suggest that there is a significant difference in the Braden QD scores from before and after virgin coconut oil of the intervention group and repositioning of the control group ($p < 0.001$).

Conclusion: Nurses are expected to be able to detect early damage to skin integrity by using the Braden QD Scale and to implement use Virgin Coconut Oil and repositioning.

KEYWORDS:

Braden QD, Pressure ulcer, Repositioning, Virgin Coconut Oil

INTRODUCTION

Pressure sores occur as a result of local injury to the tissue under the skin that occurs due to prolonged pressure.¹ The prevalence of pressure ulcers in children in Indonesia last 10 years was 2.25%.² Indonesia the incidence of pressure sores occurs due to the use of medical devices, such as the use of 13% ETT, 12% OGT, 11% NGT, and 6% oxygen saturation probe³ and the incidence of pressure ulcers in the pediatric units was in 2017 0,1% and in 2018 become 0.22%, the ulcers mostly appeared on children who had prolonged bed rest anak.⁴

Pressure ulcers are affected by tissue pressure and tolerance. Pressure intensity and the duration of being in a certain position could increase the risk of developing pressure ulcers.⁵ Pressure ulcers require a long healing process and might have risk of infection, prolonged hospital stay, decreased rest time,

increase the cost of hospitalization.⁶ One application of non-pharmacological therapy can be applied to overcome the problem of damage to the integrity of the skin, namely the administration of virgin coconut oil (VCO). VCO contains antioxidants and vitamin E.⁷ Besides that, regular repositioning could reduce pressure and prevent prolonged ischemia.⁸ it could be the most effective way to prevent pressure ulcers because it could modify pressure sores.⁴ Preventing pressure ulcers and repairing damaged tissue integrity are the main focus with regard to health services. Initial assessments are expected to prevent pressure ulcers.⁹ Early detection could be conducted by using the Braden QD Scale, which is an instrument that assesses the risk of pressure ulcers and predicts risky and risk-free clients. Nurses can use this tool to assess the risk of pressure injuries in pediatric patients.¹⁰

MATERIALS AND METHODS

The study designs were quasi experiment pre test and post test nonequivalent control group. The researcher assigned respondents into two groups. The intervention group was given virgin coconut oil and the control group was regular repositioning with 2-hourly repositioning should be given regularly within 24 hours. The provision of VCO is genuine coconut oil that has BPOM RI certification, Good Manufacturing Practice (GMP), ISO Factory Quality Management, and Halal Assurance Certificate. VCO is given to the back area, heels and areas of the body that are pressed against the surface, done once every day for 14 days or until the child can go home. The respondents were selected through a nonprobability sampling technique by consecutive sampling. The inclusion criteria were being aged between 1 month and 18 years and having a treatment length of 24 hours. The exclude criteria were children who were anxious, lacked cooperation, edema, and had previous pressure ulcers. The total sample of this innovation project involved 86 children. The instrument used in this study to collect data on questionnaire and Braden QD scores. The data analysis comprised univariate and bivariate analyses.

DISCUSSION

The study designs were quasi experiment pre test and post test nonequivalent control group. The researcher assigned respondents into two groups. The intervention group was given virgin coconut oil and the control group was regular repositioning with 2-hourly repositioning should be given

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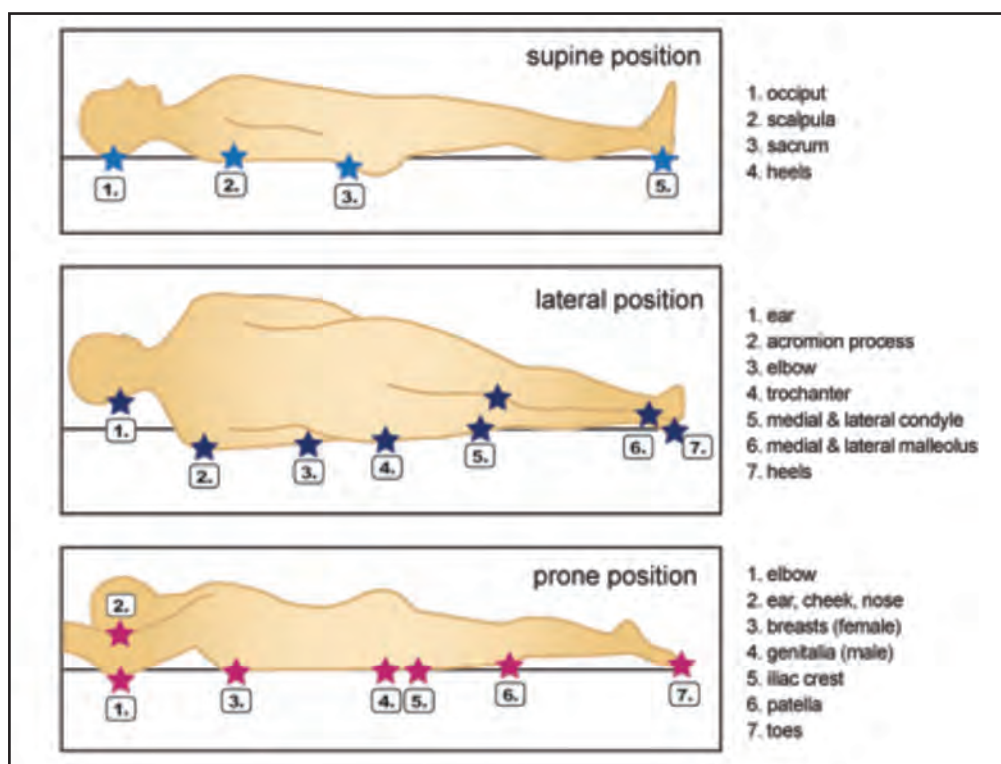
Table I: Respondents Braden QD Score

Group	Mean $\pm$ SD	CI 95%
Intervention		
Before	10.09 $\pm$ 2.266	9.40 – 10.79
After	8.44 $\pm$ 1.803	7.89 – 9.00
Control		
Before	10.02 $\pm$ 1.655	9.51 – 10.53
After	8.07 $\pm$ 1.470	7.62 – 8.52

Table II: Differences in Braden Q Scores Before and After Given Virgin Coconut Oil and Repositioning

Variable	Intervention			p	Control			p
	Mean	SD	95%CI		Mean	SD	95%CI	
Braden QD Score								
Before	10.09	2.266	1.266 ; 2.036	<0.001*	10.02	1.655	1.574 ; 2.333	<0.001*
After	8.44	1.803			8.07	1.470		

*Significant at $p < 0.05$



Locations at risk for pressure sores:

regularly within 24 hours. The provision of VCO is genuine coconut oil that has BPOM RI certification, Good Manufacturing Practice (GMP), ISO Factory Quality Management, and Halal Assurance Certificate. VCO is given to the back area, heels and areas of the body that are pressed against the surface, done once every day for 14 days or until the child can go home. The respondents were selected through a nonprobability sampling technique by consecutive sampling. The inclusion criteria were being aged between 1 month and 18 years and having a treatment length of 24 hours. The exclude criteria were children who were anxious, lacked cooperation, edema, and had previous pressure ulcers. The total sample of this innovation project involved 86

children. The instrument used in this study to collect data on questionnaire and Braden QD scores. The data analysis comprised univariate and bivariate analyses.

Based on the results of this study, it was found that giving VCO was effective in reducing the Braden QD score and there was a significant difference in the Braden QD score before being given VCO (10.09) and after (8.44) with a value of $p < 0.05$ and in the control group too there is a significant difference in the Braden QD score before (10.02) and after (8.07) with a $p > 0.05$. The intervention group was pediatric patients who received VCO given every day. VCO functions as an antioxidant and anti-stress, anti-inflammatory, analgesic, antipyretic, accelerates wound healing, repairs

damage to VCO contains 50.33% lauric acid, 14.32% capric acid, 10.25% caproic acid, 12.91% myristic acid and 4.92% palmitate which function as antimicrobials and are rich in vitamin E to prevent skin infections.¹³ Treatment by giving VCO to the back of the body is effective in reducing the risk of pressure sores in patients with chronic diseases who are treated in the inpatient unit.¹⁴

Positioning is one of the nursing interventions that nurses can perform independently to prevent the risk of damage to the integrity of the skin in children, especially in children who are immobilized due to neurological disorders, such as children with a medical diagnosis of encephalitis and hydrocephalus. In this study, those who experienced impaired motor function, so that nurses or parents needed patience in changing positions every 2 hours so that pressure sores did not occur.

The results of this study explained that in the intervention group with VCO administration there was a significant difference before being given VCO which was 10.09 and after giving VCO 8.44. Whereas in the control group with two hours of repositioning there was also a significant difference in the Braden QD score before that was 10.02 and after treatment 8.07 ($p < 0.05$). This shows that giving VCO and repositioning every 2 hours is effective in reducing the incidence of pressure sores in children.

The intervention group was pediatric patients who received VCO given every day. According to some experts, VCO has many health benefits, including being an antioxidant and anti-stress, anti-inflammatory, analgesic, antipyretic, accelerating wound healing, repairing damage to skin integrity, can lower blood pressure, increase immunity, can control blood sugar and reduce weight. bodies.⁷ VCO is pure coconut oil which is produced from processed meat on coconuts without heating so that they are protected from free radicals and are clear in color. VCO contains 50.33% lauric acid, 14.32% caprylic acid, 10.25% caproic acid, 12.91% myristic acid and 4.92% palmitate.¹³

Treatment by giving VCO to the back of the body is effective in reducing the risk of developing pressure sores in patients with chronic diseases who are treated in inpatient rooms.¹⁴ Other studies also explain that using VCO can prevent the incidence of pressure sores in patients in the Intensive Care Unit.¹⁵ VCO contains Medium Chain Fatty Acids (MCFA) which are fatty acids consisting of lauric acid, oleic acid, capric acid and caproic acid and functions as an antimicrobial. VCO that is used topically will react with skin bacteria to form free fatty acids such as those contained in sebum. Sebum consists of medium chain fatty acids such as those in VCO so that it protects the skin from the dangers of pathogenic microorganisms. Free fatty acids help create an environment which is acidic on the skin so that it can kill disease-causing bacteria.¹⁶ VCO also functions as an antioxidant which is rich in polyphenolic vitamin E which is useful for preventing skin infections and treating skin damaged by free radicals.¹³

Besides that, repositioning is also an effective step to prevent pressure sores, by positioning the client regularly to different positions, it can modify the area of pressure points. If the body is repositioned regularly, the lack of oxygen in the tissues will not last too long so that the risk of developing pressure sores is reduced. Every child who is at risk of experiencing prolonged bed rest in the hospital will be given a decubitus mattress. Provision of a decubitus mattress must still be accompanied by comprehensive care, without ignoring the risk of pressure sores due to prolonged bed rest. Therefore, giving decubitus mattresses alone is not enough as a measure to prevent pressure sores, but intervention by giving VCO and repositioning every 2 hours with attention to comfort in children needs to be done to avoid pressure sores in children.

The intervention group was given virgin coconut oil and the control group was regular repositioning with 2-hourly repositioning should be given regularly within 24 hours. The advantage of these two modalities is that they are equally easy to apply. Does not require special skills and can be applied by the patient's family. the disadvantage of providing VCO is that it requires additional costs by buying VCO oil, but it does not require expensive costs and is easy to obtain. Whereas for regular positioning every 2 hours does not require additional costs and tools, it only requires cooperation and discipline from parents who support the success of the intervention. The authors recommend these two interventions so that they can be applied as independent nursing interventions in preventing pressure sores in children.

CONCLUSION

Avoiding the occurrence of pressure sores and improving tissue integrity is the main focus of health services. An important implementation in preventing pressure sores is identifying the risk of pressure sores. The measurement tool used to assess damage to skin integrity is the Braden QD Scale which can predict the incidence of pressure sores in children which can predict the incidence of pressure sores in children which consists of 7 subscales, each subscale with a score of 0, 1, and 2. Values ≥ 13 patients are said to be at risk of HAPI (Hospital Acquired Pressure Injury). Administration of virgin coconut oil and two hours of repositioning effectively reduced Braden's QD score and thus these two interventions could be performed to prevent hospitalized children from developing pressure sores. The results of this evidence-based practice can be implemented as a nursing intervention to prevent pressure ulcers in children. The limitation of this study is that it requires the cooperation of parents to apply virgin coconut oil and 2-hour repositioning because it requires the cooperation of parents in providing regular repositioning every 2 hours.

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Preparation of decaffeinated coffee extract: study of the effectiveness of decaffeinated coffee extract toward lowering blood sugar in type 2 diabetes mellitus patients

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ABSTRACT

Introduction: Diabetes mellitus is a disease characterized by an increase in blood sugar levels due to abnormalities in the insulin hormone system. The number of people with this disease is expected to increase every year. Therefore, it is necessary to develop diabetes mellitus drugs that have effective performance in reducing blood glucose level. Coffee contain chlorogenic acid and caffeine. Chlorogenic acid play a role in increasing insulin sensitivity. However, the caffeine causes a decrease in glucose tolerance. The removal of caffeine or the decaffeination process is expected to improve the quality of coffee as an anti-diabetic drug. The aim of this study was to investigate the effectiveness of decaffeinated coffee extract in reducing blood sugar.

Materials and Methods: Green or roasted coffee extract was decaffeinated using activated charcoal. Decaffeinated coffee extract with the lowest caffeine and the highest chlorogenic acid based on HPLC measurement was used for anti-diabetic test. The anti-diabetic test was conducted with 52 DM type 2 patient selected by purposive sample. The test were divided into two groups: intervention (26 respondents) and control group (26 respondents). The data were analysed by Paired and Independent t test.

Results: Decaffeinated green coffee extract is very suitable for use as a drug to lower blood sugar in DM type 2 patients than decaffeinated roasted coffee extract because of higher in chlorogenic acid and lower in caffeine (Figure 2). Treatment by decaffeinated green coffee extract for 3 weeks showed a significant decrease in average fasting blood glucose level from 144.7 g/dl to 92.23 g/dl. All statistical tests showed a p value = 0.001 (below the significant value), this value proves the success of reducing blood glucose by decaffeinated green coffee extract.

Conclusion: The decaffeinated green coffee extract decreases fasting blood sugar significantly.

KEYWORDS:

Green coffee, roasted coffee, chlorogenic acid, blood sugar

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease caused by insulin resistance and pancreatic B-cell dysfunction.

According to WHO, DM affects 463 million patients worldwide¹, a number expected to grow to 592 million by 2035.² DM is high risk for stroke, kidney disease, heart and vascular disease, thus seriously affecting the quality of life and even death.¹ However, the cost of treating diabetes is relatively expensive.³ Therefore, it is necessary to develop inexpensive and effective diabetes drugs to lower blood sugar. Coffee is a commonly consumed beverage around the world; it consists of two main components, caffeine and chlorogenic acid. Raw coffee beans without the roasting process are generally called green coffee. Green coffee contains lower caffeine than roasted coffee.⁴ Meanwhile, the content of CA in green coffee is much higher than roasted coffee.⁵ Studies related to the effect of caffeine on lowering glucose have been carried out. Caffeine causes a decrease in insulin sensitivity, causing a decrease in glucose tolerance.⁶ Meanwhile, CA plays a role in preventing insulin resistance so that it triggers a faster decrease in blood sugar.^{7,8}

Decaffeination is a caffeine adsorption process so that there is a decrease in caffeine levels in solution. Several studies showed the ability to absorb caffeine using activated carbon.⁹⁻¹¹ The ability to absorb activated carbon is due to the pores spread over the entire surface, large surface area, and the presence of functional groups such as hydrosil (OH), carboxylate (COOH) and carbonyl (C=O).¹¹⁻¹³

In this study, the effectiveness of decaffeinated coffee extract was tested in reducing blood sugar of patients with type 2 diabetes mellitus. Treatment was carried out for 3 weeks. Blood sugar measurement using a glucometer before and after treatment with decaffeinated coffee extract.

MATERIALS AND METHODS

Material

This study uses Aceh Gayo green and roasted coffee, activated charcoal and demineralised water.

Methods

Preparation of Decaffeinated Coffee Extract

Green coffee and roasted coffee are ground using a grinder to a size of 20 mesh. Finely ground coffee weighed 200 g. Fine coffee grounds are dissolved in 80°C demineralized water. The stirring process was carried out for 30 minutes. The coffee solution obtained is filtered to separate the insoluble coffee grounds. The filtered coffee solution was added with 200 g of

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Table I: Distribution of respondents based on age (n = 52)

	Intervention group	Control group
Mean	55.1	46.09
Standar Deviasi	13.69	10.62
Min – Max	22 - 87	26 - 65
CI 95 %	49.63 - 60.68	41.79 - 50.37

Table II: Analysis of the effect of decaffeinated coffee extract in the intervention group

Glucose level	Intervention group (g/dL)			Control group (g/dL)	
	Pre-treatment	Post-treatment		First	Post
Mean	144.7	92.23	Mean	151.73	128.35
SD	26.35	16.38	SD	38.30	38.53
Min–Max	112–201	52–132	Min-Max	76–200	61–200
95 % CI	134.09–155.37	92.01–105.85	CI 95 %	135.2–167.20	112.78–143.91

Table III: Analysis of differences in fasting blood glucose level between intervention and control groups

Group	Mean	SD	SE	p value	N
Intervention	99.23	16.38	3.21	0.001	26
Control	128.35	38.53	7.55		26

Table IV: Analysis of differences in fasting blood glucose level between pre and post treatment

Group	Mean	SD	SE	p value	N
Pre Treatment	148.23	32.73	4.54	0.001	26
Post treatment	99.23	16.38	3.21		26

activated charcoal. Stirring the mixture of coffee and activated charcoal solution was carried out for 30 minutes at 80°C. After 30 minutes, the decaffeinated coffee solution is refrigerated for 8 hours to maximise caffeine adsorption. After 8 hours of standing, the decaffeinated coffee solution was separated from the undissolved activated charcoal with Buchner filter. Then continued by HPLC testing, which was used to determine the levels of chlorogenic acid and caffeine before and after decaffeination.

Anti-diabetic Test of Decaffeinated Coffee Extract

The Quasy Experiment, pre-post with control group, was conducted among 52 respondents (type 2 DM) that were selected by purposive sampling. Decaffeinated Green coffee was carried out orally on 26 respondents who suffered from type 2 of DM for 3 weeks with a dose of 4 tablespoons every day. Blood sugar was measured with a glucometer before and after treatment (day 21). Paired t test was conducted to determine the effect of giving decaffeinated green coffee extract in the intervention group.

RESULTS

Preparation of Decaffeinated Coffee Extract

Based on Figure 1, the dissolved caffeine in roasted coffee (729.16 ppm) is higher than in green coffee (214.46 ppm). This is because the caffeine content in green coffee beans is lower than roasted coffee beans.^{4,14} Caffeine content decreased after decaffeination. Caffeine in roasted coffee extract decreased from 729.16 ppm to 442.54 ppm. Caffeine

in green coffee extract decreased from 214.46 ppm to 163.61 ppm. The porous surface and the content of hydroxyl (-OH) and carboxylate (-COOH) functional groups in activated charcoal play a role in the adsorption of caffeine in coffee extract.¹⁵ The possible interaction is hydrogen bonding between the -OH group in activated carbon with the C=O group or the N atom in caffeine.⁹

Green coffee extract showed more chlorogenic acid content than roasted coffee (Figure 2). These results are in accordance with research conducted by previous studies.⁵ This is because chlorogenic acid is a phenolic compound that is very sensitive to temperature. Roasting will cause damage to the structure of chlorogenic acid.⁷ Figure 2 also shows that caffeine in roasted coffee extract is higher than green coffee extract. However, the content of chlorogenic acid in green coffee extract showed a higher value than roasted coffee. Decaffeinated green coffee extract is very suitable for use as a drug to lower blood sugar in DM patients than decaffeinated roasted coffee extract. Therefore, Antidiabetic testing of type 2 DM patients will only be carried out using decaffeinated green coffee extract.

Anti-diabetic Test of Green Coffee Extract

Based on Table I, the average age of the respondents in the intervention group was 55 years with a SD of 13.69 years, the youngest age was 22 years, and the oldest was 87 years. While in the control group, the average age of respondents is 46 years with a SD of 10.62 years, the youngest age is 26 years and the oldest is 65 years.

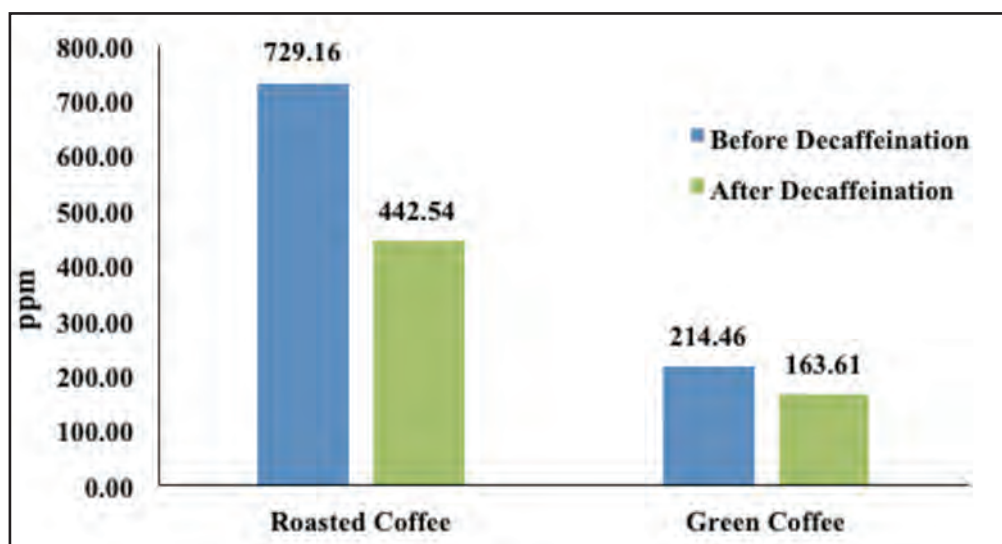


Fig. 1: Comparison of caffeine level before and after decaffeination

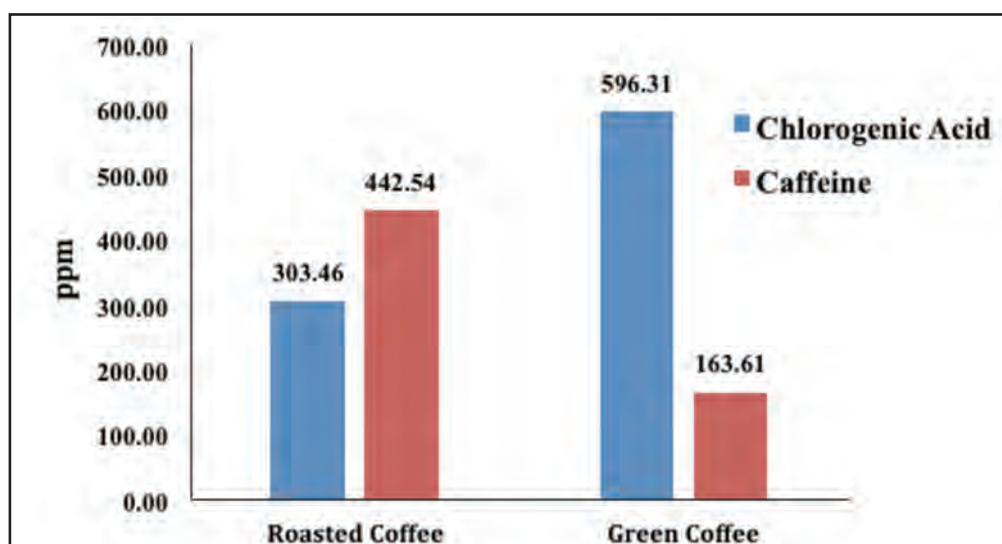


Fig. 2: Comparison of chlorogenic acid and caffeine after decaffeination

Table II showed that the the average of intervention group fasting blood glucose level before treatment was 144.7 g/dl and decreased to 92.23 g/dl. The average of fasting blood glucose level in control group was 151.73 g/dl then in the post decreased to 128.35 g/dl.

Table III showed the average fasting blood glucose level of the intervention group was 99.23 gr/dl with a standard deviation of 16.38 gr/dl, while in the control group the average fasting blood glucose level was 128.35 gr/dl with a standard deviation of 38.53 gr/dl. The results of the statistical test obtained a p value of 0.001. It can be concluded that there is a significant difference in the fasting blood glucose level of intervention group and the control group. So it can be concluded that the treatment of decaffeinated green coffee extract has an effect on decreasing fasting blood glucose level.

Table IV showed the average fasting blood glucose level in the pre-intervention measurement was 148.23 gr/dl with a standard deviation of 32.73 gr/dl, while in the post-intervention measurement the average fasting blood glucose level was 99.23 gr/dl with a standard deviation of 16.38 gr/dl. The results of the statistical test obtained a p value of 0.001 so it could be concluded that the treatment of decaffeinated green coffee extract had an effect on decreasing fasting blood sugar.

DISCUSSION

There was a decrease in blood sugar after giving decaffeinated green coffee extract in the treatment group. Decaffeinated green coffee extract contains chlorogenic acid with low caffeine. Chlorogenic acid inhibits the activation of the glucosidase enzyme so that there is a decrease in the breakdown of carbohydrates into glucose.¹⁶⁻¹⁸ Caffeine has a negative effect in the form of decreasing insulin sensitivity

which interferes with glucose tolerance and increases blood glucose.^{6,16} Therefore, the low caffeine in green coffee extract increases its activity in lowering blood sugar.⁷ Chlorogenic acid prevents insulin resistance so that it triggers a faster decrease in blood sugar.^{7,8} Chlorogenic acid also repairs the pancreas damaged by diabetes.¹⁹ This compound is useful to prevent insulin resistance so that it triggers a faster decrease in blood sugar levels.²⁰ Chlorogenic acid reduces blood glucose adsorption by interfering with the active transport of glucose and increasing insulin secretion by pancreas. However, Chlorogenic acid has low stability and bioaccessibility, resulting in slower metabolism.²¹

This study is in line with research conducted by Zuñiga et al. (2018), Chlorogenic Acid also played a role in reducing fasting blood sugar that occurred in 15 patients with diabetes melitus type 2 who had been treated 3 times a day for 12 weeks in a randomized, double-blind, placebo-controlled clinical trial. In another clinical trial conducted by Roshan et al. (2018), chlorogenic acid also played a role in reducing fasting blood sugar in 21 patients with diabetes melitus type 2 with treatment 2 times a day for 8 weeks.

If a comparison is made to some of the literature, this study is superior based on the time of decreasing fasting blood sugar. Some literature shows that decreasing fasting blood sugar with chlorogenic acid treatment takes more than 1 month. Meanwhile, in this study it only took 3 weeks. This proves that the process of removing caffeine (decaffeination) is very influential on the speed of decreasing fasting blood sugar. However, this study was limited to type 2 diabetes mellitus patients. Treatment of patients with type 1 diabetes mellitus needs further research. Type 1 diabetes mellitus shows more severe pancreatic damage so that insulin production cannot be done at all.

CONCLUSION

Decaffeinated roasted coffee extract contains lower CA than green coffee extract. Decaffeinated green coffee extract showed a significant decrease in fasting blood sugar level on the Paired t test. There is a difference in blood sugar reduction between respondents in the intervention group and the control group based on the Independent t test.

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The impact of COVID-19 pandemic: daily work stress and work performance between work from home (WFH), work from office (WFO) and hybrid in Indonesia

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ABSTRACT

Introduction: The purpose of this research aimed to investigate the difference between daily work stress and work performance in respondents who work from home (WFH), office (WFO), or vice versa on a scheduled basis during the pandemic COVID-19 period.

Materials and methods: A total of 400 respondents were recruited, from all over the province in Indonesia. Instruments utilized were structured questionnaires including a demographic questionnaire, work performance scale (WPS), daily work stress scale. The design used was cross-sectional with a nonprobability sampling method and the data analysis with Chi-Square. The respondents were 400 respondents.

Results: Shows that both respondents who had high, moderate, and low-stress levels on work from home ($p>0.001$), work from office ($p>0.001$), and Hybrid ($p>0.001$). Respondents also had good work performance with all varied work methods.

Conclusions: Based on this research, each worker has more varied work stress, even though they still carry out their jobs well, and have good performance.

KEYWORDS:

Pandemic COVID-19, Daily Work Stress, Work Performance, Mental Health Workers

INTRODUCTION

The 2019 Corona Virus Disease (COVID-19) was declared a Covid-19 Pandemic by the World Health Organization (WHO) on March 11, 2020.¹ President of Indonesia through Presidential Decree of the Republic of Indonesia Number 12 of 2020 concerning the Determination of Non-Natural Disaster of the Spread of COVID-19 as a National Disaster.^{2,3} When there is a change in the scheduling of working from home and in the office, four problems arise, namely the psychological contract, the emergence of mistrust which the individuals feel distrusted that they are working, third, the emergence of workplace disruptions and finally the conflict between work life and home life.⁴ Stress also arises due to repetitive or monotonous behaviors, such as the stress of performing office work at home with the distraction of the home environment, reduced physical activity, and increased

screen viewing.⁵ Some things that cause stress when working in an office, especially a service, tourism, or hospitality office during a pandemic such as, anxiety over work termination, a quiet work environment, work boredom due to decreased mobility.⁶ Research conducted in the United States shows that from 1,165 workers, around 17.8% reported having anxiety and depression, as many as 5.8% experienced only symptoms of anxiety, and 4.5% experienced symptoms of depression. Predictors that cause this to happen are the fear of transmission from life-threatening COVID-19, family financial threats, because during the COVID-19 period there were many employee termination, and the third is the stressful atmosphere of the office or workplace.⁷ Stress that occurs due to working during the COVID-19 pandemic can cause anxiety that reduces sleep quality, which reduces work quality.⁸

This will affect the work performance of workers. Individual work performance is influenced by the type of work profession performed, work shift, work pressure, work-family conflict, practice environment satisfaction, and salary satisfaction.⁹ Or on the contrary, the COVID-19 pandemic has also changed working methods that can improve the performance of workers, especially young workers because based on research that the signatures faced by workers are difficulties in getting up early, using public transportation etc. can be resolved by working at home.¹⁰

MATERIALS AND METHODS

This research is a quantitative study with a cross-sectional method. This study aims to see the relationship of stress experienced by workers to the work performance of workers in Indonesia, whether WFO, WFH, or scheduled WFO and WFH during the COVID-19 Pandemic. Research respondents were workers from 34 provinces in Indonesia with inclusion criteria outside who did not experience shift changes at work during the Pandemic. Sampling using random sampling with respondents who participated in this study were 400 respondents. Respondent data received was processed using the univariate test, namely the frequency distribution test and central tendency and bivariate test using the chi-square test. This research was conducted for approximately one year and data collection started in May 2021.

The questionnaires used were three questionnaires, namely questionnaire A of respondent characteristics, the

Table I: Overview of impacts experienced by workers during WFH and WFO in Indonesia (n=400)

Variable	Total	Percentage (%)
The impacts felt during WFH		
Saturated	193	48.25
Working over working hours	192	48
Gadget addiction	144	36
Difficult to manage time	141	35.25
Decreased eye health	126	31.5
Workload increased	113	28.25
Increased daily cost of living	113	28.25
Weight gain	90	22.5
Work not finished	76	19
No barriers	15	3.75
The impact felt during the WFO		
Worried about the health of yourself and your family	336	84
Lots of health protocols	172	43
Cost of purchasing personal supplements (excluding the company's responsibility)	149	37.25
Routine swabs	107	26.75
Difficult to coordinate staff scheduling	45	11.25
No barriers	5	1.25

Table II: Analysis of the relationship between daily work stress and work performance in WFH (n=57)

Variable Independen Daily Work Stress	Variable Dependen Work Performance		p value
	Pre-treatment	Post-treatment	
Moderate	2 (18.2)	9 (81.8)	0.809
Low	7 (15.2)	39 (84.8)	
Total	9 (15.8)	48 (84.2)	

Table III: Analysis of the relationship between daily work stress and work performance in WFO (n = 143)

Variable Independen Daily Work Stress	Variable Dependen Work Performance		p value
	Moderate, No (%)	Good, No (%)	
High	0	1 (100)	0.006
Moderate	7 (46.7)	8 (53.3)	
Low	2 (1.6)	125 (98.4)	
Total	9 (6.3)	134 (93.7)	

Table IV: Analysis of the relationship of daily work stress with work performance in scheduled work methods between WFO and WFH (n=200)

Variable Independen Daily Work Stress	Variable Dependen Work Performance		p value
	Moderate, No (%)	Good, No (%)	
High	0	2 (100)	0.336
Moderate	4 (10.3)	35 (89.7)	
Low	7 (4.4)	152 (95.6)	
Total	11 (5.5)	189 (94.5)	

questionnaire B was a questionnaire to measure work performance developed by Koopmans 20141 has a Cronbach alpha value of 0.92 and $r = +0.83$ with a total of 21 questions. This questionnaire has been used and adapted in research in Indonesi. Questionnaire C is a questionnaire that measures daily work stress developed by Lait & Wallace this questionnaire has six questions and has an alpha-Cronbach value of 0.921. This research also pays attention to ethical principles, and has been reviewed.

DISCUSSION

The impact of Work From Home experienced by workers at the top of the list is that workers feel bored (48.25%), work beyond working hours (48%), dependence on gadgets (36%), difficulty managing time between work and distractions that occur at home (35.25%), and decreased eye health (31.5%). This is in accordance with the results of research conducted by Woodruff that stress also arises due to repetitive or monotonous behavior, this will lead to boredom, by doing the same activities every day and doing it at home,

distraction when doing work can cause individuals to find it difficult to do work, decreased activity, only looking at the gadget screen so that the majority of activities are carried out sitting so that weight increases and eye health decreases because in a day of working hours or even more just looking at the screen. The results of this study also show that WFO workers are worried about the health of themselves and their families (84%), many health protocols (43%), the cost of purchasing personal supplements (outside of company coverage) (37.25%), routine swabs (26.75%), difficult coordination of staff scheduling (11.25%)¹¹ States that 75% of IDN Times survey results for workers in Indonesia show that they think working from the office provides easy coordination, communication, more focused, and life between work and home is not mixed. WFO causes anxiety about their own health and family status, death threats, paranoid thinking to colleagues, who suspect the viruses until it appears absent problem and continues by declining the work performance.¹²⁻¹⁴ Even this concern caused 5.8% of anxiety, 4.5% of depression due to the fear of being infected by the virus, but workers must continue to work for the sake of their economic survival.⁷

The results of this study are very interesting because both individuals who have moderate, low and high stress levels by working WFO, WFH, or alternate entry scheduling have good work performance. Another study also mentioned that both working at home and in the office have the same efficiency in achieving performance.¹⁵ There are several things that cause workers to continue to have good work performance such as concerns about not having a job or termination of employment, 6, Professions/job desk, work shifts, work pressure, work-family conflict, practice environment satisfaction, and salary satisfaction.⁹ So it can be said that stress is only one of the factors that influence but not the main problem, there are other things that may be the cause of why in this study work performance remains good, further research needs to be done to find out other factors that cause work performance to always be good.

The important thing to note from the results of this study is that there are workers who experience high stress, but still carry out tasks well, this could be because respondents have good stress management or good emotional intelligence.¹⁶ Stress that occurs based on this research cannot be ignored or not handled by the company because stress can become anxiety and develop into depression and other psychiatric problems. In the end the company will lose workers due to physical or psychological health problems. WFH workers can still achieve the expected work targets and in terms of benefits, the company can also consider efficiency in the aspect of energy by around 25% compared to before the Covid-19 pandemic. Emissions dropped 7 times smaller than emissions in 2009 where it is estimated to be the lowest emission period, namely the economic crisis.¹⁷⁻²⁰ From the aspect of workers, many workers also hope to continue working by telecommuting even though the COVID-19 pandemic has ended because it is considered more efficient and not time consuming to get to the office.²¹ Other research also states that both working at home and in the office have the same efficiency in achieving performance.¹⁵ Moreover, providing the option to WFH to workers may encourage them

to act in their own best interest and remain committed to their employers, increasing employees' intrinsic motivation and reciprocal behavior.²²

CONCLUSION

This study illustrates that there is no significant relationship between daily work stress and Work Performance in workers. Work performance of workers is in good condition despite high levels of stress. However, the company must also pay attention to the mental health of workers because untreated stress will drag on into severe psychological problems and result in burn out. Good work performance from each method can be considered as a determination to become a provision that has a standard implementation procedure.

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Factors associated with the functional balance among diabetes mellitus patients in Padang, Indonesia

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ABSTRACT

Introduction: One of the common problems in patients with diabetes mellitus is a decrease in balance stability. A decrease in balance stability will result in functional limitations, an increased risk of falling and injury and a decrease in patient productivity. This study aimed to analyse the factors associated with functional balance in diabetes mellitus patients in Padang, Indonesia.

Materials and Methods: This research design is cross-sectional. The number of samples in this study was 132 diabetes mellitus patients. Chi-square test and binary logistic regression were used to examine the factors associated with functional balance in diabetes mellitus patients.

Results: Factors associated with functional balance in diabetes mellitus patients were age.

Conclusion: This study highlights that age, gender and degree of neuropathy are significant factors associated with functional balance in diabetes mellitus patients. Nurses must enhance health education about prevention and risk factors that affect functional balance in diabetes mellitus patients.

KEYWORDS:

Diabetes mellitus, functional balance

INTRODUCTION

In 2019, the International Diabetes Federation (IDF) estimates that there will be 436 million people aged 20–70 years in the world suffering from type 2 DM in 2019 or equivalent to 9.3% of the total world population at the same age.¹ The prevalence of type 2 DM in Indonesia in 2020 reached 6.2%, meaning that there are more than 10.8 million people suffering from type 2 DM in 2020.¹

Increased blood glucose levels (hyperglycaemia) in patients with type 2 DM can cause various problems in patients. Exposure to chronic hyperglycaemia results in ischaemia of the nerves and changes in nerve function, causing functional balance disorder. Functional balance is the body's ability to maintain balance in a certain position or perform movements either statically or dynamically.² Balance processes that are regulated by the cooperation of sensory nerves, motor and biomechanical processes experience

changes due to hyperglycaemia. The sensory system which consists of the vestibular system, proprioceptive system and visual system has decreased function in DM. Nerve damage in DM patients includes microangiopathy complications.³ Chronic hyperglycaemia conditions cause vestibular dysfunction in maintaining body balance.⁴

Functional balance disorder in diabetes mellitus patients is one of the causes of the risk of falling in diabetic patients.⁵ The results of previous studies showed that many patients with diabetes experienced functional balance disorders. The balance score with the Berg Balance Scale (BBS) in diabetic neuropathy patients was lower, namely 40.5. This means that patients with diabetic neuropathy experience functional balance disorders, because the normal functional balance based on BBS is 46 – 56.⁶ The results of Asif and Batool's research 75.5% of DM patients show balance disorder based on the results of the Timed Up and Go (TUG) test. The results of a study by Cordeiro et al in 2009 showed that factors related to functional balance in elderly people with diabetes were age, daily activities, step strategy, and proprioceptive sensitivity.⁷ Several research results have explained that balance disorders are more common in patients with diabetes, but are still limited in explaining the factors that influence these functional balance. Based on the existing problems, this study will look further at the factors related to functional balance in DM patients.

MATERIALS AND METHODS

In this cross-sectional, non-interventional study, we enrolled 132 patients previously diagnosed with type 2 diabetes, attending scheduled visits in the Dr. M. Djamil Hospital, Padang, Indonesia. Purposive sampling was used for data collection. At the time of the screening patients, the following were considered exclusion criteria: not ability to provide informed consent, patients with foot edoema, patients with foot ulcers, patients with hearing loss.

The instrument used in this study was a respondent characteristic questionnaire which included age, gender and duration of DM. Blood glucose control is seen based on the HbA1C value. HbA1C <6.5% is defined as controlled blood glucose. The degree of neuropathy is the severity of neuropathy based on the result of a physical examination using MNSI (Michigan Neuropathy Screening Instrument) guidelines. Physical examination consisting of examination of foot appearance, ankle reflexes, vibration perception and

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foot sensitivity. Each physical examination item has a score range of 0 – 1, so the total score range is 0 – 10. The degree of neuropathy is categorized based on total score. The total score >2 – 4.5 is categorized as mild, >4.5 – 7.5 as moderate and >7.5 as severe neuropathy. Functional balance is the body's ability to maintain a position statically or dynamically. Functional balance is assessed with the BBS instrument (Berg Balance Scale). The subject was ordered to make movements and maintain positions according to BBS guidelines. The Berg Balance Scale consists of 14 assessment items and has a score range of 0 to 4 per item. Total score 0 – 56. The total score 46 – 56 is categorized as normal and 0 – 45 as disorder. The study design, protocol and informed consent form were reviewed and approved by the Ethics Committee of Faculty of Nursing, Indonesian University (Number : 0417/UN2.F12.D/HKP.02.04/2016); all patients provided written informed consent prior any study procedure or activity.

Statistical Analysis: IBM SPSS statistics version 26.0 was used to analyse the data. The data were presented descriptively. Chi-square test was used for bivariate analysis. Logistic regression analysis determined the association between the independent variables and identified determinant factors associated with functional balance in diabetes mellitus patients.

RESULTS

A total of 132 diabetes mellitus patients were recruited in this study. The prevalence of functional balance disorder among respondents was 40,90% (54 out 132 respondents). The univariate and bivariate analysis result of this study can be seen in the following table :

The univariate and bivariate analysis in Table I shows that the majority of the respondents with functional balance disorder were aged > 65 years old (51.06%), duration of DM > 5 years (42.85%), female (50.70%), uncontrolled blood glucose (45%), overweight (47.80%) and severe neuropathy degree (76.30%). The majority of the respondents with normal functional balance were aged > 65 years old (48.94%), duration of DM > 5 years (57.14%), male (70.49%), uncontrolled blood glucose (55%), normal BMI (73.60%) and mild neuropathy degree (85.50%).

The multivariate analysis in Table II shows age (OR = 6.89 95% CI = 2.03–23.46, $p = 0.002$), gender (OR = 2.58 95% CI = 1.02–6.53, $p = 0.046$) and degree of neuropathy (OR = 4.48 95% CI = 2.47–8.11, $p = 0.000$) are significant factors associated with functional balance in diabetes mellitus patients.

Table I: Univariate and bivariate analysis of factors associated with the functional balance in patients with diabetes mellitus (N=132)

Factors	Functional balance				p value
	Normal		Disorder		
	n	%	n	%	
Age					0.000
< 65 years	32	84.21	6	15.79	
> 65 years	46	48.94	48	51.06	
Duration of DM					0.281
< 5 years	14	70.00	6	30.00	
> 5 years	64	57.14	48	42.85	
Gender					0.014
Male	43	70.49	18	29.51	
Female	35	49.30	36	50.70	
Blood glucose control					0.040
Controlled	18	78.30	5	21.70	
Not controlled	60	55.00	49	45.00	
BMI					0.010
Underweight	4	33.30	8	66.70	
Normal	39	73.60	14	26.40	
Overweight	35	52.20	32	47.80	
Neuropathy degree					0.000
Mild	53	85.50	9	14.50	
Moderate	16	50.00	16	50.00	
Severe	9	23.70	29	76.30	

Table II: Multivariate analysis of factors associated with the functional balance in diabetes mellitus patients (n=132)

Factors	B	Wald	p value	OR	95% CI
1	Age	1.93	9.55	0.002	6.89 2.03–23.45
2	Duration of DM	–0.48	0.47	0.492	0.62 0.16–2.41
3	Gender	0.95	3.97	0.046	2.58 1.02–6.53
4	Blood glucose control	0.17	0.05	0.820	1.18 0.28–5.02
5	BMI	0.49	3.29	0.069	1.63 0.96–2.76
6	Neuropathy degree	1.49	24.42	0.000	4.48 2.47–8.11

DISCUSSION

In this study, factors associated with functional balance in diabetes mellitus patients were age, gender, and degree of neuropathy. Nemmers and Miller's research in 2008 showed that age had a significant relationship with the Berg Balance Scale score with a value of $r=-0.438$ and $p<0.0001$. Increasing age shows a decrease in the Berg Balance Scale score, meaning that increasing age increases functional balance disorders.⁸ Increasing age will cause a decrease in the function of the body's systems, including the body's function in controlling balance. The decline in balance ability with age is caused by changes in the sensory, motor and central nervous system. The process of degeneration in the vestibular system will result in balance disorders in the elderly.^{9,10}

In this study, it was also found that the percentage of balance disorders was higher in women than men. Theoretically, there is no effect of gender on functional balance disorders. Research by Chaiwanichsiri et al in 2008 showed that gender was not related to balance function and the incidence of falls in the elderly. But if it is associated with changes in bone metabolism in women when they enter menopause, it is found that the decrease in estrogen affects the occurrence of bone fragility. Fragility of the bones in the feet causes an increased risk of injury or falls in postmenopausal women.¹¹

The results showed that the degree of neuropathy affects the functional balance of diabetic patients. Palma et al. study in 2012 concerning postural control and functional balance in patients with diabetic neuropathy showed that there was a relationship between the severity of neuropathy and the occurrence of functional balance disorders in diabetic neuropathy patients.¹² The research results of Lim et al. in 2014 regarding a comparison of the ability to maintain balance between type 2 DM patients with neuropathy and without neuropathy in 60 respondents concluded that there was a decrease in dynamic balance stability in DM patients.¹³ The process of body balance is regulated by the cooperation of the sensory, motor and biomechanical nervous systems. In neuropathy, the sensory nervous system which consists of the vestibular system, proprioceptive system and visual system experience decreased function. This decrease in the function of the nervous system will lead to a decrease in the ability to regulate balance functions.^{2,12}

CONCLUSION

Factors related to functional balance in DM patients are age, gender and degree of neuropathy. The most dominant factor affecting functional balance in DM patients is age. To reduce functional imbalance, patients need to control the complications of neuropathy which can lead to functional imbalance. Nurse must enhance health education about prevention and risk factors that affect functional imbalance.

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CONFLICT OF INTEREST

Conflicts of interest have not been disclosed by any authors.

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The differences in development between stunting and normal children at the age of 3–72 months

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ABSTRACT

Introduction: Globally, there were around 22% of children under the age of 5 suffer from stunting. The Asian region contributes around 21.8% of the world's stunting cases. This study aims to looked at the differences in development between stunted and normal children at the age of 3–72 months.

Materials and methods: This type of research used an analytic observational approach with a cross-sectional design. The research variables were the child development and stunting. The sample were 130 respondents. Data were analysed with chi-square test.

Results: The results showed that stunted children were 5.525 times more at risk of getting “deviated/doubtful” development screening results than normal children (OR= 5.525; 95% CI= 2.488–12.268; p-value <0.001).

Conclusion: It can be concluded that there were developmental differences between stunted children and normal children.

KEYWORDS:

Child development, stunting, normal

INTRODUCTION

Globally, there are 149.2 million children or almost a quarter of the number of children under the age of 5 suffering from stunting. Asia contributed to as many as 79 million stunting cases of the world's stunting cases.¹ Likewise, what is happening in Indonesia, especially in the West Sumatra province, is known that in 2021, the highest cases of stunting occurred in Pasaman Regency with the prevalence of short toddlers is 30.2%.^{2,3} In Primasari et al, out of 12 sub-districts in Pasaman Regency, the Pegang Baru Public Health Center in Panti District has a fairly high stunting percentage of 16.8%.⁴

In accordance with the Guidelines for Implementation of Stimulation, Detection and Early Intervention on Child Growth and Development at the Basic Health Service Level, Child Development Monitoring can be assessed with Kuisisioner Pra Skrining Perkembangan (KPSP) instrument. The KPSP instrument recommended by the Ministry of Health of the Republic of Indonesia.⁵ Stunting is a condition where a

child's growth is stunted, which is caused by chronic malnutrition which can make a child shorter than his age. Chronic malnutrition causes failure to thrive in children. Failure to thrive in children can cause cognitive, language and motor developmental disorders in children that are not in accordance with the child's developmental age.⁶ To optimize children's development, every child needs to be given stimulation to stimulate cognitive, language and motor skills. Stimulation to children can be given by mothers, fathers and other family members. Children's brain tissue, especially at the age of five, which gets stimulation can develop 80% at the age of 3 years. If a child never gets stimulation, his brain tissue may shrink or not develop optimally.⁷ Based on the results of Primasari et al, it was found that there were differences in the development of fine motoric and gross motoric skills between stunted toddlers and normal toddler.⁴ According to the Kuisisioner Pra Skrining Perkembangan (KPSP) instrument, children's development is assessed based on four aspects, namely, fine motoric, gross motoric, social independence and speech language.⁵ So, in this study, the researchers wanted to see the differences in the development of stunted children and normal children related to these four aspects.

MATERIALS AND METHODS

This study used an analytic observational approach with a cross-sectional design. This research has the scope of looking at the differences in development between stunted and normal children at the age of 3–72 months. This research was conducted in The Working Area of The Pegang Baru Public Health Center, Pasaman Regency. The sample size in this study was calculated using the following Daniel's formula.⁸ The number obtained from the results of the minimum sample calculation was 130 respondents. The time of the research was carried out from April to September 2020. The sampling technique was carried out by accidental sampling. That was carried out on children who came to Posyandu during the data collection process on August, 10–13th 2020. The research variables were the child development and stunting.

The operational definition of stunting in children in this study was seen from resulting in low height-for-age at <-2SD. Height-for-age is one of the indices for measuring nutritional status (Body Length per Age) which is a way of determining the incidence of stunting with the results of examinations

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with categories namely very short (< -3 SD), short (-3 SD to -2 SD) and normal (-2 SD to 2 SD) and high (> 2 SD). The operational definition of child development in terms of 4 aspects (fine motoric, gross motoric, social independence and speech language), that's measured by KPSP instrument. The KPSP measurement results consist of deviations if the number of yes answers < 6 . Doubtful if the number of yes answers = 7-8 and normal if the yes answer = 9-10.⁵ Inclusion criteria in this study were willing to become respondents, aged 3-72 months according to the age category measured on the KPSP questionnaire, healthy children, children and parents cooperative during the examination. Exclusion criteria in this study were children who did not come to posyandu at the time of data collection. There was no drop out in this study. The statistical test used was chi-square test with a 95% confidence level ($\alpha=0.05$). Data were analysed using SPSS 17.

RESULTS

From the 130 respondents in this study, 46 people were identified as stunted and 84 people were normal. The characteristics of the respondents can be seen in Table I and Table II. Based on table I can be known that the average age of children, who be respondent is 33.33 ± 19.24 months. The smallest age of respondent is 3 months and the highest is 72 months.

From Table II, it is known that more than half respondent have male gender, both in groups children identified as stunting (54.3%) and normal children (51.2%). More than half (63.8%) of the children who became respondent was 1st and 2nd child on number of siblings. Viewed from history of birth weight there were 3.1% (4 people) of children who experienced in Low Birth Weight (LBW) < 2500 grams, 3 of them found in children with stunting category and 1 of them in normal children. In the group of children with stunting, there were 37% had very short height and 63% with height short in accordance her/his age.

From Table III, it is known that the results of KPSP screening, on stunting children were found almost half (41.3%) have "doubtful" fine motoric screening results and "doubtful" developmental screening results were also found in a small part (6%) of normal children. In the gross motor development screening results for the group of children with stunting, 4.3% found the results "deviation" and 34.8% "doubtful". Whereas in the group of normal children there were no "deviation" screening results, however, there was a small proportion (14.3%) whose screening results were "doubtful". In the aspect of social development and independence, 2.2% of stunted children were found with "deviation" screening results and 8.7% "doubtful". In normal children's screening results there were no "deviations" screening results, it's just that in normal children there were 9.5% with "doubtful" screening results. Viewed from the screening results for language and speech development, 21.7% of the results were "doubtful" in the stunting group and 9.5% of the results were "doubtful" in normal children.

In terms of the results of the KPSP assessment as a whole, it was found that a small portion (8.7%) had "deviation" results and almost half (47.8%) had "doubtful" results in the

stunting group. Whereas normal children are not found with the results of the screening "deviations", but there was found a small proportion (19%), with "doubtful" screening results. From Table IV, it can be seen that the statistical test results show that stunted children are more at risk of 5.525 times getting the results of the "deviation/doubtful" development screening compared to normal children (OR= 5.525; 95% CI= 2.488–12.268; p -value < 0.001).

DISCUSSION

Stunting is a condition of failure to thrive in children under five resulting from chronic malnutrition so that children are short for their age. This period of malnutrition occurs since the baby is in the womb and in the early days after the baby is born. However, stunting conditions only appear after the baby is 2 years old.⁶ Stunting reflects chronic malnutrition and can have long-term impacts, including growth retardation, decreased cognitive, motor, language development and mental abilities, susceptibility to disease, low-economic productivity, and low reproductive quality.⁹

The results of the bivariate test were obtained (p -value < 0.001), meaning that there was a statistically significant difference in the development of stunted and normal children. The test results also show that stunted children are 5.525 times more at risk of getting "deviation/doubtful" developmental screening results than normal children (OR= 5.525; 95% CI= 2.488–12.268). This is supported by the results of research by several experts including the results of research by Probosiwi et al. (2017) who found stunting to have a relationship with child development, marked OR = 3.9 (1.7–8.9), meaning that among the development of suspect children. It is likely that children with stunting are 3.9 times more at risk than children with normal development.¹⁰ The results of the study Migang (2021) also found stunted toddlers were at risk of 22 times experiencing developmental delays compared to normal toddlers (p -value < 0.001 ; OR = 22,176; 95%CI= 2,661–184,798).¹¹

Stunting can cause children to lose their curiosity about the environment, make them lazy to do interact with the environment, so that there is a possibility of failure in achieving motor development when compared to normal children.¹² Stunting will also result in low cognitive and intellectual development, behavioral problems and poor school performance, physical abilities and low productivity, which can last into adulthood.^{7,13} The results of the study of Wahidamunir stated the opposite, namely that there was no significant relationship between the incidence of stunting and the level of development of children aged 48–59 months (p value 0.37).¹⁴ This is because the child's growth and development are related to the environment in which the child is born and lives. Development is also influenced by environmental stimuli including parenting, education level and family socio-economic.¹ There are several limitations that need to be considered in this study namely, the cross-sectional design of this study poses limitations to the causal relationship between the variables studied. Also, the data in this study were only processed a bivariately, since the differences in development seen were from the KPSP screening results combining four aspects (fine motoric, gross

Table I: Description of Respondent's Age (in month)

Respondents	N (N= 130)	Min	Max	Means	Standard Deviation
Stunted Children	46	9	60	35.43	14.98
Normal Children	84	3	72	32.18	21.22
Whole Respondents	130	3	72	33.33	19.24

Table II: Frequency distribution of respondent characteristics

Characteristics respondents	Stunted (N= 46)		Normal (N= 84)		Whole respondents (N= 130)	
	f	%	f	%	f	%
Sex						
Man	25	54.3	43	51.2	68	52.3
Woman	21	45.7	41	48.8	62	47.7
What order are you in family						
1 st child and 2 nd child	28	60.9	55	65.5	83	63.8
> 3 rd child	18	39.1	29	34.5	47	36.2
History of birth weight						
LBW (< 2500 grams)	3	6.5	1	1.2	4	3.1
Normal weight (> 2500 g)	43	93.5	83	98.8	126	96.9
Height-for-age category						
Very short	17	37.0	0	0	17	13.1
Short	29	63.0	0	0	29	22.3
Normal	0	0	84	100.0	84	64.6

Table III: Frequency distribution of the results of the KPSP assessment

Characteristics respondents	Stunted (N= 46)		Normal (N= 84)		Whole respondents (N= 130)	
	f	%	f	%	f	%
KPSP results of fine motoric						
Deviation	0	0	0	0	0	0
Doubtful	19	41.3	5	6.0	24	18.5
Normal (according to age)	27	58.7	79	94.0	106	81.5
KPSP results of Gross Motoric						
Deviation	2	4.3	0	0	2	1.5
Doubtful	16	34.8	12	14.3	28	21.5
Normal (according to age)	28	60.9	72	85.7	100	76.9
KPSP results of social and independence						
Deviation	1	2.2	0	0	1	0.8
Doubtful	4	8.7	8	9.5	12	9.2
Normal (according to age)	41	89.1	76	90.5	117	90.0
KPSP results of speech and language						
Deviation	0	0	0	0	0	0
Doubtful	10	21.7	8	9.5	18	13.8
Normal (according to age)	36	78.3	76	90.5	112	86.2
KPSP Results						
Deviation	4	8.7	0	0	4	3.1
Doubtful	22	47.8	16	19.0	38	29.2
Normal (according to age)	20	43.5	68	81.0	88	67.7

LBW: Low Birth Weight, KPSP Results: Results of child development assessment of four aspects (fine motoric, gross motoric, social independence and speech language).

Table IV: Developmental differences in stunting and normal children aged 3–72 months

Child Development (KPSP Result)	Stunted (N= 46)		Normal (N= 84)		Total (N= 130)		p-value	OR (95%CI)
	f	%	f	%	f	%		
Deviation/Doubtful	26	61.9	16	38.1	42	100	<0.001	5.525 (2.488–12.268)
Normal (according to age)	20	22.7	68	77.3	88	100		
Total	46	35.4	84	64.6	130	100		

motoric, social independence and speech language). It has not been examined further from each aspect separately and also this research has not explored further about the causes of stunting, it is suggested that future researchers can study it further.

CONCLUSION

It can be concluded that there are developmental differences between stunted children and normal children. In the stunting children group, it was found that a small proportion had "deviation" KPSP measurement results and almost half had "doubtful" KPSP results. Whereas normal children group were not found with the results of the screening "deviations", but there was found a small proportion with "doubtful" screening results. Stunted children are predicted to experience obstacles in the future and have low physical, intellectual and productivity abilities. However, child development is not only influenced by stunting conditions but is also influenced by other factors such as the environment where the child was born, where the child lives and environmental stimuli, including parenting style, level of education and family socio-economic status. This research has not explored further about the causes of stunting, It is hoped that future researchers can study it further.

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Education package based on family centered maternity care to increase self efficacy and knowledge of breastfeeding mothers in the covid pandemic

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ABSTRACT

Introduction: Exclusive breastfeeding is still below the set target. Breastfeeding behavior is influenced by knowledge and self-efficacy. Training packages based on family centered maternity care are needed to boost mothers' efficacy and knowledge about breastfeeding. The aim of this study is to evaluate the effect of an online education package based on Family Centered Maternity Care on the self efficacy and knowledge of breastfeeding mothers.

Materials and methods: This Study used a pre-experimental design method with a One-Group Pre-Post test design approach. We recruited 60 breastfeeding mothers in Padang, Indonesia, selected with consecutive sampling. Online Education Based On Family Centered Maternity Care was provided for the respondent. Data were collected using the Breastfeeding Self efficacy Scale ShortForm (BSE-SF) and The Breastfeeding Knowledge (BKQ) Questionnaires.

Results: The respondents had significant differences in self-efficacy and knowledge before and after the health education Based On Family Centered Maternity Care ($p < 0.001$).

Conclusion: After Education Package Based On Family Centered Maternity Care influenced the Self Efficacy And Knowledge of Breastfeeding Mothers. It could be provided as a nursing intervention to assist Breastfeeding Mothers.

KEYWORDS:

Breastfeeding, Education package, Family Centered Maternity Care

INTRODUCTION

Early breastfeeding initiation and exclusive breastfeeding aid in a child's survival and development of the antibodies necessary for illness defense. According to the World Health Organization, the coverage of exclusive breastfeeding in 2018 worldwide was only around 36% during the 2007-2014 period¹. The proportion breastfeeding in infants In West Sumatra the coverage of exclusive breastfeeding in 2016 was 75.1% with a target of 83 %².

Breastfeeding that does not reach the target can harm the baby's health³. The COVID-19 Pandemic period impacted all

aspects, including breastfeeding rates in Indonesia. According to the 2020 WHO, due to the COVID-19 pandemic, access to essential services such as breastfeeding counseling in hospitals, health clinics, and through home visits has been disrupted. The inaccurate information about breastfeeding safety has reduced the rate of breastfeeding mothers because postpartum mothers fear passing the disease on to their babies. Even though according to research, mothers who are suspected or confirmed of SARS-CoV-2 infection give birth to babies with negative test results or no results, it is recommended to breastfeed if possible, unless the mother's condition is seriously ill or in the ICU¹⁵.

In Indonesia, there was a decrease in the rate of breastfeeding during the COVID-19 pandemic. According to the 2021 Basic Health Research data, 52.5 percent or only half of the 2.3 million babies aged less than six months were exclusively breastfed in Indonesia, or decreased 12 percent of the 2019 figure. The early breastfeeding initiation rate has also decreased from 58.2 percent in 2019 to 48.6 percent in 2021¹⁶.

Self-efficacy and knowledge are the main factors to increase the behavior of exclusive breastfeeding⁴. The self-efficacy of mothers who feel they are unable to breastfeed is the main factor for mothers not to exclusively breastfeed or stop breastfeeding prematurely⁶. During the COVID-19 pandemic, the self-efficacy of breastfeeding mothers can decrease because the forming factors cannot be achieved with maximum. Self efficacy is influenced by mother's knowledge about breastfeeding. Increasing knowledge can be done by providing online education based on family centered maternity care.

Some online education is carried out by researchers and is effective for supporting breastfeeding mothers during a pandemic but there are still drawbacks to this method because it does not involve husbands and families as support for mothers while at home, so a more appropriate strategy is needed to increase mothers' confidence in breastfeeding.

Family Centered Maternity Care is a concept of providing family-centered maternity nursing care⁵. The combination of online education with the concept of family centered maternity care is a strategy to increase family participation in caring for postpartum mothers. Education package is given to postpartum mothers accompanied by the family,

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such as husbands or parents, as a support system for mothers in exclusive breastfeeding. According to Asmuji in 2016 the postnatal education model with the FCMC approach has several dimensions, including providing postnatal education by providing a discharge planning format, involving the closest family for postpartum mothers (eg husband, mother and in-laws) as social support, paying attention to the stages of the postpartum period consisting of: from the immediate postpartum phase (0-24 hours first), early postpartum (> 24 hours-1 first week) and late postpartum (> 1 week- 6/8 weeks), paying attention to the characteristics of postpartum mothers and families, including the culture used by them, educational topics tailored to the needs of mothers related to the stages of the postpartum period⁶.

This education package is designed while taking into account health protocols during the COVID-19 pandemic. Online education is carried out using the Zoom Cloud Meeting and WhatsApp Messenger applications because these applications are easily accessible and understandable for postpartum mothers. This education package is an innovation in providing health education that pays attention to health protocols during a pandemic.

The education package consists of several educational topics arranged based on the postpartum phase. the immediate postpartum phase includes pain adaptation and early mobilization. Topics in the early postpartum phase include breast care, oxytocin massage, correct breastfeeding techniques, nutrition during breastfeeding, perineal care, personal hygiene, rest needs, postpartum gymnastics, exclusive breastfeeding, newborn care (bathing, umbilical cord care, and changing diapers). While topics in the late postpartum phase include contraception, sexuality, infant immunization, getting to know baby's behavior, baby's growth and development and baby's safety'. With increased knowledge and self-efficacy of mothers, the problem of low exclusive breastfeeding can be overcome.

The aim of this study is to evaluate the effect of an online education package based on Family Centered Maternity Care on the self-efficacy and knowledge of breastfeeding mothers in West Sumatra, Indonesia during the COVID-19 pandemic. Specific objectives include comparing rates of exclusive breastfeeding, assessing changes in self-efficacy, and evaluating knowledge acquisition before and after the implementation of the education package.

MATERIALS AND METHODS

This research used pre-experimental design because they provide little or no control of extraneous variables in the form of one-group pretest-posttest design. This research used pre-test and post-test to see the result of the treatment. We recruited 60 breastfeeding mothers in Lubuk Begalung Public health center Padang, Indonesia, and selected with consecutive sampling. Respondents' inclusion criteria in this study were early postpartum mothers (24 hours until one week postpartum) who were not infected with the corona virus, able to communicate well, the respondent sight and informed consent sheet. Exclusion criteria were mothers who

had breast problems in breastfeeding, mothers who were sick. Data were collected using the Breastfeeding Self Efficacy Scale ShortForm (BSE-SF) and The Breastfeeding Knowledge (BKQ) Questionnaires. The BSES-SF consists of 14 statements covering techniques interpersonal thinking, and support (support). Every statement items are positive with a total score range of 14-70. Reliability test the BSES-SF instrument uses the Cronbach alpha coefficient and corrected items total correlation coefficient to test its validity. Results obtained is 0.94 with a mean of 55.8 (SD=10.85). While the results of the reliability test on the translated instrument shows the Cronbach alpha value coefficient of 0.872. The Breastfeeding Knowledge Questionnaire (BKQ) was used to assess participants' knowledge of breastfeeding [24]. This 26-item questionnaire has eight subscales: benefits (four items), component (two items), lactation mechanism (four items), skills (five items), breast problem management (three items), neonatal problem management (four items), contraindication (one item), and breast milk preservation (three items). Each correctly answered item was assigned a score of 1, and incorrectly answered items were assigned a score of 0. A previous study demonstrated that this scale has satisfactory psychometric properties. Cronbach's α for the BKQ used in this study was 0.80.

An online education and self-administered questionnaire were sent out between October 2020 and November 2020 via zoom and WhatsApp, and respondents were recruited on a voluntary basis. We conducted an educational package for 60 minutes with the frequency of 4 online meetings. The first online educational meeting on demonstrations of breastfeeding techniques that serve to create direct breastfeeding experiences, the second online educational meeting on breastfeeding videos which are expected to provide knowledge and model strategies for effective breastfeeding. The third online education in the form of verbal persuasion regarding exclusive breastfeeding is expected to motivate mothers to achieve exclusive breastfeeding success. The fourth online education about stress management is an intervention given to create positive coping strategies so that mothers have positive views and beliefs about their ability to breastfeed successfully. The pretest and posttest were carried out one day before and after the intervention using a questionnaire made in the form of a Google form that is easily accessible to respondents.

Information about the responders remained confidential and non-attributable. This study was approved by the Faculty of Medicine, Andalas University, and registered with ID 937/UN.16.2/KEP-FK/2020.

DATA ANALYSIS

Data collected were analyzed using the software Statistical Package for the Social Sciences (SPSS) version 26. Categorical variables are presented as frequency and percentage (%). The parametric Paired t-test was used to do a bivariate analysis with a 95% level of confidence. The use of this test is based on the normality test. the Asymp.sig significance value was 0.993, which means that the data is normally distributed.

RESULTS

We recruited 60 breastfeeding mothers in Lubuk Begalung Public health center Padang, Indonesia. The respondents are early postpartum mothers (24 hours until one week postpartum) who were not infected with the corona virus. The research result can be seen in the following table:

The result from the total 60 breastfeeding mothers, the average self-efficacy before treatment was 41.05. The average self-efficacy after treatment was 57.48. while knowledge before treatment was obtained at 14.55 and after treatment was obtained at 22.98. Table II describes the results of the paired T-test data analysis. It was found that there was an effect of education packages based on family-centered maternity care on self-efficacy and knowledge of breastfeeding mothers with a p-value < 0.001.

DISCUSSION

The results of the Cheema et al study in 2020 explained that breast milk should not be withheld from infants because of the overall safety of breast milk and the short and long term nutritional, immunological, and developmental benefits of breast milk for newborns. During a pandemic, the mother's care arrangements, the severity of the mother's infection and the availability of resources may influence breastfeeding decisions, the role of joint decision-making about breastfeeding between mother and doctor needs to be emphasized¹⁵. This condition supports the mother's self efficacy to maintain breastfeeding.

This study was not in line with the results of research conducted by Pradinie (2015) regarding the breastfeeding self-efficacy education package and the success of breastfeeding in postpartum mothers, showing that there was no difference between the treatment and control groups after being given breastfeeding support package intervention

($p=0.410$)⁷. Differences can occur due to differences in sample characteristics. The majority of samples in previous studies had previous breastfeeding experience. Mothers who have had direct experience with breastfeeding tend to be more confident in continuing to breastfeed, especially since the beginning. Most respondents have high enough breastfeeding self-efficacy to make them more persistent in continuing breastfeeding⁸.

Self-efficacy and knowledge in breastfeeding mothers are very important. This is evidenced by research by Zakiah (2012), which states that mothers with high self-efficacy breastfeed longer than those with low self-efficacy and there is a positive correlation between self-efficacy on the first day of breastfeeding and the length of breastfeeding at two months breastfeeding⁹.

In this study, the intervention was carried out with innovations from previous studies. Combining online education with family-centered maternity care is a strategy to increase family participation in postpartum maternal care. Family-centered maternity care is a concept of providing family-centered maternity nursing care¹⁰.

This model has the advantage that in optimizing a mother's understanding of her role and function in maternal adaptation and newborn care, the family is actively involved in this effort¹¹. The impact of the increased understanding of postpartum mothers will have the ability to competent mothering optimally¹².

The results of this study are also by the theory put forward by Lunenburg (2011) that breastfeeding self-efficacy can be influenced by four factors: performance accomplishment, vicarious experiences, verbal persuasion, and physiological response. Physiological responses¹³. The online education method with the concept of family-centered maternity care

Table I: Demographic characteristics

Variable	Category	Frequency	Percentage
Age	< 25	12	20
	25 – 35	21	35
	> 35	27	45
Parity	<2	33	55
	≥ 2	27	45
Education Level	low education	26	43.3
	secondary education	30	50
	higher education	4	6.7
employment status	housewife	46	76.7
	employee	14	23.3

Table II: Differences in average self efficacy and knowledge of respondents before and after being given an Education Package based on family centered maternity care

Variable	Measurement Time	mean	N	Std. Deviation	95% CI	P value
Self efficacy	Pretest	41.05	60	4.188	39.97-42.13	0.000
	Posttest	57.48	60	4.742	56.26-58.71	
Knowledge	Pretest	14.55	60	2.27	13.96-15.13	0.000
	Posttest	22.98	60	2.03	22.45-23.51	

includes the verbal persuasion factor, which is additional support from the husband and is expected to increase self-efficacy further. Verbal persuasion is support from other influential people such as friends, family, lactation consultants, and health practitioners. Reinforcement or advice given by influential people is a source of strength for mothers to breastfeed their babies¹⁴.

Health services always conduct education as one of the health promotion work programs. Health workers explain how important it is to give breast milk exclusive breastfeeding, nutrients or ingredients in breast milk as well as the benefits of breast milk which include cheap breast milk, no hassle to make it, as an anti-infection factor, and can establish a closer loving relationship between mother and child. There is a special record at the health center regarding babies who are given exclusive breastfeeding. To find out the number of babies who are getting exclusive breastfeeding, the health worker usually makes a mark on the examination book or immunization book baby about development and breastfeeding. Before the Pandemic, special and face-to-face counseling about exclusive breastfeeding and even counseling about proper breastfeeding methods had also been carried out in the Health Service Area.

The limitation of this research is that the number of respondents is only 60 people, of course it is still lacking describe the real situation. In the data collection process, the information obtained through questionnaires sometimes does not reflect the opinions of the respondents actually, this happens because sometimes there are differences in thinking, assumptions and different understanding of each respondent, as well as other factors such as honesty factor in filling out the opinions of respondents in the questionnaire.

CONCLUSION

This study concludes that there is an effect of online education packages based on Family Centered Maternity Care on self-efficacy and knowledge of breastfeeding mothers. There is a difference in the average acquisition of knowledge before and after the implementation of the education package.

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CONFLICT OF INTEREST

We have no conflicts of interest.

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Current advances in the development of meniscus tissue engineering: narrative review

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ABSTRACT

Introduction: The meniscus plays an important role in maintaining homeostasis to facilitate the normal function of the knee joint. It is one of the most commonly injured areas of the knee joint. Meniscal-related injuries can lead to significantly decreased athletic ability, and their incidence has increased yearly. It has been found that most meniscal injuries are irreparable, and meniscectomy can increase the predisposition to knee osteoarthritis. Tissue engineering technology on meniscus repairing and transplantation has received widespread attention recently. This review aimed to analyse the scientific literature regarding the potential applications of tissue engineering on meniscus repairing and transplantation procedures.

Method and Materials: The electronic search was carried out using PubMed/MEDLINE®databases with the keywords “tissue engineering AND meniscus” spanning the period of publications from Jan 1980 until Dec 2022.

Results: The literature search identified 405 references in PubMed/MEDLINE, and 179 were selected following the eligibility requirements. The research analysis showed that the existing meniscal tissue engineering studies used a wide variety of seed cells, cytokines, bioactive materials and 3D structures. Each showed distinct advantages and disadvantages in terms of biocompatibility, degradability, mechanical strength, porosity, and etc. It was noted that 3D printing technology is promising for tissue engineering meniscus research. In addition, the optimal use of compression and hydrostatic pressure to markedly improve the functional properties of tissue-engineering meniscal can serve as an useful strategy.

Conclusion: This review analysed the different approaches employed for meniscus tissue engineering and regeneration. Meniscal tissue engineering still faces several major challenges in terms of seed cells, choice of materials and 3D printing strategies, which should be effectively overcome to harness the full potential of this technology.

KEYWORDS:

Stem cells; biomaterials; tissue engineering; meniscus

INTRODUCTION

The meniscus is a critical component of the knee joint that absorbs oscillation. It conducts load and increases the stability of the knee joint, in addition to lubricating the joint and preventing degeneration of the articular cartilage, which is of considerable importance in ensuring the normal function of the knee joint.¹ The principal components of the meniscus are water (72%), collagen (22%) collagen and glycosaminoglycans (GAGs) (0.8%). The fibres and fascicles in the meniscus are distributed in various arrangements, depending on the location of the tissue.² The inner component of the meniscus is composed of small and irregular radial collagen fibrils with a structure similar to that of hyaline cartilage.³ Conversely, the outer region is composed of organised interweaved collagen fibrils, fibres and fascicles with a circumferential orientation.³

The ability of the meniscus to regenerate following an injury is minimal due to the nature of the blood supply. Clinical management depends on multiple factors, especially age, concurrent chondral injury and the time between injury and surgery.⁴ Surgical treatment options include meniscal sutures, partial or complete meniscectomy and meniscal allograft transplantation. Meniscectomy and debridement are more traditional, earlier and widely used interventions. However, this induces functional loss after resection and abnormal weight distribution, causing patients to suffer from osteoarthritis (OA) at an early age.⁴ Meniscal allograft transplantation of the damaged meniscus has been reasonably successful and has proven safe. However, the poor durability of allografts gives rise to a high reoperation rate.⁵ Hence, using biomaterial scaffold meniscus may be advantageous compared to meniscal allograft transplantation.

However, progress in strategies to replace the function of this structure has lagged behind other tissue engineering endeavours.⁶ Notably, the principal problems in meniscus

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tissue engineering include the complexity of the three-dimensional (3D) structure with individualised size characteristics, the high compressive and tensile requirements and the inadequacy of the blood supply. There is emerging evidence of the capability and efficacy of tissue engineering, especially with the use of stem cell technology and different clinical adjuvants, e.g., cytokines and newer biomaterials, that will be outlined in this review.

MATERIALS AND METHODS

The electronic search was carried out using PubMed/MEDLINE®databases with the keywords “tissue engineering AND meniscus” spanning the period of publications from Jan 1980 until Dec 2022.

RESULTS

The literature search identified 405 references in PubMed/MEDLINE, and 179 were selected following the eligibility requirements. The research analysis showed that the existing meniscal tissue engineering studies used a wide variety of seed cells, cytokines, bioactive materials and 3D structures. Each showed distinct advantages and disadvantages in terms of biocompatibility, degradability, mechanical strength, porosity, and etc. It was noted that 3D printing technology is promising for tissue engineering meniscus research. In addition, the optimal use of compression and hydrostatic pressure to markedly improve the functional properties of tissue engineering meniscal can serve as a useful strategy.

The traditional aim of meniscus healing is the preservation and repair of the original meniscus as far as possible. With the advent of novel technologies and materials, researchers have utilised tissue engineering techniques to repair an injured meniscus or even reconstruct the entire meniscus, providing alternatives for patients who require the removal of the whole meniscus. Seed cells, scaffold materials and growth factors are the three essential factors in tissue engineering.⁷

Seed Cells for Meniscus Tissue Engineering

The ideal seed cells should be available from abundant sources, be easy to harvest, proliferate and induce to undergo differentiation, secrete sufficient extracellular matrix (ECM) and have a stable phenotype. The development of stem cell therapies has provided a novel direction for meniscal injury repair because they display all these characteristics.^{3,7}

The meniscus has variations in fibre anisotropy, regionally different cells and various ECM components.^{1,3} Meniscal cells are broadly classified into three varieties, including fibroblast-like cells, superficial zone cells and meniscus fibrochondrocytes (MFCs) (Figure 1).⁸ Fibroblast-like cells, principally located in the most lateral 1/3 of the meniscus, exhibit elongated cellular morphological characteristics and are encapsulated in a fibre network composed of collagen type I (COL I).⁹ Superficial zone cells are characterised as CD34⁺, CD31⁻ and SMA⁺ and are located in the superficial surface of the meniscus, displaying a flattened, fusiform morphology without cell extensions. Several reports suggested that the superficial zone cells are potential

progenitor cells with therapeutic and regenerative properties.^{1,3,7} However, no studies have been published on the application of meniscus surface cells for stem cell therapy or meniscal tissue engineering. MFCs predominantly located in the 2/3 of the most medial meniscus. They are morphologically round and often surrounded by a network of fibres woven by COL I and COL II (at a ratio of 2:3).^{1,9} As self-seeded cells repair meniscal injuries, MFCs can be obtained through minimally invasive surgery through rapid expansion *in vitro*, generating a fibrocartilagenous matrix. Typically, the most common source of MFCs is a badly injured meniscus or the lateral side of a meniscus, in numbers that can satisfy the needs of the majority of patients after propagation. However, propagated MFCs always display dedifferentiation, and the capacity to generate cartilaginous ECM decreases with age.^{1,9} The addition of fibroblast growth factor (FGF) could potentially solve this problem by inhibiting cellular dedifferentiation and promoting the secretion of the ECM.²

BMSCs (Bone marrow mesenchymal stem cells) possess the potential to differentiate into osteoblasts and chondrocytes and have high expansion capability *in vitro* with low immunogenicity. Therefore, BMSCs have commonly been used as seed cells in meniscal tissue engineering research.^{10,11} In a study with scaffolds fabricated with collagen type I that compared the potential to engineer meniscus-like tissue using BMSCs and MFCs, the BMSCs expressed higher levels of COL2A1, ACAN, COL10A1 and GAG content than MFCs.¹⁰ BMSCs may directly participate in tissue repair or indirectly induce the repair response in the host via the paracrine pathway.¹¹ BMSCs injection also showed graft versus host disease inhibition because of the significant effect of modulating the immune response and reduced impediment to immune rejection of allografts.¹² BMSCs injection also enhanced the prognosis of meniscal allograft transplantation. Struijk et al.¹³ injected doses of BMSCs (>0.1 million) in meniscus allograft tissue, and the results showed prominent cell proliferation and migration in 14 days and ideal cell survival in 28 days. Attachment of BMSC to the scaffold material facilitates the fixation of BMSC at the site of the meniscus injury and results in a better repair. Whitehouse et al.¹⁴ implanted autologous bone marrow MSCs (Mesenchymal Stem Cells) seeded into collagen-coated scaffolds into non-vascular meniscal injuries in a clinical trial of five patients. After 24 months of follow-up, the symptoms of injury in those patients were significantly improved. Symptoms were entirely relieved in three patients, while the symptoms did not improve in the other two patients 15 months after transplantation, who required meniscal resection. No adverse reaction was observed in these patients, confirming the potential of BMSCs to repair meniscal injury. The technique of BMSCs therapy for meniscal injuries needs to be combined with biomaterials to have better results. However, *in vivo* studies on BMSC biomaterials are generally performed in animal models. Many of these animal models (small animals) have knee joints that differ significantly from those of humans. More clinical studies are needed to obtain more reliable data and establish a more comprehensive understanding.

From the results of gene similarity analysis, gene expression in SMSCs is closer to meniscal cells than to bone BMSCs.¹⁵

Table 1: Application of growth factor in meniscus tissue engineering.11,20, 22

Growth factor	Cell types	In vitro/ In vivo	Biomaterials/scaffold/explants	Delivery systems	Effects
TGF-β1	Rabbit meniscus cells	In vivo	Poly-L-lactic acid (PLLA)	Not available	Increased collagen and GAG
TGF-β1	Rabbit mesenchymal stem cells	In vivo	Situ crosslinked hydrogel	Not available	Stimulated cell differentiation
TGF-β3	Human bone marrow mesenchymal stem cells (hBMSCs)	In vitro	Meniscus-derived matrix (MDM)	Not available	Enhanced production of proteoglycans
TGF-β3	Cow meniscus cells	In vitro	Meniscus tissue block	Three-armed TMPE-(TMC2-HDI)3 adhesive and hyper-branched CA-4PEG-(TMC2)2-HDI adhesive	Enhanced cell proliferation
TGF-β3, bFGF	Bovine meniscus cells	In vitro	Electrospun produced by poly (ε-caprolactone) (PCL) and N, N-dimethylformamide (DMF) scaffolds	Not available	TGF-β3 increased proteoglycan content in the explants
TGF-β3, CTGF	Synovial MSCs	In vitro	CTGF-loaded fibrin glue mixed with glycolide acid (PLGA) microspheres	Not available	Induced recruitment and step-wise differentiation of synovial mesenchymal stem/progenitor cells
TGF-β3	Tonsil-derived MSCs	In vitro	Riboflavin-induced photo cross-linked collagen-hyaluronic acid (COL-RF-HA) hydrogels	Not available	Stimulated the expression of COL2, SOX9, ACAN, COL1 and production of ECM
TGF-β3, CTGF	Without cells	In vivo	3D printing PCL scaffold	PLGA microspheres	No adverse response
TGF-β3, CTGF	MSCs	In vitro	Meniscus explant model	PLGA microspheres	High CTGF dose and slow TGFβ3 release were most effective for integrated healing of avascular meniscus
TGF-β, Matrilin-3	Adipose-derived mesenchymal stromal cells	In vitro	Not Available	Methacrylated hyaluron (MAHA)	Increased expression of the chondrogenic marker, and decreased the mRNA marker for hypertrophy and protein expression
TGF-β1, chondroitinase-ABC (C-ABC)	Articular chondrocytes and meniscus cells from calves	In vitro	Agarose	Not Available	Increased compressive modulus
TGF-β	Meniscus fibrochondrocytes	In vitro	Polyurethane (PU)	Not Available	Enhanced cell proliferation and ECM production
TGF-β	Meniscus cells	In vitro and vivo	Silk fibroin sponge	Platelet-rich gel (PRG)	Enhanced in vitro cytocompatibility, and in vivo cell infiltration
TGF-β3, CTGF	Meniscus fibrochondrocyte-like cells and MSCs	In vitro and vivo	3D printing PCL scaffold	PLA/PGA	Enhanced cell proliferation, ECM production and mechanical properties
SDF-1	Human cartilage mesenchymal progenitor cells (C-PCs)	In vitro	Hydroxypropyl cellulose (HPC)	Not Available	Enhanced cell migration
IGF-1	Bovine meniscal fibrochondrocytes	In vivo	Alginate cross-linked with calcium sulfate	Not Available	Improved mechanical and biochemical properties, increased glycosaminoglycan (GAG) and collagen
Platelet-derived growth factor (PDGF-BB)	Meniscal and synovial cells	In vitro	Electrospun nanofibers	Not Available	Increased cell viability, proliferation and infiltration, upregulated key genes OF ECM
PDGF-AB, PDGF-BB, IGF-I, TGF-β1	Ovine meniscal chondrocyte (OMC)	In vitro	Polyglycolic acid (PGA)	Not Available	Increased collagen type I, and decreased collagen type II production

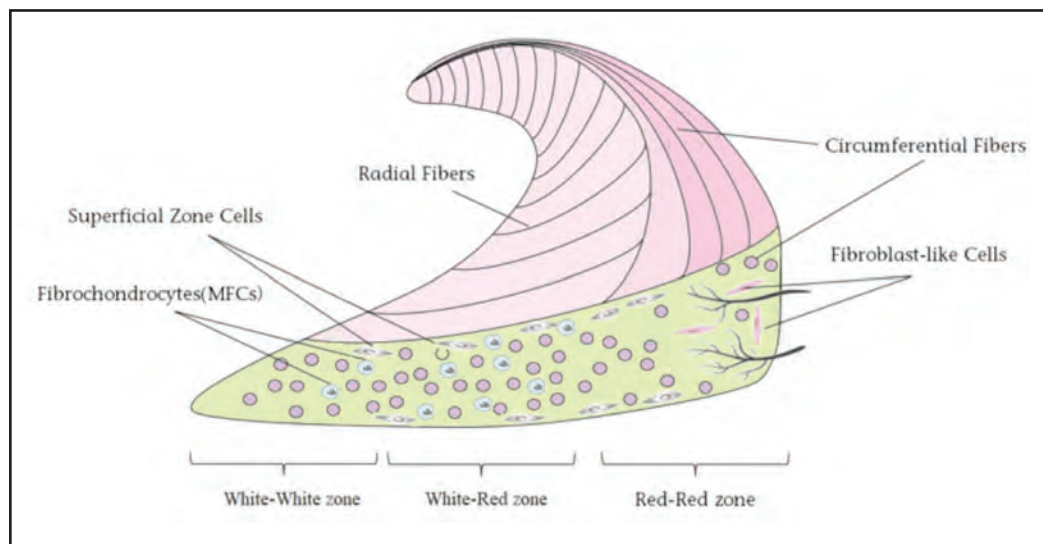


Fig. 1: Structure of the meniscus

SMSCs possess more significant potential to form colonies and can migrate to the site of defects in the meniscus; SMSCs have gradually become a focus of research attention in tissue engineering. *In vivo* studies in pigs and mice have shown that SMSCs, when injected into a defect, promote the proliferation and differentiation of native meniscus chondrocytes to self-repair.¹⁶

Adipose tissues are widely distributed throughout the human body and can harvest easily. They are widely used in a variety of fields in regenerative medicine. The application of ADSCs (Adipose tissue-derived stem cells) in meniscus repair must also attach to the scaffold material. A study in a rabbit model demonstrated that sheets of ADSCs promote meniscus regeneration, but the collagen component of the ADSCs sheet-treated tissue differs depending on the defect site.¹⁷ Nevertheless, several reports suggest that ADSCs produce factors that inhibit chondrocyte proliferation and stimulate chondrocyte apoptosis, while other research shows ADSCs exhibiting tumour-enhancement properties.¹⁸ In addition, several researchers report that ADSCs isolated from different anatomical sites and from donors of different genders and ages display variable differentiation potential.¹⁹ The study of ADSCs in meniscus repair is limited to animal experiments.

A majority of research efforts have focussed on developing novel methods, including gene editing and culture techniques in recent years, on improving the efficiency of seed cells in regenerating meniscus tissue.²⁰ Cytokines play a significant role in cell proliferation, migration and differentiation, and related genes are often used as editing targets for meniscus tissue engineering seed cells. Frequently used target genes in meniscus tissue engineering include FGF-2, TGF- β , insulin-like growth factor I (IGF-I), tumour necrosis factor- α (TNF- α), hepatocyte growth factor (HGF) and activin receptor-like kinases 5 (Alk5)^{21,22} and serve different functions to promote meniscal tissue repair (Table I). Noteworthy, *in vitro* gene editing studies have aimed to determine the precise control mechanism of gene expression that promotes the release of cytokines.²²

- Promote proliferation: TGF- β , FGF-2, IGF-I, platelet-derived growth factor (PDGF), CTGF, calcitonin gene-related peptide (CRGF);
- Modulate cell migration: TGF- β , stromal cell-derived factor 1(SDF-1), Chondroitinase ABC;
- Stimulate anabolic pathways: TGF- β , FGF-2, IGF-I, PDGF, hepatocyte growth factor (HGF), bone morphogenetic protein-7 (BMP-7);
- Modulate cell differentiation: TGF- β , FGF-2, bone morphogenetic protein-2(BMP-2), cartilage-derived morphogenetic protein (CDMP-2);
- Inflammatory response and catabolic/catabolism pathways: TGF- β , Interleukin (IL)-1, matrix metalloproteinases (MMP) family, TNF- α .

Biomaterials for Meniscus Tissue Engineering

Tissue engineering of the meniscus should be capable of supporting axial impact, rotational forces and shear forces in the knee joint. Biomaterials should provide a microenvironment conducive to cell adhesion, proliferation and matrix synthesis. The meniscus scaffolds should process suitable pore size and porosity, excellent biocompatibility and ideal biodegradability.

Tissue engineering materials used to generate a meniscus includes two types: natural biomaterials and synthetic materials.²³ Natural biomaterials include decellularised meniscus, collagen, hyaluronic acid (HA), chitosan, gelatin and bacterial cellulose. Synthetic materials include polyglycolic and polylacticcolic acids.

The ECM of the meniscus has a complicated 3D structure that supports the morphology, behaviours and function of cells, such as migration, proliferation, secretion and differentiation.²⁴ The internal microenvironment of the artificial meniscus tissue engineering scaffold should be similar to natural ECM to provide biocompatibility and degradability.²⁵ The meniscus is predominantly composed of collagen and proteoglycans. Natural biomaterials have similar components making biological compatibility and

biochemical active. Thereby promoting the regeneration of meniscus tissue²⁶ based on the monomer units and structure, most natural biomaterials are categorised as protein/polypeptides (e.g., collagen, gelatin, silk) or polysaccharides (e.g., HA, alginate, agarose, GAGs, chitin, chitosan). Proven commercial products that are natural biomaterials have been used in the clinic. CMI® is an FDA-approved cell-free scaffold derived from bovine Achilles tendon collagen. At 1-year follow-up after transplantation in acute/chronic meniscus injury patients, CMI® showed acceptable biocompatibility and was able to consolidate to the host meniscus.²⁷ At 10-year follow-up, all of the 25 patients reported pain relief and improved function and most patients did not experience degenerative disease of the knee joint.²⁸ Natural biological materials are suitable for the growth, development and metabolism of seed cells. However, natural biological materials have some limitations, e.g., collagen lacks flexibility, has low tensile strength, has poor initial stability and degrades quickly. HA and alginate lack anti-pressure ability, unable to adapt to changes in gravity and are slowly degraded.²⁰ All these limitations warrant consideration for synthetic materials for meniscus tissue engineering.

Synthetic materials are organic polymers with several advantages, including strong mechanical properties and ease of production. These characteristics allow the materials to adapt to the needs of different tissues by adjusting the molecular weight and relative proportions of the components so they can be widely used to produce scaffolds in meniscus tissue engineering.²⁹ Synthetic materials commonly used in meniscus tissue engineering include polyglycolic acid (PGA), polylactic acid (PLA), polylactide glycolide acid (PLGA), polycaprolactone (PCL), polyurethane (PU), polyvinyl alcohol (PVA) and new nanomaterials.^{2,3} Typically, scaffolds that consist of more than two kinds of composite materials are called composite scaffolds, such as PGA/PLGA and HA/PCL. These materials are biocompatible and have good mechanical strength. Notably, the degradation rates of these materials can be controlled by changing the proportion of polymers, molecular weight and crystallinity. Synthetic materials can be produced under controlled conditions to obtain predictable mechanical and physical characteristics such as strength, degradation rates, porosity and Young's modulus. Natural biomaterials have been used in commercial products in the clinic. Actifit® (Orteq Sports Medicine, London, UK) is an improved PU scaffold consisting of 20% PU and 80% of PCL. Actifit® has been approved for use in Europe.³⁶ In a clinical study, patients showed improved mobility with cartilage tissue growth into the scaffold.³⁰ At a follow-up of 5 years, MRI showed that the Actifit® meniscal implant had an intermediate signal and was reduced size in all patients. These data indicate that Actifit® still has limitations as it deforms and undergoes atrophy following long-term use.³¹ NUSurface® is a cell-free anisotropic synthetic biomaterial comprising polycarbonate urethane (PCU).³⁰ At a follow-up of 2 years, patients reported pain relief and had a lower rate of knee reconstructive procedures compared to the control group.³² However, larger prospective trials are required to validate these findings. Compared to natural biomaterials, synthetic materials can lack surface cell adhesion sites on the surface and can be less

biocompatible. Researchers have combined synthetic and natural materials to solve these problems to produce meniscal tissue engineering materials. Natural biomaterial hydrogels have been shown to have good histocompatibility and absorption properties and have been applied in repairing knee cartilage and the meniscus by injection treatments.²⁰ Chen et al.³³ injected a hydrogel produced by decellularised meniscus ECM into a 3D-printed PCL scaffold which was implanted into the knee of a New Zealand rabbit undergoing total medial meniscectomy. Six months after implantation, the meniscus was regenerated and had a similar microstructure, biochemical composition and biomechanical properties to the natural meniscus.

Natural biomaterials can also be combined with synthetic materials for 3D-printed tissue-engineered scaffold structures. Cengiz et al.³⁴ blended PCL with silk fibroin (SF) and entrapped it in a 3D-printed cage scaffold. Human meniscocytes and ADSCs have shown satisfactory cell adhesion, metabolic activity and proliferation on scaffolds after being seeded *in vitro*. The scaffold was shown to have ideal biomechanical properties after subcutaneous implantation in nude mice. Combining natural and synthetic polymers (bioartificial combination) is a multipurpose method to design more successful biomaterials that enhance physical and biological features, such as biocompatibility.³⁵ They have been combined to take advantage of their favourable properties to overcome the disadvantages of each particular type of material.

Advancements in Biomaterial Techniques of Meniscus Tissue Engineering

Cytokines can guide cell proliferation, migration and differentiation through biochemical signals and have been widely used *in vitro*. Cytokines commonly used in meniscal tissue engineering and cell therapy include TGF- β , FGF-2, IGF-I and Chondroitinase ABC.^{26,36} *In vitro* and signalling pathway studies have found that many other cytokines have potential roles in meniscus repair. Cytokines are sensitive to variations in temperature, pH and other factors within the microenvironment.²⁰ They are also prone to denaturation, inactivation and decomposition. Therefore, strategies to maintain the activity of cytokines and obtain controlled and sustained release need to be developed to optimise tissue engineering meniscus technologies. The biomaterial's molecular weight, solubility, surface charge and degradation rate are key factors that determine the rate of cytokine release.²² Current biomaterials for tissue engineering delivery and the loading of cytokines or other active substances include hydrogels, acellular matrices and composite scaffolds (PCL, PLGA, agarose). These materials have strong biocompatibility but are suboptimal in terms of mechanical strength, degradation rate and cytokine-controlled release. Research is being conducted to develop 3D printing technology in meniscus tissue engineering.^{22,34}

Meniscal tissue engineering has high requirements on the mechanical structure, molecular weight, porosity, fibre anisotropy, degradation rate, surface roughness, stiffness, hydrophilic/hydrophobic ratio and surface charge of biomaterials.²⁰ In recent years, the design of tissue engineering meniscus trying to mimic the microstructure and

chemical properties of human meniscus.. Currently, physical and chemical methods are used for meniscus tissue engineering (e.g., freeze-frying, melt moulding, solvent casting, particulate leaching and gas foaming) that provide an ideal microenvironment for cell culture in which the degradation rate is controllable to a certain extent.³⁷ However, pore size, porosity and surface charge are difficult to control. Electrospinning can be used to produce nanoscale fibres that mimic collagen. However, this technique has many limitations relating to porosity and precise microstructural control.³⁸ Moreover, the composition, structure and cell types of the inner and outer regions of the meniscus are significantly different.^{37,38} This is difficult to recreate in a single material preparation and scaffold construction method using a single cell type.

Recently, 3D bioprinting has attracted significant research attention. 3D bioprinting is an automated, organisation friendly manufacturing method that accurately simulates the microscopic columns of a target tissue enabling the precise construction of tissue blocks with specific shapes and structures.²⁵ Commonly used bioprinting techniques for meniscus tissue engineering include direct ink writing, fused deposition modelling (FDM) and extrusion-based bioprinting.^{37,39} High extrusion temperatures result in FDM technology producing materials with poor surface quality and difficulties combining biopolymers.³⁹ Extrusion bioprinting techniques are the most commonly used techniques in meniscus tissue engineering. Recently, this technique has been employed to produce structures with high yields and structural integrity for easy modification. Zhang et al.⁴⁰ printed meniscus-shaped scaffolds with PCL using the melt deposition technique and transplanted the scaffolds into New Zealand white rabbits after seeding BMSCs. The regeneration and mechanical properties of the implanted tissues were assessed, and rough and microscopic observations assessed the degeneration of the articular cartilage at 12 and 24 weeks after surgery. The study showed that the 3D-printed scaffolds seeded with MSCs promoted fibrocartilage tissue regeneration and increased the mechanical strength of the tissue. This approach may provide a functional replacement of the meniscus to reduce postoperative damage to knee cartilage.

Meniscus scaffold should show high mechanical strength to hold the weight, good porosity to satisfy cell colonisation requirements and excellent biocompatibility to prevent cytotoxicity. Still, only some types of biomaterials meet all these requirements.³⁹ Researchers print polymeric as the backbone and fill it with biological materials combined with growth factors to promote cell proliferation and the matrix-forming phenotype of the cells to build an adjustable scaffold to solve this challenge. Chen et al.³³ produced synthetic 3D-printed conditioned scaffolds by PCL and hydrogel derived from meniscus extracellular matrix to reproduce native ECM-like environments. The scaffold yielded outstanding biomechanical strength that was close to those of the native meniscus. They implanted the MFCs-loaded scaffold into the knee joints of New Zealand rabbits. They found that the cell-loaded scaffold exhibited better physical appearance and ability of cartilage protection than the acellular scaffold.

CONCLUSION

To summarise the type of seed cells and biomaterials that are used in meniscus tissue engineering, we reviewed all the existing literature in this field and discussed the unique characteristics of each of them. Insufficiency in current meniscal repair techniques to halt the development and progression of the disease has accelerated the development of tissue engineering strategies. The goal of meniscus tissue engineering is to create new tissue that is similar to meniscus tissue in vivo and suitable for cell proliferation or differentiation, readily integrates into surrounding native tissues and ensures positive outcomes regardless of biological variability and the age of the patient. A big leap in research progress in the field of stem cell sources, biomaterials and the application of stimuli methods to develop tissue engineering techniques for meniscus repairing can be observed to produce therapeutic strategies with lasting effects for meniscus injury. The biomechanical properties of the existing tissue-engineered meniscus still need to be improved. Numerous clinical trials of stem cell-based tissue engineering meniscus have been carried out.

The complex mechanics of the knee joint and the lack of blood supply to the meniscus make 3D-printed meniscus with stem cells the best choice for tissue engineering scaffolds. The bio-ink should possess the characteristic of ideal printability, proper mechanical strength and a mild curing process for cell protection. Single material can only meet these requirements in the studies so far. Part of the researchers choose materials of high mechanical strength as bio-ink to print the backbone of the meniscus and use materials with high biocompatibility to fill the void, exploring a promising technological route. Still, finding the ideal type of biomaterials, the most suitable growth factor and the ideal additive manufacturing method pose enormous challenges.

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Route delivery of nutrition in patients with enterocutaneous fistula

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ABSTRACT

Malnutrition is one of the most frequent effects of an enterocutaneous fistula (ECF). There are some factors that contribute to it including inadequate intake, fluid loss via fistula and underlying disease. The role of nutrition is very important as a part of ECF therapy to give adequate nutrition, maintain fluid and electrolyte state and increase the likelihood of fistula closure spontaneously. Therefore, it is anticipated that adequate nutrition management will lower morbidity and mortality while enhancing clinical results. Nutritional requirements and nutritional route, whether oral, enteral and parenteral nutrition in ECF management, are influenced by the anatomical, physiological and aetiology of the fistula. The purpose of this review was to highlight the evidence based on nutritional therapy in ECF patients by calling attention to nutritional route selection based on the anatomy and physiology fistula to prevent malnutrition.

KEYWORDS:

Enterocutaneous fistula, malnutrition, enteral, parenteral nutrition

INTRODUCTION

Enterocutaneous fistula (ECF) is a feared complication after gastrointestinal surgery. ECF incidence is unknown but has been estimated at less than 0.5 patients per 100,000 citizens.¹ Approximately, 75% of all ECF is caused by open surgery or laparoscopy, and the rest (25%) is caused by diverticular disease, inflammatory bowel disease (IBD), malignancy and radiation therapy.² As cited by Teixeira et al, 1.5% of the patients developed an ECF after acute trauma laparotomies and the most common site of ECF was a colon (69%), followed by small bowel (53%), duodenum (36%) and stomach (19%). This complication exerts a significant negative impact on length of stay, longer intensive care unit utilisation and higher hospital costs.³

The classic triad describes the problems of ECF: sepsis, malnutrition, fluid and electrolyte imbalance.⁴ Subsequently, 55–90% of patients become severely malnourished.¹ Factors that cause malnutrition in ECF are underlying disease, inadequate intake, increased protein requirements related to systemic inflammation and increased fluid loss, including nutrients through the fistula.⁵

Optimal nutritional support plays a major role in preventing malnutrition, reducing morbidity and mortality.⁶ Without optimal nutrition, ECF patients can experience delayed wound closure and worse overall outcome.⁷ ECF patients who

received 1,500–2,000 calories per day had a lower mortality rate and a higher rate of fistula closure. Otherwise, patients who only received <1,000 calories per day had a higher mortality rate and lower fistula closure rate.⁴ To provide optimal nutritional support, the selection of a nutritional route—oral, enteral or parenteral—should be considered.

Dudrick et al. reported that providing total parenteral nutrition (TPN) could treat malnutrition in patients with severe nutritional debility or complex gastrointestinal disease.⁸ Although 60–70% ECF patients ultimately require TPN, it is preferred to administer enteral nutrition (EN) via a nasogastric tube or percutaneous endoscopic gastrostomy device.⁹ Only a few studies have investigated outcomes associated with the use of enteral or parenteral nutrition in ECF patients and the discussion about which is the better nutritional route is still ongoing. A cohort study from Levy et al (1989) of 335 ECF patients with high output fistula have reported though many patients received TPN as initial stabilisation, 85% of patients were maintained exclusively with EN. In 38% of patients, the fistula closed spontaneously and the mortality rate was only 19% in 234 patients who managed conservatively.¹⁰ A study conducted by Li et al for 30 years on 1,168 patients showed that 86.4% of patients receiving EN found it effective. Only 13.6% of patients received parenteral nutrition exclusively. The mortality rate was very low, and overall closure rates were high. EN can even be used successfully in patients with high-output fistulas when combined with elemental formulas, anti-motility drugs, and fibre-bulking agents.¹¹

Given the high risk of malnutrition in ECF patients, an optimal nutritional medical therapy approach was needed to reduce morbidity and mortality. The anatomy and physiology of ECF also affect the nutritional route selection to support nutrition therapy. This review will go through the nutrition dietary aspects of ECF therapy, with a particular emphasis on the nutritional route selection.

Definition and Classification

ECF is an abnormal connection between the gastrointestinal tract and external skin.² ECF can be classified according to the anatomy, aetiology and physiology that contribute to morbidity, mortality and the possibility of spontaneous fistula closure.¹² Based on the anatomy, ECF is divided according to the organ of origin: type I (abdominal, esophageal, gastroduodenal fistula), type II (small intestinal fistula), type III (large intestine fistula) and type IV (entero-atmospheric fistula, regardless of origin).¹² Based on the

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Table I: Prognostic factors of ECF2

Favourable	Unfavourable
Albumin >3 g/dL	Undernutrition
Diverticular fistula	Short fistula, multiple, complex fistula
Single fistula	Large enteral defect (>1 cm), visible mucosa
Intestinal continuity	High output (>500 mL/day)
	Prior radiation
	Multiple prior operations

Table II: Pros and Cons nutritional routes in ECF

Nutritional Route	Pros	Cons
Parenteral	- Useful in high-output fistula - Ability to reduce gastrointestinal secretion 30-50%, therefore potentially decreasing mortality rate and helping spontaneous closure in 70% of patients	- Catheter-related complications - Risk of hyperglycaemia
Enteral	- Can initiate immediately if the patient is stabilised and sepsis is controlled - Lower cost - Greater availability - Fewer complications - Useless in high-output fistula	- Contraindicated if there are intestinal discontinuity, ileus, short bowel length, enteral feeding intolerance
Combination Enteral and Parenteral	- To achieve the caloric requirement - Could be applied if enteral feeding was accessible but not well tolerated (keeping 20% of the required calories achieved by enteral and 80% by parenteral)	
Oral	- Only useful when the patient enable to tolerate fluids and solid food	- May increase the output of the fistula, especially
Fistuloclysis	- Useful in patients with intact intestinal absorption ability distal to the infusion site - Beneficial in patients with complications associated to TPN (infection, venous access problem, liver failure).	- Difficult to perform - Complication can occur because the peristaltic activity of the small intestine moves the fistula catheter into the distal small intestine

etiology, ECF is classified into iatrogenic (75–85%) and spontaneous (15–25%). Spontaneous fistulas occur in patients with IBD, malignancy, appendicitis, diverticulitis, post-irradiation, tuberculosis and ischaemia.¹³ Based on physiology, fistulas are classified according to the volume of fistula output, namely high output (>500 mL/day), moderate (200–500 mL/day) and low output (<200 mL/day).¹⁴

Prognostic Factor

Patients with a proximal fistula, high output and hypoalbuminaemia (<3g/dL) have more complications and a less likely tendency for spontaneous fistula closure. In contrast, patients without comorbidities who have fistula after surgery and are low output tend to have higher rates of spontaneous closure.² There are some factors that favour spontaneous closure, such as small enteric defects (<1 cm) and long fistula tracts (>2 cm). Factors influencing the failure of spontaneous fistula closure include bowel discontinuity, radiation therapy, adjacent abscess, stricture or inflammation of the bowel, distal obstruction and foreign body.⁵ These factors are presented in Table I.

Nutritional Route in ECF Patients

In the majority of ECF patients, adequate oral intake is not possible. As an alternative to providing an optimal nutrition, nutrients can be provided either by enteral route (via nasogastric or nasojejunal tube, or via gastrostomy or jejunostomy, or fistuloclysis into the distal small bowel) or parenterally (via a peripheral or central vein).¹⁵ The selection

of the nutritional route is influenced by several factors, namely patient tolerance, the origin of the fistula, the length of the intestine that functions well to absorb, and the volume of fistula output.^{6,16} EN can be chosen if the intestine is functioning properly to perform the absorption (no sign of intra-abdominal sepsis) and the volume can be controlled. On the other hand, if the volume of the fistula is high, parenteral nutrition may be used.⁶

ASPEN recommends the use of an oral diet or EN in patients who have passed the fluid and electrolyte stabilisation phase if the ECF output is low (<500 mL/day) and there is no distal obstruction. In patients with a high-output fistula (>500 mL/day), intestinal obstruction, impaired ECF drainage that interferes with wound and skincare or impaired fluid and electrolyte balance, parenteral nutrition may be required. This aims to meet the needs of nutrition, fluids and electrolytes and support spontaneous closure of the ECF.⁵

Parenteral Nutrition

Nutrition in the resuscitation phase begins with TPN. This step is taken for a short period to avoid complications related to the use of a central route, with a caloric requirement of 30–40 kcal/kg, 1.5–2 g of protein per kg, 30–40 mL of water per kg. During nutrition administration, it is necessary to monitor blood glucose levels tightly to prevent hyperglycaemia.⁶ The ratio of calories between carbohydrates, fats and proteins in TPN should be adjusted to the patient's medical history, such as a history of diabetes

mellitus or lung disease. Patients with lung disease required to adjust macronutrient composition by increasing the percentage of fat and decreasing the percentage of dextrose to reduce the production of carbon dioxide by dextrose oxidation.⁶

After fluid and electrolyte resuscitation and drainage of percutaneous infection or surgery, patients with high-output fistula (>500 mL/day) are initiated with parenteral nutrition. Other indications for parenteral nutrition include intestinal obstruction or ECF drainage that would interfere the wound and skincare or disturb fluid and electrolyte balance.⁵ The concept of 'bowel rest' in TPN based on the observation that providing TPN especially in high-output fistulas will reduce gastrointestinal secretions by 30–50% thereby aiding closure of the fistula, reducing the incidence of dehydration and electrolyte imbalances.^{2,13,17}

Providing TPN not only reverses the catabolic state of the patient but also allows the fistula to close spontaneously. If the fistula does not close spontaneously, the patient can undergo surgery without infection and is likely to have a good outcome.⁴ Parenteral nutrition is the only option in high output or bowel failure due to diffuse disease.¹³ Parenteral nutrition can be used independently or in conjunction with enteral feeding to meet the nutritional requirement of the patient and to allow minimal enteric flow through fistula.¹⁸ MacFadyen et al (1973) reported that TPN decreased the mortality rate to 6.45%, and among 70% of subjects had spontaneous fistula closure.⁶ Nowadays, most centers use a combination of TPN and enteral feeding. Study by Li et al that analyse therapeutic results among 1,168 subjects with ECF showed the combination of TPN and enteral feeding had a better outcome. Only 13.6% of patients received only TPN.¹¹

Patients commonly receive parenteral nutrition formulas containing intravenous lipid emulsion, representing a major source calories and essential fatty acids.^{1,15} The first commercially intravenous lipid emulsion was soybean-oil based, containing high of essential and long-chain polyunsaturated fatty acids (PUFA). Its product have high content of omega-6 PUFA, which has pro-inflammatory effect.¹⁵ Long-term use of soybean-oil based has been associated with the development of parenteral nutrition-related liver disease.¹⁹ As an alternative, it has been developed partial replacement of soybean oil with other lipid emulsion such as medium-chain triglycerides (MCT), olive oil, and fish oil. Both MCT and olive oil-rich emulsions are less prone to lipid peroxidation than PUFA, while fish oil contains omega-3 PUFAs that have immunomodulatory and anti-inflammatory effect.¹⁵ Patients who receive little or no EN need to receive micronutrients such as selenium and zinc via parenteral nutrition.¹⁹

TPN causes several other side effects, such as catheter-related bloodstream infection (BSI), hyperglycaemia, central venous thrombosis and refeeding syndrome.⁴ Marra et al reported that 80.9% of patients who received long-term TPN developed BSI and 78.9% of patients had more than one episode of BSI.²⁰ Refeeding syndrome could occur when TPN is administered rapidly and characterised by metabolic and electrolyte abnormalities induced by rapid repletion of elements that the

body has adapted to be scarce.²¹ Parenteral nutrition is contraindicated in cases of liver dysfunction or failure, difficulty in vascular access or infection in the vascular access device.¹³

Enteral Nutrition

Enteral nutrition (EN) has been identified as an independent factor associated with fistula closure.⁴ Although initial bowel rest may be useful for early control and minimisation output of the fistula, if the patient is stabilised and sepsis is under control, EN is recommended to be initiated immediately.^{4,21} EN has a number of benefits including lowering infection incidence, lowering costs and improving immune function compared to parenteral nutrition.² Achieving a caloric requirement of at least 20% via the enteral route can help to maintain intestinal flora, mucosal barrier integrity, hormonal signaling and reduce bacterial translocation.^{2,13} To achieve moderate success using EN, ECF patients should have at least 4 feet (1.2 meters) of healthy bowel from the ligament of Treitz to the external fistula opening.¹³ However, in multiple organ dysfunction syndrome, gut function may be compromised and EN is not always tolerated.¹ If nutritional requirements cannot be achieved via enteral or if the fistula output is high, then parenteral nutrition is given.⁶

EN is contraindicated in conditions such as short bowel (small bowel length less than 75 cm), bowel discontinuity, ileus, perforation, inaccessible enteral access, intolerance to enteral feeding and high fistula output.^{6,15} When gastrointestinal blood flow is compromised during haemodynamic instability phases, EN also will be contraindicated.¹⁵ Complications associated with EN include aspiration, nasogastric tube misplacement, diarrhoea, nausea, vomiting and obstruction (ileus).¹

Total calorie requirement can be met on the first day by enteral feeding. However, in some cases, enteral feeding takes 5–10 days to meet the total daily requirement. To provide optimal nutritional support, a combination of EN and parenteral nutrition is required. This combination may also be given when access to EN is available but is not well tolerated. Therefore, 20% of the total calories required are fulfilled by enteral and 80% by TPN. This combination can protect mucosal integrity as well as maintain immune and hormonal function.⁶

In proximal duodenal fistulas, a percutaneous jejunostomy tube (PEJ) can be used, while in distal ileal or colonic fistula, patients may be able to obtain nutrition via mouth or gastric tube.⁷ In the acute phase, continuous EN via nasogastric, gastrostomy or jejunostomy tube may be better tolerated than bolus feeds, although there are benefits in bolus feeds after the patients have stabilised.¹⁹ Feeding tube volumes and concentrations are usually low at the start of the administration, then increased gradually to achieve a tolerable target.⁶ EN can be started at a rate of 20 mL/hour in the first 24–48 hours then gradually increased based on the patient's ability to tolerate feeding. If tolerable, the maximum rate of EN is 120 mL/hour per day.⁴

Administration of EN in ECF patients has shown good results. A cohort study by Levy et al (1989) of 335 ECF patients with high output fistula reported that, though many patients

received TPN as initial stabilisation, 85% of patients were maintained exclusively with EN. 38% of patients had spontaneous fistula closure, and the mortality rate was only 19% in 234 patients who were managed conservatively.¹⁰ A study conducted by Li et al for 30 years on 1168 patients showed that 86.4% of patients receiving EN found it effective. EN can even be used successfully in patients with high-output fistulas when combined with elemental formulas, anti-motility drugs and fibre-bulking agents.¹¹ Yuan et al in their 10-year retrospective studied the benefit of early EN on the fistula outcome. They reported that patients who received early EN within 14 days of hospital admission had earlier fistula closure and fewer complications compared to patients who received EN more than 14 days after hospital admission.²²

The polymeric formula is the most frequently used formula for patients requiring EN support. This formula is designed to resemble the general diet by providing carbohydrates, proteins and fats in a non-hydrolysed form. The source of carbohydrates in this formula comes from maltodextrin and solid corn syrup. The protein source comes from protein isolate, sodium and calcium caseinate while the fat source comes from canola, soybean or safflower oil. The use of this polymeric formula requires a normal digestive function.²³

In patients who have malabsorption disorders and/or have difficulty digesting and absorbing standard polymeric formulas, elemental and semi-elemental formulas are used more often. The composition of hydrolysed macronutrients in these formulas is useful for increasing absorption. The carbohydrate source comes from hydrolysed cornstarch, maltodextrin or fructose. Sources of protein are amino acids and dipeptides or tripeptides (hydrolysed casein, whey or soy protein isolate) and fat sources are fatty acid esters or MCTs.²³

The majority of ECF patients can typically receive adequate nutrition by administering standard polymeric enteral formulas. However, elemental or semi-elemental formulas should be available in patients with a very short bowel or patients who cannot tolerate polymeric formulas or if polymeric feeds cause diarrhea. In addition, in high-output fistula, the elemental formulas should be considered as they have been shown to be related with an 80% reduction in fistula effluent.²⁴

Based on the location of the fistula, the elemental formula can be applied to a distal fistula that provides pre-digested nutrients (glucose, amino acid, MCTs).²⁵ This will result in decreased output fistula, but it should be noted that drainage around the fistula should be in good condition.^{4,25} Otherwise, in very proximal ECF, EN can be administered distally to the fistula using the remaining bowel. If all pancreatic secretions exit through the fistula, elemental formulas are required unless the fistula output itself is reintroduced distally. This approach will minimise the loss of electrolyte, calorie and bile salt/cholesterol even though it is impractical.²⁵ The enteral formula is generally initiated at a rate of 30–50 mL/hr, increased over 24–48 hours as gastric aspiration decreases and tolerance increases until the target is reached.²⁵

Hafejee et al conducted a prospective study by providing nutritional therapy to 63 patients with high-output fistula. In

this study, the nutritional regimen was divided into three categories, namely TPN, a combination of TPN and EN, and EN only. The formula used in EN is an elemental low-residue formula. The results of this study suggested that a low-residue elemental diet is beneficial in ECF without the risk of sepsis and other complications associated with TPN.²⁶ Enteral immuno-nutrition supplementation such as arginine, omega-3 fatty acids and nucleotides in critically ill patients and infants has been shown to reduce infection and length of stay but not mortality.¹

Oral Nutrition

Oral feeding is started when the patient can tolerate fluids and solid food. The selection of a diet that is high in calories, high in sodium, low in fibre and high in residue is explained to patients.^{6,9} Regular meals as well as oral nutritional supplements should be considered.¹⁵ In some cases, even if the patient has normal intestinal absorption, the administration of oral feedings especially with solid foods may increase fistula output. If the fistula output is increased, then providing food orally is not beneficial.⁶ Datta et al reported that oral nutrition could be made in high output fistula with the following modification: (1) limit intake of low sodium fluids to 500 mL/day, (2) provide oral solution with high sodium (90–120 mmol/L sodium content), (3) small volume fluid intake with solid foods and (4) administration of protein pump inhibitor, octreotide and anti-motility drugs.²⁷

Fistuloclysis

Fistuloclysis (distal feeding) is a method that allows the administration of nutritional formula into the normal intestine distal to the ECF.¹⁵ Nutrition can be given as the formulas, fluid, or chyme (effluent re-fed distally from a proximal fistula).²⁸ Fistuloclysis is indicated when the fistula is located in the small intestine and is not distal enough to allow adequate enteral absorption or in patients where TPN is contraindicated.⁶ Before initiating fistuloclysis, anatomy of the bowel and fistula must be established to ensure that there are no distal enterotomies or obstruction. This technique has been for centuries and even though it is difficult, it is considered efficient, efficacious and successful.²⁸ ASPEN recommends the use of fistuloclysis in patients with intact intestinal absorption ability distal to the infusion site and when the ECF is not expected to close spontaneously.⁵

Fistuloclysis has been demonstrated in some trials to preserve nutritional status, water and electrolyte balance, which can reduce and replace parenteral nutrition requirements. As cited from Teubner et al, fistuloclysis can provide effective nutritional support by successfully replacing TPN in 11 of 12 ECF patients and showed no complication associated with fistula.²⁹ Coetzee et al reported that about half of patients with enteric fistula by fistuloclysis is feasible and can eliminate the need for parenteral nutrition.³⁰

Fistuloclysis is helpful in patients with complications associated with TPN including infection, venous access problems or liver failure. In high-output ECF with distal mucocutaneous limb, fistuloclysis may be an adjunct to standard EN.² Administration of nutrition begins with a polymeric formula, but if the patient is intolerable, it can be changed to an oligomeric formula (semi-elemental). Polymeric nutrition was started at a rate of 30 mL/day and

increased by 20 mL/hour daily until the target was reached. If EN reaches a rate of 90 mL/hour then parenteral nutrition can be discontinued.⁵ Complications such as obstruction can occur as peristaltic activity of the small intestine moves the fistula catheter into the distal small intestine.²

Monitoring and Evaluation

During nutritional therapy, it is necessary to monitor and evaluate the patient. Assessment of nutrition tolerance and the ability to provide targeted nutrition should be done routinely.⁵ Assessment of nutrition intake is very important in ECF patients by calculating calories and protein requirements, assessing feeding tolerance, modifying feeding methods, adjusting needs with changing clinical conditions and observing complications during nutritional therapy.⁶ In intensive care patients, investigations and procedures may cause interruption in feeding, especially in the case of EN, resulting in a clinically relevant difference between prescribed and delivered nutrients.¹⁵

Fluid status in ECF patients should be assessed daily, and all sources of intake and output should be monitored.¹³ To adjust the initial target caloric intake and follow the patient's progress, laboratory tests such as albumin, prealbumin, transferrin and CRP in stable patients are required at least weekly during hospitalisation.¹³ Transferrin levels greater than 140 are associated with an increased rate of spontaneous fistula closure and reduced mortality.²

Hypertriglyceridaemia is often found in ECF patients. Therefore, lipid profile examination should be done especially in patients who received parenteral nutrition. A study by Visschers et al showed that high triglyceride levels in ECF patient were associated with sepsis, small bowel fistula with high output, use of the parenteral route and underlying disease with inflammation as the etiology.³¹

Serum electrolytes, glucose, urea nitrogen, creatinine, calcium, magnesium and zinc levels are taken during the first week to resolve the deficiency quickly and to maintain metabolism.³² Nitrogen balance calculations with correction for enteric loss should be performed to ensure and maintain a positive nitrogen balance. A positive nitrogen balance indicates a negative transient anabolic state, inadequate caloric intake, unresolved sepsis and excessive gastrointestinal fluid loss. The examination is carried out with urine levels for 24 hours to measure urea nitrogen levels. However, it should be noted that these nitrogen balance calculations are significantly meaningful in patients who have recovered from sepsis.¹³ If the nitrogen balance result is negative, nutritional therapy needs to be modified. Monitoring the fistula is also required to see if there is a possibility of spontaneous closure of the fistulas. Generally, 90% of fistulas are resolved without surgery within 5 weeks with medical management.³³ If medical management does not result in spontaneous fistula closure within 4–6 weeks, then surgical treatment may be considered.^{4,33}

CONCLUSIONS

To prevent medical problems, especially malnutrition, in ECF patients, nutritional route selection should be considered

based on the anatomy and physiology of fistula. Nutrients can be provided either by enteral route (via nasogastric or nasojejunal tube, or via gastrostomy or jejunostomy, or through fistuloclysis into the distal small bowel) or parenterally (via a peripheral or central vein). The selection of the nutritional route is influenced by patient tolerance, the origin of the fistula, the length of the healthy intestine to absorb the nutrients and the volume of fistula output.

EN is a preferable route compared to parenteral nutrition unless there is a clear contraindication. It enhances the functional and structural integrity of the gastrointestinal tract, prevents bacterial invasion into intestinal epithelial cells, stimulates the secretion of immunoglobulin A and supports the mass of gut-associated lymphoid tissue (GALT).⁴ However, EN is contraindicated in short bowel (small bowel length less than 75 cm), bowel discontinuity, ileus, perforation, inaccessible enteral access, intolerance to enteral feeding, high fistula output and during hemodynamic instability phases. High-output fistula is contraindicated because EN may increase gastrointestinal secretion and increase fistula output, which will delay the fistula's closure. If enteral feeding is available but cannot be well tolerated, or unable to meet the nutritional requirement, a combination of EN and parenteral nutrition is required. This combination can protect mucosal integrity, maintain immune and hormonal function, increase the rate of spontaneous fistula closure and decrease mortality rate. To lower the risk of catheter-related infection while utilising parenteral nutrition, the infusion line must be carefully managed and treated.

Monitoring and evaluation, including assessment of food intake and EN tolerance, are necessary during nutritional therapy. Furthermore, laboratory tests such as albumin, prealbumin, transferrin, CRP, serum electrolytes, glucose, urea nitrogen and creatinin are required to adjust the initial target caloric intake and follow the patient's progress. Monitoring the fistula is also required to see if there is a possibility of spontaneous closure of the fistulas.

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A Tête-à-tête with ChatGPT on the impact of artificial intelligence in medical education

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ABSTRACT

Chat Generative Pre-Trained Transformer (ChatGPT) is an artificial intelligence (AI) language model developed by OpenAI. It is trained to process vast amounts of text and engage in human-like conversational interaction with users. Being accessible by all, it is widely used and its capabilities range from language translation, summarising long texts and creative writing. This article explores the potential role of ChatGPT in medical education and the possible concerns about the misuse of this technology through a conversation with ChatGPT itself via text prompts. The implications of this technology in medical education as told by ChatGPT are interesting and seemingly helpful for both the students and the tutors. However, this could be a double-edged sword considering the risks of compromised students' integrity and concerns of over-reliance. This also calls for counter strategies and policies in place to mitigate these risks.

KEYWORDS:

Artificial intelligence, ChatGPT, medical education

INTRODUCTION

Chat Generative Pre-Trained Transformer (ChatGPT), the brainchild of OpenAI, an artificial intelligence (AI) firm based in California has taken the world by storm since its launch in November 2022. ChatGPT is developed as a large language model (LLM) that uses deep learning algorithms. It is trained to process a gargantuan amount of text and optimised to engage in human-like conversational interaction with users based on their prompts.¹ The capabilities of ChatGPT can be diverse from language translation, sentiment analysis, summarising long texts and creative writing to assisting with programming languages and coding. One can sign up for a free ChatGPT account at OpenAI's website and it is accessible across various operating systems including Microsoft Windows, Mac, iOS and Android platforms.

While this technology can help students in their studies by providing quick, reliable information, assisting with research and helping them practice and prepare for exams, it could be a double-edged sword.² There are worldwide concerns from academia considering the possibilities of misuse of this technology to generate essays, reports without original creative thinking, and compromise of students' integrity during online exams.^{3,4}

Recent preprints have demonstrated modest performance of ChatGPT in the United States Medical Licensing Examination (USMLE) accentuating its role as an effective medical education tool.^{5,6} To understand the implications of this technology in the teaching and learning of medical students, the authors had a conversation with ChatGPT (Jan 30, 2023 version- Free research preview) on 3rd February, 2023 using a Macbook (macOS Ventura 13.2) using the following text prompts.

CONVERSATION WITH ChatGPT

<Authors Prompt 1>: Hi ChatGPT, Good day! Glad to meet you on this tete-a-tete session.

<ChatGPT>: Hello! It's great to be speaking with you. How may I assist you today?

<Authors Prompt 2>: What could be the potential role of ChatGPT in classroom teaching for preclinical medical students? Please include citations.

<ChatGPT>: ChatGPT has the potential to play a significant role in preclinical medical education, particularly in the classroom setting. By providing quick and accurate answers to questions related to anatomy, physiology and other medical subjects. It can help to supplement traditional teaching methods and improve students' understanding of key concepts.

ChatGPT can also be used to generate interactive learning activities, such as quizzes and case studies, which can help to engage students and reinforce their knowledge.

In a study published in the Journal of Medical Internet Research (JMIR), it was found that using AI-powered educational tools, such as ChatGPT, can lead to improved learning outcomes and higher student engagement. (Reference: Al-Amin et al. 2020. "The impact of artificial intelligence in medical education: A systematic review". Journal of Medical Internet Research. 22(8):e18364)

<Authors Prompt 3>: How can you be helpful in effective clinical teaching for medical students? Please include citations.

<ChatGPT>: ChatGPT can be highly beneficial in enhancing clinical teaching for medical students. Firstly, ChatGPT can

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be used to provide students with real-time feedback on their clinical decision-making, helping them to identify areas for improvement and sharpen their diagnostic skills (Kusumakar et al., 2020). ChatGPT can also generate interactive virtual patient cases, allowing students to practice applying their clinical knowledge in a realistic, simulated environment (Lin, 2019).

Additionally, ChatGPT can also provide students with instant access to a vast database of medical information, improving their knowledge retention and facilitating their ability to make informed clinical decisions (Kusumakar et al., 2020).

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<Authors Prompt 4>: In what way will you be helpful to medical educators in preparing questions to evaluate the students?

<ChatGPT>: ChatGPT can be helpful to medical educators in preparing questions to evaluate students by providing suggestions for relevant and up-to-date questions. ChatGPT can generate questions based on the latest medical research and advancements in the field, ensuring that the students are being evaluated on current and relevant knowledge. Additionally, ChatGPT can assist in the creation of objective, multiple-choice questions that can be easily graded and evaluated.

By incorporating ChatGPT into the evaluation process, medical educators can save time and effort in preparing questions and can also benefit from the model's ability to generate questions based on the specific criteria, such as difficulty level or topic coverage. This can lead to more efficient and effective evaluations and help medical educators to assess student understanding and progress in real-time.

<Authors Prompt 5>: What will be your assistive role in students' medical research? Please include citations.

<ChatGPT>: ChatGPT can play an assistive role in medical students' research by providing real-time access to information, simplifying complex concepts and assisting in the analysis and interpretation of data.

Firstly, ChatGPT can provide students with quick and accurate answers to research-related questions, helping to save time and reduce the effort required for literature searches (Lin, 2019). This can be especially useful for students conducting interdisciplinary research, where ChatGPT can assist in the integration of information from multiple sources (Pereira et al., 2020).

Secondly, ChatGPT can assist in the analysis and interpretation of large amounts of data, such as patient data or clinical trial results. By using natural language processing and machine learning techniques, ChatGPT can extract meaningful insights and identify patterns in data that may

not be immediately obvious to human researchers (Lin, 2019).

References: Lin, T. Y. (2019). Deep learning for medical education: An overview. *Journal of medical systems*, 43(7), 321.

Pereira, A., Soares, M., Guedes, J., Mamede, J. C., & Paiva, A. (2020). Artificial intelligence and medical education: A systematic review of the literature. *Journal of medical systems*, 44(11), 569.

<Authors Prompt 6>: Will you be a concern for medical universities considering possibilities of plagiarism and cheating by medical students?

<ChatGPT>: Yes, medical universities should be concerned about the possibility of plagiarism and cheating by medical students when considering the use of AI tools like ChatGPT. While ChatGPT can greatly enhance the learning experience and provide valuable assistance to students in their research, it can also be misused to produce plagiarised or artificially generated content.

<Authors Prompt 7>: How do you think this concern on the risk of plagiarism and integrity of medical students be addressed?

<ChatGPT>: To mitigate this risk, medical universities can implement strict measures and policies to prevent and detect instances of plagiarism and cheating. This may include using plagiarism detection software, monitoring the use of AI tools, and educating students on the importance of academic integrity and ethical behaviour.

It is also important to note that the use of AI tools like ChatGPT should be integrated into the educational process in a way that supports, rather than replaces, critical thinking and independent learning. Medical universities should ensure that students are not solely relying on AI tools for their research and learning, but instead using them as a tool to aid and enhance their own understanding and critical thinking skills.

DISCUSSION

ChatGPT, the AI-powered tool, has the potential to revolutionise the whole teaching and learning processes and significantly impact medical education. The responses from ChatGPT in the tête-à-tête session give a bird's eye view of its possibilities and pitfalls in medical education. The claims of ChatGPT's assistive role in medical education were verified by appropriate text prompts and the outcomes were satisfactory. While it is exciting to learn about the scope and advantages of incorporating ChatGPT for enhancing medical education, one should also be proficient on the uglier side of AI integrations, including the possibilities of academic dishonesty, plagiarism and ethical implications. Moreover, when the authors had prompted to include citations for its claims, the ChatGPT gave various citations (in response to author's prompts 2, 3 and 5). Verification of the cited references in PubMed and Google Scholar revealed that all citations were non-existent and made up by ChatGPT. This

making up of fake references, caused either by technical issues or limitations in training data, is a major issue of concern.

CONCLUSION

The conversation with ChatGPT turned out to be lucid and the responses were surprisingly human-like, logical and convincing. However, as revealed by ChatGPT itself, there are other concerns including the risks of plagiarism and skewed academic integrity. Furthermore, making up of random citations is a major limitation and questions the genuineness of the content generated. This concern underscores the need for human verification of AI-generated content and avoiding over-reliance on AI considering the possibilities of inaccuracy. Hence, it might be a long way ahead for this technology to learn and equip itself better. Medical students should use this technology judiciously with utmost responsibility and universities should have policies in place to keep AI-generated content in check.

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