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Original Articles

Case Report

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Original Articles

177 The Effect of Giving A Vibrator with A Cooler on Pain Level in Childhood with Venipuncture in Tidore Kepulauan Hospital

Fadila Abdullah, Nursanti Anwar
Ternate Health Polytechnic Department of Nursing, Ternate Indonesia

The results of the statistical test show that there was a significant difference in pain in the intervention group and the control group (p=0.013). The use of a cooling vibrator can be an alternative to reduce pain in children during venipuncture.

183 Association of Neuropathic Pain Improvement and hs-CRP Changes among Trigeminal Neuralgia Patients Experienced Radiofrequency Ablation 60° and 65° Celcius: 6 Months Follow Up

Yani Arlina, Trianggoro Budisulistyo, Dwi Pudjonarko, Dodik Tugasworo, Herlina Suryawati, Elta Diah Pasmanasari
Department of Neurology, Faculty of Medicine Diponegoro University / Dr. Kariadi Hospital Semarang, Indonesia

The LANSS scores changes observed significant improvement in all groups, which mentioned if the neuropathic pain syndromes might be better under each treatment. The Hs-CRP levels improvement is better in the neuro ablation groups than analgesic drugs treatment. Even though the Hs-CRP are following of systemic nonspecific inflammation, NT is a focal inflammation.

191 Comparison of Modified OTAGO Training Program and Walking Training on Physical Performance in Pre-Frail Elderly

Nura Eky Vikawati, Hari Peni Julianti, Novita Sari Dewi, Endang Sri Mariani
Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Diponegoro University Semarang, Indonesia

Both modified OTAGO and walking training intervention can improve the physical performance of pre-frail elderly. The modified OTAGO training is not superior in improving physical performance compared to walking training.

198 The Relationship between Serum Folic Acid Levels with The Cognitive Function of The Elderly

Hermanto, Hexanto Muhartomo, Amin Husni, Maria Immaculata Widiastuty, Herlina Suryawati, Arinta Puspita Wati
Department of Neurology Faculty of Medicine Diponegoro University / Kariadi Hospital Semarang, Indonesia

There is a significant relationship between serum folic acid levels and cognitive function in the elderly. Higher educational status in the elderly is associated with better cognitive function.

203 Analgesic Potency of Ibuprofen, Paracetamol, and Mephenamic Acid: A Randomized Controlled Trial

Christin Rony Nayoan[1,2], Nur Syamsi[2]
[1]Departement of Ear, Nose, and Throat-Head and Neck Science of Medical Faculty of Tadulako University – Undata General Hospital, Palu, Indonesia
[2]Departement of Farmacology of Medical Faculty of Tadulako University, Palu, Indonesia

Paracetamol 600 mg, mefenamic acid 500 mg and ibuprofen 600 mg have equal analgesic potency.

209 Effect of Fixed Dose Combinations Antituberculosis and Separate Formulations on Clinical Symptoms, Weight Gain, Adverse Effect and Plasma Concentration in Tuberculosis and HIV Coinfection Cases

TTiti Sundari[1], Nina Mariana[2], Debby Intan Permatasari[2], Adria Rusli[1], Pompini Agustina Sitompul[1], Rosamarlina[1], Aninda Dinar Widiantari[2], Siti Maemun[2], Vivi Lisdawati[2]
[1]Department of Pulmonology, Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia
[2]Department of Research, Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia

There was not significant different between Fixed Dose Combinations and Separate Formulations groups on improvement of clinical symptoms and weight gain in intensive phase of therapy, the highest of adverse effects was gastrointestinal syndrome, and all subjects had normal reference ranges of rifampicin concentrations, and isoniazid and pyrazinamide below the normal range.

217 Cytokine Storm score (CSs) in COVID-19 Patients Smokers at Dr. Saiful Anwar Malang

Resti Fitriani Yuliawati,Tri Wahju Astuti, Yani Jane Sugiri
Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Brawijaya University / Dr. Saiful Anwar Hospital, Malang, Indonesia

Cytokines Storm scores (CSs) increased significantly in COVID-19 patients who smoked, D-dimer and CRP levels were significantly higher in smoking COVID-19 patients compared to non-smokers.

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Editorial

Welcome

It still revolves around Covid-19 and policy regulations regarding how to deal with the status of endemicity in the pattern of the spread of this virus. Several studies are still able to use data related to Covid-19 not only about the virus itself but also how humans deal with the consequences it causes. Management and monitoring of events similar to diseases caused by this virus are still being carried out and are a good source of research.

Diseases caused by infection are still a topic that is never finished being discussed. Based on any point of view capable of producing good research. Especially in Indonesia, there is a uniqueness because of the large number of cases and the increasing incidence of infectious diseases. This opened up many breakthroughs to develop the science of infectious diseases. Tuberculosis and hepatitis, are still able to make the enthusiasm of the researchers aroused. Challenges in the management of the disease make a lot of research done.

In line with infectious diseases, studies in the field of medicine still open up great opportunities to obtain useful research outcomes. Medicines, both antibiotics and other supporting medicines, related to treatment goals, are always interesting to discuss.

Whatever it is, in terms of research it should still follow standard principles in composing research. With discipline in the mastery of research methodology, supported by the availability of data and the use of appropriate analysis, writing will undoubtedly be formed that can be utilized in related scientific fields.

Especially in a situation of confusion over the new rules in health law, it is only appropriate that the scientific field must continue to be put forward. The era of globalization is increasingly open and demands that every activist in health and medical engineering have more innovation, a passion for development, and the ambition to always keep up with the times. The attitude of not being trapped in pragmatism when the new Health Law was enacted is an attitude that must always be developed. There are still many fields of knowledge that require the touch of health workers in Indonesia, apart from being concerned about the development of the situation regarding the future fate of health workers.

Happy working.

Editor.

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Original Article

Nephrotoxicity and Kidney Fibrosis Due to Gentamicin in Wistar Rats

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Abstract

Background : Gentamicin is an aminoglycoside used as a treatment for various infections. One of the side effects reported on the use of gentamicin is nephrotoxic. However, there are still many uses of gentamicin that have not been precisely indicated. This study was aimed to analyze the nephrotoxic effects leading to renal fibrosis due to gentamicin induction in Wistar rats.
Methods : This research is an in vivo experimental study, pre- and post-test control group design, conducted in September and October 2022 at the Animal House Laboratory of the Faculty of Medicine, Sriwijaya University, and the Palembang Health Laboratory Center. There were 4 treatment groups: Group I, placebo; Group II, gentamicin-induced (GIG I) at 80 mg/kgBW; Group III, gentamicin-induced (GIG II) at 120 mg/kgBW; and Group IV, gentamicin-induced (GIG III) at 240 mg/kgBW. Gentamicin was administered intraperitoneally for 7 days, to 8 Wistar rats per group. Blood was taken from all Wistar rats in each group on days 0, 3, 7, and 14. The results of the study were tested for normality with the Shapiro-Wilk test and homogeneity with the Levene's test. The ANOVA test and the Post-Hoc test were used to conduct the analysis.
Results : Induction of gentamicin in the GIG I and GIG II groups was significant in increasing the mean creatinine and urea levels on day 0 and day 14 of treatment ($p<0.05$). In the GIG III group there was a 50% mortality in experimental animals showing a Lethal dose of 50 (LD50) at that dose.
Conclusion : GIG I and GIG II have significant nephrotoxic effects in increasing creatinine and urea levels which lead to renal fibrosis.

Keywords : Gentamicin, Renal Fibrosis, Nephrotoxic, Wistar Rat

INTRODUCTION

Nephrotoxicity is defined as kidney injury or decreased kidney function[1] caused directly or indirectly by drugs[2] and other chemicals.[3] Drug-induced nephrotoxicity can affect the vascular, glomerulus, and renal tubules.[4] Some antibiotics are nephrotoxic that cause acute renal injury (AKI)[5] and chronic kidney disease (CKD) which leads to renal fibrosis.[3,6] The class of antibiotics that cause nephrotoxicity and renal fibrosis is the aminoglycoside group.[6]

Gentamicin is one example of an aminoglycoside[7] used to treat infections caused by gram-negative bacteria.[8] Gentamicin can cause nephrotoxic adverse effects in the majority of patients. Nephrotoxicity due to gentamicin also involves an inflammatory role through cell infiltration, increased cytokine production and capillary hyperpermiability.[9] The inflammatory response that was originally thought to be a defense mechanism will contribute to kidney failure.[10]

Initial inflammation of the kidneys then increases cystacin-c and inflammatory mediators in the kidneys. Increased cystacin-c and inflammatory mediators, which further increases the expression of intercellular adhesion molecule-1 (ICAM-1) and P-selectin from endothelial cells,[11] resulting in increased attachment of inflammatory cells especially netrophil cells. This leads to an increase in reactive oxygen species (ROS), leading to cell necrosis and increasing creatinine and ureal levels which are used as biomarkers to assess kidney damage.[3]

The kidneys are known to be able to regenerate, but with a cell damage rate of up to 50%, it will be difficult to restore the physiological function of the kidneys. This has prompted many researchers to investigate various drugs, especially antibiotics, that have the potential effect of causing nephrotoxicity. Gentamicin can have nephrotoxic effects, which can result in renal fibrosis, a disorder known as end-stage renal disease (ESRD). Numerous investigations have shown that gentamicin is nephrotoxic and can result in renal fibrosis, for example, at low doses of 10 mg/kg body weight over the course of several months[2], at high doses of 60 mg/kg body weight within 10 days, doses of 100 mg/kg body weight within 8 days.[12] Toxicity was known to occur at gentamicin doses ten times the safe dosage in Wistar rats. Administration of gentamicin 100 mg/kgBW i.p. to wistar rats for 8 days showed a toxicity effect on the glomerulus and renal tubules.[13]

In a study conducted by Awodele O. *et al*., it was determined that induction of gentamicin 80 mg/kgBW for 7 days caused necrosis and fibrosis of the kidney due to the progression of kidney damage; specifically by examining the nephrotoxicity effect that leads to renal fibrosis by analyzing the parameters of urea and creatinine.[14] Therefore, a research is required to evaluate kidney function parameters such as urea and creatinine in order to analyze the nephrotoxic effect causing renal fibrosis in Gentamicin-induced Wistar rats.

METHODS

Preparation of Experimental Animals

This research is an experimental research conducted in vivo with a pre and post test control group design. The research sample was Wistar rats weighing 150–200 grams with a rat age of 12–16 weeks.

The research was carried out in September October 2022 at the Animal House Laboratory, Faculty of Medicine, Universitas Sriwijaya and Palembang Health Laboratory Center. Before the study, all rats were allowed to adapt for 7 days in stainless steel cages with a minimum required volume of 500 cm^2 for two rats and a minimum required cage height of 20 cm with a room temperature of 22±1°C, 12 hours of light-dark cycles, and given ad libitum access to drinking water and food.

The sample was taken by simple random sampling and divided into four groups with 8 mice per group. Group I placebo, given aquadest; group II gentamicin-induced (GIG I) of 80 mg/kgBW; group III induced gentamicin (GIG II) of 120 mg/kgBW; group IV induced gentamicin (GIG III) of 240 mg/kgBW. Wistar rats were induced for 7 days intraperitoneally.

Nephrotoxic Effects Assessment of Gentamicin and Statistical Analysis

All Wistar rats in each group were taken blood samples from the retroorbital plexus in the eyes of mice on days 0, 3, 7, and 14. Blood samples are checked for creatinine and ureum levels by a measurement procedure using a clinical spectrophotometer.

Data analysis processing using IBM SPSS Statistic 26 application. The homogeneity and normality of the data were examined. Nephrotoxic effect is determined by Paired T test. Differences in nephrotoxic effects are determined by the Independent T test. The dose match between gentamicin and placebo was determined by PostHoc Test.

A certificate of research ethics has been obtained from the Medical and Health Research Ethics Commission (KEPKK) of the Faculty of Medicine, Sriwijaya University with certificate number 281-2022.

RESULTS

This study is an invio experimental study using 8 wistar rats each group (32 wistar rats). Group 1 (placebo), II (gentamicin 80mg/kgBW), group III (gentamicin 120mg/kgBW) and group IV (gentamicin 240mg/kgBW). In group IV, gentamicin injection 240 mg / kgBW on day 2, caused the death of 6 rats which means death in > 50% of experimental animals (Lethal Dose 50 / LD 50) at a dose of 240 mg / kg BW.

TABLE 1
Inter-Group Weight Homogeneity Test

Rat group	Rat body weight Mean ± SD (gram)	p value
Placebo group	158.57 ± 6.502	0.198
GIG I (80 mg/kgBW)	164.33 ± 2.958	
GIG II (120 mg/kgBW)	179.33 ± 2.291	
GIG III (240 mg/kgBW)	168.67 ± 9.709	

*Levene Test, p = 0.05

TABLE 2
Homogeneity Test of Creatinine and Urea Levels Before Inter-Group Treatment Intervention

Rat group	Treatment group	Mean ± SD (gram)	p value
Creatinine level	Placebo group	33.29 ± 2.431	0.290
	GIG I (80 mg/kgBW)	31.88 ± 1.387	
	GIG II (120 mg/kgBW)	32.86 ± 2.494	
Ureum level	Placebo group	7.18 ± 1.447	0.356
	GIG I (80 mg/kgBW)	5.88 ± 0.975	
	GIG II (120 mg/kgBW)	6.71 ± 1.573	

*Levene Test, p = 0.05

Homogeneity Test

The homogeneity test was conducted to determine the homogeneity of the data on the body weight of rat before treatment. In the levene test, rat body weight was obtained, p value = 0.198 ($p > \alpha$) which showed no difference in the mean body weight of rat before treatment between treatment groups. Thus, the body weight of the rats had homogeneous data variance (Table 1).

Homogeneity tests were also performed to determine homogeneity in creatinine and ureum levels before treatment (day 0). The results of statistical tests with levene test statistical tests obtained rat creatinine levels p = 0.290 ($p > \alpha$) and rat ureum levels p = 0.356 ($p > \alpha$) which showed that there was no difference in the mean creatinine and ureum levels of rats before treatment between treatment groups (Table 2).

Normality Test

Table 3 showed the results of the normality test of serum creatinine and ureal levels before treatment in each group with the Shapiro Wilk test, it was found that serum creatinine and ureum levels before treatment were normally distributed ($p > \alpha$) with a value of $\alpha = 0.05$.

The nephrotoxic effect of gentamicin in the group on creatinine and ureum levels can be seen using the statistical test Paired T-Test. Table 4 shows the mean creatinine levels before treatment and day 14 of treatment in the placebo, GIG I and GIG II groups showed significant differences in mean creatinine levels.

Table 5 shows that the mean ureum levels on day 0 and day 14 after induction in the placebo group showed no difference in mean ureal levels, while GIG I and GIG II showed significant differences in mean ureal levels,

Intergroup Nephrotoxic Effects on Creatinine and Ureal Levels

The nephrotoxic effect of gentamicin in the group on creatinine and ureal levels can be seen using the statistical test Paired T-Test. In Table 4 which shows the mean creatinine levels before treatment (day 0) and day 3 of treatment in the placebo group there is no difference in the mean creatinine levels, while in GIG I and GIG II show a significant difference in mean creatinine levels.

In Table 4 also showed mean ureum levels before treatment (day 0) and day 3 after induction in placebo, GIG I, and GIG II groups there were differences in mean ureum levels.

Table 6 demonstrates that the placebo group had no significant differences in mean ureum levels on day 0 and day 14 of treatment, whereas GIG I and GIG II had significant differences in mean ureum levels. Table 5 also

TABLE 3
Normality Test on Creatinine and Ureal Levels between Intervention Groups

Rat group	Treatment group	p value
Creatinine level	Placebo group	0.873
	GIG I (80 mg/kgBW)	0.739
	GIG II (120 mg/kgBW)	0.484
	GIG III (240 mg/kgBW)	0.220
Ureum level	Placebo group	0.755
	GIG I (80 mg/kgBW)	0.093
	GIG II (120 mg/kgBW)	0.577
	GIG III (240 mg/kgBW)	0.388

* Shapiro Wilk test, p = 0.05

TABLE 4
Nephrotoxic Effects of Gentamicin on Creatinine Levels at Day 0 and Day 14 between Intervention Groups

Rat group	Creatinine level		p value
	day-0	day-14	
Placebo group	33.29 ± 2.43	38.28 ± 1.32	0.301
GIG I (80 mg/kgBW)	31.88 ± 1.38	227.07 ± 3.43	0.000
GIG II (120 mg/kgBW)	32.86 ± 2.49	405.81 ± 0.57	0.003

*Paired T test, p = 0.05

TABLE 5
Nephrotoxic Effects of Gentamicin on Creatinine and Ureum Levels on Day 0 and Day 3 between Intervention Groups

Rat group	Creatinine level		p value	Ureum level		p value
	Day-0	Day-3		Day-0	Day-3	
Placebo group	33.29 ± 2.43	34.38 ± 2.10	0.301	7.18 ± 1.44	9.94 ± 2.76	0.022
GIG I (80 mg/kgBW)	31.88 ± 1.38	33.21 ± 1.65	0.000	5.88 ± 0.97	6.39 ± 1.00	0.000
GIG II (120 mg/kgBW)	32.86 ± 2.49	34.98 ± 2.55	0.003	6.71 ± 1.57	8.80 ± 0.99	0.010

*Paired T test, p = 0.05

shows that the mean ureum levels on day 3 and day 7 of treatment in the placebo, GIG I, and GIG II groups showed differences in mean ureum levels.

Table 7 shows that there was no difference in mean creatinine levels on day 7 and day 14 after induction in the placebo group, whereas GIG I and GIG II showed significant differences in mean creatinine levels. Table 6 also demonstrates that there was no difference in the placebo group's mean urea levels on the seventh and fourteenth days after treatment, whereas GIG I and GIG II exhibited significant differences in mean urea levels.

Table 8 demonstrates that there was a significant difference between the placebo, GIG I, and GIG II groups' mean creatinine levels before and after induction. Table 7 demonstrates that there was no difference in the placebo group's mean urea levels before and after treatment, whereas GIG I and GIG II exhibited significant differences in their mean urea levels.

TABLE 6
Nephrotoxic Effects of Gentamicin on Creatinine and Ureal Levels at Day 3 and Day 7 between Intervention Groups

Rat group	Creatinine level		p value	Ureum level		p value
	Day-3	Day-7		Day-3	Day-7	
Placebo group	34.38 ± 2.10	34.15 ± 3.79	0.873	9.94 ± 2.76	8.03 ± 2.14	0.003
GIG I (80 mg/kgBW)	33.21 ± 1.65	156.01 ± 1.31	0.000	6.39 ± 1.00	21.19 ± 1.23	0.000
GIG II (120 mg/kgBW)	34.98 ± 2.55	228.36 ± 2.21	0.000	8.80 ± 0.99	34.04 ± 1.84	0.000

*Paired T test, p = 0.05

TABLE 7
Nephrotoxic Effects of Gentamicin on Creatinine and Urea Levels on Day 7 and Day 14 between Intervention Groups

Rat group	Creatinine level		p value	Ureum level		p value
	Day-7	Day-14		Day-7	Day-14	
Placebo group	34.15 ± 3.79	38.28 ± 1.32	0.058	8.03 ± 2.1	7.57 ± 0.63	0.650
GIG I (80 mg/kgBW)	156.01 ± 1.31	227.07 ± 3.43	0.000	21.19 ± 1.23	40.39 ± 3.99	0.000
GIG II (120 mg/kgBW)	228.36 ± 2.21	405.81 ± 0.57	0.000	34.04 ± 1.84	47.00 ± 1.88	0.000

*Paired T test, p = 0.05

TABLE 8
Nephrotoxic Effects of Gentamicin on Creatinine and Urea Levels on Day 0 and Day 14 between Intervention Groups

Rat group	Creatinine level		p value	Ureum level		p value
	Day-0	Day-14		Day-0	Day-14	
Placebo group	33.29 ± 2.43	38.28 ± 1.32	0.005	7.18 ± 1.44	7.57 ± 0.63	0.610
GIG I (80 mg/kgBW)	31.88 ± 1.38	227.07 ± 3.43	0.000	5.88 ± 0.97	40.39 ± 3.99	0.000
GIG II (120 mg/kgBW)	32.86 ± 2.49	405.81 ± 0.57	0.000	6.71 ± 1.57	47.00 ± 1.88	0.000

*Paired T test, p = 0.05

Differences in Nephrotoxic Effects Between Groups on Creatinine Levels

The Independent T-Test statistical measure can be used to identify differences in creatinine levels between groups. Table 9 demonstrates a significant difference in creatinine levels between the placebo group and GIG I and GIG II (p) and significant difference in creatinine levels between GIG I and GIG II.

Differences in Nephrotoxic Effects Between Groups on Ureum Levels

Differences between groups on urea levels with the Independent T-Test in Table 10 showed that there were significant differences in urea levels after treatment in the placebo group compared to GIG I and GIG II ($p<\alpha$) and there were significant differences in mean urea levels after treatment in GIG I compared to GIG II.

Conformity Test of Gentamicin Induction on Creatinine Levels in Wistar Rats

The results of the dose compatibility tests for GIG I, GIG II, and placebo were analyzed using the PostHoc Test (Tukey), and it was revealed that GIG I and GIG II had distinct nephrotoxic effects than the placebo group in increasing creatinine levels (Table 11).

TABLE 9
Comparison of the Nephrotoxic Effects of Gentamicin on Creatinine Levels after Intervention (Day-14)

Group	Comparison	p value
Placebo group (38.28 ± 1.322)	GIG I (227.07 ± 3.435)	0.000
	GIG II (405.8 ± 0.579)	0.000
GIG I (227.07 ± 3.435)	Placebo group (38.28 ± 1.322)	0.000
	GIG II (405.8 ± 0.579)	0.000
GIG II (405.8 ± 0.579)	Placebo group (38.28 ± 1.322)	0.000
	GIG I (227.07 ± 3.435)	0.000

*Independen T test, p = 0.05

TABLE 10
Comparison of the Nephrotoxic Effects of Gentamicin on Ureum Levels after Intervention (Day-14)

Group	Comparison	p value
Placebo group (7.57 ± 0.635)	GIG I (40.39 ± 3.991)	0.000
	GIG II (47.00 ± 1.886)	0.000
GIG I (40.39 ± 3.991)	Placebo group (7.57 ± 0.635)	0.000
	GIG II (47.00 ± 1.886)	0.000
GIG II (47.00 ± 1.886)	Placebo group (7.57 ± 0.635)	0.000
	GIG I (40.39 ± 3.991)	0.000

*Independen T test, p = 0.05

Conformity Test of Gentamicin Induction on Ureum Levels in Wistar Rats

The results of the dose conformity tests for GIG I, GIG II, and placebo using the PostHoc Test (Tukey) revealed that GIG I and GIG II had distinct nephrotoxic effects than the placebo group in increasing ureum levels (Table 12).

DISCUSSION

This study aims to assess the nephrotoxic effect that leads to renal fibrosis by induction of gentamicin doses of 80 mg/kgBW, 120 mg/kgBW, 240 mg/kgBW. Nephrotoxic effects seen from creatinine and urea levels. The results of statistical analysis showed that all doses of gentamicin increased creatinine and urea levels ($p<0.05$). Gentamicin increased urea and creatinine levels at doses of 80 mg/kgBW, 120 mg/kgBW, 240 mg/kgBW.

At the time of the study, six rats induced by gentamicin 240 mg/kgBW died within 24 hours after the first dose was administered. This shows that a dose of 240 mg/kgBW of gentamicin has a toxic effect on >50% of experimental animals in GIG III, and has reached a Lethal Dose of 50 (LD50).The results of 240 mg/kgBW gentamicin induction contradicted previous studies conducted by Awodele O., *et al* which showed that rats induced by 280 mg/kgBW gentamicin for 14 days had a nephrotoxic effect and showed renal fibrosis due to progressive kidney damage but did not show any death in rat. Differences in research results reaching death in >50% of experimental animals (LD50) can be caused by differences in age in each experimental animal.[15] The value of creatinine and ureum in the early stages of an individual's life tends to be higher due to growth, development, and high metabolic processes. Along with increasing age and maturity until aging, this value will decrease due to the ongoing process of high metabolism. In this study, however, creatinine and urea levels increased due to gentamicin's toxic effect. Consequently, the nephrotoxic effect varies according to the age of rats.[16,17]

According to The Kidney Disease: Improving Global Outcomes (KDIGO), the increase in serum creatinine in AKI conditions is up to 1.5 times the initial value in the first 7 days. An increase in creatinine levels twofold from normal can be used as an indication of a 50% decrease in kidney function and a three-fold increase in creatinine levels can be used as an indication of a 75% decrease in kidney function. Based on the results of the

TABLE 11
Conformity test of the Nephrotoxic Effects of Gentamicin on Creatinine Levels

Variable	Placebo group	GIG I (80 mg/kgBW)	GIG II (120 mg/kgBW)
Placebo group	–	0.000	0.000
GIG I (80 mg/kgBW)	0.000	–	0.000
GIG II (120 mg/kgBW)	0.000	0.000	–

*PostHoc Test (Tukey), p = 0.05

TABLE 12
Conformity test of the Nephrotoxic Effects of Gentamicin on Ureum Levels

Variable	Placebo group	GIG I (80 mg/kgBW)	GIG II (120 mg/kgBW)
Placebo group	–	0.000	0.000
GIG I (80 mg/kgBW)	0.000	–	0.000
GIG II (120 mg/kgBW)	0.000	0.000	–

*PostHoc Test (Tukey), p = 0.05

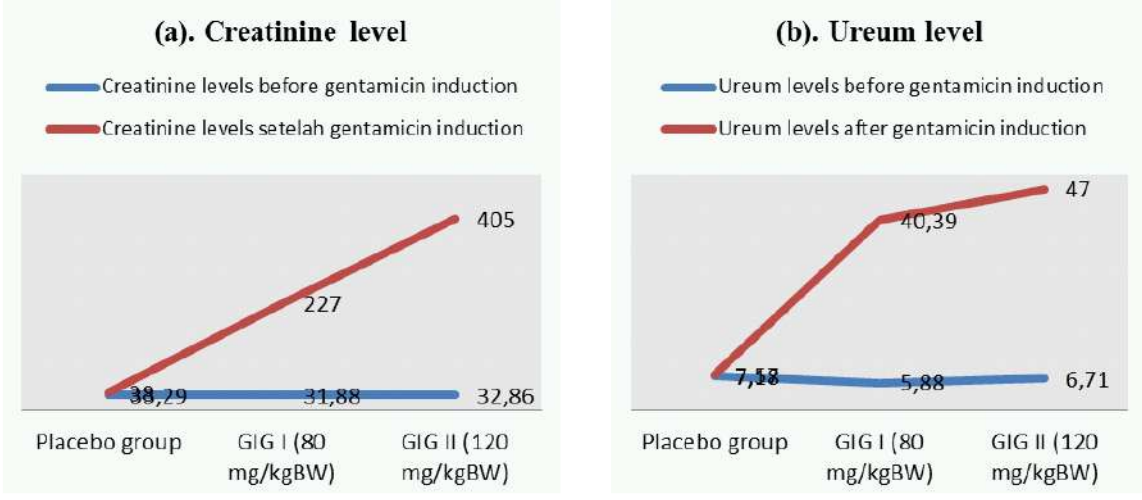

Figure 1. Nephrotoxic effects of gentamicin on the kidney
(a). Creatinine level (b). Ureum level

study, by assessing the mean comparison of creatinine levels on day 0 and day 14, it increased up to seven times in GIG I, and 12 times in GIG II. This indicates a decrease in kidney function up to stage III due to the induction of GIG I (80 mg/kgBW) and GIG II (120 mg/kgBW). Comparison was also seen in the mean urea level on day 0 and day 14, which increased up to seven times in GIG I and GIG II. In this condition, the kidney has led to a state of renal fibrosis and ends in a state of End Stage Renal Disease (ESRD).[18]

Gentamicin induction exerts a toxic effect on the renal tubular epithelium, the vascular system, and the renal glomeruli. The accumulation of gentamicin in the proximal tubule causes the transport of protein and cation molecules (megalin and cubilin complexes) in the proximal tubule by endocytosis. Gentamicin binds to membrane phospholipids and causes a condition called phospholipidosis. When the concentration of gentamicin in the GIG I group (80 mg/kgBW), GIG II (120 mg/kgBW), and GIG III (240 mg/kgBW) in the endosomal structure exceeds the threshold, the cell membrane and its contents will be disrupted which then exits into the cytosol. Gentamicin in the cytosol then binds to mitochondria and activates the intrinsic pathway of

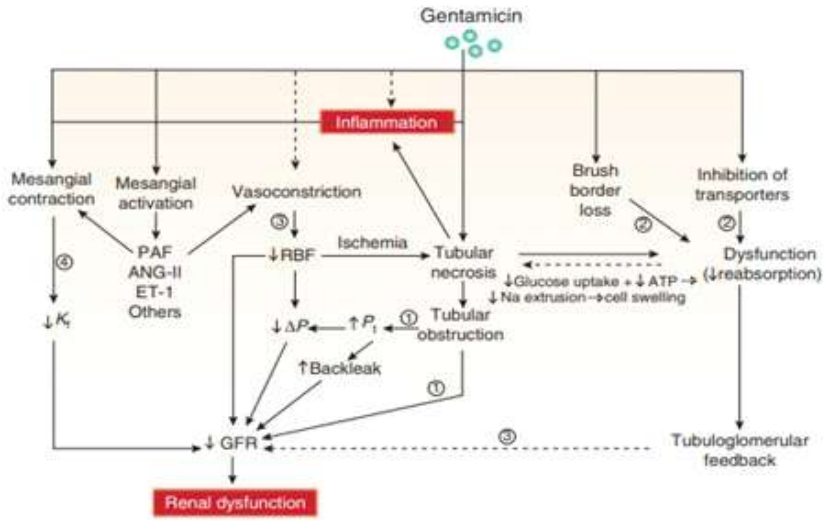

Figure 2. Integration of Gentamicin Nephrotoxicity Mechanisms[9]

apoptosis, affects the respiratory pathway, increases hydroxy radicals and superoxide anions resulting in oxidative stress in cells, and results in inhibition of Adenosine Triphosphate (ATP) production. Gentamicin also binds to mitochondria and causes an increase in Bax level (Bcl 2 binds to protein X) 4 through inhibition of proteosomal degradation. Increased Bax levels cause activation of a protease enzyme called cathepsin which can induce cell death.[11] Gentamicin also inhibits protein synthesis in the endoplasmic reticulum causing the translation process to be disrupted. Ultimately, there is activation of the Calcium-Sensing Receptor (CaSR) with gentamicin which causes apoptosis in kidney tubular cells and indicates cell death.[4] Nephrotoxicity due to gentamicin also involves an inflammatory role through cell infiltration, increased production of cytokines and capillary hyperpermeability. Inflammation is a major factor in the occurrence of kidney damage due to ischemia and nephrotoxicity.[9]

Inflammation due to the toxic effects of gentamicin plays a role in the fibrotic response of kidney tubular cells which causes the progression of kidney disease towards CKD. Continuous injury to the kidney leads to accumulation of scar tissue in the tubular epithelial cells.[19] In renal fibrosis, the tubular epithelial cells lose their polarity and transform into mesenchyme in the process of Epithelial-to-Mesenchymal Transition (EMT).[20] Tubular cells lose tubular markers, such as E cadherin and zonula occludens-1 and express mesenchymal proteins, such as α-SMA and vimentin.[21] TGF-β induces changes in the morphology of the renal tubular epithelium by increasing expression of collagen types I and IV and fibronectin[22] and increasing matrix production.[23] The contractile nature of scar tissue will cause dysfunction so that fibrosis can end in end-stage renal failure.[24,25] This study proves that a dose of 80mg/kgBW can cause nephrotoxicity which leads to kidney fibrosis. In this study, histopathological features of the kidneys of Wistar rats were not shown, however, data on increased levels of urea and creatinine indicated impaired kidney function in the form of nephrotoxicity leading to renal fibrosis.

CONCLUSION

Gentamicin doses of 80 mg/kgBW (GIG I) and 120 mg/kgBW (GIG II) substantially raised the levels of ureum and creatinine, indicating that gentamicin induction result in nephrotoxicity and kidney fibrosis in Wistar rats.

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Original Article

Coping Strategies and Dass Scores among Nurses on Duty in Covid-19 Isolation Room: A Cross-Sectional Study

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Abstract

Background : Nurses are at risk for mental health problems while caring for Corona Virus Disease 2019 (COVID-19) patients. The COVID-19 pandemic had impacted not only on emotions but also nurses' coping strategies. The difference between this study and previous research in this study adds up the total DASS 42 (Depression Anxiety Stress Scale) scores as parameter to assess mental health problems of the subjects. The objectives of this study was to determine the association between coping strategies and the DASS score among nurses on duty in the COVID-19 isolation room of Dr. Kariadi Hospital.

Methods : This cross-sectional study involved nurses who treated patients in the COVID-19 isolation ward, the COVID-19 intensive room, and the COVID-19 emergency room. All participants were involved by the consecutive sampling method. The research instrument used a sociodemographic questionnaire, the Brief COPE, and the DASS 42. Inclusion criteria included nurses who served in the COVID-19 isolation room and aged 22-60 years. Higher DASS score indicates that the subject is experiencing general psychological distress compared to subjects with a lower score.

Results : Most of the respondents in this study (n=112 subjects) had problem-focused coping strategies. The mean DASS score on the subjects is 14.29 ± 13.25. There was an association between coping strategies ($p=0.048$), sex ($p < 0.001$), place of work ($p = 0.041$), and DASS score.

Conclusion : There was a relationship between coping strategies and the DASS score of nurses on duty in the COVID-19-19 isolation room. Further research needs to explore environmental factors and social support, also examine physical illnesses in more detail.

Keywords : Coping strategies; DASS; nurses; COVID-19; mental health

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was first detected in Wuhan, China. Based on the official website of World Health Organization (WHO), on February 13, 2021, there were around 410,876 new cases of patients infected with COVID-19 globally.[1] Based on data from the Ministry of Health of the Republic of Indonesia (Kemenkes RI), it is known that the total confirmed cases of COVID-19 globally as of February 11, 2021, there were 106,991,090 cases with 2,347,015 deaths and a Case Fatality Rate (CFR) of 2.2%.[2,3] One of the most needed case-control efforts is the preparation of facilities and infrastructure for the management of cases that require an isolation room that meets the requirements. Therefore, the Dr Kariadi Hospital was appointed as one of the COVID-19 referral hospitals in Central Java.[3]

Nurses are medical professionals involved in handling COVID-19 and are prone to mental health problems.[4] Nurses' occupational stress has been found to decrease the health and well-being of nurses and may put patient safety at risk and has been linked to patient errors. Stress management in health care worker, especially nurse, is needed to sustain and grow healthy and fiscally viable health care organizations that provide safe, high-quality care.[5] One of the studies by Lai *et al* found that nurses who are directly involved in the care of COVID-19 patients are at higher risk of developing mental health problems, such as depression and anxiety disorder.[6] One instrument that can be used to assess mental health problems is the DASS 42 (Depression Anxiety Stress Scale).[7]

Study on depression, anxiety, and stress among nurses during COVID-19 lockdown has been conducted in Nepal which shown some degree of depression, anxiety and stress were prevalent among nurses during the COVID-19 pandemic.[8] Another cross-sectional study in 8 European countries during peak COVID-19 months had a considerable proportion of the participants, which is medical professionals, showed high values for depression, anxiety, and stress.[9] A similar study was also conducted at the COVID-19 Referral Hospital in Aceh, Indonesia which focused on mental distress among nurses in regular ward and COVID-19 ward.[10] However, these two studies used DASS-21 which is the shortened version of DASS-42.

COVID-19 not only has an impact on emotions but also changes coping strategies. The use of good coping strategies will help individuals manage stress and reduce negative emotions, but the association between nurses' coping strategies and emotional responses due to infectious diseases such as COVID-19 still requires further research.[11] We would like to investigate not only mental health problem, but also coping strategies among nurse in the setting of COVID-19 pandemic. This study was to determine the association between coping strategies and the DASS score among nurses on duty in the COVID-19 isolation room of Dr. Kariadi Hospital.

MATERIALS AND METHODS

This research is a quantitative study with a cross-sectional approach at Dr. Kariadi Hospital. Data collection was carried out in July 2021. Inclusion criteria included: nurses who served in the COVID-19 isolation room and aged 22–60 years. Exclusion criteria included: history of having or being treated by a psychiatrist and starting to suffer from mental problems with or without taking medication from a psychiatrist since before the COVID-19 pandemic; and use alcohol, narcotics, and psychotropic substances.

Using a consecutive sampling technique, 168 subjects were obtained as respondents. Each respondent filled out the informed consent, sociodemographic questionnaire, COPE Brief questionnaire, and DASS 42 questionnaire. The DASS scores, age, gender, education, workplace, job position, medical condition, and coping strategies were obtained using a questionnaire. Coping strategy as measured by COPE Brief is obtained by adding up each question. The coping strategy's dimensions consists of problem-focused, emotional focused, and dysfunctional coping which then categories to 14 coping stategies. This questionnaire is a self-rating consisting of 28 questions, using a Likert scale where the answer choices are always (SL) = score 4, often (SR) = score 3, sometimes (KK) = score 2, never (TP) = score 1.12 The DASS questionnaire consists of 42 items to measure three scales, namely depression, anxiety and stress each of which has 14 statement items. The answer to this DASS test consists of 4 choices arranged on a scale, namely 0 = never, 1 = sometimes, 2 = often, 3 = very often. The value obtained from the subjects' response was totalled.[7]

Data were analyzed by univariate and bivariate using the SPSS program. Univariate analysis to determine descriptive data and description of sociodemographic characteristics such as mean value, standard deviation, maximum value, minimum value, and percentage. Bivariate analysis used to find the association between variables and DASS scores. Numerical data was analyzed using the Spearman correlation test, while categorical data was analyzed using the Chi square or Fisher's exact with a significance value of <0.05 with a 95% confidence interval.

Participants provided electronic informed consent prior to starting the survey. The research was authorized by the Ethical Committee of the Faculty of Medicine Universitas Diponegoro (No. 832/EC/KEPK-RSDK/2021).

RESULT

This study involved 168 nurses in the COVID-19 isolation room at Dr. Kariadi with an age range of 22-57, the mean age is 32.27 ± 6.27, and the mean is 31. A total of 112 subjects used problem-focused, 55 subjects used emotionally focused, and one used dysfunctional (Table 1).

The mean DASS score for the subjects was 14.29 ± 13.25, with the lowest score being 0 and the highest being 60, and the median score was 10 (Table 2). There were 159 (94.6%) subjects who had DASS scores at a low level and 107 (63.7%) of them used problem focused coping strategies. Only 9 (5.4%) subjects had a DASS score (GPD) at the moderate level, and 5 (3%) of them used problem-focused coping strategies. Therefore, problem-focused coping strategies was used by majorities of the subjects.

The subject's coping strategies varied as shown on Table 3. The average number of the subject using active coping was 6.99 ± 1.2 subjects, and 6.4 ± 1.3 using instrumental support. On the emotion-focused dimension, the average subject who used religion was 7.8 ± 0.6 and used humor was 3.59 ± 1.7. On the dysfunctional dimension, the mean of subjects using self-distraction were 6.01 ±1.3 and 2.11 ± 0.6 subjects using substance use.

There was a significant association between the sex

TABLE 1
Sociodemographic characteristics of research subjects

Characteristics	F (%)	Mean ± SD; Median (min-max)	Group		
			Problem-focused (n=112)	Emotion-focused (n=55)	Dysfunctional (n=1)
Age; (year)		32.27± 6.27;31 (22–57)	32.70 ±6.1;32 (22–57)	31.44 ± 6.63;31 (22–57)	31
Gender; (%)					
Man	67 (39.9%)		46 (27.4%)	21 (12.5%)	0 (0%)
Woman	101 (60.1%)		66 (39.3%)	168.67 ± 9.709	1 (0.6%)
Marital status					
Not married yet	26 (15.5%)		14 (8.3%)	12 (7.1%)	0 (0%)
Married	139 (82.7%)		96 (57.1%)	42 (25.0%)	1 (0.6%)
Divorced	3 (1.8%)		2 (1.2%)	1 (0.6%)	0 (0%)
Level of education					
D3	104 (61.9%)		68 (40.5%)	36 (21.4%)	0 (0%)
Nurse Practitioner	64 (38.1%)		44 (26.2%)	19 (11.3%)	1 (0.6%)
Work place					
Isolation Ward	92 (54.8%)		56 (33.3%)	35 (20.8%)	1 (0.6%)
ICU Isolation	49 (29.2%)		36 (21.4%)	13 (7.7%)	0 (0%)
ER Isolation	27 (16.1%)		20 (11.9%)	7 (4.2%)	0 (0%)
Medical Condition					
Hypertension/DM	4 (2.4%)		2 (1.2%)	1 (0.6%)	1 (0.6%)
None	164 (97.6%)		110 (65.5%)	54 (32.1%)	0 (0%)
Working Position					
Head nurse	6 (3.6%)		4 (2.4%)	2 (1.2%)	0 (0%)
Staff nurse	162 (96.4%)		108 (64.3%)	53 (31.5%)	1 (0.6%)
History of suffering from COVID-19					
Once	61 (36.3%)		46 (27.4%)	15 (8.9%)	0 (0%)
Never	107 (63.7%)		66 (39.3%)	40 (23.8%)	1 (0.6%)

TABLE 2
DASS Score Characteristics

Characteristics	F (%)	Mean ± SD; median (min-max)	Group		
			Problem-focused (n=112)	Emotion-focused (n=55)	Dysfunctional (n=1)
DASS score (GPD) (mean ± SD; Median (min-max))		14.29 ± 13.25; 10 (0–60)			
Low	159 (94.6%)		107 (63.7%)	51 (30.4%)	1 (0.6%)
Currently	9 (5.4%)		5 (3%)	4 (2.4%)	0 (0%)

TABLE 3
Characteristics of the brief COPE subscale used by research subjects

Dimension	Subdimension	Average±SD
Problem-focused coping	Active Coping	6.99 ± 1.2
	Planning	6.68±1.2
	Using instrumental support	6.4 ± 1.3
Emotion-focused coping	Acceptance	6.89 ± 1.1
	Humour	3.59 ± 1.7
	Religion	7.8 ± 0.6
	Using emotional support	6.79 ± 1.2
	Positive reframing	6.9 ± 1.1
Dysfunctional coping	Denial	4.01 ± 1.6
	Self-distraction	6.01 ± 1.3
	Behavioural disengagement	2.86 ± 1.2
	Substance use	2.11 ± 0.6
	Venting	5.29 ± 1.5
	Self-blame	4.3 ± 1.54

variable and the DASS score (p<0.000), the workplace variable and the DASS score (p=0.041), and coping strategies with the DASS score (p=0.048). There was no significant association between age, marital status, education level, medical condition, work position, and history of suffering from COVID-19 on the DASS score (Table 4).

DISCUSSION

The characteristics of the research subjects, which include age, gender, marital status, education level, medical condition, work position, history of suffering from COVID-1919, can be said to be relatively homogeneous. The average DASS score for nurses was 14.29 ± 13.25, with the lowest score being 0 and the highest score being 60 and 159 (94.6%) subjects having a low DASS score. This may be due to the COVID-19 pandemic that has lasted more than one year. Thus, nurses have already adapted to the conditions of the circumstance. Most of the nurses in this study have received vaccines that can increase their immunity, have received training on COVID-19, received incentives, and the isolation room has provided standardized PPE (Personal Protective Equipment) for nurses.[10]

There are variations of coping strategies in research subjects with problem-focused coping being the most widely used. Coping strategies are ways for

TABLE 4
The association between variables on the DASS score (GPD)

Characteristics	F (%)	Mean ± SD; Median (min-max)	p ¥	r
Age; (year)		32.27 ± 6.27;31.00 (22–57)	0.624	-0.038
Gender; (%)			<0.001*	0.268
Man	67 (39.9%)	10.06 ± 10.65;6 (0–44)		
Woman	101 (60.1%)	17.09 ± 14.08;14 (0–60)		
Marital status			0.119	-0.121
Not married yet	26 (15.5%)	18.54 ± 14.72;17 (0–48)		
Married	139 (82.7%)	13.53 ± 12.94;9 (0–60)		
Divorced	3 (1.8%)	12.33 ±10.79;17 (0–20)		
Level of education			0.666	0.054
D3	104 (61.9%)	14.09 ±13.32;9 (0–48)		
Nurse Practitioner	64 (38.1%)	14.61 ±13.22;11 (0–60)		
Work place			0.041*	-0.126
Isolation Ward	92 (54.8%)	11.18 ± 11.06;9 (0–42)		
ICU Isolation	49 (29.2%)	16.01 ± 13.79;11.5 (0–48)		
ER Isolation	27 (16.1%)	14.04 ± 13.39;11 (0–60)		
Medical Condition			0.177	-0.105
Hypertension/DM	4 (2.4%)	29.25 ±25.26;27.5 (2–60)		
None	164 (97.6%)	13.92 ±12.75;10 (0–48)		
Working Position			0.224	0.094
Head nurse	6 (3.6%)	7.67 ±8.41;4.5 (2–24)		
Staff nurse	162 (96.4%)	14.53 ±13.35;11 (0–60)		
History of suffering from COVID-19			0.387	-0.067
Once	61 (36.3%)	15.62 ±13.81;14 (0–60)		
Never	107 (63.7%)	13.52 ± 12.92;9 (0–48)		
Coping strategy			0.048*	-0.034
Problem-focused	112 (66.7%)	13.25±13.11;9 (0–46)		
Emotion-focused	55 (32.7%)	14.58±13.22;11 (0–60)		
Dysfunctional	1 (0.6%)	38		

individuals use in solving problems, dealing with changes that occur, and threatening situations, both cognitively and behaviorally. There are three types of coping strategies. Problem focused coping has the goal of solving a problem or taking action to change the status quo. Emotional focused coping focuses on emotions and aims to reduce emotional distress related to stressful situations. Lastly, dysfunctional coping is a coping strategy that tends to be unhelpful in reducing stress and usually involves denial, self-distraction, behavioral disengagement, substance use, venting and self-blame.[11]

Significant association between coping strategies

and DASS score was found, despite a very weak correlation, with negative correlation. This result shows the more often subjects use problem focused coping strategies, the lower the DASS score. This finding is in line with the theory that stressful pandemic conditions can affect many people, but the response and impact on individuals vary according to the coping strategies. Coping strategies are influenced by environmental factors (external) and personal characteristics (internal). The use of adaptive coping is one factor that influences the resilience or protective factor of nurses in dealing with the COVID-19 pandemi.[13,14] Individuals who do not use adaptive coping are more prone to experiencing mental health problems.[15] Si *et al* found that problem-focused coping can help reduce the occurrence of adverse psychological symptoms such as depression, anxiety and stress thereby reducing nurses' DASS scores.[16] Successful coping strategies will help individuals manage events that cause stress and negative emotions that can affect the DASS score.[11,17] Also, using adaptive coping strategies can reduce the incidence of mental problems in nurses in dealing with the COVID-19 pandemic.[18]

Physiological differences, susceptibility to stress, and self-concept between genders result in different responses to stressors which ultimately would affect the DASS score. This study found a significant association between gender and nurses' DASS scores with women had higher average DASS score. This is in line with research by Alnazly *et al*., which states that there is an association between gender and nurses' DASS scores.[19] In general, women are more prone to suffer from mental problems because physiological differences between women and men (i.e. genetic susceptibility, hormone and cortisol levels and others) can be reflected emotionally and behaviorally. Women are more susceptible to stress and pain than men, so they are prone to experience greater sadness and anxiety.[20]

There was no significant association between education and DASS score of subjects who served in isolation rooms. In the organizational structure of nursing management, nurses are divided into clinical managers and working nurses. Clinical managers are expected to have professional skills in managing nursing care while working nurses have professional practice skills. So that nurses with a higher level of education have higher responsibilities and leadership roles, while nurses with D3 education have an active role in nursing care so that they come into direct contact with Covid-19 patients. This situation shows both groups have a heavy workload which can be trigger for stress. This study is in line with research conducted by Cheung *et al*., which found no significant association between education and nurses' DASS scores.[21]

Nurses in this study had different workplace including ICU, ward, and emergency room. This study found a significant association between workplace and DASS score. Subjects who work in the intensive care unit has higher average DASS score than subjects who work in the emergency room or ward. That may be due to nurses on duty in the intensive care unit have more complex nursing care, such as administering medication and monitoring the patient's vital signs continuously compared to nurses who work in other places. In addition to that, this study result is also in line with Muliantino, where they found a significant association between the workplace and the DASS score.[22]

Contrary to workplace, no significant association was found between the work position and nurses' DASS scores. It may be partly explained by the fact that the mental health of the head nurses and the staff nurses are both affected by the COVID-19 pandemic. Staff nurses have a high risk of contracting the disease and are prone to psychological problems, while the head nurses can still be infected by his co-workers who directly handle COVID-19 patients. The majority of the subjects of this study are staff nurses. This finding is in line with Chowdhury, which they also did not find the association between the work position and mental problems of nurses during the COVID-19 pandemic calculated by the DASS score.[23]

The study also found no significant association between physical illness and nurses' DASS scores. This is because this study did not assess physical illness in detail so that as many as 164 (97.6%) subjects did not have a physical illness with an average DASS score of 13.92 ± 12.75. It appears that the distribution between subjects who have and do not have a physical disease is not equal. It can be concluded that physical illness is not the only factor associated with the DASS score.[24] This study is in line with Cheung *et al*., who investigated the association between physical illness and symptoms of depression, anxiety, and stress using the DASS on nurses in Hong Kong.[21]

This study has two limitations. First, environmental factors and social support were not examined, eventhough these could influence nurses' coping strategies and DASS scores. Second, data on physical illness were lacking in detail.

CONCLUSION

The study results concluded there was an association between coping strategies, gender, workplace, and the DASS score of nurses who served in the COVID-19 isolation room at Dr Kariadi Hospital. There were variations in coping strategies for nurses who work in the COVID-19 isolation room, with problem focused as the most widely use. As nurse well-being is important for safety and patient care, mental health services are needed for nurses who are constantly in stressful work condition. Further research needs to be carried out on environmental factors and social support that can affect

nurses' coping strategies, depression, anxiety, and stress also examine physical illnesses in more detail.

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Original Article

The Wistar Rat Parietal Lobe Cell and Pain Perception Changes after Frequent of Mobile Phone Electromagnetic Wave Expose

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Abstract

Background : The increasing number of mobile phone users raises concerns about the effects. Mobile phone electromagnetic wave radiation harms pain perception due to granular cell changes in the cerebral parietal cortex. The aimed of this study was to determine the effect of exposure to electromagnetic waves mobile phone on pain perception due to changes in the granular cells of the cerebral parietal cortex Wistar rats.
Methods : Experimental research using randomized posttest with control group design. Samples were 28 rats divided into 4 groups. The control group was not exposed, the treatment group was exposed to 2100 MHz electromagnetic waves for 2 hours/day with a distance of 3 cm for 15 days in treatment group 1, for 30 days in treatment group 2, and 45 days in treatment group 3. Measurement of pain onset using the hot method. Changes in pain threshold were taken from the difference in pain onset after exposure to before exposure. Granular cell changes in the cerebral parietal cortex were assessed from the total score with the provisions of normal cells (sumx0), hydropic degenerated cells (sumx1), and necrotic cells (sumx2).
Results : The longer the exposure to mobile phones, the higher the pain threshold and the cerebral parietal cortex granular cell damage score. There was a significant difference in pain threshold and changes in cerebral parietal cortex granular cells between groups (p=0.000). There was a significant relationship between changes in the parietal cerebral cortex granular cells and pain threshold in Wistar rats exposed to electromagnetic waves (p=0.000).
Conclusion : Exposure to mobile phone electromagnetic waves affects pain perception due to changes in the granular cells of the cerebral parietal cortex in wistar rats.

Keywords : mobile phone, electromagnetic, pain threshold, granular cells, parietal lobe

INTRODUCTION

In the COVID-19 pandemic situation starting in 2020 which requires people to keep their distance from each other and not communicate directly, causing the use of mobile phone, especially the internet, to increase by around 7% or ±875,000 new users every day around the world, raising concerns about the effects.[1] Mobile phone electromagnetic wave radiation has side effects or negative impacts that have the potential to interfere with health.[2] The negative impact of mobile phones on the brain from previous research shows that exposure to 900 MHz electromagnetic waves at a short distance causes an increase in brain tissue temperature.[3] Prolonged exposure to 837.8 MHz electromagnetic waves can increase brain glucose metabolism in the area closest to.[4,5] Excessive smartphone use is likely to fail cognitive control during emotional processing, and this impairment might be influenced on emotional processing related to social interaction.[6] Exposure to a mobile phone when it is placed 5 cm from the head causes less brain activation than when the mobile phone is placed next to the ear/head on both sides.[7] Exposure to 900 MHz electromagnetic waves in the brain can increase oxidative stress due to an increase in free radicals, causing changes in the histopathological structure of the brain in the form of shrinkage of pyramidal neurons, mild perivascular and perineural edema, vacuolation of neurons and glial cells of the cerebral cortex and rat hippocampus.[8,9] Reduction of Purkinje cells, vacuolization of neurons and glial cells, interstitial edema in the cerebellum and apoptosis of glial cells in the frontoparietal lobe of the cerebral cortex.[8,10] The cerebral parietal lobe, which plays an important role in pain perception, might interfere due to structural changes following mobile phone electromagnetic exposure. Recently the brain wave activities seemed to raise in the frontal and temporal lobes.[7] Whereas the cellular structure changes remain not much has been explored, and the pain symptoms are influenced by mood or individual perception. The pain involved multifactorial subjective experience, which developed from a neuromatrix brain working. Meanwhile, the affective-cognitive as the neuroanatomical function also plays role in it.[11] Based on it, we thought that pain perception might be important to learn, so it is necessary to observe the perception of pain due to changes in the granular cells of the cerebral parietal cortex.

METHODS

This is an experimental study conducted from January 2022 – March 2022 at the Experimental Animal Laboratory of Medical Faculty UNDIP and the Anatomical Pathology Laboratory of the Diponegoro National Hospital by using the randomized posttest method with a control group design. The 28 healthy male Wistar rats (Rattus norvegicus) with the age of 24 weeks and body weight of ± 200 g were divided into 4 groups, and each was placed in a different cage with the dimension measured 7cm x 20cm x 5cm. The control group was only placed in a treatment cage for 2 hours/day for 45 days, and the treatment group was exposed to 2100 MHz electromagnetic waves for 2 hours/day with a distance of 3 cm for 15 days (Group 1), for 30 days (Group 2), and 45 days (Group 3). Pain threshold might be assessed for all samples by placing them on a hot plate with a temperature of 55°C. The initial

Figure 1. The mobile phone devices are placed within a 3 cm distance from the cage which the electromagnetic exposure effect observe.

time exams of pain sensations were counted by stopwatch and recorded when the rats pulled or licked their feet. Thus reflected pain sensation feeling according to the grimace rat scale (GRS),[12,13] and its record as base line time of pain threshold sensation. The delta changes in pain intensity presented as the differentiation between the baseline data before mobile phone exposure, and the time recorded after the duration time of exposure as the groups divided.

Immediately after completion of the last mobile phone exposure, the rats will be decapitated according to each group, then the brain tissues carry out for the parietal cortex histological tissue preparation. It will be stain with Haematoxylin Eosin and examine by pathology anatomy (PA) experts for observing and counting the pathologic cell finds. PA experts observe granular cells in the granular layer of the parietal cortex, and its carried out in 5 fields of view under of 400x magnification light microscope. Assessment of cell morphology was carried out using a scoring system with the provisions of normal cells (number x0), cells undergoing hydropic degeneration (number x1), and cells undergoing necrosis (sum x2).[9] Statistical tests were used to determine the significance of differences in changes in the granular cells of the cerebral parietal cortex and pain threshold between groups and the significant relationship between changes in the granular cells of the parietal cortex and the pain threshold in Wistar rats exposed to electromagnetic waves. This research was approved by Medical Faculty Diponegoro University Semarang with an ethical clearance no 01/EC/H/FK-UNDIP/I/2022.

RESULTS

The following are histopathological description of the parietal cortex of all groups. Higher parietal cell changes were observe in groups with increase duration time of mobile phone exposures. It presented the hydropic degenerated cells alteration or even went to the necrosis stage (Table 1).

The longer exposed time duration presented of higher mean score of granular cells damage in the granular layer of the parietal cortex (Table 2). The non-parametric Kruskal-Wallis with p = 0.000, which meant the significant differences of the parietal cortex cells histology exposed by mobile phone in accordance to the time exposed duration (Group 1, 2, and 3). Whereas the Control group with no parietal cortex cellular changes.

The longer duration time exposure to mobile phones might increase the average time to reach the pain threshold. Our study showed significant differentiation of pain threshold altered between samples exposed by mobile phones and those not frequently exposed (the one-

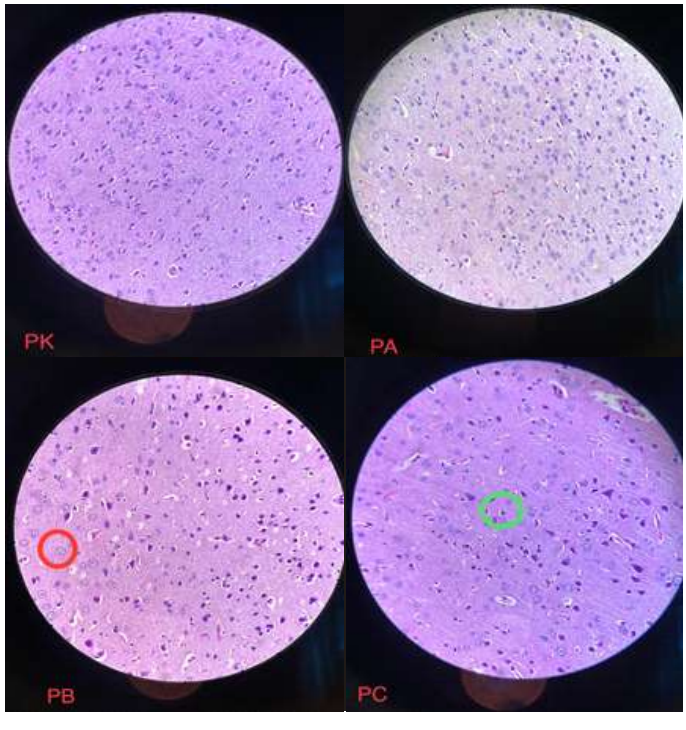

Figure 2. PK: histopathological picture of the cerebral parietal cortex in the control group; PA: histopathological picture of the cerebral parietal cortex in treatment group 1; PB: histopathological picture of the cerebral parietal cortex in treatment group 2 with red circles in the form of granular cells that experienced hydropic degeneration; PC: histopathological description of the cerebral parietal cortex in treatment group 3 with a green circle in the form of granular cells undergoing necrosis.

TABLE 1
Description of the mean of hydropic degeneration and necrosis cells in all groups

Group	The mean of hydropic degeneration cells	The mean of necrosis cells
Control	0	0
Group 1	1.2	0
Group 2	2.2	0
Group 3	2.1	1

TABLE 2
Description of the histopathological scores of the parietal cerebral cortex of wistar rats in all groups

	Histopathological scores of the parietal cerebral cortex		
Group	Mean ± SD	Median (min–max)	p
Control	0 ± 0	0 (0–0)	0.000
Group 1	1.28 ± 0.48	1 (1–2)	
Group 2	1.71 ± 0.75	2 (1–3)	
Group 3	4.28 ± 1.25	4 (3–6)	

Note: *p : Kruskal-Wallis, significant (p < 0.05)

TABLE 3
Description of changes in the pain threshold of wistar rats in all groups

	Changes in the pain threshold		
Group	Mean ± SD	Median (min–max)	p
Control	4.85 ± 3.48	5 (1–11)	0.000
Group 1	36 ± 8.86	36 (23–49)	
Group 2	60 ± 9.79	59 (48–75)	
Group 3	91.71 ± 14.46	87 (77–114)	

Note : * p : One way ANOVA, significant (p < 0.05)

way ANOVA test, p = 0.000). When the time duration is exposed more frequently, the pain threshold will raised (Table 3). The Spearman test showed significant association between the parietal cell changes and of and the pain threshold alteration due to exposure to electromagnetic waves exposure of mobile phones (p= 0.000). The Correlation Coefficient value is 0.906, reflecting a strong and positive correlation between the higher score of the parietal changes and the pain treshold changes.

DISCUSSION

The longer the exposure to mobile phones might caused of higher mean score of granular cell damage in the deep granular layer of the rat cerebral parietal cortex. In Groups 1, 2, and 3, the cells were dominated by hydropic degeneration, while in Group 3 the necrosis cells began to appear. In the treatment group, there was structural damage marked by histopathological changes in the form of degeneration which is a reversible injury, and cell death which is an irreversible injury. Hydropic degeneration occurs when cells cannot maintain ionic and fluid homeostasis (mainly due to ion pump activity in the plasma membrane). If the cause of the injury persists, granular cells that have been injured can experience tearing of the plasma membrane and changes in the cell nucleus so that the cells die or are necrotic.[14] The Kruskal-Wallis comparative test analysis showed significant (p=0.000), so there were significant differences

in the histopathological features of the parietal cerebral cortex in rats exposed to mobile phone electromagnetic waves with difference duration exposure time and those not exposed. Recently the striking effects on neuronal damage of the hippocampus were observed underwent a single 2-hours exposure to a 915 MHz mobile phone. Thus with the average whole-body specific energy absorption rates (SARs) as low as 2, 20, or 200 mW/kg.[15] After exposure to 1,375 MHz mobile phone radiation at 3 cm from the cage for 72 hours, the pyramidal cells might shrinkage, mild perivascular and perineural edema are founded, and the neurons and glial cortex cells with vacuolization are present. There was also a reduction in Purkinje cells, vacuolization of neurons and glial cells, and interstitial edema in the cerebellum.[8] On the other hand, the 900 MHz mobile phone exposed at a distance of 1 cm for 2 hours/day, showed apoptosis of frontoparietal glial cells after 10 months followed up.[10]

The granular cells damage can be caused by continuous exposure to mobile phone electromagnetic waves, thereby increasing free radical activity in cells and disrupting the metabolism of Reactive Oxygen Species (ROS) by increasing the production of ROS such as increased NMDA and MDA or decreased activity. antioxidants such as catalase, SOD, and GSH.[16,17] In normal circumstances, the ROS formed will be neutralized by antioxidants in cell tissue, but if the production of ROS increases abnormally such as due to exposure to electromagnetic waves, the antioxidants in the body tissues are unable to neutralize everything which ultimately leads to oxidative stress.[18] As a result of oxidative stress, there will be consequences for granular cells in the granular layer in the cerebral parietal cortex through several mechanisms, namely increased lipid peroxidation in cell membranes, oxidative damage to DNA, including modification of purine or pyrimidine bases, protein damage that causes conformational changes, polymerization and protein fragmentation, as well as the induction of apoptosis and necrosis.[16,18,19]

The pain threshold changes showed significantly different in Groups 1, 2, and 3, and the long-term mobile phone exposure might be a cause of the threshold increase (ANOVA test, p= 0.000). Thus higher threshold alteration could be implicated in lesser pain sensitivity. It means when the threshold gets higher, the rats might not be as sensitive as the lower threshold state. Mobile phone electromagnetic exposed might promote a significantly thermal pain sensation reduction (Mann-Whitney p=0.001).[13] The electromagnetic waves originated from mobile phones with amplitude modulation setting on 73.5 MHz and SAR 0.4 w/kg for 45 days (2 hours/day), observed delayed retraction response of the rat's hind limb after noxious stimuli (p=0.01). Otherwise, the tail withdrawal response might not statistically significant (p=0.2).[20] Those phenomenon based on the increasing pain threshold in association with the pain impulses interferes, as the mobile phone electromagnetic exposure leads to the primary sensory alteration, and the pain perception changes due to the threshold increase.[21–23] The histopathological examinations of the parietal cortex and the pain threshold changes seemed significantly related (Spearman test, p=0.000). The Correlation Coefficient is 0.906, which means the strength of the relationship is strong and positively correlated (the higher the histopathological picture score of the parietal cerebral cortex, the higher the change in pain threshold). The granular cells' damage plays a role as a pain impulse receiver from the thalamus (the thalamocortical tracts), which with responsible for the intensity and location of the pain. Structural cell damage might cause an increase in the pain threshold.[21–23]

CONCLUSION

Exposure to mobile phone electromagnetic waves affects pain perception due to changes in the granular cells of the cerebral parietal cortex of Wistar rats. The longer the exposure to mobile phones might caused higher granular cell damage in the deep granular layer of the rat cerebral parietal cortex. Further study will need to be perform in order to know whether the changes in cerebral parietal cortex granular cells are reversible or irreversible.

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Original Article

The Effect of 1% Povidone Iodine Mouthwash on The Incidence of Oral Mucositis and Odynophagia in Patients with Head and Neck Malignancy

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Abstract

Background : Oral mucositis is an injury of normal mucosal tissue with an acute inflammation of the oral, tongue, and pharyngeal mucosa after exposure to chemo-radiotherapy. Post chemoradiotherapy oral mucositis is commonly accompanied by painful swallowing or odynophagia. Povidone iodine 1% is an antiseptic mouthwash that widely used to prevent infections in the oral cavity. The aim of this study was to determine the effect of 1% povidone iodine mouthwash on the incidence of oral mucositis in patients with head and neck malignancy at Dr. Kariadi General Hospital Semarang.
Methods : This study was single random blinded experimental study, with total samples of 44 patients with head and neck malignancy after chemoradiotherapy. The samples divided into treatment group of 22 samples with 1% povidone iodine mouthwash and control group of 22 samples with NaCl 0.9% recruited using single random sampling at Dr. Kariadi Semarang General Central Hospital in 2022. The effect of 1% povidone iodine mouthwash on the incidence of oral mucositis and odynophagia was analyzed using the Fischer Exact and Mann Whitney test.
Results : In the 1% povidone iodine mouthwash group day 15th, 21 patients (95.5%) were found without mucositis and 1 patient (4.5%) with mucositis oral grade I. In the 1% povidone iodine mouthwash group, 21 people (4.5%) were found without odynophagia and 1 people (4.5%) had odynophagia. There was an association between oral mucositis and odynophagia on povidone iodine 1% group ($p < 0.05$).
Conclusion : Povidone iodine 1% mouthwash can affect the incidence of oral mucositis in patients with head and neck carcinoma. Povidone iodine 1% mouthwash can reduce the incidence of oral mucositis and odynophagia compared to placebo in patients with head and neck carcinoma.

Keywords : oral mucositis, povidone iodine 1%, odynophagia, head and neck malignancy

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INTRODUCTION

Head and neck carcinoma is a malignant tumor in organs around the head and neck such as the mouth, throat, sinuses, respiratory tract and salivary glands. Treatment for head and neck carcinoma may include radiation, chemotherapy, or a combination of the two. Treatment of head and neck carcinoma often has side effects such as oral mucositis.[1–3]

Oral mucositis is an injury to normal mucosal tissue that occurs secondary to inflammatory and cytotoxic effects after exposure to chemoradiotherapy lasting between 7 to 98 days.[4,5] The incidence of oral mucositis in patients with head and neck malignancy receiving chemotherapy, radiotherapy and chemoradiotherapy respectively is 20%– 40%, 80% and 80% – 100%, respectively.[4,6] Oral mucositis is generally characterized by erythema, edema, mucosal ulceration and pseudomembrane formation in the oral cavity and oropharynx.[5–7] Severe oral mucositis causes pain, reduces oral nutrition intake, impairs quality of life, increases secondary infection due to loss of protective epithelial barrier and basal membrane, and affects medication adherence.[8]

Painful swallowing or odynophagia is also the most common symptom found in patients with head and neck malignancy who receive radiotherapy and/or chemotherapy. Odynophagia due to oral mucositis causes chewing, swallowing, and speaking disturbances, leading to many complications including malnutrition, dehydration, aspiration, respiratory infections, increasing the number of days of hospitalization, and even death.[7]

Povidone iodine mouthwash is a mouthwash with an active iodine complex that is popular, easy, inexpensive, safe, and effective in reducing inflammation and infection. Povidone iodine mouthwash is considered to have the broadest spectrum of antimicrobial action compared to other common mouthwash antiseptics such as chlorhexidine, octenidine, polyhexanide and hexetidine which show efficacy against gram-positive, gram-negative bacteria, bacterial spores, fungi, protozoa and some viruses. The antimicrobial activity of povidone iodine originates from the strong oxidizing ability of free iodine towards amino acids, nucleotides and double bonds, as well as unsaturated free fats which cause povidone iodine to damage protein and microbial DNA. The ability of povidone iodine is also found to inhibit interleukin-1 beta (IL-1β) and interleukin-8 (IL-8), thus reducing inflammation.[9–13]

Oral mucositis requires a highlight, especially for clinicians because it is strongly associated with the quality of life of patients with head and neck malignancy after receiving chemoradiotherapy. Previous research discussing the effect of 1% povidone iodine mouthwash in patients with head and neck malignancy with complaints of oral mucositis after administration of chemoradiotherapy in Indonesia is still very limited. This study assessed the effect of giving povidone iodine 1% mouthwash for the prevention of oral mucositis due to side effects of chemoradiation in patients with head and neck malignancy at Dr. Kariadi General Central Hospital, Semarang.

METHODS

This study was random single blinded experimental study. The total samples of this study were 44 samples distributed into two groups; 22 samples in control group using NaCl 0.9% and 22 samples in treatment group with *povidone iodine* 1% mouthwash given. The sample was chosen using simple random at Dr. Kariadi General Central Hospital Semarang in 2022. The inclusion criteria for this study were patients with ECOG performance status I and II, aged ≥ 18 years, willing to undergo the study procedure, and diagnosed with head and neck carcinoma except for oropharyngeal carcinoma (tonsil, tongue, and palate carcinoma). Exclusion criteria in this study were the patients with history of systemic diseases such as diabetes mellitus, SLE, HIV, history of taking antibiotics and immunosuppressants ≥ 5 days. The independent variable was 1% povidone iodine, while the dependent variable was the degree of oral mucositis and the degree of odynophagia. The degrees of oral mucositis is divided into grade 0 (no complaints), grade 1/mild (hyperemia and burning sensation in the mouth), grade 2/moderate (oral erythema, single ulceration, and still able to eat solid food), grade 3/severe (multiple ulceration and only able to eat liquid food), and degree 4/life threatening (patients can't eat and drink). The degree of odynophagia was determined based on the Visual Analog Scale (VAS) divided into no pain (VAS 0) and mild pain (VAS 1-3). The association between variables were analyzed using Fischer Exact and Mann Whitney tests. The study protocol was approved by the Health Research Ethics Commission at Dr. Kariadi General Central Hospital Semarang (1032/EC/KEPK-RSDK/2022) with research permit (DP.02.01/I.11/2170/2022).

RESULTS

This study involved 44 head and neck carcinoma patients who previously received chemoradiation divided into control group (22 patients) using NaCl 0.9% gargle and treatment group (22 patients) with 1% povidone iodine with the characteristics of the samples shown in Table 1.

Table 1 shows that the majority of the control and treatment groups were male. The average age of the subjects in this study was 18 to 75 years with an average age of 48 years with the most common type of head and neck carcinoma was nasopharyngeal carcinoma. The

TABLE 1
Characteristics of Samples

Demographic Characteristics	Group A (NaCl 0.9%; n=22 samples)	Group B (povidone iodine 1%; n=22 samples)	Total (Group A dan B; n=44 samples)
Sex			
Male	16 (72.7)	16 (72.7)	32 (72.7)
Female	6 (27.3)	6 (27.3)	12 (27.3)
Age (mean) (Min–Max ± SD)	53 (24–75 ± 11.51)	43 (18–63 ± 12.72)	48 (18–75 ± 12.96)
Type of Carcinoma			
Nasopharyngeal	11 (50.0)	17 (77.3)	28 (63.6)
Laringeal	5 (22.7)	3 (13.6)	8 (18.2)
Sinonasal	5 (22.7)	2 (9.1)	7 (15.9)
CAE	1 (4.6)	0 (0.0)	1 (2.3)
Degree of Oral Mucositis			
Not found	2 (9.1)	17 (77.3)	19 (43.2)
Grade I	15 (68.2)	5 (22.7)	20 (45.4)
Grade II	5 (22.7)	0 (0.0)	5 (11.4)
Grade III	0 (0.0)	0 (0.0)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)
Microbiological Findings			
Gram-positive and -negative bacteria	4 (18.2)	0 (0.0)	4 (9.1)
Gram-positive and -negative bacteria, and fungal	1 (4.5)	0 (0.0)	1 (2.3)
Not found	17 (77.3)	22 (100)	39 (88.6)

microbiological findings in this study were a combination of gram-positive, negative, and fungal bacteria. Side effects of chemoradiation found in this study included odynophagia, tongue stiffness, and loss of taste.

Table 2 shows the degree of oral mucositis in the control group and the 1% povidone iodine mouthwash treatment group at 0^{th}, 5^{th}, 10^{th}, and 15^{th} chemoradiations. These findings were significantly different between the degrees of oral mucositis in head and neck carcinoma patients who received 1% povidone iodine mouthwash at the 15^{th} chemoradiation ($p = 0.019$).

Table 3 shows odinophagia in the control group and 1% povidone iodine mouthwash treatment group. The result of this study showed no significant difference in swallowing pain between patients with head and neck carcinoma who received 1% povidone iodine mouthwash at the 5^{th}, 10^{th}, and 15^{th} chemoradiation.

Table 4 shows the association between the degree of oral mucositis and the degree of odinophagia. A significant association was found between the degree of oral mucositis and the degree of odynophagia ($p < 0.05$) in patients with head and neck carcinoma receiving 1% povidone iodine mouthwash at the 10^{th} and 15^{th} chemoradiation.

DISCUSSION

Povidone iodine 1% mouthwash is a mouthwash that is currently widely used to prevent oral infections due to its antiseptic effect.[10–12] In this study, the control group using NaCl 0.9% and treatment group with 1% povidone iodine mouthwash samples were dominated by male, which was in accordance with previous studies which showed that there were generally more patients with head and neck carcinoma in males.[13,14] Nasopharyngeal carcinoma is one of the most common types of head and neck

TABLE 2
The degree of oral mucositis in control group and 1% povidone iodine mouthwash treatment group at 0th, 5th, 10th, and 15th chemoradiation

Degree of Mucositis	Day of Chemoradiation							
	0th		5th		10th		15th	
	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)
(–)	20 (90.9)	22 (100)	18 (81.8)	20 (90.8)	16 (72.7)	20 (90.9)	15 (68.2)	21 (95.5)
I	2 (9.1)	0 (0)	3 (13.6)	2 (9.1)	4 (18.2)	2 (9.1)	5 (22.7)	1 (4.5)
II	0 (0)	0 (0)	1 (4.5)	0 (0)	2 (9.1)	0 (0)	2 (9.1)	0 (0)
III	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IV	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
p value	0.244£		0.365‡		0.107‡		0.019‡	

Fisher exact test (£); Mann Whitney (‡), *Significant (p < 0.05);

TABLE 3
The degree of odynophagia in control group and 1% povidone iodine mouthwash treatment group at 0th, 5th, 10th, and 15th chemoradiation

Odynophagia (VAS)	Day of Chemoradiation					
	5th		10th		15th	
	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)
Painless (VAS 0)	19 (86.4)	21 (95.5)	17 (77.3)	19 (86.4)	18 (81.8)	21 (95.5)
Mild pain (VAS 1–3)	3 (13.6)	1 (4.5)	5 (22.7)	3 (13.6)	4 (18.2)	1 (4.5)
p	0.303		0.349		0.172	

Analyzed using Fisher exact test; * Significant (p < 0.05); A: control group, B: povidone iodine 1% mouthwash treatment group

carcinoma and is endemic in Southeast Asia. According to the International Agency for Research on Cancer, there were 129,079 new cases of nasopharyngeal carcinoma in 2018, more than 70% of new cases of nasopharyngeal carcinoma were reported in East and Southeast Asia.[15–17]

Mucositis oral occurring throughout radiation therapy is due to multifactor etiologies.[12] Infection plays a significant role in the pathophysiology of oral mucositis. Oral microorganisms can cause infections of the oral mucosa and antiseptic agents can reduce the incidence and severity of these infections by reducing the number of these microorganisms.[11,12]

Microbiological findings in this study included gram-positive bacteria, Streptococcus viridans and Staphylococcus aureus. Findings of the fungal component include the finding of pseudohyphae (a sausage-like appearance) and yeast which known as pathognomonic signs in commensal Candida albicans infections which are usually found in the oral mucosa and in the lumen of the digestive tract which are responsible for more than 80% of head and neck infections that more commonly found in control group compared to 1% povidone iodine group.[12,18]

Chemotherapy or radiotherapy procedure, especially when combined, can increase the incidence of acute side effects, such as oral mucositis, followed by odynophagia, loss of taste, tongue stiffness, xerostomia, nausea, vomiting and fatigue. All of these can lead to significant dehydration and weight loss.[15,19,20]

In this study, the incidence of oral mucositis was mostly found in the first to second weeks of chemoradiotherapy with predominance of grade I–II. These findings are in accordance with previous studies which showed that most patients with head and neck malignancy who received chemoradiotherapy had grade I–II oral mucositis. Grade III and IV mucositis were frequently observed in the fourth and sixth (last week) weeks, which can lead to discontinuation of treatment or even hospitalization.[16,17] Some literature had observed a significant reduction in the incidence, severity, and

TABLE 4
Correlation between the degree of oral mucositis and the degree of odinofagia in the control group and povidone iodine 1% mouthwash treatment group at the 5th, 10th and 15th chemoradiation

Degree of Mucositis	Odynophagia Degree at the Day of Chemoradiation					
	5th		10th		15th	
	Painless	Mild Pain	Painless	Mild Pain	Painless	Mild Pain
(–)	35 (92.1)	5 (83.3)	35 (97.2)	1 (12.5)	36 (100)	3 (37.5)
I	3 (7.9)	1 (16.7)	1 (2.8)	7 (87.5)	0 (0)	5 (62.5)
P	0.456		<0.001*		<0.001*	

Analyzed using Fisher exact test; * Significant (p < 0.05)

duration of oral mucositis during chemoradiation in a group of patients using the common mouthwash of povidone iodine solution.[11,12] The results of this study showed a decrease in the degree of oral mucositis in the 1% povidone iodine mouthwash treatment group compared to the control group at the 15th chemoradiation (p = 0.019). The results of this study are in accordance with previous studies which showed that among 76 samples, patients in the povidone iodine group had significantly lower mucositis scores when compared to the control group from the first week, saline/soda solution, and chlorhexidine from the fourth and fifth weeks after radiotherapy, respectively.[11]

In this study, there was no significant association between the use of mouthwash and odynophagia. These results are in line with previous studies which showed that mouthwash tolerability (assessed at VAS 1–5) was significantly better in the normal saline group than in the povidone iodine group.[11,15]

This study showed a correlation between the degree of oral mucositis and the degree of swallowing pain in both the control group and the 1% povidone iodine mouthwash treatment group (p<0.05). The severity of oral mucositis including odynophagia/dysphagia can be reduced by oral hygiene care (to reduce oral infections with opportunistic pathogens that can exacerbate mucositis) through gargling activities with antiseptic solutions, one of which is povidone iodine.[10–12] Previous research showed that 50% of patients reported dysphagia/odynophagia in the first week after cancer therapy (25% with VAS 1 odynophagia and 25% with VAS 3 odynophagia) with 30% of these patients experiencing grade I and II oral mucositis in the same week. The study also showed that there was a transition in the severity of oral mucositis and odynophagia/dysphagia at 2–3 weeks in patients who did not perform oral hygiene care with mouthwash so understanding the natural course of acute oral complications is important by informing patients about the importance of maintaining adequate oral hygiene to help minimize symptoms of acute oral complications.[16]

The limitation of this study was the short evaluation time. The research findings required to be thoroughly interpreted to reduce research bias.

CONCLUSIONS

Povidone iodine 1% mouthwash can affect the incidence of oral mucositis in patients with head and neck carcinoma. Povidone iodine 1% mouthwash can reduce the incidence of oral mucositis and odynophagia compared to placebo in patients with head and neck carcinoma.

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Original Article

Fetal Growth Cut-Off Point to Predict Neonatal Outcome in Pregnancy with Normal and Deficient Vitamin D Levels: Intergrowth-21, World Health Organization Fetal Growth Curve, and Hadlock's Estimated Fetal Weight

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Abstract

Purpose : Analyze the cut-off point of fetal growth based on the Intergrowth-21, World Health Organization (WHO), and Hadlock's estimated fetal weight (EFW) in pregnant women with normal or deficient vitamin D levels to predict neonatal outcomes.
Methods : This cross sectional study to develop a diagnostic test, included 120 of pregnant women who completed follow up until children aged 2 years, divided into normal and deficient vitamin D group. Ultrasound and maternal vitamin D level examined during the second trimester of pregnancy. EFW was calculated using Hadlock's formula and plotted on the Intergrowth-21 and WHO curves. The reference standards were the neonatal outcome, LBW, stunting, and neurocognitive impairment. Significant odds ratio (OR) value and area under the curve (AUC) of 0.6 are used to determine the cut-off point to be used.
Results : Fetal growth curve was based on the WHO at the 5th percentile to predict LBW to have an AUC of 0.6 and OR of 6, 95% confidence interval (CI) of 1.36–26.45. The AUC for predicting LBW based on Intergrowth and Hadlock were 0.45 and OR not significant. As well as the AUC estimated stunting based on Hadlock, the Intergrowth-21 and the WHO fetal growth curves is <0.6 with OR not statistically significant. The AUC predicted neurocognitive impairment based on WHO's chart was 0.6 but OR not statistically significant.
Conclusion : The WHO fetal growth curve can be used to predict LBW. The cut-off point of the fetal growth curve and which percentile is determined by the neonatal outcome.

Keywords : Fetal growth curve Cut-off Point, 25(OH)D, Stunting, Neurocognitive impairment

INTRODUCTION

Guidelines for performing an ultrasound (USG) examination to assess the estimated fetal weight (EFW) were published by the International Society of Ultrasound in Obstetrics and Gynecology, but plotting the growth curve during biometric measurements or EFW to determine the need for close monitoring is very important.[1] Fetal growth charts of normal pregnancies in a large population were published by several studies.[2–4] However, more specific fetal growth charts are needed concerning neonatal outcomes, especially low birth weight (LBW) infants, stunting, and neurocognitive impairment of children in special populations, as well as pregnant women with normal and deficient vitamin D levels.[5]

Vitamin D is a micronutrient that has calciotrophic (skeletal) and non-calciotrophic (extraskeletal) biological actions. Calciotrophic biologic action is important for calcium homeostasis regulation, which in turn contributes to intrauterine-initiated bone growth that contributes to fetal growth.[6] The main sources of vitamin D are sunlight and food.[7] Vitamin D deficiency is expressed by the 25-hydroxy vitamin D (25(OH)D) level in the blood. Vitamin D deficiency is a public health problem worldwide, especially concerning these two biological actions.[8]

Vitamin D deficiency during pregnancy affects the fetal growth and the bones of the child because of the calciotrophic biologic action of vitamin D. Research on vitamin D deficiency during pregnancy on fetal growth and birth weight gives inconclusive results.[9–12] A study linked vitamin D deficiency during pregnancy with the incidence of stunting, associated with fetal and child growth in the First Thousand Days of Life.[13]

Stunting is a condition in children with body length based on age and z score of <−2 according to the World Health Organization (WHO). Intrauterine fetal growth (IUGR) is one of the factors that influence the incidence of stunting in Indonesia.[14] The 2018 Basic Health Research data reported a 29.2% incidence of stunting in children aged 2 years and 30.8% in children aged 5 years.[15] This incidence decreased to 37.2% in children under 5 years old in 2013.[16] The 2019 Indonesian Toddler Nutrition Status Survey reported a decline in stunting incidence by 27.67%. These incidences have not met the WHO standard, which states that the incidence of stunting should be <20%, although it has decreased.[17]

One of the effects of vitamin D deficiency during pregnancy, as a non-calciotrophic biologic action, is the nervous system's development and function. Neurodevelopment includes cell differentiation and synaptic formation. Neurological functions include gene expression, metabolic regulation, neurotrophic-neurotoxicity, and a protective role against brain inflammation. Research on the relationship between maternal vitamin D status during pregnancy and children's cognitive function remained lacking. A study revealed that vitamin D levels during normal pregnancy affect the neurocognitive function of children.[18] Therefore, analyzing the cut-point of EFW in the second and third trimesters of pregnancy (based on Intergrowth 21, WHO, and Hadlock) is necessary in particular cases with vitamin D deficiency, LBW, stunting, and neurocognitive impairment.

METHODS

Research subject

This retrospective cohort study aimed to develop a diagnostic test, included 385 participants of the First 1000 Days of Life Medical Faculty Diponegoro University's research. A total of 120 pregnant women who had normal (n = 60) and deficient vitamin D (n = 60) levels had complete data until the child was 2 years old. The cut-off point was determined based on maternal vitamin D levels, LBW, stunting, and neurocognitive impairment. Sixty subjects, each group (normal and deficient vitamin D consist 30, conducted Capute Scale examination. The inclusion criteria included normal and singleton pregnancies. Exclusion criteria were fetal congenital abnormalities and premature birth. The data for children included gender, birth weight, stunting, and neurocognitive impairment when the child age 2 years old. Other data such as age, weight, height, body mass index, education and socioeconomic status of the mother were also collected.

Fetal growth classification

USG examination to assess EFW is conducted by obstetrics and gynecology specialists who have a basic USG examination certification from the Indonesian Obstetrics and Gynecology Association. The examining physician was blinded from the maternal vitamin D levels and fetal outcomes upon examination. The examination was conducted in the second trimester of pregnancy. The USG parameters assessed included biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), and EFW according to Hadlock 1984.[19] Fetal growth cut-off point according to growth chart and EFW was assessed by reference standard maternal vitamin D levels and neonatal outcomes. Neonatal outcomes include LBW, stunting, and neurocognitive impairment when the child aged 2 years old. Fetal growth charts used Intergrowth-21 and WHO.[20]

Reference standard: Maternal vitamin D levels and fetal outcomes

Vitamin D levels were assessed from maternal blood 25(OH)D levels during the second trimester with a cut-off point of 20 ng/ml. Fetal outcomes were assessed for LBW,

wasting or stunting, and neurocognitive disorders when the child was 2 years old. LBW is a baby who is born weighing <2,500 g and is classified as normal and low. Criteria for classifying children age 2 years into stunting was according to the WHO. Neurocognitive impairment were considered on a full scale (part of the examination Capute Scale) if the score less than 75.

Statistical analysis

Descriptive analysis was used to assess the characteristics of the subject of the mother and child. The cut-off point is assessed based on the receiver operating characteristic (ROC) curve and calculated Youden's index for each neonatal outcome based on vitamin D levels during pregnancy. Odds ratio (OR), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed. The percentile fetal growth chart or EFW was selected based on significant OR values and an area under the curve (AUC) of 0.6.

RESULT

A total of 120 pregnant women, including 60 pregnant women each with normal and deficient vitamin D levels. Table 1 shows the patient characteristics. The average age of the mother is 29(5) years, and 39% have obesity. The average gestational age at the USG examination is 22 weeks. The number of babies born to boys and girls was 59 and 61 babies, respectively. Eight neonates were born with LBW, 15 with a stunting, and 5 with suspected neurocognitive impairment.

Table 2 shows the patient characteristics based on maternal vitamin D levels and nepnata; outcomes. No significant difference was found between gestational age, EFW on USG, and birth weight based on maternal vitamin D levels, and fetal outcome (LBW, stunting, and neurocognitive disorders).

Figure 1 shows the ROC curves of fetal growth and maternal vitamin D levels. All AUC values based on

TABLE 1
Patient characteristics based on ultrasound examination

Characteristics	n (%)	Median (min–max)	Mean (SD)
Mother			29.87 (5.57)
Age (years)		30 (17–44)	60.14 (12.27)
Mother's weight at measurement (kg)		57.25 (40.9–102.5)	26.06 (4.97)
Maternal body mass index (kg/m^2)		25.48 (18.30–49.18)	25.48 (18.30–49.18)
Underweight	15 (12.5)		
Normal	66 (55)		
Overweight	39 (32.5)		
Education			
Elementary School	9 (7.6)		
Junior High School	28 (23.3)		
Senior High School	70 (58.3)		
Associate degree	7 (5.8)		
Bachelor degree	6 (5)		
Socioeconomic			
Middle	74 (61.7)		
Low	46 (38.3)		
Maternal vitamin D level (ng/ml)		19.59 (4.94–37.65)	19.60 (5.2)
Deficient	60 (50)		
Normal	60 (50)		
Child			
Gestational age at ultrasound (weeks)		22.5 (1627)	22.5 (1627)

TABLE 1. Continued.

Characteristics	n (%)	Median (min–max)	Mean (SD)
Gender			
Boy	59 (49.2)		
Girl	61 (50.8)		
How to give birth			
Vaginal	63 (52.5)		
Caesarean section	57 (47.5)		
Baby's birth weight (grams)		3045 (2000–3900)	3066 (408)
< 2500	8 (6.67)		
>2500	112 (93.3)		
Z score PB/U (2 years)		−1.1 (−3.46–2.56)	−1.04 (0.96)
Tall	2 (1.7)		
Normal	103 (85.8)		
Short	13 (10.8)		
Very short	2 (1.7)		
Neurocognitive			
Suspected impairment	5 (1.9)		
Normal	57 (22.1)		

growth curves and EFW were 0.5.

Figure 2 shows the ROC curve of fetal growth and LBW. The AUC value of fetal growth curve based on the WHO growth curve was 0.6. Based on Youden's index, the cut-off fetal growth curve according to the WHO growth curve is the 5th percentile.

Figures 3 and 4 show the ROC curves of fetal growth and neonatal outcomes in terms of stunting and neurocognitive impairment at 2 years of age. The AUC value was 0.6 for neurocognitive disorders based on the WHO growth curve. Based on Youden's index, the cut-off fetal growth curve according to the WHO growth curve is the 35th percentile for neurocognitive impairment.

Table 3 shows the sensitivity, specificity, PPV, and NPV values for each fetal growth chart to predict maternal vitamin D and fetal outcomes. High sensitivity and NPV values on the Intergrowth-21 and fetal growth charts of the WHO predict maternal vitamin D, with a significant OR value. Likewise, the specificity and high NPV values on the WHO fetal growth chart predict LBW, with a significant OR value. The sensitivity, specificity, and NPV values were high on all fetal growth charts to detect stunting and neurocognitive impairment at the age of 2 years, but without significant OR values.

DISCUSSION

Based on the AUC and OR value, the WHO fetal growth curve can predict LBW in children. The growth curve according to the WHO has high specificity and NPV, which is appropriate for making the diagnosis. The AUC value of 0.6 is congruent with other study results. The RADIUS study on 9,409 pregnant women concluded that the fetal growth curve based on Intergrowth-21 and WHO had an AUC of 0.5–0.59.[21] A study of 3,437 African-American pregnant women comparing eight fetal growth charts, including Intergrowth-21 and WHO could not predict a poor combined perinatal outcome at the 10th percentile (AUC of 0.55) and a sensitivity of only 22%.[22] The Intergrowth-21 growth curve at the 10th percentile had an AUC of 0.52 in 1054 pregnant women in the United States.[23] Another study revealed similar results when comparing EFW based on Hadlock and Intergrowth-21 growth curves.[24] A study on 10,366 pregnant women that compared Hadlock, Intergrowth-21, and WHO revealed an AUC value of 0.54.[5]

Ultrasound during second or third trimester obtain estimate of fetal weight. But, ultrasound examination in the second trimester has been done to evaluate fetal anatomy. So, ultrasound in second

TABLE 2
Patient characteristics based on maternal vitamin D levels and neonatal outcomes

Variables	n (%)	Gestational age (week)	Estimated fetal weight (grams)	Baby's birth weight (grams)
			Mean (standard deviation)	
Vitamin D levels				
Normal	60 (50%)	22.27 (2.34)	553.7 (199.82)	3090.92 (403.37)
Deficient	60 (50%)	22.52 (2.32)	550.25 (192.82)	3062.92 (416.38)
Baby's birth weight				
<2500	8 (6.67)	23.33 (1.80)	574.88 (187.455)	2182.50 (372.24)
>2500	112 (93.3)	22.32 (2.35)	550.34 (196.81)	3130.09 (330.93)
Category z scores children aged 2 years				
Stunting	15 (12.5)	22.93 (1.83)	569.53 (175.26)	3018.33 (437.38)
Normal	105 (87.5)	22.31 (2.39)	549.47 (198.9)	3073.86 (406.63)
Neurocognitive				
Impairment	5 (8.06)	23.2 (3.34)	503.80 (121.08)	3208.4 (286.78)
Normal	57 (91.94)	22.28 (2.34)	536.58 (191.57)	3061.05 (409.58)

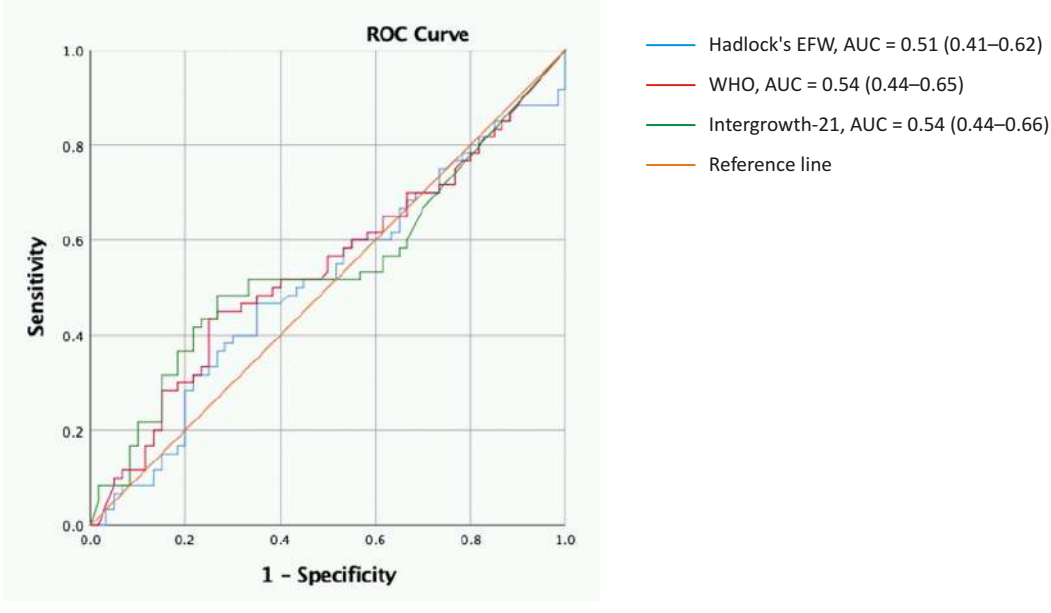

Figure 1. ROC curve of fetal growth based on maternal vitamin D levels

trimester is undergone for many more pregnant women than third trimester, especially in mid second trimester (18 – 22 weeks of gestation). Intrauterine fetal growth restriction in the mid second trimester of pregnancy related with neonatal outcomes. Fetal growth is linked to the placenta. The placenta is the organ that connects the fetus and the uterus. Various nutrients, hormones, and other endogenous metabolites from the mother will be transported via the placenta to the fetus. The cell that lines the outermost layer of the placenta is the syncytiotrophoblast, which is the smallest unit cell in the placenta and plays a role in fetal growth.[25] Vitamin D receptor is previously reported in trophoblasts; thus, vitamin D plays a role in fetal growth. The role of vitamin

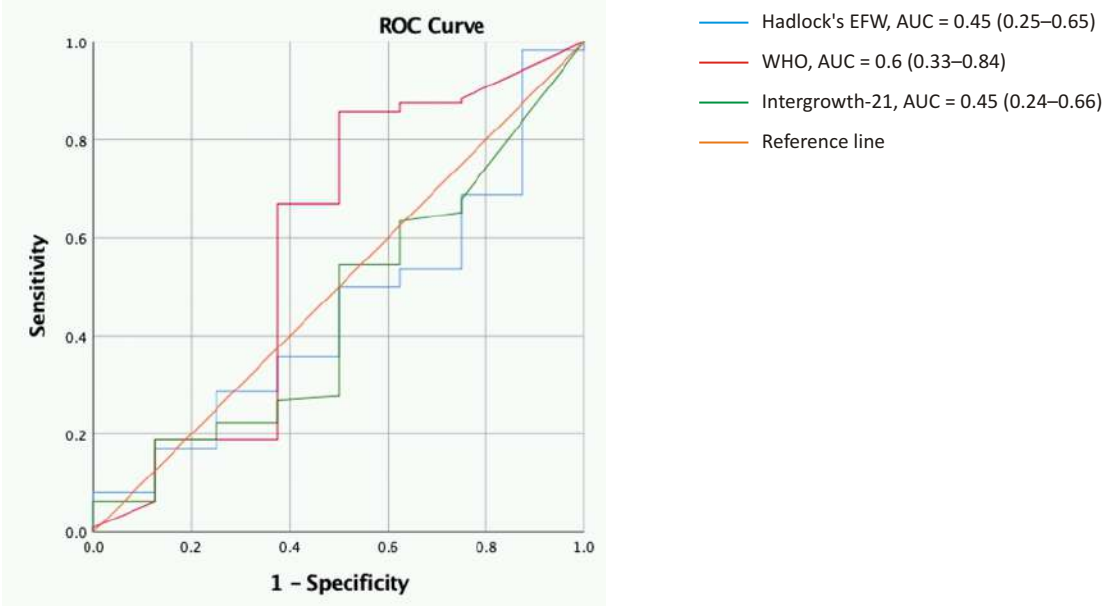

Figure 2. ROC curve of fetal growth and LBW

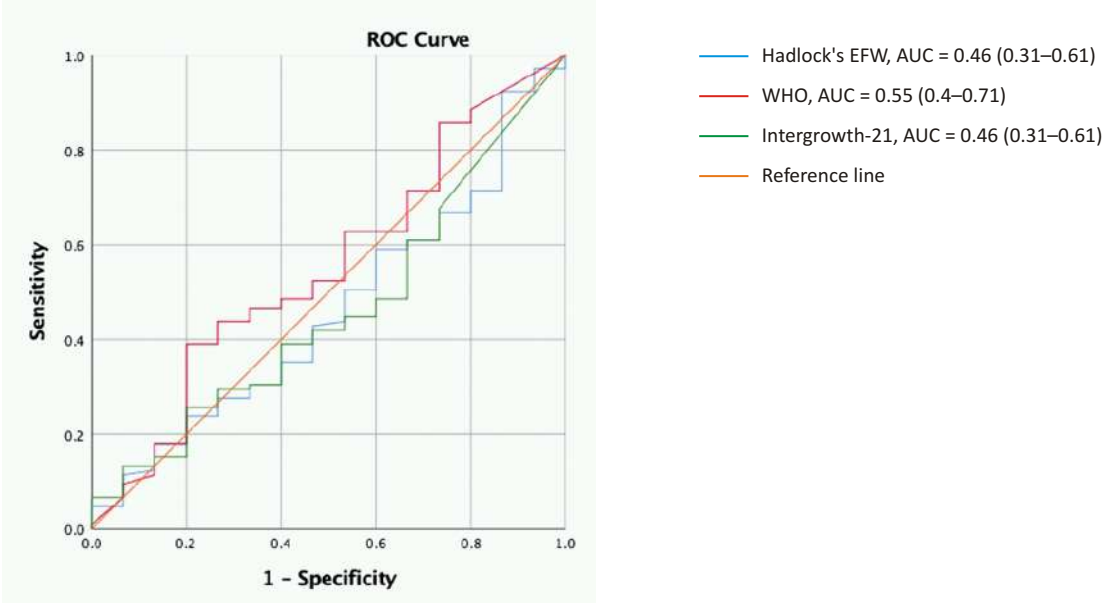

Figure 3. ROC curve of fetal growth and LBW

D during pregnancy on fetal growth includes calcium metabolism[26] and bone growth, as well as altered placental function.[27] Therefore, this study was conducted on specific participants, including pregnancies with normal and deficient vitamin D levels.

A study in Indonesia revealed that vitamin D deficiency in the first trimester was associated with low fetal BPD and AC.[28] Other studies linked vitamin D deficiency to low FL measures.[29] One study in Iraq found that vitamin D deficiency affected the weight and anthropometry of newborns.[30] Studies in Singapore revealed that vitamin D levels did not affect the anthropometry of newborns and postnatal, but this was because the incidence of vitamin D deficiency was only 1.6%.[31] Additionally, meta analysis studies supported the hypothesis that vitamin D deficiency is associated with LBW.[32] A study in Kenya linked vitamin D deficiency to stunting. A prospective cohort study in India included 250 primigravidas with normal pregnancies and examined vitamin D levels at 34 weeks of gestation. The

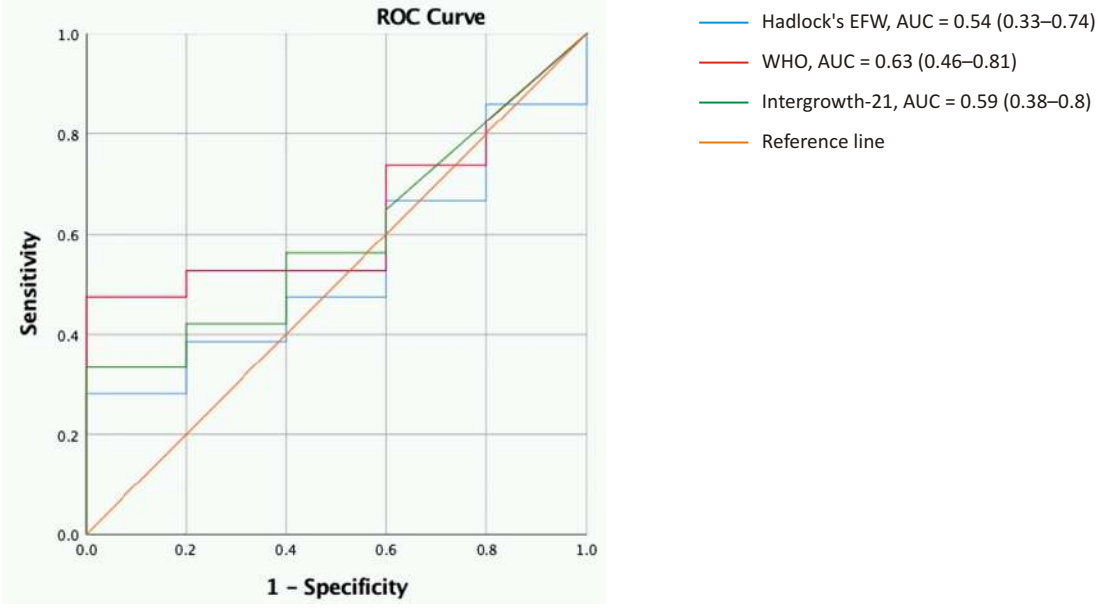

Figure 4. ROC curve of fetal growth and neurocognitive impairment at 2 years of age

study concluded that vitamin D deficiency affects fetal FL and birth length, but does not affect BPD and birth weight.[33] Another study revealed different results, no relationship was found between maternal vitamin D levels with birth weight, body length, and HC.[34]

Research on the effect of fetal growth on the incidence of stunting and birth weight remained lacking. The incidence of stunting is related to bone growth that supports the child's height. Bone is the greatest nutritional priority compared to fat and muscle because bone plays an important role in maintaining mineral balance, providing structural support, and hematopoiesis.[35] A prospective British cohort study that included 628 pregnancies who are followed up to 4 years of age concluded that fetal growth (AC measurement) in the second half of pregnancy was associated with bone mineralization at birth, and growth in children younger than 2 years of age was associated with bone mineralization at 4 years of age.[36] A prospective cohort study by the same investigators in 380 pregnancies revealed that fetal growth (AC and FL measurements) in the second half of pregnancy was associated with bone mineralization at 4 years of age.[37] A prospective cohort study of 399 females with normal pregnancies revealed that birth weight correlated with child length at 6, 12, and 24 months of age; FL at 20 weeks of measurement correlated with infant FL at birth; infant FL at birth correlated with FL at 6 months and 24 months.[38] The mechanism of the effects of bone growth on fetal growth and birth weight remained unknown but may be related to leptin, growth hormone, and cortisol.[39]

Stunting is also associated with neurocognitive disorders in children. Pregnancy is a critical phase of brain growth and development which includes the growth and differentiation of neuron cells, neuron migration, dendritic arborization, synaptogenesis, gyrus formation, myelination, and apoptosis. A cross-sectional study was conducted on 170 normal pregnancies and children aged 3–30 years who had undergone magnetic resonance imaging (MRI) 1022 times. The results revealed that the greater the birth weight of the baby, the greater the total volume of the brain, cerebral cortex, white matter, and gray matter. The volume of the cerebral cortex is related to the surface area of the cerebral cortex. The hypotheses included the following: a migration of neurons from the subventricular area to the cortex when RFW can be easily influenced by external stimuli, occurs in the second trimester of pregnancy. Hence, EFW disruption will affect the migration of neurons. The prefrontal area of the cortex is associated with later neurocognition.[40] A study of 756 neonates who underwent MRI at 2 weeks of age concluded an association between the increase of 500 grams of birth weight and the 4% increase in intracranial volume, which is the total volume of gray matter, white matter, and cerebrospinal fluid. MRI examination in early neonates is associated with neurocognitive disorders.[41]

Therefore, this is the first study that included the population of pregnant women with normal and deficient vitamin D levels to know the graph and percentile of fetal growth that will be chosen to predict LBW because previous research publications are unavailable. Additionally, the observation time is sufficient because at the time of first 1000 days. However, further research is needed with a bigger sample size before its application in daily practice.

TABLE 3
Fetal growth cut-off point for predicting maternal vitamin D levels and neonatal outcomes (OR, sensitivity, specificity, PPV and NPV)

Cut-off point	Proportion < cut-point n (%)	OR (95%IK)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Vitamin D Intergrowth-21	75 (62.5)	2.57 (1.25.52)	73.33 (60.34–83.93)	59.21 (47.33–70.35)	58.67 (50.98–65.95)	73.77 (63.99–81.66)
WHO	79 (65.8)	2.29 (1.05–4.98)	75 (62.14–85.28)	43.33 (30.59–56.76)	56.96 (50.38–63.31)	63.41 (50.62–74.56)
EFW	54 (45)	1.14 (0.56–2.35)	46.67 (33.6–760)	56.67 (43.24–69.41)	51.85 (42.02–61.54)	51.52 (43.45–59.50)
LBW Intergrowth-21	85 (70.8)	0.38 (0.9–1.6)	50 (15.78–4.30)	27.68 (19.64–36.93)	4.71 (2.39–9.06)	88.57 (78.46–94.28)
WHO	20 (16.7)	6 (1.36–26.45)	50 (15.78–4.30)	85.71 (77.84–91.61)	20 (9.85–36.40)	96 (92.28–97.97)
EFW	54 (45)	0.38 (0.07–1.99)	25 (3.19–65.05)	53.57 (43.9–63.05)	3.7 (1.13–11.49)	90.91 (86.61–93.92)
Stunting Intergrowth-21	59 (49.2)	0.47 (0.15–1.47)	33.33 (11.82–61.62)	48.57 (38.75–8.53)	8.47 (4.23–16.25)	83.61 (77.22–88.74)
WHO	76 (63.3)	2.56 (0.68–9.64)	75 (47.62–92.37)	71.93 (58.46–83.03)	42.86 (31.21–55.36)	91.11 (60.91–82.39)
EFW	32 (26.7)	0.38 (0.08–189)	13.33 (1.66–40.46)	71.43 (61.79–79.82)	6.25 (1.74–20.06)	85.23 (82.06–87.92)
Neurocognitive Intergrowth-21	41 (66.1)	2.16 (0.23–20.67)	80 (28.36–99.49)	35.09 (22.91–48.87)	9.76 (6.28–14.85)	38.71 (26.60–51.93)
WHO	35 (56.5)	0.85 (0.7–40.9)	100 (47.82–100)	47.82 (33.98–61.03)	14.29 (11.53–17.57)	–
EFW	41 (66.1)	2.16 (0.23–20.67)	80 (28.36–99.49)	35.09 (22.91–48.87)	9.76 (6.28–14.85)	95.24 (76.98–99.17)

CONCLUSION

The WHO fetal growth curve can be used to predict LBW. The cut-off point of the fetal growth curve and which percentile is determined by the neonatal outcome.

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Original Article

Correlation Between Visceral Fat and Lipid Profile in Myocardial Infarction Patients

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Abstract

Background : Previous studies reported that visceral fat plays an important role in cardiovascular disease, even in non-obese individuals. Bioelectrical impedance analysis (BIA) is a non-invasive and radiation-free method for assessing visceral fat. Not much is known whether visceral fat correlates with lipid profile in myocardial infarction (MI) patients in Indonesian population. The purpose of this study was to analyze the correlation between visceral fat and serum lipid profile in MI patients.
Methods : This is a correlational study on 32 MI patients hospitalized at the ICCU of RSUP Dr. Kariadi Hospital recruited with consecutive sampling. Visceral fat was measured by BIA SECA mBCA 525 series, data regarding levels of total cholesterol, triglycerides, low density lipoprotein (LDL), and high density lipoprotein (HDL) were gathered from medical record. The data were normally distributed, then the hypothesis was tested with the Pearson.
Results : The mean age of the subjects was 55 ± 9.88 years, with 87.5% being male. As many as 81.3% of subjects experienced ST-elevation myocardial infarction (STEMI). The average body mass index (BMI) was 26.2 ± 3.68 kg/m², in which 40.6% of subjects were classified as grade 1 obesity. The majority of subjects (93.8%) had high visceral fat. As many as 68.8% of subjects had high LDL levels with an average of 120.5 ± 38.84 mg/dL. HDL average was 35±13.55 mg/dL with 62.5% of subjects having low HDL levels. More than half of the subjects (56.3%) experienced hypertriglyceridemia with an average of 157.4 ± 55.84 mg/dL. Visceral fat was significantly related to total cholesterol and triglycerides (r=0.40; p=0.02 and r=0.36; p=0.04).
Conclusion : There is a significant correlation between visceral fat and total cholesterol and triglycerides in MI patients.

Keywords : myocardial infarction, body composition, visceral fat, lipid profile.

INTRODUCTION

The main pathology of cardiovascular disease is the development of atherosclerosis. Several studies have reported that the accumulation of visceral fat plays an important role in the development of chronic inflammation in the arteries leading to atherosclerosis. Modifiable risk factors for MI include dyslipidemia and obesity as well as their interaction. Reducing and evaluating adiposity can be a promising intervention approach in the management of cardiometabolic risk. Body mass index (BMI) does not accurately describe fat distribution. Assessment of fat distribution, especially visceral fat is important in determining the risk of cardiovascular disease. A number of studies have reported that visceral fat and dyslipidemia are risk factors for cardiovascular disease but studies investigating correlation between visceral fat and lipid profiles in patients with a diagnosis of MI is rare.[1–3]

Diagnostic imaging using computed tomography (CT) and magnetic resonance imaging (MRI) can accurately measure body composition, visceral fat accumulation, and ectopic fat distribution, but these tests are expensive and involve radiation exposure, making them ineffective in everyday practice. Dual-X-ray absorptiometry (DXA) expose relatively low radiation, but visceral fat measurements tend to have lower values in individuals with normal weight and tend to have higher values in obese individuals compared to MRI. Visceral fat dysfunction contributes to metabolic syndrome and cardiovascular disease. Bioelectrical impedance analysis (BIA) is relatively simple, fast, and non-invasive which can provide a more reliable picture of body composition with minimal variability between examiners and fast examination results, with an examination error of <1% on re-examination.[4–6] BIA examination was reported in previous studies to have better results in estimating visceral fat despite differences in BMI, age group, and sex. A study in a population in Taiwan reported that visceral fat had a positive correlation with risk factors for cardiovascular disease (blood pressure, glucose levels, and lipid profile), after adjusting for age and abdominal circumference, with the strength of the relationship being stronger in women than in men. The purpose of this study was to analyze the correlation of visceral fat and lipid profile in IM patients.

METHODS

This is a correlational study with consecutive sampling. The sample size uses the following formula:

$$n = \left\{ \frac{(Z\alpha + Z\beta)}{0{,}5 \ln \{(1+r)/(1-r)\}} \right\}^2 + 3$$

It is determined that the magnitude of type I error (α) = 5%, then the value of Zα is 1.64. The type II error (β) is set at 20% (β=0.2), so the value of Zβ is 1.28. The minimum correlation that was considered significant (r) from the lipid profile in previous studies was obtained by a value of r = 0.475, so the minimum sample size was 32 people.[7]

Data is in the form of secondary data taken from ICCU patients at RSUP Dr. Kariadi as many as 32 subjects. The inclusion criteria are inpatients in the ICCU of RSUP Dr. Kariadi with a diagnosis of IM during the study period, age >18 years, not pregnant and complete medical record data. Exclusion criteria were patients with edema, pregnant patients, or patients with malignancy. The independent variable used is visceral fat. The dependent variables are total cholesterol, triglycerides, HDL, and LDL. The confounding variables that influenced the study were age, HbA1C, fasting glucose, and blood pressure. Data processing uses SPSS version 25. Data with a nominal or ordinal scale is displayed in the form of amounts (n) and percentages (%), data with a ratio or interval scale is displayed in the form of mean and standard deviation (SD). The normality test using Shapiro-Wilk and data distribution of variables was normal, then test the correlation was tested with the Pearson test (r values, p values with 95% confidence intervals). This research has gained permission from the Health Research Ethics Committee of RSUP Dr.Kariadi Semarang No.1111/EC/KEPK-RSDK/2022.

RESULTS

The subjects of this study were 32 patients with a diagnosis of MI treated at RSUP Dr. Kariadi Semarang according to the time of the study that met the inclusion and exclusion criteria. The basic characteristics of the research subjects are described in Table 1.

The youngest age of this research subject is 33 years and the oldest is 71 years. The independent variable in this study was visceral fat as measured by the BIA SECA mBCA 525 tool, visceral fat was grouped based on the cut-off value contained in the tool, namely the normal group <1.4L, the increased group <2.2L and the high group ≥2, 2L. Confounding variables include age, incidence of diabetes mellitus (DM), and incidence of hypertension. The characteristics of the research subjects are described in Table 2.

Variables are normally distributed, so the visceral fat correlation test with lipid profiles using the Pearson test can be seen in Table 3.

The scatter plot graph between visceral fat and lipid profile can be seen in Figure 1.

The correlation of visceral fat with lipid profile shown in Table 3 and Figure 1 shows that there is a unidirectional correlation between visceral fat and total cholesterol and triglycerides, but there is no significant correlation between visceral fat, HDL and LDL.

TABLE 1
Basic characteristics of research subjects

Subject Characteristics	Mean± SD	n (%)
Age (Years)	55 ± 9.9	–
<60 years	–	21 (65.6)
≥60 years	–	11 (34.4)
Gender	–	–
Male	–	28 (87.5)
Female	–	4 (12.5)
Miokardial infraction	–	–
STEMI	–	26 (81.2)
NSTEMI*	–	6 (18.8)

*non ST-elevation myocardial infarction

TABLE 2
Characteristics of research subjects

Subject Characteristics	Mean±SD/ Median	n (%)
BMI (kg/m^2)	26.2 ± 3.68	–
Underweight	–	–
Normoweight	–	5 (15.6)
Overweight	–	9 (28.1)
Obese 1	–	13 (40.6)
Obese 2	–	5 (15.6)
Viseral fat (L)	3.9 ± 1.34	–
Normal	–	1 (3.1)
Increased	–	1 (3.1)
High	–	30 (93.8)
DM	–	–
Yes	–	13 (40.6)
No	–	19 (59.4)
HbA1C (%)*	5.9	–
<6.5	–	19 (59.4)
>6.5	–	13 (40.6)
Fasting Glucose (mg/dL)	122	–
<126	–	18 (56.3)
>126	–	14 (43.8)
Hypertension	–	–
Yes	–	14 (43.5)
No	–	18 (56.3)

TABLE 2. Continued.

Subject Characteristics	Mean±SD/ Median	n (%)
Sistole (mmHg)	118.2 ± 17.91	–
<120	–	22 (68.8)
120–139	–	6 (18.8)
≥140	–	4 (12.5)
Diastole (mmHg)	75.5 ± 10.68	–
<80	–	20 (62.5)
80–89	–	8 (25)
≥90	–	4 (12.5)
Total cholesterol (mg/dL)	177.5 ± 45.97	–
Normal	–	20 (62.5)
Hypercholesterolemia	–	12 (37.5)
LDL (mg/dL)	120.50 ± 38.84	–
Normal	–	10 (31.3)
High	–	22 (68.8)
HDL (mg/dL)	35 ± 13.55	–
Low	–	20 (62.5)
Normal	–	12 (37.5)
Triglyseride (mg/dL)	157.6 ± 55.84	–
Normal	–	14 (43.8)
Hypertriglyseride	–	18 (56.3)

*Hemoglobin A1C

TABLE 3
Correlation of visceral fat with lipid profile

Variable	R	p value
Total cholesterol	0.400	0.023
Triglyseride	0.363	0.041
HDL	-0.272	0.133
LDL	0.326	0.068

The results of the visceral fat correlation test with confounding variables using the Pearson test can be seen in Table 4.

The scatter plot graph between visceral fat and confounding variables can be seen in Figure 2.

The correlation of visceral fat with all confounding variables shown in Table 4 and Figure 2 shows no significant correlation between visceral fat and all confounding variables.

DISCUSSION

Myocardial infarction is the most common cardiovascular disease, based on the results of th electrocardiogram, MI consists of STEMI and NSTEMI. RISKESDAS data in 2018 shows that the number of people with heart disease is more in men than women, as well as the British National Report in 2014, the prevalence of MI in men is 3x higher than that in women. Research in

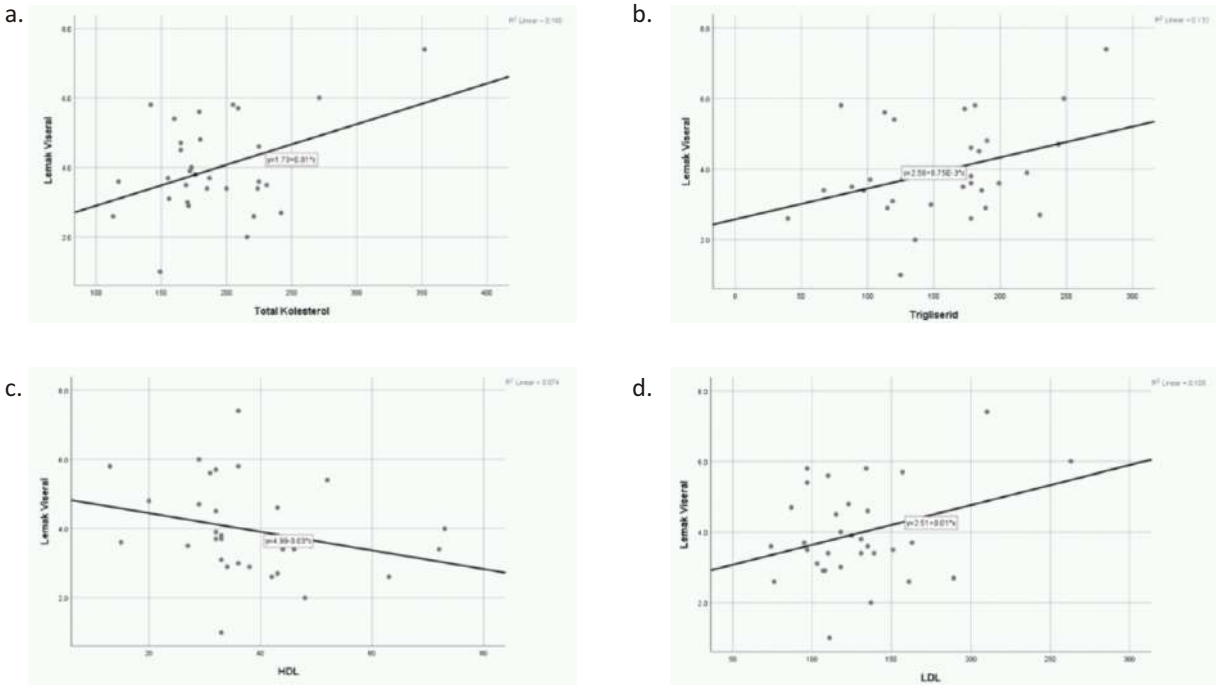

Figure 1. Scatter plot between visceral fat and (a) total cholesterol; (b) triglycerides; (c) HDL; and (d) LDL

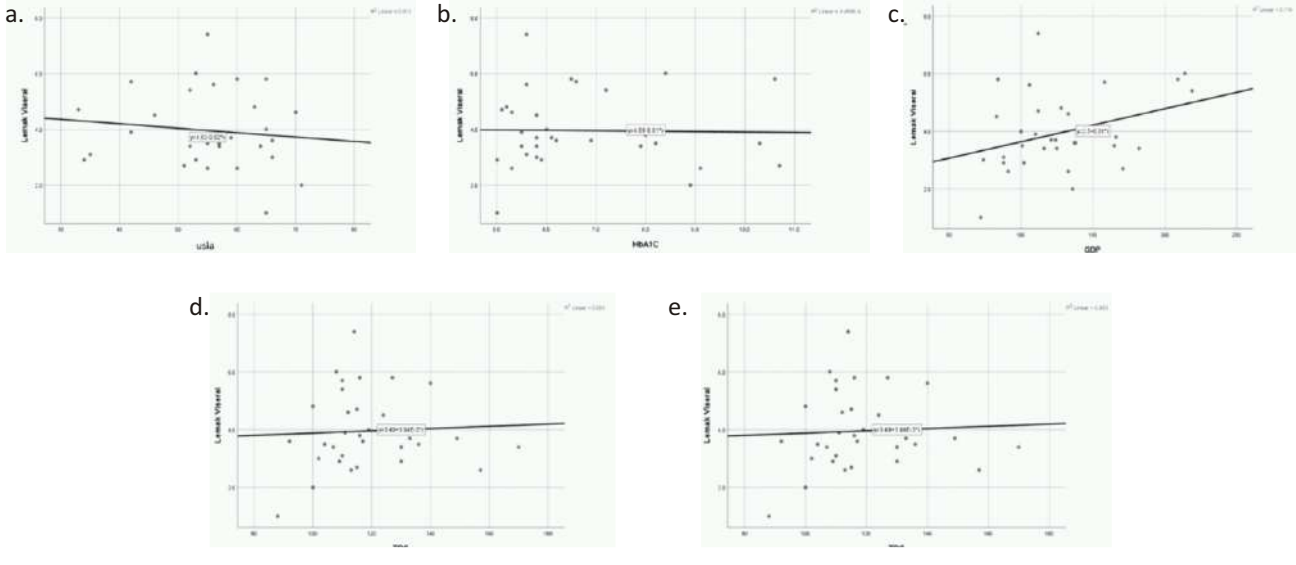

Figure 2. Scatter plot between visceral fat and (a) age; (b) HbA1C; (c) Fasting glucose; (d) diastole; and (e) systole

2020 at Dr. Kariadi General Hospital reported similar thing, 72.9% of MI patients were male. Sex hormones play an important role in the regulation, distribution and function of adipose tissue. Women have more total body fat and subcutaneous fat while men have more visceral fat. Population studies report that high testosterone concentrations are associated with increased visceral fat in women and decreased in men. In hypogonadal males, low testosterone concentrations are associated with accumulation of visceral fat.[8–10]

This study reported an average BMI of 26.22 ± 3.68 kg/m² and 40.6% of the study subjects were grade 1 obese. An increase in BMI was directly related to an increased risk of MI. Subjects in the normoweight group were 15.6%, this is in line with the Yajnik-Yudkin hypothesis (Y-Y paradox) stating that there is "thin fat", namely a significant difference in fat composition between Asian and Caucasian ethnic groups with the same BMI. The BMI anomaly of the Asian population is in the form of a slimmer physical appearance but the body

TABLE 4
Correlation of visceral fat with confounding variables

Variable	R	p value
Age	- 0.115	0.532
HbA1C	- 0.019	0.920
Fasting glucose	0.338	0.059
Diastole	0.204	0.262
Sistole	0.052	0.776

scan results show a high ratio of total fat to body weight.[11,12]

The mean visceral fat in this study was 3.9 ± 1.34 L where 93.8% of the subjects had high visceral fat. Fat distribution, especially visceral fat plays an important role in increasing the risk of cardiovascular disease. A number of studies indicate that obese patients with metabolic disorders such as insulin resistance and dyslipidemia indicate excess visceral fat. Fat distribution is very different in racial and ethnic groups and reflects differences in anthropometry of each ethnicity, Asian populations tend to have an "apple shape" body shape, which indicates a high prevalence of abdominal fat accumulation. Studies in Korea report important evidence that in individuals who appear normal and are assessed for cardiovascular risk only by anthropometry, there is a dramatic increase in cardiovascular disease without a significant increase in BMI, supporting the relevance of fat distribution. So the main target of therapy is reducing visceral fat with physical activity and healthy food. The Asian population has more visceral fat accumulation but lower BMI values.[11–13]

Visceral fat was significantly related to total cholesterol (r=0.400, p=0.023) and triglyceride (r=0.363, p=0.041), but visceral fat was not related to HDL (r= -272, p=0.133) and LDL levels (r=0.326, p=0.068). Accumulation of fat mass in obesity causes infiltration of marophages and becomes a site for the production of proinflammatory cytokines such as tumor necrosis factor (TNF) which has been shown to induce insulin resistance in adpository tissue and inhibit the synthesis and secretion of adiponectin. The decrease in adiponectin is associated with a decrease in HDL levels. The relationship between visceral fat and HDL is negative indicating that with an increase in visceral fat, HDL levels will be lower, this is in line with the results of this study, the average HDL level in this study was 35 ± 13.55 mg/dL with 62.5% subjects had low HDL levels (<40 mg/dL). HDL has anti-arterogenic effects in the form of the ability to remove cellular lipids and better cell survival. Decreased HDL levels and function are secondary to hormonal changes, inflammatory processes caused by food intake, smoking habits, and alcohol consumption were not examined in this study. Visceral fat accumulation has metabolic consequences and visceral fat may predict cardiovascular risk better than BMI even in non-obese individuals. The form of cholesterol circulation is bound to lipoproteins, the 4 main fractions of lipoproteins are divided based on density namely very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL and HDL. Cholesterol and TG from the liver are carried by apolipoprotein B (ApoB) in the form of VLDL, which then undergo hydrolysis by lipase becoming IDL and LDL. VLDL cannot enter the tunica intima of the arteries, so lipase modifies it into smaller particles, so that it can enter the tunica intima of the arteries and is arteriogenic. Measurement of LDL levels is quite useful in evaluating the risk of cardiovascular disease, but this parameter only provides information about the amount of cholesterol bound to the LDL fraction, but does not provide information about the concentration of LDL particles. A number of studies highlight the missing link between LDL and cardiovascular events. A cohort study from the lipid research clinical prevalence study reports that men with LDL levels <100 mg/dl had an increased cardiovascular mortality compared to men with LDL levels of 100-130 mg/dl. A cohort study in patients with the metabolic syndrome shows that they had larger areas of visceral fat but lower LDL levels than patients without the metabolic syndrome. In line with this study, 93.8% of patients were in the high visceral fat group and the relationship between visceral fat and LDL was not significant (r=0.326, p=0.068). ApoB examination can accurately measure LDL concentrations, with this method patients with central obesity with LDL levels within normal limits but have metabolic abnormalities such as hypertriglycerides and decreased HDL levels, have 20–25% higher ApoB levels. This explains that eventhough LDL levels do not increase, patients still have a risk of cardiovascular disease because they still have high concentrations of LDL particles. The clinical practice of assessing LDL particle size is fasting triglyceride levels, which have shown to be negatively correlated with LDL particle size. This negative

correlation describes the activity of the cholesterol ester protein transfer enzyme due to hypertriglycerides, namely the exchange of triglyceride molecules from VLDL to LDL. This exchange results in a relative increase in LDL triglyceride content, which is further hydrolyzed by hepatic lipase. The end result is the formation of small particle LDL cholesterol. This explains that the accumulation of visceral fat is associated with increased TG levels and causes the formation of LDL which has small and dense particles, then develops into insulin resistance and cardiovascular disease. Assessment of cardiovascular disease risk in clinical practice can examine the levels of TG, HDL and the TK:HDL ratio.[9,14–21]

The age of the research subjects was dominated by <60 years old, which was 65.6%. This indicates a tendency for lipid profile disturbances to occur at a young age. This is in line with a study in Japan for 3 decades (1985–2014) which reported a significant increase in the age group ≤59 years. One of the most important health issues in Asia Pacific is cardiovascular disease, where there are increasing rates of dyslipidemia, DM, obesity and hypertension due to rapid urbanization, a shift in diet to a "western" diet, smoking, and decreased physical activity. Observational studies report that intake of fruit, dairy products, and fiber has a protective effect, whereas intake of fried and fatty foods, alcohol, red and processed meats, sugary drinks, processed flour and foods with a high glycemic index are associated with high visceral fat mass. Excess consumption of processed foods that contain high energy and low nutrient content combined with a sedentary lifestyle is a risk factor for cardiovascular disease. Dietary factors such as increased intake of fat and alcohol even in non-obese individuals will trigger the accumulation of visceral fat, which is characterized by high lipogenic activity and high lipolytic activity. Visceral fat circulates in the portal vein system and is directly related to the liver, where high lipolytic activity will cause insulin resistance due to increased levels of free fatty acids in the liver. Glucose intolerance is related to lipid peroxidation with consequent DNA damage. DNA damage can be used as a biological marker in the detection, monitoring and prognosis of degenerative diseases such as atherosclerosis. Increased oxidative stress causes endothelial dysfunction by increasing vascular superoxidation anion production, and in turn will decrease nitric oxide (NO). Endothelial dysfunction is associated with cardiovascular disease risk factors such as smoking, accumulation of visceral fat and fasting or postprandial hypertriglycerides. A study in England compared Asian and Caucasian ethnicity, found that the Asian population was diagnosed younger. Study in Korea on non-obese adult males reported that visceral fat was most significantly associated with impaired postprandial lipid response, lipid peroxidation, DNA damage and endothelial dysfunction, which associated with the risk of morbidity and mortality from cardiovascular disease.[13,22–26]

Visceral fat accumulation has been shown to cause glucose intolerance resulting in insulin resistance. Several studies have reported that the combination of visceral fat and lipid dysregulation is associated with high sugar intake. A study in South Korea showed a significant relationship between visceral fat and HbA1C in the pre-DM patient group. HbA1C is reported to be useful in assessing long-term glycemic control in DM patients. HbA1C levels are affected by the number of erythrocytes, so in anemic patients the HbA1C value cannot be used. There was no relationship between visceral fat and HbA1C in this study, this could be due to the subject being anemic. Anemia conditions and DM treatment history were not examined in this study. The high prevalence of DM in patients with cardiovascular disease among Asian population causes them to feel no any classic symptoms of MI, so that the percentage of "silent killers" is higher in the Asian population.[27,28]

Hypertrophy occurs in fat cells, especially visceral fat in obese individuals, causing a decrease in adiponectin and insulin sensitivity which develops into insulin resistance. Fasting blood sugar is one of the most sensitive parameters for detecting DM. Fasting glucose levels increase with age and visceral fat in overweight and obese individuals. In patients with acute myocardial infarction, there is a stress response in the form of excessive secretion of steroid hormones, adrenaline, glucagon and free fatty acids. Acute hyperglycemia can disrupt the prothrombotic phase, increase inflammation and oxidative responses, damage endothelial cells and microcirculatory function and eventually lead to massive myocardial infarction. There was no relationship between visceral fat and fasting glucose levels ($r=0.338$; $p=0.059$) in this study, possibly due to the use of insulin therapy in patients with high blood sugar levels at admission. In this study there was no data on the time of sampling for examination of fasting glucose levels, so it was not known whether it was the fasting glucose level after admission or the evaluation fasting glucose level.[29,30]

Visceral fat has been reported to be associated with blood pressure. Several mechanisms of visceral fat are associated with increased blood pressure, namely, adipokine secretion, free fatty acids derived from visceral fat circulating in the portal vein, cardiac sympathetic activity is higher in visceral obesity and visceral fat is associated with activation of the renin-angiotensin-aldosterone system. The results of this study found no relationship between visceral fat, TDS and TDD as no hypertension therapy before the subject experiencing MI or the time of blood pressure examination.[31,32]

Limitations of this study is no data on therapy either before treatment or during treatment is available, so that it affects the levels of lipid profiles, fasting blood sugar, and blood pressure. The research subjects were

ICCU patients where there was a change in the hypercatabolic state to be very different from the healing phase, so the time for data collection greatly influenced the results of the study. Future studies need a larger sample size using the cohort method.

CONCLUSION

This study shows that there is a significant correlation between visceral fat and total cholesterol and triglycerides in MI patients. All confounding variables (age, HbA1C, fasting glucose, and blood pressure) were not correlated with visceral fat in this study. Visceral fat assessment is very important as an effort to prevent non-communicable diseases, especially cardiovascular disease, with a relatively easy and fast examination with BIA, can describe metabolic risk. The BIA examination also evaluates more accurately than conventional anthropometric examinations, where BMI cannot describe the risk of fat distribution, thus causing underdiagnosis.

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Original Article

The Effect of Giving A Vibrator with A Cooler on Pain Level in Childhood with Venipuncture in Tidore Kepulauan Hospital

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Abstract

Background : A traumatic care is therapeutic care that is carried out as part of an intervention to remove or suppress psychological or physical stress suffered by a child. The act of minimizing pain, stress and trauma to children when given at the time of blood collection is part of the principle of atraumatic care. One of the atraumatic actions that can be performed on children is the use of a vibrator with a cooler to minimize pain when stabbing a vein. The aims of this study was to determine the effectiveness of giving a vibrator accompanied by a cold compress against pain in children when taking venous blood.
Methods : The design of this research is true experimental with a post-test only control group design. Researchers divided into 2 groups, namely the intervention and control groups were taken randomly. Then the researcher made a vibrator with a cooler that had been previously tested on 30 adults, then after being declared to have passed the ethical study it would be applied to children when taking venous blood, assessing children's pain using the FLACC instrument (face, legs, activity, cry and controllability). The study was conducted at the Tidore Islands Hospital. Data processing was carried out previously by testing the homogeneity and normality test, if normally distributed it will use the independent t-test to assess the difference in the average of the two groups, while if it is not normally distributed it will be tested with Mann-Whitney.
Results : The results of this study indicate that the characteristics of respondents according to age are mostly 4 years old. In the control group the average age of children is 3.87 while in the intervention group the average age of children is 3.93. Most of the experience of having blood drawn in both groups had blood drawn before. Based on gender characteristics, most of the control and intervention groups were women. There are differences in pain scores in the control and intervention groups. The mean pain score in the intervention group was 3.13 and the mean pain score in the control group was 7.87. The results of statistical tests using Mann Whitney showed that there was a significant difference in pain during venipuncture in the intervention group and the control group (p=0.013).
Conclusion : The results of the statistical test show that there was a significant difference in pain in the intervention group and the control group (p=0.013). The use of a cooling vibrator can be an alternative to reduce pain in children during venipuncture.

Keywords : Atraumatic care, pain, children, cooling vibrator. Venipuncture

INTRODUCTION

A healthcare facility or hospitalization is an environment that is foreign to both children and their parents, a condition which can lead to feelings of anxiety, fear, helplessness, anger and loss of control. Treatment procedures performed in hospitals are generally considered a threat to children. Efforts can be made to prevent and reduce the physical stress experienced by children and families, and nurses and other health workers recommend an atraumatic treatment approach.[1]

The condition of the disease that causes the child to require various diagnostic procedures, treatment and hospitalization. One procedure that is often performed is venipuncture (drawing venous blood). Pain is a common experience and serves as an important sign that the body is damaged.[2] Several studies show that the pain experienced by children when taking blood is sometimes ignored so that the treatment given becomes inadequate. Children who are admitted to the hospital often undergo various invasive procedures that need to be carried out. Venous puncture is an invasive procedure that is often carried out by nurses or laboratory personnel in hospitals, where this action is carried out by inserting a needle into a child's blood vessel which can cause pain.[3]

A punctured venous blood examination is the second source of pain most felt by children after their illness.[4] Inappropriate pain management can have a major impact on a child's life. Pain can cause difficulty sleeping, reduce the child's interest in activities, and increase anxiety. Failure to reduce pain can result in helplessness and hopelessness.[3]

To reduce pain, pharmacological therapy can be done, namely using drugs and non-pharmacological therapy without using drugs such as relaxation, hypnosis, guided imagery, massage, music therapy, warm compresses and cold compresses.[5] Giving cold compress therapy is a suitable therapy given before a venous puncture examination is carried out. The cold effect caused can cause numbness before pain occurs. Cold compress therapy can provide a local anaesthetic effect on puncture wounds during infusion.[6] Cold compresses using ice can slow the conduction of peripheral nerve fibres and reduce the release of inflammatory mediators and nociceptors, causing a faster skin anaesthetic effect.[7] The act of reducing pain, trauma and feelings of pressure in children when taking blood is part of the principles of atraumatic care.

The principle of atraumatic care can be applied both pharmacologically and non-pharmacologically. Pharmacological techniques can be done in various ways, including the use of EMLA cream, lidocaine and L.M.X.4. Management of pain relief non-pharmacologically when taking blood includes various physical and cognitive-behavioural pain management strategies. Various non-pharmacological physical intervention efforts include distraction, massage, hot and cold compresses, acupressure techniques, and contralateral stimulation.[8]

Non-pharmacological methods to reduce pain during blood collection procedures have been proven to be effective and efficient to be applied to pediatric patients.[9] Distraction is the most frequently performed action, however, the use of cold compresses and vibrators has been studied to reduce pain in children. The action of cold compresses provides a cold sensation and reduces pain by inhibiting conduction and nerve impulses, which results in numbness, increases the pain threshold and causes an anaesthetic effect.[10] Research conducted by[11] concluded that the use of ice cubes was significantly more effective in reducing pain than the use of vapour coolant spray when conducting a skin test as an injection drug. Another study conducted by[10] found that the use of a cooling vibrator was more effective in reducing pain than the standard procedure when performing venipuncture in children aged 4–18 years. Different things were expressed by[12] who researched 47 children aged 4–17 years, the results of the study found that there was no significant difference between the combination of using cold compresses and vibrations with the control group using standard procedures. Younger children have different cognitive development from older children, this will affect the ability to tolerate pain.[13]

Research on the use of cold compresses and vibrators is effective in reducing pain in children aged 4–18 years, but research in the early childhood group or commonly called early childhood (1–4 years) needs further studies. This is following the recommendation of[12] to conduct research on a more uniform age group. In addition, actions that combine various methods to reduce pain and reduce children's distress need to be taken.[9] Based on a preliminary study conducted at the Tidore Hospital, the action of reducing the pain of taking blood for children was only limited to involving parents, namely by holding and inviting children to talk. The act of giving cold compresses has not been carried out. So researchers are interested in conducting research on the effect of vibrators with cooling on pain in children when blood is drawn in the Tidore Islands Hospital area.

RESEARCH METHODS

This research uses true experimental with a post-test-only control group design. Researchers divided into 2 groups, namely the intervention and control groups were taken randomly.

Group design	Treatment	Post Test
Intervention	X	I–1
Control		C–1

I-1 = Measurement of the dependent variable in the cold pack and vibration intervention group
X = Vibration and cold compresses intervention
C-1 = Measurement of the dependent variable in the control group

The population in this study were all children who had blood drawn at Tidore Kepulauan Hospital.

The sample in this study was selected using random allocation. Determination of the intervention group and the control group is taken randomly, the sample will be given an explanation before being included in the study.

For simple experimental research using experimental groups, a minimum of 10–20 samples each can be used. The research will use 30 child respondents and 30 adult respondents for the preliminary study. The inclusion criteria in this study were children aged 1–7 years, children who were not in a critical condition or decreased consciousness, children who did not suffer from red sickle cells, children who did not experience skin abrasions in the tool attachment area. Meanwhile, the exclusion criteria are if the parent/guardian resigns during data collection.

The place where this research was conducted was at the Tidore Kepulauan Hospital. Previously, a preliminary study would be carried out at the hospital.

The research process began in March 2022 starting with the process of assembling the tool, testing it on adults. Data collection was carried out September–November 2022. The preparation and reporting of research results was carried out in December 2022.

Research Ethics in this research conducted by considering ethical principles aimed at protecting research subjects. By paying attention to the basic principles of research ethics.[14] The respondent's right to autonomy includes the right to agree or refuse to participate in this study. Respondents (children and parents) received an explanation of the research procedures, benefits and risks of this study before being included in the study.

a. Right to justice

The principle of treating fairly relates to selecting respondents based on sample criteria. The intervention group in this study received cold compresses and vibration treatment, while the control group received interventions as usual at the Tidore Kepulauan Hospital.

b. The right to privacy

This research protects the privacy and dignity of the respondents, during the research, the confidentiality of the respondents is maintained. This right is fulfilled by not telling other parties all the problems of the respondent and treating them kindly. Therefore the research data is coded, and the identity of the respondent will not be included in the intervention results report.

Researchers made a vibrator with a cooler that would be tested previously on 30 adults, then after being declared to have passed the ethical study it would be applied to children when taking venous blood.

Data collection instrument using a questionnaire containing questions related to the respondent's identity, including age, gender, previous blood sampling experience. The data collection tools used in this study included a vibrator accompanied by a cooling compress, stationery, observation sheets to assess pain and a video recorder.

Data collection method : for the control group, a vibrator accompanied by cooling was placed in the vein puncture area for approximately 30 seconds to 60 seconds. Then during the puncture, the tool is shifted 1–2 cm above the vein puncture area.

During the venous puncture, the child's pain response was observed. To support pain assessment, during the procedure, a video recording was also carried out by a data collector who was not involved in the procedure.

Data analysis used in this study are Univariate analysis Used to determine the description of age, gender, previous experience of blood collection and pain level when the child is pierced by a vein and Bivariate analysis of the research was carried out to prove the hypotheses that had been formulated. Prior to the bivariate analysis, homogeneity and normality tests were carried out first. If it is normally distributed, the independent t test is used to find out the mean difference between the two groups, while if it is not normally distributed, the Mann Whitney test is used.

RESULTS

Characteristics of Respondents

Table 1 shows the mean age of children who underwent venipuncture at Tidore Hospital in the control group was 3.87 years (3–5; 95% CI: 1.41–4.42), the youngest age in the control group was 3 years and the oldest age was 5 years. The mean age in the intervention group was 3.93 years (3–5; 95% CI: 1.38–4.37), the youngest age in the intervention group was 3 years and the oldest age was 5 years.

Table 2 shows that the experience of having previous blood drawn at Tidore Kepulauan Hospital mostly had blood drawn before. In the control group, 9 people had blood taken, while in the intervention group, 11 people had blood taken. Based on gender characteristics, the control group and the intervention group were mostly women (53% and 60%).

TABLE 1
Characteristics of Respondents Based on Age in Tidore Kepulauan Hospital

Variable	Median	Min–Maks	Mean	SD	95% CI Lower-Upper
Control group Child's					
Age (Years)	4	3–5	3.87	2.78	1.41 – 4.42
Intervention Group					
Child's Age (Years)	4	3–5	3.93	2.76	1.38 – 4.37

TABLE 2
Characteristics of Respondents Based on Experience with Previous Blood and Gender

Variable	Intervention Group		Control Group	
	n	%	n	%
Blood drawn experience				
Ever	11	73%	9	60%
Never	4	27%	6	40%
Sex				
Male	7	47%	6	40%
Female	8	53%	9	60%

TABLE 3
Distribution of Pain Scores in the Intervention Group and Control Group in Children with Venipuncture at Tidore Kepulauan Hospital

Variable	n	Median	Min–Maks	Mean	SD	95% CI Lower–Upper
Control Group	15	8	6–10	7.87	1.15	1.15
Intervention Group	15	4	1–5	3.13	1.50	1.50

TABLE 4
Analysis of Pain Differences in the Intervention Group and Control Group at Tidore Hospital

Group	n	Mean Rank	p value
Control Group	15	23.00	0.013
Intervention Group	15	8.00	

Overview of Pain Levels in the Control and Intervention Groups during Venapuncture

Data collection in this study used the FLACC instrument with 5 assessment components, namely face (facial expression), legs (leg movement), activity (activity), cry (crying) and controllability (ability to be entertained).

Based on the results of the analysis in Table 3, the control group's average pain score obtained was 7.87 (6-10; 95% CI: 7.20 - 8.52), while in the intervention group the average pain score obtained was 3.13 (1-5; 95% CI: 2.27 - 3.99).

Analysis of Differences in Pain (Comfort) in the Control Group and the Intervention Group

The following presents the differences in pain in the intervention group and the control group in Table 4.

Based on Table 4, the Sig Value or P-Value is 0.013 <0.05. If the p-value < the critical limit of 0.05, then there is a significant difference between the two groups or which means that H1 is accepted.

DISCUSSION

Overview of Pain Levels in the Intervention Group and Control Group

The results of statistical tests showed that there was a difference in the average pain score in the intervention group and the control group. The control group's average pain score obtained was 7.87 (6–10; 95% CI: 0.58–0.95), while in the intervention group the average pain score obtained was 3.13 (1–5; 95% CI: 0.75–2.38). The results of this study are in line with research conducted[15], that cold compresses can relieve pain by slowing the speed of nerve conduction and inhibiting nerve impulses, causing numbness and increasing the pain threshold and can cause an anaesthetic effect. Cold therapy is widely used to reduce the process of swelling, pain, muscle spasm and the risk of cell death. Cold therapy is used in the form of ice massage, ice packs, cold bath/water immersion and vapour coolant sprays.

Assessing the level of pain can be done by looking at the response directly or indirectly. Indirect assessment includes facial expressions, crying, motor activity, and simple and complex behaviour. Assessment of physiological symptoms includes respiratory rate, heart rate, blood pressure and sweating and direct assessment using self-reporting or projection methods. This study uses the FLACC instrument which includes 5 assessment components, namely face (facial expression), legs (leg movement), activity (activity), cry (crying) and controllability (ability to be entertained). This instrument is not only able to determine pain but also can determine the comfort of the child when taking blood. Difficulty in assessing pain when the child is afraid and cries first before taking blood.

Differences in Pain Levels in the Control Group and the Intervention Group

The results of statistical tests using Mann Whitney showed that there was a significant difference in pain in the intervention group and the control group (p = 0.013). Cold compresses have a mechanism of pain that is transmitted from the peripheral nervous system to the central nervous system and is modulated by the gating system in the dorsal horn of the spinal cord. More specifically, the afferent nervous system which is pain receptors (A-delta fibres carry acute pain and myelinated C fibres transmit pain slowly) is blocked by nonnoxious fast-moving (A-beta) nerves. The cold sensation stimulates C fibres and blocks the A-delta which carries pain signals so that the pain felt will be reduced.[10] Cold compresses and vibrations are considered effective for reducing pain in children during a venous puncture procedure .[16,17]

The results of this study are in line with previous research. Research conducted by I Gusti Ayu Putu Satya Laksmi stated that the pain level of children in the control group was moderate pain. Meanwhile, the level of pain in the treatment group was included in the category of mild pain. The test results show that there is an effect of cold compresses on the level of pain during infusion in school-age children.[18] Lingga Liwa Ati said that babies who get measles immunization will experience pain that can cause excessive anxiety and even trauma, therefore it is necessary to take atraumatic care measures such as ice packs to reduce pain so that excessive anxiety and even trauma will not arise.[19] The inhibition of transmission and duration of pain impulses that occur in the dorsal door are based on gate control theory so as to minimize the pain sensation formed due to needle insertion during anesthesia.[20]

CONCLUSION

There are differences in pain scores in the control and intervention groups. The mean pain score in the intervention group was 3.13 and the mean pain score in the control group was 7.87.

The results of statistical tests using Mann Whitney showed that there was a significant difference in pain during venipuncture in the intervention group and the control group (p=0.013).

Recomendation for service institutions, the results of this study are expected to provide input for nursing service providers to approach atraumatic care in taking blood in children. The treatment room is expected to be more optimal in reducing pain in children according to the child's developmental stage.

For nursing science, the results of this study are expected to be evidence-based practice in the practice of nursing children with venipuncture.

For further research, in this study, researchers only used ages 1–7 years, it is hoped that further research will pay attention to the developmental age of children more equally so that the interventions provided are more equal. Future research is expected to use a larger sample. The next research is expected to be able to develop a vibrator and cooler with a more compact form using battery resources.

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Original Article

Association of Neuropathic Pain Improvement and hs-CRP Changes among Trigeminal Neuralgia Patients Experienced Radiofrequency Ablation 60° and 65° Celcius: 6 Months Follow Up

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Abstract

Background : Trigeminal neuralgia (NT) is a neuropathic pain that involves the trigeminal nerve in the face. The first-line medical management of patients with NT is Carbamazepine (CBZ). Radiofrequency ablation (RFA) procedure is a minimally invasive procedure using a high-frequency current-generating device that produced heat ablate of C-fibers with effectiveness around 76% for 10 yeas follow-up. Inflammed trigeminal nerve (TG) or the branch(es) might be one of the underlying mechanisms unless vascular compression is a common etiology. The heat effects might be according to the temperature set up varies recently from 60°C to 95°C.
Methods : This observational study enrolled 75 severe NT subjects without satisfactory improvement of treatments, divided into 3 groups: analgesics prescription (Control), RFA 60, and RFA 65 Groups. The LANSS scores and hs-CRP levels were followed-up before (baseline), 2 weeks, 3, and 6 months experienced the treatments. Subjects ages in the range of 48.32 ± 12.73 to 50.88 ± 14.59 years old, and the duration of illness from 4.48 to 10.32 months.
Results : The LANSS score >12 before treatments showed significance improvements ($p<0.001$), as in the Control (64% with neuropathic pain), RFA 60 (100% with neuropathic pain), and RFA 65 group (92% with nociceptive pain) at 2 weeks followed-up. At 3 and 6 months observed 100% subjects with nociceptive pain but without significancies. Even though the hs-CRP levels observed reduced for all groups, especially RFA 60 and RFA 65, but have no significances.
Conclusion : The LANSS scores changes observed significant improvement in all groups, which mentioned if the neuropathic pain syndromes might be better under each treatment. The Hs-CRP levels improvement is better in the neuro ablation groups than analgesic drugs treatment. Even though the Hs-CRP are following of systemic nonspecific inflammation, NT is a focal inflammation.

Keywords : Trigeminal neuralgia, neuropathic pain, inflammation, LANSS score, Hs-CRP

INTRODUCTION

Trigeminal neuralgia (NT) or tic douloureux is a neuropathic pain that involves the trigeminal nerve in the face. Based on existing studies, the prevalence of neuropathic pain in NT in France and England is around 6% to 8%, while data from 13 hospitals in Indonesia ranges from 21.8%. Several epidemiological studies show that the prevalence of NT sufferers in the European region ranges from 0.16 to 0.3%, in Asia it ranges from 0.3 to 0.4%, and the prevalence rate in the world ranges from 12.6 to 27.0 per 100,000 people per year. From several studies, it can be concluded that female sufferers are more often affected (60%) than men (40%) with a ratio of 1.5: 1.1. The age group between 50 and 70 years is a frequent case.[1]

According to The International Association for the Study of Pain (IASP), NT is defined as a recurrent, severe, brief, and sharp pain in one or more division of trigeminal nerves. While the International Headache Society (IHS) defines NT as unilateral facial pain, characterized by facial pain such as electric shock, which is brief and limited to the distribution of one or more divisions of the trigeminal nerve. NT can involve bilateral trigeminal nerve abnormalities although it is rare.[2] The pathophysiology of NT events is still unclear, but the theoretical basis behind the occurrence of NT which is most found around 80% is the theory that vascular compression by vascular tissue generally occurs around the area of entry of the trigeminal nerve to the pons. Trigeminal nerve compression is most caused by arteries (64% of cases), with the Superior Cerebellar Artery (SCA) in 75%, while the remaining 25% is compression of other small arteries and veins.[3,4]

Treatment of NT can be done in 2 ways, namely non-operative and operative. In non-operative management, intervention can be done through drugs or radiofrequency therapy. The first-line medical management of patients with NT according to the European Federation of Neurological Societies (EFNS) and the American Academy of Neurology (AAN), is Carbamazepine (CBZ) with an effectiveness of 70% to 80% with an initial dose of 200–300 mg/day with a maximum dose of 1200 mg/day.[5,6]

Radiofrequency ablation (RFA) procedure or can be called rhizotomy is a minimally invasive procedure using a high-frequency current-generating device that produces heat with the aim of making lesions on a tissue, including nerve tissue.[7,8] RFA is very relevant for the management of trigeminal neuralgia according to the 2019 EAN (European Academy of Neurology) guidelines. Radiofrequency energy utilization can use 2 methods, namely: pulsation or ablation. Pulsed radiofrequency (PRF) has a lower clinical improvement effectiveness than RFA, but the potential for side effects or complications is minimal. Based on case studies, RFA showed better effectiveness with greater potential for side effects. There is no specific standard for temperature selection in RFA. A literature shows that the temperature for RFA varies widely between studies (60°C to 95°C). The long-term analgesic effect of RFA at elevated temperatures (80°C) is not superior to those at relatively low temperatures (60–75°C). Therefore, we recommend a low temperature RFA (60–75°C) for the treatment of NT.[8,9]

The effectiveness of RFA reaches 3 to 10 years after the procedure, about 76% of subjects are pain free without medical therapy, 5% are on a reduced drug dose, and 15% of subjects require high doses of drugs or surgery.[8] Although there are some complications, RFA is still an effective procedure that can instantly relieve pain in 90–100% of NT cases. The proportion of patients who had no pain for 5 years and did not require oral treatment was 57.7%, after 15 years, 42.2% of patients still had no relapse, after 2 years the RFA was as high as 97.2%, after 8.8 years only 7.6%, and the rate of pain improvement after 11 years 52%.[8,10]

Clinical trials and effective pain management require valid and reliable assessments, one of which is using a measuring tool such as the Leedes Assessment of Neuropathic Symptoms and Sign Scale (LANSS), which is the first screening tool made for the diagnosis of neuropathic pain and consists of 5 aspects that describe symptoms and 2 aspects of clinical examination. LANSS has a sensitivity and specificity of 82–91% and 80–94%. If the score is 12 the patient suffers from neuropathic pain.[11]

Some recent studies have indicated the close relationship of inflammation with NT, and some inflammatory factors have been reported to induce neuropathic pain. Inflammation is suggested to exert a certain effect on nociceptor sensitization, and some studies have shown that the pro-inflammatory cytokines that have been produced at the time of inflammation can activate the nerve endings of polymodal nociceptor. Consequently, such kind of peripheral nociceptor sensitization will result indifferent pain quality and duration from the inflammatory tissues.[12]

High sensitivity C-Reactive Protein (Hs-CRP) is used as a marker of choice in monitoring the inflammatory response in the acute phase and can also be used in the chronic phase associated with depression, because in several studies the concentration of Hs-CRP increased thousands of times over time. 48 hours after the onset of inflammation compared to basal concentrations. The CRP test is not a specific test, it only shows inflammation in the body but cannot tell you exactly where it is.[13] The normal reference value for Hs-CRP is 0–0.30 mg/dL. Hs-CRP levels are influenced by proinflammatory cytokines, namely interleukin 1 (IL1), interleukin 6 (IL6), Tumor Necrosis Factor (TNFα), Substance P (SP) and Calcitonin Gene Related Peptide (CGRP).[14] In the study of Lakoski SG *et al*. said overall women had significantly higher median CRP levels than

men (2.56 mg/L: 1.43 mg/dL).[15]

This study aims to determine the effect of low-grade and high-grade RFA and medical therapy on changes in LANSS scores and Hs-CRP levels in NT patients.

METHODS

This is a cohort retrospective observational study with that conducted in the Department of Neurology Dr. Kariadi Hospital in Semarang that conducted for 5 months from May 2022 to September 2022. Participants were NT sufferers who received adequate analgesics prescription, but without any satisfaction of improvement. Subjects definitely carry out tumors, multiple sclerosis, or vascular malformation in regards to FIESTA 3D Head MRI examinations. The dropout criteria include patients who refer for surgeries or RFA re-intervention or died during the study. Seventy-five NT subjects were collected and divided into 3 groups: analgesics medication only (Control), RFA 60°C (RFA 60), and RFA 65°C (RFA 65). LANSS scores and Hs-CRP levels are measured before intervention and after undergoing RFA intervention (2 weeks, 3, and 6 months). RFA procedures were done by a Neurologist Pain and Minimally Invasive physician, who experienced more than 3500 cases of intractable pain. All procedures have done in Operation Theater of Dr. Kariadi Hospital Semarang, by guiding fluoroscope and under local anesthesia. Subjects will refer to the recovery room for 30 minutes to monitor post-intervention. They might monitor for 24 hours then, and be hospitalized for as long as 3 days. The LANSS score <12 means nociceptive pain, while a score >12 was neuropathic pain. The Hs-CRP level was assessed using a venous blood sample. Measurement results were grouped into normal (0–0.3 mg/dL) and high (> 0.3 mg/dL). This study has received ethical approval from the Ethics Commission with the number 1013/EC/KEPK-RSDK/2020.

The data were processed using SPSS statistical software version 26. Nominal data will be expressed as a distribution of frequencies and proportions. For each variable, a normality test was performed. Univariate analysis to see a description of all research data. Bivariate analysis was carried out to test each variable on the output results. Numerical data, consisting of age, are tested using the ANOVA test and Spearman correlation. Nominal data, consisting of gender, was tested using chi-square and Fischer exact. Ordinal data, consisting of long-time of suffering, LANSS score, and Hs-CRP levels, were tested using Kruskal Wallis. The significance result test results are said to be significant if $p < 0.05$.

RESULTS

The 75 subjects enrolled in this study with ages in the range of 48–56 years old, and the duration of illness from 4.48 to 10.32 months. There was no drop outed subject in this study until 6-month follow-up.

All subjects were considered for neuropathic pain concerning LANSS score with improvement at week 2, such is 36% of the Control group showed nociceptive pain, the RFA60 group still the same 100% still neuropathic pain, and in the RFA65 group 92% with nociceptive pain. Then months 3 and 6 showed 100% subjects in all groups with nociceptive pain, and no significant difference ($p = 1.000$).

Even though the Hs-CRP levels observed reduced for all groups, especially RFA 60 and RFA 65, but have no significance. Mild facial numbness gradually improve after RFA was performed, and no serious complications. Analgesics prescribed observed dose reduction, except

TABLE 1
Characteristics of research subjects

Variable	Control	RFA60	RFA65	p
Age (years)	50.88 ± 14.59; 56 (21–74)	50.56 ± 13.16;55 (27–72)	48.32 ± 12.73;48 (20–69)	0.767τ
≤ 50 years	11 (44%)	10 (40%)	13 (52%)	
> 50 years	14 (56%)	15 (60%)	12 (48%)	
Gender				1·000¥
Male	10 (40%)	10 (40%)	11 (44%)	
Female	15 (60%)	15 (60%)	14 (56%)	
Long-time of suffering (months)	4.48 ± 4.68; 3 (1–24)	5.88 ± 5.23;4 (1–24)	10.32 ± 15.84;5 (1–60)	0.123£
≤ 3 months	15 (60%)	8 (32%)	8 (32%)	
> 3 months	10 (40%)	17 (68%)	17 (68%)	

τ = ANOVA, £ = Kruskal wallis, ¥ = Chi Square, *significant p<0.05

TABLE 2
Differences in LANSS scores before and after the 2nd week of treatment, 3rd month and 6th month of the medical group, RFA60, and RFA65

	Control	RFA60	RFA65	p
Pre-treatment				1.000£
Nociceptive	0	0	0	
Neuropathic	25 (100%)	25 (100%)	25 (100%)	
2 weeks				<0.001£*
Nociceptive	9 (36%)	25 (100%)	23 (92%)	
Neuropathic	16 (64%)	0	2 (8%)	
3 months				1.000£
Nociceptive	25 (100%)	25 (100%)	25 (100%)	
Neuropathic	0	0	0	
6 months				1.000£
Nociceptive	25 (100%)	25 (100%)	25 (100%)	
Neuropathic	0	0	0	

£ = Kruskal wallis, *significant p<0.05

TABLE 3
Differences in Hs-CRP levels before and after the 2nd week, 3rd month and 6th month of treatment in the Medical, RFA60, and RFA65 groups

	Control	RFA60	RFA65	p
Pre-treatment				0.048£*
Normal	3 (12%)	10 (40%)	10 (40%)	
High	22 (88%)	15 (60%)	15 (60%)	
2 weeks				0.928£
Normal	5 (20%)	7 (28%)	7 (28%)	
High	20 (80%)	18 (72%)	18 (72%)	
3 months				0.686£
Normal	10 (40%)	16 (64%)	16 (64%)	
High	15 (60%)	9 (36%)	9 (36%)	
6 months				0.834£
Normal	20 (80%)	22 (88%)	23 (92%)	
High	5 (20%)	3 (12%)	2 (8%)	

£ = Kruskal wallis, *significant p<0.05

the Control group is remain analgesic doses.

Increased hsCRP levels correlated with an increase in the LANSS score before therapy, but no correlation was found after the intervention was given. It is suspected that the intervention given has more effect on reducing the LANSS score than reducing hsCRP levels.

DISCUSSION

The neuropathic pain syndromes might establish due to nociceptors activation both in peripheral and central nervous systems, although without clear trigeminal compression or lesions. Neurotransmitter and vasoactive

TABLE 4
The correlation of LANSS score and Hs-CRP levels among subjects

	Hs-CRP pre	Hs-CRP at week 2	Hs-CRP at month 3	Hs-CRP at month 6
Control Group				
LANSS pre	p= 0.230, r= 0.249			
LANSS at week 2		p= 0.217, r= -0.256		
LANSS at month 3			p= 0.195, r= 0.268	
LANSS at month 6				p= 0.973, r= 0.007
RFA60 Group				
LANSS pre	p<0.001, r= 0.692			
LANSS at week 2		p=0.783, r= 0.058		
LANSS at month 3			p=0.511, *r= -0.138	
LANSS at month 6				Not Definited
RFA65 Group				
LANSS pre	p= 0.002, r= 0.592			
LANSS at week 2		p= 0.992, r= 0.002		
LANSS at month 3			p= 0.67, *r= -0.285	
LANSS at month 6				Not Definited

substances lead to a threshold decreased, so both nociceptive and non-nociceptive impulses play a role in pain transmission generation. It continued to the higher centers that will interpret a pain sensation. Nerve injury or resonance vibration near the TG might promote nerve cell hyperexcitation and abnormal transmission. This can be caused by facial pain occurrence even though without noxious stimuli performed.[25] Our study with similarities to the recent that observed female NT subjects more find than males (3: 2.28. This could be associated with smaller TG volume in females than males, as 0.74 mm3 (range 0.35–1.71 mm3) in females and 0.88 mm3 (range 0.42–1.4 mm3) in males. By advancing ages the TG volumes might gradually shrink more related to the degeneration process or atrophy.[26,27] Persistent vascular compression to TG might lead to demyelinated changes, wherein myelin might act as an insulator to facilitate pain transmission.[27] Hormones state play an important role in pain intensity in women. As estrogen can stimulate both central and peripheral sensitization[28], progesterone reduces the pain threshold.[18,29] A common females suffering from NT is slightly more depressed and anxious[30], and tend to be more excessive to express pain than males.[31]

Recently the Numerical Rating Scale (NRS) showed significant improvement underwent RFA by setting the temperatures <70°C (0.88±2.21), 75°C (0.61±1.88), or >80°C (0.57±1.47) ($p < 0.05$). The 75°C set up of radiofrequency might be the optimal temperature set up, that reduced the pain intensity and minimal facial numbness or dysesthesia complications. When the temperature is slightly lower than 75°C, so can cause pain improvement while the long-term effectiveness could be shorter.[32] The successful outcomes described as the severity of pain might reduce at least 50% than before for more than 6 months follow up.[33]

Our study with similar results to the previous study presented a 70-year-old woman suffering from trigeminal neuralgia. She underwent 3 cycles of ablation that increased gradual temperature to 65°C, 70°C, and 75°C RFA for 60 seconds duration respectively, so she has lowering analgesics prescribed. And she gradually pains reduction, and it was completely free after 8 months.[34] The RFA set up at 60°C to 65°C for 90 seconds improved pain among NT patients (91.7%) within 10 days afterward. Only 2 patients (8.3%) showed delayed pain intensity reduction at 8 weeks later.[35] Another study's conclusion of immediate pain relief might reach approximately 91% o 94.8%, with a recurrence of around 18% to 22% after 2 to 9 years of follow-up, and reduced analgesics prescription. A three cycles RFA treatment at 70°C temperatures each for 60 seconds has shown improvement of pain around 67% at three months follow up.[36] The continuous low-grade RFA performed from 50°C to 68°C for 180 seconds for NT patients, observed gradual improvement on the next day with 95%, at 1 week and 1 month 100%, 1 month, 3 months, 6 months, and

1 year of action were 95%, 100%, 100%, 95%, 85%, and 85%.[37] The results are similar to this study that observed significance pain reduction when following up at 2 weeks, 3 months, and 6 months underwent RFA treatments. The reason for selecting the RFA intervention with low temperature is to create a lower degree of post-operative inflammation while still providing benefits similar to standard operational RFA in general.

Those, Control, RFA60, and RFA65 groups did not show significant differences in Hs -CRP levels before and after treatments (2 weeks, 3 and 6 months) (Table 3). NT disorders are associated with local nerve damage or inflammation than systemic events, but the hs-CRP might be following a nonspecific inflammation.[38] It is a non-systemic inflammatory mediator frequently analyzed of association between pain attack among migraine patients and Hs-CRP levels. Increasing levels of Hs-CRP (10.00–20.00 mg/l) correlate to the risks of a chronic migraine attack, but remais of controversy results. Increasing of Hs-CRP levels was associate to frequent attacks of migraine (≥7 days/month) but not for <7 days/month. The 11-years of follow-up mentioned of higher Hs-CRP levels are associated with the risk of chronic migraine. Thus elevation levels might affect on peripheral and/or central general pain sensitization.[39] It is in accordance to the oxidative stress, leukocyte activation, vasodilation, and inflammatory cytokines increased during migraine attacks.[21] The elevated hs-CRP (> 0.3 mg/L) could be related to other comorbidities, such are depression due to chronic pain or systemic inflammation due to advanced body mass index. Whereas this study observed no significant improvement in Hs-CRP levels, although the blood examination showed reduce. Subjects in this study observed no vascular offense to the TG, so the local inflammation from vessel compression is absent. Commonly Hs-CRP had been analyzed as mediators involved in migraine attacks that bring sensitivity (70%) and specificity (73%).[40,41]

In the Control group, there was no correlation between changes in the LANSS score and Hs-CRP levels before and after treatment. At week 2 observed of negative correlation as the LANSS score increased while Hs-CRP levels decrease. This can be understanding that the neuropathic pain syndrome is remains even though the inflammation states reduced. Whereas at months 3 and 6 after the intervention with a positive correlation, as increasing of LANSS score accompanied by Hs-CRP levels increase. The RFA60 and RFA65 groups showed a moderately positive correlation, which the LANSS scores in and Hs-CRP levels increased both at week 2 and month 3 (Table 4). It was might be following post-neuro ablation inflammation, as the performed of radiofrequency neuro ablation the temperature of the surrounding tissue might increase or the frictional heating happen too. Radiofrequency ablation is aimed to interfere with the pain impulses by forming denervating nerves, so immediately can lead to inflammation surrounded.[42] At week 2 observed only the RFA65 group remained with 2 subjects (8%) with neuropathic pain syndromes, even though the LANSS improvement was significant. Whereas after 6 months post neuro ablation the LANSS score showed of null or zero cause might be neuropathic pain syndromes are absented.

Moreover, NT might be an association with inflammation which the nociceptive sensitization activated. When the disorders get prolonged also the inflammation tends to chronic stages, so the polymodal nociceptor and peripheral sensitization activation might increase. By those events, the satellite glial cells and sensory ganglion release the pro-inflammatory mediators, then the nerve excitability might increase and chronic pain appears. The primary sensory trigeminal afferents near the entry zone will be demyelinated, then it can be baed on the NT etiology. The macrophage and mast cells can be found in trigeminal roots, and this with related to the inflammation and NT present.[43] Nonetheless, we realize that limitations remain in this study. We had not analyzed of patient's comorbidities, as they might play the role in the pain perceptions of each subject. NT might be underly by inflammation and degeneration process events, so might be analyzing of cytokines involvement or the neurophysiology examinations.

CONCLUSION

The decrease in LANSS scores and clinical improvement in postoperative pain was greatest in the RFA60 group, starting from the 2nd week. The decrease in postoperative Hs-CRP levels was greatest in the RFA60 dan RFA65 group.

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AUTHOR CONTRIBUTIONS

TB designed the study and proceed with the RFA, TB and YA collected and follow up with the subjects, DP and ED formally analyzed the results. YA wrote the original article draft, and TB write and edited the article.

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Original Article

Comparison of Modified OTAGO Training Program and Walking Training on Physical Performance in Pre-Frail Elderly

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Abstract

Background : Multicomponent training program like OTAGO is considered to improve the physical performance of pre-frail elderly, thereby reducing risk of fall. The Short Physical Performance Battery (SPPB) is a combination test that assesses physical performance and becomes a fall risk screening test for pre-frail elderly. This study aimed to compare the modified OTAGO to walking training on physical performance as measured by SPPB in the pre-frail elderly.
Methods : This was an observational study with a cross-sectional design. The data were taken from the previous study including pre-frail subjects in Prolanis, Gunung Pati area, Semarang before and after giving intervention (modified OTAGO vs walking training) for 6 weeks. The SPPB score was measured from balance function test, chair stand test, and 4-meter walking test before and after the intervention. Data analysis was using SPSS ver 20.0. Paired sample T-test and Wilcoxon signed ranks test were used to analyze the SPPB score before and after interventions in the modified OTAGO and walking training group, respectively. Mann-Whitney U was used to analyze the difference in the average improvement of SPPB score.
Results : There was a significant improvement in SPPB score before and after interventions either in modified OTAGO (p=0.013) or walking training (p=0.013). No significant difference was found in the average improvement of SPPB score in both groups (p=0.826).
Conclusion : Both modified OTAGO and walking training intervention can improve the physical performance of pre-frail elderly. The modified OTAGO training is not superior in improving physical performance compared to walking training.

Keywords : Modified OTAGO training, Walking training, Pre-frail, SPPB

INTRODUCTION

Physical and cognitive functions are known to decline with age. These are worsened by other deteriorations in various functions needed for optimum physical performance, thereby increasing the risk of falling and other risks related to falls.[1,2] Falls in the elderly cause loss of independence, hospitalization due to trauma, death related to injuries and fractures, decreased quality of life, and increased health care costs.[3] The prevalence rate of falls in pre-frail elderly is higher than in frail elderly. It is because they spend more time walking than frail elderly. Pre-frail elderly was diagnosed based on the Fried Frailty Phenotype criteria, 1 to 2 out of 5 criteria (grip strength, walking speed, fatigue, physical activity, unexplained weight loss).[4,5] Meanwhile, frailty is a dynamic process, where a person can experience a transition to frailty status, namely fit/robust, pre-frailty, and frailty. Pre-frailty is a predisposing condition before frailty occurs. A recent systematic review of the global prevalence of elderly people with pre-frailty and frailty in the community ranged from 34.6–50.9% and 4.9–27.3%, respectively. Asian countries record a higher prevalence range of pre-frailty (40-72%) and frailty (5-28%) than the global range.[6] This condition is consistent with the findings of a multicenter study in Indonesia which found a pre-frail prevalence of 61.6% and 25.2% of frail.[7]

One of the combined tests used to assess physical performance and become a fall risk screening test in the elderly is the Short Physical Performance Battery (SPPB). This test measures several physical performance tasks (such as chair stand or sit to stand, standing balance or balance function, and gait speed during walking).[8] The SPPB is highlighted as a diagnostic criterion for geriatric syndromes.[9] In a multicenter study, the SPPB (score ≥3 and ≤9) was used to detect low physical performance in physical frailty and sarcopenia.[10] The SPPB is also recommended by the European Working Group on Sarcopenia in Older People (EWGSO2) as a measure to identify declines in physical performance (SPPB score ≤ 8 points) as part of the algorithm for screening and diagnosing severe sarcopenia.[11]

The exercise programs designed to improve physical performance and prevent falls in the elderly have been investigated in several substantial studies in recent decades. Clinical evidence of the effectiveness of fall prevention–specific exercise types and minimum interventions has been summarized in systematic reviews.[6,7] However, determining the best training program design for individual sub–groups is still challenging. A type of multicomponent exercise program (strengthening, balance, and resistance training) with specific doses according to the recommendation (at least twice per week) is the modified OTAGO training program.[12–14] Based on a quasi-experimental study that compared the control group and the multicomponent exercise group concluded that this exercise program is safe and possible to be given to pre-frail elderly and can improve frailty status, functional performance and muscle strength.[15] A previous randomized controlled trial concluded that OTAGO exercise can reduce the incidence of falls, improve balance and physical performance in elderly people over 65 years old.[16] The OTAGO exercise is a multicomponent exercise consisting of resistance, balance, and aerobic exercise (walking). The walking training on the OTAGO exercise program target the duration up to 30 minutes, at a normal pace, divided into several shorter sessions, for example three 10-minute sessions, at least twice a week.[17] Walking is a form of the simplest aerobic exercise that can be given to the pre-frail elderly. To the best of our knowledge, there is no study that compare modified OTAGO training (including resistance, balance, and walking exercises) and walking training only in pre-frail elderly.

Thus, this study aims to compare the modified OTAGO training and walking training intervention on the physical performance measured by SPPB score in pre-frail elderly.

METHODS

This was an observational study with a cross-sectional design. Samples of this study were data from the previous study conducted in May – June 2021 which investigated a comparison between the modified OTAGO training program and walking training on balance function, including the chair stand test, and gait speed. In the previous study mentioned, subjects who were actively participated *in Program Pengelolaan Penyakit Kronis (Prolanis)* at the Gunung Pati Clinic and Gunung Pati Primary Care Center, Semarang and met the inclusion criteria were recruited. There were 31 pre-frail subjects who were recruited and randomized using sealed envelope randomization to be divided into the OTAGO training group and walking training group.

The data that did not meet the complete information of age, sex, amount of medication, body mass index (BMI), mini nutritional status (MNA), frailty phenotype as well as data of balance function, chair-stand, and 4-meter walk test before and after intervention were excluded from this study.

The assessment of physical performance by using SPPB was obtained from previous data on the balance function, 5 times chair stand, and 4-meter walking. The balance function data had a range of scores 0 to 4. The 4-meter walking data had a score range of 1-4 points (score 1 if > 8.7 seconds, 2 if 6.21–8.7 seconds, 3 if 4.82–6.2 seconds, 4 if <4.82 seconds). The 5 times chair stand test had a range of score from 0-4 points (point 4 if the time data obtained was <11.19 seconds, point 3 if it was 11.2–13.69 seconds, point 2 if it was 13.7–16.69 seconds, 1 if it was >16.7 seconds, and 0, if it was >60 seconds). Thus, the highest SPPB score was 12 and the lowest was 0.

The SPPB data were obtained from all the data before and at the end of the 6th week of the intervention.

The data gathered were analyzed descriptively and analytically using IBM SPSS Version 20.0 software. The paired-sample T-test and Wilcoxon signed ranks test were used to analyze the SPPB score data before and after modified OTAGO training and walking training intervention, respectively. The Wilcoxon test was also used to analyze the frailty phenotype score before and after intervention in each group. The Mann-Whitney U was used to analyze the differences in the mean increase of SPPB score and frailty phenotype score reduction in both groups.

This study has been reviewed and approved by the Health Research Ethics Commission (KEPK), Faculty of Medicine, Diponegoro University with Document No. 417/EC/KEPK/FK-UNDIP/XII/2022. The data gathered in this study was part of a previous study conducted in May-June 2021 with Document No. 76/EC/KEPK/FK-UNDIP/III/2021.

RESULTS

Thirty-one data of pre-frail elderly of Prolanis Gunung Pati Semarang were gathered. Five out of 31 data were excluded due to incomplete data (no data of post intervention). The consort diagram of data sample selection was shown in Figure 1.

The previous data on demographic and clinical characteristics in both groups were shown in Table 1. The table showed the results of the homogeneity test of demographic characteristics consisting of age, sex, number of medications, MNA (Mini Nutritional Assessment), and frailty phenotype score which indicates pre-frail. There was no significant difference between the modified OTAGO training group and the walking training group, with a p-value >0.05. Demographic characteristics in both groups were homogeneous.

The mean of frailty phenotype score in the two groups before intervention was not significantly different, with a p>0.05 (p = 1.000). The data result of frailty phenotype scores before and after intervention showed a significant difference in the modified OTAGO group (p=0.001), but not in the walking group (P=0,023). The delta reduction of frailty scores in the OTAGO and walking groups was -1.00 ± 0.43 and -0.38 ± 0.51, as it was shown in Figure 2. The delta reduction was significantly different between modified OTAGO and walking group (p=0.005).

The analysis result of the SPBB score data before and after the modified OTAGO training and walking training intervention can be seen in Table 2. The mean or average value of the test before and after the modified OTAGO training intervention was 7.69 and 8.77, respectively. Paired samples correlations of SPPB score data of the modified OTAGO training intervention was 0.666 with a probability value of 0.013. A correlation of 0.666 indicates a moderate relationship before and after the modified OTAGO training intervention. While in walking training, the mean value of the test before and after the intervention was 7.62 and 8.85, respectively. This shown a significant improvement of SPPB score before and after walking training with the probability value of 0.013.

The analysis of differences in the average improvement of SPPB score in both groups yielded a p-value of >0.05 as it was shown in Table 3.

The analysis result did not show a significant difference of SPPB score improvement between the modified OTAGO and walking control groups.

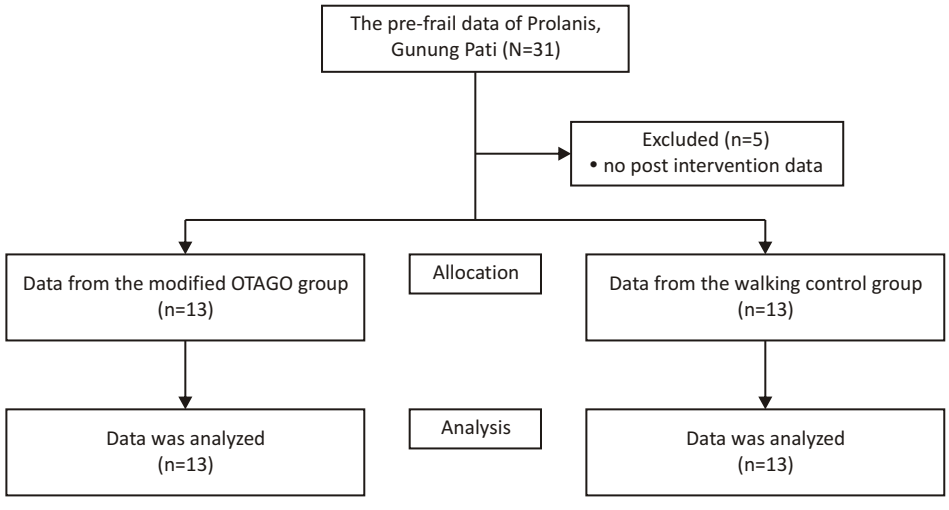

Figure 1. Consort diagram of data sample selection

TABLE 1
The characteristics of previous data subjects

Variable	Group		p
	Modified OTAGO group	Walking control group	
Age	65.00 ± 3.85	65.15 ± 5.97	0.659‡
Sex			
Male	5 (38.5%)	6 (46.2%)	0.691¥
Female	8 (61.5%)	7 (53.8%)	
Amount of medication	2.46 ± 1.27	2.69 ± 1.18	0.605‡
BMI	23.94 ± 3.32	23.65 ± 2.63	0.804§
MNA	12.38 ± 1.39	12.08 ± 1.12	0.426‡
Frailty Phenotype Score	1.31 ± 0.48	1.31 ± 0.48	1.000‡

*Significant (p<0.05); ¥Chi square; §Independent t; ‡Mann Whitney; BMI : Body mass index; MNA: Mini Nutritional Assessment

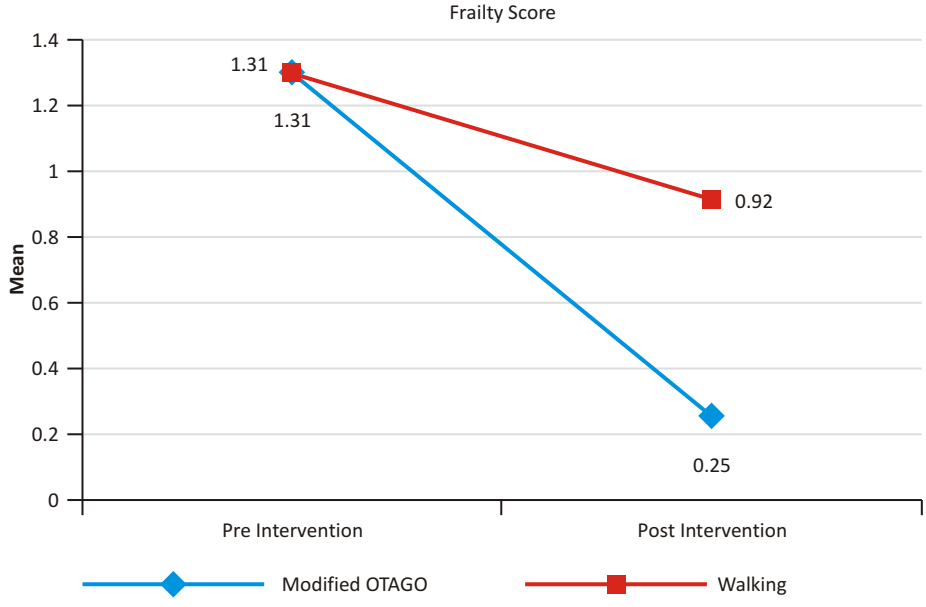

Figure 2. The mean of delta reduction of frailty scores pre- and post- intervention

DISCUSSION

The mean age of subjects in our study was 65 years old. Our previous mentioned study applied more than 60 years old as one of the inclusion criteria. The previous study stated that the prevalence of pre-frail in Indonesia at the age of more than 60 years is 61,6%.[7]

The gender data revealed that female was frequent than male, in both modified OTAGO group and walking control group. Our finding was consistent with data from the Indonesian Central Bureau of Statistics in 2020 that states the prevalence of female elderly is higher than that of male, which is 52.35%. Life expectancy and the percentage of health complaints were also found to be higher in female elderly by 52.31% compared to male.[18]

The maximum number of drugs used by subjects in both groups is 4 drugs. This amount is less than the limit for the number of drugs that might affect the SPPB score. Drug use of ≥ 5 drugs per day can cause drug interactions, and disease interactions that affect balance control, increase the risk of falling in the elderly, and indirectly affect the SPPB score.[19–21]

Body mass index between the two groups in this study is comparable. Previous investigator did not include BMI as inclusion criteria specifically, where BMI data was integrated in the MNA scoring section. From the

TABLE 2
Analysis of SPPB score in modified OTAGO and walking group data

Groups	SPPB score		P-value
	Before	After	
Modified OTAGO training	7.69 ± 1.84	8.77 ± 1.09	0.013*
Walking training	7.62 ± 1.71	8.85 ± 1.41	0.013*

*Significant (p<0.05); ¥Chi square; §Independent t; ‡Mann Whitney; BMI : Body mass index; MNA: Mini Nutritional Assessment

TABLE 3
Difference of average improvement of SPPB score in modified OTAGO and walking training

Groups	SPPB score improvement#	P-value
Modified OTAGO training	1.08 ± 1.38	0.826
Walking training	1.23 ± 1.30	

#Score improvement = SPPB score after intervention – SPPB score before intervention

data, it is shown that the average pre-frail elderly classified as overweight based on Asia-Pacific classification. Meanwhile, the MNA score did not show a malnutrition status in both groups. The presence of malnutrition significantly affects the development of frailty. It is also related to dynamic balance performance and physical performance in the elderly.[22]

Comparison of the delta score of frailty phenotype before and after intervention between the two groups showed that the subjects who received the modified OTAGO experienced statistically significant reduction score of frailty phenotype compared to the walking group. This result is in line with the study on multicomponent training in which the components of exercise are similar to modified OTAGO training. That training consisting of aerobic exercise, resistance exercise using *Theraband* and balance exercise showed an improvement in frailty phenotype scores after 12 and 24 weeks of training when compared to the control group.[23]

In this study, the two intervention groups showed a significant correlation between the improvement of SPPB scores before and after each training. A previous study on pre-frail elderly that evaluated using a graphic sensor and SPPB score found that there was a slower decline of performance in the OTAGO group than in the control group, even though the capacity of both groups increased.[21] Meanwhile, a study with 65 elderly in the community who measured physical performance by SPPB separately found no improvement in the static balance between groups. There was a decreasing time performance of the chair stand test and no improvement in the walking speed.[24] Our study did not measure SPPB scores separately but compared the total data scores obtained before and after the intervention.

Few studies have provided walking therapy for pre-frail elderly. A study involving 81 participants in 9 nursing homes in Spain provided walking training as a control in a multicomponent exercise intervention. In that previous study, it was found that walking training did not give better improvement on SPPB score than multicomponent training.[25] Different from the walking training given in the modified OTAGO group, our previous investigator gave the walking training group a step-based walking, recorded with a pedometer, and supervised every week. Our previous investigator only provided the number of steps during walking training but did not consider the daily number of steps.

Both data from modified OTAGO and walking training in our study showed a significant improvement in SPPB scores. The difference in score improvement between groups did not show a significant result. Providing physical activity in various forms can improve the SPPB score. The Lifestyle Interventions and Independence for Elders (LIFE) Study involving 1635 adults aged 78.9±5.2 years who were given moderate levels of physical activity showed a significant improvement in SPPB scores compared to the group that was only given health education.[26]

In this study, it is shown that the group given the modified OTAGO training experienced a significantly greater reduction in frailty phenotype scores than the group that was given the walking training only. However, both groups showed a significant improvement in physical performance scores as measured by SPPB. As mentioned in the previous review studies that the structured physical activity not only improves physical performance but also offers other benefits like increasing mobility.[27,28] We believe that the

multicomponent training like the modified OTAGO which include the walking training as one of its components will be more beneficial in improving the physical performance as well as reduction of frailty phenotype score. Apart of that, other factors such as habits, availability of the equipment, compliance and clinical conditions of each elderly can influence the selection of the appropriate training for them.

Nevertheless, this study has some limitations in terms of the small number of data collected from our previous study. Some of the data collected are not complete due to unavailable data of post-intervention. The components in the SPPB score are not analyzed separately and other factors that cannot be ruled out may affect the physical performance of pre-frail elderly.

CONCLUSION

Both modified OTAGO and walking intervention can improve the physical performance of pre-frail elderly. Compared to walking training, the modified OTAGO training is not superior in improving physical performance in pre-frail elderly.

Studies that compare modified OTAGO training and walking training with more objective measurements involving bigger samples and considering other factors affecting SPPB scores are still needed.

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Original Article

The Relationship between Serum Folic Acid Levels with The Cognitive Function of The Elderly

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Abstract

Background : Cognitive decline is a common condition that occurs in the elderly. One of the early indicators of senility is a decrease in cognitive function. Folic acid is thought to protect the arteries from damage because of homocysteine by converting homocysteine into cysteine and then excreted in the urine. Increased levels of homocysteine can interfere with vascular function and cause toxic effects on neurons thereby increasing the risk of cognitive decline. The objectives of this study was to determine the relationship between serum folic acid levels and cognitive function of the elderly.
Methods : Analytical descriptive research with a cross-sectional approach. The research subjects were the elderly who met the inclusion criteria and did not have exclusion criteria. The research was conducted from May to July 2022 at the Pucang Gading Nursing Home, Semarang. Serum folic acid levels were examined using the ELISA (Enzyme-linked immunosorbent assay) method. Cognitive function was assessed using the Indonesian version of the Montreal Cognitive Assessment (MoCA) simultaneously on the subject. Cognitive function is normal if the MoCA-INA value is ≥ 26 and it is said to be cognitive dysfunction if the MoCA-INA value is < 26. Data were analyzed using the Spearman test. Results are considered significant if the value of $p < 0.05$.
Results : There is a strong positive correlation between serum folic acid levels and cognitive function in the elderly ($r=0.914$, $p<0.001$). There is a relationship between educational level and cognitive function ($r=0.922$, $p<0.001$) where higher education correlates with increased cognitive function in the elderly.
Conclusion : There is a significant positive correlation between serum folic acid levels and cognitive function in the elderly.

Keywords : Cognitive function, MoCA-INA, Serum Folic Acid Levels

INTRODUCTION

The elderly are aged > 60 years, at which age it generally occurs a degenerative aging process that triggers a decrease in various body functions, one of the consequences is a decline in cognitive function. The progressive decline in cognitive function can affect the social function and daily life of the elderly. In Indonesia, the number of elderly tends to increase from 7.6% in 2010 to 8.03% in 2014. Central Java is the province with the second highest number of elderlies after the Special Region of Yogyakarta. In 2015, the number of elderly in Central Java reached 11.7% and increased in 2017 to 12.59%. This shows an increase in the Life Expectancy (UHH) of the world population including Indonesia.[1–3]

According to the Indonesian Ministry of Health in 2009, the age categories of the elderly are divided into early elderly (46–55 years old), late elderly (56–65 years old), and elderly period (≥65 years old). The Delphi Consensus published that there is a 10% increase in the prevalence of cognitive impairment compared to previous publications. In Southeast Asia, the number is expected to increase from 2.48 million in 2010 to 5.3 million in 2030.[2]

The lack of folic acid intake is one of the factors leading to decreased cognitive function. Folic acid is a nutrient needed to maintain homocysteine levels in normal conditions. The increased amount of homocysteine levels will disrupt vascular function and cause toxicity to neurons, so it can increase the risk of cognitive decline.[4]

Until now, checking folic acid levels is not a routine test in health facilities. This may be due to the limited examination services and high cost. Therefore, there is no data on folic acid levels in the elderly, especially in Semarang City.

Although many studies have discussed the relationship between serum folic acid levels and cognitive function in the elderly, the results vary. In addition, there is not enough data on folic acid levels in the elderly community in Semarang City. Therefore, the researcher was interested in conducting a study of the problem. This study aims to determine the relationship between serum folic acid levels and cognitive function in the elderly in Semarang City. Especially in Pucang Gading nursing home in Semarang.

METHODS

This study is an analytical descriptive study with a cross-sectional approach that was conducted at Pucang Gading Wredha Home Semarang from May–July 2022. The research subject is elderly who meet the inclusion criteria (elderly people over 56 years of age who can read and write, can speak Indonesian, conscious and cooperative subjects) and had no exclusion criteria (subjects with depressive disorders, disturbed diet due to impaired intake, impaired absorption, patients with a history of stroke, history of tumor/carcinoma, dementia, and a history of taking drugs).

This study assessed serum folic acid levels with the cognitive function of the elderly. Examination of cognitive function by using MoCA-INA instrument. The confounding factors in this study were age, gender, education level, cholesterol level, BMI, history of diabetes mellitus, and high blood pressure. Examinations are carried out by general practitioners who have understood and received instructions regarding how to collect data.

This research has received approval from the Medical Research Ethics Commission of FK UNDIP/RSDK with No. 30/EC/KEPK-RSDK/II/2022. Statistical analysis using the "SPSS for Windows version 26" program. Data analysis included descriptive analysis and statistical analysis. The first stage was a univariate analysis of descriptive statistics to determine the basic characteristics of the research subjects. While statistical analysis is to see correlation and comparison. Comparative tests used the Chi-Square and Spearman correlation tests for numerical data. Meanwhile, to determine the significance of the strength of the relationship after controlling for confounding variables using the partial correlation test.

RESULTS

This study required a minimum number of samples of 30 research subjects. This study involved 35 subjects, most of whom were > 65 years old as many as 25 subjects (71.4%). The education level of the research subjects was found to be mostly elementary school 12 subjects (34.3%). Most of the subjects were female, namely 22 subjects (62.9%). Most subjects had normal cholesterol levels (71.4%), normal BMI (77.1%), no DM (22.9%), and no hypertension (68.6%).

The analysis was carried out between the variables of folic acid levels on the cognitive function of the elderly, there was a significant correlation between the two variables with a strong positive correlation level. This means that increased folic acid levels are associated with increased cognitive function in the elderly.

Based on the risk factor analysis, there was a relationship between the MoCA-INA score on gender ($p=0.019$) and level of education ($p=0.001$). Women tend to experience cognitive dysfunction compared to men. Subjects without education up to junior high school education had a higher incidence of cognitive dysfunction than high school subjects.

After controlling the variables of gender and level of education, there was still a correlation between serum folic acid levels on cognitive function in the elderly ($p<0.001$; $r= 0.862$ (controlling for sex) and $r= 0.922$ (controlling for level of education)).

TABLE 1
Relationship between serum folic acid levels and cognitive function in the elderly

Variable	Elderly Cognitive Function	
	r	p
Folic Acid Levels	0.914	<0.001$^{\$*}$

Description: * p < 0.05 significant, $^{\$}$ SpearmanTest

TABLE 2
Relationship between confounding variables and cognitive function in the elderly

Variable		MoCA-INA			
		Normal (≥26)	Disturbed (<26)	P	OR (95% CI)
Age	56–65 years	1 (10%)	9 (90%)	0.436$^{\&}$	0.444 (0.45–4.37)
	> 65 years	5 (20%)	20 (80%)		
Level of education	No school Junior High School	0 (0.0%)	25 (100%)	0.001$^{*!}$	–
	Senior High School	6 (60%)	4 (40.0%)		
Gender	Man	5 (38.5%)	8 (61.5%)	0.019$^{*\&}$	13.125 (1.321–130.424)
	Woman	1 (4.5%)	21 (95.5%)		
Cholesterol Levels	Normal	4 (16.0%)	21 (84.0%)	0.564$^{\&}$	0.762 (0.116–5.006)
	Tall	2 (20.0%)	8 (80.0%)		
BMI	Underweight	0 (0.0%)	5 (100%)	0.200$^{!}$	–
	Normal	5 (18.5%)	22 (81.5%)		
	Overweight	0 (0.0%)	1 (50.0%)		
	Obese	1 (50.0%)	1 (50.0%)		
History DM	Yes	1 (12.5%)	7 (87.5%)	0.580$^{\&}$	0.629 (0.062–6.328)
	No	5 (18.5%)	22 (81.5%)		
History of Hypertension	Yes	1 (9.1%)	10 (90.9%)	0.371$^{\&}$	0.38 (0.393–0.713)
	No	5 (20.8%)	19 (79.2%)		

Description: * p < 0.05 significant, $^{\$}$ Chi-Square Test, $^{\&}$ Fisher's Exact Test, $^{!}$Kruskal-Wallis

DISCUSSION

The mean serum folic acid level of the 35 study participants was 7.09 ± 2.55 mg/mL. The minimum value is 2.40 mg/mL, and the maximum value is 9.62 mg/mL. The average was 8.09 mg/mL. 3 mg/mL is the normal serum folic acid level. There was no discrimination between men and women.[5–7]

Only 5 (17.2%) of the 35 study participants had a decrease in serum folic acid levels. This could be because the study was conducted on the elderly in nursing homes, where the residents' health and psychological factors, as well as their dietary patterns, are likely to be well maintained. Morris *et al* (2010) research found that low folate levels and high homocysteine levels are risk factors for depression and dementia, including Alzheimer's disease and vascular dementia.[7] High homocysteine levels can impair cognitive performance via a variety of mechanisms such as oxidative stress, apoptosis, and senile plaque.[8,9] Increased plasma homocysteine causes faster shrinkage of the medial temporal lobe, resulting in.[8,9]

The Moca-INA score obtained an average of 21.4 ± 4.6 on the Moca-INA examination, with the lowest score being 14 and the highest score being 30. The median value is 22. Folic acid deficiency has been linked to

TABLE 3
Correlation test for the relationship between serum folic acid levels and cognitive function in the elderly with control over gender and education

Variable	Correlation between serum folic acid levels and cognitive function in the elderly	
	Rho	P
Gender	0.862	<0.001$
Education	0.922	<0.001$

Description: p <0.05 significant, $Partial Correlation Test

neurological disorders such as depression and dementia, as well as demyelinating myelopathy. Folic acid is a nutrient that is required to maintain normal homocysteine levels. Increased homocysteine levels will disrupt vascular function and cause neurotoxicity, increasing the risk of cognitive decline.[4,10,11,12]

The subjects in this study had a lower-than-normal MoCA-INA score (26), indicating that their serum folic acid levels were low. As a result, cognitive function suffers. This is according to Mengyue L *et al* (2020) found a significant relationship between folic acid intake and cognitive function. The correlation value (r) is positive, indicating that taking folic acid for 6 months can improve cognitive function significantly.[13]

The strength of the relationship between serum folic acid levels and cognitive function in the elderly was discovered in this study. After controlling for gender, no significant changes with the same correlation strength were found; this is consistent with a study that stated menopause is a natural part of aging. Menopause and the loss of ovarian hormones are two factors that contribute to memory loss. As a trophic agent, the hippocampus secretes hormones such as estrogen in adults. However, a lack of estrogen during menopause causes neurons to become more fragile, resulting in memory loss.[14] After controlling for education, changes in the strength of the relationship between serum folic acid levels and cognitive function in the elderly revealed changes in the strength of the correlation. This is consistent with the findings of Yao *et al* (2009) who discovered that "changes in the shape and function of the post-maturity brain are primarily the result of experience and education"[15] routine and continuous cognitive skill development such as logic and reasoning, abstract thinking, and the ability to prevent and enhance neuronal connections.[16]

This study has several limitations, including the fact that it was only conducted in one elderly home, so the results do not represent the general population; brain structural abnormalities were not excluded by supporting examinations; and no further follow-up on folic acid serum levels and cognitive function was performed. examined in the elderly.

CONCLUSION

There is a significant relationship between serum folic acid levels and cognitive function in the elderly. Higher educational status in the elderly is associated with better cognitive function.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Original Article

Analgesic Potency of Ibuprofen, Paracetamol, and Mephenamic Acid: A Randomized Controlled Trial

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Abstract

Background : Analgesics are a group of drugs to relieve pain. The use of analgesics is quite high, around 22.8% is used per year. Selection of analgesic drugs having adequate potency and minimal side effects is needed. Common analgesics publicly known involve paracetamol 500 mg, mefenamic acid 500 mg, and ibuprofen 400 mg. This study aims to compare the analgesic potency of paracetamol 600 mg, ibuprofen 600 mg and mefenamic acid 500 mg.
Methods : This study used a double blind randomized control trial. The study population was healthy subjects. The study sample consisted of 30 subjects with the inclusion criteria involve normal vital signs, while the exclusion criteria involve history of allergy to NSAID class drugs. This study consisted of three groups namely group 1 (K1)= paracetamol 600 mg, group 2 (K2)= mefenamic acid 500 mg, group 3 (K3)= ibuprofen 600 mg. Each subject was given medication according to the group and their pain latency (the time of onset of constant and unbearable pain) was measured every 30 minutes
Results : The repeated ANOVA test shows P= 0.1507 meaning that no significantly different analgesic potency was found between groups.
Conclusion : Paracetamol 600 mg, mefenamic acid 500 mg and ibuprofen 600 mg have equal analgesic potency.

Keywords : Analgesic, Parasetamol, Ibuprofen, Mefenamic Acid

INTRODUCTION

Analgesic derives from the word an – meaning not and algesia meaning pain, so analgesia means no pain. One of analgesic class is Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).[2] NSAIDs work by inhibiting the action of the cyclooxygenase enzyme disrupting the biosynthesis of prostaglandins . Some of analgesics in the NSAID class are acetaminophen/paracetamol, mefenamic and meclofenamic acids, and ibuprofen.[3]

Mild to moderate acute pain can be treated with NSAIDs as first-line agents. Acetaminophen or commonly known in Indonesia as paracetamol, is a non-opioid antipyretic analgesic which is very popular in the community to relieve mild to moderate pain. Paracetamol is different from other NSAIDs as it has less anti-inflammatory activity. The usual dose of paracetamol is 500 mg per consumption.[4] Mefenamic acid is an NSAID included in BCS (Biopharmaceutic Classification System) class II having low solubility with high membrane penetration.[5] Mechanism of action mefenamic acid is by inhibiting the cyclooxygenase enzyme.[6] Mefenamic acid and other NSAIDs can cause gastrointestinal disturbance involving stomach irritation if used in high doses or in the long period. The general dose of mefenamic acid for adults and children over 14 years is 500 mg per consumption.[7] Ibuprofen is also well known in Indonesia having anti-inflammatory and antipyretic effects, with a general dose of 400 mg effective for relieving pain. Ibuprofen is an NSAID considered having the least side effects and the safest NSAID among others.[8]

A report from The Oxford League Table of Analgesic Efficacy in 2006, NSAIDs have varying strength profiles. This study recorded data on the number needed to treat (NNT) or the value of the proportion of patients who are pain free within 4–6 hours compared to placebo, where the patients suffered from moderate to severe pain. NSAIDs involving ibuprofen 400 mg and paracetamol 500 mg have NNT 2.5 and 3.5 respectively,[9] while data on mefenamic acid has not been stated for its analgesic potency, whereas some of these NSAIDs is a non-selective class of NSAIDs commonly used by health care facilities in Indonesia.[10]

Research data in Brazil in 1 year found the overall analgesic consumption was 22.8%. Of them, 25.9% of analgesics was cumsumed by adults (18 years and over). The data for the use of non-opioid analgesics is 18.5%, NSAIDs 6.9%, and 0.5% opioid analgesics. The most widely used drugs were metamizole (37.8%) then paracetamol (25.3%). The prevalence of analgesic use may increase in certain conditions such as presence of chronic disease (regardless of the number of analgesic combinations ranging from one to three or more), five or more medication consumption (besides analgesics), possession of health insurance, use of emergency services within last year, or hospitalization within las year.[11] Based on the 2013 Riskesdas regarding data on NSAID use in Indonesia, the province with the highest NSAID consumption was East Java with 94%, followed by West Java province with 56%.[12] NSAIDs have been available for decades and their use has been described in many guidelines. Most guidelines recommend that "choice of a particular NSAID should be based on a balance between benefits and risks for the individual patient". However, studies are often incomplete.[13] The common side effect of NSAIDs is gastrointestinal disturbances with peptic ulcer as the most severe side effect. In the United States, 100,000 cases of peptic ulcers occurs due to NSAIDs consumption, so assessment of the NSAID potency is important so appropriate medication is selected and no NSAID with the same mechanism of action and potency is combined.[14] For that reason, this study aims to compare the analgesic potency of paracetamol, mefenamic acid, and ibuprofen as NSAIDs commonly used by the public.

METHODS

This research is a double blind randomized controlled trial. The study was conducted at the Pharmacology Laboratory of the Medical Faculty of Tadulako University and the Ear, Nose and Throat–Head and Neck, Functional Medical Unit of Undata General Hospital, Palu. The population is healthy subjects, not suffering from any illness. The sample size formula used is the Federer formula and the results are 9 subjects per group plus 10 percent of the drop out to 10 subjects per group. The inclusion criteria were willing to participate and signing consent to become s reserarch subject and having normal vital signs. The exclusion criteria were having a history of allergy to NSAIDs, history of taking NSAIDs within <24 hours before study, history of taking corticosteroid and gastrointestinal disturbance. This research was approved by the research ethics committee of the Medicine faculty of Tadulako University number 7245 A / UN 28.1.30 / KL / 2022. Informed consent and physical examination were carried out for each subject. The medication used in this study were paracetamol 600 mg, mefenamic acid 500 mg and Ibuprofen 600 mg. These medictions were chosen as they were the most widely used analgesics by public.[15] The dosage was adjusted according to a report from The Oxford League Table of Analgesic Efficacy regarding the effectiveness rates of various kinds of analgesics and adjusted for the doses available at the pharmacy. The 500 mg mefenamic acid and 400 mg ibuprofen is a common dose in the community, while the 600 mg paracetamol was chosen as previous study reported the use of this dose for acute pain.[15]

Based on the number of medications studied, this study divided subjects into 3 treatment groups: Group 1 (K1)= 600 mg paracetamol, Group 2 (K2)= 500 mg mefenamic acid, Group 3 (K3)= 600 mg Ibuprofen.

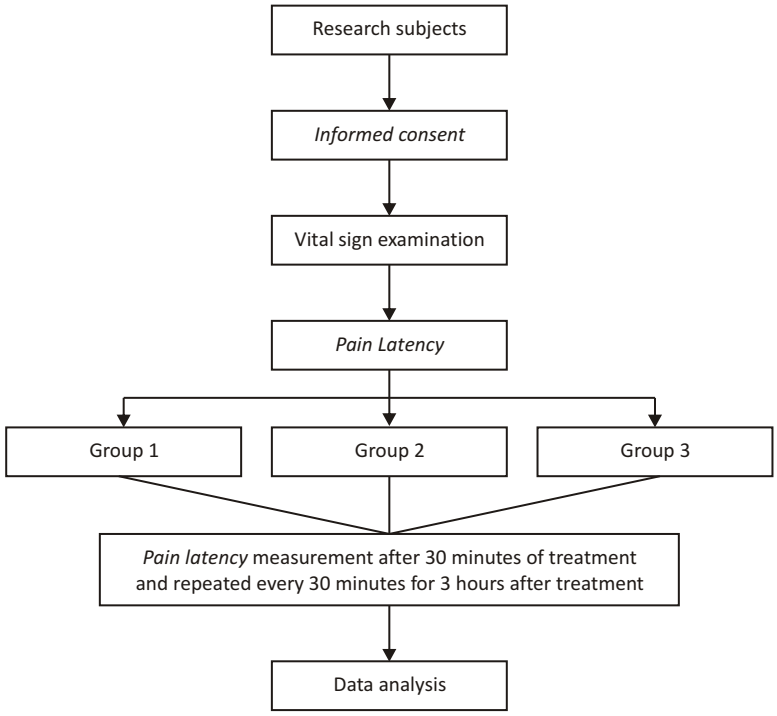

Figure 1. Consort diagram

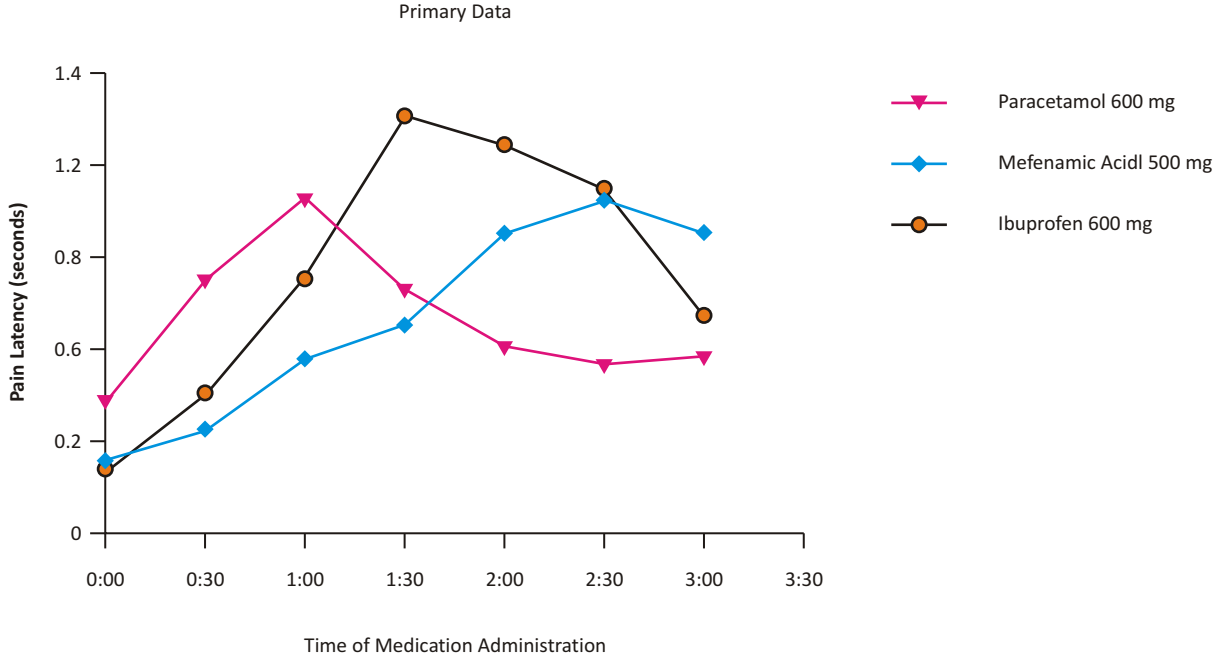

Figure 2. Comparison of the effect of three medications on pain latency (onset of constant pain since the introdution of pain) and time of observation

Thermometer, sphygmomanometer and smartphone were used to assess vital signs, specifically the sphygmomanometer was used to provoke pain in the subject arm by means of a sphygmomanometer cuff installed and pumped up to 180 mmHg and maintained at that pressure, then subjectds were assessed how long it takes to reach constant and unbearable pain (pain latency). Pain latency time was assessed before treatment

TABLE 1
Comparison of Mean Pain Latency in all groups

	Mean pain latency in seconds	P value
Paracetamol 600 mg	62.57	0.1507
Mefenamat acid 500 mg	64	
Ibuprofen 600 mg	67.86	

*Significant P < 0.05

TABLE 2
Comparison between groups

Bonferroni's Multiple Comparisons Test	95.00% CI of Diff	Adjusted P Value
Parasetamol 600 mg vs. Asam Mefenamat 500 mg	-10.31 to 9.965	>0.9999
Parasetamol 600 mg vs. Ibuprofen 600 mg	-15.55 to 4.722	0.5957
Asam Mefenamat 500 mg vs. Ibuprofen 600 mg	-15.38 to 4.894	0.6393

*Significant P < 0.05

(drugs administration) and every 30 minutes up to 3 hours after treatment. Data regarding pain latency time is the primary measurement data analyzed in this study. Research data were analysed using the PRISMA application. The data normality test used the Shapiro-Wilk normality test. The data normality test is to find out whether the data is normally distributed or not. Comparison test used repeated ANOVA and Bonferroni post hoc tests. The consort diagram is shown in Figure 1.

RESULTS

This research has been carried out at Pharmacology Department of Medical Faculty of Tadulako University to prepare materials and tools for research, followed by Functional Medical Unit of Ear, Nose and Throat–Head and Neck of of Undata General Hospital in June 2022. The population involved healthy subjects willing to participate and giving consent as research subjects. The sample size was 30 people based on predetermined inclusion and exclusion criteria. Samples were divided into 3 treatment groups namely Group 1 (K1)= 600 mg paracetamol, Group 2 (K2)= 500 mg mefenamic acid , and Group 3 (K3)= 600 mg Ibuprofen.

The study sample consisted of 40 subjects. Anamnesis and examination of vital signs were carried out and informed consents were signed then followed by provoking pain in the arm by inflating sphygmomanometer cuffs, pain latency was measured by using a Visual Analoque Scale (VAS). Subsequently, the treatment was carried out by adminisering medications in a double-blind manner, and measurements were repeated every 30 minutes with a total of 6 measurements during 3 hours of observation. After that, all research results were collected and primary data analysis was carried out.

The Figure 2 shows the onset of the three medications. Paracetamol shows a rapid onset but shorter duration than ibuprofen and mefenamic acid. Normalily test was carried out using the Shapiro–Wilk normality test showing that the research data is normally distributed. A repeated ANOVA was carried out to answer research objectives (Table 1) and Bonferroni's post hoc was carried out to compare groups (Table 2).

The repeated ANOVA (Table 1) showed no significant difference between all groups (p>0.05). The research data was analyzed to compare groups and obtained a P value> 0.05 (Table 2) meaning that no significant difference was found between medications studied. No subject complained any side effects from the medication during 24 hours of observation.

DISCUSSION

Seven observations were conducted and repeated every 30 minutes for 3 hours involving once before medication administration and six times after medication administration, then data were collected and analyzed. The results of this study cfound no significant differences between groups. It was found that paracetamol 600 mg, ibuprofen 600 mg and mefenamic acid 500 mg had equivalent analgesic potency.

The Oxford League Table of Analgesic Efficacy (2007) reported that NSAIDs have varying strength

profiles. This report shows the number needed to treat or the value of the proportion of patients who are free of pain within 4–6 hours compared to placebo, the pain used is moderate to severe pain. Several NSAIDs administered at clinical doses involving ibuprofen 400 mg and paracetamol 500 mg have a number needed to treat of 2.5 and 3.5 respectively. The medication in this study used larger dose involving ibuprofen, increased by a half, and paracetamol, increased by one fifth. As a result, there is a similarity in their analgesic potency.

Different Research findings were put forward by a study comparing visual analogue scale (VAS) in administering oral mefenamic acid, ibuprofen and paracetamol before circumcision. This study found that the ibuprofen group had the lowest VAS followed by mefenamic acid group and paracetamol respectively. Ibuprofen is more potent in treating post-circumcision pain as it strongly inhibits prostaglandins in peripheral tissues, sites of injury during circumcision.[16] Different study findings may arise as this study uses a larger dose, different from that used in other studies.

The side effect of these three drugs is on the gastrointestinal tract. The three drugs tested in this study were NSAIDs (3). A meta-analysis of the variability of the risk of complications of NSAIDs found that ibuprofen has the lowest risk of gastrointestinal complications followed by diclofenac, azapropazone and tolmetin. Ketoprofen and piroxicam showed the highest risk of gastrointestinal complications whereas indomethacin, naproxen, sulindac and aspirin showed moderate risk. High-dose of ibuprofen carries the same risk of gastrointestinal complications as naproxen and indomethacin.[17] No drug side effect was noted during this study as patients was only monitored for 3 hours for data collection and 24 hours for nay side effects. The medication administration is not repeated and the period is very short to cause severe side effects.

A study conducted at a puskesmas (literally means community health centre) in 2017 – 2019, paracetamol was used the most frequently used followed by ibuprofen and mefenamic acid respectively,[18] while a study regarding pattern of osteoarthritis treatment at hospitals found that mefenamic acid is the most frequently used pain killer followed by paracetamol and ibuprofen respectively. These two studies show that these three drugs are widely used and various types of analgesic are used depending on the case. In term of price, ibuprofen 600 mg is the most expensive which costs Rp 2285 followed by paracetamol 600 mg and mefenamic acid 500 mg which cost Rp 650 and Rp 360 respectively.

The limitation of this study is that assessment only uses a simple and subjective parameter. For further research, several objective measurement parameters can be added, such as for assessing bioavailability in the blood.

CONCLUSION

This study concluded that paracetamol 600 mg, mefenamic acid 500 mg and ibuprofen 600 mg had equal analgesic potency. This study recommends administration of NSAIDs should consider their potency as well as provision of several analgesics should not combine analgesics with the same mechanism of action.

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Original Article

Effect of Fixed Dose Combinations Antituberculosis and Separate Formulations on Clinical Symptoms, Weight Gain, Adverse Effect and Plasma Concentration in Tuberculosis and HIV Coinfection Cases

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Abstract

Background : Fixed Dose Combination (FDC) was aimed to simplify TB therapy and facilitate physician and patient compliance. This study was aimed to evaluate the effect of FDC antituberculosis and separate formulations (SF) on clinical symptoms, weight gain, adverse effect and plasma concentration in TB/HIV cases during the intensive phase.
Methods : Prospective cohort study was conducted in public hospital, Jakarta. We recruited TB-HIV patients in May 2018-May 2019. Patients (over than 18 years old) diagnosed with TB-HIV who consumed either FDC or SF and had not received antiretroviral. A total of 36 subjects were included in this study, 20 subjects in FDC group and 16 subjects in SF group.
Results : There was not significant different between FDC and SF groups with an improvement of clinical symptoms (P = 0.70) and weight gain (P = 1.00). Gastrointestinal syndrome was 75% in FDC group; 62.5 % in SF group. Mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration after 2 weeks therapy in FDC group were 5.49 mg/L (±3.40 mg/L), 1.35 mg/L (±1.20 mg/L), 19.87 mg/L (±17.00 mg/L), respectively. Mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration in SF group were 6.42 mg/L (±4.80mg/L), 0.87 mg/L (±0.70 mg/L), 5.03 mg/L (±7.60 mg/L), respectively.
Conclusion : There was not significant different between FDC and SF groups on improvement of clinical symptoms and weight gain in intensive phase of therapy, the highest of adverse effects was gastrointestinal syndrome, and all subjects had normal reference ranges of rifampicin concentrations, and isoniazid and pyrazinamide below the normal range.

Keywords : coinfection TB-HIV, fixed dose combination, separated formulation.

INTRODUCTION

Tuberculosis (TB) is an infectious disease which causes second most death in the world after HIV. Indonesia was one of the 30 highest TB burden country in the world, including coinfection TB-HIV.[1,2] Moreover, strains of Mycobacterium tuberculosis that are resistant to standard anti-TB therapy are emerging in almost all areas reporting to the World Health Organization (WHO). The large number of tablets used in the treatment regimens of TB, long-term treatment and nonadherence to treatment regimen are believed to be major contributing factors to this public health problem.[3] Fixed Dose Combination (FDC) was aimed to simplify TB therapy and facilitate physician and patient compliance with treatment recommendations. A previous study from Indonesia showed that patient's adherence of the use of FDC was 72.7% compared to the use of SF was 65.5%, there was no difference of the adherence between FDC and SF groups (p = 0.601).[4] Al-Shaer *et al* mentioned that effectiveness was not different between FDC and SF as shown by mean time to sputum conversion (29.9±18.3 vs. 35.6±23 days, p=0.12). Similarly, there was no difference in the incidence of adverse events, except for visual one that was higher in SF group. Fixed-dose combination (FDC) formulations are currently recommended for the treatment of active tuberculosis (TB) Meanwhile, concerns were raised about adequate bioavailability of the component drugs, particularly rifampicin (RIF) due to its enhanced decomposition in the presence of isoniazid (INH). In addition, a systematic review showed that the use of FDC increased the risk of tuberculosis recurrence compared to the use of SF.[5] Therefore, we aimed to evaluate the effect of FDC antituberculosis and separate formulations (SF) on clinical symptoms, weight gain, adverse effect and plasma concentration in TB/HIV cases during the intensive phase.

METHODS

Prospective cohort study was conducted in public hospital, Sulianti Saroso infectious disease hospital, Jakarta. It recruited TB-HIV patients in May 2018–May 2019. The inclusion criteria were patients (over than 18 years old) diagnosed with TB-HIV who received anti-tuberculosis medications (either as FDC or SF) and had not received antiretroviral. The exclusion criteria were the patients had renal disease and or creatinine/urea and elevated of LFT (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] values) including total bilirubin).

The subjects received first-line anti-TB medications (rifampicin, isoniazid, pyrazinamide, and ethambutol), either as FDC (rifampicin 150, isoniazid 75, pyrazinamide 400, and ethambutol 275 mg/tablet) or SF (rifampicin 450 or 600, isoniazid 300, pyrazinamide 500, and ethambutol 500 mg/tablet). The dose was calculated based on the patient's weight. We used the survival estimate formula to calculate the sample size. It was estimated that 23 evaluable patients in each group were included, considering an expected drop-out rate of 10%.

The effect was defined as an improvement of clinical symptoms (improved or deteriorated) and weight gain (no loss or weight loss) during the intensive phase (after 2 months therapy. We noted the clinical symptoms of subjects such as a persistent cough, chest pain, fatigue, loss of appetite, fever. Adverse effect was also defined as a clinical symptom and increased alanine transaminase (ALT) and aspartate transaminase (AST), assessed closely at each visit during the first and second weeks of the intensive phase therapy. Normal reference ranges were 0 to 45 IU/L; 0 to 35 IU/L for ALT and AST, respectively.

Plasma concentrations of FDC antituberculosis and SF were measured after 2 weeks therapy when the drug reached in steady-state. Blood samples were collected in the morning on EDTA tubes, 2 ± 2 hours after the subjects administered the FDC antituberculosis or SF. After centrifugation, plasma was transferred and stored at -80ºC until analysis. Plasma concentrations of FDC antituberculosis and SF were determined using liquid chromatography (LCMS/MS) method with UV detection at Pharma Metric laboratories, Jakarta.

Statistical analysis, categorical data were reported as frequency and percentages. Fisher test to compare categorical data between the two groups of comparison. We set the significance level of 0.05. All statistical analyses were performed using SPSS 19. The study protocol was approved by Sulianti Saroso Infectious Disease hospital ethics committee (No. 33/XXXVIII.10/VII/2018). All involved subjects signed informed consent forms.

RESULTS

A total of 36 subjects were included in this study (Table 1). Twenty subjects received FDC antituberculosis and 16 subjects received SF. Overall the subjects was on clinical stage-1 and 2 of HIV.

At baseline, positive smear pulmonary tuberculosis were 5 subjects (10% in FDC group and 18.8% in SF group), while they achieved sputum conversion at the end of the intensive phase (after 2 months therapy). In the FDC group, 2 (10%) subjects passed away, 3 (15%) subjects were discontinued therapy due to increased LFT and allergies, and 2 (10%) subjects were lost to follow up after 2 months therapy (intensive phase). Figure 1 showed the flow chart of recruited subjects.

There was not significant different between FDC and SF groups with improving clinical symptoms (P = 0.70) and weight gain (P = 1.00), Table 2 and 3. Table 4 showed all of subjects had normal range of AST/ALT

TABLE 1
Demographic and clinical characteristics of the study subjects

Variables	FDC group (N=20 subjects)	SF group (N=16 subjects)
Age (year)		
>35	7 (35)	7 (43.8%)
≤35	13 (65)	9 (56.3)
Sex		
Male	17 (85)	4 (75)
Female	3 (15)	4 (25)
Body Weight Index		
Low, n (%)	9 (45)	7 (44)
Normal, n (%)	11 (55)	9 (56)
Clinical stage of HIV		
I, n (%)	0	0
II, n (%)	0	0
III, n (%)	15 (75)	11 (68.75)
IV, n (%)	5 (25)	5 (31.25)
Opportunistic infection		
Yes	12 (60)	6 (37.5)
None	8 (40)	10 (62.5)
Smear-positive pulmonary tuberculosis at baseline		
Positive	2 (10)	3 (18.8)
Negative	18 (90)	13 (81.3)

results in the first week and second week of intensive phase. Gastrointestinal syndrome was 75% in FDC group; 62.5 % in SF group. Adverse effect of FDC and SF groups were presented in Figure 2.

Six (30%) subjects out of 20 subjects in FDC group and 9 (56,25%) subjects from 16 subjects in SF group, the plasma concentration at 2 hours (C2h) were measured after 2 weeks therapy. Only half of subjects was measured the plasma concentration at 2 hours due to financial reasons. Plasma concentration at 2 hours were described in Figure 3 and 4. Several studies stated that the lower concentration at 2 hours was defined as rifampicin (< 8 or < 4 mg/L); (isoniazid) < 3 or < 1.5 mg/L; and (pyrazinamide) < 35 or < 20 mg/L.6,7 In this study, mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration in FDC group were 5.49 mg/L (±3.40 mg/L), 1.35 mg/L (±1.20 mg/L), 19.87 mg/L (±17.00 mg/L), respectively. Mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration in SF group were 6.42 mg/L (±4.80mg/L), 0.87 mg/L (±0.70 mg/L), 5.03 mg/L (±7.60 mg/L), respectively.

DISCUSSIONS

This study evaluated an improvement of clinical symptoms and weight gain during the intensive phase. There was not significantly different between FDC and SF groups with improvement of clinical symptoms and weight gain. We assumed that the FDC product had a bioequivalence to the SF for each of its active components, including rifampicin.[8] Therefore strongly recommended that the product of FDC must be ensured that qualified active ingredients and excipients should be used.[8] However, our subjects were newly diagnosed TB/HIV and the use of FDC or SF antituberculosis in the first 2 months of treatment had not been relieved clinical symptoms and body weight. Meanwhile, in this study showed the proportion of deteriorated and weight loss

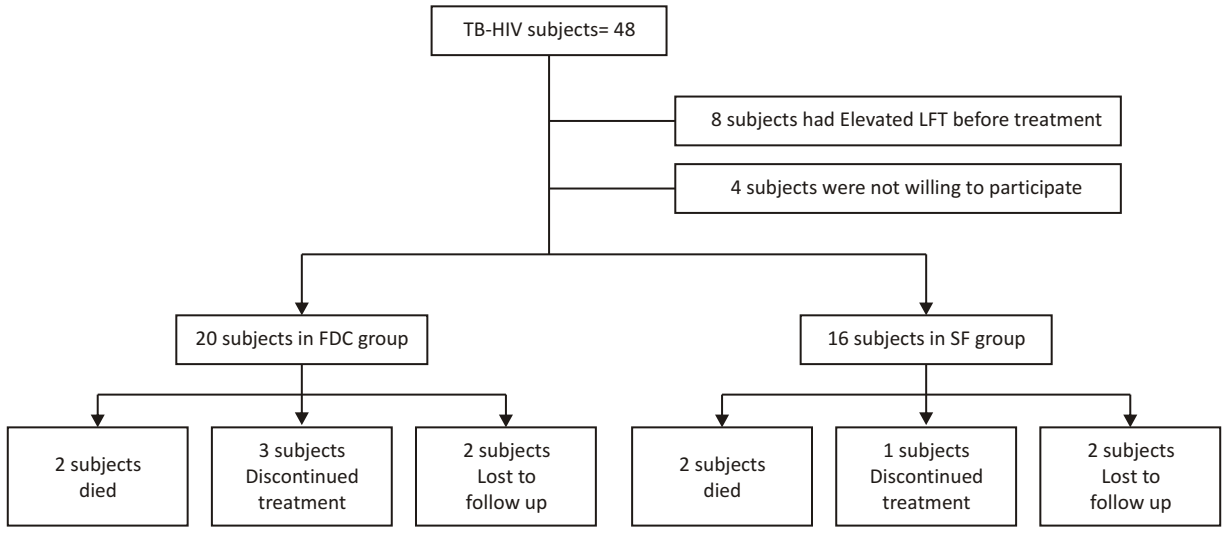

Figure 1. Flow diagram of subjects

TABLE 2
The proportion of subjects with an improvement of clinical symptoms during the intensive phase therapy

	Improved	Deteriorated	*P**	OR	CI 95%
FDC group	6 (30)	14 (70)	0.70	1.857	0.38 – 9.0
SF group	3 (18.8)	13 (81.3)			

*Fisher Exact

TABLE 3
The proportion of subjects with weight gain during the intensive phase therapy

	No loss (weight gain)	Weight loss	*P**	OR	CI 95%
FDC group	7 (35)	13 (65)	1.00	0.897	0.229 – 3.521
SF group	6 (46.2)	10 (62.5)			

*Fisher Exact

were higher. Weight loss is a major feature of TB/ HIV, which may affect both the severity and outcome of the disease. There was a hypothesis that the pathogens products can stimulate the production of proinflammatory mediators and cytokines. It stimulates the acute phase of the host response, which leads to anorexia.[9,10]

We did not evaluate acid-fast bacilli (AFB) sputum smear conversion as an outcome of the therapy due to the proportion of smear-negative was higher (over than 50%). Leandro *et al* showed that high prevalence of smear-negative (65.2%) among patients with TB in a tertiary care hospital of south of Brazil with high TB/HIV prevalence.[11] Previous studies demonstrated that TB/HIV patients are more likely to have smear-negative pulmonary tuberculosis, and this probability increases as immunosuppression increases.[12]

In this study, we evaluated adverse effect, particularly altered alanine transaminase (ALT) and aspartate transaminase (AST). We assessed closely at each visit during the first and second weeks in the intensive phase compared to the baseline ALT/AST. Baseline liver function are one of the risk factors for the development of drug induce hepatitis and these inform monitoring and management of these patients.[13] We did not find the elevation of ALT/AST of ≥ 3 during 2 weeks of intensive phase.[8] A small subject might contribute the results. However, hepatotoxicity attributed to FDC or SF

TABLE 4
Laboratory results (AST/ALT) at each visit during the first and second weeks of the intensive phase therapy

	FDC group n (%)	SF group n (%)
The first week of the intensive phase therapy (n= 36 subjects)		
Normal range of AST/ALT	20 (55)	16 (45)
Elevated of AST/ALT	0	0
The second weeks of the intensive phase therapy (n= 21 subjects)		
Normal range of AST/ALT	13 (62)	8 (38)
Elevated of AST/ALT	0	0

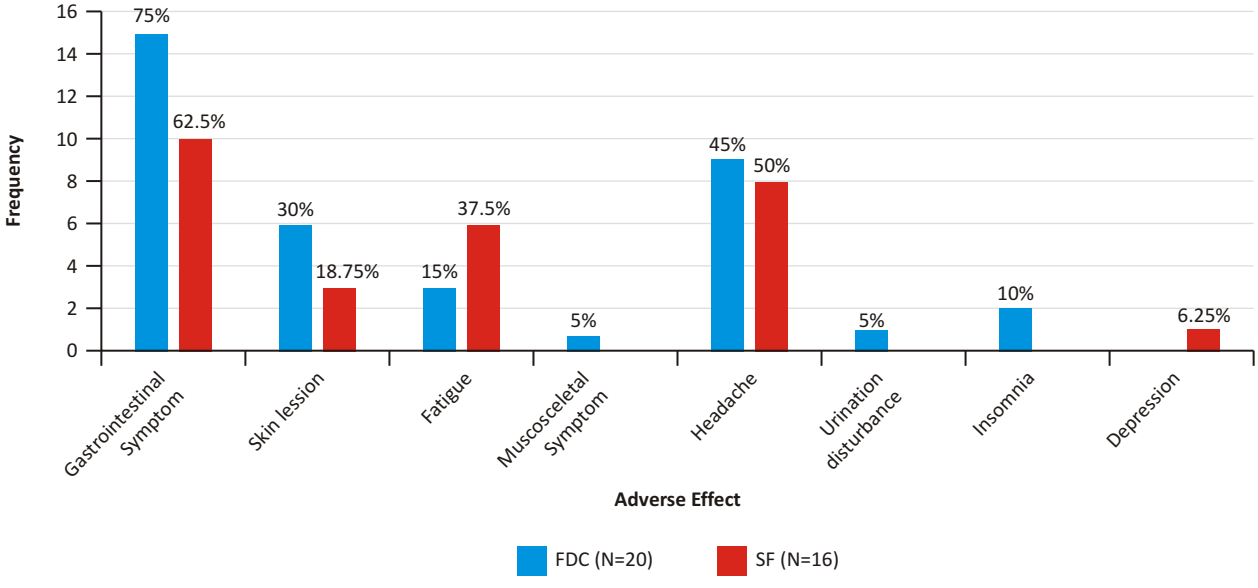

Figure 2. Adverse effect of FDC and SF groups

of antituberculosis has been reported in 5%–28% of people treated with antituberculosis drugs.[8,13] Another adverse effect such as gastrointestinal syndrome and headache are common in each group. Majdoub *et al* mentioned that urticaria, thrombocytopenia and leukopenia were common in patients treated with FDC due to significant difference in isoniazid and rifampicin in both groups.[14] Treatment regimen for TB is same in both HIV positive and HIV negative patients. However, HIV causes poor treatment outcomes of antituberculosis. Since this virus impairs immune system of the host therefore adverse effects due to antituberculosis are more common where there is an increase prevalence of HIV.[14]

Plasma concentrations are measured to evaluate the appropriate dose for subjects who are slow to respond to therapy, have multidrug resistance, are at risk of drug-drug interactions or have concomitant disease conditions that significantly complicate the clinical situation or failed to therapy.[15,16] This study showed that the subjects had normal reference ranges of rifampicin concentrations, and lower ranges isoniazid and pyrazinamide, in both groups. Sekai *et al*, showed that of 225 of pulmonary TB patients, low pyrazinamide plasma concentration was associated with poor treatment outcome than normal plasma concentration ($p < 0.01$).[17] However, we did not evaluate an association between low plasma antituberculosis concentrations and clinical outcome and adverse effect because of a small number of blood sampling, the blood sampling was collected from 7 subjects of FDC group and 10 subjects of SF groups. Moreover, we only collected one sample that we expected C2h of rifampicin, isoniazid and pyrazinamide might provide information of completed of drug absorption and was accepted as an estimated C-max.[18,19] Meanwhile, C2h

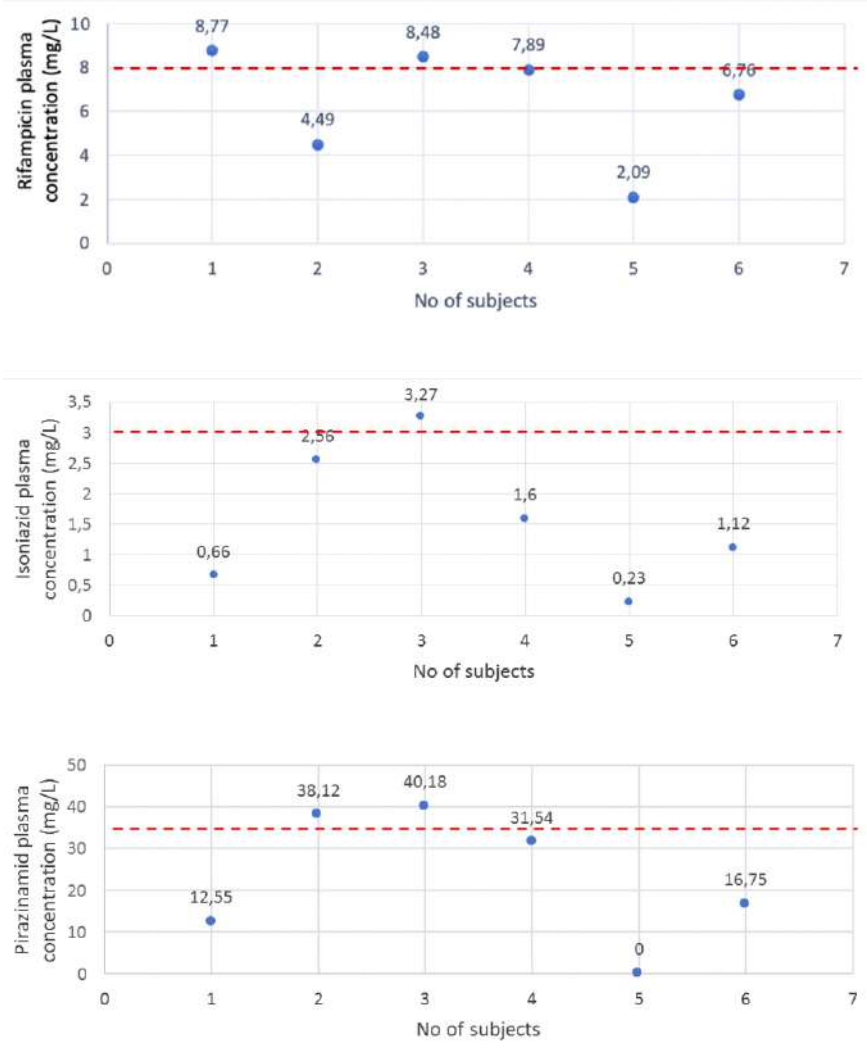

Figure 3. Mean plasma Rifampicin, Isoniazid, Pyrazinamide concentration (mg/L) in FDC group. The results of mean plasma Rifampicin, Isonizaid, Pyrazinamide concentration (mg/L) in each subject is showed by blue dots. The lower normal range in each drug is showed by horizontal a red dot line.

values cannot differentiate between the delayed absorption or malabsorption and a low peak concentration, ideally a second sample, often collected at 6-hour (C6h), can confirmed between delayed absorption and malabsorption.[16,18] From a prospective observational study at India mentioned that low C2h of isoniazid was 71%, rifampicin was 58%, ethambutol was 46%, pyrazinamide was 10% and both isoniazid and rifampicin were 45% of the patients. Therapy failure occurred more frequently in both isoniazid and rifampicin were below the normal ranges (p=0.013).[19] Um SW *et al* founded that among 69 enrolled TB patients had low C2h of antituberculosis drugs. The plasma concentrations of isoniazid, rifampicin and pyrazinamide were positively associated with dose per kilogram of body weight ($P < 0.05$), meanwhile isoniazid concentration was associated with acetyl isoniazid/isoniazid ratio. We know that metabolism of isoniazid, especially acetylation by liver N-acetyltransferase. Isoniazid can be acetylated to form acetyl isoniazid. Thus, the ratio of the plasma concentrations of acetyl isoniazid and isoniazid as a determinant of the type of slow or rapid acetylator.[16,20]

Previous studies demonstrated the important to compare of FDC and SF formulations. Abraham *et al* conducted a randomized clinical trial comparing FDC with SF which FDC appeared to be as effective and safe as SF, although the proportion of HIV patients was only 5%.[21] Wu JT *et al* mentioned that serum bilirubin concentrations at the peak level, at week 4, and at week 8 were significantly higher for FDC than SF (p=0.04, and 0.03, respectively).[2]

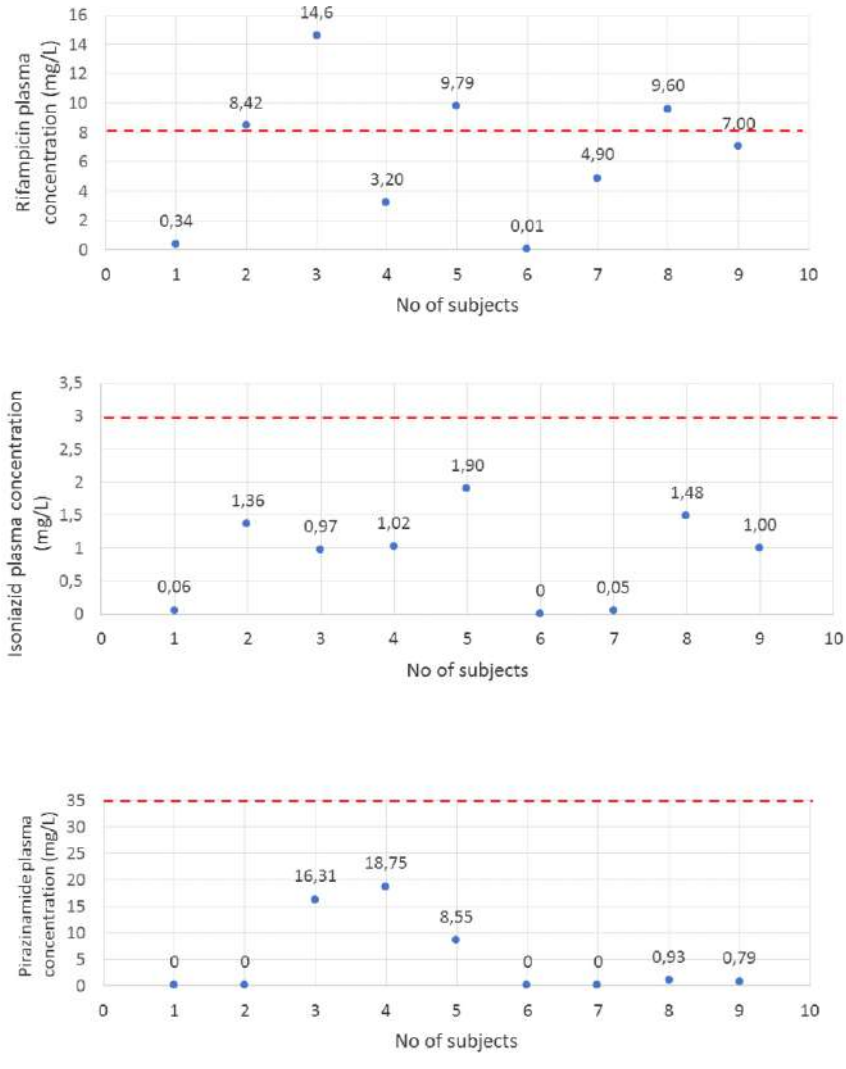

Figure 4. Mean plasma Rifampicin, Isoniazid, Pyrazinamide concentration in SF group. The results of mean plasma Rifampicin, Isonizaid, Pyrazinamide concentration (mg/L) in each subject is showed by blue dots. The lower normal range in each drug is showed by horizontal a red dot line.

Limitations of the study, to begin with our sample size was too small and cannot reach an estimated number in each group. Therefore, it might be difficult to find significant relationships from the data. In addition, we only collected one sample as C2h, which might miss the actual peak concentration. We suggest that further research with better designs are needed.

In conclusion, in intensive phase of therapy, there was not significant different between FDC and SF groups on improvement of clinical symptoms and weight gain, the highest of adverse effects was gastrointestinal syndrome, and all subjects had normal reference ranges of rifampicin concentrations, and isoniazid and pyrazinamide below the normal range. However, we should be directly observing patients with TB/HIV in intensive phase to complete their appropriate treatment.

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Conflict of Interest

We declare no conflict of interest in this study.

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Original Article

Cytokine Storm score (CSs) in COVID-19 Patients Smokers at Dr. Saiful Anwar Malang

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Abstract

Background : After 3 years of the COVID-19 pandemic, its escalation is still causing a critical global health problem. Cytokine storm is a severe complication of COVID-19, and smoking is a risk factor for death. The prevalence of smoking in Indonesia is very high, but there is still little research on the effect of smoking on the occurrence of cytokine storms. The Cytokines Storm Score (CSs) is a quick and simple method for detecting cytokine storms early by utilizing D-dimer, lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) parameters. The objectives of this study was to evaluate CSs in COVID-19 patients smokers

Methods : Retrospective analysis of 120 confirmed COVID-19 patients in November 2020–2021, divided into 2 groups (60 smokers and non-smokers), male, without comorbidities. analysis using Chi-square and Mann-Whitney. Prior to the CSs examination, lymphopenia is required. CSs were positive if at least two of the D-dimer, LDH, or ferritin levels were elevated. The CRP level is measured if there is an increase in only one of these values. Elevated CRP, lymphopenia, and impaired D-Dimer, LDH, or ferritin will result in positive CSs.

Results : CSs were significantly higher in smokers than non-smokers (54.5% vs. 45.5%, p = 0.024). D-dimer and CRP levels were significantly higher in smokers than non-smokers (1620 ng/mL vs. 1002.5 ng/mL, p = 0.001; and 13.8 mg/dL vs. 7.75 mg/dL, p = 0.001). Lower LDH and higher ferritin levels were not significant in smokers compared to non-smokers (405.5 IU/L vs. 418 IU/L, p = 0.160; and 886.65 ng/mL vs. 790.5 ng/mL, p = 0.203).

Conclusion : Cytokines Storm scores (CSs) increased significantly in COVID-19 patients who smoked, D-dimer and CRP levels were significantly higher in smoking COVID-19 patients compared to non-smokers.

Keywords : cytokine storm; COVID-19; Cytokine Storm score (CSs); smoker

INTRODUCTION

After three years, the COVID-19 pandemic is still causing serious problems for global health. Since June 2020, more than 7.26 million cases have been reported in 215 countries, with over 423,000 deaths and a global mortality rate of 5.6 percent.[1] Cytokines storm syndrome is a severe COVID-19 complication with smoking as a potential risk factor that can lead to death.[2] In these circumstances, a pandemic is critical for identifying risk factors, such as smoking, which is a risk factor for a variety of infections caused by bacteria and viruses.[3] Although smoking is very common in Indonesia, there is moderate little research on the link between smoking and cytokine storm incidents. Smoking in COVID-19 patients, such as adding an ingredient and burning it, could Improve the regulation of the angiotensin-converting enzyme-2 (ACE-2) receptor used by SARS-CoV-2 to enter the cell host, so that the more viruses that enter, the more Cytokines are activated, potentially leading to more symptoms in COVID-19 patients.[3] According to a study conducted at the hospital Saiful Anwar Malang, smoking is associated with a higher risk of COVID-19 development and mortality in COVID-19 patients who are hospitalized.[4] Based on the foregoing, a faster, simpler, and more accurate method of detecting cytokines storm is required, namely the Cytokines Storm score (CSs) with D-dimer, LDH, ferritin, and CRP parameters.

The Cytokine Storm score (CSs) is a biomarker guide that can be used as a prediction tool to identify patients at various stages of hyperinflammation, which may be useful for early intervention, early therapy, and disease progression prevention.[5] CSs were considered positive if lymphopenia was found and at least two of the serum levels of D-dimer, ferritin, or LDH were elevated.[6] D-dimer is a degradation product of fibrin, a small protein fragment that is present in the blood after the blood clot is degraded by fibrinolysis. Although the mechanism of this complication is still unknown, D-dimer shows relevance to the impact of smoking on the endothelium and COVID-19.[7] *Lactate Dehydrogenase* (LDH) is an intracellular enzyme involved in anaerobic glycolysis that catalyzes the oxidation of pyruvate to lactate.[8] The results showed that there was a significant increase in serum antioxidant enzymes, namely LDH, in the smoker group compared to the non-smoker group.[9] Ferritin is an acute-phase protein, a major iron storage protein. Based on research through *Bronchoalveolar Lavage* (BAL), it was found that in vitro ferritin release increased for 20 hours in alveolar macrophages obtained from mild smokers ($p<0.05$) and severe smokers ($p< 0.001$).[10] C-Reactive Protein (CRP) is an acute-phase inflammatory protein produced by the liver that can rise in a variety of conditions, including inflammation, cardiovascular disease, and infection.[11] Research shows that there is a dose-response relationship between CRP levels and the intensity and/or duration of smoking.[12]

This study aims to evaluate the CSs between smokers and non-smokers in COVID-19 patients using a scoring system based on a minimum of 2 from D-dimer, LDH, ferritin, or CRP levels (which meet the requirements).

METHODS

The design of this study was analytic retrospective, samples were obtained from 120 patients who were divided into 2 groups (60 smokers and 60 non-smokers). The research was conducted at the Dr. Saiful Anwar Malang in November 2020–2021. The inclusion criteria were: patients treated in the Integrated Covid Installation Room (intensive and non-intensive) as confirmed cases (RT-PCR Sars Cov 2 or TCM); age >18 years; male sex; smoker, former or non-smoker; Lymphocytes/Absolute Lymphocyte Count (ALC) <1000 (x103/mmc), and no comorbidities.

Data were analyzed using the one-sample Kolmogorov-Smirnov test for normality, the Chi-Square test for the categorical scale, and the Mann-Whitney test for the numerical scale. Lymphopenia was selected as a prerequisite for CSs, then if at least two levels of serum D-dimer > 1000 ng/mL, LDH > 300 IU/L, and ferritin >500 ng/mL were found, then CSs was considered positive. But in patients with lymphopenia and interference from only one of the D-dimer, ferritin, or LDH levels, then the CRP level is measured. If CRP is >10 mg/dL along with lymphopenia and increased D-dimer, ferritin, or LDH, then CSs is considered positive.

RESULTS

Characteristics Sociodemography CSs (+) in Smokers Based on the Brinkman Index (BI)

Sociodemographic characteristics with CSs (+) in smokers based on the Brinkman Index(BI): There were 55 subjects who were divided into 3 groups, namely mild, moderate, and severe (BI), as can be seen in Table 1.

Based on age with a mild Brinkman Index (BI), there were 5 (27.8%) aged 18–39 years, 11 subjects (61.1%) aged 40–64 years, and 2 subjects (11.1%) aged ≥ 65 years. In moderate (BI) there was 1 subject (3.2%) aged 18-39 years, 21 subjects (67.7%) aged 40–64 years, and 9 subjects (29.0%) aged ≥ 65 years. In severe (BI) there were no subjects aged 18–39 years, and 3 subjects (50.0%) aged ≥40–64 years.

Based on education with mild (BI), there were no subjects with elementary school education, 4 subjects (22.2%) in junior high school, 3 subjects (16.7%) in high school, and 11 subjects (61.1%) in undergraduate. In

TABLE 1
Sociodemographic Characteristics of CSs (+) in Smokers based on the Brinkman Index (BI)

Variables	Brinkman Index (CSs (+))						p value
	Mild		Moderate		Severe		
	(n=18)	%	(n=31)	%	(n=6)	%	
Age (year)							
18–39 years	5	27.8%	1	3.2%	0	0.0%	0.035
40–64 years	11	61.1%	21	67.7%	3	50.0%	
≥ 65 years	2	11.1%	9	29.0%	3	50.0%	
Education							
Primary School	0	0.0%	4	12.9%	3	50.0%	0.021
Junior High School	4	22.2%	5	16.1%	2	33.3%	
Senior High School	3	16.7%	10	32.3%	0	0.0%	
Bachelor	11	61.1%	12	38.7%	1	16.7%	
Profession							
Not working, retired, student	4	22.2%	11	35.5%	1	16.7%	0.256
Laborers, farmers, drivers	3	16.7%	6	19.4%	4	66.7%	
Entrepreneur, trader	4	22.2%	8	25.8%	1	16.7%	
Private sector employee	4	22.2%	5	16.1%	0	0.0%	
Health workers	1	5.6%	1	3.2%	0	0.0%	
Civil servants, lecturers, teachers	2	11.1%	0	0.0%	0	0.0%	

TABLE 2
Comparison of CSs in COVID-19 Patients Smokers and Non-Smokers

Smoker status	CSs (+)		CSs (-)		p value
	(n=101)	%	(n=19)	%	
Smoker	55	54.5%	5	26.3%	0.024
Non smoker	46	45.5%	14	73.7%	

If the value of p <0.05 = significant, Data analysis was performed using the Chi square test (categorical scale), CSs: *Cytokines Storm score*

moderate (BI), there were 4 subjects (12.9%) from elementary school, 5 subjects (16.1%) from junior high school, 10 subjects (32.3%) from senior high school, and 12 subjects (38.7%) from undergraduate school. In severe (BI), there were 3 elementary school subjects, 2 junior high school subjects, no subjects with high school education, and 1 subject (16.7%) was an undergraduate.

Based on work with mild (BI), it was found that 4 subjects (22.2%) had similarities, namely (not working, retirees and students), (self-employed and traders), and private employees, as many as 3 subjects (16.7%) laborers, farmers and driver, 1 subject (5.6%) health workers, 2 subjects (11.1%) lecturers, teachers, and civil servants. In moderate (BI), 11 subjects (35.5%) do not work, retirees and students, 6 subjects (19.4%) laborers, farmers and drivers, 8 subjects (25.8%) entrepreneurs and traders, 5 subjects (16, 1%) private employees, 1 subject (3.2%) health workers, no subjects as lecturers, teachers, and civil servants. In severe (BI), 1 subject (16.7%) has similarities: (not working, retired and students) and (self-employed and traders), 4 subjects (66.7%) are laborers, farmers, and drivers, there are no subjects as (employees private sector), (health workers) and (lecturers, teachers, and civil servants).

TABLE 3
Comparison of CSs in Smokers Based on Brinkman Index (BI)

Brinkman Index	CSs (+)		CSs (-)		p value
	(n=55)	%	(n=5)	%	
Mild	18	32.7%	2	40.0%	0.733
Moderate	31	56.4%	2	40.0%	
Severe	6	10.9%	1	20.0%	

If the value of p <0.05 = significant, Data analysis was performed using the Chi square test (categorical scale), CSs : *Cytokines Storm score*

TABLE 4
Levels of D-dimer, LDH, ferritin, and CRP in COVID-19 Patients: Smokers and Non-Smokers

Variables	std. Deviation	Minimum	Maximum	Median	p value
D-dimer (mg/L)					
Smoker	9858.37	450	37200	1620	0.000
No smoker	868.79	139	3720	1002.5	
Total	7379.63	139	37200	1311.25	
LDH U/L					
Smoker	433.11	142	2250	405.5	0.160
No smoker	327.29	103	1448	418	
Total	385.16	103	2250	411.75	
Ferritin ng/mL					
Smoker	1165.01	246.3	6665	886.65	0.203
No smoker	635.07	127	2173	790.5	
Total	947.29	127	6665	838575	
CRP (mg/dL)					
Smoker	11.25	0.9	57.9	13.8	0.000
No smoker	5.92	0.3	24.1	7.75	
Total	9.54	0.3	57.9	10.775	

If the value of p < 0.05 is significant, data analysis was performed using the Mann–Whitney test (numerical scale). Because the distribution is not normal, the median value (minimum-maximum) is used

Comparison of CSs in Smoker and Non-Smoker COVID-19 Patients

In the comparison of CSs in smoking and non-smoking COVID-19 patients, there were 120 subjects, consisting of 60 smokers and 60 non-smokers. The data uses a categorical scale, so the Chi-Square test is carried out with the results as described in Table 2.

Based on the data from the Table 2, it shows a significance value of (p = 0.024), so it can be interpreted that there is a significant difference between subjects who experience CSs (+) and CSs (-) in the smoker and non-smoker groups. The incidence of CSs (+) was significantly higher in smokers compared to non-smokers: 5 subjects (54.5%) vs. 46 subjects (45.5%). While the incidence of CSs (-) was significantly lower in smokers compared to non-smokers: 5 subjects (26.3%) vs. 14 subjects (73.7%).

Comparison of CSs in Smokers COVID-19 Patients Based on the Brinkman Index (BI)

Comparison of CSs in smokers based on the Brinkman Index obtained as many as 60 subjects, using categorical scale data, so that the Chi-Square test was carried out with

the results as described in Table 3.

The results of the comparison of the Brinkman Index between subjects who experienced CSS (+) and CSs (-) showed a significance value of 0.733 (p >0.05), so it could be interpreted that the results of the comparison of the Brinkman Index between subjects who experienced CSS (+) and CSs (-) did not find a meaningful difference. The incidence of CSs (+) was not significantly higher in moderate (BI) 31 subjects (56.4%) compared to mild (BI) 18 subjects (32.7%) and severe (BI) 6 subjects (10.9%). Meanwhile, the incidence of CSs (-) was not significantly higher in mild and moderate (BI) in 2 subjects (40.0%) compared to 1 subject (20.0%) in severe (BI).

D-dimer, LDH, ferritin, and CRP Levels in COVID-19 Smoker and Non-Smoker Patients

The results of the data normality test for D-dimer, LDH, ferritin, and CRP levels in smokers and non-smokers as described in Table 4.

In Table 4, the comparison of D-dimer between smokers and non-smokers shows a significance value of 0.000 (p <0.05), significant, whereas in smokers with a median D-dimer of 1620 ng/ml, it is higher than in non-smokers with a median D-dimer of 1002.5 ng/ml.

The results of the comparison of the LDH of patients between smokers and non-smokers show a significance value of 0.160 (p >0.05), significant, where smokers' median LDH of 405.5 IU/L is lower than the median LDH of non-smokers, which is 418 IU/L.

Ferritin comparison results between smokers and non-smokers COVID-19 patients showed a significance value of 0.203 (p >0.05), so it can be interpreted that there is no significant difference in the ferritin comparison between smokers and non-smokers. A median of 886.65 ng/mL was higher than in non-smokers, with a median of 790.5 ng/mL.

The results of the comparison of CRP in smokers and non-smokers with COVID-19 patients showed a significant value of 0.000 (p <0.05), so it can be interpreted that the results of the comparison of CRP in patients between smokers and non-smokers showed a significant difference. The median CRP level in smokers was 13.8 mg/dL, higher than the median CRP in non-smokers, which was only 7.75 mg/dL.

DISCUSSION

Sociodemographic Characteristics of CSs (+) smokers based on the Brinkman Index (BI)

Sociodemographic characteristics in this study were divided into 3 groups, namely the mild, moderate, and severe Brinkman Index. Of the 55 CSs (+) smoking patients, there was a significant difference (p = 0.035). Most people between the ages of 18 and 39 have mild (27.78%), 40 to 64 years have mostly moderate (67.74%), and 65 years have mostly severe (BI) (50.0%). The Brinkman Index in CSs (+) COVID-19 patients increased with age, according to this study. It is possible that the older and the longer smoking the incidence of CSs is higher.

Based on the level of education, there was a significant difference (p = 0.021) in the Brinkman Index (BI), namely at the elementary and junior high school education levels, where the (BI) was the highest (50.0% and 33.33%). At the high school level, the majority were classified as moderate (BI) (32.26%), and those not found (BI) were severe. At the undergraduate level, most of them had mild (BI) (61.11%). From this study, it was found that the Brinkman Index in CSs (+) COVID-19 patients was getting worse in line with the low level of patient knowledge. This is not in accordance with the RISKESDAS data that, based on the level of education, the higher the level of education, the higher the amount of cigarette and tobacco consumption; however, the difference in prevalence is not significant.[13]

Based on work, it was found that CSs (+) in COVID-19 patients who worked as civil servants, lecturers, and teachers mostly had mild (BI) (11.11%), no moderate (BI), and no severe (BI). Jobs as health workers have similarities with jobs as private employees, namely mild (BI) (5.56% and 22.22%) and no severe (BI). Jobs as self-employed and traders have similarities with those of patients who are not working, students, and retirees, mostly in moderate (BI) (25.81% and 35.48%). Most of the patients who worked as laborers, farmers, or drivers had severe (BI) (66.7%). The degree of Brinkman Index may be influenced by the high mobility and social environment in which the patient works.

CSs in Smoking and Non-Smoking COVID-19 Patients

The comparison of smoker status between patients who have CSs (+) and CSs (-) shows a significance value of 0.024, so it can be interpreted that the results of the comparison of smoker status between patients who have CSs (+) and CSs (-) show a difference, which means that the incidence of CSs (+) is higher in smokers (54.5%) than non-smokers (45.5%), while in contrast, patients with CSs (-) are lower in smokers (26.3%) than non-smokers (73.7%).

These results are consistent with the previous theory that smoking is like adding fuel to the fire because smoking can upregulate the receptor angiotensin-converting enzyme-2 (ACE-2) used by SARS-CoV-2 to enter host cells so that more and more viruses enter. further increases the risk of cytokine storms, which can worsen the condition of COVID-19 patients.[3] Furthermore, these findings are consistent with previous research indicating that the value of CSs is considered positive if two biomarkers, namely serum D-dimer, ferritin, LDH, or CRP levels, have increased.[6]

CSs in Smoking COVID-19 Patients Based on the Brinkman Index

The incidence of CSs (+) was not significantly (p=0.733) higher in moderate (BI), namely 31 subjects (56.4%) compared to mild (BI), 18 subjects (32.7%), and 6 subjects (10.9%) in severe (BI). This is inconsistent with previous research that cigarette smoke induces epigenetic modifications of the bronchial epithelium, which causes metaplasia of mucus (goblet) cells, so that the more cigarettes are smoked, the more ACE2-producing goblet cells in the lungs will increase, which is the receptor used by SARS-CoV-2 to enter host cells.[14] However, in that study, there were various comorbidities, whereas in our study, we excluded all existing comorbidities, so from the results of this study, we suspect that the CSs (+) incident has actually occurred at a moderate degree.

Comparison of D-dimer, LDH, ferritin, and CRP Levels in Smoker and Non-Smoker COVID-19 Patients

The comparison of D-dimer levels between smokers and non-smokers with COVID-19 patients was significantly (p = 0.001) higher in smokers than non-smokers with COVID-19 patients (median: 1620 mg/L vs. 1002.5 mg/L). The results of these D-dimer levels are in line with previous research that indicates that increasing D-dimer levels in smokers can increase the incidence of thromboembolic coagulopathy, causing worsening in patients with confirmed COVID-19.[15] And according to the results of other studies, high D-dimer levels correlate with the severity of COVID-19. Reports of D-dimer levels vary, but the median level of D-dimer levels is around 1000 ng/Ml.[6]

The comparison of CRP levels between smoking and non-smoking COVID-19 patients revealed significantly (p = 0.001) higher levels in smokers than non-smokers (median: 13.8 mg/dl vs. 7.75 mg/dl). The results of this study are in accordance with the theory in the form of a meta-analysis test, which shows that smoking history and CRP are parameters that can be used to evaluate the severity of COVID-1916 and another meta-analysis showed that levels were higher at >10 mg/L in smokers than non-smokers.[11]

The LDH level of smokers in COVID-19 patients was lower (405.5 ng/ml) compared to non-smokers (411.75 ng/ml), but not significantly (p = 0.160). These results are inconsistent with the literature, which suggests that smokers have increased LDH levels, which are useful for counteracting excess free radicals from the effects of smoking, so that they will increase serum antioxidant enzymes (LDH) in the blood compared to non-smokers.[9] However, the results of this study's LDH levels are in accordance with other studies where there is an increase in LDH levels > 245 U/L, which is related to the worsening of COVID-19.[17]

Ferritin levels were higher in smokers with a median of 886.65 ng/ml compared to non-smokers (790.5 ng/ml), but not significantly (p = 0.203). Although not significant, these results are in accordance with previous studies in multivariable regression analysis showing that the median ferritin level increased with smoking status, namely in former or active smokers, and increased with the number of smokers in all subgroups of patients who were categorized according to spirometry results.[18] Based on a meta-analysis of 27 laboratories, it was concluded that the level of severity can be determined from inflammatory markers, and the most prominent difference is ferritin, with levels of 423.13 ng/mL (281.41–582.85).[19]

CONCLUSION

Cytokines Storm scores (CSs) increased significantly in COVID-19 patients smokers. D-dimer and CRP levels were significantly higher in smoking COVID-19 patients compared to non-smokers. Ferritin levels were higher and LDH lower but not significant in smokers with COVID-19 patients compared to non-smokers.

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Original Article

Comparison of ROX Index and Surfactant Protein-D with HFNC Outcome in COVID-19 Patients

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Abstract

Background : In COVID-19, severe clinical deterioration can lead to respiratory distress. High Flow Nasal Cannula (HFNC) is an oxygenation treatment recommended in severe COVID-19 patients, with various studies showing decreased recovery time and intensive care needed. However, instruments to predict HNFC outcomes, specifically in COVID-19, are not yet widely studied. ROX index is a practical instrument proven effective in predicting HFNC outcome in pneumonia while showing high variabilities of optimum time of assessments and cut-off values in COVID-19. Surfactant Protein-D (SP-D) is an alveolar protein showing potential as a biomarker in acute lung injury and respiratory distress. In this study, we analyzed ROX index and SP-D potential as HFNC outcome predictors in COVID-19 patients.

Methods : This prospective study recruited severe and critical COVID-19 patients treated with HFNC. Patient characteristics, laboratory values including initial serum SP-D values, and ROX index were recorded. Significant differences were analyzed using Chi-Square and Mann-Whitney tests. Receiver operating characteristic (ROC) analysis was used to determine HFNC outcome predictive abilities of ROX index and serum SP-D.

Results : 31 subjects with successful HFNC outcomes in 19 subjects and failed HFNC outcomes in 12 subjects were included in this study. ROX index and SP-D value were significantly higher in subjects with successful HFNC compared to failed HFNC ($p < 0.05$). ROX index at 6, 12, and 24 hours showed good HFNC outcome predictive ability (AUC > 0.7, $p < 0.05$).

Conclusion : Successful HFNC outcome in COVID-19 was significantly related to higher ROX index and serum SP-D values. ROX index also showed good potential as an HFNC outcome predictor in COVID-19 patients.

Keywords : Surfactant Protein-D, COVID-19, High Flow Nasal Cannula, ROX index

INTRODUCTION

COVID-19 infection can cause various degrees of clinical manifestation, ranging from mild to critical clinical conditions. Fever, cough, and shortness of breath are the main symptoms of COVID-19, with other accompanying symptoms such as myalgia, lethargy, and gastrointestinal manifestation, including diarrhea and vomiting. In severe cases, progressive clinical deterioration happens, leading to acute respiratory distress, septic shock, metabolic acidosis, and coagulation dysfunction in a few days.[1]

High Flow Nasal Cannula (HFNC) is an oxygenation treatment recommended in severe and critical COVID-19 patients. HFNC is also recommended in COVID-19 patients without clinical improvement after the first hour of treatment. Previous studies showed HFNC's feasibility as a treatment strategy, with 60.3% of subjects weaned from HFNC and 67.7% of weaned subjects did not require intensive care treatment.[2] Another study showed that HFNC treatment decreased recovery time and the need for mechanical ventilation.[3]

ROX index is a practical instrument previously proven effective in predicting HFNC outcomes in pneumonia patients.[4] In COVID-19, a meta-analysis study showed good predictive ability of ROX index in HFNC outcome. However, high variabilities were found in the ROX index time of assessment and cut-off value to best predict HFNC outcome in COVID-19 patients.[5]

Surfactant Protein-D (SP-D) is a protein secreted by type 2 alveolar cells. SP-D is important in various immunological functions such as agglutination and opsonization. In COVID-19, an SP-D level increase was found to be correlated with COVID-19 severity.[6] A previous study showed SP-D potential as a biomarker in acute lung injury and respiratory distress because of its protective role in various etiologies of acute lung injury.[7] Although recommended as an oxygenation treatment in severe and critical COVID-19 patients, instruments to predict HNFC outcome, specifically in COVID-19 are not yet widely studied. In this study, we analyzed ROX index and SP-D potential as HFNC outcome predictors in COVID-19 patients.

METHODS

This prospective study was conducted in Saiful Anwar General Hospital, Malang, Indonesia, between May 2021 to August 2021. This study's research protocol was accepted by the Ethics Commission of Saiful Anwar General Hospital (Approval No: 400/244/K.3/102.7/2022). Patients confirmed with COVID-19 were classified based on clinical severity. Severe and critical patients who were ≥18 years old, fully alert, able to communicate, were not on a ventilator, with a respiratory rate of 20–30 times/min and oxygen saturation of ≥90% were included in this study. Subjects using ventilator from the start of the treatment were excluded from this study. Subjects were gathered using consecutive sampling method.

Data such as patient characteristics (age, gender, and comorbidity) and laboratory values (initial SP-D, LDH, CRP, procalcitonin, D-dimer) were recorded. ROX index at 1, 2, 6, 12, and 24 hours after HFNC were calculated and recorded. ROX index is defined by the ratio of oxygen saturation per inhaled oxygen fraction divided by respiratory rate ((SpO2/FiO2)/RR). SP-D is analyzed using enzyme-linked immunosorbent assay (ELISA) (Human SP-D ELISA Kit, Elabscience).

Categorical variables are shown by number and percentage and analyzed with Chi-Square test. Numerical variables are shown in Mean ± Standard Deviation and Median (Minimum – Maximum values), analyzed with Mann-Whitney test. HFNC outcome predictive model of ROX index and SP-D levels were analyzed using receiver operating characteristic (ROC) analysis to determine predictive abilities and optimum cut-off values.

RESULTS

Thirty-one subjects were included in this study, with successful HFNC outcomes in 19 subjects and failed HFNC outcomes in 12 subjects. Subjects with failed HFNC outcomes are all male and older compared to successful HFNC subjects, but these findings were insignificant. No subject had coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) as comorbidity. Subject characteristics can be seen in Table 1.

Respiratory findings showed varying results. There was no significant difference in P/F ratio between each HFNC outcome group, while significant differences were found in ROX index at all times of analysis. Laboratory values show insignificant findings between successful and failed HFNC outcomes in C-Reactive Protein (CRP), Procalcitonin, D-Dimer, and lactate dehydrogenase (LDH). A significant difference was found between each HFNC outcome group in surfactant protein D (SP-D).

Figure 1 showed a significantly higher SP-D value in successful HFNC patients. Aside from significantly higher ROX index values found in successful HFNC patients compared to failed HFNC patients at all times of assessments, an upward pattern of ROX index was found at each time of assessment in successful HFNC patients. In contrast, a downward pattern of ROX index was found at each time of assessment in failed HFNC patients.

ROC analysis showed that although ROX index at all times of assessments and SP-D showed good potential as a predictor of HFNC outcome (AUC > 0.7), Significant ROC findings were found in ROX index evaluated at 6, 12,

TABLE 1
Subject Characteristics between Each HFNC Outcome

Variables	Successful (N=19)	Failed (N=12)	p
Age (mean+SD)	50.9 + 12.4	56.8 + 16.0	0.239
Gender, n (%)			
Male	13 (41.9)	12 (38.7)	0.030*
Female	6 (19.4)	0	
Comorbidity, n (%)			
Diabetes	2 (10.5)	4 (33.3)	0.117
Hypertension	7 (36.8)	5 (41.7)	0.788
Heart Failure	0	1 (8.3)	0.201
P/F Ratio, Median (Min – Max)	169.30 (95.30–270.00)	148.50 ± 40.32	0.166
ROX Index, Median (Min – Max)			
1 hour	4.40 (3.16–5.02)	3.70 (2.32–4.94)	0.024*
2 hours	4.35 (3.31–5.24)	3.60 (2.21–5.44)	0.030*
6 hours	4.50 (3.33–5.80)	3.52 (2.21–5.44)	0.011*
12 hours	4.45 (3.33–6.10)	3.30 (2.02–6.87)	0.025*
24 hours	4.60 (3.39–6.30)	2.95 (2.32–4.20)	0.000*
Laboratory Values, Median (Min-Max)			
C-Reactive Protein	9.47 (1.2–30.49)	9.68 (0.34–35.04)	0.675
Procalcitonin	0.2 (0.03–1.36)	0.46 (0.07–2.95)	0.110
D-Dimer	0.7 (0.29–23.8)	1.24 (0.32–6.25)	0.367
Surfactant Protein D	4.05 (0.69–26.24)	0.79 (0.54–1.37)	0.000*
Lactate Dehydrogenase	416 (0–870)	490 (0–687)	0.454

*$p < 0.05$

and 24 hours ($p < 0.05$). The cut-off value with the highest sensitivity and specificity was found in 24 hours ROX Index, with a cut-off value of 3.63 ng/ml (Sensitivity: 84.21%; Specificity: 83.33%).

DISCUSSION

In this study, subjects with successful HFNC outcomes had significantly higher ROX Index and SP-D. A significant gender difference was found between different HFNC outcomes, with significantly higher male subjects with failed HFNC outcomes. Although previous studies showed a worse prognosis for males compared to females in COVID-19 outcomes, a significant gender difference in this study can also be attributed to the lack of subject gender variance (25 males vs. 6 females).[8] Subjects with failed outcomes were also found to be older, although not significant. This finding is similar to a previous meta-analysis study that showed an insignificant association between age and COVID-19 outcome after factoring in confounding factors such as age-related comorbidity (diabetes, hypertension, renal disease). This meta-analysis found that independently, age only increased the outcome risk of COVID-19 by 2.7% in two studies and found no increase in the other five studies.[9]

This study found a significantly higher ROX index at all times of assessments in subjects with successful HFNC outcomes. ROX index formula is adjusted to the fraction of oxygen received, and the respiratory rate of the patient. This can result in a more accurate assessment of the patient's clinical outcome, hence reflected in this study's findings. This finding is similar to a previous study by Prakash *et al.*, showing ROX index's ability to help predict subjects with worse outcomes. Predicting a patient with a worse outcome helps clinicians better

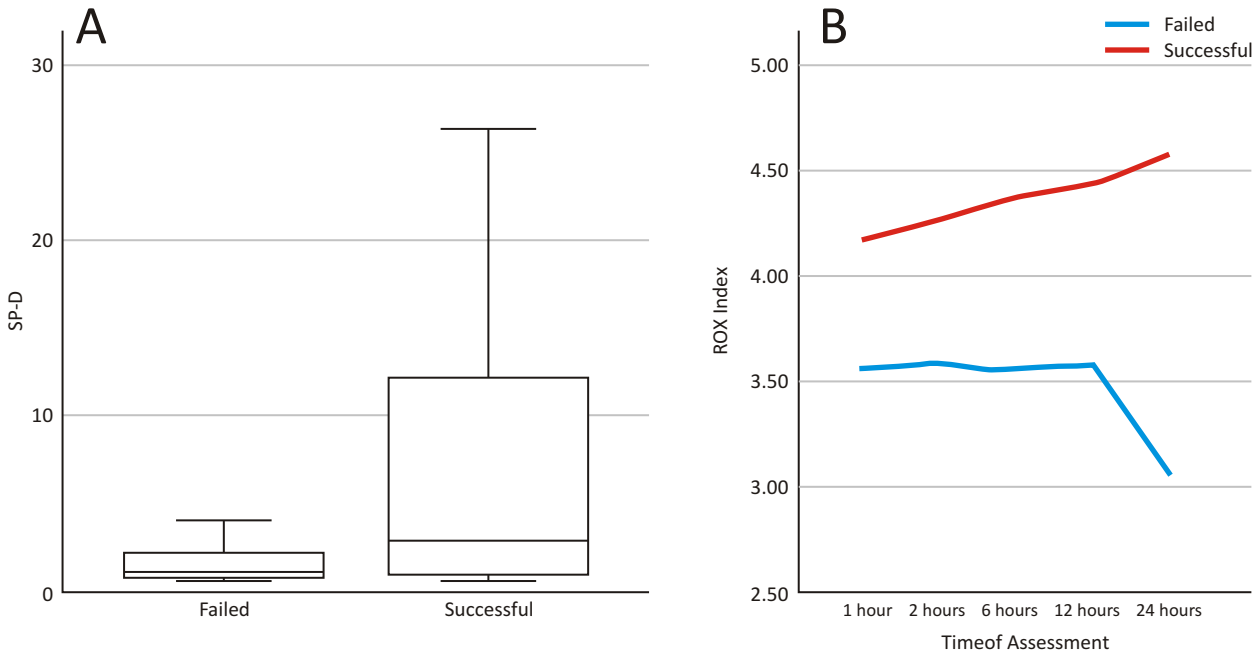

Figure 1. Graphical Representation of (A) SP-D and (B) ROX Index Pattern between HFNC Outcomes

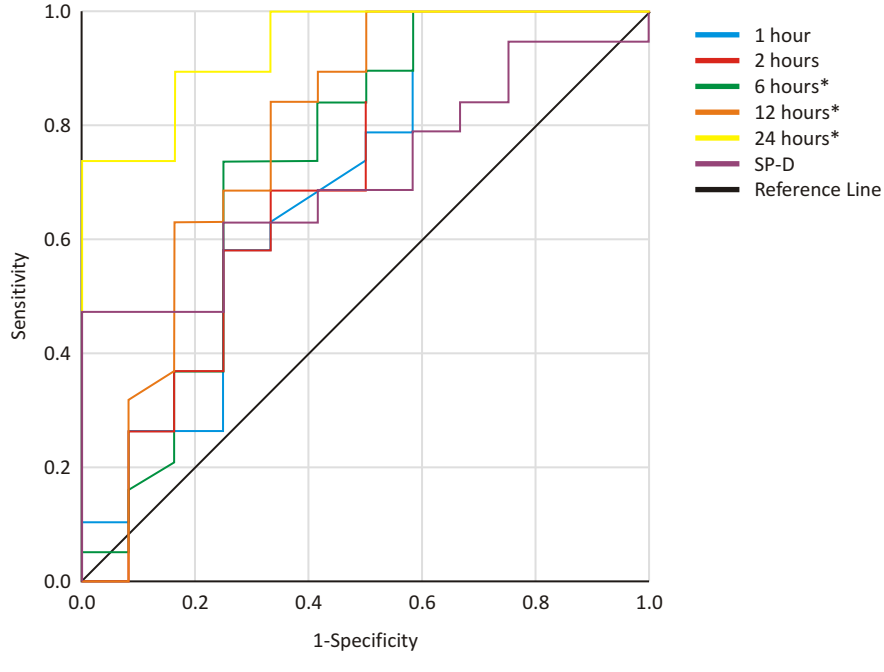

Figure 2. ROC Analysis of ROX Index and SP-D to Predict HFNC Outcome. *p < 0.05

prepare for various treatments, such as early invasive mechanical ventilation.[5] ROX index was also an excellent HFNC outcome predictor in other respiratory diseases. In a previous study, ROX index was proven to be an excellent HFNC outcome predictor in intensive-care pneumonia patients.[4]

A meta-analysis study showed that HFNC has a good predictive outcome ability, with high variance in time of assessment and cut off points. Although cumulatively proven to have a good predictive ability (sAUC: 0.81, sensitivity: 70%, specificity: 79%), there were wide variance of optimal cut-offs (3.63–3.99 ng/ml) and

TABLE 2
Cut-off Values, Sensitivity, and Specificity of ROX Indexes and SP-D to Predict HFNC Outcome

Variables	Cut-off	Sensitivity (%)	Specificity (%)
ROX Index			
1 hour	3.85	63.16	66.67
2 hours	3.90	68.42	66.67
6 hours	3.82	73.68	75.00
12 hours	3.99	68.42	66.67
24 hours	3.63	84.21	83.33
SP-D	1.14	84.20	83.30

time of assessments (1 to 24 hours) found in previous studies. Various potential confounding factors such as publication bias, comorbidity (diabetes, hypertension, heart disease), and subject characteristics (age, gender) were not found to cause these variabilities.[5] However, population difference is a potential confounding factor that can be further studied with an increasing number of studies in various populations. Future studies with a larger and more diverse population can contribute to a better understanding of ROX index predictive ability of HFNC outcome.

This study found higher serum SP-D values in patients with successful HFNC outcomes. This study is the first to analyze serum SP-D values and HFNC outcomes in COVID-19. A previous study showed higher SP-D values in COVID-19 patients with a worse clinical outcome, such as ARDS.[6] This finding is suggested to be related to the protective effect of SP-D. SP-D is known to be released by type II alveolar cells. Increased alveolar vascular permeability allows alveolar SP-D to be released to systemic circulation. SP-D contributes to various immune functions involving alveolar macrophage and dendritic cells, such as agglutination and opsonization of various microbes. In COVID-19, SP-D production increases in response to the pulmonary SARS-CoV-2 virus. This increase in production, accompanied by increased alveolar vascular permeability caused by the inflammatory condition, increased serum SP-D values in COVID-19.[7]

COVID-19 patients treated with HFNC are already in severe or critical clinical conditions. In these patients, serum SP-D values were similarly high in relation to high pulmonary viral load. High viral load and perialveolar inflammation resulted in high serum SP-D values.[10] In this study, patients with successful HFNC outcomes have higher SP-D values. This finding can be attributed to the more severe destruction of type II alveolar cells in patients with failed HFNC outcomes, which resulted in lower overall SP-D production. Higher SP-D production also helps with pulmonary immune function, which leads to a better clinical course in patients with successful HFNC outcomes.

The limitation of this study is the exclusion of smoking status and smoking history, both of which can influence the outcome and SP-D levels of the subjects. Further study with serial SP-D measurements must be conducted to know the correlation between SP-D values and the clinical course of COVID-19 patients with HFNC. Further multicenter study with a more significant number of samples is also necessary to conclude the most optimal time of assessment and cut-off value of ROX index to predict HFNC outcome.

CONCLUSION

This study showed a significant association between ROX index, SP-D values, and HFNC outcome in COVID-19 patients. This study also showed significant HFNC outcome predictive ability of ROX index in COVID-19 patients.

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Original Article

Relationship between Serum Albumin Levels and Pulmonary Edema in Glomerulonephritis Patients

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Abstract

Background : Glomerulonephritis is an inflammatory disease of the glomerulus that causes changes in permeability, changes in kidney's structure, and function of the glomerulus. Hypoalbuminemia in glomerulonephritis can decrease oncotic pressure resulting in extravasation of fluid into the interstitium. In severe hypoalbuminemia, extravasation of fluid can result in pulmonary edema. The subjective of this study was to analyze the correlation between serum albumin and the incidence of pulmonary edema by chest x-ray in patients with glomerulonephritis.
Methods : The samples of this study were collected by purposive sampling using secondary data from the medical records of Dr. Kariadi Hospital in Semarang with a total of 46 subjects from January 2016–January 2021. The serum albumin was categorized as normal if serum albumin was >3,5 g/dL, mild hypoalbuminemia if serum albumin was 2.5–3.5 g/dL and severe hypoalbuminemia if serum albumin was <2.5 g/dL.
Results : Mann Whitney test showed a significant relationship between between serum albumin and the incidence of pulmonary edema by chest x-ray in patients with glomerulonephritis (p = 0.016). A higher mean rank was found in patients with pulmonary edema compared to patients without pulmonary edema.
Conclusion : There is a significant relationship between serum albumin and the incidence of pulmonary edema by chest x-ray in patients with glomerulonephritis. Patients with lower serum albumin have a greater tendency to develop pulmonary edema than patients with higher serum albumin.

Keywords : Chest X-Ray; Glomerulonephritis; Serum Albumin; pulmonary edema; Serum albumin

INTRODUCTION

Glomerulonephritis is an inflammatory disease of the glomerulus that causes changes in permeability, changes in kidney's structure, and function of the glomerulus. Kidneys have a vital function to regulate the volume and regulate chemical composition of blood by selectively excreting metabolic wastes and water. Therefore, if there is an abnormality, it can cause abnormalities in the volume and composition of blood and body fluids.

Classification of glomerulonephritis based on its etiology, divided into primary glomerulonephritis and secondary glomerulonephritis. Based on the histopathological lesion, glomerulonephritis is divided into non-proliferative and proliferative glomerulonephritis. Glomerulonephritis which included in the non-proliferative glomerulonephritis are minimal lesion glomerulonephritis, focal segmental glomerulosclerosis, and membranous glomerulonephritis, Which are often found with clinical manifestations of nephrotic syndrome. Meanwhile, proliferative glomerulonephritis includes proliferative membranous glomerulonephritis, crescentic glomerulonephritis, and mesango-proliferative glomerulonephritis.

Data from the Indonesian Nephrology Association (Pernefri) shows that glomerulonephritis is the cause of end-stage kidney disease undergoing hemodialysis with an incidence of 39% in 2000. Pulmonary edema that causes the sudden accumulation of fluid in the interstitial tissue and alveoli of the lungs. It is due to its high intravascular pressure or the increased permeability of its capillary membranes (non-cardiogenic pulmonary edema). That causes rapid extravasation of the liquid. Then a gradual change in respiration in the alveoli causes hypoxia.[5]

The incidence rate of primary glomerulonephritis worldwide ranges between 0.2–2.5/100.000 people/year. Glomerulonephritis IgA nephropathy is the most common type obtained by adults, as much as 2.5/100.000 people/year. For children, glomerulonephritis minimal type change disease has the highest incidence, 2/100,000 people/year. The primary and secondary glomerulonephritis incidence rate in the U.S is 57 and 134/100,000 people/year.[6]

Data on the epidemiology of glomerulonephritis in Indonesia is still very little. Several hypertension and kidney centers aim to report their study and becomes a report of every hypertension and kidney center. The study by Himawan S. *et al*. in Jakarta reported based on 729 renal biopsies of nephrotic syndrome patients, 276 cases (48.9%) were glomerulonephritis of minimal change type. Proliferative mesangial type glomerulonephritis and focal segmental glomerulosclerosis reported 81 (14.4%) and 62 cases (11%). From the data obtained, 36.5% showed manifestations of clinical nephrotic syndrome. 19.2% acute nephrotic syndrome, 3.9% rapid progressive glomerulonephritis, 15% with hematuria, 19.3% proteinuria, and 6.8% hypertension.[7]

This study aims to examine more deeply and find out about correlation between serum albumin and the incidence of pulmonary edema by chest x-ray in patients with glomerulonephritis at Dr. Kariadi Hospital Semarang

METHODS

The study was conducted after obtaining ethical approval and ethical clearance in the form of ethical clearance number 125/EC/KEPK/FK-UNDIP/IV/2021 from the Medical Health and Research Ethics Commission (KEPK) Faculty of Medicine, Diponegoro University.

This study was conducted with an analytic type of observational research. The design used was cross-sectional. The research location was in the Medical Record Installation section of RSUP Dr. Kariadi Semarang, during June 2021–July 2021. Inclusion criteria include: Glomerulonephritis patient age ≥18 years. They were female and men with proteinuria and hematuria. They performed a chest x-ray and serum albumin test. All patients were recieved the same therapy, with the same drug doses, and duration of therapy during therapy on the ward. The exclusion criteria were secondary glomerulonephritis patients due to multiple myeloma, Hodkin's lymphoma, other malignant diseases. Also, glomerulonephritis patients who had diabetes mellitus and a chronic renal failure concomitant disease.

The consecutive sampling method was to take samples where the data was available, and the criteria met were then inputted into the research until the subject needed was appropriate. According to the large formula of samples in the cross-sectional design, 46 samples as a minimum sample size. The serum albumin was categorized as normal if serum albumin was >3.5 g/dL, mild hypoalbuminemia if serum albumin was 2.5–3.5 g/dL and severe hypoalbuminemia if serum albumin was <2.5 g/dL.

The data that had been collected was analyzed using electronic statistical applications. Hypothesis testing in this study used the univariate test for descriptive data of each variable and the bivariate test in the form of the Chi-Square correlation test and Mann Whitney test, which showed a significant relationship if p-value <0.05.

RESULTS

The samples studied were glomerulonephritis patients who were receiving treatment at RSUP Dr. Kariadi Semarang. The number of male patients was 33, and the number of female patients was 13. References from the

study by Akirov *et al*.[8] divided hypoalbuminemia into mild hypoalbuminemia (2.5–3.5 g/dL) and severe hypoalbuminemia (<2.5 g/dL). The sampling used was consecutive. It means that this study included all medical record with selection criteria until the required sample size reached the minimum sample size for this study has been met.

TABLE 1
Characteristic Distribution of Research Subjects

Variables	F	%
Age		
18–33	30	65.2
34–49	8	17.4
50–65	7	15.2
≥66	1	2.1
Gender		
Male	33	71.7
Female	13	28.3
Glomerulonephritis		
Acute	26	56.5
Chronic	20	43.4
Serum albumin		
Hypoalbuminemia	42	91.3
Mild (2.5–3.5 g/dL)	9	21.4
Severe (<2.5 g/dL)	33	78.6
Normal	4	8.7
Pulmonary Edema		
Yes	35	76.1
No	11	23.9

According to the Table 1, the subjects studied are most in the range of 18–33 years (65.2%), where the youngest is 18 years, and the oldest is 68 years. The most studied subjects were male, namely 33 patients (71.7%), while female were 13 patients (28.3%).

According to the Table 1, 42 patients experienced hypoalbuminemia (91.3%), nine patients had mild (21.4%), and 33 patients had severe (78.6%), and four patients had normal albumin levels (8.7%) and there were 35 (76,1%) glomerulonephritis with pulmonary edema.

According to the Table 2, Mann-Whitney test showed a significant relationship beetwen incidence of pulmonary edema and serum albumin in glomerulonephritis patients, with p=0.016 (p < 0.05). It can be concluded that there is a significant relationship between pulmonary edema and serum albumin in glomerulonephritis patients in RSUP Dr. Kariadi Semarang in January 2016–January 2021.

From the mean rank above, it was also found that pulmonary edema (25.61) had a higher mean than non-pulmonary edema (16.77). Since the codes used for the statistical test were: normal (1), mild hypoalbuminemia (2) and severe hypoalbuminemia (3), higher rank indicate lower serum albumin. Thus, glomerulonephritis patients with lower serum albumin tend to have a higher tendency of pulmonary edema compared to patients with higher serum albumin.

DISCUSSIONS

According to medical records data studied in January 2016–January 2021, there were 46 glomerulonephritis patients. Most research subjects were from the 18–33 year-old group of 30 patients (65.2%). At the same time, the most gender percentage was male, 71.3% (33 patients).

Furthermore, the results also found that the incidence of pulmonary edema in glomerulonephritis patients was 35 patients (76.1%). It also obtained 42 patients with hypoalbuminemia (91.3%). Nine patients had mild hypoalbuminemia (21.4%), and 33 patients had

TABLE 2
Result of Correlation Test Between Serum Albumin and Pulmonary Edema

Variables	Pulmonary Edema				p value
	Yes		No		
	n	%	n	%	
Normoalbumin	1	25.0	3	75.0	0.016*[M]
Mild Hypoalbuminemia	6	66.7	3	33.3	
Severe Hypoalbuminemia	28	84.8	5	15.2	
Total	35	76.1	11	23.9	

*Significant [M]Mann-Whitney; Mean rank pulmonary edema 25.61; Non pulmonary edema 16.77

severe hypoalbuminemia (78.6%) and 4 patients had normal albumin levels (8.7%).

Based on the Mann-Whitney test between serum albumin and the incidence of pulmonary edema, it was found that the correlation level between these variables was significant ($p = 0.016$: $p < 0.05$). It is in line with that done in 2005 by Sudung O. Pardede *et al*.[9] In acute glomerulonephritis, patients found 87% of patients with clinical manifestations of edema and 14% of patients with pulmonary edema radiology. It follows Starling's laws, where several things, namely vascular permeability, influence the transfer of fluid from intravascular to interstitial space. Some pressures, such as intravascular hydrostatic, interstitial space hydrostatic, intravascular oncotic, and interstitial space oncotic.[10] Thus, hypoalbuminemia is the cause of pulmonary edema. This condition lowers the oncotic pressure in the blood so that intravascular fluid moves into the interstitial.[5] Thus, the condition of hypoalbuminemia is a cause of pulmonary edema because this condition lowers the oncotic pressure in the blood so that intravascular fluid moves into the interstitial.

Research conducted by Hassan *et al*. in 2005[11] also revealed that Pulmonary edema is associated with the accumulation of excess extracellular fluid after impaired excretion of fluids and solutes. Under normal conditions there is an exchange of fluids, colloids and solutes from the blood vessels into the interstitial space. Pulmonary edema occurs when there is a shift of fluid from the blood into the interstitial spaces or into the alveoli that exceeds the amount of fluid returned to the blood vessels and fluid flow to the lymphatic system.[12]

In this study, it was also found that glomerulonephritis patients with higher serum albumin had a lower tendency to develop pulmonary edema than glomerulonephritis patients with lower serum albumin. This is in accordance with the research of Feng Li *et al*. in 2015 who conducted a study with 220 hypoalbuminemia patients and this study stated that serum albumin was associated with the severity of disease and prognosis in hypoalbuminemia patients with pulmonary complications. In this study, it was found that the mortality rate increased by 89% with a decrease in serum albumin of 1 g/dL.[13] In a study conducted by Akirov *et al*. also stated that the lower the patient's serum albumin, the longer the length of stay in the hospital.[8] Likewise with the study by Bassoli *et al*. which found a negative correlation between serum albumin and disease severity with $p<0.0001$. This study also stated that in inflammatory conditions transcapillary leakage can occur which is stimulated by an increase in interleukin-2, interferon and interleukin-6. Damage to the vascular endothelium results in leakage of albumin into the interstitial space of the lung.[14]

However, our study's limitation is that the study was conducted with secondary data using medical records of patients with glomerulonephritis.. This study also only took chest X-ray samples and serum albumin at one time, namely when the first examination of the patient was performed. The cross-sectional method limited our study to analyze the correlation between serum albumin and the incidence of pulmonary edema after therapy. In this study also did not use other laboratory data such as protein, ureum, and serum creatinine.

CONCLUSION

There is a strong relationship between serum albumin and pulmonary edema in glomerulonephritis patients and in patients with severe hypoalbuminemia (serum albumin < 2.5 g/dL) have a greater tendency to develop pulmonary edema.

In future studies, researchers suggest using more variables to get better and more reliable results. Future research is necessary to do further research by considering the involvement of other factors that can affect the condition of pulmonary edema in glomerulonephritis such as hypertension, ureum, and serum creatinine.

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Original Article

Relationship of Serum Hemoglobin and Vitamin D Levels with Postural Balance

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Abstract

Background : The population of the elderly in Indonesia has increased significantly in recent years. The incidence of falls is influenced by postural balance. Vitamin D and hemoglobin deficiency are associated with decreased muscle function and postural balance. This study is to investigate the relationship between vitamin D and hemoglobin levels with postural balance in the elderly.
Methods : The study used a cross-sectional design with the participation of 33 patients (aged 64.94±5.42 years). The study sample was elderly individuals who fulfilled the inclusion criteria at Semarang Elderly Posyandu. Patients performed postural balance test, with Sharpened romberg and tandem gait test. The examination of vitamin D and hemoglobin was taken from the patient's venous blood. Vitamin D was measured using ELISA.
Results : The results of the independent sample t-test analytic test revealed a P value of vitamin D (0.007) and a P value of hemoglobin of (0.021) ($p<0.05$). There is a meaningful relationship between vitamin D and hemoglobin levels with postural balance in the elderly.
Conclusion : Decreasing Haemoglobine and Vitamin D impair the postural balance.

Keywords : Haemoglobine, Postural balance, vitamin D

INTRODUCTION

In recent years, the number of elderly people in Indonesia has increased significantly. According to the Indonesian Central Bureau of Statistics in 2020, the elderly in Indonesia have touched 9.92% of the entire Indonesian population or around 26.82 million people, an increase of 0.32% (1 million people) from the previous year.[1]

The incidence of falls in the elderly is caused by two things, which are intrinsic factors and extrinsic factors. Intrinsic factors such as vision, hearing, neuromuscular and extrinsic factors such as tripping, slipping, and falling due to loss of balance as well as elements that are not directly related include the help of environmental factors in seeing the surroundings (example: indoor light intensity), and safety equipment.[2]

The incidence of falls in the elderly is due to intrinsic factors, one of which is a disorder of the limb system. Limb system disorders such as muscle wasting and osteoporosis provide complications in the form of postural balance disorders. Physical activity plays a role in maintaining postural balance. In the literature proposed by Habut, M. Y. *et al* that a person who has strenuous physical activity has good postural balance.[3]

Included in any of the geriatric syndromes, postural balance disorder is defined as the inability to integrate sensory input and determine body oscillations in an upright position while simultaneously maintaining balance.[5,6]

Low hemoglobin levels contribute to a variety of adverse health outcomes, including not only decreased muscle strength, but also impaired walking; increased fatigue, anxiety, and depression; and decreased quality of life in the elderly.[7–11] Iron deficiency has a substantial effect on muscle function, oxidative energy metabolism, immunity, and the nervous system.[12,13]

Vitamin D (calcitriol) or 1,25-dihydroxyvitamin D3 (1,25 (OH) 2D3) is a major hormone that regulates the homeostasis of calcium phosphate and bone mineral metabolism. Some literature mentions that vitamin D is implicated in the regulation of the immune system, cardiovascular system, oncogenesis, and cognitive function. Low serum levels of vitamin D are associated with decreased muscle strength and physical function. Previous studies have shown that increased muscle strength and decreased body sway in response to vitamin D can reduce the incidence of falls. Vitamin D levels in the body are measured by knowing the concentration of serum 25(OH) vit D levels. Vitamin D that enters the body and is produced cutaneously is converted to 25 (OH) vit D, but in serum only a fraction of 25 (OH) vitamin D is converted to 1,25 (OH) 2 vitamin D. Thus measuring serum 25 (OH) vitamin D levels is the best test to assess vitamin D stores. The researcher's aim is to determine whether there is an association between vitamin D levels, hemoglobin, and balance disorders in the elderly to establish a basis for future clinical intervention trials.

METHODS

Descriptive analytical studies with case control. A total of 33 respondents aged 60 years or older were at the Posyandu of Kalipancur Village in Semarang City for the period September November 2021. This research has received approval from KEPK No.282/EC/KEPK/FKUNDIP/XII/2020. History of diseases issued by respondents that affect postural balance such as Parkinson's disease, stroke, seizures, epilepsy; the presence of motor neurological deficits such as paresis or orthopedic problems such as amputations and critical osteoarthritis; intake of sedatives; taking vitamin D supplements.

As a postural balance test, a modified Romberg test (SR = Sharpened Romberg) and a tandem gait test were performed. SR requires that the subject stand in a tandem position (heel to toe), first with eyes open and then with eyes closed while the examiner observes body shake or the subject's inability to maintain position. A Tandem gait test was conducted with respondents asked to fold their arms on their chests and walk as fast as possible along 5 m then turn back to their original place. Respondents walked in a pattern of heel-to-toe steps on ribbons or ropes. Results were unbalanced for the tandem gait test when the subject went off the track. For the Romberg test when the subject moves from a standing place. It is said to be unbalanced if the results of both tests of the subject cannot maintain postural balance or one of the two tests cannot maintain postural balance.

Blood samples were taken from the respondents' venous blood. Blood was taken for measurement of hemoglobin and vitamin D. The serum 25 (OH) D level was measured using the ELISA method. Statistical analysis was done by computer using a data analysis program. The normality of the data was verified using Shapiro-wilk, then tested for the descriptive statistics and then analysed using the Independent-t test and the non-significant data was continued with the Mann-Whitney test. The outcome is meaningful if the value of $p<0.05$ is obtained.

RESULTS

Based on Table 1, out of 33 respondents, all respondents were elderly at the Kalipancur Elderly Posyandu, Semarang City, where 8 (24.2%) respondents were male and 25 (75.8%) other respondents were female. Respondents aged 60–74 years were 29 (87.9%) and respondents aged 75–90 years were 4 respondents (12.1%). Respondents who have the results of balanced 27 (81%) and unbalanced 6 (19%) on the balance test results.

TABLE 1
Characteristics of the subject (Age, Hemoglobin, Vitamin D, Balance test results)

Variable	Average (SD)
Age (year)	64.94±5.42
Hemoglobin (gr/dl)	12.71±1.50
25 (OH) D (ng/ml)	21.73±4.89
Sex type	
Man	8
Woman	25
Balance posture	
Balanced	27
Not balanced	6

TABLE 2
Result vitamin D level and hemoglobin

Variable	Balance posture	Non balance posture	P-value
Vitamin D level	16.03±4.89	10.63±0.29	0.007
Hemoglobin	12.71±1.50	11.90±0.58	0.021

From the results obtained from the independent sample t-test analytical test, the P value designated by Sig (2-tailed) is 0.007 ($p < 0.05$) from this it can be said that there is a meaningful relationship between vitamin D levels and postural balance in elderly. From the results of the independent sample t-test analytical test, the P value designated by Sig (2-tailed) is 0.021 ($p < 0.05$), it can be said that there is a significant relationship between hemoglobin levels and postural balance in the elderly.

DISCUSSION

The study was screened first. Among 60 respondents who have been tested with a health questionnaire, there were 33 respondents who met the inclusion criteria from the Kalipancur Elderly Posyandu, Semarang City. Statistical test of relationship between vitamin D levels with postural balance obtained p value = 0.007 ($p < 0.05$) it shows there is a significant relationship between vitamin D levels with postural balance in the elderly. This is in accordance with the research hypothesis that there is a relationship between vitamin D levels and postural balance in the elderly. These results show the suitability of research that has been conducted by Akdeniz *et al* where in the study it was found that respondents with serum 25 (OH) D levels higher than 50.0 nmol / l in women aged 60 years and over experienced significantly better improvements in patients in postural balance, gait, chair stand performance and Short Physical Performance Battery (SPPB).[21–23]

The correlation statistical test between hemoglobin and postural balance obtained a value of $p = 0.021$ ($p < 0.05$), it shows that there is a significant relationship between hemoglobin and postural balance of the elderly. Research published by Zakai, *et al* mentioned that a decrease in blood hemoglobin levels up to 0.4 g/dl can increase the risk of morbidity and mortality of the elderly. A decrease in hemoglobin can represent the development of new diseases, such as cardiovascular disease, kidney disease, or inflammation in the elderly. Inflammation that occurs in the elderly has adverse effects on physical function. According to research conducted by Cesari, one of the symptoms of anemia is fatigue. This causes the most problems and limitations in physical function in the elderly. Another research mentioned that the decreased hemoglobin affects its deliveries to the skeletal muscles, thus disrupting the performance of the muscles. [24,25]

Research published by Nakamura, *et al* mentioned that Vitamin D levels are not longitudinally associated with impaired postural sway in older women. Mean subject age and serum 25(OH)D levels were 73.3 years (SD 3.7) and 61.0 nmol/L (SD 16.9), respectively. No significant association was found between 25 (OH) D

levels and changes in postural sway velocity (adjusted P for trend=0.72). Women with 25 (OH) D <30 nmol/L tended to have lower Δpostural sway velocity than those with 25(OH)D ≥30 nmol/L (mean, -0.59 vs 0.37 cm/s, respectively; adjusted P=0.13).[26]

The limitation of this research is that vitamin D supplementation has not been given so it is not known whether vitamin D supplementation will affect postural balance.

CONCLUSION

In conclusion, the researchers found a significant relationship between the postural balance with the levels of vitamin D and hemoglobin in the elderly. Explanatory mechanisms regarding the relationship between vitamin D and hemoglobin levels of patients with postural balance can be used as future research.

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Original Article

The Effect of Effleurage along with Moisturizing Application on Skin Elasticity

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Abstract

Background : A decrease in skin elasticity is a problem often complained of, especially by women. Changes in some of the structure and elasticity of the skin occur with age as a result of reduced production of natural oils and skin collagen. There are several ways to increase skin elasticity, including by stimulating collagen. One of them is by using topical skin care such as using a moisturizer that suits skin type. This study intends to determine the effect of effleurage in the application of moisturizer on skin elasticity.
Methods : The research design was a randomized controlled-trial with two groups pre and posttests conducted on 30 students of the Physiotherapy Department Surakarta randomly selected and divided into two groups. The treatment group applied moisturizer to the skin using the effleurage technique, while the control group applied only moisturizer. The groups were intervened for two weeks. Skin elasticity was measured using the EH-900U skin analysis system.
Results : The Pre-Posttests of group one's skin elasticity with the Paired Samples T-Test yielded a p value = 0.013, which means that there is an effect of effleurage in applying moisturizer on skin elasticity. The Pre-Posttests of group two's skin elasticity with the Wilcoxon Test yielded a p value = 0.551, which means that there is no effect of topical moisturizer on skin elasticity. There were significant differences in the treatment and control groups.
Conclusion : The application of moisturizer along with effleurage for skin elasticity is more robust than applying only topical moisturizer.

Keywords : Effleurage, Moisturizer, Skin elasticity

INTRODUCTION

The skin is the largest organ of the body and has a very important role. The skin is the outermost organ and covers the entire surface of the body with an area of approximately 600 m2 and a weight between 2700 grams to 3000 grams.[1] The thinnest skin is located on the eyelids while the skin on the soles of the feet is the thickest part with a thickness of up to 0.6 cm.[2] In addition to its functional role as a protector, the skin is also a "determining factor" of one's appearance in terms of one's aesthetics or beauty.[3] The beauty of the skin has a psychosocial role in a person's life, especially women. With this very important role, skin care is absolutely a concern because if the skin has problems, it will have a very big impact on self-confidence and appearance.[4]

One problem that often arises is decreased skin elasticity, namely the skin's ability to stretch and return to its normal state. Skin elasticity in young adults is better than in old adults.[5] This is related to the thickness of the dermis where the dermis layer is thinning in older people. Several factors cause the skin to lose its elasticity, including: age, genetics, UV exposure, stress and diet.[6]

As people get older, there are changes in some of the structure and elasticity of the skin as a result of reduced production of collagen and the skin's natural oils. This can be exacerbated by exposure to accumulated irritants such as UV exposure, stress and diet. This causes the skin to thicken, dry to sores.[7] There are several ways to increase skin elasticity, including by stimulating collagen or preventing inflammation that leads to the breakdown of structural proteins in the skin.[8] One of them is by using topical skin care such as using a moisturizer according to skin type.[9]

The applications of skin moisturizer in the form of lotion is expected to be done properly and correctly to get maximum effect. One of its applications is the massage technique in the form of an effleurage technique.[10] Massage effleurage is able to yield effect to the skin. Massage effleurage has the effect of releasing adhesions and removing small thickenings in the tissue located under the skin so absorption can be improved.[11] For that reason, researchers are interested in conducting research studies related to the effect of effleurage in applying moisturizer on skin elasticity.

METHODS

This research is a two groups pre and post test design, involving subjects divided into two groups, and measurements taken before and after treatment administration. The first group as the treatment group applied moisturizer (Kaila hand and body lotion) to the skin of each arm using effleurage technique while the second group as the control group applied topical moisturizer to the skin of each arm.

The research was conducted from August to September 2022 at the Physiotherapy Department, Health Polytechnic, Ministry of Health, Surakarta. The subjects were randomly allocated. The subjects involved female students who meet the criteria. The inclusion criteria were female aged 25–30 years who had no allergies to moisturizers and were willing to participate in the study. The drop out criteria involve having hypersensitivity, and unable to join the program for 3 times in a row. The independent variable is effleurage while the dependent variable is skin elasticity.

Effleurage is a light massage using palms and moisturizing cream applied on the arms starting from the bottom to the top. Skin elasticity is a measure of the skin's ability to stretch and return to its normal shape. The measuring instrument uses the EH–900U skin analysis system.

The total subjects consisting of 30 participants divided into 2 groups. The first group received the effleurage intervention and topical moisturizer to the arm skin for 5 minutes. The second group received only topical lotion to the arm skin. The intervention was carried out 2 times a day for 2 weeks. The skin analysis tool was employed to examine the skin elasticity level. Ethical clearance with number 4288/B.1/KEPK-FKUMS/VI/2022 was obtained from the Health Research Ethics Commission, Faculty of Medicine, University of Muhammadiyah Surakarta.

SPSS was employed to process and analyze research data. The subject characteristics based on age distribution, and skin elasticity values before and after treatment are presented. Normality test was conducted with Shapiro Wilk. The first group's data was normally distributed ($p>0.05$) so hypothesis analysis used a parametric test, while the second group's data was not normally distributed ($p<0.05$), so the hypothesis analysis used a non-parametric test. The Paired T-Test was used for analysis of different tests before and after intervention in the first group, while the Wilcoxon Test was used in the second group with.

RESULTS

A total of 30 female graduate students at the Physiotherapy Department of Health Polytechnic of the Health Ministry were recruited and allocated in 2 groups (Diagram 1). The age range of the subjects was 25–30 years. The average age of the first group is 26 years, while that of the control group is 25 year.

The average value of skin elasticity before and after treatment in the first group were 33.8 and 42.87 respectively (Figure 1 and Table 1). The average value of skin elasticity before and after treatment in the second group were 40 and 37 respectively (Figure 2 and Table 1).

Statistical analysis begins with a prerequisite test, namely the data normality test. The number of subjects is

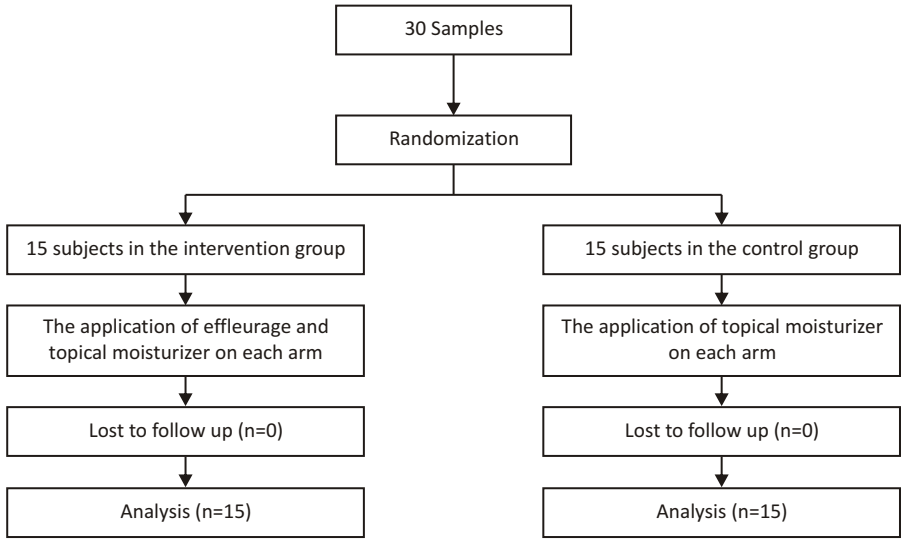

Diagram 1. Consort Diagram

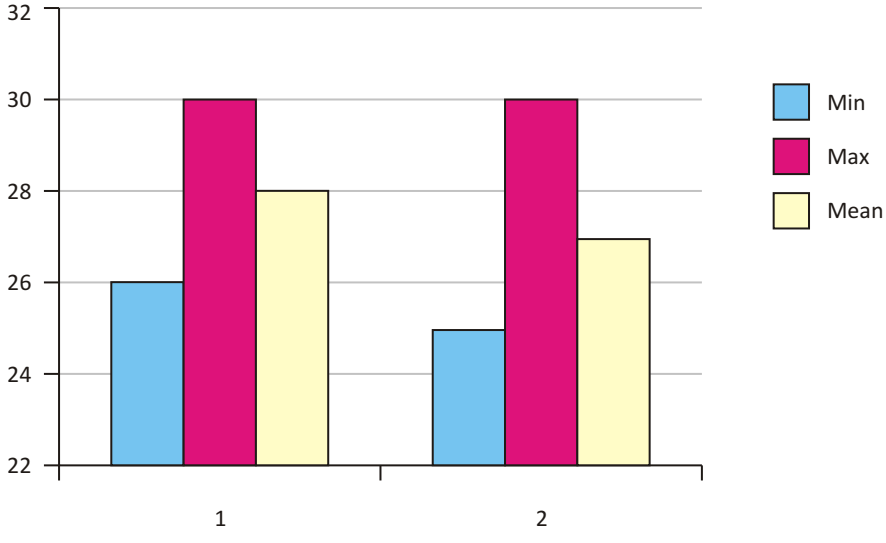

Figure 1. Data distribution of research subjects based on age (1 = intervention group; 2= control group)

30 so Shapiro Wilk was employed for data normality testing. The first group's data was normally distributed ($p>0.05$), while the second group's data was not normally distributed ($p<0.05$) (Table 2).

Homogeneity test with Levene's test aims to determine the distribution of research subject data in each group. The results of the homogeneity test with a p value > 0.05 means that the distribution of moisture and elasticity values between the first and second groups is equally distributed (Table 3).

Paired samples t-test of the first group shows $p <0.05$ which means that there is difference elasticity value between before and after treatment (Table 4).

The Wilcoxon test in the second group shows $p > 0.05$ which means that there is no different elasticity value between before and after treatment (Table 5).

DISCUSSION

This study found that the group given moisturizing treatment with effleurage showed more significant changes compared to the group that was only given topical moisturizer.

Effleurage on the skin can also increase elasticity so that the skin will look younger. Massage using the effleurage technique can improve texture, wrinkles, and sagging skin. Effleurage is believed to help bring oxygen to the area.[12] Effleurage in the form of a structured series

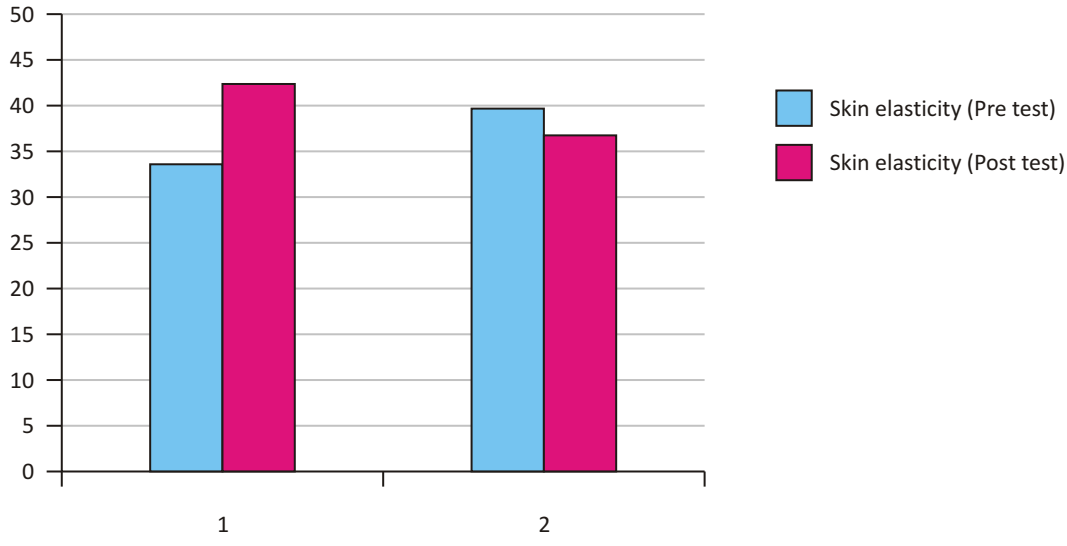

Figure 2. Data distribution of averaged skin elasticity before and after intervention

TABLE 1
Decribtive statistik of pre and posttests

	N	Minimum	Maximum	Mean	Std. Deviation
Group 1					
Pretest	15	25	48	33.80	5.735
Posttest	15	28	64	42.87	10.743
Valid N (listwise)	15				
Group 2					
Pretest	15	31	60	40.07	8.447
Posttest	15	27	61	37.80	7.930
Valid N (listwise)	15				

TABLE 2
Normality test

	Kolmogorov–Smirnov[a]			Shapiro–Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pretest						
Group 1	.153	15	.200*	.932	15	.294
Group 2	.263	15	.006	.852	15	.019
Posttest						
Group 1	.169	15	.200*	.912	15	.147
Group 2	.191	15	.147	.851	15	.018

TABLE 3
Homogeneity test

Pretest	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Equal variances assumed	1.953	.173	-2.377	28	.025	-6.267	2.636	-.867	-.867
Equal variances not assumed	.263	15	-2.377	24.644	.026	-6.267	2.636	-.833	-.833

TABLE 4
Paired samples t-test of the first group

Pair 1	Paired Differences							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
Pre – Posttest	-9.067	12.314	3.179	-15.886	-2.247	-2.852	14	.013

TABLE 5
Wilcoxon test of the second group

	Posttest – Pretest
Z	-.597[b]
Asymp. Sig. (2-tailed)	.551

of touch and/or hand pressure on the soft tissues of the body stimulates sensory receptors and subcutaneous tissue in the skin.[13] The effleurage massage technique improves local circulation and reduces dryness of the skin.[14]

Effleurage technique can promote blood circulation and increase metabolic processes. The effect resulting from massage can help accelerate the absorption of moisturizer into the skin so that it improves skin health and restores facial elasticity.[15]

CONCLUSION

Analysis of the research data found that the application of effleurage along with moisturizer improves skin elasticity. For further research, there is a need to control the activity and several areas of the subject's body. The application of interventions in research subjects is better not only on the skin of the arms but several other parts of the body that are often exposed to sunlight.

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Case Report

Palliative Care Case Report: A Man with End Stage Lung Cancer with Brain Metastases

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Abstract

Background : Lung cancer accounts for 13% of malignancies in the world and the most common type of cancer suffered by men in Indonesia. The 5-year survival rate for patients with lung cancer is only 18.1%. About 25–30% will develop brain metastases. Overall palliative care is needed including biologically targeted therapy, chemotherapy, stereotactic radiosurgery (SRS), surgery in selected cases, and whole brain radiotherapy treatment (WBRT). Rare studies that take into account surgical palliation in advanced NSCLC. It has been demonstrated that metastaticectomy generally improves survival and, in some patients, even long-term survival.
Case Report : A 65-year-old male patient with Non-Small Cell Carcinoma favor Lung Adenocarcinoma and cerebellum metastases. The patient underwent surgery to remove a brain tumor. The patient received 8 radiotherapies and Erlotinib chemotherapy for 4 cycles for 6 months. The dose of Erlotinib 150g/24 hours was used in the first month. The dose was reduced in the 2nd to 6th month to 100g/24 hours. Assessment of palliative care was carried out using the Karnopsky Questionnaire, Fatigue Severity Scale (FSS), and Palliative Performance Scale (PPS).
Conclusion : Despite major improvements in the way lung cancer patients are treated in recent years, morbidity and death rates are still high. Palliative care (PC) is an approach to treating patients with life-threatening diseases, one of which is lung cancer.

Keywords : Brain Metastases, Lung Cancer, Palliative Care

INTRODUCTION

Lung cancer is one of the most common malignancies worldwide, accounting for 13% of all cancer cases. Lung cancer also causes 1/3 of all cancer-related deaths in men. By 2030, there will be an estimated 26 million deaths from lung cancer.[1] In the United States, lung cancer was the leading cause of cancer-related deaths, with a prevalence of 25.9% of all cancer-related deaths in 2017.[2]

According to data from the World Health Organization (WHO), the most common type of cancer found in men in Indonesia is lung cancer, which is the fifth most common cancer in women.[1] Based to the 2018 Riskesdas, the prevalence of cancer in Indonesia increased from 1.40% in 2013 to 1.79% in 2018. Indonesia experienced an increase in the number of cancer cases from 2013–2018, namely from 1.4–1.8 per mil. The province with the most cases of permil is the province of the Special Region of Yogyakarta, namely 4.9 permil in 2018.[3]

Lung cancer can take many forms, ranging from asymptomatic or minimally symptomatic disease with a mild burden and/or moderate progression to aggressive and rapidly progressing disease with severe symptoms. Survival rates and quality of life tend to be worse in patients with advanced lung cancer who experience more severe symptoms.[4] Symptoms of lung cancer include pain, nausea, dyspnea, fatigue, anorexia/cachexia, depression, and confusion/delirium.[5] Due to the high prevalence and symptom burden of the disease, the impact of palliative care on lung cancer patients has attracted a great deal of research attention in recent years.[6]

Currently, the anticipated 5-year survival rate of patients with lung cancer is only 18.1%. Even for patients with stage 1 Non-Small Cell Lung Cancer (NSCLC), the 5-year overall survival rate is 73–90%, whereas for patients with stage 4 NSCLC, it is only 0–10%.[7] A meta-analysis involving more than 5,000 patients with lung cancer showed that the median survival time of patients not receiving antineoplastic treatment was approximately 7 months.[8] Although the incidence and mortality of lung cancer are declining, the prevalence remains high, with more than 500,000 patients in the United States currently suffering from this disease. For patients with advanced lung cancer, disease burden, consequences, and side effects of treatment can dramatically reduce quality of life.[9]

Among several types of lung cancer, approximately 7.4% of patients with Non-Small Cell Lung Cancer (NSCLC) will have brain metastases (BM) at the time of first diagnosis and 25–30% will develop brain metastases during the course of their disease. The life expectancy of these patients is poor, with a median survival of only 3.4 months.[10] In addition, many patients lose autonomic impairment due to neurocognitive and functional deficits and morbidity associated with drugs such as steroids and anti-epileptic drugs.[11]

Advances in the ability to study genomes in recent years have driven the concept of personalized medicine based on the molecular classification of oncogenic addictive tumors. The identification of (Epidermal Growth Factor Receptor (EGFR), translocation Reactive Oxygen Species-1 (ROS1), and anaplastic lymphoma kinase-positive (ALK+) has revealed tumor subsets of NSCLC that are responsive to targeted treatment.[12] Concomitantly, the strategies used to treat patients with brain metastases have also progressed. Treatment modalities include biologic targeted therapy, chemotherapy, stereotactic radiosurgery (SRS), case-selected surgery and Whole Brain Radiotherapy Treatment (WBRT). The approach adopted for a particular patient will depend on the performance status, molecular classification of the tumor and distribution intracranial and extracranial diseases.[11]

Substantial evidence supports the adoption of a palliative care approach in patients with lung cancer. Palliative care aims to prevent and relieve suffering by identifying and treating debilitating symptoms early; supporting patients and their families to optimize coping and active living; and addressing physical, psychosocial, and spiritual problems. Most research shows that introducing palliative care at an early stage will give benefit to patients with advanced malignancies, including advanced lung cancer. WHO defines palliative care as a treatment approach designed to improve the quality of life of patients with long-term fatal illnesses and their families by identifying, preventing, and eliminating suffering as early as possible, as well as addressing physical, psychosocial, and spiritual problems. Key features of palliative care include a team-based approach that provides pain and symptom relief, supports patients and their families in optimizing coping and active living, and addresses the psychological and spiritual aspects of care. Palliative care can be provided at any stage of the illness and is used in combination with other treatments designed to cure the disease or prolong survival.[6]

CASE REPORT

A 65 year old male patient visited the hospital polyclinic complaining of a headache. The initial complaint was a month ago with symptoms of spinning sensation, and the felt that this was caused by vertigo because the patient had a history of vertigo. However, at this time, the vertigo did not improve with medication, so the patient decided to receive inpatient care at Telogorejo Hospital, Semarang. Previously, the patient had a history of lung – cancer carcinoma in situ of the Bronchus and Lung, with a histological diagnosis of Non-Small Cell Carcinoma for Adenocarcinoma of the Lung, which was diagnosed in

June 2022. Pathological examination of the anatomy with fine needle aspiration biopsy (FNAB) in 2022 revealed that non-small cell carcinoma favors Lung Adenocarcinoma and continues with EFGR mutation examination. EFGR mutation examination revealed positive mutations in exon 21 (L858R) and exon 20 (S7681). The patient then received erlotinib chemotherapy in six cycles for six months, but in the fourth month, the patient stopped undergoing chemotherapy. In the first month, the erlotinib dose was 150 mg/24 hours. The dose was reduced from the 2nd month to the 6th month to 100g/24 hours.

Paliative Care

The complaints of spinning sensations are not improving, and patients experience nausea and vomiting. This raises suspicion of metastatic lung tumors in the brain. From the patient's family history, it was found that the mother also had vertigo. The patient lives at home with his family and claims to have a jogging hobby. During this period, the patient had a vegetable and fruit diet menu. The patient was a contractor and had built shop bussines. The patient is currently feeling irritated because the disease is not improving and is not recovering, and the patient admits to experience emotional exhaustion, irritability, and despair. The patients also felt that their physical condition was not the same as before. The patient feels that he rarely tells his family about his illness, feels that he does not sleep well, often wakes up in the middle of the night, and cannot go back to sleep. Currently, the patient does not have a wife because the patient's wife has died, and the relationship between the patient and other families is harmonious, judging by the communication between the father and his son, who is also an internist. The patient already knows the neighbors around his house well, because since birth, the patient has lived in that neighborhood and some of his neighbors are still relatives/family members of the patient and often play with their peers near the house.

On physical examination, the general condition of the patient was weak, with composmentis awareness (E4V5M6), body weight 70 kg, which decreased by 5 kg from the previous month, pulse 108 ×/min, RR 22 ×/min, temperature 37.2º C per axillary, SpO2 96 %, and good nutritional status. In generalist status, no abnormalities were found on the head and neck examinations. Examination of the lungs revealed movement of the right chest that was the same as the left on inspection, the same right and left chest fremitus on palpation, sonor sounds in both lung fields on percussion, and vesicular base sounds in both lung fields without any additional sounds on auscultation. Cardiological, abdominal, and extremity examination revealed no abnormalities.

On supported examinations, complete blood count, X-ray, ECHO cardiography, and MRI were performed. From laboratory tests, Hb was 12.8 gr/dl, leukocytes 11,800/ul, platelets 331,000, albumin 3.1 gr/dl, uric acid 2.7 mg/dL, blood sugar 437 mg/dL, and total cholesterol 227 mg. /dL. On ECHO examination, left ventricular hypertrophy (LVH) was observed without enlargement of the other heart chambers. Magnetic resonance imaging (MRI) revealed a cerebellar tumor.

The Hospital Anxiety and Depression Scale (HADS) questionnaire was used to assess palliative parameters, namely, anxiety and depression, with an anxiety score of 0 and a depression score of 6, indicating that the patient did not have anxiety or depression disorders. To assess quality of life, an evaluation was carried out using the Karnopsky Questionnaire with a final score of 80, which indicates that the patient is able to carry out activities and work normally and does not need special assistance. Patients were also assessed using the Fatigue Severity Scale (FSS) with a result of 36 which indicated that the patient was not fatigued. For the parameters of palliative care, patients were examined using the Palliative Performance Scale (PPS) questionnaire, and a 90% result was obtained. This indicates that there are no subjects in the risk group

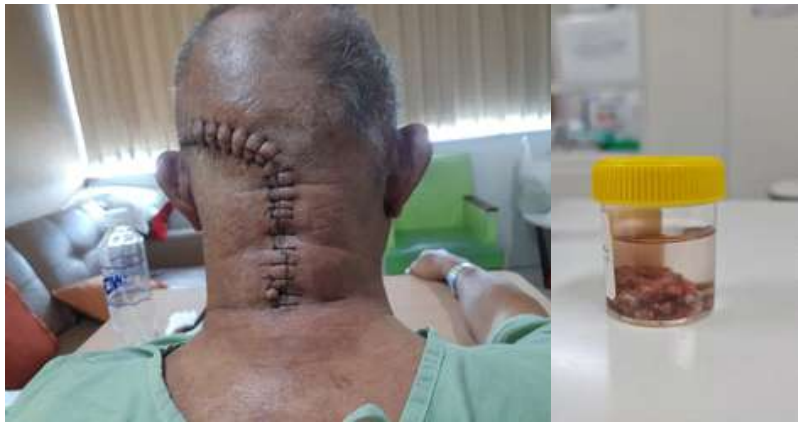

Figure 1. Post surgery and brain metastases specimens

required observation.

Based on the considerations of the palliative team, the patient underwent surgery to remove the tumor (Figure 1). After surgery to remove the tumor, the patient underwent radiotherapy. This therapy was performed by the patient for 1 month, starting on August 17, 2022, with a total of 7 times radiation. After the 8th irradiation, the headache persisted. Currently, the patient is able to perform activities independently. After irradiation, the patient was scheduled to receive a chemotherapy program. The drugs the patient is currently taking are Lapigim (Glimepiride 2 mg and Metformin 500 mg) because the patient has type-2 DM and Gabapentin, Erlotinib Hydrochloride 100 mg. Patients receive palliative care since the diagnosis of cancer is enforced in 2022 in the form of supportive psychotherapy, occupational therapy (patients continue to work while undergoing chemotherapy), clerical assistance, and advance care planning.

DISCUSSION

Lung cancer is characterized by uncontrolled growth of cancer cells in the lung tissue due to malignancy originating from outside the lung or from the lung itself.[13] Uncontrolled growth causes mutations in the essential genes that regulate cell division. Finally, it converts normal cells into cancer cells. Mutations can occur spontaneously or be inherited.[14] Lung cancer often appears hidden and asymptomatic until it reaches an advanced stage. In general, there are currently no suitable screening methods for lung cancer. The recommended screening methods for lung cancer detection are limited to high-risk patient groups. The high-risk group included patients aged >40 years with a smoking history of ≥30 years and who had quit smoking 15 years before the examination, or patients aged ≥50 years with a smoking history of ≥20 years and having at least one other risk factor.[15]

The exact etiology of lung cancer is still not known. Long-term exposure or inhalation of carcinogens is a significant risk factor, along with other risk factors such as immunity and genetics.[16] Several references have reported that the etiology of lung cancer is closely related to smoking habits. Lombard and Doering studies reported a higher incidence of lung cancer in smokers than nonsmokers.[17]

Symptoms and signs of lung cancer vary based on the location, size of the cancer, degree of obstruction, and presence of regional or distant metastases. The most common symptoms are cough or chronic cough changes. Hemoptysis or sputum mixed with blood may also be present. Lung cancer can cause various complications, including pleural effusion, neurological disorders, and heart disease. Lung cancer can also cause other problems such as chest pain, coughing, shortness of breath, coughing up blood, nausea, pain, and fatigue.[18] Based on the 2018 National Cancer Control Committee, systemic clinical symptoms that are sometimes encountered are weight loss in a short time, loss of appetite, and intermittent fever. Symptoms associated with neurological disorders (headache and weakness/paresis) are encountered if they have spread to the brain or spinal cord. Bone pain is often the first symptom of cancer that spreads to the bones. Other symptoms include paraneoplastic symptoms, such as musculoskeletal pain, hematology, vascular, neurology, and others.[15]

Several supporting modalities suitable for diagnosing lung cancer include laboratory tests, imaging, transthoracic biopsy (TTB), fine-needle aspiration biopsy (FNAB), and histopathological examination. Lung cancer therapy can be classified based on its type, namely, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Treatment is usually based on the stage of the cancer, with therapeutic modalities including surgery, radiotherapy, and chemotherapy. Chemotherapy modality is standard therapy for stage III A lung cancer patients and for palliative treatment.[17]

Tyrosine Kinase Inhibitors (TKI), such as gefitinib and erlotinib, have been shown to be effective in patients with mutational activation of EGFR and ALK genes, such as NSCLC lung cancer cases. Despite its efficacy in controlling systemic disease, its effectiveness in patients with brain metastases has not been well established because data on the use of erlotinib or gefitinib are available from retrospective non-randomized studies with a limited number of patients.[19] A Chinese study of 136 NSCLC patients with resected brain metastases identified mutations EGFR in 57% of brain metastases, with a concordance rate of 93.3% in EGFR mutation status between primary tumor and brain metastases. This suggests that the EGFR status of the primary tumor is an excellent surrogate for the EGFR mutation status of brain metastases.[20] There is mounting evidence that treatment with TKI results in high response rates (70%–89%), improvement and progression-free survival (PFS) (12.9–19.8 months and 6.6–23.3 months, respectively) which demonstrated better clinical outcomes in a selected population of EGFR-mutated NSCLC patients with brain metastases.[21] Therefore, EGFR and ALK -TKI are valid options for patients with asymptomatic brain metastases from NSCLC, especially for those with EGFR-activating mutations or ALL+.

There are no well-defined treatment timing guidelines for NSCLC patients with EGFR mutations and asymptomatic brain metastases who do not require emergency therapy. In a retrospective study of patients with asymptomatic brain metastases without previous TKI treatment, first-line brain radiotherapy failed to improve long-term survival in patients with NSCLC with EGFR mutations and TKI therapy with asymptomatic brain metastases.[22]

Whether erlotinib or gefitinib can delay or obviate the need for brain radiation is considerable interest. To answer this question, a meta-analysis was performed in NSCLC patients with EGFR mutations and brain metastases. The authors reported improvement in PFS and OS with advanced use of cranial radiotherapy, although with more neurologic side effects compared to TKI alone.[22] Negative results have been recently reported with the use of advanced EGFR-TKIs, with suspension of SRS or WBRT resulting in lower OS in NSCLC patients with EGFR-mutantion and brain metastases. Similarly, no significant difference in OS was reported in 110 patients with EGFR-mutant lung adenocarcinoma who underwent erlotinib versus RT for brain metastases (median, 35 vs. 26 months; P = 0.62). The results of this study suggest that local therapy may still be important for the treatment of brain metastases in patients with EGFR mutations.[23]

Owing to continuous innovation and advances in medical treatment with targeted therapy and immunotherapy in the last decade, the survival of patients with advanced NSCLC has been extended, making it possible and clinically beneficial for radiotherapy to play a more active role in a highly selected subpopulation. For some patients initially unable to tolerate aggressive treatment because of severe symptoms caused by metastases (including lung, bone, and brain) and/or tumor emergencies [such as superior vena cava syndrome (SVCS), malignant spinal cord compression (MSCC), and hemoptysis], timely radiotherapy can significantly improve their general condition and performance status (PS) scores, giving them opportunities for more aggressive treatment and longer survival.[24]

To provide timely palliative care, ASCO guidelines recommend that palliative care be initiated within eight weeks of advanced lung cancer diagnosis. Historically, with palliative care as the primary goal, local treatment including surgery and radiotherapy was the standard of care for NSCLC patients with brain metastases because of the poor ability of chemotherapy drugs to cross the blood-brain barrier (BBB). Stereotactic radiosurgery (SRS) and whole brain radiotherapy treatment (WBRT) were performed according to the number and size of brain metastases. With the emergence of various small-molecule TKIs that exhibit increased penetration of the BBB, promising survival results have been reported in patients with brain metastases with anaplastic ALK or EGFR mutations. Pre-clinical studies have uncovered reasons for the synergistic anti-cancer effects of TKIs combined with radiotherapy. Accumulating data suggest that cranial radiotherapy, when performed in selected subgroups of oncogene-addicted NSCLC patients with brain metastases using the right radiation technique at the right time, not only contributes to symptom control but can also lead to longer survival. Based on data from previous studies, radiotherapy has immunomodulatory qualities that can enhance the antitumor immune response, making the integration of radiotherapy with immunotherapy as new therapeutic option for advanced NSCLC.[24]

According to Fitri *et al*., cancer is a terminal or palliative disease and patients with advanced conditions require services that can improve the quality of life of patients and families through palliative care. Palliative care is a form of health care that aims to improve the quality of life for patients and families with life-threatening illnesses, with prevention and eradication through early detection, appropriate assessment, and treatment of pain and physical problems, as well as psychosocial and spiritual problems.[25] In the National Consensus Project (NCP) Clinical Practice Guidelines for Quality Palliative Care in 2009, defines palliative care as "medical care provided by an interdisciplinary team, including medicine, nursing, social work, chaplaincy, counselling, nursing assistants, and other health care professions that focus on eliminating suffering and support for the best quality of life for patients facing serious life-threatening illnesses and their families. Palliative care included pain management, management of other physical complaints, psychological support, nursing care, social support, cultural and spiritual support, as well as assistance in preparation for and during bereavement. In this case, the patient received palliative care since the diagnosis of cancer was made in the form of supportive psychotherapy, occupational therapy, chaplain assistance, and advance care planning. The assessment and evaluation of patient complaints require the knowledge and attitudes of nurses related to palliative care. Nurse collaboration with various scientific team members can develop and implement a comprehensive treatment plan to improve the patient's quality of life.[26]

CONCLUSION

Palliative care is an approach for treating patients with life-threatening illnesses, including lung cancer. If introduced at an early stage, it can relieve symptoms and improve the quality of life. ASCO guidelines recommend that palliative care be started within 8 weeks of the diagnosis of advanced lung cancer. Palliative care should involve a combination of treatment methods based on available resources, and patients' responses should be monitored regularly. Providing proper holistic care will give patients the opportunity to live with the best quality of life for as long as possible.

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Case Report

A 71-year Old Male Patient with 20 Hour Onset of Infarct Stroke that was Performed with Intra-Arterial Thrombolysis, Mechanical Thrombectomy, Balloon Angioplasty, and Carotid Stenting: A Case Report

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Abstract

Background : For above 2 decades, the definitive management for acute ischemic stroke is intravenous or intra-arterial thrombolysis (IAT), using recombinant tissue-type plasminogen activator. Recently mechanical thrombectomy (MT) was developed to overcome the problem that intravenous thrombolysis is only effective in removing large artery occlusions in the range of 10–30%. Early treatment with intra-arterial thrombolysis, permanent stent insertion and clot extraction devices evolved into the stent-retriever device used in most of the important trials and, recently, emerged aspiration tool. This case report presented 71-year-old male patient with infarct stroke who performed with MT.
Case presentation : This case report presented 71-year-old male patient with the main complaint of right limbs weakness. A non-contrast head CT scan found infarction in the cortical-subcortical left parietal lobe, posterior pericornu of the right lateral ventricle and right temporal cornu periventricular; lacunar infarction in the right and left paramedian pons; old lacunar infarction in the left and right centrum semiovale, left corona radiata, right internal capsule, right parietal lobe white matter, left lentiform nucleus, left posterior crus of the internal capsule-thalamus, right thalamus, right lateral ventricular pericornu and left paramedian pons. The patient underwent cerebral digital substraction angiography (DSA), as well as IAT, MT, balloon angioplasty, and carotid stenting with good clinical outcome.
Conclusion : With the overwhelming positive results of studies evaluating the safety, efficiency, and efficacy of mechanical thrombectomy; the standard of care for the treatment of patients with anterior circulation vessel occlusion is becoming clear.

Keywords : balloon angioplasty, carotid stenting, case report, intra-arterial thrombolysis, mechanical thrombectomy.

INTRODUCTION

Every year, there are about 800,000 stroke cases in the United States and 1 million cases in the European Union. Although stroke deaths have declined over the previous 1 decade, they still rank as the most cause of the mortality.[1,2] Additionally, stroke is the most etiology cause of permanent disability and the frequent causes of dementia in developed countries. Stroke patients and their relatives are often burdened with highly cost rehabilitation, financial and productivity difficulties, and limitations in daily activities. Treatment and intervention in golden time period can reduce long-term disability by preserving at-risk penumbra areas and reducing morbidity and mortality.[1]

For above 2 decades, the definitive management for acute ischemic stroke is intravenous or intra-arterial thrombolysis (IAT), using recombinant tissue-type plasminogen activator (rtPA).[1,3] Recently mechanical thrombectomy (MT) was developed to overcome the problem that intravenous thrombolysis is only effective in removing large artery occlusions in the range of 10-30%. Early treatment with intra-arterial thrombolysis, permanent stent insertion and clot extraction devices, such as the Mechanical Embolus Removal in Cerebral Ischaemia (MERCI) device, evolved into the stent-retriever device used in most of the important trials and, recently, emerged aspiration tool.[3,4]

This change in pace in treatment for the large number of people with major stroke requires a sizeable infrastructure to be put in place and will inevitably involve further centralization of services for hyperacute stroke.[3] This case report reports a patient with infarct stroke who underwent intra-arterial thrombolysis, mechanical thrombectomy, balloon angioplasty, and carotid stenting.

CASE PRESENTATION

This case report reports the case of a 71-year-old male patient who came to the emergency room with the main complaint of weakness in the right limbs. Approximately 20 hours before admission to the hospital, the patient was found by his family who had suddenly fallen on the floor, the patient was unconscious, had difficulty communicating, there was weakness in the right side of the limbs, both eyes glanced to the left side all the time. Other complaints such as headaches and seizures were previously denied.

The patient's family brought the patient to the emergency room at the Kariadi General Hospital. While in the emergency room, the patient had opened his eyes spontaneously but there was no eye contact. The patient tended to be restless, eyes only glance to the left side, unable to speak. The left limb looked more active than the right limb, the mouth appeared to droop on the left side.

The patient had hypertension by regularly taking amlodipine 10 mg/24 hours and history of previous stroke in 2020 (mouth drooping, slurred speech, and limb weakness), hospitalization at private hospital in Semarang. The family did not know the patient's history of taking blood thinner drugs. The patient had a history of coronary heart disease in 2000. The patient has a habit of smoking since 20 years ago, in a day can be used up 1-2 packs. The history of diabetes mellitus and dyslipidemia was denied.

The patient then underwent mechanical thrombectomy from the emergency room. In stroke unit, the patient was still sedated by general anesthesia. The patient had no seizures, the limbs on the right side appeared weaker. There was no nausea and vomiting.

In physical examination, the patient's general condition as seriously ill, with GCS scoring E2M5Vguedel (still under sedation after general anesthesia), blood pressure 150/123 mmHg, pulse rate 97x/minute, respiratory rate 20x/minute, temperature 36.5°C, oxygen saturation 96% with nasal cannula 3 liters per minute. The NIHSS score in the emergency room was 18 which was included in severe neurological deficits, while the NIHSS in stroke unit could not be assessed because the patient was still under sedation. Eye examination revealed a 3mm/3mm isochoric spherical pupil, direct light reflex +/+, conjugate deviation to the left. There was no neck stiffness, examination of the cranial nerves revealed right XII nerve parese of the central type. Motor examination of the upper and lower extremities on the right side revealed the impression of hemiparese dextra (could not move spontaneously) and there was hypertonicity. Physiological reflexes within normal limits, pathological reflexes negative such as Babinski, Chaddock and Gondor reflexes positive on the right side, sensibility of both extremities within normal limits.

The supporting examinations in the form of a non-contrast head CT scan on 20 January 2023 found infarction in the cortical-subcortical left parietal lobe, posterior pericornu of the right lateral ventricle and right temporal cornu periventricular; lacunar infarction in the right and left paramedian pons; old lacunar infarction in the left and right centrum semiovale, left corona radiata, right internal capsule, right parietal lobe white matter, left lentiform nucleus, left posterior crus of the internal capsule-thalamus, right thalamus, right lateral ventricular pericornu and left paramedian pons; no bleeding or signs of increased intracranial pressure; aging cerebral atrophy. Examination of thorax plain radiography gives the impression of a normal heart shape and location, calcification of the aortic arch, and no visible pulmo spots. The blood laboratory results could be seen in Table 1.

The patient was diagnosed clinically with decreased consciousness, spastic right hemiparesis,

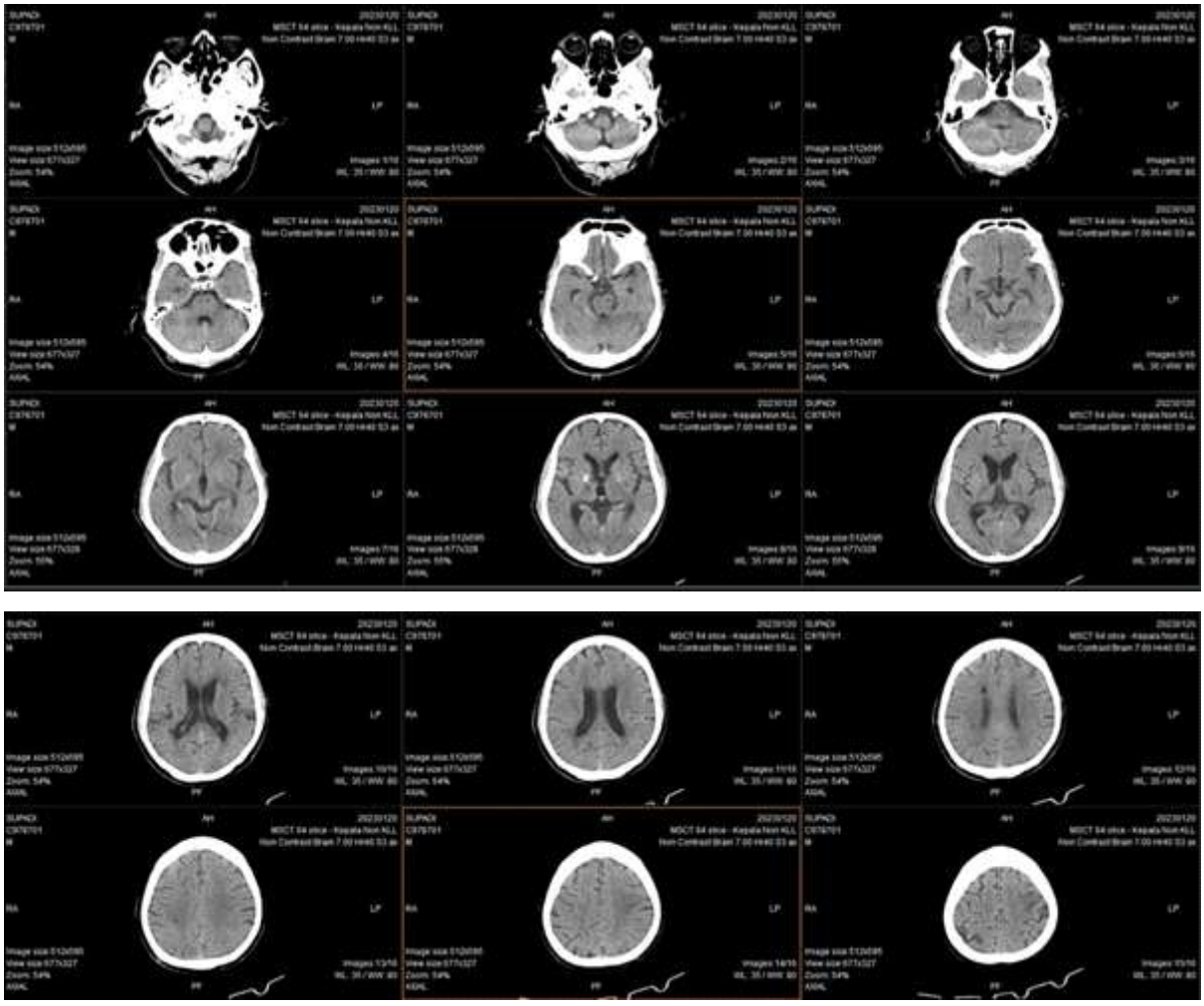

Figure 1. Non-Contrast Head CT Scan from the patient

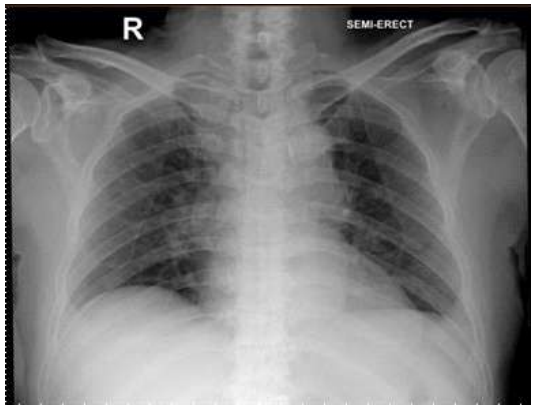

Figure 2. Thorax Plain Radiography from the patient

global aphasia, paresis of right facialis nerve. The topically diagnostic in centralcortical-subcortical left parietal lobe, etiologically due to infarct stroke and hypertension. Then the patient underwent cerebral digital substraction angiography (DSA), as well as intra-arterial thrombolysis, mechanical thrombectomy, balloon angioplasty, and carotid stenting. In this case the DSA procedure was carried out through branchial access.

The procedure went well, after the procedure the patient had an improvement in consciousness, the patient

TABLE 1
Blood laboratory results

Laboratorium	Normal Range	Results (20/01/2023)
Hemoglobin	13.2–17.3	15.6
Hematocrite	32–62	46.8
Erytrochyte	4.4–5.9	5.15
Leukocyte	3.800–10.600	7.100
Thrombocyte	150.000–400.000	417.000
Blood glucose	80–160	102
Urerum	15–39	24
Creatinin	0.6–1.3	1.2
Calsium	2.12–2.52	2.4
Natrium	136–145	141
Kalium	3.5–5.0	4.0
Chlorida	95–105	105

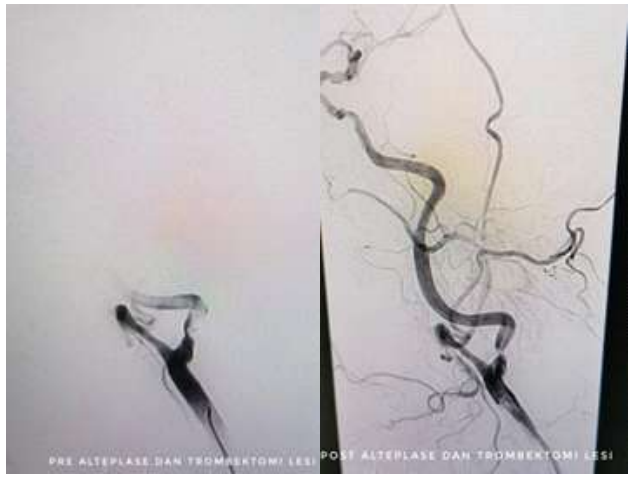

Figure 3. Results of cerebral DSA pre and post IA thrombolysis + mechanical thrombectomy

opened his eyes spontaneously but had not made maximum contact, the limbs on the right side could be moved. 1 day after the procedure, the right limb began to be lifted and awareness slowly improved. After the procedure, the patient was given therapy 30-degree head up position, oxygen via nasal canule 3 liters per minute, ringer lactate infusion 20 drops per minute, Diltiazem intravenously 5–20 mcg/kgBW/minute through syringe pump, injection of ranitidine 50 mg/12 hours intravenously, vitamin B12 500 mcg/12 hours intravenously, clopidogrel 75 mg/24 hours per oral. The patient was programmed to sleep on lying position, placed a sand pillow over the puncture site (right brachial) for 6 hours, the right arm must straight and couldn't move for 6 hours on the arm that was punctured, and within 24 hours it couldn't get out of bed. Patients are monitored every hour for 6 hours in the form of monitoring of general condition, vital sign, GCS, neurological deficits, signs of bleeding, and artery brachialis pulsation.

DISCUSSION

Intravenous tissue plasminogen activator (tPA) is the only recanalization therapy approved for the treatment of acute ischemic stroke but because of the narrow

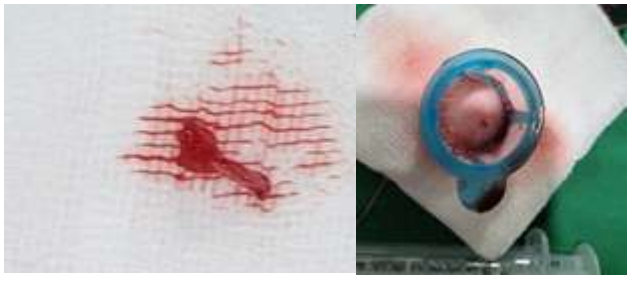

Figure 4. Evacuated thrombus

treatment time of 3 to 4.5 hours, it is used in a minority of acute ischemic stroke patients.[1] Moreover, its benefit is limited, with respect to clinical efficacy and recanalization, especially for great vessel occlusion, the most common cause of severe and fatal acute ischemic stroke. The traditional time window for intra-arterial thrombolysis is less than 6 hours and 8 hours for mechanical embolectomy. Duration of ischemia is a major predictor of neurologic outcome but with modern penumbra imaging, patient selection for intra-arterial thrombolysis (IAT) may be time dependent.[1,5]

IAT, once the first-line therapy for large vessel occlusion before the advent of mechanical thrombectomy (MT), has reemerged with a new potential role in the modern endovascular era. Recent studies have shown promising results of IAT recombinant tissue plasminogen activator (rtPA) in the context of MT.[3,5,6]

Findings from a number of studies suggest that IAT may be a plausible alternative to intravenous thrombolysis (IVT). In some studies, IAT is associated with a higher rate of recanalization than IVT.[7] There are several potential advantages to IAT, such as planning angiography to tailor therapy, locoregional injections, and the ability to use mechanical devices to accelerate the rate of recanalization. Delays in treatment with IAT and delays may reduce the benefits of this procedure, because time to treatment is a major predictor of acute stroke outcome.[5,7]

One of the risks of IAT is intracranial hemorrhage; Another is the risk of procedural complications such as anaphylaxis and systemic bleeding.[5,7] In one of the early clinical trials of IAT, the prevalence of intracranial hemorrhage (ICH) at 24 hours and death at 90 days was 42% and 27%, respectively. Trials and subsequent studies report mortality rates of 7% to 29%, and bleeding rates ranging from 0% to 33%. In a study of patients receiving IAT (along with other endovascular treatment) after ≥8 hours documented an estimated rate of 33% for death at 90 days and imminent bleeding (subarachnoid and intracranial.[7]

The risk of ICH with IAT can be related not only to the thrombolytic dose used during IAT, but also to the severity of the stroke.[8] Regarding other complications, the PROACT II trial reported that 1% of patients receiving IAT with recombinant prourokinase developed anaphylaxis and 7% experienced systemic bleeding. Several studies have found that there are no significant differences between treatments in the proportion of patients who live without disability, have bleeding symptoms, or die. Another study found that IAT showed clinical benefit over venous thrombolysis for some of these outcomes.[7,8]

Since January 2015, 11 RCTs on mechanical thrombectomy in the anterior circulation have been published, which have led to a revolution in the care of patients with large artery occlusion.[9] Patients with significant deficits as manifested by a National Institutes of Health Stroke Scale (NIHSS) score between 8 and 20 have better outcome with endovascular treatment (EVT) reperfusion.[9,10]

Based on the current trial, American Heart Association guidelines provide evidence of a level of 1A for EVT candidates with NIHSS score ≥6.[8] However, there is a significant proportion of patients with acute ischemic stroke and great vessel occlusion who may present mild stroke severity (NIHSS score <8). EVT appears to be effective and safe in individuals with mild to moderate stroke severity and proximal great vessel blockage, despite the lack of relevant RCT evidence.[8,11]

The time window for EVT plays a significant part in clinical outcome, as demonstrated that its efficacy is time dependent: in anterior circulation stroke, the role of successful thrombectomy is beneficial in the first 3 to 4.5 hours after stroke compared to the treatment after 5 to 8 hours.[9] Although thrombolysis is the treatment option ≤4.5 hours after stroke onset, additional or primary EVT can be performed over a longer timeframe: in a recent RCT, only a few patients were unable to puncture within 6 hours. Therefore, the positive results of the trial were affected mostly by individuals admitted within 6 hours of symptom onset.[9,11]

A meta-analysis of recent RCTs demonstrated that in subjects who got substantial reperfusion with EVT, every 1-hour delay to reperfusion was related with adverse rates of disability and reduced functional impairment, but mortality rates remained unchanged.[7] Posterior circulation and brainstem stroke caused by vertebral or basilar artery occlusion may be less

susceptible to hemorrhagic complications than reperfusion therapy. Safe recanalization of occluded posterior circulation vessels has been reported ≤24 hours after brainstem infarction.[7,11]

In subjects with clinical features suggestive of great vessel occlusion and who may be candidates for EVT, a comprehensive examination should be performed using multimodal computed tomography (CT) or multimodal magnetic resonance imaging (MRI) techniques.[9] The main advantage of CT over MRI is that it is widely available and stroke imaging protocols consisting of non-contrast CT and CT angiography (CTA) can be performed in only a few minutes. Brain parenchymal imaging, preferably by noncontracting CT or alternatively by MRI, should be used to diagnose intracranial hemorrhage (ICH) or stroke mimics such as tumors, infections, etc.[9,12]

The Alberta Stroke Program Early CT Score (ASPECTS) is a systematic scoring to detect early CT signs such as an insular ribbon sign or obscuring lentiform nuclei.[13] An independent meta-analysis demonstrated that EVT improved outcomes in both patients based on ASPECTS 8 to 10 (ie, minimal ischemic damage) and 5 to 7 (ie, moderate ischemic damage). In contrast, patients with ASPECTS low from 0 to 4 showed no benefit of treatment with EVT, suggesting that EVT has little or no efficacy in patients with large ischemic nuclei. However, the interpretation of ASPECTS is still debated even among stroke experts. Standardized and automated assessment of ischemic damage may be useful in future clinical practice.[12,13]

Arterial imaging of the cerebral circulation, preferably by CTA or alternatively by magnetic resonance angiography, is essential for assessing a patient's eligibility for EVT. CTA is widely available, with fast, thin-section, volumetric spiral CT images obtained during bolus injections of time-optimized contrast material for vascular opacities.[9] The entire region from the aortic arch to the circle of Willis can be covered in one data acquisition. CTA confirms the presence of great vessel occlusion, allows localization of occluded vessels, and may facilitate intervention by obviating the need for non-targeted vessel cerebral angiography. In addition, it can identify collateral circulation and clot length. Collateral circulation may improve stroke outcomes by limiting the rate of cerebral infarction.[9,12,13]

Endovascular diagnostic and therapeutic procedures are generally performed via the femoral artery. Some of the reasons for this common approach are its location, easy approach to puncture and hemostasis, and low complication rate.[12,13] The femoral puncture also allows access to almost any area of the artery and provides the operator with favorable ergonomics in most cases. However, in some situations, femoral access may be difficult or even contraindicated, such as absence of a palpable femoral pulse, severe generalized femoral occlusion disease, recent femoral intervention or surgery, femoral aneurysm/pseudoaneurysm, and in some cases, presence of prosthetics. Access via other vessels, such as the brachial, radial, and ulnar, has been used when femoral access is not available. Many studies have noted that this approach has excellent technical results and a low incidence of complications.[13]

However, the use of brachial artery access for non-coronary interventions has received little attention.[12–14] Despite its utility as an adjunct technique and sometimes mandatory, some endovascular surgeons are reluctant to expand its use for fear of an increased complication rate. Several series have documented complication rates as high as 11%.[14]

A development in the interventional management of acute stroke was performed in 2008 with the use of a stent-like thrombectomy device now called a stent retriever. The aspiration technique can be performed as an alternative treatment to stent retriever devices.[8] The stent retriever technique allows a high recanalization rate with reduced recanalization time and a low complication rate. Retractable stents are self-expanding stent-like devices that are completely retractable. Therefore, this device combines the benefits of fast flow recovery and mechanical thrombectomy. Excellent recanalization results can be achieved with this technique with Thrombolysis rates in Grade 2a/b or 3 flow Cerebral Infarction (TICI) as high as 90%. The results of this prospective study show a high rate of clinical outcome within 3 months.[8,12,13]

The better clinical outcome with the restorative appliance is due to the rapid and effective removal of the clot and the possibility of temporary flow restoration. In addition, the use of a stent retriever device is related with a lower rate of ICH symptoms and a lower rate of death.[9] The low mortality rate reflects the low rate of ICH symptoms and demonstrates the safety of flow restoration devices compared to thrombectomy devices in the past. This was confirmed in all RCTs. In the stent retriever technique, the target vessel is inserted with a 0.014-inch guide wire and a suitable microcatheter between 0.018 and 0.027 inches. The thrombus is crossed with a guidewire, and a microcatheter is placed distal to the thrombus. The stent retriever is advanced to the distal end of the microcatheter. Then, the microcatheter is removed to spread the device under fluoroscopy. A control angiogram is performed after the device opens successfully. Stent retriever device sizes range from 3.0×15 mm to 6.0×30 mm; however, usually 6.0 mm devices are used. After a while, the device is withdrawn with continuous aspiration. This procedure is repeated until a TICI level of 2b or 3 is reached.[9,12,13]

Clinical experience has exhibited situations that are resistant to recanalization of stent retrievers. These situations include occlusions located at the terminal internal carotid artery (ICA) and bifurcation of the

middle cerebral artery and trifurcation thrombi, as well as hard thrombus configurations.[13] The aspiration technique was an early feature in the history of mechanical thrombectomy, and its use has been demonstrated in a large number of trials and clinical experience. During the last few years, new aspiration devices were developed including internal distal diameter change of the distal catheter; therefore, the aspiration technique in some centers is used as the primary treatment for intracranial artery occlusion.[9,12,13]

Recent studies, included in 1 randomized trial, demonstrated that the primary aspiration technique is a safe and effective EVT method with clinical outcomes comparable to stent retriever devices.[8] The main advantages of the aspiration technique are the quick procedure time and the high rate of favorable clinical outcome. When the aspiration technique is used, the thrombus is passed with a microwire and microcatheter, and the aspiration catheter is placed directly proximal to the thrombus. The microwire and microcatheter were removed. The catheter is then removed under constant negative pressure to avoid loss of the thrombus. After each removal of the clot fragment, the procedure is repeated until a TICI level of ≥2 or 3 is reached.[8,9,12,13]

A tandem occlusion is a combination of the extracranial segments of the ICA occlusion with the concomitant occlusion of the intracranial segments. Tandem occlusions are uncommon but show a challenging therapeutic setting in the setting of acute ischemic stroke.[13] Only a small number of patients with tandem occlusions were included in the recent EVT RCT. The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials Collaboration) meta-analysis showed that EVT may also be beneficial in this subgroup of patients. Acute occlusion of extracranial ICA segments resulting in ischemic stroke is different from other forms of acute occlusion of cerebral vessels.[9,12,13]

The pathophysiological processes in acute extracranial ICA occlusion, are close to those observed in acute coronary artery occlusion, most of which are ruptured atherosclerotic plaques and overlapping thrombus.[14] Therefore, in these subjects, acute extracranial ICA stenting should be performed for vessel recanalization. Intervention in a patient with a tandem occlusion consists of 2 steps: the first step is revascularization of the extracranial ICA segment with stent implantation, as in the management of atherosclerotic stenosis. The second step is mechanical recanalization of the occluded intracranial arteries by stent retriever or aspiration techniques.[11,14]

All RCTs reported an increased recanalization success rate, which was explained as a TICI level of 2b or 3 and varied between 59% and 88%.[11,15] Most significantly, these technical successes translate into clinical improvements as it appears that the probability of a good outcome increases with better recanalization. Recently, the long-term results of 2 RCTs exhibited that the positive effects of EVT at 1 to 2 years were similar to those reported at 3 months without any difference in mortality.[15]

The consensus conference on intracranial atherosclerotic disease concluded that there are no clear data available to support the efficacy of primary angioplasty over stent placement for the treatment of intracranial atherosclerotic stenosis.[16] Both primary angioplasty alone and angioplasty with self-expanding stents have been evaluated in nonrandom trials with satisfactory results and with recurrent ischemic events no worse than lesions treated by medical management alone. But the current treatment paradigm is based on operator preference and experience. In most practice, reports of dissection, vessel rupture, recoil of the lesion, and restenosis observed with angioplasty using balloon catheters designed for use in coronary arteries have undermined the role of primary angioplasty as the treatment of choice for intracranial atherosclerotic disease.[16–18]

Traditionally, carotid endarterectomy (CEA) has been the main method of treating asymptomatic and symptomatic carotid artery stenosis. Carotid endarterectomy involves exposure of the carotid artery and removal of plaque, usually from the carotid bulb and proximal internal carotid artery, through a neck incision. However, in vascular surgery, like many other surgical specialties, minimally invasive techniques have evolved over the years.[16] Carotid artery stenting (CAS) is one such technique, which can be performed via a transfemoral approach or a transcarotid approach. CAS is a reasonable alternative to CEA in selected patients with high-grade asymptomatic (greater than 70%) or symptomatic carotid artery stenosis. Indications for CAS include a patient's high risk of surgery, such as severe pulmonary disease, recent myocardial infarction, unstable angina, or severe congestive heart failure; previous history of neck radiation making open surgical dissection difficult; history of damage to the contralateral vocal cords; presence of tracheostomy, contralateral carotid occlusion; and previous CEA with recurrent stenosis.[16,19,20]

In a recent study, balloon angioplasty was associated with periprocedural stroke, a mortality rate of 5% and a technical success of up to 92%. In patients with hemodynamic compromise as a mechanism of ischemia, a marginal opening of 10% or 20% of the lesion in intracranial atherosclerotic disease may be thought to be beneficial because a small increase in vessel diameter can result in a large increase in perfusion. These patients should demonstrate post-procedure symptom improvement and future prospective studies should evaluate this hypothesis.[15,20]

Ultimately compared with medical therapy and intracranial stenting, endovascular treatment of intracranial atherosclerotic disease with balloon

angioplasty is relatively safe with periprocedural morbidity and mortality estimated at 5% in this study. A randomized controlled study to evaluate between the 3 treatment modalities is needed to understand the optimal treatment for patients with symptomatic intracranial atherosclerotic disease.[20,21]

CONCLUSION

With the overwhelming positive results of studies evaluating the safety, efficiency, and efficacy of mechanical thrombectomy; the standard of care for the treatment of patients with anterior circulation vessel occlusion is becoming clear. However, these benefits should not be limited to certain patients. Patients with occlusion of the posterior circulation and distal vessels have been shown to benefit from mechanical thrombectomy. The future of this field is bright and the exploration of endovascular recanalization is uncharted, to push the boundaries of current therapy in a sensibly and systematic manner.

CONFLICT OF INTEREST

No conflict of interest to declare.

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Case Report

CT Scan Imaging in Tuberculosis and Lung Cancer: A Case Report in Lung Hospital

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Abstract

Background : Tuberculosis is a contagious infectious disease that attacks various organs, especially the lungs. Chest CT scan modalities have a role in helping the diagnosis of tuberculosis and lung cancer. This case report presents a rare case of two women diagnosed with tuberculosis and lung cancer.
Cases Presentation : Two women aged 43 and 42 years came to the radiology department with a history of chest pain, loss of appetite, and cough, and underwent tuberculosis therapy by taking medication for two months. The patient underwent chest x photo thorax, abdominal ultrasound, thoracic CT scan, and a biopsy was performed with CT scan guiding.
Discussion : The findings of this case are consistent with previous studies which explained that radiological CT scans found tuberculosis with lung cancer. In the lung window, CT scan chest contrast found cystic bronchiectasis. Other results showed an encapsulated pleural effusion in the right hemithorax, compression atelectasis, and multiple lymphadenopathies.
Conclusion : CT scan imaging simultaneously can show the occurrence of tuberculosis and lung cancer. Lung cancer that worsens can cause adenocarcinoma with metastasis spreading to other organs.

Keywords : computed tomography, tuberculosis, lung cancer

INTRODUCTION

Tuberculosis is a contagious infectious disease caused by Mycobacterium tuberculosis (Mtb) which attacks various organs, especially the lungs.[1] Tuberculosis may coexist with malignancy or manifest as lung malignancy.[1] In 2022, it is the second leading cause of death in the world after COVID-19,[2] and is highly contagious especially in poorly ventilated environments and crowded places.[3] Tuberculosis is a significant risk factor for lung cancer, and continues to increase steadily for years after the diagnosis of tuberculosis, and may reflect the effects of inflammation. Chronic lung disease and scarring resulting from tuberculosis.[4] According to the World Health Organization (WHO) the highest incidence was detected in Southeast Asia at 45% and in the African region by 25% of the total incidents.[5] In Indonesia tuberculosis lung disease is endemic disease number two.[6] In 2020 there were 11,993 deaths out of an estimated total of 842,000 cases,[7] increasing to 969,000 cases in 2021 with a mortality rate of 345 per 100,000 population.[8]

Tuberculosis and lung cancer are often known to coexist.[9] Case study findings suggest that tuberculosis may predispose to lung cancer.[10] Previous studies provide strong evidence of an increased risk of lung cancer among individuals with tuberculosis, and it increases further with coexisting COPD or other smoking-related cancers.[11]

Modalities such as chest scan play a role in assisting the diagnosis of tuberculosis.[12,13] However, cases of tuberculosis dissertation of lung cancer are rare, so case reports discussing tuberculosis biopsies guided by CT scans are important to report. This article reports on two women with tuberculosis dissertation lung cancer.

CASES PRESENTATIONS

This paper presents two cases of tuberculosis and lung cancer dissertation. A 43 year old woman, with a history of chest pain, loss of appetite, and cough for two months. The second woman is 42 years old with the same complaint, namely shortness of breath, and atelectasis lung on chest radiograph, with suspicion of clinical lung cancer tuberculosis. Both patients are new to therapy tuberculosis by taking medication for two months. The patient came to the radiology department to do a chest x-photo, abdominal ultrasound, and chest CT scan. Both patients then had a biopsy performed with CT scan guiding, to be sent to the anatomical pathology laboratory. Laboratory results showed non-small cell lung cancer.

RESULTS

The results of the second biopsy of the patient found adenocarcinoma. The first case was more severe because of adenocarcinoma with distant metastases to the liver, right and left pleural effusion, bronchiectasis in segments 2 and 2 of the right lung and segment 6 of the left lung, thoracic vertebrae, lumbar and thyroid organs left lobe. In addition, metastases were found in the left lobe of the thyroid organ, enlarged lymph nodes in the tracheal, subaortic, right and left axilla. The largest lymphadenopathy with a size of 2.0 cm is in the paratrachea. This condition indicates that the cancer has spread to various tissues.

X-ray imaging results thorax found a picture of pneumonia, underlying (underlying disease-principal disease) and tuberculosis lungs. Furthermore, the patient underwent abdominal ultrasound with the results obtained multiple nodules in the liver, which are liver metastases from lung cancer adenocarcinoma. Ultrasound of the abdomen also found right pleural effusion, which is also a metastasis from adenocarcinoma cancer, and multiple nodules. This is metastatic lung cancer adenocarcinoma.

Chest CT scan with contrast of CT scan imaging results found a solid mass in segment 10 in the left lung, size 3.75 x 3.28 x 4.11 cm, multiple solid nodules in the segment right lung 5, 6, 8, 9, 10. The largest size of the nodule is 1.24 x 1.35 x 1.10 cm, on the right 10th segment. In segment 5,6,8,9,10 the right lung is the largest in size on the right, and a solid nodule is also found on the left 10th segment. In the lung window CT scan chest contrast found cystic bronchiectasis in segment 1, 2 right lung, and segment 5 left lung. On CT scan of the chest, multiple lymph nodes were also found lymphadenopathy in the upper-lower, paratracheal, subavic, interlobar, right and left axilla with the largest size of 2.00 x 1.40 cm in the lower paratrachea. CT scan results also found duplex pleural effusion. Lesions were found on the bone window sclerotic partially lytic on coccus paper thoracic 2, 4, 10, 12. In the mediastinum window found a solid nodule in the gland left lobe measures 0.83 x 0.86 cm. The impression from this CT Scan shows tuberculosis lung and a solid mass in the lung with metastases to the liver, vertebrae, and duplex pleural effusion (see Figure 1).

The results of the adenocarcinoma biopsy in the second patient found right pleural effusion, but no metastases were found in the liver or thoracic and lumbar spine. There was also atelectasis in segment 3 of the right lung, but no bronchiectasis was found. Another finding is the presence of lymphadenopathy in the paratrachea, subcarina, right and left axilla.

CT scan imaging results in the second patient were found in the right lung pattern bronch-vascular looks increased, no spot appear. Lesion looks isodens lobulated at 3,5 segments right lung (±7.9 x 5.3 x 7.1 cm in size), accompanied by a narrowing of the right middle bronchus, attached to the right inferior bronchus. Right inferior pulmonary, post-contrast injection appears

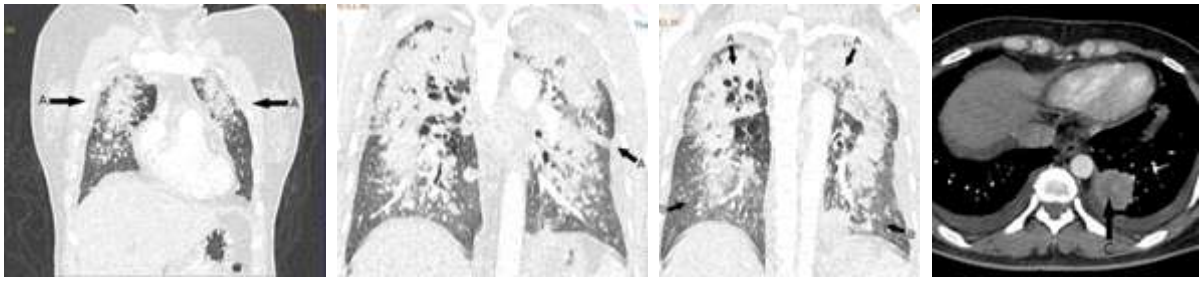

Figure 1. The first patient's CT scan results found tuberculosis lung (A), lung nodule in bilateral lung (B), solid mass in left lung (C).

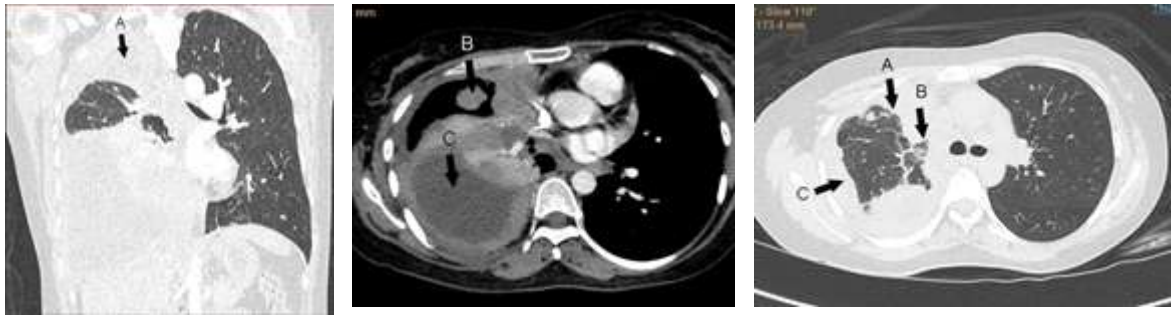

Figure 2. CT scan of the second patient, found tuberculosis lung (A), nodule / mass in lung right (B), right pleural effusion (C).

enhancement. Pleural effusion was seen in the right hemithorax with thick walls. Compression atelectasis of the 3rd segment of the right lung. The left lung has a pattern bronchovascular looks normal, no spot, and nodules and atelectasis. The trache doesn't look pushed, the left bronchus doesn't look narrow, and the esophagus doesn't widen, the walls don't look thick, and no masses are visible. Other results showed that the left and right thyroid did not appear enlarged and no mass was seen. Furthermore, the shape and location were normal, the aorta was not dilated and calcification was not seen. Another finding was multiple lymphadenopathies in the right and left upper-lower paratrachea, subcarina, and right and left axilla (Figure 2).

The impression obtained in the second patient was a solid lobulated mass in segment 3.5 of the right lung with a size of ±7.9 x 5.3 x 7.1 cm, accompanied by a narrowing of the right medial bronchus, attached to the right inferior bronchus, encased pulmonary artery right inferior, and suspected right lung tumor. In addition, there is an encapsulated pleural effusion in the right hemithorax accompanied by compression atelectasis in the 3rd segment of the right lung. Other results are multiple lymphadenopathies in the upper-lower paratrachea right and left, subcarinal, and there are right and left axillae.

DISCUSSION

This case report describes the discovery of tuberculosis with lung cancer in Lung Hospital dr. Ario Wirawan, Salatiga. This finding is consistent with a previous study by Thattaamuriyil Padmakumari,[9] that CT scan radiology has the ability to differentiate tuberculosis and lung cancer,[14] and evaluates the potential predictive role of clinical parameters. CT scan radiology has become one of the most influential topics in quantitative imaging research. This is because CT scan radiology is a method applied to imaging that allows the extraction of thousands of quantitative ultrastructural parameters from pixels.[15]

In the first case report, there was an adenocarcinoma with metastases in both pleural effusions. Further findings revealed that metastases had spread to various body tissues such as the liver, thyroid lobe, lymph glands, and others. These results indicate that tuberculosis that is already severe is more difficult to treat and often leads to death.[16–18] According to Dacosta, the incidence of tuberculosis lesions is significantly associated with carcinoma, being the main cause of death in many countries around the world.[19] Previous research by Cukic explained that lung tuberculosis patients are at risk of bronchial drainage carcinoma, peripheral lung carcinoma, and cavernous carcinoma.[20] It is possible that pulmonary tuberculosis enhances the risk of lung cancer.[21] This supports the statement of Hui *et al* that there is a direct relationship between tuberculosis and lung cancer, especially adenocarcinoma.[22]

In the second patient, it was found that the right lung had an increased bronch-vascular pattern, accompanied by narrowing of the right median bronchus, and attached to the right inferior bronchus. On the left

lung, the bronch-vascular pattern appears normal, no spots were seen, and nodules or atelectasis. According to Hors *et al* incidental non-nodular lung findings can broadly be characterized as an airway or airspace related disorder and a diffuse parenchymal abnormality.[23]

In the lung window CT scan chest contrast found cystic bronchiectasis. This is consistent with previous findings that CT scores bronchiectasis peripherals have added value to pulmonary function tests in monitoring cystic fibrosis lung disease.[24] Tuberculosis lung can coexist with carcinoma squamous cell lung at the same time.[25] Lung cancer and pulmonary tuberculosis are two major public health problems related to clinical and radiological presentations.[26,27] The result of Park *et al* show that pulmonary tuberculosis is a risk factor for developing chronic obstructive pulmonary disease and lung cancer.[28] An investigation by Qin *et al* explained that tuberculosis is an important risk factor for lung cancer, which originates from chronic inflammation and infection.[29]

CT Scan results showed that there was an encapsulated pleural effusion in the right hemithorax accompanied by compression atelectasis, and multiple lymphadenopathy, which are common radiological findings in many thoracic diseases.[30] Characteristics of lung cancer in tuberculosis patients the most common fibrothorax or empyema is squamous cell carcinoma.[31] Radiological findings of CT scans can find tuberculosis and cancer in the lungs and can be used to stop cancer at an early stage.[26]

CONCLUSION

Based on the biopsy results and CT scan radiological findings, it can be concluded that tuberculosis and lung cancer can coexist in these patients. Lung cancer that worsen can cause adenocarcinoma with metastases spreading to the liver, pleura, thoracic vertebrae, and lumbar spine.

CONFLICT OF INTEREST

No conflict of interest to declare.

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This work did not receive any grand from funding agencies in the public, commercial, or not-for-profit sectors.

ETHICAL APPROVAL

Approval was not required.

INFORMED CONSENT

The informed consent approval by the family patient. The authors declare that this case report does not contain any personal information that could lead to the identification of the patients.

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Research manuscript should adhere guidelines as follow:

Title :
1. Is neither too long nor too short, approximately 12–14 words
2. Describes research design
3. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, method, result, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (research justification): what have been known and what need to be added. The second paragraph consists of hypothesis or research aim.
2. Is supported by relevant and strong references

Methods :
1. Explains research design, settings and time
2. Explains population and sample, sampling technique, sample size (equation doesn't need to be enclosed), inclusion and exclusion criteria.
3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
4. Thoroughly explains method, instrument, measurement technique and data collection
5. Explains data analysis with proper tests according to data, significance and confidence interval
6. Explains computer program (software) used
7. Explains ethical clearance and informed consent

Results :
1. Is presented in a logical sequence
2. Presents subject characteristics (in a table). For clinical trial, subject characteristic of each group before trial are presented
3. Explains subjects who drop out and the reasons. If possible, provides consort diagram
4. Maximum 3-4 tables
5. Provides hypothesis without commentary

Discussion :
1. Discusses all relevant findings and its association with practice. There is no redundant repetition of findings already presented in the results section.
2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

Conclusion :
1. Should answer research question
2. Should be based on research findings, not quotation
3. Can provide suggestion for future research

References :
1. Uses Vancouver style (see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*) www.icjme.org

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1. Present complete name of authors without academic title along with office/institution/work place address under the title
2. Provide correspondences
   The main author provides a statement explaining that article has never been published nor sent for publication to other journals and has already been approved by all co-authors evidenced by a statement sheet. All sent articles are reviewed by profession groups (peer reviewers) and editors. All articles should provide ethical clearance issued by Ethical Review Board and 2 sheets of inform consent form already signed in "pdf" format.

CASE REPORT

Title :
1. Is neither too long nor too short, approximately 12-14 words
2. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, case report, discussion, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (justification of the case report). The second paragraph consists of aim of case report emphasizing diagnose/pathogenesis/therapy.
2. Is supported by relevant and strong references

Case report :
1. Presents short case involving medical history, physical examinations, and investigations.
2. Stresses new or rare cases or new therapies or procedures
3. Provides patient's picture (if necessary), investigations such as radiology or laboratory or others as needed. Pictures/photos size minimum 300 dpi.
4. Obtains patients' or families' informed consent for publication for patients with easily identified features. Editors may conceal physical features considered unnecessary.
5. Contains maximum four photos/pictures for each article.

Discussion :
1. Provides epidemiology data showing that rare cases occur or new procedures are conducted.
2. Provides relevant discussion according to aim of the case report emphasizing diagnose/pathogenesis/therapy comparing/relating to other cases and providing LoE (Level of Evidence).

Conclusion and suggestion :
1. Are in line with the aim of case report.
2. Suggestion consists of improvement for case management.

Reference :
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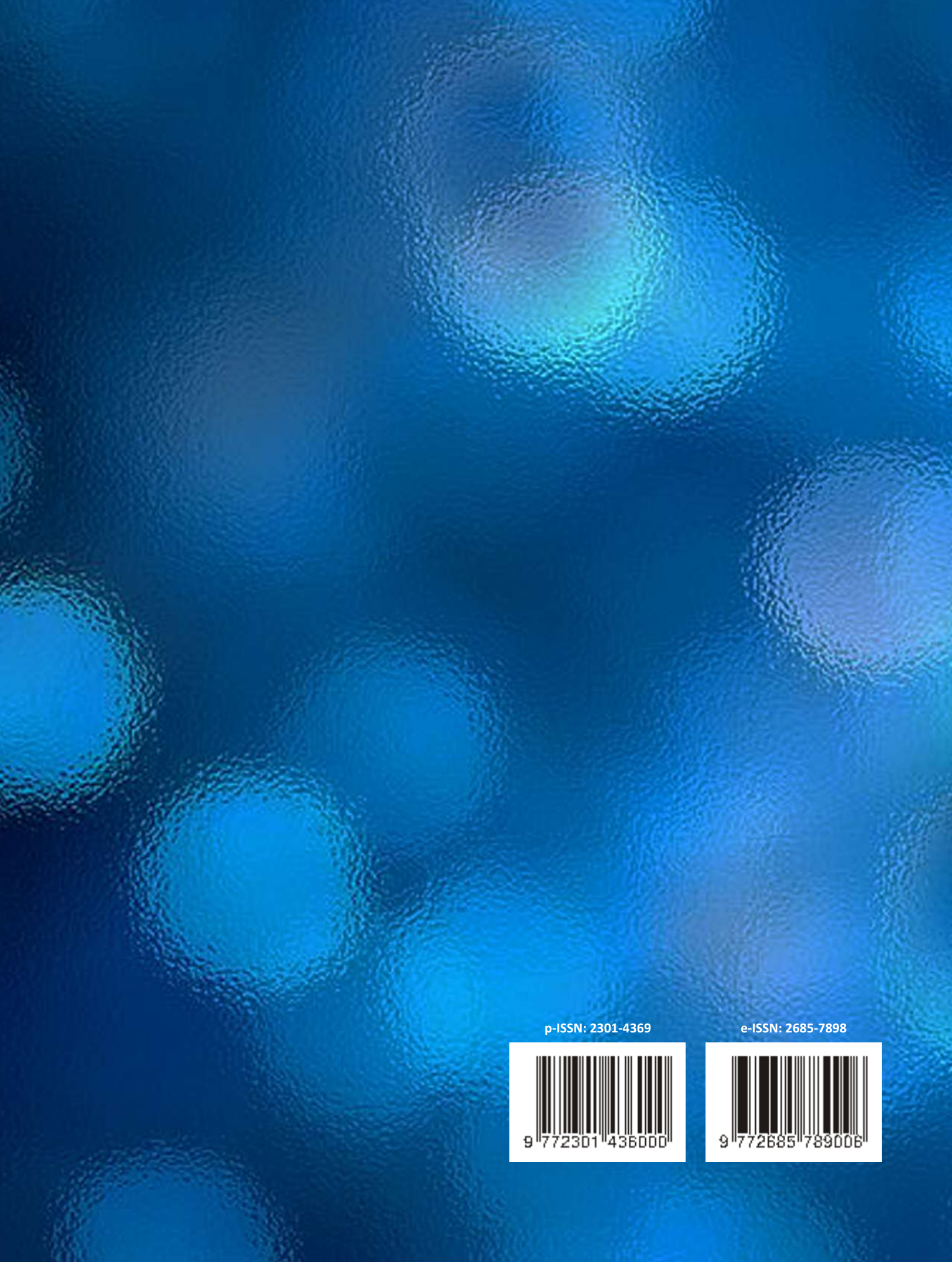

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