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Effect of carvedilol rapid up-titration on malondialdehyde levels in patient with heart failure reduced ejection fraction

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ABSTRACT

Background: Malondialdehyde (MDA) is a marker that can assess the level of oxidative stress. Studies support that this marker can reflect the severity of heart failure. Carvedilol is a third-generation beta-blocker with antioxidant effects. Slow titration may contribute to the suboptimal dose use and therapeutic effect due to improved left ventricular systolic function and reduced dose-dependent mortality.

Aim: To determine the effect of rapid titration of carvedilol compared with standard titration according to standard guidelines on MDA levels in HFrEF (heart failure reduced ejection fraction) patients.

Methods: This study is a single-centre experimental study with a randomized, double-blind control trial conducted from October to December 2021. A total of 26 HFrEF patients undergoing treatment at UNS Hospital Sukoharjo were sequentially included in the study and then randomly divided into the rapid titration group carvedilol given an initial dose of 2 x 3.125 mg and increased every day with a target dose of 2 x 25 mg (or the maximum tolerated dose). The control group was given carvedilol dose titration according to standard guidelines. Blood plasma was taken on the first day before treatment and on the day the patient was discharged. MDA levels were checked by the ELISA method.

Results: The decrease in mean MDA levels was greater in the carvedilol rapid titration group than in the control group (2.84 $\pm$ 1.00 vs. 3.59 $\pm$ 2.55). However, these results were not statistically significant ($p = 0.590$). In the rapid titration group, carvedilol also showed a change in post-pre-MDA with a larger mean decrease (-0.55 $\pm$ 1.01) although not statistically significant ($p = 0.157$).

Conclusion: Rapid up-titration of carvedilol in patients with HFrEF during hospitalization can reduce MDA levels better than titration according to standard guidelines but is not statistically significant.

Keywords: Carvedilol; HFrEF; MDA.
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INTRODUCTION

The condition of heart failure involves oxidative stress in its clinical development. Oxidative stress is defined as a dysregulation between reactive oxygen species (ROS) and endogenous antioxidant defence mechanisms.[1] In insignificant amounts, ROS plays an important function in cell homeostasis. However, in substantial amounts, it will cause cell dysfunction, protein, lipid peroxidation, deoxyribonucleic acid (DNA) damage, and cell death.[2] Malondialdehyde (MDA) is a marker that can be used to assess the level of oxidative stress. Studies support that this marker may reflect the severity of heart failure.[3]

Beta-blocker is a core component of standard HFrEF (heart failure reduced ejection fraction) therapy. In patients with HFrEF, beta-blockers have shown to be beneficial in reducing morbidity and mortality in several randomized clinical trials.[4] Carvedilol is a third-generation beta-blocker that has an antioxidant effect.[5] The direct antioxidant effect of carvedilol may contribute to the reduction of oxidative stress.[6] Titration of carvedilol according to standard guidelines is conducted in not less than two weeks.[5] Slow titration may contribute to suboptimal dose and therapeutic effects due to improvement in left ventricular systolic function and reduced dose-dependent mortality.[7] Therefore, the researchers investigated the effect of the administration of carvedilol with rapid titration on MDA levels in hospitalized HFrEF patients.

METHODS

This research was a randomized, double-blind study with pre- and post-evaluations. This study is based on the core research, namely Effect of Carvedilol Rapid Up-Titration in Patients with Heart Failure with Reduced Ejection Fraction (ClinicalTrials.gov Identifier:

NCT05179070), approved by the ethics committee of the Faculty of Medicine, Universitas Sebelas Maret (UNS).[8] This study was conducted at the UNS Hospital, Sukoharjo, Central Java, from October to December 2021.

This study was conducted on 26 HFrEF patients undergoing treatment in the inpatient room using a consecutive sampling method. There were 13 patients in the carvedilol rapid titration group and 13 in the standard guideline titration group. The patient gave written consent to participate in this study.

The independent variable in this study was the rapid titration of carvedilol, and the dependent variable was MDA levels. Rapid titration is the administration of carvedilol starting at a dose of 2 x 3.125 mg and increasing daily (double dose) to a target dose of 2 x 25 mg (or the maximum dose the patient can tolerate) during treatment. The inclusion criteria were HFrEF patients who had never received carvedilol therapy or were on beta-blocker therapy at a dose that was not optimal, established by history, clinical symptoms, physical examination, echocardiography, age > 18 years, and heart rate > 50 beats per minute. The exclusion criteria were cardiogenic shock and/or requiring inotropic therapy, grade 2 or 3 atrioventricular block without a pacemaker, acute asthma, malignancy, chronic renal failure, and sepsis.

The patients were randomly divided into two groups. Group I was given 2 x 3.125 mg of carvedilol and titrated two times daily up to a maximum dose of 25 mg or the maximum dose the patient could tolerate. Group II was given an initial dose of 2 x 3.125 mg and titrated according to standard guidelines. MDA levels through intravenous blood samples were measured at the patient's initial arrival and pre-discharge. MDA levels were checked using the ELISA method in the biomedical laboratory of the Faculty of Medicine, UNS.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 22. The normality test of the data distribution was done on continuous variables with the Shapiro-Wilk test. To determine the mean difference between the treatment and control groups before and after treatment,

Table 1. Basic Characteristics of Research Subjects

Basic Characteristics	Group		*p-value*
	Group I (Carvedilol Rapid Titration) (n=13)	Group II (Control) (n=13)	
Demographic Characteristics			
Gender[a]			1.000
Male	9 (69.2%)	9 (69.2%)	
Age[b]	58.69 ± 8.89	56.62 ± 8.89	0.557
Comorbid factors			
Hypertension[a]	10 (76.9%)	9 (69.2%)	1.000
Diabetes Mellitus[a]	5 (38.5%)	4 (30.8%)	1.000
CHD[a]	5 (38.5%)	5 (38.5%)	1.000
Atrial Fibrillation[a]	2 (15.4%)	2 (15.4%)	1.000
Smoking[a]	8 (61.5%)	9 (69.2%)	1.000
Dyslipidemia[a]	5 (38.5%)	2 (15.4%)	0.378
Revascularization[a]	0 (0.0%)	1 (7.7%)	1.000
Hyperthyroid[a]	2 (15.4%)	2 (15.4%)	1.000
Gout[a]	1 (7.7%)	4 (30.8%)	0.322
Rehospitalization[a]	1 (7.7%)	1 (7.7%)	1.000
Therapy during Treatment			
ACE-I[a]	13 (100%)	13 (100%)	1.000
MRA[a]	13 (100%)	13 (100%)	1.000
Furosemide[a]	13 (100%)	13 (100%)	1.000
Amlodipine[a]	3 (23.1%)	5 (38.5%)	0.637
Statin[a]	10 (76.9%)	11 (84.6%)	1.000
Ivabradine[a]	4 (30.8%)	9 (69.2%)	0.050*
Physical Examination			
SBP (mmHg)[b]	132.77 ± 21.86	137.31 ± 26.67	0.639
DBP (mmHg)[b]	89.15 ± 14.52	87.15 ± 15.41	0.736
Heart Rate (per minute)[b]	100.69 ± 13.25	86.54 ± 14.98	0.017*
Laboratory Examination			
Hb (g/dL)[b]	13.52 ± 1.09	12.86 ± 1.45	0.207
Hct (%)[b]	39.23 ± 3.00	37.92 ± 4.50	0.392
AE (million/uL)[c]	24.74 ± 72.49	4.77 ± 0.78	0.700
AL (thousand/uL)[b]	8.73 ± 2.90	8.33 ± 2.36	0.699
AT (thousand/uL)[c]	193.54 ± 98.88	241.57 ± 101.40	0.158
Ur (mg/dL)[c]	36.46 ± 13.88	44.85 ± 29.37	0.857
Cr (mg/dL)[b]	1.03 ± 0.33	1.21 ± 0.62	0.352
Echocardiography			
EF (Simpson) (%)[b]	21.33 ± 5.43	23.58 ± 8.48	0.428
TAPSE (mm)[c]	1.54 ± 0.50	2.14 ± 1.49	0.383

Remark: The results of the observation of categorical data were described by frequency distribution (%). The results of the observation of numerical data were described by mean ± SD, [a]unpaired group difference test shows categorical data using the chi-square test/Fisher exact test. [b]unpaired group difference test shows numerical data passing the normality condition (t independent sample), unpaired group difference test shows numerical data not passing the normality requirement (Mann Whitney). *) significant if the test produces $p \leq 0.05$. CHD: coronary heart disease, ACEi: angiotensinogen converting enzyme inhibitor, MRA: mineralocorticoid receptor antagonist, SBP: systolic blood pressure, DBP: diastolic blood pressure, Hb: hemoglobin, Hct: hematocrit, AE: erythrocyte number, AL: leukocyte number, AT, platelet count, Ur: urea, Cr: creatinine, EF: ejection fraction, TAPSE: tricuspid annular plane systolic excursion.

the independent sample t-test was used if the data distribution was normal (if the data is not normal, the Mann-Whitney test is performed). To determine the mean difference between before and after treatment in one group, paired sample t-test was used if the data distribution was normal (if it is not normal, the Wilcoxon test is performed). $p < 0.05$ was considered to indicate a significant difference.[9]

RESULT

A total of 30 patients were diagnosed as HFrEF during the study period, but four were excluded since they met the exclusion criteria. There was one patient discharged at his request, two patients refused to participate in the study, and one patient died from thyroid storm in less than 24 hours. During hospitalization, monitoring of complaints, blood pressure, heart rate, lung rhonchi, ECG, and echocardiography was conducted every day. All study samples successfully passed the hospitalization without worsening and went home on the fifth day without any side effects of treatment.

Based on the basic characteristics of the research subjects (Table 1) shows that all patients in the two study groups used ACE-I, MRA, and furosemide therapy, while the use of amlodipine ($p = 0.637$) and statins ($p = 1.000$) did not show a significant difference. The therapy showing a significant difference was the use of ivabradine ($p = 0.050$) with $p < 0.05$. In group II, nine patients (69.2%) used the therapy, while only four patients in group I (30.8%) used the therapy. In general, the treatment therapy used by the two treatment groups was homogeneous except for the use of ivabradine therapy.

Physical examination of heart rate (HR) ($p = 0.017$) showed a significant difference between groups I and II, where group I had a higher average HR than group II (100.69 ± 13.25 vs. 86.54 ± 14.98).

Pre- and Post-Heart Rate (HR) Differences and Post-Pre-Difference in Group I and Group II

The results of the examination of pre and post-HR differences and post-pre differences between the treatment and control groups can be seen in Table 2. The paired difference test in group I (p

Table 2. HR Difference Test between Group I and Group II

Group	HR (per minute)		*p-value*	HR Difference
	Pre	*Post*		
Group I (n=13)	100.69 ± 13.25	70.92 ± 12.80	< 0.001*[b]	-29.77 ± 19.59
Group II (n=13)	86.54 ± 14.98	83.54 ± 16.01	0.632[b]	-3.00 ± 22.00
p-value	0.017*[a]	0.036*[a]		0.003*[a]

Remark: The results of the observations are described by mean ± SD, [a]unpaired group difference test passed the normality requirement (t independent sample), [b]paired group difference test passed the normality requirement (paired-sample t). *) Significant if the test produces $p < 0.05$.

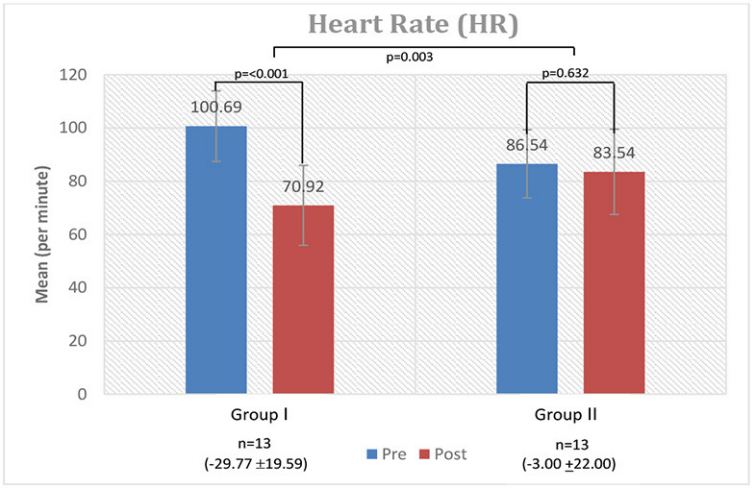

Figure 1. Bar Chart of Changes in HR between Group I and Group II

Table 3. MDA Difference Test between Group I and Group II

Group	MDA (nmol/mL)		*p-value*	MDA Difference
	Pre	*Post*		
Group I (n=13)	3.39 ± 1.21	2.84 ± 1.00	0.072[c]	-0.55 ± 1.01
Group II (n=13)	3.61 ± 2.03	3.59 ± 2.55	0.701[d]	-0.02 ± 0.84
p-value	0.959[b]	0.590[b]		0.157[a]

Remark: The results of the observations are described by mean ± SD, [a]unpaired group difference test passed the normality requirement (t independent sample), [b]unpaired different group test did not pass the normality requirement (Mann Whitney), [c]paired group difference test passed the normality requirement (paired t sample). [d]paired difference test did not pass the normality requirement (Wilcoxon rank test). *) Significant if the test produces $p < 0.05$.

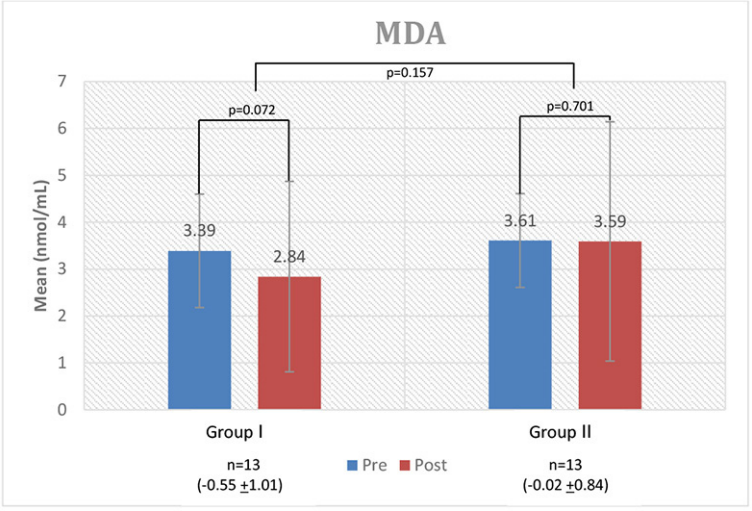

Figure 2. Bar Chart of Changes in MDA between Group I and Group II.

Table 4. MDA Subgroup Analysis Difference Test between Group I and Group II

Group	MDA (nmol/mL)		*p-value*	MDA Difference
	Pre	*Post*		
Group I (n=9)	3.70 ± 1.30	2.59 ± 0 .99	< 0.001[b*]	-1.11 ± 0 .55
Group II (n=8)	3.16 ± 0.84	2.61 ± 0 .92	0.003 [b*]	-0.55 ± 0 .35
p-value	0.336 [a]	0.972 [a]		0.028[a*]

Remark: The results of the observations are described by mean ± SD, [a]unpaired group difference test passed the normality requirement (t independent sample), [b]paired group difference test passed the normality requirement (paired-sample t). *) Significant if the test produces p < 0.05.

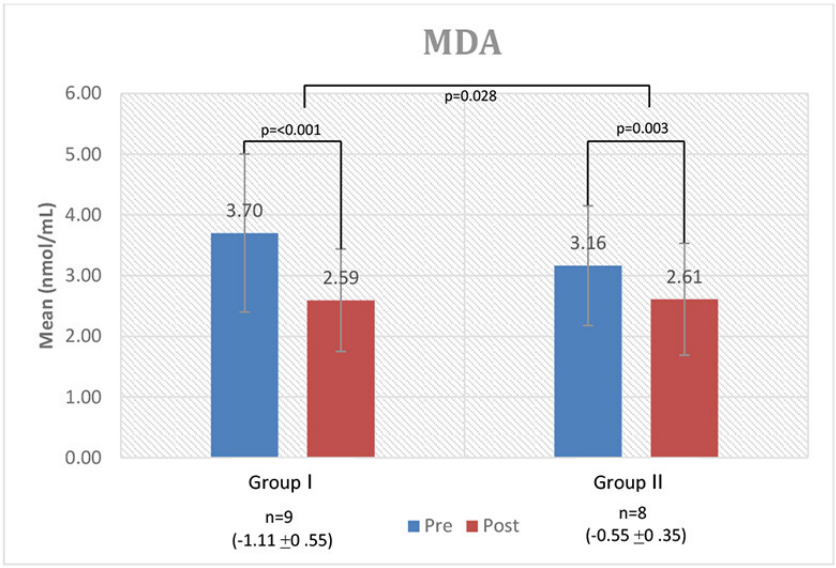

Figure 3. Bar Chart Analysis of Subgroup Changes in MDA between Group I and Group II.

= <0.001) got p < 0.05, which means that group I had a significant decrease in HR, and group II (p=0.632) got p > 0.05 meaning that group II there had no significant change in HR. Subjects in group I had a greater decrease in HR than group II. Carvedilol rapid titration treatment was effective and significant in reducing HR. This is evidenced in the unpaired difference test at the post-pre difference value (p = 0.003) with p < 0.05. Changes in HR between group I and group II can be seen in Figure 1. The carvedilol rapid titration in patients with HFrEF during hospitalization can reduce HR better than standard titration according to standard guidelines, and the results are statistically significant.

Pre- and Post-MDA Differences and Post-Pre-Difference in Group I and Group II

The results of the examination of pre, post, and post-pre-MDA differences between the treatment and control groups can be seen in Table 3. Paired difference test in group I (p = 0.072) and group II (p = 0.701) obtained p > 0.05 which means that there were no significant changes in MDA. Subjects in group I had a greater decrease in MDA than group II, but the administration of carvedilol rapid titration did not significantly reduce MDA as evidenced in the unpaired difference test on the difference in the post-pre values (p = 0.157). Changes in MDA between group I and group II can be seen in **Figure 2**.

Subgroup Analysis in Group I and Group II

In the study sample, four patients from group I and five from group II had a higher post-MDA value than the pre-MDA. The researchers analyzed a total of 9 patients from both groups. These patients had more comorbid factors. Four patients in group I had comorbid factors including hypertension, diabetes mellitus, atrial fibrillation, smoking, dyslipidemia, and hyperthyroidism. Meanwhile, five patients in group II had comorbid factors such as hypertension, diabetes mellitus, CHD, smoking, atrial fibrillation, and hyperthyroidism. Overall, 6 out of 9 patients had three comorbid factors, two patients had two comorbid factors, and one patient had one comorbid factor. Thus, the researchers conducted a subgroup analysis by eliminating patients with increased post-MDA values. The subgroup analysis results of the examination of pre, post, and post-pre-MDA differences between the treatment and control groups can be seen in Table 4.

Paired difference test in group I (p =< 0.001) and group II (p = 0.003) obtained p < 0.05 which means that group I and group II had a significant decrease in MDA. Subjects in group I had a greater decrease in MDA than group II. Carvedilol rapid titration treatment in subgroup analysis was significant in reducing MDA. This is evidenced in the unpaired difference test on the post-pre difference value (p = 0.028). Changes in MDA between group I and group II in the subgroup analysis can be seen in Figure 3. The carvedilol rapid titration in patients with HFrEF during hospitalization can reduce MDA levels better than standard titration according to proven standard guidelines, although statistically not significant.

DISCUSSION

This experimental study aims to determine the effect of carvedilol rapid titration in patients with HFrEF during hospitalization on the reduction of MDA levels. Carvedilol is a third-generation beta-blocker that can improve left ventricular systolic function, reduce hospitalization, and reduce mortality.[10] In addition, carvedilol has direct antioxidant properties that contribute to the reduction of oxidative stress.[6]

Despite these advantages, the use of beta-blockers at suboptimal doses may reduce the therapeutic effect. Therefore, the therapeutic effect is related to the dose of the drug used [7]. Standard guidelines recommend beta-blockers starting at the initial dose and titrating the dose every two

weeks if no contraindications are found.[5,11] However, increasing the dose takes at least eight weeks and could take longer in clinical practice. This can potentially decrease the efficacy of beta-blockers.[7] According to research by Ouwerkerk et al.[12] HFrEF patients who received therapy at doses less than 50% of the standard guideline recommendations had a higher risk of death and/or hospitalization due to heart failure than those who reached the optimal dose.

This study found that the average decrease in MDA levels was greater in group I compared to group II after the carvedilol rapid titration (2.84 ± 1.00 vs. 3.59 ± 2.55). However, this result was not statistically significant (p = 0.590). Group I also showed a change in post-pre-MDA with a larger mean decrease (- 0.55 ± 1.01) although not statistically significant (p = 0.157).

The researchers performed a subgroup analysis by excluding patients with increased post-MDA levels. A total of 4 patients in group I and five patients in group II experienced an increase in post-MDA. This group of patients had multiple comorbidities with 6 of 9 patients having three comorbid factors, two patients with two comorbid factors, and one patient with one comorbid factor. The analysis was performed by eliminating patients with an increase in post-MDA. It was found that carvedilol rapid titration treatment in subgroup analysis was significant in reducing MDA. This is evidenced in the unpaired difference test with the post-pre difference value (-1.11 ± 0.55 vs. - 0.55 ± 0.35; p= 0.028).

Comorbid factors such as hypertension, diabetes mellitus, CHD, atrial fibrillation, smoking, dyslipidemia, and hyperthyroidism can cause oxidative stress. The study by Kumar et al.[13] in 250 hypertensive patients and 250 control patients showed a significant increase in MDA levels in the hypertensive patient group (p < 0.001). The study of Sunita et al.[14] compared a group of patients with diabetes and those without a significant increase in MDA levels (p = 0.000). Research by Reza et al.[15] found a significant increase in patients with diabetes mellitus with CHD compared to those with diabetes mellitus alone (p = 0.000). Negreva et al.[16] found that MDA levels were significantly increased in atrial fibrillation patients (p < 0.001). Research by Shah et al.[17] in 120 male patients found that smoking significantly increased MDA levels (p < 0.001). The study by Singh et al.[18] in 50 dyslipidemic patients and 50 control patients showed that there was a significant increase in MDA levels in dyslipidemic patients (p = 0.001). The study by Olia et al.[19] in 35 hyperthyroid patients and 35 control patients showed a significant increase in MDA levels in hyperthyroid patients (p = 0.001). This shows that the presence of multiple comorbidities will lead to higher MDA levels. Thus, stricter control of comorbid factors is needed to control MDA levels.

In the study of Castro et al.[20] performed taht 30 HFrEF patients had a significant decrease in MDA levels after administration of carvedilol according to standard guidelines for six months (p < 0.001). This indicates that the evaluation in this study can be conducted longer to obtain more optimal results. Carvedilol rapid titration during the hospitalization was well tolerated in this study. These results are consistent with the findings of Selles et al.[7] which involved 611 patients with a left ventricular ejection fraction < 40%. The study concluded that carvedilol rapid titration was safe during hospitalization in heart failure patients with decreased ejection fraction.

HR at discharge, ≥ 90 times per minute could predict cardiovascular mortality independently (OR = 8.47, p = 0.016). Administration of beta-blockers was inversely associated with combined cardiovascular mortality and hospitalization at six months in patients with heart failure. Patients who received HR-modulating therapy on discharge showed low mortality and rehospitalization rates.[21] This study showed a significant decrease in HR after treatment between group I and group II (70.92 ± 12.80 vs. 83.54 ± 16.0, p = 0.036). Group I also showed a decrease in HR which was significantly better than group II (p = 0.003). This implies that carvedilol rapid titration can reduce HR better than titration according to standard guidelines.

LIMITATION

This study has several limitations; first, this study was only conducted in a single center. Second, the duration of the MDA evaluation was short during hospitalization. Third, further research is needed regarding clinical outcomes such as worsening heart failure, rehospitalization, and death. To provide more optimal results, it is necessary to conduct multicenter studies and longer MDA evaluations.

CONCLUSION

Increased carvedilol rapid titration in patients with HFrEF during hospitalization can reduce MDA levels better than titration according to standard guidelines but is not statistically significant. Rapid titration increases were well tolerated by HFrEF patients during hospitalization.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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ETHICAL CLEARANCE

This study's ethical clearance was provided by Health Research Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret No. 84/UN27.06.6.1/KEP/EC/2021.

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