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The effect of antihypertensive monotherapy and combination on blood pressure in stroke patients

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ABSTRACT

Background: Stroke is a syndrome characterized by loss of focal and function of the rapidly developing CNS. Furthermore, hypertension is a known risk factor that occurs approximately 70% of the time, and lowering systolic BP from 1 to 3 mmHg effectively reduces the risk of stroke by 20 to 30%.
Methods: An observational analytic design, using a retrospective medical record data collection in Malang City Hospital. A total of 113 patients met the inclusion criteria. In addition, the inclusion criteria include hospitalized patients with a primary diagnosis of stroke, ischemia or bleeding as evidenced by a head CT scan, having comorbid hypertension, and having received antihypertensive therapy. Meanwhile, the exclusion criteria were the BP data of the patient measured only once.
Results: The results showed the ability of antihypertensive monotherapy and combinations to lower systolic BP by 33.62 ± 30.15 mmHg and 30.50 ± 29.47 mmHg ($p = 0.744$) in ischemic patients. In comparison, diastolic BP decreased by 6.86 ± 13.18 mmHg and 11.50 ± 16.26 mmHg (0.291), respectively. Moreover, the administration in bleeding stroke patients resulted in a decrease to 16.95 ± 17.89 mmHg and 22.82 ± 23.91 mmHg, ($p = 0.029$) for systolic, and 8.63 ± 14.63 mmHg and 8.71 ± 17.17 mmHg ($p = 0.647$) for diastolic BP, respectively. Furthermore, a combination of 4 antihypertensives drugs showed a better decrease in systolic BP in both patients (44.50 ± 21.63) compared to monotherapy, and a mixture of 2 as well as three drugs, by 27.02±27.05, 25.65 ± 29.97, and 25.37 ± 25.08 ($p = 0.027$), respectively.
Conclusions: Combination therapy is recommended in stroke patients because BP can be better controlled.

Keywords: hypertension, stroke, antihypertensive therapy.
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INTRODUCTION

Stroke is a syndrome characterized by the functional loss of the focal and global central nervous system, which is believed to develop rapidly and whose symptoms last longer than 24 hours. This disease is fatal and has a high tendency, which might result in death, requiring immediate emergency treatment. The main cause is a blockage in the blood supply to the brain or a rupture of the vessels, which is believed to disrupt oxygen and nutrients, causing damage to nerve cells, affecting brain function, and developing stroke symptoms.[1-2] Based on anatomic pathology, strokes are classified into ischemic and bleeding, where the former encompasses brain tissue damages due to poor blood flow. At the same time, the latter is characterized by uncontrolled bleeding, determined to destroy cerebral cells.[3]

Hypertension is a risk factor for cardiovascular diseases, including stroke, with an incidence rate of 70%. Furthermore, only 29% of patients receive antihypertensive therapy, while barely 45% experience controlled conditions.[4] Several studies have shown that high systolic and diastolic blood pressure (BP) increases the risk of cardiovascular disease. However, it is known that a 1 to 3 mmHg decrease in systolic BP reduces the relative risk of stroke by 20 to 30%.[5]

Antihypertensive therapy helps control BP and prevent recurrent stroke. However, it is important to gradually lower the high values by considering the patient's special conditions, including the BP value and the type of stroke. Furthermore, the classes of antihypertensive drugs also include Diuretics, Angiotensin-Converting Enzyme Inhibitors (ACEI), Calcium Channel Blockers (CCB), β-Blockers (BB), Angiotensin Receptor Blockers (ARB), α-Blockers, and direct vasodilators.[6]

In Indonesia, there is minimal research to evaluate antihypertensives' use in ischemic and bleeding strokes. Therefore, this research aims to evaluate the use of antihypertensives in ischemic and bleeding stroke patients. Furthermore, numerous stroke treatments require BP monitoring when using antihypertensive to ensure better control through a routine medium.

RESEARCH DESIGN AND METHODS

Study design and participants

An observational design with retrospective data collection was used, including patients with the inclusion and exclusion

criteria. During the sampling processes, secondary data from the medical records of BP examination of stroke patients using antihypertension are used. Furthermore, the inclusion criteria include hospitalized patients with a primary diagnosis of ischemic or bleeding stroke as evidenced by head CT scans, hypertension, and those receiving antihypertensive therapy. Meanwhile, the exclusion criteria include individuals with BP data measured on it once. This research was declared ethic-worthy by the Health Research Ethics Commission of the Regional General Hospital (RSUD), Dr. Saiful Anwar, with ethical number 400/038/K.3/302/2019.

The study was conducted from March to May 2019 at RSUD Dr. Saiful Anwar Malang and Malang Muhammadiyah University Hospital. The instrument used includes a data recording sheet containing information acquired from medical records and demographics data (name, gender, and age), treatment received (type, dose, frequency, administration route and time, and also treatment duration), diagnosis, history of the disease, clinical data, and BP.

Statistical analysis

The data obtained include the BP measurement and the type of antihypertension used. These were subjected to statistical analysis using an unpaired T test to monitor the difference in the effect of monotherapy and the combination of 2 and 3 drugs on systolic and diastolic BP in both ischemic and bleeding strokes. Furthermore, a one-way ANOVA test was used to analyze the effect of each treatment separately and to compare monotherapy with an antihypertensive blend of systolic and diastolic BP in stroke patients. In addition, a transformation was performed to filter out data that was believed not to meet the one-way ANOVA requirements. However, an alternative test, called Kruskal-Wallis, was conducted under circumstances where previous processes did not fulfill the stipulated requirements. The resulting data were statistically significant at a p-value < 0.05.

RESULTS

The antihypertensive drugs used by

Table 1. Distribution of patients based on antihypertensive groups use

Antihypertensive Drug Classes		Sample (n)*	Percentage (%)
Calcium Channel Blockers (CCB)			
Amlodipine		80	74.1
Nifedipine		2	1.9
Nimodipine		16	14.8
Nicardipine		9	8.3
Diltiazem		1	0.9
	Total	108	95.6**
Angiotensin Receptor Blockers (ARB)			
Valsartan		65	92.9
Candesartan		4	5.7
Irbesartan		1	1.4
	Total	70	61.9**
β-Blockers (BB)			
Bisoprolol		6	100.0
	Total	6	5.3**
Angiotensin Converting Enzyme Inhibitors (ACEI)			
Lisinopril		6	85.7
Captopril		1	14.3
	Total	7	6.2**
Diuretics			
Furosemide		8	53.5
Hydrochlorothiazide (HCT)		6	40.0
Spironolactone		1	6.7
	Total	15	13.3**

Description:
*one patient received more than one type of antihypertensive
** the percentage calculation method is the total number of drug users in each drug class divided by the number of patients (113 patients)

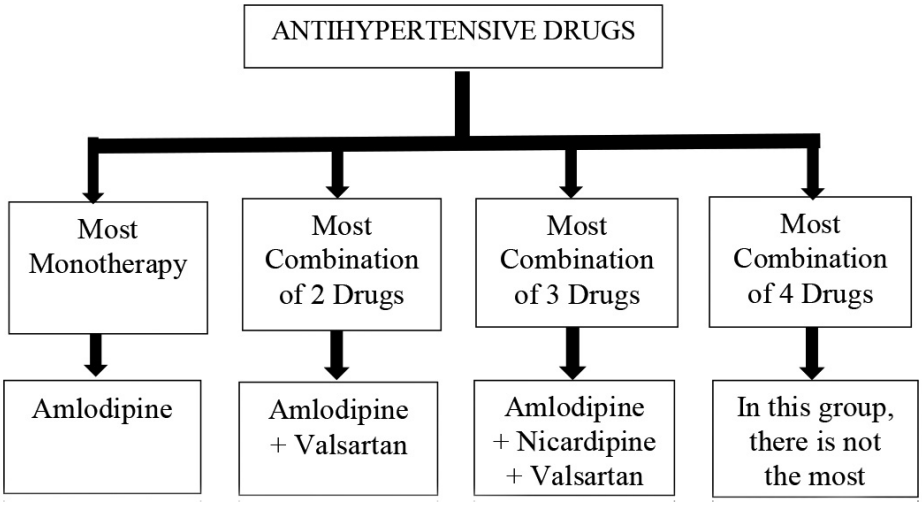

Figure 1. The most common use of monotherapy and combination antihypertensive

each patient are different. The profile of the antihypertensive drug usage can be seen in Table 1. The most widely administered antihypertensive group was the CCB group, which was 108 patients (95.6%), followed by the ARB group of 70 patients (61.9%). In the CCB class, amlodipine was the most frequently administered, with a total of 80 patients.

In this study, the administration of antihypertensives was grouped into the use of monotherapy and the combination, as shown in Table 2. Based on antihypertensive drugs, the combination of antihypertensives was administered more (57.5%) than monotherapy (42.5%). The most frequently administered combination of drugs was a combination of two, namely the CCB and ARB groups, which were 36 patients (31.9%). The most widely used antihypertensive monotherapy and the combination can be seen in Figure 1. The most commonly used antihypertensive drug from the monotherapy group is amlodipine; from the two-drug combination group, the most widely used is amlodipine + valsartan; from the three-drug combination group, the most commonly used is amlodipine + nicardipine + valsartan, while, from the four-drug combination group, no drug combination was most widely used.

Table 3 shows the effect of using antihypertensive drugs on systolic and diastolic BP in both ischemic and bleeding stroke patients. The results of the unpaired T-test showed that either monotherapy or combination antihypertensive provision could reduce systolic and diastolic BP. However, a statistically significant decrease in BP was seen in systolic BP from combination antihypertensive administration in hemorrhagic stroke patients ($p = 0.029$).

In this study, a One-Way ANOVA and Kruskal Wallis test was also conducted to determine the differences in BP in each treatment group, namely the monotherapy group, the combination of 2 drugs, the combination of 3 drugs, and between monotherapy and combination. For a combination of 4 drugs, the test cannot be carried out because in each combination there is only one data. The results of the One-Way ANOVA and Kruskal Wallis analysis for each drug group are presented

Table 2. Distribution patterns of antihypertensive monotherapy and combination use

Antihypertensive Drug Classes		Sample (n)	Percentage (%)
Monotheraphy			
CCB			
Amlodipine		23	71.9
Nimodipine		8	25.0
Nicardipine		1	3.1
	Total	32	28.3*
ARB			
Valsartan		9	75.0
Candesartan		3	25.0
	Total	12	10.6*
ACEI			
Lisinopril		4	100.0
	Total	4	3.5*
Combination of two drugs			
CCB + ARB			
Amlodipine + Valsartan		30	83.3
Amlodipine + Irbesartan		1	2.8
Nifedipine + Valsartan		1	2.8
Nimodipine + Valsartan		3	8.3
Nicardipine + Valsartan		1	2.8
	Total	36	31.9*
CCB + Diuretic			
Amlodipine + Furosemide		3	100.0
	Total	3	2.7*
ARB + ACEI			
Candesartan + Lisinopril		1	100.0
	Total	1	0.9*
ARB + Diuretic			
Valsartan + Furosemide		1	100.0
	Total	1	0.9*
CCB + CCB			
Amlodipine + Nicardipine		1	100.0
	Total	1	0.9*
Combination of three drugs			
CCB + ARB + Diuretic			
Amlodipine + Valsartan + Furosemide		3	50.0
Amlodipine + Valsartan + HCT		2	33.3
Dilitiazem + Valsartan + HCT		1	16.7
	Total	6	5.3*
CCB + CCB + ARB			
Amlodipine + Nimodipine + Valsartan		3	33.3
Nimodipine + Nicardipine + Valsartan		1	11.1
Amlodipine + Nimodipine + Candesartan		1	11.1
Amlodipine + Nicardipine + Valsartan		4	44.4
	Total	9	8.0*
CCB + BB + ARB			
Amlodipine + Bisoprolol + Valsartan		3	100.0
	Total	3	2.7*
CCB + BB + ACEI			
Amlodipine + Bisoprolol + Lisinopril		1	100.0
	Total	1	0.9*
Combination of four drugs			
CCB + CCB + BB + ARB			
Amlodipine + Nicardipine + Bisoprolol + Valsartan		1	100.0
	Total	1	0.9*
CCB + ARB + Diuretic + Diuretic			
Amlodipine + Candesartan + Furosemide + Spironolactone		1	100.0
	Total	1	0.9*
CCB + BB + ARB + Diuretic			
Amlodipine + Bisoprolol + Valsartan + HCT		1	100.0
	Total	1	0.9*
CCB + CCB + ARB + Diuretic			
Amlodipine + Nifedipine + Valsartan + HCT		1	100.0
	Total	1	0.9*

Description:
* the percentage calculation method is the total number of drug users in each drug class divided by the number of patients (113 patients)

Table 3. Results of unpaired T test for BP in stroke patients

BP Systolic/Diastolic	Type of Therapy	n	Mean Change BP ± SD (mmHg)	p
Ischemic Stroke				
Systolic	Monotheraphy	30	33.62 ± 30.15	0.744
	Combination	21	30.50 ± 29.47	
Diastolic	Monotheraphy	30	6.86 ± 13.18	0.291
	Combination	21	11.50 ± 16.26	
Hemorrhagic Stroke				
Systolic	Monotheraphy	19	16.95 ± 17.89	0.029*
	Combination	45	22.82 ± 23.91	
Diastolic	Monotheraphy	19	8.63 ± 14.63	0.647
	Combination	45	8.71 ± 17.17	

Description:
* p value < 0.05 shows statistically significant results.
The difference between the systolic and diastolic BP values (+) shows that blood pressure decreases after the administration of antihypertensive drugs.
The difference between systolic and diastolic BP values (-) indicates increased BP after antihypertensive provision.

in Table 4.

The effect on changes in systolic and diastolic blood pressure was observed with each administration of drug groups to patients with stroke. Based on the One Way ANOVA test results, it is known that the three-drug combination groups showed a statistically significant change in diastolic BP (p = 0.026), as presented in Table 4. Based on these results, it can be seen that the combination of 3 drugs that can lower diastolic BP the most is CCB + BB + ARB, namely 16.67 ± 20.82 mmHg. However, based on the post-hoc test in Table 5, the results showed that the combination of 3 drugs that showed a difference in diastolic BP reduction was

Table 4. Analysis result of one-way ANOVA and Kruskal Wallis for BP of the stroke patient

BP Systolic/Diastolic	Drug Classes	n	Mean Change BP ± SD (mmHg)	p
Monotheraphy Drugs Group				
Systolic	CCB	32	28.66 ± 30.28	0.064
	ARB	12	23.33 ± 20.93	
	ACEI	4	25.00 ± 17.32	
Diastolic	CCB	32	8.72 ± 13.69	0.806
	ARB	12	5.33 ± 13.16	
	ACEI	4	5.00 ± 32.00	
2 Drugs Combination Group				
Systolic	CCB + ARB	36	22.81 ± 28.83	0.447
	CCB + Diuretic	12	63.33 ± 32.15	
	ARB + ACEI	3	20.00 ± 0.00	
	Diuretic + ARB	1	0.00 ± 0.00	
	CCB + CCB	1	46.00 ± 0.00	
Diastolic	CCB + ARB	36	7.44 ± 15.53	0.085
	CCB + Diuretic	12	26.67 ± 5.77	
	ARB + ACEI	3	10.00 ± 0.00	
	Diuretic + ARB	1	-10.00 ± 0.00	
	CCB + CCB	1	2.00 ± 0.00	
3 Drugs Combination Group				
Systolic	CCB + ARB + Diuretic	6	25.00 ± 21.68	0.440
	CCB + CCB + ARB	9	18.67 ± 21.73	
	CCB + BB + ARB	3	16.67 ± 15.28	
	CCB + BB + ACEI	1	0.00 ± 0.00	
Diastolic	CCB + ARB + Diuretic	6	5.00 ± 10.49	0.026*
	CCB + CCB + ARB	9	7.50 ± 19.94	
	CCB + BB + ARB	3	16.67 ± 20.82	
	CCB + BB + ACEI	1	-30.00 ± 0.00	
Monotherapy and Combination Group				
Systolic	Monotherapy	48	27.02 ± 27.05	0.027*
	2 Drugs Combination	42	25.65 ± 29.97	
	3 Drugs Combination	19	25.37 ± 25.08	
	4 Drugs Combination	4	44.50 ± 21.63	
Diastolic	Monotherapy	48	7.56 ± 13.64	0.746
	2 Drugs Combination	42	8.33 ± 15.56	
	3 Drugs Combination	19	10.26 ± 20.03	
	4 Drugs Combination	4	19.25 ± 19.55	

Description:
* p value < 0.05 shows statistically significant results.
The difference between the systolic and diastolic BP values (+) shows that blood pressure decreases after administration of antihypertensive drugs.
The difference between systolic and diastolic BP values (-) indicates an increase in BP after antihypertensive provision.

Table 5. Analysis result of post-hoc for BP at stroke patient

Drug Classes	Mean Difference	95%CI		p
		Minimum	Maximum	
Group of 3 Drugs Combination				
CCB + ARB + Diuretic vs CCB + CCB + ARB	-11.11	-30.87	8.65	0.251
CCB + ARB + Diuretic vs CCB + BB + ARB	-11.67	-38.18	14.85	0.365
CCB + ARB + Diuretic vs CCB + BB + ACEI	35.00	4.38	65.62	0.028*
CCB + CCB + ARB vs CCB + BB + ARB	-0.56	-25.55	24.44	0.963
CCB + CCB + ARB vs CCB + BB + ACEI	46.11	16.80	75.42	0.004*
CCB + BB + ARB vs CCB + BB + ACEI	46.67	12.44	80.90	0.011*
Monotherapy and Combination				
Monotherapy vs 2 Drugs Combination	1.38	-0.624	0.70	0.100
Monotherapy vs 3 Drugs Combination	1.65	-0.147	0.84	0.167
Monotherapy vs 4 Drugs Combination	-17.48	-1.912	-0.02	0.045*
2 Drugs Combination vs 3 Drugs Combination	0.27	-0.478	0.53	0.924
2 Drugs Combination vs 4 Drugs Combination	-18.86	-2.238	-0.34	0.008*
3 Drugs Combination vs 4 Drugs Combination	-19.13	-2.311	0.03	0.010*

Description:
* p value < 0.05 shows statistically significant result.

CCB + BB + ACEI. Still, the combination of 3 drugs caused an increase in diastolic BP by 30.00 mmHg. Based on Table 4 and **5**, it can also be seen that giving a combination of 4 drugs (44.50 ± 21.63 mmHg) can reduce systolic BP the best compared to monotherapy (27.02 ± 27.05 mmHg), a combination of 2 drugs (25.65 ± 29.97 mmHg), and a combination of 3 drugs (25.37 ± 25.08 mmHg) with p-value = 0.027.

DISCUSSION

This study obtained data from 113 ischemic and bleeding stroke patients receiving antihypertensive treatment, which consists of 64 males (56.6%) and 49 females (43.4%). The results showed that men are dominantly affected by stroke. This is corroborated by reports from the American Heart Association, where a 41% higher incidence was recorded.[7]

Regarding the age of the patients, the results showed an age distribution of 33 to 88 years in patients with stroke and comorbid hypertension. The majority were between 51-60 years, consisting of 32 patients (28.3%). Furthermore, this risk is doubled every decade between the age 45-85. Therefore, this result is confirmed by Choudhury *et al.* (2015) report of the highest risk ratio in the age range of 55-64.[8]

Based on history, approximately 91 patients (80.5%) developed hypertension, a major risk factor for stroke reported in 17 cases (15.0%) and was variable with good BP control. The wall structure and composition of the cerebral blood vessels change at high levels, and uncontrolled hypertension has been linked to recurrent strokes. This is possibly attributed to the development of atherosclerotic plaque leading to vessels blockages and ischemic strokes, or aneurysms, which are considered hemorrhagic.[9]

According to the inclusion criteria, all participants had comorbid hypertension, and the second highest comorbidity experienced by 38 patients (33.6%) was dyslipidemia, which was characterized by a high lipid profile. This condition occurs due to metabolic and immunological mechanisms in which fatty acids form clots that are believed to play an important role in atherosclerosis development. Therefore, the results show activation of inflammatory cells, endothelial damage, and smooth muscle proliferation.[10]

The observation data were obtained from 113 patients comprising 49 (43.4%) with ischemic stroke and 64 (56.6%) with hemorrhagic. Jane *et al.* (2012) posited a greater prevalence of ischemic strokes (77.6%) than hemorrhagic (22.4%), and the inverse was recorded in this current investigation.[11] This was due to the active treatment of recruited patients with antihypertensives. Meanwhile, not all ischemic stroke patients could be recruited in this research. Those that did not receive antihypertensive therapy cannot be included in the sample.

A study showed that using the CCB group can reduce the risk of stroke by 10%, although this is not significant compared to other groups. This class of drugs can also reduce the risk of stroke by 13.5% compared to Diuretics and β-Blockers.[12] The combination therapy of two to four antihypertensive drugs has significantly reduced BP better than monotherapy. This may be due to the combination of a different antihypertensive drug that works by different mechanisms and can reduce the potential for side effects. In general,

combination therapy is more effective in lowering BP than increasing monotherapy doses.[13]

The extensive nanotherapeutic use of CCB groups was observed in 32 patients (28.3%). Amlodipine was also common because of the numerous beneficial effects, including the reduction of diastolic BP to the target (71%). In particular, this treatment reduces the risk of stroke by 50% and is not involved the side effects, including tachycardia. Furthermore, a study affirms an upsurge in the effects of nitric oxide, with proven benefits. Therefore, amlodipine is preferable in patients with cardiovascular diseases compared to ARBs.[14]

The drug combination administered mainly comprises CCB + ARB. These provide potential BP reduction effects through several mechanisms, as the ARBs influence the Renin Angiotensin Aldosterone System (RAAS) by inhibiting the angiotensin II type 1 receptor. Furthermore, vasodilation is stimulated by the excretion of sodium and water. This pathway improves cardioprotective and renoprotective properties, while CCB inhibits calcium channels in vascular smooth muscle cells and reduces peripheral vascular resistance. In addition, over 50% of patients treated with this combination therapy attain the BP target within two weeks. This is evident by the 35.8 mmHg and 28.6 mmHg decline in systolic and diastolic BP, respectively.[15]

Our results showed that the provision of antihypertensive, either monotherapy or in combination, reduces systolic and diastolic BP in both ischemic and bleeding stroke patients. However, only the 3-drug combination group showed statistically significant changes in diastolic BP. These results align with research conducted by Noubiap (2015), that the combination of antihypertensives can significantly reduce systolic BP and the incidence of stroke compared to monotherapy.[16]

The three-drug combinations that showed the greatest difference in diastolic BP reduction were CCB + BB + ARB. Meanwhile, the three-drug combination containing ACEI, consisting of CCB + BB + ACEI, showed an increase in diastolic BP. This can be caused by the absence of ARB content in the three-drug combinations but instead contained ACEI. ACEI in this combination is thought to be less effective in reducing BP because it only inhibits the formation of angiotensin II indirectly in the Angiotensin Converting Enzyme (ACE) pathway. Meanwhile, a non-ACE pathway can result in the formation of angiotensin II, which ACEI does not inhibit; therefore, the vasodilation effect is less than optimal because there are many vasoconstrictors of angiotensins II. This is different from ARB, which works by directly inhibiting the formation of angiotensin II. Therefore, the ability of ARB to reduce BP is better than ACEI.[15]

The provision of CCB + ARB + Diuretic or CCB + CCB + ARB therapy reduces diastolic BP to the target level without increasing side effects. Furthermore, CCB and ARB potentially reduce BP through several mechanisms: calcium channel blocking in vascular smooth muscle cells and angiotensin II receptors inhibition, respectively.[17] The results show that the provision of a four antihypertensive drug combination has the best ability to reduce systolic BP compared to monotherapy, two-drug combination, or three-drug combination. Therefore, a combination of antihypertensives should be administered to lower blood pressure in patients with ischemic and bleeding strokes.

CONCLUSION

This study concluded that combining antihypertensive drugs resulted in better BP lowering than monotherapy.

ABBREVIATIONS

ACE, Angiotensin Converting Enzyme; ACEI, Angiotensin Converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; ANOVA, analysis of variance; BP, blood pressure; BB, β-Blockers; CCB, Calcium Channel Blockers; CNS, central nervous system; RAAS, Renin Angiotensin Aldosterone System; SD, standard deviation.

AUTHOR CONTRIBUTION

All authors contributed to all stages of the research process starting from drafting the research concept, collecting data, analyzing the results, compiling the research paper, and approving the publication of this research manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL

This research has been ethically approved by the Health Research Ethics Commission of the Regional General Hospital (RSUD), Dr. Saiful Anwar, with ethical number 400/038/K.3/302/2019

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