INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

CHANGES IN PLATELET AGGREGATION AND NIHSS AFTER ANTI-PLATELET THERAPY FOR ACUTE ISCHEMIC STROKE PATIENTS AT H. ADAM MALIK GENERAL HOSPITAL MEDAN

Novi Apriani*[1], Puji Pinta O. Sinurat[2] & Alfansuri Kadri[2]
[*1]Resident Department of Neurology, Faculty of Medicine, University of North Sumatera
[2]Department of Neurology staff, Faculty of Medicine, University of North Sumatera

DOI: https://doi.org/10.29121/ijrsm.v7.i8.2020.8
Keywords: Platelet Aggregation, NIHSS, Acute Ischemic Stroke.

Abstract
Background: Acute ischemic stroke is caused by blockage of the cerebral arteries due to thrombus originating from excessive clotting of platelets. Increased platelet activity impacts the risk of atherothrombosis. The clinical impact of this blockage can be seen in changes in platelet aggregation and *NIHSS* after anti-platelet administration.
Objectives: This study aims to determine changes in platelet aggregation and *NIHSS* after administration of anti-platelet therapy in acute ischemic stroke patients.
Methods: This study was a *Quasi Experimental Study* with the method of *Pre and Post-test Only Group* selected by consecutive *non-random sampling* technique, in which patients diagnosed with ischemic stroke treated at H Adam Malik General Hospital Medan. The study began from March to July 2020.
Results: The study was conducted on 38 samples consisting of 18 men and 20 women with an average age of 58.92(±7.539) years. There was a significant change between platelet aggregation and *NIHSS* ($p<0.001$). There was a significant relationship between platelet aggregation with *NIHSS* the first day before the administration of anti platelets ($p=0.018$) and correlation test ($r=0.339$) positive direction (unidirectional). There was no significant relationship between platelet aggregation with *NIHSS* in the seventh day after anti platelet administration ($p=0.394$).
Conclusions: There were significant changes between platelet aggregation and *NIHSS* scores. There was a significant relationship between platelet aggregation and *NIHSS* the first day before anti platelet administration. There was no significant relationship between platelet aggregation and *NIHSS* in the seventh day after anti platelet administration.

Introduction
Stroke is actually the second leading cause of death and third rank disability worldwide. In Europe stroke is the second highest cause of death in the incidence of 1.1 million deaths per year.[1] In America, stroke is currently the fourth cause of death.[2] Data in Indonesia, stroke is in the third position of the degenerative disease group after heart disease and malignancy.[3]

Ischemic stroke is the most common, accounting for 80% of all strokes.[4] Acute ischemic stroke is caused by blockage or occlusion of the cerebral artery caused by blood clots (thrombus) that comes from excessive clotting of platelets.[5,6] Aggregation is the ability of platelets to stick together to form a blockage. Initial aggregation caused by surface contact and liberation *Adhenosinediphospate* (*ADP)* from another platelets attached to the surface of endothelial this is called primary aggregation wave. The more platelets involved, the more *ADP* is released, resulting in a secondary aggregation wave accompanied by more platelet recruitment.[7,8]

Increasing health services will increase the life expectancy of ischemic stroke patients.[9] *The National Institutes of Health Stroke Scale* is a quantitative measurement of stroke neurological deficits that has been shown to be justified and has predictive validity for long-term stroke *outcome*.[10]

Aspirin or acetylsalicylic acid is a non-steroidal anti-inflammatory drug that has a strong anti-platelet effect. Aspirin is an antithrombotic which works by irreversibly acetylating the cyclooxygenase (COX-1) enzyme to inhibit the conversion of arachidonic acid to prostaglandins, which will then form thromboxane A2 (TXA2) so that platelet aggregation cannot occur.[11]

There is still very little research data that looks at changes in platelet aggregation values and functional outcomes using *NIHSS* in acute ischemic stroke associated with anti-platelet use. There are several studies, including by

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Kusnardi and Mahfoed (2013) which found that there is a strong positive correlation with r=0.661 between platelet aggregation against *Adhenosinediphospate (ADP)* and functional outcome in acute ischemic stroke.[12] A study by Rosita et al (2011) used the Gajah Mada Stroke Scale as a measurement of clinical outcome of ischemic stroke in patients who were examined for platelet aggregation. The results of his research found that stroke patients with acute infarction with high platelet aggregation will give a relative risk of 2.15 times the occurrence of poor clinical outcomes compared to patients without clotting excess platelets.[13] Research by Ick et al (2014) looked at the comparison of platelet aggregation values in patients who were given aspirin and not given aspirin in hypertensive patients. The results of his study showed that the average platelet aggregation value given aspirin was lower than those who were not given aspirin in hypertensive patients.[14]

Method

Study sample

The research subjects were taken from the patient population of H. Adam Malik General Hospital Medan. The research subjects were determined according to the consecutive *non-random sampling* method. This research subject consisted of all fisrt ever acute ischemic stroke patients confirmed by head *CT-scan* and gave consent to participate in this study.

Study design

This research is a *Quasi Experimental Study* with the method of *Pre and Post-test Only Group.* There is treatment by anti-platelet therapy to all acute ischemic stroke patients who undergo treatment at the *Stroke Corner, High Dependency Unit* and *High Care Unit* H. Adam Malik Hospital Medan.

Statistical analysis

Data were analyzed is statistically with the aid of a computer program *Windows SPSS* (*Statistical Product and Science Service*) version 25.0. To see the changes in platelet aggregation and *NIHSS* after anti-platelet therapy, the relationship between platelet aggregation and *NIHSS* on the first and seventh day.

Result

Ischemic stroke patients who underwent treatment at H. Adam Malik General Hospital Medan from March 2020 to July 2020, there were 38 ischemic stroke patients who met the study criteria. This stroke patient was the first ever acute ischemic stroke.

Based on the characteristics of the 38 research subjects, it was found that the age of all study subjects had a mean of about 58.92±7.54 with the largest age range at the age of 55–<65 years, namely 21 subjects (55.3%). Most of the research subjects were female, as many as 20 subjects (52.6%). The educational level of research subjects was at most senior high school as many as 22 subjects (57.9%) and the least was primary school and undergraduate as many as 5 subjects (13.2%). The occupational status of respondents at most did not work as many as 20 subjects (52.6%) while respondents who worked were 18 subjects (47.4%). Most of the respondents ethnicity is the Batak ethnic group as many as 25 subjects (65.8%). For complete data regarding the characteristics of the subject of this study are presented in table 1 below.

Table 1. Description of the Characteristics of Research Subjects

Characteristics respondents	Average	n (38)	Percentage (%)
	58.92(±7.54)		
Age (years)			
• 45-<55 years		12	31.6
• 55-<65 years		21	55.3
• 65->75 years		5	13.2
Gender			
• Male		18	47.4
• Women		20	52.6
Education			
• Primary school		5	13.2
• Junior High school		6	15.8
• Senior High school		22	57.9
• Bachelor		5	13.2

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Job		
• Unemployment	20	52.6
• Work	18	47.4
Ethnic Group		
• Batak	25	65.8
• Malay	8	21.1
• Java	4	10.5
• Aceh	1	2.6

Descriptive analysis of the characteristics of the platelet aggregation score in this study showed that the platelet aggregation value on the first day was the hyperaggregation category of 28 subjects (73.3%). Value platelet aggregation on seventh day with the characteristics of the most widely aggregation is normoagregasi category as many as 37 subjects (97.4%). This can be seen in table 2 below.

Table 2. Characteristics of Platelet Aggregation Score

Characteristics of PlateletsAggregation	**N (38)**	**Percentage (%)**
Aggregation day 1		
• Normoaggregation	10	26.3
• Hyperaggregation	28	73.3
Aggregation day 7		
• Normoagegation	37	97.4
• Hyperaggregation	1	2.6

Descriptive analysis of the characteristics of the *NIHSS* score in this study used the median (minimum-maximum) value because the data were not normally distributed. Obtained the *NIHSS* score first day was 11.50(4-21), with the characteristic neurological deficits that most of the categories were as many as 19 subjects (50.0%). The *NIHSS* value on the seventh days was 6.50(1 - 17), with the most characteristic neurological deficits in the moderate category as many as 21 subjects (55.3%). This can be seen in table 3 below.

Table 3 . Characteristics of the NIHSS Score

Score characteristics	**Median (min-max)**	**n (38)**	**Percentage (%)**
NIHSS score on day 1	11,50(4-21)		
• Mild		3	7.9
• Moderate		19	50.0
• Severe		16	42.1
NIHSS score on day 7	6,50 (1-17)		
• Mild		16	42.1
• Moderate		21	55.3
• Severe		1	2.6

This study was to determine the changes between the first day of platelet aggregation and the seventh day after the administration of anti-platelet therapy to test *Wilcoxon* to 38 research subjects showed that there is influence significantly after administration of anti-platelet therapy to changes in platelet aggregation (p<0.001). It can be explained that there was no negative change, namely a change from normoaggregation to hyperaggregation. There were 27 subjects experiencing positive changes, namely changes from hyperaggregation to normoaggregation. Furthermore, there were 11 subjects experiencing no changes (ties), namely from hyperaggregation to

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

hyperaggregation as much as 1 subject and from normoaggregation to still being normoaggregated by 10 subjects. This can be seen in table 4 below.

Table 4. Changes in Platelet Aggregation

PlateletsAggregation	Aggregation Change		Change		*p*
	D1	D7			
	n	n		n	
Normoaggregation	10	37	Negative change	0	
Hyperaggregation	28	1	Positive change	27	<0.001
			Ties	11	

D1 : Platelet aggregation on first day before anti platelet therapy, D2 : Platelet aggregation on seventh day after anti platelet therapy. With *Wilcoxon test*

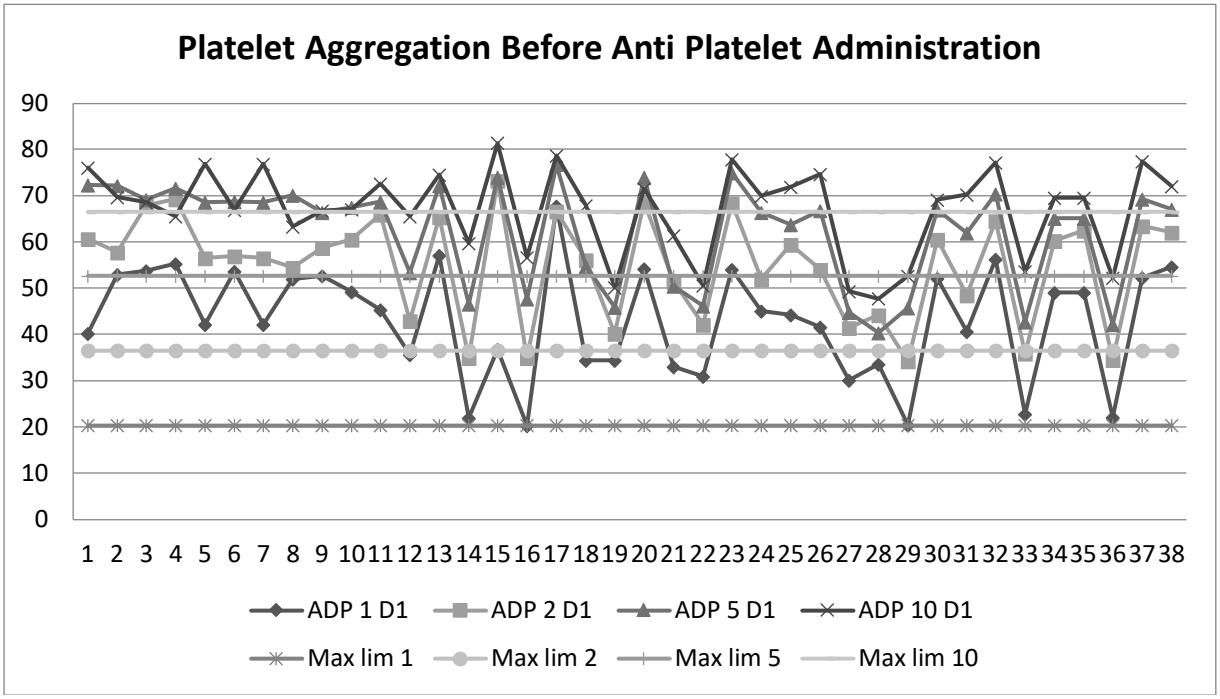

Figure 1. Shows that the platelet aggregation values with ADP mediator 1, 2, 5 and 10 µm before anti-platelet administration in ischemic stroke patients are above normal values. ADP 1 D1 = Adhenosinediphospate 1µm before anti-platelet administration, ADP 2 D1 = Adhenosinediphospate 2µm before anti-platelet administration, ADP 5 D1 = Adhenosinediphospate 5µm before anti-platelet administration, ADP 10 D1 = Adhenosinediphospate 10µm before anti-platelet administration

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

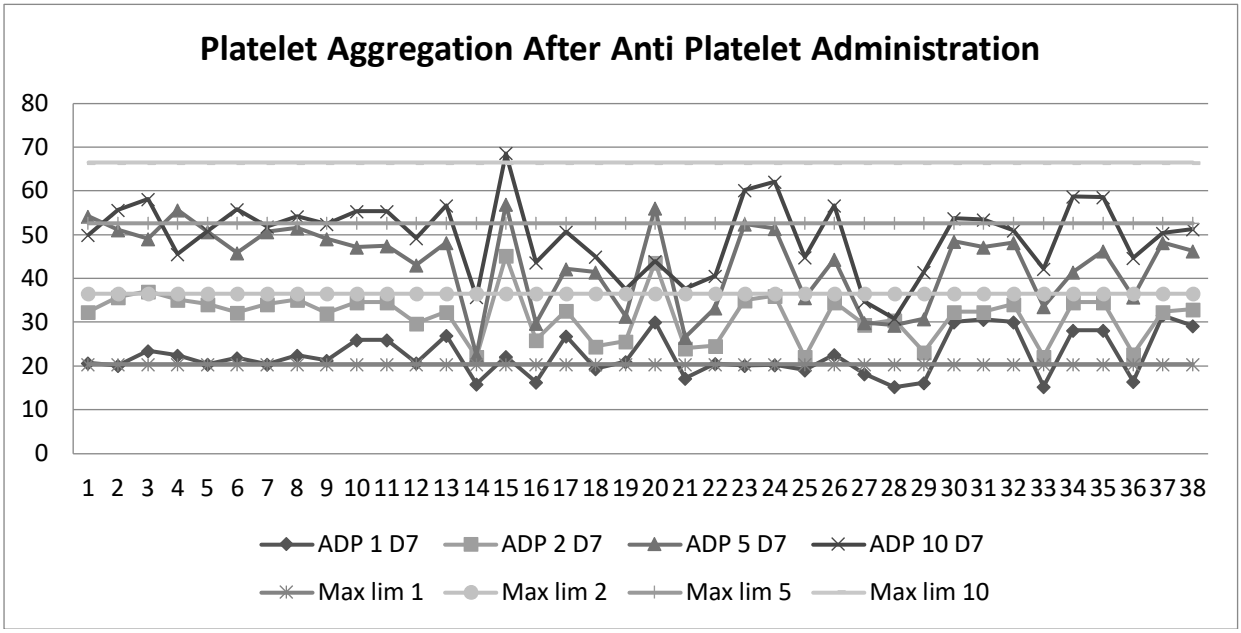

Figure 2. Shows that there is a decrease in the platelet aggregation values with ADP mediators of 1,2,5 and 10 µm after anti-platelet administration. ADP 1 D7 = Adhenosinediphospate 1µm after anti-platelet administration, ADP 2 D7 = Adhenosinediphospate 2µm after anti-platelet administration, ADP 5 D7 = Adhenosinediphospate 5µm after anti-platelet administration, ADP 10 D7 = Adhenosinediphospate 10µm after anti-platelet administration.

In this study is also to determine the change in *NIHSS* the first day and the seventh after anti-platelet therapy following administration of *Wilcoxon test* to 38 research subjects showed that there is influence significantly after administration of anti-platelet to change the prognosis using the *NIHSS* ($p<0.001$). It can be explained that there was no negative change, namely the change in *NIHSS from* mild to moderate or severe as well as from moderate to severe. There were 28 subjects experiencing positive changes, namely the change from severe to moderate *NIHSS* scores by 15 subjects and there were moderate to mild changes as many as 13 subjects. Furthermore, there were 10 subjects experiencing no changes (ties), namely 1 subject from severe *NIHSS* remained to severe, while 6 subjects from moderate *NIHSS* remained to moderate and from mild *NIHSS* to mild as many as 3 subjects. This can be seen in table 5 below.

Table 5 .NIHSS changes

NIHSS	***NIHSS* changes**		**Change**		***p***
	D1	**D7**			
	n	**n**		**n**	
Mild	3	16	Negative change	0	
Moderate	19	21	Positive change	28	<0.001
Severe	16	1	Ties	10	

D1 : *NIHSS* on first day before anti platelet therapy, D2 : *NIHSS* on seventh day after anti platelet therapy
With Wilcoxon test

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

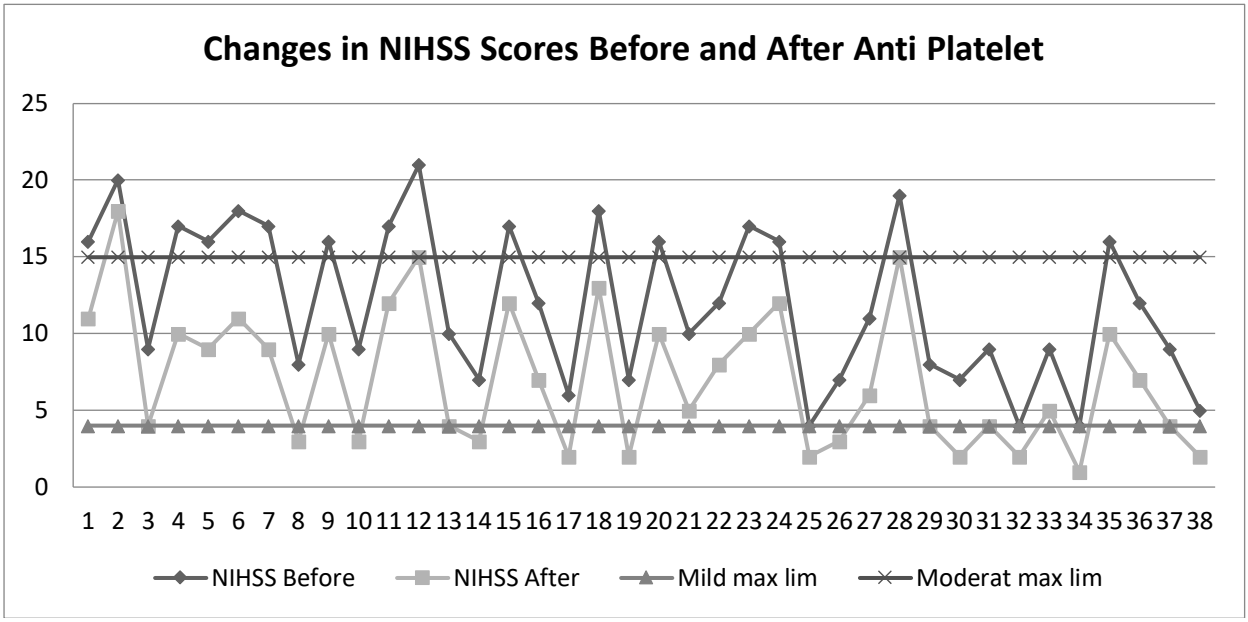

Figure 3 Shows that there is a change in the NIHSS value after anti-platelet administration. NIHSS before : The National Institutes of Health Stroke Scale before anti-platelet administration. NIHSS after : The National Institutes of Health Stroke Scale after anti-platelet administration. Mild max lim : the maximum limit for the mild group NIHSS value. Moderat max lim : the maximum limit for the moderat group NIHSS value.

In this study, to determine the relationship between platelet aggregation and *NIHSS* the first day before the administration of anti-platelet therapy , the *Mann-Whitney* test was performed on 38 study subjects.The results showed that there was a significant relationship between platelet aggregation and *NIHSS* (*p=0.018)* and *correlation* test obtained *r*=0.339 in a positive direction (unidirectional), meaning that if the platelet aggregation is hyperaggregated, the *NIHSS* obtained will also get increased and vice versa. This can be seen in table 6 below.

Table 6 . Relationship between Platelet Aggregation and NIHSS first day before Anti Platelet Therapy

Platelet Aggregation on the first day	*NIHSS* the first day						Total		*r*	*p*
	Severe		Moderate		Mild					
	n	%	n	%	n	%	n	%		
Hyperaggregation	15	53.5	10	35.7	3	10.7	28	100	0.339	0.018
Normoaggregation	1	10	9	90	0	0	10	100		

Mann-Whitney test

In this study to determine the relationship between platelet aggregation with *NIHSS* the seventh day after the administration of anti platelet therapy, *Mann-Whitney test* to 38 research subjects showed that no correlation were significant between platelet aggregation with *NIHSS* after administration of anti platelet (*p*=0.394). It is different from the previous point which saw the relationship between platelet aggregation and *NIHSS* before giving anti-platelet therapy which has a significant relationship. This can be seen in table 7 below.

Table 7 . Relationship between Platelet Aggregation and NIHSS seventh day After Anti Platelet Therapy

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Platelet Aggregation on the seventh day	*NIHSS* the seventh day						Total		*p*
	Severe		Moderate		Mild				
	n	%	n	%	n	%	n	%	
Hyperaggregation	0	0	1	100	0	0	1	100	0.394
Normoaggregation	1	2.7	20	54.1	16	43.2	37	100	

Mann-Whitney test

Discussion

Based on the characteristics of 38 research subjects, it was found that the ages of all ischemic stroke subjects in this study had a mean of 58.92±7.54 with the largest age range of 55–<65 years, namely 21 subjects (55.3%). The results of this study are relevant to previous research conducted by Rambe et al (2013) which stated that the mean age of stroke patients was 59 years (age range 20–95 years) and the highest number of subjects was 40–59 years.[15] In a study conducted by Ick et al (2014), it was found that the characteristics of the most ischemic stroke subjects were in the age group >60 years as many as 20 people (66.7%). Increasing the age of more than 60 years found the risk of developing hypertension by 11,340 times when compared to those aged less than 60 years.[14] Research conducted by Kusnardi et al (2013) also shows the results mean age relevant to the research that is equal to 63.70±9.84 with an age range 50-85 years.[12]

The research subjects were female as many as 20 subjects (52.6%) more than men as many as 18 subjects (47.4%). The results of this study is relevant to the research conducted by Rambe et al (2013) shows the demographic characteristics of more women in the amount of 52.7% compared to men. Women have several unique risk factors that differ from men, including use of oral contraceptives, pregnancy, menopause and hormone replacement therapy.[15] One meta-analysis study found that the use of oral contraceptives in women will increase the incidence of ischemic stroke three times greater. In pregnant women there will be changes in hemostasis which will result in an increase in blood clotting factors, decreased anticoagulants and fibrinolytic activity so that it can increase the risk of thrombosis.[16]

The characteristics of the educational level of the research subjects in this study were mostly high school students as many as 22 subjects (57.9%). This research is relevant to the research Sembiring et al, (2017) which says education is the most research subjects senior high school (45%), followed by junior high school (35%) and the smallest is an undergraduate (8.3%).[17] It is slightly different from the study by Rosita et al. (2011) that the highest level of education is primary school as many as 40 subjects (40%), but if we look at this research, it has the same thing that most of the subjects did not continue their education to university.[13]

The employment status in this study is divided into two, namely working and not working. Most of the work status in this study was not working as many as 20 subjects (52.6%). This is relevant to the research conducted by Rosita et al (2011) which found that the most occupational statuses were unemployed as many as 36 subjects (43%).[13] According Riskesdas in 2018 the prevalence of stroke was higher in people with the status of the economy is low is not working based diagnostic healthcare or symptoms as much (21.8%).[3]

Respondent ethnicity is divided into Batak as many as 25 subjects (65.8%), Malay as many as 8 subjects (21.1%), Javanese as many as 4 subjects (10.5%) and Aceh as many as 1 subject (2.6%), so that It was concluded that most of the respondents with ischemic stroke in this study came from the Batak tribe. This is relevant to the research of Rambe et al. (2013) in the ischemic stroke group that was found (40.7%) of the Batak tribe.[15] The cause of the high incidence of stroke in the Batak tribe compared to the non-Batak ethnic group may be due to non- modifiable risk factors, namely genetically and modifiable stroke risk factors.[18] Batak specialties also contain lots of cholesterol levels.[19] The Batak tribe has the characteristic of eating more than other tribes so that it is more likely

to be obese and the Batak tribe is more temperamental and emotional than other tribes (Nainggolan et al, 2015) so that it can cause blood pressure to increase more easily.[20]

In this study, the platelet aggregation value was obtained on the first day before giving anti-platelet therapy with the most platelet aggregation characteristics in the hyperaggregation category as many as 28 subjects (73.3%). The platelet aggregation value on the seventh days after giving anti-platelet therapy with the most aggregation characteristics was the normoaggregation category as many as 37 subjects (97.4%). This is relevant to a study conducted by Rosita et al (2011) who conducted a study to examine the value of platelet aggregation before administering anti-platelets. This study found that the highest aggregation was hyperaggregation of 48 subjects (57.14 %).[13] Another study by Ick et al (2014) obtained platelet aggregation values using ADP 10 µM and 5 µM in hypertensive patients who were not given aspirin with a mean of 58.53 and 50.47, while in hypertensive patients who were given aspirin a mean of 36.20 and 32.33. This shows that there is a decrease in platelet aggregation when given anti-platelet therapy in hypertensive patients, which is one of the risk factors for ischemic stroke.[14]

In this study, the *NIHSS* value on the first day was obtained with a median of 11.50(4-21), with the most characteristic neurological deficits in the moderate category as many as 19 subjects (50.0%). The *NIHSS* value on the seventh day with a median of 6.50(1-17), with the most characteristic neurological deficit was in the moderate category as many as 21 subjects (55.3%). This is relevant to the study of Kusnardi et al. (2013) who obtained the *NIHSS* value before administering anti-platelet therapy with the most moderate category of 18 subjects (60%).[12] Another study by Lok et al (2017) found that the initial *NIHSS* value in the examination was a median of 6(1-18), while after anti-platelet therapy the median was 4.5(1-16). This explains that the highest *NIHSS* value at the beginning of the examination of patients undergoing treatment is in the moderate category.[21] In the study of Arisoy et al (2016) who examined the *NIHSS* value of ischemic stroke patients on admission and discharge of care. The highest *NIHSS* score at entry was the moderate category at 71.12% and the highest *NIHSS* when going home was the moderate category at 57.8%. The results of this examination show that the outgoing *NIHSS* value is better than the *NIHSS* value at entry.[22]

In this study is getting a significant influence on changes in platelet aggregation and the first day to the seventh day after the administration of anti-platelet therapy to 38 subjects ($p<0.001$). It can be explained that there was no negative change, namely a change from normoaggregation to hyperaggregation. There were 27 subjects experiencing positive changes, namely changes from hyperaggregation to normoaggregation. This study is relevant to other studies by Yi et al. (2017) who also had a significant effect on subjects who were given aspirin and not given aspirin with a value ($p<0.001$). This study did not compare before and after giving aspirin but divided the groups that were given and not given aspirin with values of 58±18.6 and 47.6±16.4, respectively. It is hoped that aspirin will give normoaggregation results so as to prevent the incidence of cardiovascular and cerebrovascular disease. This is because aspirin works by acetylating cyclooxygenase *(COX-1*), thereby inhibiting the formation of thromboxane A_2 (TXA_2). Thromboxane A_2 is a potent platelet aggregator that will strengthen platelet aggregation.[23]

The change between *NIHSS* on the first day and *NIHSS* on the seventh day after administering anti-platelet therapy to 38 study subjects was significant ($p<0.001$). It can be explained that there was no negative change, namely the change in the *NIHSS* value from mild to moderate or severe as well as from moderate to severe. There were 28 subjects who experienced positive changes, namely a change from severe to moderate *NIHSS* values as many as 15 subjects and changes from moderate to mild category as many as 13 subjects. This study is relevant to another study by Meyer et al (2008) which also obtained a significant change in prognosis ($p<0.002$) from baseline before anti-platelet therapy and after seven days of anti-platelet therapy with a mean of 6 and 3 in acute ischemic stroke. This suggests that the administration of anti-platelet therapy in acute ischemic stroke patients will improve the *outcome.*[24]

In this study is to get the result that there is a significant association between platelet aggregation with *NIHSS* first day before the administration of anti-platelet therapy ($p=0.018$) and correlation test obtained ($r=0.339$) in the positive direction (unidirectional), meaning that if the value of the aggregation platelets are hyperaggregated so the *NIHSS* is increased and vice versa. This is relevant to the study of Kusnardi et al. (2013) who found a significant relationship between platelet aggregation and *NIHSS* before anti-platelet therapy ($p<0.001$) and the strength of the correlation was 0.661. This shows that the higher the platelet aggregation value against *ADP*, the higher the *NIHSS* value. This research is supported by the theory of thrombus formation involving *ADP* mediators.

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Thrombus formation begins with platelet aggregation caused by platelet activation. This process can be caused by the release of several chemicals, including *ADP*, collagen, epinephrine, arachidonic acid, serotonin and prostaglandins, so that *ADP* will cause the thrombus to get worse, as a result the brain ischemic will become heavier and result in poor functional outcome in ischemic stroke patients.[12]

In this study this indicates the absence of a significant association between platelet aggregation with *NIHSS* seventh day after the administration of anti-platelet therapy to 38 research subjects (p=0,394). As we know that the mean volume of platelets is a marker of platelet function which is highly correlated with platelet activity, platelet aggregation, resulting in thromboxane A2, *platelet factor 4* and β thromboglobulin. This study is relevant to research conducted by Haungsaithong et al. (2015) which found that there was no statistically significant relationship between platelet aggregation and *NIHSS* for 4 weeks of anti-platelet administration with a value (p=0.429).[25] This can occur because of various factors, including researched by Lok et al. (2017) which states that there are several factors that play a role in the prognosis of stroke including pro-inflammatory status, inflammatory processes, hormones, prothrombotic conditions and markers of platelet membrane aggregation or protein and premorbid blood vessel disease.[21] Research by Wouters et al (2018) also argues that there are various factors that influence stroke outcome including treatment with thrombolysis, age, gender, blood sugar levels, diseases such as diabetes, hypertension, ischemic heart disease, atrial fibrillation, hyperlipemia and smoking history.[26]

This study has several limitations, namely this study only focuses on changes in platelet aggregation and *NIHSS* after administration of anti-platelet therapy without further analyzing other factors that can affect prognosis in acute ischemic stroke patients. This study also only focused on the use of one type of anti-platelet, namely acetylsalicylic acid , and a brief stroke prognosis assessment.

Conclusion

There were significant changes between platelet aggregation and NIHSS scores. There was a significant relationship between platelet aggregation and *NIHSS* the first day before anti platelet administration. There was no significant relationship between platelet aggregation and NIHSS in the seventh days after anti platelet administration.

Suggestion

Future studies are expected to analyze other factors that can affect prognosis in acute ischemic stroke patients. Future studies are expected to use other anti-platelets such as clopidogrel and others. Future studies are expected to increase the time to assess the prognosis in ischemic stroke patients

References

[1] Nichols, M., Townsend, N., Scarborough, P. and Rayner, M. 2012. European Cardiovascular Disease Statistics. 2012 edition. Europiean Heart Network and European Society of Cardiology. Brussel.

[2] Jauch, E.C., Saver, J.L., Adams, H.P., Bruno, A., Connors, J.J., Demaerschalk, B.M., et al. 2013. Guidelines for the Early Management of Patients with Acute Ischemic Stroke : A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association. *Journal of American Heart Association*. 44(3):870-947.

[3] Riset Kesehatan Dasar. 2018. Badan Penelitiandan Pengembangan Kesehatan Kementerian Kesehatan Republik Indonesia.

[4] Chiba, T. and Umegaki, K. 2013. Pivotal Roles of Monocytes/ Macrophages in Stroke. *Hindawi Publishing Corporation*. 2(1):1-10.

[5] Fedin, A.I. and Badalyan, K.R. 2019. Review of clinical guidelines for the treatment and prevention of ischemic stroke. *Journal of neurologi and psychiatry*. 119(8):95-100.

[6] Lamsudin. 2010. Pertemuan Ilmiah Nasional Perdossi : Stroke, Neurosonology, Neuroimaging, dan Neurointervention serta Pertemuan Asean Stroke Advisory Panel. Yogyakarta.

[7] Nneka, N.I., Uchenna, M.A., Chinyere, E.C., Ikechukwu, E.A., Onyemaechi, O.O.,and Nwobi, E.J. 2012. Platelet activity in patients with type 2 diabetes in eastern Nigeria. *Res. J. Pharmacol.* 6(3):48-51.

[8] Madan, R., Gupta, B., Saluja, S., Kansra, U.C., Tripathi, B.K. and Guliani, B.P. 2010. Coagulation profile in diabetes and its association with diabetic microvascular complications. *Journal Association of Physicians of India*. 58(1):481-84.

[9] Kwakkel, G., Veerbeek, J.M., van Wegen, E.E., Nijland, R., Harmeling-van der Wel, B.C. and Dippel, D.W. 2010. Predictive value of the *NIHSS* for *ADL* outcome after ischemic hemispheric stroke: does timing of early assessment matter ?. *Journal of the neurological sciences*. 294(2):57-61.

[10] Meschia, J.F., Bushnell, C., Boden, A.B., Braun, L.T., Bravata, D.M., Chaturvedi, S., et al. 2014. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association / American Stroke Association. *Journal of American Heart Association*. 45(12):3754-832.

[11] Wilmana, P.F. dan Gan, S. 2012. Analgesik-Antipiretik, Analgesic Anti-inflamasi Nonsteroid, dan Obat Gangguan Sendi Lainnya. Dalam: Gunawan S.G., Setiabudi, R., Nafrialdi. Dan Elysabeth, editor. *Farmakologi dan Terapi*. Edisi ke-5.Hal: 234-35. FK UI. Jakarta.

[12] Kusnardi, B. dan Mahfoed, M.H. 2013. Korelasi Antara Agregasi Trombosit terhadap Adenosine Diphosphate Dengan Keluaran Fungsional Stroke Iskemik Akut. *Neurona*. 30(2):1-5.

[13] Rosita, L., Usi, S. dan Budi, M. 2011. Status Penggumpalan (Agregasi) Trombosit Sebagai Faktor Prognostik Tejadinya Keluaran Klinis Stroke Infark Mendadak. *IJCP & ML*. 17(2):86-96.

[14] Ick, B.L., Mongan, A.E. danMemah, M. 2014. Perbandingan Nilai Agregasi Trombosit pada Pasien Hipertensi yang diberi Aspirin dan Tidak diberi Aspirin di RSUP. Prof. Dr. R. D. Kandou Manado. *Jurnal e-Biomedik (eBM)*. 2(2):1-9

[15] Rambe, A.S., Fithrie, A., Nasution, I. dan Tonam. 2013. Profil Pasien Stroke pada 25 Rumah Sakit di Sumatera Utara 2012 :Survei Berbasis Rumah Sakit. *Neurona*. 30(2):1-7.

[16] Appelros, P., Stegmayr, B. and Terent, A. 2009. Sex Difference in Stroke Epidemiology : a Systematic Review. *Journal of American Heart Association*. 40(4):1082-90.

[17] Sembiring, N., Rambe, A.S. dan Sinurat, P.P.O. 2017. Perbandingan Tingkat Akurasi Siriraj Stroke Score, Allen Stroke Score, Besson Stroke Score danAlgoritma Stroke Gajah Mada Dalam Menentukan Jenis Stroke Pada Fase Akut. http://repository.usu.ac.id/handle/123456789/64936 di peroleh tanggal 15 Juli 2020

[18] Sjahrir, H., 2003. Stroke iskemik. YandiraAgung. Medan.

[19] Manurung, M., Diani, N. danAgianto. 2015. AnalisaFaktorRisiko Stroke padaPasien Stroke Rawat di RSUD Banjarbaru. *Jurnal DK*. 3(1):74-85.

[20] Nainggolan, T., Pasaribu, J. B., Simanjuntak, M. S. E. dan Simorangkir, M. S. E. 2015. Karakter Batak: Masa Lalu, Kini, dan Masa Depan. Yayasan Pustaka Obor Indonesia: Jakarta.

[21] Lok, U., Gulacti, U., Ekmekci, B., Bulut, T. and Celik, M. 2017. Predictive and Prognostic role of Mean Platelet Volume in Patient with First Ever Acute Ischemic Stroke. *Neuro Sciences*. 22(2):119-126.

[22] Arisoy, Y.M., Maja, J. dan Runtumene, T. 2016. Gambaran *NIHSS* pada pasien stroke di ruangan rawat inap neurologi Prof. Dr. R.D Kandau Manado periodeJuli 2014 – Juni 2015. *Jurnal e-Clinic*. 4(1):1-4

[23] Yi, X., Lin, J., Wang, C., Huang, R., Ham, Z. and Li, Y. 2017. Platelet Function Guided Modification in Platelet Therapy After Acute Ischemic Stroke is Associated with Clinical Outcome in Patients with Aspirin Nonresponse. *Oncotarget*. 8(63):106258-69.

[24] Meyer, D.M., Albright, K.C., Allison, T.A. and Grota, JC. 2008. LOAD : A Pilot Study of the Safety of Loading of Aspirin and Clopidogrel in Acute Ischemic Stroke and Transient Ischemic Attack. *J Stroke Cerebrovasc*. 17(1):26-29.

[25] Haungsaithong, R., Udommonghol, C., Nidhinandana, S., Chairungsaris, P., Chinvarun, Y., Suwantamee, J., et al. 2015. The Changes in Mean Platelet Volume After Using of Antiplatelet Drug in Acute Ischemic Stroke : A Randomized Controlled Trial. *J Med Assoc Thai*. 98(9): 852-7.

[26] Wouters, A., Nysten, C., Thijs, V. and Lemmens, R. 2018. Prediction of Outcome in Patient with Acute Ischemic Stroke Based on Initial Saverity and Improvement in the First 24 h. *Front Neurol*. 9(308):1-6.