The Changes in Mean Platelet Volume after Using of Antiplatelet Drugs in Acute Ischemic Stroke: A Randomized Controlled Trial

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Objective: *To measure the changes of mean platelet volume (MPV) after using four antiplatelet drugs in acute non-cardioembolic ischemic stroke patients and assess the association of antiplatelets and MPV and stroke outcome.*
Material and Method: *Ischemic stroke survivors with National Institute of Health Stroke Scale (NIHSS) ≤8 were randomly allocated into four groups, receiving aspirin, clopidogrel, combined aspirin and dipyridamole, and cilostazol. The change of MPV, NIHSS, and modified Rankin Scale (mRS) were recorded at baseline and week 4 in all studied groups. MPV was measured using the standard automated blood test for complete blood count.*
Results: *Twenty-one subjects were included in this study. They comprised of five cases in each antiplatelet group, except for aspirin, which had six subjects. Male was 57%, and hypertension was the most common risk factor (61.9%). Most of participants (76%) had small vessel disease. At 4-week, MPV was reduced and NIHSS, mRS were improved in every studied group. Clopidogrel significantly reduced NIHSS score ($p = 0.003$), and it produced the greatest reduction in MPV compared to others.*
Conclusion: *Every type of antiplatelets included in this study reduced MPV, NIHSS, and mRS in acute non-cardioembolic stroke patients. Clopidogrel improved NIHSS the most.*

Keywords: *Mean platelet volume (MPV), Stroke, Antiplatelet drugs*

J Med Assoc Thai 2015; 98 (9): 852-7
Full text. e-Journal: *http://www.jmatonline.com*

Platelet size, measured as mean platelet volume (MPV), is a marker of platelet function and is positively associated with indicators of platelet activity, including aggregation and release of thromboxane A_2, platelet factor 4, and beta-thromboglobulin[1,2]. Previous studies have documented above average levels of MPV among patients with acute stroke[3-6], myocardial infarction[7,8], chronic vascular disease[9,10], or vascular risk factors[11,12]. Larger platelets are more reactive than smaller or normal size platelets due to their greater content in granules[13,14]. Interestingly, higher mean platelet volume (MPV) values have also been found in patients with stroke than in control subjects[3-5]. From literature reviews, previous studies have shown the effect of some drugs, such as rosuvastatin[15], amlodipine[16] and nevibolol[17], on mean platelet volume. The results of these studies demonstrated their effects on significant decreasing of MPV, which might be associated with better stroke prevention and outcome.

We, therefore, would like to study about the changing of MPV in acute ischemic stroke using a variety of antiplatelets. We hypothesized that antiplatelets would reduce MPV and be able to improve outcome after the event. We also compared how different between each kind of antiplatelet on MPV and clinical outcome which this would help us to understand more stroke mechanism and to choose the proper antiplatelets in high-risk individuals.

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Material and Method

Participants

We enrolled ischemic stroke patients admitted to Neurology or Internal Medicine wards, Phramongkutklao Hospital between March 2011 and September 2011. The inclusion criteria were age greater than 45 years, and diagnosed with first-ever acute ischemic stroke presenting within 24 hours. The exclusion criteria were individuals with 1) cardioembolic evidences, 2) recurrent ischemic stroke, 3) pregnancy or lactation, 4) severe medical

illnesses such as liver or renal impairment, malignancy, hematologic disease, or cardiac disease, 5) the patient had been taking rosuvastatin, amlodipine and nevibolol prior to the event (as these medication have been reported on MPV reduction), and 6) NIHSS >8 (as individuals with large stroke would require more aggressive medical or surgical interventions or even anticoagulation therapy).

Procedures and randomization

The participants were hospitalized and evaluated for severity of stroke by National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) within 24 hours. Blood chemistries, complete blood count (CBC) including mean platelet volume (MPV), and computerized tomography of the brain were performed. MPV was obtained from CBC automate analysis, blood sample (4 ml) was preserved in K3E K3 EDTA 0.04 mg tube and was analyzed by COULTER Hmx Hematology analyzer, COULTER LH 750 within two hours. All of the participants were classified types of ischemic stroke based on Trial of Org 10172 in Acute Stroke Treatment (TOAST). In the first week, as a standard treatment every patient received aspirin 300 mg/day[18] and simvastatin 40 mg/day.

After eligibility assessment, patients were randomly assigned using the block randomization to receive one antiplatelet (aspirin 81 mg/day, clopidrogrel 75 mg/day, aspirin 50 mg/day with dipyridamole 200 mg/day, and cilostazol 200 mg/day)[19-21]. Aspirin 300 mg commenced in the first week of stroke was discontinued. Other medications were continued without changing their dosage for at least four weeks. It was inappropriate to have a placebo group because of Ethical consideration. Blood chemistry, automated CBC including MPV, NIHSS, and mRS were re-assessed at 4-week after admission. Primary outcome was the change in MPV at week-4 from baseline in each antiplatelet drug. Meanwhile, secondary outcome was the association between types of antiplatelet and stroke functional outcome (NIHSS and mRS).

The present study was approved by the Institutional Review Board of Royal Thai Army Medical Department (IRB, RTA, MD) in February 2011. Informed consent was obtained from patients before the procedure was undertaken.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 15.0. The results were expressed as mean, standard deviation, number, and percentage. Pre- and post-treatment differences in MPV, NIHSS, and mRS were analyzed using paired t-test. Analysis of co-variant was used to compare mean among groups. The *p*-value of <0.05 was determined as statistically significant difference.

Results

Twenty-one patients were enrolled and randomly assigned to four difference antiplatelet groups. There were six individuals for the aspirin, five each for the clopidogrel, combination of aspirin and dipyridamole, and cilostazol group. Baseline demographic characteristics of our studied patients are shown in Table 1. Patients were predominantly male (57%). The mean age was 60 years and the most common risk factor was hypertension (61.9%). The other common risk factors were dyslipidemia (47.6%) and smoking (42.9%). Small-vessel disease classified by TOAST was 76% of all the participants. Platelet counts were normal in all participants. Baselines MPV, mRS, NIHSS of overall patient were 8.4, 1.24, and 3.81 respectively. There was no significant difference of baseline characteristics between the four groups.

All antiplatelets reduced mean platelet volume (Table 2). It was noted that clopidogrel had the greatest reduction in MPV compared to others (difference of 0.46). However, the reduction of MPV did not create a statistically significant difference as compared with the other three types of antiplatelets (*p*-value = 0.343). For functional outcome assessment, modified Rankin Scale was evaluated which the lower scores represents the better functional outcome. The result showed that 4-week after stroke event, mRS was reduced in all studied groups; however, there was no statistical significance (*p*-value 0.329). The details of mRS of each antiplatelets were shown in Table 3. Finally, decreasing in NIHSS was found in the four groups receiving different antiplatelets (Table 4). Nevertheless, significant NIHSS improvement was observed in only the clopidogrel group (*p*-value = 0.003).

Discussion

Ischemic stroke is a very common and a burden condition worldwide. To prevent, modify, and treat this condition appropriately would help individuals at risk from their disability and mortality. Therefore choosing the right antiplatelets would be beneficial in general practice. Mean platelet volume would provide

Table 1. Baseline characteristics

	Total (n = 21)	Aspirin & dipyridamole (n = 5)	Clopidogrel (n = 5)	Cilostazol (n = 5)	Aspirin (n = 6)	*p*-value
Age (SD)	60.0 (11.1)	59.0 (12.7)	56.0 (7.5)	68.0 (12.35)	57.5 (10.6)	0.329
Sex (M:F)	12:9	4:1	3:2	1:4	4:2	0.249
Hypertension	13 (61.9%)	4 (80%)	3 (60%)	4 (80%)	2 (33.3%)	0.324
Diabetes	6 (28.6%)	1 (20%)	1 (20%)	2 (40%)	2 (33.3%)	0.862
Dyslipidemia	10 (47.6%)	2 (40%)	3 (60%)	1 (20%)	3 (50.0%)	0.907
Smoking	9 (42.9%)	2 (40%)	2 (40%)	1 (20%)	4 (66.7%)	0.477
TOAST (lacunar:large:others)	16:3:3	5:0:0	3:1:1	3:1:1	5:0:1	0.687
MPV (SD)	8.40 (0.9)	7.88 (0.44)	8.56 (0.99)	8.66 (0.78)	8.46 (1.10)	0.510
mRS (SD)	1.24 (0.4)	1.20 (0.45)	1.20 (0.45)	1.40 (0.55)	1.17 (0.41)	0.843
NIHSS (SD)	3.81 (1.7)	4.80 (3.11)	3.80 (1.30)	3.40 (0.55)	3.33 (1.21)	0.541

M = male; F = female; SD = standard deviation; TOAST = trial of Org 10172 in acute stroke treatment; MPV = mean platelet volume; mRS = modified Rankin scale, NIHSS = National Institute of Health Stroke Scale
p-value: one way ANOVA

Table 2. Change in MPV from baseline to week 4 in each antiplatelets

Drugs	MPV at onset	MPV at week 4	Difference	*p*-value
Aspirin	8.47	8.22	-0.25	0.429
Aspirin & dipyridamole	7.88	7.64	-0.24	0.523
Clopidogrel	8.56	8.10	-0.46	0.189
Cilostazol	8.66	8.34	-0.32	0.550
Overall	8.40	8.22	-0.18	0.343

MPV = mean platelet volume
p-value: paired t-test

Table 3. Change in mRS from baseline to week 4 in each antiplatelet drug

Drugs	MRS at onset	MRS at week 4	Difference	*p*-value
Aspirin	1.17	1.33	-0.17	0.363
Aspirin & dipyridamole	1.20	1.00	-0.20	0.374
Clopidogrel	1.20	1.00	-0.20	0.374
Cilostazol	1.40	1.20	-0.20	0.374
Overall	1.24	1.14	-0.10	0.329

mRS = modified Rankin scale

Table 4. Change in NIHSS from baseline to week 4 in each antiplatelet drug

Drugs	NIHSS at onset	NIHSS at week 4	Difference	*p*-value
Aspirin	3.33	2.83	-0.50	0.656
Aspirin & dipyridamole	4.80	2.60	-2.20	0.086
Clopidogrel	3.80	1.80	-2.00	0.003
Cilostazol	3.40	2.60	-0.80	0.099
Overall	3.81	2.48	-1.33	0.004

NIHSS = National Institute of Health Stroke Scale

us a new insight about stroke mechanism in the future[3-6]. The MPV measure is very simple as we can get the value from a simple automated complete blood count, which is always available in any hospitals. MPV reduction at 4-week was demonstrated in each antiplatelet groups compared with at the entry. Similarly, mRS and NIHSS were changed in the same way. Thus, MPV would be a novel marker for improving of stroke. Although we could not explain exactly why MPV reduces after stroke treatment, we hypothesized that this would be an acute phase reactant and that it increases in size at the time of stroke onset. Therefore, the reduction would indicate stroke improvement, which we could compare among different treatment groups[9-11].

In different antiplatelet groups, they demonstrated that there were varieties of changes in MPV, mRS, and NIHSS reduction. In patients receiving clopidogrel, MPV and stroke severity assessed by NIHSS seemed to be significantly reduced, while other antiplatelets did not have that effect. Larger platelets are more reactive than smaller or normal size platelets due to their greater content in granules[13,14]. In addition, higher MPV values have also been found in patients with stroke as compared to control subjects[3-5]. Our study indicated that clopidogrel might be better on stroke treatment. However, this finding might be because of the small sample size. Furthermore, combining aspirin and dipyridamole, clopidogrel, and cilostazol had better result of MPV changes in all parameters than aspirin alone. This interesting outcome would guide clinicians to select a proper antiplatelet in treating patients at high-risk of recurrent ischemic stroke, especially in those with high MPV.

This study has the following weaknesses, a small sample size, mainly the small vessel disease was studied, and a short duration of follow-up (4 weeks). For future direction, we suggested that the next study should enroll more participants and with variety in etiologies to represent all types of ischemic stroke. However, to our knowledge, this small randomized trial was the first study to demonstrate the association between antiplatelet and stroke outcome in acute ischemic stroke.

Conclusion

All types of antiplatelet medications reduced MPV, NIHSS, and mRS in acute non-cardioembolic stroke. Clopidogrel would be more beneficial in improving stoke outcome at one month.

What is already known on this topic?

Larger platelets are more reactive than smaller or normal size platelets. Some of medications for preventing stroke have demonstrated a reduction of MPV suggesting that smaller MPV may be a marker of stroke outcome.

What this study adds?

All studied antiplatelet reduced MPV but clopidogrel and cilostazol appeared to effect MPV more than others. However, our small study showed only clopidogrel group had a better clinical outcome based on the national institute of health stroke scale.

Acknowledgement

The authors gratefully acknowledged Neurology residents and staffs at Division of Neurology for their contributions during the enrolment periods. We also thanked our patients and their caretakers for their contributions.

Potential conflicts of interest

None.

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การเปลี่ยนแปลงของขนาดเกล็ดเลือดหลังการรักษาอัมพาตจากสมองขาดเลือดด้วยยาต้านเกล็ดเลือด

รจนันต์ ห่วงสายทอง, เจษฎา อุดมมงคล, สามารถ นิธินันทน์, ปานศิริ ไชยรังสฤษดิ์, โยธิน ชินวลัญช์, จิตถนอม สุวรรณเตมีย์, พาสิริ สิทธินามสุวรรณ

วัตถุประสงค์: *เพื่อศึกษาหาการเปลี่ยนแปลงของขนาดเกล็ดเลือดหลังการรักษาอัมพาตจากสมองขาดเลือดด้วยยาต้านเกล็ดเลือด และหาความสัมพันธ์กับผลการรักษา*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยอัมพาตจากสมองขาดเลือดที่มีค่า National Institute of Health Stroke Scale น้อยกว่าหรือเท่ากับ 8 แบ่งแบบสุ่มเป็น 4 กลุ่ม เพื่อรับยาต้านเกล็ดเลือด aspirin, clopidogrel, aspirin + dipyridamole และ cilostazol ศึกษาคะแนน NIHSS และคะแนน modified Rankin Scale (mRS) ที่ 4 สัปดาห์ เทียบกับเมื่อเริ่มการศึกษา และดูความสัมพันธ์กับค่าขนาดเกล็ดเลือดซึ่งตรวจจากการทำ complete blood count*

ผลการศึกษา: *ผู้ป่วยทั้งสิ้น 21 ราย แบ่งเป็นกลุ่มละ 5 ราย ได้รับยา clopidogrel, aspirin+dipyridamole และ cilostazol และมี 6 ราย ในกลุ่มที่ได้รับยา aspirin ผู้ป่วยเป็นเพศชายร้อยละ 57 มีความดันโลหิตสูงร้อยละ 61.9 ผู้ป่วยส่วนใหญ่เป็นอัมพาตจากหลอดเลือดฝอยตีบ ที่ 4 สัปดาห์ พบว่าค่าขนาดเกล็ดเลือด ค่า NIHSS และค่า mRS ดีขึ้นในทุก ๆ กลุ่ม นอกจากนี้พบว่าในกลุ่มที่ได้รับ clopidogrel มีค่า NIHSS ลดลงอย่างมีนัยสำคัญทางสถิติ ($p = 0.003$) ซึ่งพบว่ามีค่าขนาดเกล็ดเลือดลดลงได้มากกว่ากลุ่มที่ได้รับยาต้านเกล็ดเลือดชนิดอื่น ๆ*

สรุป: *ยาต้านเกล็ดเลือดทุกชนิดสามารถลดขนาดเกล็ดเลือด ค่า NIHSS และ mRS ในผู้ป่วยอัมพาตจากสมองขาดเลือด โดยพบว่ายา clopidogrel มีผลชัดเจนต่อคะแนน NIHSS ที่ดีขึ้น*