Efficacy and Safety of Dual Antiplatelet Treatment for Adult Moyamoya Disease: A Retrospective Cohort Study

Thon Thiraworawong, MD*

**Division of Neurology, Neurological institute of Thailand, Bangkok 10400 Thailand*

Abstract

Introduction: Moyamoya disease is a chronic intracranial vasculopathy. Current treatment guidelines recommend antiplatelet therapy, however, there is no data about dual antiplatelet treatment in Moyamoya disease. The objective of this study was to determine the outcomes of dual antiplatelet therapy for ischemic events and death in adult Moyamoya disease.

Methods: This retrospective cohort study examined the clinical, imaging data, and clinical outcomes of ischemic stroke or transient ischemic attack patients with Moyamoya disease. Univariate analysis and multiple logistic regression model of included relevant confounders and potential predictors were performed.

Results: A total of 192 adult patients with Moyamoya disease were included in this study. Adult Moyamoya patients who received dual antiplatelet treatment had higher risk of hemorrhagic stroke than patients who received single antiplatelet treatment at 12-month follow-up (odd ratio (OR), 1.96; confidence interval (95% CI), 1.62-4.73; p<0.001), but not significant in the composite of ischemic stroke, hemorrhagic stroke, and death (odd ratio (OR), 1.23; confidence interval (95% CI), 0.86-1.44; p=0.634).

Conclusion: Adult Moyamoya patients had no potential clinical benefit from dual antiplatelet treatment with an increase in the risk of hemorrhagic stroke.

Keywords: Moyamoya, Dual antiplatelet, stroke (J Thai Stroke Soc. 2023;22(2): 5-16)

Corresponding author: ***Thon Thiraworawong, MD*** *(Email: blackthn@gmail.com)*

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ประสิทธิภาพและความปลอดภัยของการใช้ยาต้านเกล็ดเลือดร่วมกันสองชนิด ในผู้ป่วยโรคโมยาโมยา

นพ.ธน ธีระวรวงศ์*

**กลุ่มงานประสาทวิทยา สถาบันประสาทวิทยา กรุงเทพมหานคร 10400 ประเทศไทย*

บทคัดย่อ

บทนำ โรคโมยาโมยาเป็นโรคของหลอดเลือดแดงในสมองชนิดหนึ่งที่มีการดำเนินโรคอย่างเรื้อรัง แนวทางการรักษาในผู้ป่วยโรคโมยาโมยาที่มีอาการของหลอดเลือดสมองขาดเลือด แนะนำให้การรักษาด้วยยาต้านเกล็ดเลือด ปัจจุบันยังไม่มีข้อมูลมากพอสำหรับการรักษาด้วยยาต้านเกล็ดเลือดสองชนิดร่วมกันในผู้ป่วยโรคโมยาโมยา วัตถุประสงค์ของงานวิจัยนี้จึงเป็นการศึกษาหาผลลัพธ์ที่ได้จากการรักษาด้วยยาต้านเกล็ดเลือดสองชนิดร่วมกันในกลุ่มผู้ป่วยโรคโมยาโมยา

วิธีวิจัย เป็นการศึกษาทบทวนข้อมูลย้อนหลังจากเวชระเบียน โดยเก็บข้อมูลอาการทางคลินิก, รายละเอียดของภาพวินิจฉัยทางสมองและหลอดเลือดสมอง, ผลลัพธ์ของการรักษาในกลุ่มผู้ป่วยโรคหลอดเลือดสมองขาดเลือดจากโรคโมยาโมยาและวิเคราะห์ข้อมูลทางสถิติ ครอบคลุมข้อมูลปัจจัยพื้นฐานของผู้ป่วย, ปัจจัยเสี่ยงและปัจจัยอื่น ๆ ที่อาจมีผลรบกวนต่อผลลัพธ์ในการรักษา

ผลการวิจัย การศึกษานี้มีผู้ป่วยป่วยโรคโมยาโมยาเข้าร่วมการศึกษาจำนวน 192 ราย ผู้ป่วยโรคโมยาโมยาที่มีอาการของหลอดเลือดสมองขาดเลือด และได้รับประทานยาต้านเกล็ดเลือดร่วมกันสองชนิดมีความเสี่ยงต่อการเกิดโรคหลอดเลือดสมองแตกเมื่อติดตามอาการในช่วงระยะเวลาหนึ่งปีมากกว่าผู้ป่วยที่รับประทานยาต้านเกล็ดเลือดชนิดเดียวอย่างมีนัยสำคัญทางสถิติ (odd ratio (OR), 1.96; confidence interval (95% CI), 1.62–4.73; p<0.001), และหากพิจารณาผลลัพธ์รวมในการป้องกันโรคหลอดเลือดสมองขาดเลือดกลับเป็นซ้ำ, การเกิดเลือดออกในสมองและการเสียชีวิต (odd ratio (OR), 1.23; confidence interval (95% CI), 0.86–1.44; p=0.634) ยังไม่พบว่ามีนัยสำคัญทางสถิติ

บทสรุป ผู้ป่วยโรคโมยาโมยาที่รับประทานยาต้านเกล็ดเลือดสองชนิดร่วมกันไม่ได้ประโยชน์สำหรับผลลัพธ์การรักษาอย่างมีนัยสำคัญ นอกจากนี้ยังเพิ่มโอกาสการเกิดเลือดออกในสมองมากขึ้น

คำสำคัญ: โรคโมยาโมยา, ยาต้านเกล็ดเลือดร่วมกันสองชนิด, โรคหลอดเลือดสมอง (J Thai Stroke Soc. 2023;22(2): 5–16)

Introduction

Moyamoya disease is a chronic intracranial vasculopathy first described in 1957 by Takeuchi and Shimizu[1]. Progressive stenosis and occlusion of intracranial arteries of the circle of Willis causing characteristic of collateral vessels. The collateral vessels give the appearance of the puff of smoke on angiography and anointed the name "Moyamoya" in 1969 by Suzuki and Takaku[2]. Moyamoya disease is usually found in bimodal age groups.[3] Current treatment guidelines recommended antiplatelet therapy[4], however, there is no data about dual antiplatelet treatment in Moyamoya disease.[5, 6] The objective of this study was to determine the outcomes of dual antiplatelet therapy for adult Moyamoya disease.

Materials and methods

Study populations

This study was a retrospective cohort study of stroke patients with Moyamoya disease from January 1, 2013. to September 30, 2022. at the neurological institute of Thailand. This study retrospectively examined the clinical, imaging data and clinical outcomes in adult patients with Moyamoya disease from medical records. Patients were tested for diagnostic imaging of the characteristic Moyamoya disease by using magnetic resonance angiography or digital subtraction angiography within 3 months after the onset of the stroke. This study excluded any children aged less than 15 years old or stroke patients with atherosclerotic risk factors or stroke patients with cardiac risk factors. This study collected demographic data, clinical risk factors, and clinical outcomes such as age, sex, history of comorbidities, type of antiplatelet medications, the severity of neurological deficit by NIH[7] stroke scale, size of infarction, size of hemorrhage, the number of patients who deteriorated neurological symptoms, the number of recurrent ischemic stroke, the number of hemorrhagic stroke, the number of intracranial or extracranial bleeding events, and the number of death.

Definitions

Acute stroke was defined as an acute neurological deficit lasting more than 24 hours with either ischemic or hemorrhagic lesions on brain imaging. The transient ischemic attack was defined as an acute neurological deficit lasting less than 24 hours and no ischemic lesion on brain imaging.

Recurrence ischemic stroke was defined as acute neurological deficit with a new ischemic lesion on brain imaging in the patient who received dual antiplatelet treatment or single antiplatelet treatment. Recurrence transient ischemic attack was defined as acute neurological deficit lasting less than 24 hours and no new ischemic on brain imaging in the patient who received either dual antiplatelet treatment or single antiplatelet treatment.

Moyamoya disease was defined by a revision of the diagnostic criteria of Moyamoya disease 2021 by the research committee on Moyamoya Disease (Spontaneous Occlusion of Circle of Willis), Japan.[8]

Diagnostic Criteria 2021:

A. Radiological Findings

Radiological examination such as cerebral angiography is essentially mandatory for diagnosis, and at least, the following findings must be present.

Especially in the case of unilateral lesions or lesions complicated by atherosclerosis, it is essential to perform cerebral angiography to exclude other diseases.

1.Cerebral angiography

(1) Stenosis or occlusion in the arteries centered on the terminal portion of the intracranial internal carotid artery.

(2) Moyamoya vessels (abnormal vascular networks) in the vicinity of the occlusive or stenotic lesions in the arterial phase.

Note: Both bilateral and unilateral cases can be diagnosed as Moyamoya disease.

2.MRI and MRA

Moyamoya disease can be diagnosed when all of the following findings are found on MRI and MRA (time-of-flight; TOF) using a scanner with a static magnetic field strength of 1.5 Tesla (T) or higher (3.0 T is even more useful).

(1) Stenosis or occlusion of the terminal portion of the intracranial internal carotid artery.

(2) Decrease in the outer diameter of the terminal portion of the internal carotid artery and the horizontal portion of the middle cerebral artery bilaterally on heavy T2-weighted MRI.

(3) Abnormal vascular networks in the basal ganglia and/or periventricular white matter on MRA.

Note: When two or more visible flow voids are present in the basal ganglia and/or periventricular white matter at least unilaterally on MRI, they can be judged as representing abnormal vascular networks.

B. Differential Diagnosis

Moyamoya disease is a disease of unknown etiology, and similar cerebrovascular lesions associated with the following should be excluded as quasi-Moyamoya disease or Moyamoya syndrome.

(1) Autoimmune disease (SLE, antiphospholipid syndrome, polyarteritis nodosa, Sjögren syndrome, etc.),

(2) Meningitis,

(3) Brain tumors,

(4) Down's syndrome,

(5) Neurofibromatosis type 1,

(6) Cerebrovascular lesions after head irradiation.

Note: Cases with hyperthyroidism can be diagnosed as Moyamoya disease.

Diagnostic Assessment

Moyamoya disease is diagnosed when (1) and (2) of A-1 or (1) to (3) of A-2 are met and B is excluded. The neuroradiologist interprets the imaging results as being compatible with Moyamoya disease.

Large infarction was defined as an area of hypodensity (for CT brain) or hyperintensity (for MRI brain) more than one-third of the middle cerebral artery infarction area.

Major bleeding was defined as life-threatening bleeding or bleeding that required blood transfusion or bleeding in vital organs such as the eye, intracranial or intra-spinal bleeding. Minor bleeding was defined as a bleeding event that does not meet the major bleeding definition.

Inclusion criteria

All acute stroke or transient ischemic attack patients with neuroimaging compatible with Moyamoya disease within 3 months after the onset of ischemic events from January 1, 2013, to September 30, 2022, and received clinical follow-up more than 1 year.

Exclusion criteria

Children aged less than 15 years old.

The patient had received clinical follow-up less than 1 year.

The patient had a hemorrhagic stroke from Moyamoya disease.

Sample size calculation

The previous study[9, 10] showed that adult patients with Moyamoya disease had an annual risk for recurrent ischemic events of about 18–23% in the first year and dual antiplatelet therapy had decreased the risk by 44–64% when compared with single antiplatelet therapy. Sample size calculation based on the following formula[11], substituted the values in the equation with

$$n_{exposure} = \left[\frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

$$p_1 = P(outcome|exposure), q_1 = 1 - p_1$$

$$p_2 = P(outcome|unexposure), q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p}, r = \frac{n_{unexposure}}{n_{exposure}}$$

p_1=0.08, p_2=0.23, alpha=0.05, beta 0.20 and r=1. Estimation of sample size needed more than 188 patients in this study to ensure 80% statistical power and thereby avoid a type 2 error, in which a difference between treatment arms is missed because of an insufficient number of the composite of ischemic stroke, hemorrhagic stroke, and death.

Study outcomes

The primary efficacy outcome was a composite event of ischemic stroke, hemorrhagic stroke, and death. Secondary outcomes were bleeding events, recurrence of ischemic stroke or transient ischemic attack events, and the number of deaths.

Statistical Analysis

Continuous variables were presented as the mean or median. Categorical variables were described as percentages. The difference in baseline characteristics between the dual antiplatelet group and the single antiplatelet group were analyzed using the Mann–Whitney U test if not normally distributed or the t-test if normally distributed; categorical variables were compared between groups with the X^2 test or, where appropriate, Fisher's exact test. Multiple logistic regression analyses were used to identify the confounding factors of the composite events in this study. Confounding factors were selected if there were statistical differences by univariate analysis. Odd ratios and a 95% confidence interval were used to illustrate the association. The level of significance was set at a value of p less than .05. All statistical analyses were performed using SPSS for windows version 16.0 (IBM, Armonk, NY).

Results

The baseline characteristics of this study are summarized in Table 1. A total of 192 adult patients with Moyamoya disease (78 men and 114 women) with a mean age of 47.8 years were included in this study. Adult patients with Moyamoya disease who presented with ischemic stroke or transient ischemic attack were included in this study. This study excluded some adult patients with Moyamoya disease who had hemorrhagic events(N=25), loss to follow-up(N=12), had comorbid with other stroke mechanisms(N=10), or had inconclusive neuroimaging data(N=5), (figure1). The combination of dual antiplatelet in this study was the proportion of the type of dual antiplatelet such as aspirin plus cilostazol, aspirin plus clopidogrel, and clopidogrel plus cilostazol

were 86.4%, 9.1%, and 4.5 %, respectively. The average mean low-density lipoprotein level (LDL) was 71.5 mg/dl. The proportion of large infarction (p=0.045) and the proportion of revascularization surgery (p=0.034) were statically significant in the univariate analysis model. However, the baseline Suzuki stage (p=0.084) and baseline NIH stroke scale(p=0.078) tends to be statistically significant in the univariate analysis model.

Table 1. Demographic data of study populations

Characteristic	Total (N=192)	Dual antiplatelet group (N=88)	Single antiplatelet Group (N=104)	p value
Gender (female, %)	114(59.4)	52(59.1)	62(59.6)	0.531
Age (years, mean)	47.8	47.1	48.4	0.756
Type of antiplatelet				-
Aspirin with Cilostazol (%)	76(39.6)	76(86.4)	-	
Aspirin with clopidogrel (%)	8(4.2)	8(9.1)	-	
Clopidogrel with Cilostazol (%)	4(2.1)	4(4.5)	-	
Aspirin alone (%)	52(27.1)	-	52(50.0)	
Cilostazol alone (%)	30(15.6)	-	30(28.8)	
Clopidogrel alone (%)	22(11.5)	-	22(21.2)	
Duration of antiplatelet therapy (months, mean)	10.2	8.6	10.8	0.266
Suzuki stage (median)	4	5	3	0.084
LDL (mg/dl, mean)	71.5	68.1	74.6	0.238
Statin use				0.452
High intensity statin (%)	17(8.9)	10(11.4)	7(6.7)	
Moderate intensity statin (%)	39(20.3)	21(23.9)	18(17.3)	
No statin or low intensity statin (%)	136(70.8)	57(64.8)	79(76.0)	
Baseline NIHSS (median)	12	8	12	0.078
large infarction (%)	53(27.6)	21(23.8)	32(30.8)	0.045
Bilateral vascular stenosis	118(61.5)	61(69.3)	57(54.8)	0.156
Type of vascular lesion				
Terminal internal carotid stenosis (%)	192(100.0)	88(100.0)	104(100.0)	-
Proximal MCA stenosis (%)	161(83.9)	77(87.5)	84(80.7)	0.766
Proximal ACA stenosis (%)	153(79.7)	74(84.1)	79(75.9)	0.532
Revascularization surgery (%)	46(24.0)	15(17.0)	31(29.8)	0.034

Figure 1. Flow of study procedure

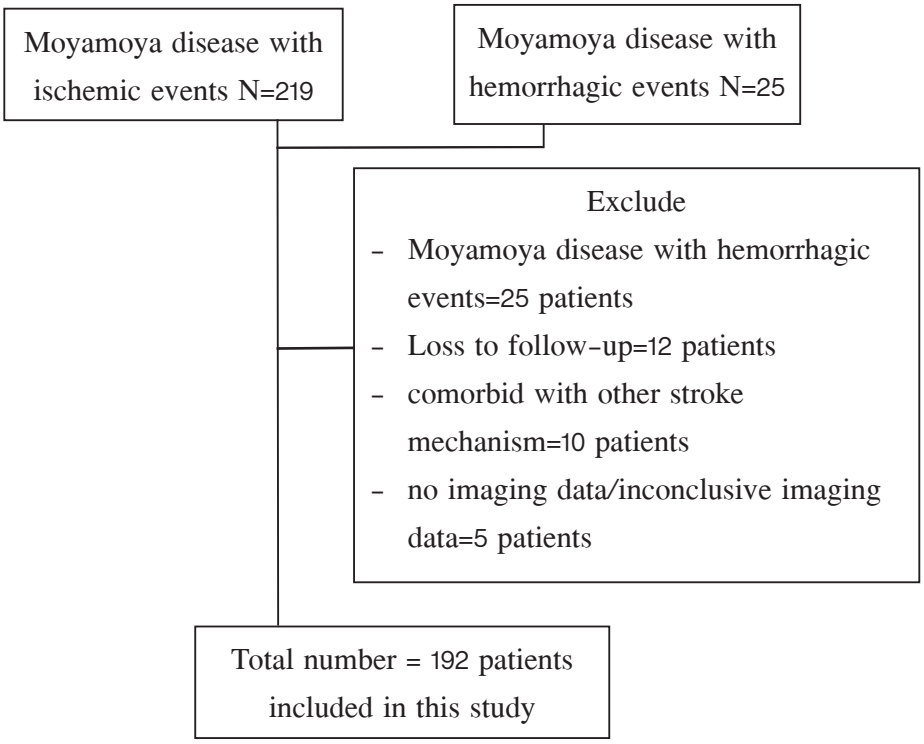

Table 2 showed the outcomes of dual antiplatelet treatment for adult patients with Moyamoya disease. Patients who received dual antiplatelet treatment had a higher risk of hemorrhagic stroke (odd ratio (OR), 1.96; confidence interval (95% CI), 1.62–4.73; p<0.001), and major bleeding (odd ratio (OR), 2.98; confidence interval (95% CI), 1.86–4.58; p<0.001) than patients who received single antiplatelet treatment, but not significant in the composite of ischemic stroke, hemorrhagic stroke, and death (odd ratio (OR), 1.23; confidence interval (95% CI), 0.86–1.44; p=0.634), the number of recurrent ischemic events (odd ratio (OR), 0.87; confidence interval (95% CI), 0.78–1.02; p=0.146) and the number of death (odd ratio (OR), 0.76; confidence interval 95% CI, 0.53–1.41; p=0.558). Figure 2 showed overall survival among Moyamoya patients who received either dual antiplatelet or single antiplatelet.

Table 3 showed a subgroup analysis of composite events by antiplatelet treatment duration. Patients who received dual antiplatelet treatment for less than 3 months or 6 months had not statistically significant in the composite of ischemic stroke, hemorrhagic stroke, and death (odd ratio (OR), 0.97; confidence interval (95% CI), 0.89–1.24; p=0.632)

Table 2. Outcomes of dual antiplatelet treatment for adult Moyamoya disease

	Dual antiplatelet group (N=88)	Single antiplatelet group (N=104)	p value	Adjusted OR(95%CI)*
Composite of ischemic stroke, hemorrhagic stroke and death (%)	37(42.0)	42(40.4)	0.634	1.23(0.86–1.44)
Bleeding events	12(13.6)	7(6.7)	<0.001	1.96(1.62–4.73)
Intracerebral hemorrhage (%)	2(2.3)	0	–	–
Subarachnoid hemorrhage (%)	5(5.7)	6(5.8)	0.442	0.98(0.76–1.12)
Extracranial bleeding (%)	15(17.0)	9(8.7)	<0.001	2.98(1.86–4.58)
Major bleeding++ (%)	4(4.72)	4(3.9)	0.568	1.02(0.88–1.32)
Minor bleeding (%)				
Recurrence ischemic stroke or transient ischemic attack (%)	17(19.3)	26(25.0)	0.146	0.87(0.78–1.02)
Number of Death (%)	6(6.8)	9(8.6)	0.558	0.76(0.53–1.41)

* Adjusted for baseline Suzuki classification, baseline NIHSS, large infarction, Previous revascularization surgery

++ Major bleeding defined by: life threatening bleeding or bleeding that require blood transfusion or bleeding in vital organs

Figure 2. Kaplan–Meier curves showing overall survival among Moyamoya patients who received either dual antiplatelet or single antiplatelet

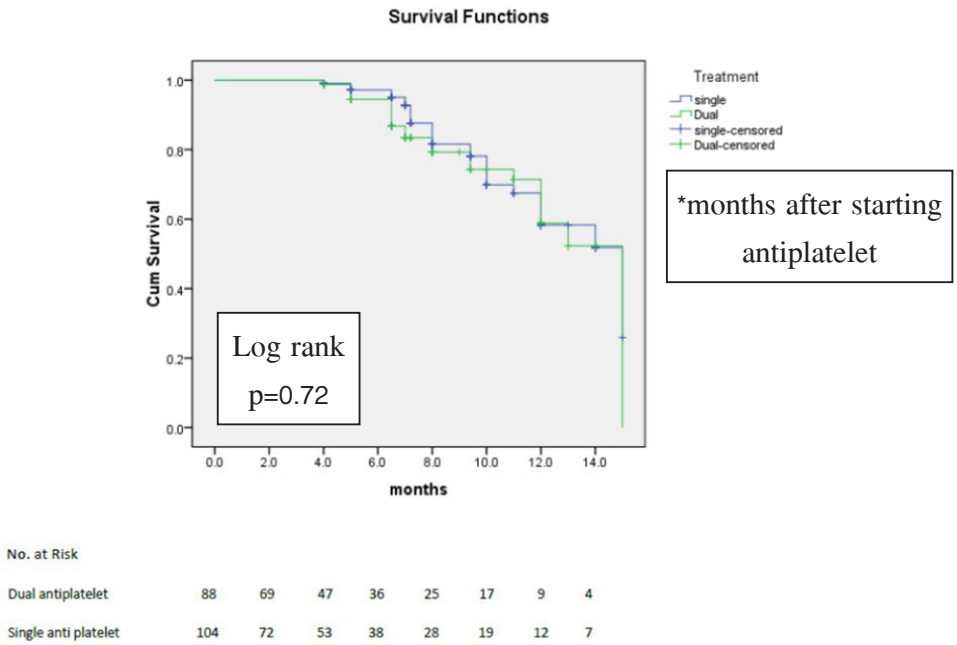

Table 3. Subgroup analysis of composite events by antiplatelet treatment duration

	Dual antiplatelet group (N=88)	Single antiplatelet group (N=104)	p value	Adjusted OR(95%CI)*
Duration less than 3 months	2(2.3)	0	-	-
Duration less than 6 months	6(6.8)	8(7.7)	0.632	0.97(0.89-1.24)

* Adjusted for baseline Suzuki classification, baseline NIHSS, large infarction, Previous revascularization surgery

Discussion

The results of this study suggested that dual antiplatelet treatment for adult patients with Moyamoya disease had no clinical benefit to preventing the composite of ischemic stroke, hemorrhagic stroke, and death (odd ratio (OR), 1.23; confidence interval (95% CI), 0.86-1.44; p=0.634), recurrent ischemic stroke or transient ischemic attack (odd ratio (OR), 0.87; confidence interval (95% CI), 0.78-1.02; p=0.146) or death (odd ratio (OR), 0.76; confidence interval 95% CI, 0.53-1.41; p=0.558).

Moyamoya disease caused ischemic events traditionally thought to result from poor perfusion, there is some evidence that ischemia in Moyamoya disease results from thromboembolic mechanism[12]. Onozuka et al.[13] found that antiplatelet use was significantly associated with good functional status on hospital admission for patients with non-hemorrhagic Moyamoya disease in Japan. Antiplatelet therapy may also be of benefit in conjunction with surgical revascularization[14] but some patients could not be a good candidate due to poor cerebral perfusion preserved.

Although Moyamoya is a rare disease and no large randomization trial for antiplatelet guide. In a previous study, the association of antiplatelet therapy, including cilostazol, with improved survival in patients with Moyamoya disease in a nationwide study[15]. Using the Korean national health insurance service database. Among 25,978 patients with newly diagnosed Moyamoya disease, the mean age was 37.6±19.9 years any antiplatelet use was associated with reduced risk of death (hazard ratio, 0.77; 95% CI, 0.70–0.84) in a multivariate model. Among individual antiplatelet agents, cilostazol was associated with a greater reduction in mortality than the 5 other antiplatelet regimens. Subgroup analysis, according to the age group and history of ischemic stroke, and sensitivity analysis, using propensity score-matched analysis, revealed consistent results. However, dual antiplatelet use in this study was just 9.3% (2,424/25978).

The main combination of aspirin plus cilostazol was used mainly in this study. In a previous study, Efficacy and Safety of Combination Antiplatelet Therapies in Patients with Symptomatic Intracranial Atherosclerotic Stenosis (TOSS 2)[16], a randomized, double-blind study in subjects with acute symptomatic stenosis in the M1 segment of the middle cerebral artery or the basilar artery were randomly allocated into either a cilostazol group or a clopidogrel group. revealed no significant differences between the 2 groups with respect to new ischemic lesions (18.7% versus 12.0%; P=0.078) and major hemorrhagic complications

(0.9% versus 2.6%; P=0.163). This trial failed to show a significant difference in preventing the progression of intracranial atherosclerotic lesions on MR angiogram and not increased hemorrhagic complication in atherosclerotic ischemic stroke patients. However, this trial was not directly studied dual antiplatelet therapy in ischemic stroke patients with Moyamoya disease who had other stroke mechanisms.

The combination of aspirin plus clopidogrel was used in this study. In a previous study, Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE study group)[17] showed that the combination of clopidogrel and aspirin was superior to aspirin alone for reducing the risk of stroke in the first 90 days and did not increase the risk of hemorrhage. However, this previous study followed up with enrolled patients within 3 months and no data on outcomes by using dual antiplatelet therapy beyond 3 months, especially, no data for adult Moyamoya disease. In a previous study, Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT study group)[18], the trial was halted after 84% of the anticipated number of patients had been enrolled because the data and safety monitoring board had determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events and a higher risk of major hemorrhage than aspirin alone at 90 days. The trial protocol differs from any previous study due to the 600 mg loading dose for clopidogrel in the dual antiplatelet arm. However, this trial was not directly studied dual antiplatelet therapy in ischemic stroke patients with Moyamoya disease. In this study, adult Moyamoya disease with ischemic events who received dual antiplatelet treatment had higher Suzuki stage and lower proportion of received revascularization surgery compared with patients who received single antiplatelet treatment. This finding might be because this study was an observational study, thus, treating physicians tended to prescribe dual antiplatelet for some selected patients who had a poor candidate for revascularization surgery and tend to increase the risk of ischemic events in the future from neuroimaging data and baseline Suzuki stage.

Moyamoya disease is associated with a high risk of recurrent cerebral ischemia. The mechanism of ischemic stroke from Moyamoya disease includes cerebral hypoperfusion, or thromboembolism[19]. The appearance of steno -occlusive changes in the region of the terminal internal carotid artery and the subsequent development of Moyamoya vessels are the characteristic findings in the initial stages (stages 1–3), whereas the compensatory development of transdural and/or transcranial anastomoses from the external carotid artery and the consequent disappearance of the Moyamoya vessels represents more advanced stages (4 and 5), followed by the disappearance of the intracranial internal carotid artery and the regression of the collateral circulation from the external carotid artery (stage 6)[20]. However, among patients with Moyamoya disease has an intrinsic nature to convert the vascular supply for the brain from the internal carotid (IC) system to the external carotid (EC) system, as indicated by Suzuki's angiographic staging established in1969 [21, 22, 23]. Insufficiency of this IC-EC conversion system could result not only in cerebral ischemia but also in intracranial hemorrhage from inadequate collateral anastomosis ('Moyamoya vessels'), both of which represent the clinical manifestation of Moyamoya disease.

Clarifying the pathophysiology of cerebral ischemia in Moyamoya disease has the potential to guide treatment decisions. Moyamoya disease

in adulthood had a variable of ischemic and hemorrhagic events and a causal relationship is not well established[24]. Whereas interventions to improve cerebral perfusion in Moyamoya disease such as revascularization surgery had the potential benefit in some cases and had no consensus criteria for a selected good candidate for surgery. The treating physician had a selection bias for balance risk of ischemic events and hemorrhagic events for patients with Moyamoya disease. However, more evidence in the future will improve the treatment plan for Moyamoya disease.

There are several limitations to this study. First, enrollment of adult patients with Moyamoya disease in this study had higher Suzuki stages in the dual antiplatelet treatment group. Patients with higher Suzuki stages were associated with unfavorable outcomes, especially hemorrhagic events. Second, Moyamoya disease is a chronic disease that tends to progress over time and stroke events either ischemic or hemorrhagic events occurred from the nature of the disease progression and masked effect of antiplatelet in late-stage Moyamoya disease, finally, the observational design meant that patient allocation to dual antiplatelet group occurred at the discretion of the treating physician rather than by randomization, creating the possibility of confounding by indication when interpreting the medication effect. This limitation was addressed by the use of a multivariate logistic regression model. However, unmeasured confounding factors could still be present.

Conclusion

Adult patients with Moyamoya disease had no clinical benefit from dual antiplatelet treatment with an increase in the risk of hemorrhagic stroke and major bleeding.

Originality and body of knowledge

Long-term use of dual antiplatelet treatment had no clinical benefit in adult patients with Moyamoya disease, especially in patients with a higher stage of Moyamoya disease.

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