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Original Research Article

The effect of dual antiplatelet therapy for improvement of extracranial and intracranial artery stenosis evaluated by digital subtraction angiography

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ABSTRACT

Background: Stroke involving extracranial carotid (ECAS), vertebral (EVAS), and intracranial arteries (IAS) contributed to an annual stroke rate of 0.1-3.3%. Even though endarterectomy and/or angioplasty and stenting had revolutionized its' management, best medical treatment (BMT) is still the mainstay of therapy to prevent secondary stroke/transient ischemic attack. This study aimed to evaluate the effect of BMT to reduce the degree of stenosis by using six-months double antiplatelet therapy (DAPT).
Methods: A retrospective cohort study was conducted in a secondary private hospital in Indonesia, in January-December 2022. Adults ≥18 years old with ECAS, EVAS, or IAS detected using digital subtraction angiography (DSA), receiving DAPT for at least six months, and those who had second DSA evaluation were included. Any subjects with other brain pathologies or recorded incompliance to DAPT were excluded. Age, gender, stenosis degree, stenosis location, and conversion of stenosis degree were recorded and compared between pre-DAPT and post-DAPT group.
Results: Of 30 subjects, there were insignificant changes (46.5±24.3% to 50.8±22.9%, p=0.09) of ECAS, EVAS, and IAS. There were 14 cases with constant stenosis (51.4±17.5%), 8 cases with decreasing stenosis (46.9±28.2% to 40.1±32.8%, p=0.012), and 12 cases with increasing stenosis (40.4±29.9% to 57.1±21.0%, p=0.002). No significant association were found among those groups related to traditional vascular risk factors.
Conclusions: There was no difference in respect to the degree of stenosis following six months of DAPT in either ECAS, EVAS, or IAS. Routine evaluation as well as recognizing features of high-risk stroke/TIA are important to help decide individual who may be candidates of endovascular procedures earlier.

Keywords: Carotid artery stenosis, Degree of stenosis, Dual antiplatelet, Intracranial artery stenosis, Vertebral artery stenosis

INTRODUCTION

Extracranial carotid artery stenosis (ECAS), extracranial vertebral artery stenosis (EVAS), and intracranial artery stenosis (IAS) have been recognized as risk factors for stroke. A study of 3,727 subjects with 4,230 asymptomatic ECAS cases in California reported that severe ipsilateral ECAS contributed to an estimated 4.7% of ECAS-related acute ischemic strokes over a 5-year period, both with and without aspirin and without surgical intervention.[1] Another study described that the annual ipsilateral stroke rate reached 0.1-1.6% in cases of mild-to-moderate asymptomatic ECAS and 2-3.3% in cases of severe asymptomatic ECAS with suboptimal medical treatment.[2]

Stenosis degree was measured and classified using the North American symptomatic carotid endarterectomy trial (NASCET) criteria into mild, moderate, and severe stenosis.[1,3] Mild stenosis was defined as stenosis of <50% whereas moderate stenosis was defined as stenosis of 50-69% and severe stenosis was defined as stenosis of 70-99%. Increased degree of stenosis, either in symptomatic or asymptomatic patients, has been recognized as a risk factor of stroke, especially in those with moderate and severe stenosis.[1-3.]

The best medical treatment (BMT), which includes lifestyle modifications, dual antiplatelet therapy, and risk factor control, remains the cornerstone of treatment for symptomatic ECAS, EVAS, and IAS to prevent long-term cardiocerebral vascular events such as myocardial infarction and stroke. Despite compliant use of BMT, some cases, especially those with moderate-to-severe stenosis (50-99%), still face a persistent risk of stroke or transient ischemic attack (TIA). Several reported risk factors include increased age, more recent stroke/TIA symptoms, male gender, more comorbidities, more severe stenosis, irregular plaque, stenosis progression of >20%, intraplaque hemorrhage on MRI, predominantly echolucent plaque, silent ipsilateral infarction on CT, increased juxtaluminal black area on computerized ultrasound plaque analysis, ≥1 microembolic signal during ≥1 hour of transcranial Doppler monitoring, contralateral stroke/TIA, contralateral occlusion, and others. Since the discovery of carotid endarterectomy (CEA) more than 20 years ago, as well as angioplasty and stenting, these endovascular procedures have been recommended in conjunction with BMT to treat symptomatic ECAS of 50-99%, symptomatic ECAS of <50%, or near occlusion with distal vessel collapse with recurrent stroke/TIA. They are also considered for EVAS and IAS with recurrent stroke/TIA following routine antiplatelet therapy.[3]

Studies comparing BMT to endovascular procedures have evolved to help determine suitable candidates for endovascular procedures and those who will benefit from BMT. BMT has been reported to be similarly effective as endovascular procedures for asymptomatic ≥50% ECAS and has shown a decrease in the annual ipsilateral stroke rate from 2-3.3% to 0.3-3.1%. Moreover, BMT has been found to provide three to eight times greater cost-effectiveness than endovascular procedures.[2] While the incidence of stroke has been the primary outcome parameter in most studies, there have been limited studies analyzing its impact on the reduction of stenosis percentage.[4] This study aimed to describe the effect of dual antiplatelet therapy on reducing the progression of stenosis in the symptomatic ECAS, EVAS, and IAS population.

METHODS

We conducted a retrospective cohort study at a secondary private hospital in Jakarta, Indonesia, from January to December 2022, to evaluate the effect of dual antiplatelet therapy on the reduction of extracranial carotid artery stenosis (ECAS), extracranial vertebral artery stenosis (EVAS), or intracranial artery stenosis (IAS).

Inclusion and exclusion criteria

The inclusion criteria encompassed adults aged ≥18 years with a diagnosis of ischemic stroke or transient ischemic attack (TIA) who had been diagnosed with ECAS, EVAS, or IAS using digital subtraction angiography (DSA), received dual antiplatelet therapy (DAPT), and underwent a second DSA at least six months later. Subjects with spinal stroke, brain vascular malformations (including arteriovenous malformation, aneurysm, Moya-Moya disease, etc.), or other structural brain etiologies (acute traumatic brain injury, brain infection undergoing therapy, or brain tumor), as well as those who underwent carotid, vertebral, or intracranial artery stenting or endarterectomy, received regimens other than DAPT (including single antiplatelet or anticoagulant therapy), or did not comply with the treatment regimen, were excluded.

This study retrospectively recorded several data from the medical record, including demographics of age and gender, cerebrovascular risk factors including hypertension, diabetes, smoking, and exercise, the final diagnosis of ischemic stroke or TIA, the use of dual antiplatelet, and the location, percentage, and degree of stenosis using pretreatment DSA expertise and DSA expertise following at least six months of DAPT.

Brain ischemic stroke was defined as a sudden focal or global neurological syndrome involving the brain or retina that could exclusively be attributed to reduced brain perfusion due to blood vessel narrowing, as confirmed by objective brain imaging expertise, excluding hemorrhagic lesions. TIA was defined as an ischemic stroke in which the symptoms resolved within 24 hours.

Blood vessel stenosis was determined using DSA expertise, considered the gold standard for diagnosing ECAS, EVAS, and IAS. The percentage of stenosis was calculated using the NASCET criteria and was recorded as documented by the experts.[1,3] Stenosis location was classified as ECAS if it occurred in the extracranial right or left internal carotid artery (ICA) or at the bifurcation between the common carotid artery and ICA, EVAS if it occurred in the extracranial right or left vertebral artery (VA), or IAS if it occurred in an intracranial artery, including the anterior cerebral artery, middle cerebral artery, posterior cerebral artery, basilar artery, intracranial VA, or intracranial ICA. The degree of stenosis was categorized as mild for 30-49% stenosis, moderate for 50-69% stenosis, and severe for ≥70% stenosis.[3]

Each subject underwent two DSA procedures with an interval of at least six months. Dual antiplatelet therapy

(DAPT) consisted of two medications to prevent platelet aggregation, including aspirin, clopidogrel, cilostazol, ticagrelor, etc., and was documented in the medical records. Age, gender, and cerebrovascular risk factors were recorded at the time of admission. The response of DAPT to the degree of stenosis was assessed with regard to the change in the percentage of stenosis location, whether single or multiple, the mean stenosis in overall cases as well as in ECAS, EVAS, or IAS cases, the change in the degree of stenosis, categorized as mild, moderate, or severe, and the mean stenosis change categorized as constant, increased, or decreased stenosis.

Using 95% confidence interval and power of 80%, the sample size was estimated to be 96. However, not every patient had DSA performed to diagnose stenosis. To maximize the sample size, total sampling during a year was carried out, which resulted in the recruitment of 30 subjects.

Data were presented as percentages for categorical data, as mean±standard deviation for normally distributed numerical data, or as median (minimum-maximum) for abnormally distributed numerical data. For bivariate comparisons between pre-DAPT and six months following DAPT, paired t-test analysis was performed. Data were analyzed using SPSS 20.0.

RESULTS

The study recruited 30 subjects with a mean age of 53.4±9.8 years, predominantly male (56.7%), and with the following risk factors: hypertension (100%), lack of exercise (60.0%), diabetes (26.7%), and smoking (26.7%). All enrolled subjects had either ECAS (33.3%), EVAS (33.3%), or IAS (36.7%). The stenosis was mostly located in a single location (96.7%), but one subject had multiple extracranial stenoses involving the extracranial carotid LCCA/LICA bifurcation and extracranial left vertebral artery ostium. Therefore, there were 30 subjects and 31 cases of stenosis in the pre-DAPT group (Table 1). The distribution of stenosis is depicted in Figure 1.

Table 1: Demographic characteristic of subjects.

Parameters	Total (N=30) (%)
Age (years)	53.4±9.8
Male (n)	17 (56.7)
Hypertension (n)	30 (100.0)
Diabetes (n)	8 (26.7)
Smoking (n)	8 (26.7)
No exercise (n)	18 (60.0)
Stenosis profile	
ECAS	10/30 (33.3)
EVAS	10/30 (33.3)
IAS	11/30 (36.7)
Stenosis location	
Single	29/30 (96.7%)
Multiple	1/30 (3.3%)

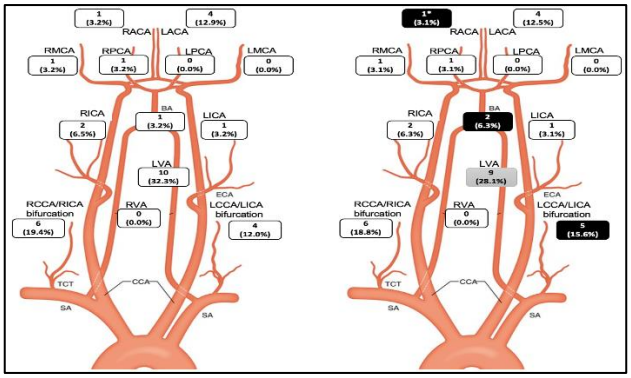

Figure 1: Distribution of stenosis in this study.
Black box indicates new stenosis, grey box indicates total resolved stenosis, and asterisk indicates one subject with new stenosis and one subject with total resolved stenosis post-DAPT.

Table 2: Comparison of stenosis parameter pre-DAPT and post-DAPT.

Parameter	Pre-DAPT	Post-DAPT	P
Stenosis location (n=30 subjects)			
No stenosis	-	2 (6.7%)	0.23
Single location	29 (96.7%)	25 (83.3%)	Ref
Multiple location	1 (3.3%)	3 (10.0%)	0.61
Mean stenosis (n=34 cases)	46.5±24.3%	50.8±22.9%	0.09
ECAS (n=11)	38.2±16.6%	45.3±12.2%	0.16
EVAS (n=10)	55.0±24.0%	56.3±26.0%	0.42
IAS (n=13)	46.9±29.8%	51.2±28.2%	0.41
Stenosis classification (n=34 cases)			
No stenosis	3 (8.8%)	2 (5.9%)	1.00
Mild stenosis	15 (44.1%)	13 (38.2%)	Ref
Moderate stenosis	9 (26.5%)	10 (29.4%)	0.77
Severe stenosis	7 (20.6%)	9 (26.5%)	0.75
Delta stenosis changes (n=34 cases)	0 (-30-50%)		
Constant stenosis (n=14)	51.4±17.5%		Ref
Increased stenosis (n=12)	40.4±29.9%	57.1±21.0%	0.002
Decreased stenosis (n=8)	46.9±28.2%	40.1±32.8%	0.012

DAPT: dual antiplatelet therapy, ECAS: extracranial carotid artery stenosis, EVAS: extracranial vertebral artery stenosis; IAS: intracranial artery stenosis.

Following six months of DAPT, there were two subjects with resolved stenosis (6.7%) and two new cases of multiple stenosis (10.0%). The resolved stenosis cases were a subject with 5% stenosis at EVAS and a subject with 30% IAS at the right anterior cerebral artery. The new multiple stenosis cases included a subject who initially had single 50% ECAS at RCCA/RICA bifurcation, which progressed to additional 50% IAS at

BA and 20% IAS stenosis at RACA and a subject who initially had single 50% EVAS which progressed to additional 50% IAS at LCCA/LICA bifurcation. Therefore, at the end of the study, there were 28 subjects with stenosis and 32 cases of stenosis, as well as 2 resolved stenosis cases (Table 2, Figure 2A).

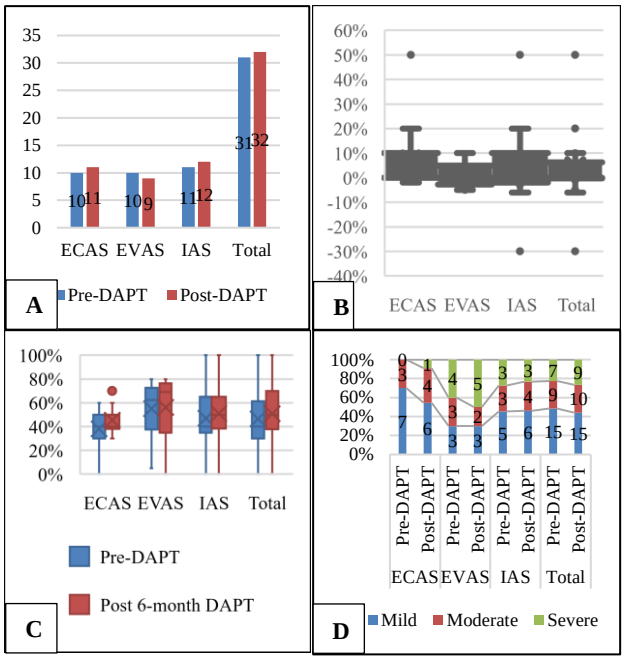

Figure 2: (A) Number of cases with stenosis in this study; (B) Stenosis difference after six months of DAPT; (C) Mean stenosis before and after DAPT; (D) Number of cases with mild, moderate, and severe stenosis prior to and following DAPT. There was no statistically significant difference in all subgroups. DAPT: dual antiplatelet therapy, ECAS: extracranial carotid artery stenosis, EVAS: extracranial vertebral artery stenosis; IAS: intracranial artery stenosis.

The mean stenosis increased slightly from 46.5±24.3% prior to DAPT to 50.8±22.9% following 6 months of DAPT (p=0.09). This pattern was consistent when analyzed within subgroups of ECAS (38.2±16.6% to 45.3±12.2% in pre-DAPT versus post-DAPT, p=0.16), EVAS (55.0±24.0% to 56.3±26.0% in pre-DAPT versus post-DAPT, p=0.42), and IAS (46.9±29.8% to 51.2±28.2%, p=0.41). In subjects with predominantly mild stenosis before DAPT, there was an increased tendency towards moderate (p=0.77) and severe stenosis (p=0.75) after DAPT. Among the subjects, 14 had constant stenosis (mean stenosis change of 0±30-50%), 12 had increased stenosis, and 8 had decreased stenosis (Table 2, Figure 2).

The difference in stenosis did not show any association with age, gender (p=0.82), diabetes (p=0.98), sedentary behavior (p=0.33), or smoking (p=0.75) (Table 3). The association between hypertension and stenosis cannot be evaluated because all subjects in this study had hypertension

Table 3: Difference in stenosis with respect to demographic characteristic of subjects.

Parameter	Delta stenosis change (%)	P value
Age	-	
Gender		0.82
Male	0 (-30-20)	
Female	0 (-5-50)	
Hypertension		-
Yes	0 (-30-50)	
No	-	
Diabetes		0.98
Yes	0 (-6-10)	
No	0 (-30-50)	
Smoking		0.75
Yes	0 (-5-10)	
No	0 (-30-50)	
Exercise		0.33
Yes	0 (-30-20)	
No	0 (-6-50)	

DISCUSSION

To date, this study is one of the few that have evaluated the dynamics of ECAS, EVAS, and IAS following DAPT using the gold standard of DSA. The study recruited adults in their fifth decade of life, with a male-to-female ratio of 3:2. The age of the subjects in this study was younger than that reported in other studies, where the subjects were typically in their seventh decade of life, but the gender ratio was similar.[5-9] According to the National Basic Health Research of Indonesia in 2018, there is a positive association between increasing age and the prevalence of stroke. The prevalence rates increased from 3.70 per 1,000 individuals in the 35-44 years age group to 14.20 per 1,000 in the 45-54 years age group, and further to 32.40 per 1,000, 45.30 per 1,000, and 50.20 per 1,000 in the 55-65 years, 65-74 years, and ≥75 years age groups, respectively.[10] The younger age of the subjects in this study may be attributed to differences in ethnicity compared to the populations in other studies.[5-9] However, it is worth noting that this study may represent older non-geriatric adults who are still in their productive years, which could have implications for reduced productivity.

The predominant risk factor in this study was hypertension, followed by sedentary behavior, diabetes, and smoking. Other studies have also reported hypertension as the most prevalent risk factor, followed by smoking, hyperlipidemia, atrial fibrillation, and diabetes. These findings remained consistent whether examining asymptomatic or symptomatic stenosis or nonsignificant or significant stenosis. Increased blood pressure variability was observed in individuals with increased age, females, diabetics, smokers, a history of previous stroke/TIA, peripheral vascular disease, or atrial fibrillation. Hypertension may contribute to endothelial dysfunction and activation, as well as increased neuroinflammation, which could play a role in the

development of vascular stenosis. It is hypothesized that a reduction in systolic blood pressure propagation, in conjunction with control of HbA1c levels and plaque remodelling with statins, may lead to decreased stenosis progression.[11,12]

This study predominantly recruited subjects with a mild degree of stenosis. After 6 months of BMT with DAPT, the study made the following observations: (1) there was no association between six-month DAPT and the degree of stenosis; (2) this nonsignificant association was not only observed in overall stenosis, but also in ECAS, EVAS, and IAS; (3) this nonsignificant association was not associated with traditional vascular risk factors such as age, gender, and comorbidities of stroke/TIA. Following 6 months of DAPT, there were 14 subjects with constant stenosis at 51.4±17.5%, and 8 subjects with decreased stenosis from 46.9±28.2% to 40.1±32.8% (p=0.012). However, there were 12 subjects with increased stenosis, which progressed from 40.4±29.9% to 57.1±21.0% (p=0.002). These findings suggest that while BMT remains the primary choice of treatment for stenosis cases, routine evaluation of plaque may be considered to detect subjects whose stenosis does not respond to BMT, allowing for earlier intervention before the occurrence of stroke/TIA.

Although there were no new stroke/TIA events at the end of the study, and the majority of stenosis cases were stabilized or reduced (64.7%), some subjects (35.3%) may not have benefited from 6 months of DAPT. A review by Kim et al highlighted other features of stenosis associated with a higher risk of stroke/TIA, including the detection of microemboli (OR 6.63, 95% CI 2.85-15.44), plaque echolucency (RR 2.48, 95% CI 1.90-3.22), stenosis progression (RR 1.86, 95% CI 1.35-2.55), especially progression of >20% (OR/HR 1.92, 95% CI 1.14-3.25), reduced cerebrovascular reserve (OR 5.27, 95% CI 1.68-16.51), intraplaque hemorrhage (HR 14.5, 95% CI 2.9-7.25), and ipsilateral silent brain infarction (HR 3.0, 95% CI 1.46-6.29).[13] Another critical review by Messas et al added clinical features such as contralateral stroke/TIA, ultrasound features of an increased juxtaluminal black (hypoechogenic) area, impaired cerebral vascular reserve, larger plaque size, and MR angiography features of a lipid-rich necrotic core to the increased risk of recurrent stroke/TIA in asymptomatic ECAS.[14] While DSA was the most superior method for assessing stenosis, the morphology of plaque was better described using ultrasound imaging or MR angiography, and the impact of silent brain infarction was better assessed using cerebral imaging. Further studies to characterize the stenosis profile may be important for making earlier decisions regarding candidates for endovascular procedures.

The strength of this study lies in its assessment of the degree of stenosis as the primary outcome following DAPT, which has been examined by only a limited number of studies. The findings of this study may contribute to earlier detection and decision-making regarding endovascular procedure management. Furthermore, the primary outcome was measured using the gold standard of DSA, adding to the robustness of the results.

However, this study has some limitations, including observation of controlled risk factors are not data included, the small sample size and constraints in the assessment of the stenosis profile. Despite utilizing a total sampling method, further studies with larger sample sizes and more inclusion data are needed to confirm and generalize the findings.

CONCLUSION

Dual antiplatelet therapy provided no significant association in attempt to decrease the degree of stenosis. While BMT remains the primary treatment approach for ECAS, EVAS, and IAS, routine evaluation, and the recognition of high-risk features in these conditions are crucial for clinicians to identify those who may benefit from earlier endovascular treatment. This individualized approach to patient care can help optimize outcomes and reduce the risk of stroke or TIA in affected individuals.

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