



Efficacy of dual antiplatelet therapy as premedication before diagnostic cerebral digital subtraction angiography

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Objective : Several studies have reported that periprocedural dual antiplatelet therapy lowers the incidence of thromboembolic complications (TEC) associated with coiling of unruptured aneurysms. We hypothesized that preprocedural administration of dual antiplatelet agents (aspirin and cilostazol) for 7 days may reduce the risk of complications associated with diagnostic cerebral digital subtraction angiography (DSA).

Methods : We retrospectively reviewed the records of patients who underwent diagnostic cerebral DSA between September 2015 and April 2018. Of the 419 patients included (149 men, 270 women, mean age 58.5 years), 221 (72 men, 149 women, mean age 57.8 years) who underwent cerebral DSA between September 2015 and June 2016 were not premedicated with antiplatelet therapy. The remaining 198 (77 men, 121 women, mean age 59.4 years) who underwent cerebral DSA between July 2016 and April 2018 were premedicated with dual antiplatelet therapy (aspirin and cilostazol). We defined ischemic stroke as a cerebral DSA-induced complication identified on magnetic resonance imaging (MRI) among patients with neurological symptoms.

Results : Of the 221 patients who did not receive antiplatelet therapy, 210 (95.0%) showed no neurological symptoms; however, 11 (5.0%) developed neurological symptoms with MRI-proven ischemic stroke, which represents a TEC. Of the 198 patients who received dual antiplatelet therapy, 196 patients (99.0%) showed no evidence of TEC. The remaining 2 (1.0%) developed diplopia and motor weakness each, and MRI confirmed acute ischemic stroke ($p=0.019$).

Conclusions : The use of dual antiplatelet agents (aspirin and cilostazol) for 7 days before DSA may reduce the risk of cerebral DSA-induced TEC.

Keywords digital subtraction angiography, antiplatelet therapy, premedication, thromboembolism

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INTRODUCTION

Following the availability of novel technology, cerebral digital subtraction angiography (DSA) is commonly used clinically to diagnose cerebrovascular abnormalities⁸. Cerebral DSA is a safe procedure; how-

ever, complications may occur in rare cases^{6,8}. Considering the widespread use of cerebral DSA as a general diagnostic modality for cerebrovascular disease, it is important to reduce the complications related to this technique.

Among the various complications of cerebral DSA

including nausea, vomiting, transient hypotension, anaphylaxis, and groin hematoma^{5,23}), we focused on neurological complications secondary to thromboembolism. Thromboembolism is the most significant complication of cerebral DSA¹⁴), which occurs secondary to thrombus formation within catheters, within pre-existing friable intravascular thrombotic plaques, or device-induced microdissections¹¹).

Antiplatelet and anticoagulant therapy effectively reduces the risk of thromboembolism^{13,18}). Several studies have reported that periprocedural antiplatelet therapy effectively lowers the incidence of thromboembolic complications (TEC) that may occur with coiling of unruptured aneurysms^{15-17,24}). However, to the best of our knowledge, no studies have been performed for diagnostic cerebral DSA. We hypothesized that pre-procedural administration of dual antiplatelet agents (aspirin and cilostazol) for 7 days may reduce the risk of complications associated with diagnostic cerebral DSA.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the records of 419 patients who underwent diagnostic cerebral DSA between September 2015 and April 2018 (Table 1). Among these 419 patients, 221 patients who underwent diagnostic cerebral DSA from September 2015 to June 2016 did not received dual antiplatelet therapy as premedication. The remaining 198 patients who underwent diagnostic cerebral DSA between July 2016 and April 2018 received dual antiplatelet therapy as premedication. We changed the strategy because the incidence of TEC was higher than we thought when no premedication was given. Patient consent was waived for this study owing to the retrospective study design. Inclusion criteria for this study were non-ruptured aneurysms, arteriovenous malformations, and arteriovenous fistulas, stenosis or occlusion of cerebral artery, as well as postoperative evaluation 1-2 years after coiling or clipping (Table 2). Patients with DSA performed for subarachnoid hemorrhage

(SAH), patients with SAH presenting for a week follow-up angiography, patients with an acute or sub-acute stroke, patients with symptoms of a transient ischemic attack within 4 weeks of the scheduled cerebral DSA, patients with evidence of intracerebral hemorrhage, those with a history of neurosurgical or interventional procedures 4 weeks prior to the study, and those with congestive heart disease or cardiac arrhythmia were excluded. We defined cerebral DSA-related TEC as the occurrence of acute ischemic stroke that was confirmed on MRI within 48 hours of testing among patients presenting with neurological symptoms.

Procedures

Cerebral DSA was performed via the transfemoral arterial approach using a dedicated biplane neuroangiography unit (RF-1000-125, Artis Zee biplane, Siemens Healthineer, Berlin, Germany) with the help of 1 type of guidewire (Terumo®, 0.035 inch, Tokyo, Japan) and 3 types of catheters – Taper (Cook, Bloomington, IN, USA), Imager (Boston Scientific, Marlborough, MA, USA), Simmons I (AngioDynamics, Queensbury, NY, USA). A non-ionic contrast medium (Iomeron 300 [ioimeprol 612.4 mg/mL], Bracco S.p.A., Milan, Italy) was used for all procedures with automatic machine injection of the contrast medium fol-

Table 1. Characteristics of the study population

	Without premedication	With Premedication	Total
Number of patients	221	198	419
Male	72	77	149
Female	149	121	270
Mean age (years)	57.8 (21-80)	59.4 (19-80)	58.6 (19-80)

Table 2. Inclusion criteria for the study

Cases in premedication	Number
Unruptured aneurysm	338 (80.67%)
Intervention evaluation	51 (12.17%)
Arteriovenous malformation	9 (2.15%)
Carotid cavernous fistula	5 (1.19%)
Moyamoya	2 (0.48%)
Stenosis/occlusion/dissection	13 (3.10%)
Atherosclerosis	1 (0.24%)
Total	419

lowed by a saline flush after each injection. The FemoSeal[®], vascular closure device, was used for hemostasis at the site of vascular access. All procedures in this series were performed by a single neurovascular surgeon (the author of this study).

Drug Protocols

Patients who underwent DSA between July 2016

and April 2018 received aspirin and cilostazol (both 100 mg/day) for 7 days. All antiplatelet therapy was discontinued post-procedure in premedicated patients who underwent cerebral DSA but did not develop TEC.

Statistical Analysis

Comparison between two groups was performed us-

Table 3-1. Correlation between risk factors and the incidence of thromboembolic complications secondary to cerebral digital subtraction angiography in non-pretreated dual antiplatelet therapy as premedication

Risk factor	Thromboembolic complication		NO	YES	p-value
	No	Yes			
Hypertension	No		110	7	0.466
	Yes		100	4	
Diabetes mellitus	No		180	9	0.720
	Yes		30	2	
Hyperlipidemia	No		191	10	0.996
	Yes		19	1	
Stroke history	No		171	10	0.426
	Yes		39	1	
heart disease	No		195	11	0.359
	Yes		15	0	
Smoking	No		185	9	0.535
	Yes		25	2	
Chronic kidney disease	No		204	11	0.57
	Yes		6	0	
Number of vessel Examined	1		35	0	0.212
	2		9	0	
	3		90	4	
	4		76	7	
	5		0	0	

Table 3-2. Correlation between risk factors and the incidence of thromboembolic complications secondary to cerebral digital subtraction angiography in pretreated dual antiplatelet therapy as premedication

Risk factor	Thromboembolic complication		NO	YES	p-value
	No	Yes			
Hypertension	No		109	1	0.874
	Yes		87	1	
Diabetes mellitus	No		168	1	0.155
	Yes		28	1	
Hyperlipidemia	No		169	2	0.572
	Yes		27	0	
Stroke history	No		160	1	0.167
	Yes		29	1	
heart disease	No		188	2	0.771
	Yes		8	0	
Smoking	No		181	2	0.684
	Yes		15	0	
Kidney disease	No		194	2	0.919
	Yes		1	0	
Number of vessel Examined	1		4	0	0.989
	2		8	0	
	3		116	1	
	4		66	1	
	5		1	0	
Type of catheter	Taper		159	1	0.358
	Imager		9	0	
	Simmon		28	1	

ing Fisher's exact test, chi-square test and independent t tests (significant level 0.05). Statistical analysis was performed using the SPSS software, version 19 (IBM SPSS Statistics, IBM Corp., Armonk, NY). A p-value < 0.05 was considered statistically significant.

RESULTS

We analyzed the complication ratio based on risk factors including hypertension, diabetes mellitus, hyperlipidemia, history of stroke, smoking, heart disease such as heart failure or arrhythmia, chronic kidney disease, and others that can affect the vascular status. Our analysis showed that these risk factors did not significantly affect the incidence of DSA-induced TEC (Table 3-1, 3-2).

There was a significant difference in the incidence of TEC between patients who took dual antiplatelet therapy and those who did not, which is consistent with our hypothesis. Of the 221 patients who did not receive antiplatelet therapy, 210 patients (95.0%) did not report neurological symptoms; however, 11 patients (5.0%) reported various neurological symptoms including motor weakness and showed MRI-proven ischemic stroke (Fig. 1), which represents a TEC. Of the 198 patients who received dual antiplatelet therapy, 196 (99.0%) showed no evidence of TEC. However, 2 (1.0%) developed diplopia (Fig. 2) and motor weakness respectively, and acute ischemic stroke was confirmed on MRI ($p=0.019$) (Table 4). Of the 13 patients diagnosed with DSA-induced TEC, 7 presented motor weakness, 4 reported visual disturbance, and 1 reported dysarthria and paresis (Table 5).

DISCUSSION

Cerebral DSA and noninvasive cerebrovascular imaging modalities have shown steady improvement over the past several decades. Presently, diagnostic cerebral DSA is commonly performed for treatment planning of endovascular or open surgical proce-

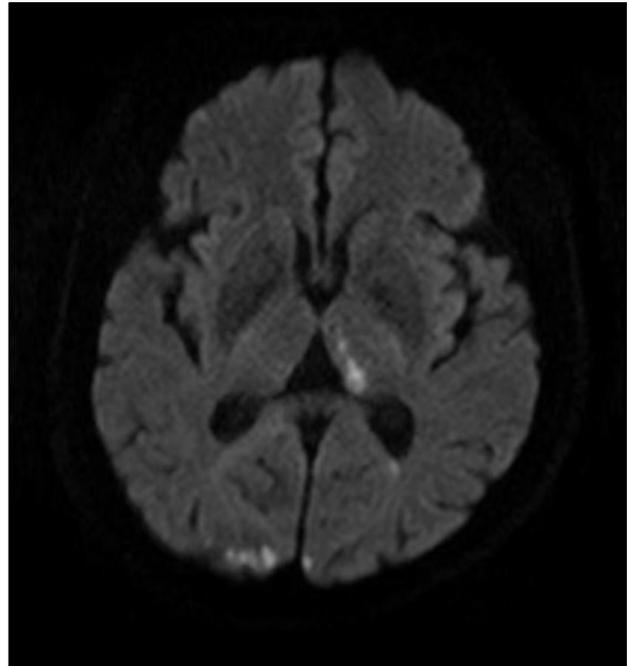


Fig. 1. Magnetic resonance image in untreated premedication
Diffusion-weighted magnetic resonance imaging scan obtained in a woman who developed right-sided motor weakness immediately after diagnostic cerebral digital subtraction angiography for an unruptured aneurysm. An acute ischemic stroke involving the left thalamus and both occipital lobes was confirmed as a thromboembolic complication. Of note, she had not been administered premedication.

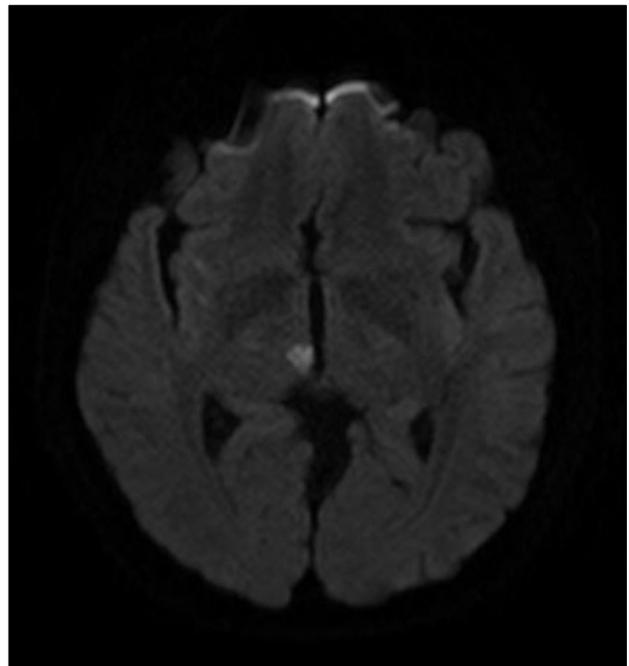


Fig. 2. Magnetic resonance image in treated premedication
Image shows a man who was premedicated with dual antiplatelet therapy and was diagnosed with an acute ischemic stroke involving the right prefrontal region. He complained of a diplopia.

Table 4. Correlation between the administration of premedication and the development of thromboembolic complications

Premedication	Thromboembolic complication		Total	p-value
	No	Yes		
No	210 (95.0%)	11 (5.0%)	221	0.019
Yes (aspirin+cilostazol)	196 (99.0%)	2 (1.0%)	198	
Total	406 (96.9%)	13 (3.1%)	419	

Table 5. Patients diagnosed with thromboembolic complications

Symptoms as thromboembolic complication	Premedication	
	No	Yes
Motor weakness	6 (46.2%)	1 (7.7%)
Ocular symptom	3 (23.0%)	1 (7.7%)
Dysarthria	1 (7.7%)	0 (0.0%)
Paresis	1 (7.7%)	0 (0.0%)
Total	11 (84.6%)	2 (15.4%)

dures⁸⁾. However, diagnostic cerebral DSA is associated with a risk of complications including TEC. To qualify as a generalized diagnostic test, cerebral DSA should be safe with a low risk of complications⁶⁾⁸⁾.

Diagnostic cerebral DSA may result in local complications such as access-site hematoma formation and systemic complications including headache, nausea, vomiting, and/or transient hypotension, nephropathy, and neurological deficits²³⁾. Among the various complications of diagnostic cerebral DSA, we focused on TEC, which can cause neurological deficits.

Thromboembolism is the most common cause of ischemic stroke, which can cause transient or permanent neurological deficit including hemiparesis, aphasia, visual symptoms, and a diminished level of consciousness, among others²⁾. Thus, thromboembolism counts as a significant complication of diagnostic cerebral DSA. Complication rates are approximately 0.55-3.2%, although these vary across studies⁶⁾⁸⁾. Most TEC occur within the first 48 hours post intervention. We defined cerebral DSA-induced TEC as the occurrence of acute ischemic stroke that was confirmed on MRI within 48 hours of testing in patients with neurological symptoms.

Presently, the key concern is to minimize diagnostic cerebral DSA-related complications and identify strat-

egies to effectively manage those that have already occurred.

The risk factors for ischemic stroke after cerebral DSA include hypertension, diabetes mellitus, dyslipidemia, cardiac disorders like heart failure or arrhythmia, a history of smoking, chronic kidney disease, the number of catheters used, types of catheters used, and the volume of contrast agent used³⁾⁵⁾²⁰⁾²²⁾²³⁾. We analyzed the effect of each risk factor on the incidence of cerebral DSA-induced complications. The association between the incidence of TEC and each risk factor was non-significant.

An ischemic stroke may occur during the cerebral DSA procedure secondary to vascular spasm or neurovascular dissection following severe vascular stenosis or occlusion. However, most instances of ischemic stroke following cerebral DSA may be associated with distal embolization of air or particulate matter¹¹⁾ secondary to disruption of a calcified plaque, which actually precipitates the clinical event. Air embolism can occur during catheter flushing, guidewire exchange, or contrast medium injection¹⁾⁸⁾, which are related to the operator's skill. Thrombus formation may occur in catheters, in pre-existing friable intravascular thrombotic plaques, or device-induced microdissections¹⁷⁾. In this study, a single neurosurgeon performed all cerebral DSA procedures, thereby minimizing the complication rate related to variations in operator's skill. However, TEC secondary to emboli originating from an existing thrombus when the device passes into the vessel cannot be avoided. We concluded that this pathomechanism of thrombus formation is a major contributor to cerebral DSA-induced ischemic stroke. Therefore, we assumed that preprocedural antiplatelet therapy could effectively reduce cerebral DSA-induced TEC. Moreover, we hypothesized that premedication using dual antiplatelet therapy could be more effective than the use of a single antiplatelet agent.

Several studies have reported that the dual antiplatelet therapy compared to single antiplatelet ther-

apy could significantly lower numerical or clinical findings associated with platelet aggregation that cause thrombus¹⁷⁾²⁵⁾²⁷⁾²⁸⁾²⁹⁾. Platelet aggregation, an important step in the process of thrombus formation, occurs through a chain of mechanisms. Antiplatelet agents are classified according to which mechanisms are inhibited. It can be divided into cyclooxygenase inhibitor, phosphodiesterase inhibitor, Adenosine diphosphate receptor antagonist, glycopeptide IIb / IIIa antagonist and serotonin receptor antagonist³⁰⁾. Simultaneous use of antiplatelet agents with these different mechanisms have shown the synergic effect²⁶⁾²⁸⁾.

Aspirin, an irreversible inhibitor of cyclooxygenase, inhibits the conversion of arachidonic acid to thromboxane A₂ and prevents vasospasm and platelet aggregation⁴⁾⁷⁾¹⁰⁾. The effect of aspirin lasts approximately 7 to 10 days corresponding to the lifespan of platelet⁷⁾. The premedication period was determined for 7 days in this study based on this fact.

Cilostazol inhibits phosphodiesterase 3, which is strongly expressed in platelets and vascular smooth muscle cells⁹⁾. Thus, cilostazol inhibits platelet aggregation and vascular smooth muscle proliferation and causes vascular dilatation¹³⁾¹⁸⁾¹⁹⁾²¹⁾. Furthermore, several reports have demonstrated the synergistic effect of cilostazol and endogenous mediators to lower the risk of hemorrhage compared with the use of clopidogrel and endogenous mediators⁹⁾. Therefore, we preferred cilostazol over clopidogrel as premedication to lower the risk of TEC. Patients who were pretreated with dual antiplatelet therapy did not report hemorrhagic related complications.

This study suggests that preprocedural dual antiplatelet therapy can significantly reduce the cerebral DSA-induced TEC rate. However, there are some limitations on this study. First, considering the effect of learning curve of operator is the limitation of this paper, further reevaluation will be needed in the future. Second, although our population is the perfect representation of our center, we could not determine whether this population was representative of the en-

tirety of population who were performed cerebral DSA. Third, this study was retrospective and consisted only of the available data at a single institution. A better designed randomized controlled trial would be needed.

CONCLUSIONS

The use of dual antiplatelet agents (aspirin and cilostazol) over a week before the procedure may reduce the risks of cerebral DSA-induced complications.

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