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Original Article

Thromboembolic complications during and after embolization of unruptured aneurysms: A chronological outcome in periprocedural thromboembolic events

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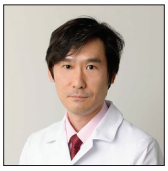

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ABSTRACT

Background: Ischemic complications develop after elective coil embolization procedures at a certain rate. The prevention of these events has been a longstanding issue for many interventional neuroradiologists. This study aimed to clarify whether procedural ischemic events after unruptured aneurysm embolization decrease over time with perioperative anti-thromboembolic treatment or surgical experience.

Methods: This study included patients with cerebral aneurysms in our institution between July 2012 and June 2020. Dual-antiplatelet therapy (DAPT) was performed (Phase 1). Thromboembolic events developed at a certain rate; thus, rivaroxaban was administered with single-antiplatelet therapy (SAPT) to improve thromboembolic results (Phase 2), showing better outcomes than in Phase 1. Subsequently, DAPT was administered again (Phase 3). Ischemic complications were evaluated in each phase or compared between the DAPT group and the direct oral anticoagulant (DOAC) with the clopidogrel (DOAC+SAPT) group.

Results: Relatively, fewer symptomatic ischemic events were noted in Phase 2 or the DOAC+SAPT group, but the outcome was not better in Phase 3 than in Phase 2. Symptomatic complications were more common in Phase 3 than in Phases 1 and 2.

Conclusion: Ischemic complications occurred at a certain rate after endovascular procedures for unruptured aneurysms. The incidence did not decrease over time; particularly, standard DAPT plus postoperative anti-thromboembolic medication did not adequately decrease complications in Phase 3 compared to Phases 1 and 2. Therefore, accumulated experience or a learning curve could not explain the results. DOAC administration might decrease the risk of these events, but further accumulation of evidence or prospective investigation is warranted.

Keywords: Direct oral anticoagulants, Dual-antiplatelet therapy, Embolization, Thromboembolic complications, Unruptured aneurysms

INTRODUCTION

The prevention of thromboembolic complications of elective endovascular procedures for cerebral aneurysms is important. A previous study reported that asymptomatic and symptomatic complications occurred in 5.5–70% and 3.8–40% of procedures, respectively.[32]

In our institution, we previously used conventional dual-antiplatelet therapy (DAPT), but we noted a certain rate of symptomatic thromboembolic events (TEs) (Phase 1). A different medication was administered to reduce TEs (Phase 2), which improved procedural results; then, conventional DAPT was performed to determine whether the result of Phase 2 was reliable, and whether our learning curve was significant (Phase 3). These outcomes were analyzed retrospectively.

MATERIALS AND METHODS

A total of 54 coiling procedures under DAPT from July 2012 to November 2015 (Phase 1), 92 procedures under 75 mg of clopidogrel and 10 or 15 mg of rivaroxaban per day from December 2015 to September 12, 2018 (Phase 2), and 75 procedures under DAPT from September 14, 2018, to June 2020 (Phase 3) were retrospectively compared. In our institution, better results were empirically observed in patients receiving warfarin or direct oral anticoagulant (DOAC) coadministration than in those receiving conventional DAPT with respect to postoperative ischemic events following carotid artery stenting. The ethics committee of our institution was consulted regarding DOAC administration, and it was approved. Three patients in Phase 1 and one patient in Phase 3 were given DOAC and 75 mg of clopidogrel. These patients had a history of nonvalvular atrial fibrillation. In Phase 2, DOAC and 75 mg of clopidogrel were administered to 55 patients, whereas 27 patients who refused coadministration received DAPT.

All patients in the DAPT group received 100 mg of aspirin and 75 mg of clopidogrel daily. The medications were started >1 week before the procedure.[13,23] During treatment, DAPT was switched to single-antiplatelet therapy (SAPT) until 2 days after the procedure, except in cases in which the operator determined that DAPT continuation was necessary, such as with stent-assisted techniques or treatment of broad neck aneurysms. With DOAC administration, the medication was also started >1 week before the procedure. Rivaroxaban use was discontinued until discharge, and subsequently, clopidogrel or DAPT was continued, as in the DAPT cases. Rivaroxaban was administered at a dose of 15 mg/day in patients with a creatinine clearance (C-Cr) >50 mL/min and at a dose of 10 mg in patients with a C-Cr >30 and <50 mL/min. These doses were approved for the prevention of ischemic stroke from nonvalvular atrial fibrillation in Japan.

All cases of elective embolization for unruptured saccular or fusiform aneurysms in the present study and re-operation for recanalization of ruptured aneurysms were included in the study. Simultaneous treatment of two or more aneurysms, procedures for coincident unruptured aneurysms in the acute stage of subarachnoid hemorrhage, and procedures using a flow diversion stent were excluded from the study.

Basically, during the procedure and the entire follow-up period, systolic blood pressure and diastolic blood pressure were controlled to <140 mmHg and <90 mmHg, respectively. Systemic heparinization was performed according to the activated clotting time and maintained from 200 s to 300 s. The addition of an optional anti-thromboembolic agent postoperatively (intravenous continuous infusion of heparin [10,000 U/day], ozagrel sodium [80 mg twice a day], or argatroban hydrate [60 mg/day]) was permitted at the operator's discretion.

No platelet aggregation test was performed in this study because platelet aggregation measurement was not available in our institution until June 2020.

All procedures were conducted after patients provided written, informed consent. The ethics committee of our institution approved the prescription of perioperative DOAC, and the study followed the principles outlined in the Declaration of Helsinki.

Evaluation of ischemic complications

Diffusion-weighted imaging (DWI) and magnetic resonance angiography were performed in all patients within 72 h after the procedure. Imaging was performed with a 1.5-T system (Infinix INFX-8000V; Canon, Tokyo, Japan). Each high-intensity signal was counted in every DWI slice. The total count was designated the "DWI count" [Figure 1]. Measurements were conducted by a neurosurgeon (H.S.) and two neurologists (T.D., T.T.) who had not observed the procedures and were not informed of the patient's personal information. Relatively, large ischemic lesions were defined as >10 mm and counted simultaneously by the same participants. A maximum diameter >10 mm was regarded as an obvious infarct lesion.[4] These DWI counts were performed in reference to the study by Park *et al.*[22]

Measurement of aneurysm size

Maximum aneurysmal diameter (Dmax) and neck and parent artery diameter (PAD) were measured on three-dimensional digital subtraction angiography, and the dome and neck ratio (D/N ratio) was calculated from Dmax/neck.

Statistical analysis

Each parameter (age, total amount of heparin, operation time, aneurysmal neck [neck], PAD, Dmax, and D/N ratio) was analyzed in each phase using a one-way analysis of variance (ANOVA). In the comparison of phases, the analysis was based on Phase 1. Comparisons of the same parameters between the DAPT and DOAC+SAPT groups were performed with the unpaired *t*-test. An analysis of DWI count was also performed to evaluate whether improvement

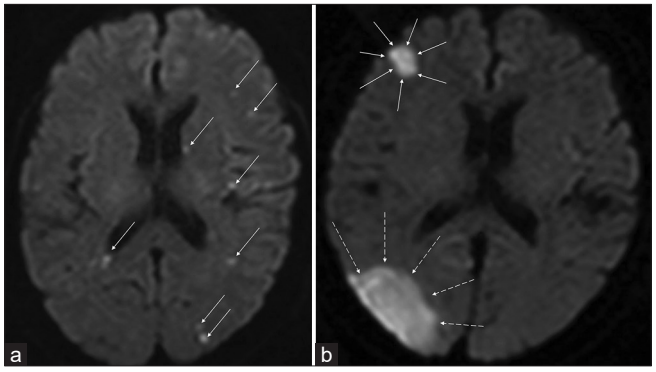

Figure 1: Method of calculating the diffusion-weighted imaging (DWI) score. Every high-intensity DWI spot (a: each indicated by an arrow) or area (b: surrounded by arrows or dotted arrows) is calculated as 1; every spot (a) is counted in each image slice, but a DWI area (b) exists over multiple slices; thus, the whole lesion over slices is counted as 1. The sum of these DWI findings is defined as the "DWI count."

in ischemic events was achieved over time across the three phases and to identify a difference between the DAPT and DOAC+SAPT groups. The number of lesions >10 mm was analyzed in each phase or compared between the DAPT and DOAC+SAPT groups using the Chi-squared test, and if the data were significant, residuals were analyzed. Logistic regression analysis was used to evaluate factors affecting DWI-positive or DWI-negative status and symptomatic complications, and multiple regression analysis was used for the DWI count. These multivariate analyses were conducted in all cases and in the DAPT and DOAC+SAPT groups because it was possible that different factors could affect ischemic events with different medications.

$P < 0.05$ was considered significant. Bell Curve for Excel version 3.22 (SSRI, Tokyo, Japan) was used for the analyses.

RESULTS

A total of 200 patients were included in the present study: 49 in Phase 1, 84 in Phase 2, and 67 in Phase 3. Of these, 14 (28.6%), 27 (32.1%), and 14 (20.9%) in each phase and 34 (24.5%) in the DAPT group and 21 (34.4%) in the DOAC+SAPT group were male. Moreover, 139 patients received periprocedural DAPT (DAPT group), and 61 received DOAC and clopidogrel (DOAC+SAPT group). Additional postoperative antiplatelet or anticoagulation treatment was performed in 7 (14.3%) patients in Phase 1, 6 (7.1%) patients in Phase 2, and 19 (28.4%) patients in Phase 3 within 24 h after the procedure.

Summary of aneurysm location

Aneurysm locations are summarized in Table 1.

Table 1: Aneurysm location.

	ACA	ICA	MCA	Posterior circulation
Phase 1	11	20	12	6
Phase 2	14	42	17	11
Phase 3	20	31	9	7
DAPT	39	62	24	14
DOAC	6	31	14	10

The phases showed no significant differences in terms of the distribution of aneurysms, with fewer ACA aneurysms being observed in the direct oral anticoagulant group (compared using the Chi-squared test, data not shown). ACA: Anterior cerebral artery, MCA: Middle cerebral artery, ICA: Internal carotid artery, DAPT: Dual-antiplatelet therapy, DOAC: Direct oral anticoagulant

Comparison of procedural techniques in each phase and between the two groups

Table 2 shows the frequency of use of the different operative techniques. The single- or double-catheter technique and balloon remodeling technique were chosen significantly more often in Phase 1, and the stent-assisted technique was selected significantly less often in the same phase. No significant technical differences were observed between the DAPT and DOAC+SAPT groups [Table 2].

Comparison of parameters among phases (one-way ANOVA) and between the DAPT and DOAC groups

The amount of heparin used during the procedure was significantly lower in Phase 2 ($P < 0.001$), and the operation time was significantly longer in Phase 2 ($P = 0.0016$) [Table 3].

Neck size and Dmax were significantly larger in the DOAC+SAPT group than in the DAPT group.

Ischemic complications and permanent deficit

Table 4 shows the assessment of areas of high-signal intensity on DWI. Scores were significantly lower in Phases 2 and 3 than in Phase 1 (one-way ANOVA). In the DAPT group, high DWI signal intensity was noted in 76 of 139 (54.7%) patients compared with 31 of 61 (50.8%) patients in the DOAC+SAPT group. The DWI count was significantly higher in the DAPT group [unpaired *t*-test, $P = 0.0224$; Table 3]. A permanent deficit was confirmed in 4 (2.9%) patients in the DAPT group and 1 (1.6%) patient in the DOAC+SAPT group. One case of permanent deficit was noted in each of Phases 1 and 2, and three cases were observed in Phase 3. TEs caused no mortality in the present study [Table 5].

Neurological symptoms occurred within 1 day postoperatively in 20 of 21 (95.2%) patients.

Table 2: Comparison of phases 1 and 3 and of the dual-antiplatelet therapy and direct oral anticoagulant groups.

	n	M (%)	F (%)	S, D (%)	Balloon (%)	Stent (%)	DOAC (%)	Inner (%)
Phase 1	49	14 (28.6)	35 (71.4)	23 (46.9)	16 (32.7)	10 (20.4)	3 (6.1)	32 (65.3)
Phase 2	84	27 (32.1)	57 (67.9)	32 (38.1)	12 (14.3)	40 (47.6)	57 (67.9)	75 (89.3)
Phase 3	67	14 (20.9)	57 (79.1)	19 (28.4)	11 (16.4)	37 (55.2)	1 (1.5)	58 (86.6)
DAPT	139	34 (24.5)	105 (75.5)	56 (40.3)	31 (22.3)	52 (37.4)		110 (79.1)
DOAC	61	21 (34.4)	40 (65.6)	18 (29.5)	8 (13.1)	35 (57.4)		57 (93.4)

The single- or double-catheter technique was used more frequently in Phase 1 than in Phases 2 and 3, whereas the stent-assisted technique was used more often in Phase 3 (compared using the Chi-squared test). No significant differences in the male: female ratio and other technical aspects were seen between the DAPT and DOAC+SAPT groups (compared using the Chi-squared test). S, D: single- or double-catheter technique, balloon: balloon remodeling technique, stent: Stent-assisted technique, DOAC: Direct oral anticoagulant with single-antiplatelet therapy (DOAC+SAPT) group, DAPT: Dual-antiplatelet therapy group, Inner: Use of intermediate catheter, *n*: Number of cases, M: Male, F: Female

Table 3: Comparison of Phases 1, 2, and 3 (one-way ANOVA) and of the dual-antiplatelet therapy and direct oral anticoagulant groups (unpaired *t*-test).

	Phase 1 (49)	Phase 2 (82)	Phase 3 (67)	*P*-value	DAPT (139)	DOAC (59)	*P*-value
Age	63.1±14.0	64.3±11.6	67.2±13.5	ns	64.3±13.3	66.4±12	ns
Heparin	3826.5±1087.6	2859.8±1366	4209.0±1108.3	*P*<0.001	4094.2±1069.7	2316.7±1104.6	*P*<0001
OP time	140.6±48	162.5±54.7	135.3±39.6	*P*=0.0016	139.0±45.0	168.6±54.3	*P*<0.001
Neck	3.8±3.1	4.0±2.6	4.3±2.4	ns	3.8±2.6	4.7±2.8	*P*=0.0259
PAD	2.9±0.9	3.1±1	3.0±0.8	ns	2.9±0.9	3.2±1.0	ns
Dmax	6.2±3.8	6.4±3.5	6.5±3.4	ns	6.0±3.4	7.2±3.7	*P*=0.0266
D/N ratio	1.8±0.6	1.7±0.6	1.7±0.6	ns	1.7±0.6	1.7±0.5	ns

Phase 2 required a lower dose of heparin and longer operation time and had a lower DWI count. A lower dose of heparin, longer operation time, larger aneurysmal neck and Dmax, and lower DWI count were observed in the DOAC+SAPT group. OP time: Operation time, PAD: Parent artery diameter, Dmax: Maximum aneurysm diameter, D/N ratio: Dome-to-neck ratio, DOAC: Direct oral anticoagulant, DAPT: Dual-antiplatelet therapy, ANOVA: Analysis of variance, ns: Not significant

Table 4: Ischemic complications by phase and treatment group.

	n	DWI+ (%)	Symptomatic (%)	DWI count	Permanent (%)	Hemorrhage (%)	>10 mm (%)
Phase 1	49	25 (51.0)	5 (10.2)	5.8	1 (2.0)	1 (2.0)	19 (38.8)
Phase 2	84	42 (50.0)	6 (7.1)	1.7	1 (1.2)	1 (1.2)	9 (10.7)
Phase 3	67	40 (59.7)	10 (14.9)	3.2	3 (4.5)	0 (0)	17 (25.4)
DAPT	139	76 (54.7)	15 (10.8)	3.8	4 (2.9)	0 (0)	37 (36.6)
DOAC	61	31 (50.8)	6 (9.8)	1.8	1 (1.6)	2 (3.3)	8 (13.1)

DWI+: High-signal intensity-positive on diffusion-weighted imaging within 72 h of the procedure, symptomatic: Postoperative ischemic neurological symptoms including transient deficit, DWI count: Total number of high signals on postoperative DWI, permanent: Permanent neurological deficit, hemorrhage: Intracranial hemorrhage, >10 mm: relatively large ischemic lesions (>10 mm), DOAC: Direct oral anticoagulant with single-antiplatelet therapy (DOAC+SAPT) group, DAPT: Dual-antiplatelet therapy group, DWI: Diffusion-weighted imaging, *n*: Number of cases

Postoperative ischemic lesions >10 mm on DWI

Table 4 shows the frequency of relatively large ischemic lesions (>10 mm) in each phase and group.

Complications not of thromboembolic origin

In this study, 11 patients developed complications not of thromboembolic origin [Table 6]. There was one case of mortality, which resulted from critical subcortical hemorrhage 2 months after the procedure. The patient received apixaban 10 mg/day for nonvalvular atrial fibrillation, and 75 mg of clopidogrel was started before the procedure using a stent.

Factors related to high-intensity DWI signals and symptomatic complications (multivariate analysis)

These analyses were conducted among DAPT and DOAC+SAPT cases [Table 7].

Patients receiving DAPT (*n* = 139)

DWI-positive findings were significantly affected by operation time and the D/N ratio. The DWI score was significantly related to operation time and Dmax. PAD and Dmax were significantly related to symptomatic complications.

Table 5: Permanent neurological deficits observed.

Phase	Age/ sex	Location	Symptom	Treatment	Sequelae	mRS	Group
Phase 1	50/F	L M1M2	Intraoperative thromboembolic M2 occlusion	Coil retrieval and clipping	Mild aphasia	0il	DAPT
Phase 2	67/M	L M1M2	Transient stent occlusion 6 days after the procedure	Conservative	Mild aphasia	0il	DOAC
Phase 3	77/F	L ICPC	Ischemia	Conservative	Transient hemiparesis	2ra	DAPT
	81/F	Acom	Ischemia	Conservative	Transient hemiparesis	0ra	DAPT
	60/M	Acom	Ischemia	Conservative	Mild hemiparesis	1em	DAPT

Permanent neurological deficits were observed in five patients, of which one was in Phase 1, one in Phase 2, and three in Phase 3. Examination of distribution by group showed four patients in the DAPT group and one patient in the DOAC group. M1M2: First bifurcation of the middle cerebral artery, ICPC: Internal carotid-posterior communicating artery, DOAC: Direct oral anticoagulant with single-antiplatelet therapy (DOAC+SAPT) group, DAPT: Dual-antiplatelet therapy group, F: Female, M: Male, mRS: Modified rankin Scale

Table 6: Summary of hemorrhagic complications.

Phase	Age/sex	Location	Complication	Treatment	Prognosis	Group
Phase 1	77/M	Acom	Femoral subcutaneous hematoma	Manual compression	Good	DAPT
	82/F	L ICPC	Femoral subcutaneous hematoma	Manual compression	Good	DAPT
	74/M	R M1M2	ICH 2 months after the procedure	Conservative	Death	DOAC
Phase 2	54/F	L IC paraclinoid	Femoral subcutaneous hematoma	Manual compression	Good	DOAC
	42/F	R Pcom	Oculomotor nerve palsy	Conservative f/u	Good	DOAC
	41/M	L PICA	R VA dissection	Conservative f/u	Good	DOAC
	58/F	L IC paraclinoid	Endothelium migration	Retrieval	Good	DOAC
	68/F	BA top	Visual disturbance (contrast encephalopathy)	Conservative f/u	Good	DOAC
	54/F	L ICPC	Femoral subcutaneous hematoma	Manual compression	Good	DAPT
	43/F	L IC aca	SAH (not aneurysmal rupture)	Conservative f/u	Good	DOAC
Phase 3	52/F	L ICPC	Femoral subcutaneous hematoma	Manual compression	Good	DAPT

All patients receiving conservative treatment showed good outcomes, except one 74-year-old man treated with 10 mg/day of apixaban who died in Phase 1. M1M2: First bifurcation of the middle cerebral artery, ICPC: Internal carotid-posterior communicating artery, DOAC: Direct oral anticoagulant with single-antiplatelet therapy (DOAC+SAPT) group, DAPT: Dual-antiplatelet therapy group, SAH: Subarachnoid hemorrhage, M: Male, F: Female, Acom: Anterior communicating artery aneurysm, Pcom: Posterior communicating artery, PICA: Posterior inferior cerebellar artery, IC: Internal carotid, BA: Basilar artery, ICH: Intracerebral hemorrhage, VA: Vertebral artery, f/u: follow-up

Patients receiving DOAC (*n* = 61)

DWI-positive findings were not significantly affected by each parameter. The DWI score was significantly related to age and the D/N ratio. The number of symptomatic complication cases was insufficient for statistical analysis. Patients administered DAPT had a larger aneurysm size and higher DWI counts ($P < 0.001$), whereas a similar tendency was not seen in patients on DOAC ($P = 0.3377$; Figure 2 regression analysis).

DISCUSSION

Due to improvements in various devices, the number of endovascular procedures performed for cerebral aneurysms is increasing. The administration of perioperative anti-thromboembolic agents helps prevent ischemic events.[32]

In the present study, 50–60% of cases in each phase showed DWI-positive lesions and symptomatic ischemic events occurred in 10.2% of cases in Phase 1, 6% in Phase 2, and 14.9% in Phase 3. All procedures were performed by experienced neuroradiologists. Unfortunately, the learning curve did not always contribute to reducing ischemic events, although the DWI count was lower in Phase 3 than in Phase 1, which may be attributed to the efficacy of postoperative optional antiplatelet or anticoagulant agents. More symptomatic complications were observed in Phase 3 than in Phase 1 or 2; therefore, the problem remains, although most ischemic complications were reversible.

Periprocedural antiplatelet treatment with systemic heparinization has been generally accepted in coil embolization. The efficacy of systemic heparinization or perioperative antiplatelet treatment has been shown by several authors.[1,22,28,36]

Brooks *et al.* reported that silent and symptomatic ischemia occurred in 43–61% and 3.8–40% of aneurysmal coil embolization procedures with DAPT and systemic

Table 7: Multivariate analysis of DWI positivity, DWI count, and symptomatic complications.

	DAPT group								
	DWI positive				DWI count	Symptomatic complication			
	OR	95% CI		*P*	*P*	OR	95% CI		*P*
Sex	0.6529	0.2673	1.5946	0.3494	0.1144	0.1236	0.0117	1.3102	0.0826
Age	1.0096	0.9857	1.0341	0.4341	0.9771	1.0033	0.9645	1.0437	0.8703
Heparin	0.9997	0.9994	1.0001	0.1424	0.1307	0.9996	0.9990	1.0001	0.1081
OP time	1.0105	1.0007	1.0205	0.0353	0.0231	1.0019	0.9875	1.0165	0.7967
Balloon	1.0988	0.4072	2.9648	0.8525	0.4218	1.3316	0.1924	9.2157	0.7717
Stent	1.3705	0.5268	3.5653	0.5182	0.7900	1.9531	0.3849	9.9102	0.4192
Inner	0.6131	0.2416	1.5556	0.3031	0.1237	2.2968	0.3563	14.8050	0.3818
PAD	1.1353	0.7415	1.7381	0.5593	0.6840	0.3447	0.1366	0.8694	0.0241
Dmax	1.0718	0.9116	1.2600	0.4012	0.0320	1.3748	1.0950	1.7261	0.0061
D/N	0.4938	0.2647	0.9215	0.0266	0.4643	0.6516	0.2481	1.7113	0.3846
	DOAC+SAPT group								
	DWI positive				DWI count	Symptomatic complication			
	OR	95% CI		*P*	*P*	OR	95% CI		*P*
Sex	0.4063	0.1038	1.5895	0.1956	0.1421	NA			
Age	1.0513	0.9956	1.1102	0.0718	0.0297				
Heparin	0.9997	0.9991	1.0002	0.2498	0.2118				
OP time	0.9937	0.9789	1.0087	0.4056	0.8037				
Balloon	4.6934	0.5682	38.7697	0.1512	0.6787				
Stent	5.6115	0.9310	33.8231	0.0598	0.7859				
Inner	0.0525	0.0025	1.0850	0.0565	0.5650				
PAD	1.1056	0.5729	2.1336	0.7646	0.3712				
Dmax	1.1070	0.8872	1.3813	0.3680	0.4612				
D/N	0.6513	0.2101	2.0191	0.4576	0.0110				

In the DAPT group, logistic regression analysis showed that shorter operation time and larger D/N ratio were associated with a significant reduction in DWI positivity, whereas a thinner PAD and larger Dmax were significantly associated with symptomatic complications (including transient symptoms). Multiple regression analysis showed that shorter operation time and larger D/N ratio were associated with a lower DWI count. In the DOAC+SAPT group, logistic regression analysis showed no parameters associated with a significant reduction in DWI positivity. Multiple regression analysis showed that older age and lower D/N ratio were associated with DWI count. The lack of symptomatic complications in the DOAC+SAPT group prevented logistic regression analysis of them. OR: Odds ratio, 95% CI: 95% confidence interval, heparin: the total amount of heparin used during the procedure, OP time: operation time, balloon: balloon remodeling technique, stent: stent-assisted technique, inner: use of intermediate catheter, PAD: Parent artery diameter, Dmax: Maximum diameter of the aneurysm, D/N: Dome to neck ratio, DOAC: Direct oral anticoagulant with single-antiplatelet therapy (DOAC+SAPT) group, DAPT: dual-antiplatelet therapy group, DWI: Diffusion weighted image, *P*: p value, NA: Not applicable

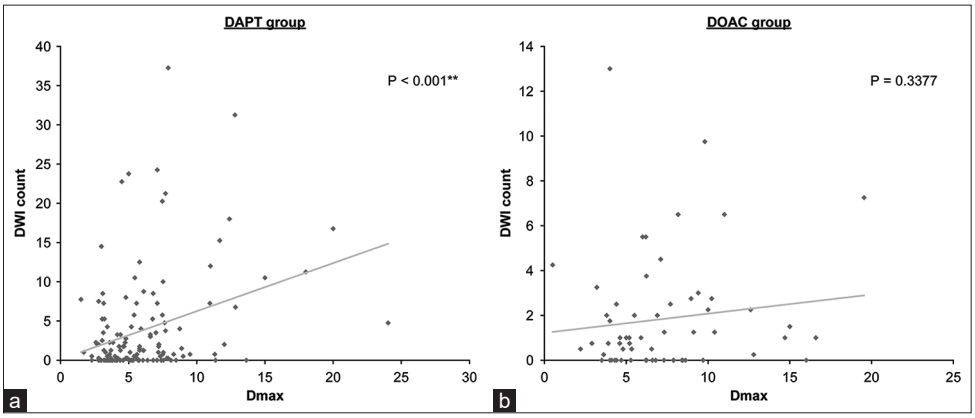

Figure 2: Relationship between diffusion-weighted imaging (DWI) count and aneurysmal maximum aneurysm diameter. (a) The regression analysis of the relationship between diffusion-weighted imaging (DWI) count (vertical axis) and Dmax (horizontal axis) shows significance in the dual-antipletelet therapy group. (b) The relationship between these parameters is not significant in the direct oral anticoagulation with single-antipletelet therapy group.

heparinization, respectively.[4] Hwang *et al*. showed a comparison of ischemic complications in simple coiling for unruptured aneurysms with or without antiplatelet treatment (single or dual).[11]

Nishikawa *et al*. found that DAPT was more effective than SAPT (aspirin) for wide-necked aneurysms.[21] Furthermore, other authors have emphasized the superiority of DAPT.[9,27] Historically, periprocedural DAPT has been considered a reasonable and optimal approach for reducing TEs in elective coil embolization.

In general, postoperative high signal intensity on DWI was noted in 10.4–64% of cases,[2-4,9,13,15,20-22,25,26,29,30,32,35] and symptomatic TEs occurred in 1.8–21.7%.[1,2,9-11,14-16,21,22,25,28,32,36] In SAPT or heparinization-only procedures, 2–15% of symptomatic TEs [1,11,22,28,36] and 1.8–8.5% of TEs were demonstrated in DAPT cases.[3,4,9,10,15,16,21,22,25,32,35] Several authors demonstrated that the incidence of hemorrhagic complications was not increased, [2,5,11,12,16,31,36] although the cumulative risk of DAPT over SAPT was reported by Diener *et al*.[6] The appropriate inhibition of platelet aggregation is essential in elective radiological interventions of unruptured cerebral aneurysms, especially in procedures using multiple catheters.[4,11,32]

In the present study, DWI findings were positive in 50–59.7% of cases through all phases, and symptomatic ischemic events, including transient symptoms, were observed in 6–14.9%. The present results were compatible with those of the previous studies, but the experience did not result in better outcomes than before, which could be interpreted as a result of the more complicated technique, larger neck, and greater aneurysmal size as a target compared with the previous reports.[14,15] The decreased DWI count might have resulted not from our technical improvement, but from additional postoperative anti-thromboembolic treatment between Phases 1 and 3. Moreover, platelet aggregation function, which is important for preventing ischemic complications, was not evaluated.[10] Preoperative evaluation of platelet aggregation function should be one of the approaches to reduce TEs. A study related to the effect of adjusted antiplatelet therapy after stenting for intracranial aneurysms[19] found a significant reduction in ischemic events after treatment of unruptured aneurysms without an increase in major bleeding.

Conversely, DOAC can possibly reduce ischemic events in aneurysmal coiling. Fewer DWI-positive findings, lower DWI count, fewer large lesions (>10 mm), and fewer symptomatic ischemic complications were seen in the DOAC+SAPT group, despite the larger aneurysmal neck size and longer operation time. Many studies have emphasized aneurysmal size, wider neck, and longer operative time as factors related to ischemic events,[9,14,15,21,22,26,33] but this tendency was not apparent in the present DOAC+SAPT group.

In Phase 2, rivaroxaban was used to prevent ischemic complications in aneurysmal coiling procedures. It was interesting that there were no parameters related to DWI positivity in the DOAC group. It was remarkable that the DWI count in the DOAC group was not significantly related to aneurysmal size.

Rivaroxaban is a direct factor Xa inhibitor that may provide more consistent and predictable anticoagulation than warfarin,[24] and it does not have an interaction with aspirin[17] or clopidogrel.[18] Antiplatelet therapy or DAPT added to DOAC did not significantly increase hemorrhagic or ischemic events, except for gastrointestinal bleeding.[5,31] Yasaka *et al*. showed that rivaroxaban may be an alternative to heparin for the treatment of acute ischemic stroke.[37] Ezekowitz *et al*. reported that, in patients with atrial fibrillation scheduled for cardioversion, there was a significant reduction in stroke development with apixaban administration compared with conventional heparin and Vitamin K antagonist treatment.[7] Flierl *et al*. reported that rivaroxaban reduced adenosine diphosphate-induced platelet aggregation in chronic heart failure; thus, it was possible that DOAC has additional efficacy that heparin does not,[8] or that DOAC might have a less unstable nature, such as heparin resistance.[34] However, whether serious hemorrhagic events, such as aneurysmal wall perforation, occur in patients administered DOAC is unknown; thus, the use of DOAC should be considered carefully. Fortunately, serious hemorrhagic events were not seen in the present patients during the procedures, although intraoperative aneurysmal perforation was reported in up to 0.7–3% of cases in the previous reports.[13,15,25,32]

Limitations

This was a retrospective study with extremely limited evidence. The antiplatelet aggregation function was not evaluated. Although a comparatively low ischemic complication rate was seen in patients administered DOAC, the reason that similar results were not achieved with suitable heparin administration remains unclear. Fewer patients receiving DOAC were treated for anterior communicating artery aneurysms than patients receiving DAPT. The present study was also subject to bias in patient selection during the acquisition of informed consent. Finally, magnetic resonance imaging was not always performed immediately before the procedures in all patients, which might be the reason that findings on postoperative DWI were not completely identified during or after the intervention.

CONCLUSION

Compared with the findings of the previous studies, the present results for unruptured cerebral aneurysm coiling in relation

to periprocedural thromboembolic complications were acceptable. However, the learning curve did not resolve the longstanding issue of reducing embolic events during or after aneurysmal embolization procedures. DOAC administration might be a possible solution for this issue, but large-scale and prospective studies are needed to confirm the present data.

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Ethical approval

The author(s) declare that they have taken the ethical approval from IRB/IEC.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that they have used artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript or image creations.

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