

Table 4 Correlation between postoperative antithrombotic treatment and ischemic complications

	Ischemic complication (-)	Ischemic complication (+)	Total	Incidence	p value			
No postoperative antithrombotic treatment	253	13	266	4.9%	p < 0.000000001	n.s.	p < 0.05	p < 0.01
Heparin	251	9	260	3.5%	p < 0.000000001	n.s.	p < 0.05	*
Argatroban	353	38	391	9.7%	p < 0.001	n.s.	*	
Ozagrel	27	4	31	12.9%	n.s.	*		
Combination	39	17	56	30.3%	*			

*: control. n.s.: no significant.

Table 5 Correlation between each factor and hemorrhagic complications

Baseline characteristics of patients	Age	≤ 49 yrs: 4.2%, 50–59 yrs: 2.8%, 60–69 yrs: 1.6%, 70–79 yrs: 2.2%, ≥ 80 yrs: 4.1%
	Sex	Male: 2.1%, female: 3.1%
	mRS at baseline	0% to 2: 2.2%, 3% to 5: 3.2%
	Previous treatment	Previously untreated: 2.8%, previously treated: 2.2%
Lesion profile	Region	IC (intracranial epidural): 1.8%, IC (intradural): 4.4%, MCA: 2.5%, VA: 3.4%, BA: 4.0%
	Symptom at diagnosis	Asymptomatic: 1.9%, symptomatic: 2.9%
	Timing of treatment (only symptomatic patients)	Nonprogressively symptomatic: 2.2%, progressively symptomatic: 6.6% (p < 0.05)
	Timing of treatment (only symptomatic patients)	Within 24 hr: 2.9%, between 24 hr and 14 days: 5.9%, after at least 15 days: 1.5% (p < 0.05*)
	Percent diameter stenosis	< 50%: 0%, 50% to 60%: 0%, 60% to 70%: 3.0%, 70% to 80%: 1.5%, 80% to 90%: 4.0%, 90% to 100%: 3.5%, 100%: 0%
	Lesion length	< 5 mm: 1.6%, 5–10 mm: 3.0%, 10–15 mm: 3.0%, ≥ 15 mm: 3.6%
	Normal vascular diameter	< 2 mm: 4.8%, 2–2.5 mm: 1.8%, 2.5–3 mm: 2.0%, 3–3.5 mm: 2.3%, 3.5–4 mm: 3.0%, ≥ 4 mm: 5.2%
	Pathology	Arteriosclerosis: 1.9%, traumatic dissection 0%, iatrogenic dissection 20%, idiopathic dissection 0%, others 0%
Treatment	Refractory to medical therapy	No: 2.7%, yes: 2.5%
	Stenting	No: 2.4%, yes: 3.2%
	Presence or absence of pre-dilatation (JR-NET2)	No: 1.6%, yes: 2.5%
	Presence or absence of post-dilatation (JR-NET2)	No: 2.3%, yes: 2.1%
	Stent + presence or absence of post-dilatation (JR-NET2)	No: 3.7%, yes: 5.0%
	Preoperative antiplatelet treatment	No: 5.4%, 1 agent: 4.8%, 2 agents: 2.0%, 3 agents: 3.2%
	Postoperative antiplatelet treatment	No: 10.0%, 1 agent: 6.0%, 2 agents: 1.3%, 3 agents: 1.0% (p < 0.000000001***)
	Postoperative antithrombotic treatment	No: 7.1%, heparin: 1.9%, argatroban: 0.8%, ozagrel: 0%, combination: 1.8% (p < 0.0001***)

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Table 5 (Continued)

	Other concurrent treatment	No: 3.0%, yes: 0.7%
Treatment situation	Diagnostic cerebral angiography	No: 3.1%, yes: 2.2%
	Emergency treatment	Planned: 2.1%, emergency: 5.7% ($p < 0.01$)
	Treatment facility	Hospital at work: 2.7%, another hospital: 3.3%
	Investigator	Supervisory physician: 3.4%, specialist: 2.4%, nonspecialist: 0%
	Scrub-in of supervisory physician	No: 2.3%, yes: 2.1%
	No. of scrub-in supervisory physicians and specialists	1: 2.0%, 2: 3.1%, ≥ 3 : 0.0%
	General anesthesia	Local anesthesia: 1.7%, general anesthesia: 4.0%
Treatment outcome	Residual stenosis immediately after treatment	$< 30\%$: 2.6%, 30% to 50% : 3.1%, $\geq 50\%$: 0%

*: Within 24 hr vs. between 24 hr and 14 days: $p < 0.05$. **: Each p-value is not shown. ***: Each p-value is not shown. JR-NET: Japanese Registry of Neuroendovascular Therapy.

Table 6 Correlation between complications and mortality

	Mortality		
	No	Yes	
Hemorrhagic complication	1.3%	23.3%	($p < 0.0000001$)
Ischemic complication	1.8%	2.3%	n.s.

n.s.: no significant.

postoperative antithrombotic treatment with heparin alone than in those who received no postoperative antithrombotic treatment (Table 4).

Correlation between each factor tested and hemorrhagic complications are shown in Table 5. The following factors were significantly correlated with hemorrhagic complications: progressively symptomatic; treatment between 24 hours and 14 days of the onset; no postoperative antiplatelet treatment; no postoperative antithrombotic treatment; and emergency treatment. In patients with hemorrhagic complications, the mortality was very high at 23.3% (Table 6).

Discussion

In this study, the incidence of ischemic complications and hemorrhagic complications was 7.7% and 2.5% in 1,133 patients who underwent angioplasty/stenting, respectively, resulting in an overall incidence of approximately 10%. Nguyen et al. reported that of 74 patients, 5% of patients who underwent angioplasty for symptomatic intracranial stenosis experienced major stroke within 30 days postoperatively.¹⁾ In the

present study, the incidence of ischemic complications and hemorrhagic complications was 6.6% and 2.4%, respectively, in patients who underwent PTA alone. The higher incidence of complications in this study may be because the complications included minor stroke, unlike in Nguyen's study.

When limited to patients who underwent stenting, on the other hand, the incidence of ischemic complications and hemorrhagic complications was relatively high at 9.7% and 3.2%, respectively, in Japan. This outcome was worse compared even with a 30-day stroke rate of 5.7% reported with Wingspan, an intracranial stent approved in the United States, at the time of approval.²⁾ This may have been due to the use of inflexible coronary stents in the present study, which was more likely to result in vascular injury at the time of access or stent deployment. In addition, since the incidence of complications was greatly different with or without stenting in this study, it is likely that there may have been problems with the device. On the other hand, the proportion of patients who had a residual stenosis of $\geq 50\%$ postoperatively was significantly lower in the stenting group, showing the usefulness of stenting in maintaining cerebral artery patency and thus warranting quick approval of flexible intracranial stents.

In this study, which had a large sample size (1,133 patients), several factors were found to be correlated with complications, and even multifactorial analysis could have been performed. However, since the data were retrospectively collected and analyzed, it is not doubtful that various biases existed. For instance, hemorrhagic complications may substantially restrict subsequent antithrombotic therapy. For significantly

biased data, it may be more important to analyze individual factors correlated with complications carefully, rather than to perform a multifactorial analysis.

In the analysis, first, several factors were correlated with ischemic complications. The incidence of complications was significantly lower in previously treated patients. Patients who experienced complications at the initial treatment often preclude retreatment for medical or social reasons, thus more patients who experienced no complications at the initial treatment might have been included in the previously treated group. In many previously treated patients, angioplasty may have been more suitable in terms of plaque characteristics or position of penetrating branches in the lesion. In addition, the intima formed after the initial treatment may have been histopathologically stable. In this study, an unexpected negative correlation was observed in patients unresponsive to medical therapy, although such patients generally have an increased risk of ischemic complications. Many of the patients enrolled with the disease refractory to medical therapy may have received not only adequate antiplatelet treatment, but also medical therapy such as statins or intensive antidiabetic treatment that can contribute to plaque stabilization. It may be hypothesized that medical therapy contributing to plaque stabilization reduced ischemic complications and is thus useful in enhancing the safety of angioplasty although this is a matter of speculation since non-antithrombotic drugs were not investigated. Additional post-dilatation following placement of balloon-expandable coronary stent was also significantly correlated with ischemic complications. Plaques excluded by repeated PTA may have impaired blood flow in the penetrating branches. As for postoperative antithrombotic therapy, the incidence of ischemic complications was significantly lower in heparin-treated patients than in untreated patients, indicating the usefulness of heparin. On the other hand, treatment with multiple antithrombotics was also positively correlated with ischemic complications. This may be because ischemic complications occurred in many of the patients who received multiple antithrombotics for the treatment of intraoperative ischemic symptoms.

In addition, some factors were found to be correlated with hemorrhagic complications. Progressively symptomatic disease, which is complicated by so-called misery perfusion, may have resulted in cerebral hemorrhage due to hyperperfusion syndrome. The higher incidence of hemorrhagic complications in patients treated between 24 hours and 14 days of the onset may be explained by the assumption that hemorrhagic changes were caused by reperfusion

of brain tissue that had just undergone irreversible ischemic changes, although there was no data on cerebral blood flow, such as single photon emission computed tomography (SPECT) or positron emission tomography (PET), in our study. Likewise, postoperative hemorrhagic complications were more likely to occur in patients who received emergency treatment, because such patients often develop acute cerebral infarction. In addition, inadequate preoperative assessment or equipment may have resulted in vascular injury during catheter manipulation or PTA in patients who received emergency treatment. A positive correlation with hemorrhagic complications was observed in patients who received no postoperative antiplatelet or antithrombotic treatment, but this may be explained by the fact that hemorrhagic complications precluded the use of these drugs.

As mentioned above, the data were retrospectively collected and analyzed in this study, requiring prospective confirmatory studies to determine whether each factor found to be correlated with complications is actually a risk factor for complications. This procedure is associated with more complications than other neuroendovascular procedures, and unfortunately the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, a randomized controlled study in the United States, failed to show the effectiveness of stenting and abandoned.³⁾ The final result of this study also showed that the early benefit of aggressive medical management over aggressive medical management plus stenting with the Wingspan stent persists during a median follow-up of 32.4 months.⁴⁾ It may be important to not only use intracranial stents, which are expected to be introduced in Japan in the near future, but also to seek to improve the treatment outcome in a multidimensional manner based on the findings of the present study.

Conclusion

Angioplasty for intracranial stenosis in Japan is almost as safe as that in the West. On the other hand, stenting using a coronary stent is associated with a higher incidence of complications, warranting quick introduction of intracranial stents.

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Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered self-reported

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