



The Usefulness of Prasugrel as Rescue Medication in Neuroendovascular Therapy

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Objective: In neuroendovascular therapy, clopidogrel resistance and thrombosis are common problems. In such cases, we use prasugrel as rescue medication, and we clarified its usefulness.

Methods: We retrospectively investigated 199 consecutive cases of neuroendovascular therapy performed at our hospital from April 2016 to March 2018, and examined the safety and effectiveness of prasugrel.

Results: There were 14 cases of prasugrel administration: six cases of coil embolization for cerebral aneurysm, five cases of carotid artery stenting (CAS), and three other cases.

The reasons for prasugrel administration were as follows: emergency stent use in four cases, intraoperative thrombosis in three cases, intra-stent thrombosis after CAS in three cases, and others in four cases. In all cases, it was used in combination with aspirin and the median duration of administration was 212 days. Regarding its safety, there was one hemorrhagic complication at the puncture site for which the involvement of prasugrel was unable to be excluded, but it was improved by conservative treatment and there was no major hemorrhage such as intracranial hemorrhage. Regarding its efficacy, in one case, the thrombus during coil embolization did not completely disappear after prasugrel administration and additional mechanical thrombolysis was required. However, no new thrombosis was observed during prasugrel administration in all 14 cases.

Conclusion: Prasugrel may be useful as a rescue medication in neuroendovascular therapy.

Keywords ► neuroendovascular therapy, prasugrel, clopidogrel resistance, thrombosis, antiplatelet drug loading

Introduction

Neuroendovascular therapy has markedly advanced. It is minimally invasive, but the number of complex surgical procedures has increased with the development of devices. In particular, attention must be paid to perioperative

thrombosis.^{1,2)} To prevent thrombosis, dual antiplatelet drugs are administered before surgery in many cases. However, some stent-inserted patients require the long-term administration of antiplatelet drugs after surgery, and hemorrhagic complications must be considered.^{1,2)} Therefore, perioperative antiplatelet drug management in neuroendovascular therapy is important.

As antiplatelet drugs, aspirin and clopidogrel are routinely used. However, the latter raises the issue of resistance. Several studies demonstrated that the incidence of thromboembolism during coil embolization of cerebral aneurysms increased in the presence of clopidogrel resistance.^{3,4)} Furthermore, prompt, accurate intraoperative antiplatelet drug loading is required in some emergency cases free from antiplatelet drug administration.

Recent studies reported the safety and efficacy of prasugrel for clopidogrel resistance or thrombosis in patients undergoing neuroendovascular therapy.⁵⁻⁷⁾ Prasugrel resistance is rare, and the interval until its effects are observed is short. However, this drug has not been approved in the cerebrovascular field.

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Table 1 Situations of prasugrel administration as a rescue medication

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- Clopidogrel resistance in preoperative platelet aggregation test
 - Intraoperative and postoperative thrombosis under other antiplatelet drugs administration
 - Emergent stent placement in cases without antiplatelet drugs administration
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At our hospital, prasugrel is employed as a rescue medication for patients who are resistant to clopidogrel during neuroendovascular therapy, those with thrombosis under antiplatelet drug administration, and those requiring emergency antiplatelet drug loading. In this study, we retrospectively investigated the use of prasugrel in our hospital to clarify its usefulness.

Subjects and Methods

The subjects were 199 consecutive patients who had undergone neuroendovascular therapy at our hospital between April 2016 and March 2018.

At our hospital, antiplatelet drugs are basically administered in perioperative period of neuroendovascular therapy as follows: when performing elective embolization of unruptured cerebral aneurysms or carotid artery stenting (CAS), dual antiplatelet therapy (DAPT) with 100 mg of aspirin and 75 mg of clopidogrel is started 7–10 days before surgery, and a platelet aggregation test (transmitted light platelet aggregation test) is conducted the day before surgery. For emergency coil embolization of ruptured cerebral aneurysms, a gastric tube is inserted after anesthesia induction, and crushed aspirin at 100–200 mg is administered through the gastric tube after the insertion of a framing coil or when a blood point becomes unclear.

Prasugrel is positively selected as a rescue medication for patients evaluated as having clopidogrel resistance on a platelet aggregation test the day before elective treatment, those with thrombosis during elective treatment (under DAPT), those in whom thrombosis developed after aspirin administration during the treatment of a ruptured cerebral aneurysm or there was no amelioration of thrombosis after aspirin administration, emergency DAPT-free patients requiring intracranial and cervical stenting, and patients with intra-stent thrombosis after CAS (**Table 1**). As an initial dose, 20 mg of prasugrel is administered. As aspirin is basically administered in advance, the administration of aspirin at 100 mg and prasugrel at 3.75 mg is continued from the day after surgery. Attending physicians are responsible for final evaluation regarding administration or the timing of discontinuation.

In this study, we retrospectively investigated the use of prasugrel in neuroendovascular therapy at our hospital to examine its safety and efficacy.

The extra-indication use of prasugrel was approved by the ethics review board of our hospital. After explaining the risks of adverse reactions and complications to the patients and their families using a document, informed consent was received.

Results

The 199 subjects consisted of 58 who had undergone coil embolization of cerebral aneurysms (unruptured: 24 patients, ruptured: 34), 41 who had undergone CAS, 62 who had undergone acute-phase revascularization, 12 who had undergone embolization of arteriovenous fistulae or arteriovenous malformation, 5 who had undergone embolization of tumor-nourishing vessels, and 21 who had undergone other procedures.

Of these, prasugrel had been administered to 15 (7.5%). However, one had continuously taken it after percutaneous coronary intervention (PCI), and this patient was excluded. As a rescue medication, prasugrel had been administered to 14 (7.0%). Their mean age was 67.6 years, and they consisted of seven men (50.0%) and seven women (50.0%; **Table 2**).

The surgeries of the prasugrel-administered patients consisted of coil embolization of cerebral aneurysms in six patients (unruptured: 1, ruptured: 4, chronic-phase ruptured: 1), CAS in five (emergency CAS: 1), acute-phase revascularization in one patient, embolization of a cavernous sinus dural arteriovenous fistula in one patient, and embolization of an internal carotid artery cavernous sinus fistula in one patient.

The reasons for prasugrel administration included clopidogrel resistance evaluated on a platelet aggregation test before CAS in one patient, thrombosis during coil embolization of ruptured cerebral aneurysms in three patients, emergency stent use during coil embolization of ruptured cerebral aneurysms in two patients, emergency stent use during acute-phase revascularization in one patient, emergency stent use during embolization of an internal carotid

Table 2 Characteristics of prasugrel-administration cases

Case	Age (y.o.)	Sex	Diagnosis	Neuroendovascular therapy	Reasons for prasugrel administration	Administration period (days)	Complications
1	83	Female	Ruptured BA trunk AN. chronic phase	Coil embolization (stent assist)	Emergency stent use	630*	None
2	72	Male	Ruptured VA-PICA AN. acute phase	Coil embolization	Intraoperative thrombus	24	None
3	64	Male	Symptomatic CCA stenosis	CAS	Postoperative in-stent thrombus	267	None
4	63	Male	BA occlusion	Thrombectomy, PTA	Intraoperative restenosis	11	None
5	49	Female	Ruptured dissecting VA AN.	Parent artery occlusion (stent assist)	Emergency stent use	36	None
6	63	Male	ICA occlusion	Thrombectomy, CAS	Emergency stent use	20	None
7	79	Male	Symptomatic ICA stenosis	CAS	Postoperative in-stent thrombus	382*	None
8	43	Male	Ruptured Acom.A. AN.	Coil embolization	Intraoperative thrombus	3	None
9	66	Female	Ruptured BA top AN.	Coil embolization	Intraoperative thrombus	14	None (need to thrombus crushing)
10	78	Female	CS dAVF	TVE (coil)	Postoperative ICA stenosis, thrombosis	309	None
11	88	Male	Symptomatic ICA stenosis	CAS	Clopidogrel resistance	186	None
12	45	Female	Direct CCF	TVE + TAE (coil, stent assist)	Emergency stent use	274	Bleeding from the puncture site
13	73	Female	Unruptured MCA AN.	Coil embolization	Postoperative thrombosis	359	None
14	81	Female	Symptomatic ICA stenosis	CAS	Postoperative in-stent thrombus	238	None

*Administration continues on the survey day. Acom.A: anterior communicating artery; BA: basilar artery; CAS: carotid artery stenting; CCF: carotid-cavernous fistula; CCA: common carotid artery; CS: cavernous sinus; dAVF: dural arteriovenous fistula; ICA: internal carotid artery; MCA: middle cerebral artery; PCI: percutaneous coronary intervention; PICA: posterior inferior cerebellar artery; PTA: percutaneous transluminal angioplasty; VA: vertebral artery; TAE: transarterial embolization; TVE: transvenous embolization

artery cavernous sinus fistula in one patient, restenosis of an atherosclerotic lesion (elastic recoil) during acute-phase revascularization in one patient, intra-stent thrombosis after CAS in three patients (asymptomatic in all patients, diagnosed on carotid artery echography 5, 6, and 42 days after surgery, respectively), and postoperative thromboembolism in two patients.

At the start of administration, prasugrel was combined with aspirin in all patients. The median administration period of prasugrel was 212 days (interquartile range: 21–300). In Case 11, in which a platelet aggregation test before CAS revealed clopidogrel resistance, the prasugrel administration period was 186 days, and DAPT was switched to monotherapy with aspirin. In the three patients with thrombosis during coil embolization of ruptured cerebral aneurysms (Cases 2, 8, and 9) and in the patient with restenosis during acute-phase revascularization (Case 4), the administration period was 3, 11, 14, and 24 days, respectively; prasugrel administration was promptly discontinued after surgery. In two (Cases 5 and 6) of four patients in whom a stent was emergently used, prasugrel was switched to clopidogrel 36 and 20 days after the start of administration, respectively. To one patient in whom intra-stent coil collapse was suspected after stent-assisted coil embolization of a ruptured basilar artery trunk aneurysm (Case 1) and to one patient in whom a stent was emergently used during embolization of an internal carotid artery cavernous sinus fistula (Case 12), prasugrel had been administered for a long period. In the three patients with intra-stent thrombosis after CAS, the administration period of prasugrel was 238, 267, and 382 days, respectively. In the two patients with postoperative thrombosis (Cases 10 and 13), it was 309 and 359 days, respectively.

Concerning the safety of prasugrel, a complication in which the involvement of this drug was unable to be excluded was noted in one patient (Case 12): retroperitoneal hematoma related to hemorrhage at the site of right femoral vein puncture after embolization of an internal carotid artery cavernous sinus fistula. However, blood transfusion was not required, and conservative treatment reduced the hematoma.

Concerning the efficacy of prasugrel, there was no stent-related thromboembolism in any of four patients in whom a stent was emergently used. In one patient with intraoperative thrombosis (Case 9), prasugrel administration did not lead to complete disappearance of the thrombus, requiring additional mechanical clot disruption. In three patients with intra-stent thrombosis after CAS,

intra-stent thrombi disappeared during follow-up at the outpatient clinic. In Case 10, thromboembolism related to stenosis of the internal carotid artery at the cavernous sinus was observed after transvenous coil embolization of a cavernous sinus dural arteriovenous fistula. New-onset thromboembolism was again noted after the administration of aspirin and clopidogrel was started. Clopidogrel was switched to prasugrel, and there has been no thromboembolism during the subsequent course. During prasugrel administration, there was no new-onset thromboembolism in any of the 14 patients, including the other 5 patients.

Discussion

For DAPT in neuroendovascular therapy, aspirin and clopidogrel are used in many cases.³⁾ However, in several studies, aspirin resistance was observed in approximately 5%, and clopidogrel resistance was noted in 20%–40%.^{3,4)} Clopidogrel is metabolized by a drug-metabolizing enzyme, cytochrome P (CYP), and its active metabolite binds to P2Y₁₂ receptors, exhibiting antiplatelet actions. This drug is primarily metabolized by CYP2C19, but it was reported that genetic polymorphism-related poor metabolizers (PMs) accounted for 3%–5% of Westerners and approximately 20% of Asians.^{8–10)} The presence of PMs markedly influences clopidogrel resistance. In such patients, the incidence of thromboembolism during PCI or neuroendovascular therapy increases,^{3,4,11)} influencing the prognosis.

In the field of cardiology, a third-generation thienopyridine, prasugrel, as a drug that replaces clopidogrel, was approved for patients with ischemic heart disease for which PCI is indicated, and favorable results have been reported. An international cooperative study of prasugrel (loading dose: 60 mg, maintenance dose: 10 mg) revealed that risk factors for massive hemorrhage included an age of ≥ 75 years, body weight of ≤ 60 kg, and history of ischemic stroke.¹²⁾ Therefore, in phase III and clinical studies in Japan, the dose was decreased (loading dose: 20 mg, maintenance dose: 3.75 mg), and there was no increase in the incidence of serious hemorrhagic complications.^{13,14)} Furthermore, a comparative study regarding the prevention of recurrent cerebral infarction using prasugrel (3.75 mg) and clopidogrel (75 mg) in Japan did not demonstrate the non-inferiority of prasugrel, but suggested that the safety and efficacy were similar between the two drugs.¹⁵⁾

Prasugrel has an action mechanism similar to that of clopidogrel. However, it is metabolized by several enzymes,

and it may not be influenced by the genetic polymorphism of CYP2C19; prasugrel resistance is rare, and this drug may not be influenced by other drugs. Several studies noted that the blood concentration of prasugrel rapidly increased regardless of the genetic polymorphism of CYP2C19, exhibiting stable inhibitory effects on platelet aggregation.^{10,16,17)}

A previous study reported that prasugrel (loading dose: 60 mg, maintenance dose: 10 mg) increased the incidence of hemorrhagic complications in neuroendovascular therapy in comparison with clopidogrel,¹⁸⁾ whereas another study found that prasugrel did not increase the incidence of hemorrhagic complications.¹⁹⁾ A recent Japanese study reported that prasugrel (loading dose: 20 mg, maintenance dose: 3.75 mg) was safe and effective in PMs of clopidogrel with endovascular therapy for unruptured cerebral aneurysms.⁵⁾ Internationally, several studies stated that low-dose prasugrel (loading dose: 20 mg, maintenance dose: 5 mg) was useful for the treatment of cerebral aneurysms.^{7,20)} A meta-analysis of these studies also demonstrated that low-dose prasugrel reduced thrombosis, and that it did not increase the incidence of hemorrhagic complications.^{21,22)}

Furthermore, it was reported that the blood concentration of prasugrel reached a peak 30 minutes after administration; the interval until its effects were observed was shorter than that for clopidogrel (1 hour).^{10,16)} Furthermore, as described above, prasugrel may exhibit more stable antiplatelet actions than clopidogrel regardless of the genetic polymorphism of CYP2C19.^{10,17)} Therefore, prasugrel may be useful when adopting a stent in DAPT-free emergency surgery patients in whom prompt, accurate antiplatelet drug loading is required.

In our series, a hemorrhagic complication at the site of venous puncture was observed in one patient (Case 12), but its direct association with prasugrel was unclear.

During prasugrel administration, there was no thromboembolism in any of the 14 patients, suggesting its safety and efficacy (loading dose: 20 mg, maintenance dose: 3.75 mg) for neuroendovascular therapy. The median administration period was 212 days. At our hospital, DAPT was continued for 6 months after CAS, so the administration period was 186 days after CAS in patient with resistant to clopidogrel. In three patients with intra-stent thrombosis after CAS, thrombosis developed under the administration of aspirin and clopidogrel, and prasugrel administration was required until thrombus disappearance and stabilization; the administration period was prolonged. In these patients, it was difficult to discontinue prasugrel or re-switch it to clopidogrel; therefore, long-term administration was considered to

be unavoidable. However, in one with intra-stent thrombosis after CAS (Case 7) and Case 1, the administration of aspirin was discontinued during the course, and monotherapy with prasugrel was performed. It may have been necessary to discontinue prasugrel and perform monotherapy using aspirin.

These results suggest the safety and efficacy of prasugrel for neuroendovascular therapy. However, in Japan, this drug has not been approved for neuroendovascular therapy, and the risk of hemorrhagic complications related to long-term administration cannot be excluded. Prasugrel should be discontinued or switched to another drug as early as possible in patients other than resistant to clopidogrel and with intra-stent thrombosis.

This study involved a small number of patients from a single institution. A randomized controlled study should be further conducted, but it is difficult considering the use of prasugrel as a rescue medication. Therefore, currently, it may be appropriate to restrict its role to a rescue medication through sufficient explanation, as at our hospital.

Conclusion

Based on our experience regarding neuroendovascular therapy involving a small number of patients, prasugrel was useful as a rescue medication. However, this drug has not been approved for neuroendovascular therapy, and its usefulness should be examined in a larger number of patients in the future.

Disclosure Statement

We declare no conflict of interest regarding this article.

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