New devices

Prevention of stent thrombosis with reduced dose of prasugrel in two patients undergoing treatment of cerebral aneurysms with pipeline embolisation devices

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Summary

Prevention of intracranial stent thrombosis with dual-antiplatelet therapy is widely used in neuroendovascular procedures. However, the rising incidence of inadequate platelet inhibition with clopidogrel may increase complications following stent placement, especially with newer devices that possess a larger total metal surface area. While there are recent reports of prasugrel as an alternative to clopidogrel, there is no clinical evidence in neurointerventional patients regarding the use of a lower maintenance dose as an alternative strategy to gain adequate platelet inhibition while possibly reducing the risk of bleeding. We present 6-month efficacy and safety outcomes of two patients undergoing elective pipeline embolisation that were found to have inadequate platelet response to clopidogrel and subsequently transitioned to prasugrel 5 mg daily for the prevention of stent thrombosis.

BACKGROUND

The pipeline embolisation device (PED) is a bare metal stent intended to treat intracranial aneurysms by providing flow diversion through the parent artery. Owing to its flexibility, the PED may be implanted into convoluted anatomy and provides a treatment option for giant, wide-neck aneurysms. Recently, researchers demonstrated that PED implantation provided complete aneurysm occlusion at 180 days in 93% of cases.¹ While this technique presents a novel approach for intracranial aneurysm treatment, the impact of inadequate platelet inhibition prior to deploying the device, which has a 30–35% total metal surface area, is unknown. Nelson *et al*¹ utilised dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel prior to PED implantation in all patients. Despite extensive use of clopidogrel in cardiology patients, there are reports of resistance due to genetic alterations that lead to impaired platelet response.² We present two cases of reduced dose prasugrel (5 mg daily) use to achieve adequate platelet inhibition following PED implantation in patients found to have clopidogrel hyporesponsiveness.

CASE PRESENTATION

A 50-year-old, 74 kg woman was admitted for planned PED placement into a giant, right cavernous internal carotid artery (ICA) aneurysm. Prior to the procedure, the patient received a 300 mg clopidogrel loading dose and 75 mg daily for 1 week. On the day of hospital admission, ADP P2Y₁₂ receptor inhibition performed via the VerifyNow assay was found to be 3%; therefore, the patient was loaded with 60 mg of prasugrel. The aneurysm was treated with two overlapping PEDs. Repeat angiography revealed a cervical petrous dissection with

flow limitation and an Acculink stent was deployed across the dissection. Final angiography demonstrated stent patency and significant stasis within the aneurysm. Owing to the cervical dissection experienced during the procedure and the high potential for intracranial bleeding, the patient was started on maintenance DAPT with prasugrel 5 mg daily. Despite the lower dose, repeat testing 24 h later showed 71% platelet inhibition, and the patient was discharged home on aspirin 325 mg and prasugrel 5 mg daily. On postoperative day 5, the patient presented with severe headache and was found to have a small, right frontal subarachnoid bleed over the convexity, remote from the aneurysm. Repeat cerebral angiography displayed significant aneurysm thrombosis when compared with the previous procedure performed 3 days prior. Owing to the small size of the bleed and the progressive aneurysm thrombosis, the patient was continued on DAPT during hospitalisation and was subsequently discharged home after observation. The patient received 6-months of DAPT and no further complications were reported.

Second, a patient with a giant, left ICA aneurysm was found to have 18% P2Y₁₂ receptor inhibition following a 300 mg clopidogrel loading dose and 5 days of 75 mg daily. The patient was loaded with prasugrel and required placement of three PEDs to adequately treat the aneurysm. The following day, the patient was discharged home on prasugrel 5 mg and aspirin 325 mg after repeat testing showed an increased platelet inhibition of 48%. No complications were reported, and a repeat angiogram at 6 months demonstrated no contrast filling inside the aneurysm and no in-stent stenosis. No genetic testing was performed on either patient.

TREATMENT

Use of reduced dose of prasugrel (5 mg daily) for the prevention of stent thrombosis in two patients undergoing PED placement.

OUTCOME AND FOLLOW-UP

Both patients received 6 months of DAPT therapy with prasugrel 5 mg and aspirin 325 mg daily. While one patient was re-admitted with a small subarachnoid bleed remote from the aneurysm, the patient was discharged home on continued DAPT due to the significant aneurysm thrombosis observed on repeat cerebral angiography. No further complications were reported.

DISCUSSION

Thromboembolism is one of the most serious complications that may occur after intracranial stenting.³ While stent thrombosis has been characterised in the cardiology literature, the occurrence rate following intracranial procedures is not well established. In the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries Study, 35% of the 61 patients experienced stent restenosis within 1 year.⁴ The preventative strategy of DAPT with aspirin and an ADP receptor antagonist has been shown in multiple reports to reduce thromboembolic rates in neurointerventional patients.⁵ A randomised, controlled trial of 47 patients with high-grade carotid artery stenosis demonstrated that DAPT with clopidogrel and aspirin reduced the 30-day incidence of adverse neurological outcomes compared with aspirin plus heparin (0% vs 25%; $p=0.02$), without an increase in bleeding.⁶ Furthermore, in a single-centre study of 162 patients enrolled in the carotid stent registry,⁷ one of the five patients treated with aspirin alone developed in-stent thrombosis and DAPT did not increase the incidence of intracranial haemorrhage.⁷

Although clopidogrel is the most commonly used ADP receptor antagonist in the cardiology literature, response rates have varied in neurointerventional procedures. Prabhakaran *et al*² evaluated clopidogrel response in 76 patients undergoing cerebrovascular stent placement and showed that >50% of patients had a clopidogrel response rate of <40% platelet inhibition. The authors concluded that routine measurement of clopidogrel response may be of clinical importance prior to intracranial stent placement and may help prevent cerebral ischaemic events. These results are consistent with a large study in cardiology patients that demonstrated a 6.3% increase in stent thrombosis in clopidogrel hypo-responders.^{2 8} While there is no standard definition of clopidogrel hyporesponsiveness in the literature, at our institution alternative antiplatelet strategies are typically explored when <30% platelet inhibition is observed with clopidogrel.

Prasugrel, an alternative third-generation thienopyridine, is known to achieve higher levels of platelet inhibition more rapidly and consistently than clopidogrel.⁹ The faster and more complete conversion of prasugrel to its active form resulted in improved efficacy in patients with acute coronary syndrome undergoing PCI; however, prasugrel has been associated with a 30% increase in the relative risk of bleeding when compared with clopidogrel.⁹ Although this newer agent may be an alternative option

for use in cerebrovascular procedures, there is limited evidence available to support its use and the increase risk of bleeding is worrisome to many clinicians. A 2011 case reported successful use of prasugrel in the treatment of a patient with acute stent thrombosis during elective stent-assisted aneurysm coiling. In their report, the authors of this case encouraged a more rigorous assessment of the medication's role in intracranial stenting.¹⁰

Recently, Akbari *et al*¹¹ presented their experience with prasugrel and aspirin in a cohort of 25 patients undergoing neurointerventional procedures, including nine patients undergoing PED placement. In this study, patients treated with prasugrel were loaded with 60 mg and then treated with a 10 mg daily maintenance dose. They observed an increased rate of haemorrhage (19.4% vs 3.6%; $p=0.02$) and no difference in thromboembolic complications in patients treated with prasugrel compared with 51 patients treated with clopidogrel. Two patients undergoing PED placement experienced serious adverse bleeding events including the following: a right cervical carotid artery haematoma following perforation, a right groin haematoma requiring surgical intervention, an upper gastrointestinal bleed with severe anaemia requiring transfusion of 6 units of packed red blood cells and an asymptomatic intraparenchymal haemorrhage. Overall, the authors of this report concluded that DAPT with prasugrel and aspirin might predispose to a higher risk of haemorrhage during neurointerventional surgery.¹¹

This small study provides further insight into the use of prasugrel in neurointerventional patients and the potential for increased bleeding; however, many questions remain regarding the medication's role in therapy, including dosing strategies. The current medication labelling recommends a dose reduction from 10 to 5 mg daily in patients weighing less than 60 kg or who are greater than 75 years of age. With *in vitro* research showing a dose-dependent inhibition of platelet aggregation with prasugrel, the dose reduction is assumed to reduce the risk of bleeding in populations of patients shown to have the highest incidence of the adverse effect in previous trials.¹² Despite the assumption that lowering the dose will result in a lower percentage of platelet inhibition,¹² no studies assessing the impact of the lower dose on clinical outcomes are currently available.

We report 6-month efficacy and safety outcomes of reduced dose prasugrel use in two patients following PED placement, one of which later developed a small subarachnoid haemorrhage that did not require further intervention, negatively on impact the patient's neurological function, or require cessation of DAPT. Our report highlights the use of a lower daily maintenance dose of prasugrel, which may provide clinicians with an alternative strategy to maintain stent patency without the increased risk of severe bleeding. As newer stenting technologies are approved, adequate platelet inhibition prior to stent deployment may become increasingly important. While the PED is a promising treatment option for cerebral aneurysms, many questions regarding antiplatelet therapy and the device remain unanswered. For example, there are no data available regarding the placement of the PED in the absence of DAPT or in poor clopidogrel responders who are not transitioned to an alternative antiplatelet agent.

Despite the increased risk of bleeding seen in previous studies with prasugrel, the clopidogrel hyporesponsiveness dilemma has created the need for an alternative antiplatelet agent following intracranial stenting, especially with newer devices that have a higher metal surface area. While reduced dose prasugrel may serve as an alternative antiplatelet strategy, no clinical evidence regarding the overall clinical efficacy and safety in neuroendovascular patients is available and further research is warranted.

Learning points

- ▶ Impact of inadequate platelet inhibition prior to placement of higher metal surface area stents, such as the pipeline embolisation device (PED), is not widely known.
- ▶ While clopidogrel is widely used as part of dual-antiplatelet therapy (DAPT) therapy prior to device implantation, recent research suggests a high prevalence of hyporesponsiveness that may lead to inadequate platelet inhibition.
- ▶ Prasugrel, an alternative third-generation thienopyridine is known to achieve platelet inhibition more rapidly and consistently; however, the agent is associated with significantly higher bleeding rates.
- ▶ Despite this increased risk of bleeding, further research is needed to determine the role of prasugrel as part of DAPT therapy prior to PED placement in patients with clopidogrel hyporesponsiveness.
- ▶ Although recent studies have utilised the 10 mg daily dose of prasugrel, no clinical reports exist regarding the use of the lower maintenance dose of 5 mg to achieve adequate platelet inhibition while potentially reducing the rates of serious bleeding.

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