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FULL PAPER

Safety of Prasugrel loading in ruptured blister like aneurysm treated with a Pipeline device

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Objective: Blister like aneurysm (BLA) is extremely challenging to treat; endoluminal reconstruction has emerged as the most promising treatment method. When to treat after the ictus, the timing of administration of antiplatelet and causal relationship between platelet function testing results and thrombo-embolism is unclear. We theorized that Prasugrel with a lower incidence of resistance may be a safe suitable alternative to clopidogrel in patients treated with a flow diverter (FD).

Methods: Prospectively collected data from consecutive patients treated for a ruptured blister with an FD was reviewed. Device deployment was timed to be at 2 h following Prasugrel loading. Thrombo-embolic and hemorrhagic complications, and occlusion rates were documented.

Results: Nine patients were included. Most were females (55%); the median age was 55 (43, 65). The median Fischer grade was 3 (2, 4). A single pipeline device was deployed in all within 24 h of admission; the median time from ictus to device deployment was 4 days (2, 30). There were no thrombo-embolic or hemorrhagic complication. Complete occlusion was noted in 89% ($n = 9$).

Conclusion: Prasugrel loading timed 2 h prior to stent delivery did not increase thrombo-embolic or hemorrhagic complications. Single stent that is well apposed against the wall appears to be an effective treatment strategy to treat BLA.

Advances in knowledge: Treatment of acutely ruptured BLA with a single pipeline device deployed at 2 h after Prasugrel loading appears to be safe.

INTRODUCTION:

Blister like aneurysm (BLA) typically occurs at non-branching sites and is commonly located at the dorsal supraclinoid internal carotid artery (ICA).¹ Morphologically, they resemble a blood blister and their characteristic geometry is that of a broad base with a small aspect ratio. Histopathologically, they differ from saccular aneurysms in that they lack the intima and media and are considered to be dissecting in etiology.² Diagnosis can be challenging and three-dimensional rotational angiography appears to be the gold standard in detecting these aneurysms.³ BLA account for approximately 0.5 to 2% of all ruptured aneurysms.⁴ Natural history of BLA appear to be aggressive in that they tend to grow and rebleed; in patients managed conservatively from the outset, 20% died predominantly due to rebleed and in a further 68% growth of the aneurysm or repeat bleed necessitated treatment.⁴ Frequent rebleeding and/or regrowth of the dome after the neck clipping was observed by Satoh et al.⁵ The friable nature of BLA and their complex geometry pose unique challenge to both surgical and endovascular management. In a systematic review, combined surgical morbidity and mortality amounted to 37.8%.⁶

Endovascular methods to treat BLA could be either deconstructive or reconstructive. Parent artery occlusion (PAO) following balloon test occlusion has been undertaken and is very effective in achieving immediate aneurysm occlusion. However, the downside are that of occlusion of side branches and consequent negative impact on vasospasm due to reduced perfusion pressure, and lack of access to perform intra-arterial therapy.⁷ Additionally, these aneurysms do not appear to be suitable for conventional coiling and the reported combined morbidity and mortality was high (34%). A variety of reconstructive techniques have been described to treat BLA. The combined morbidity and mortality was low with stent assisted coiling and overlapping stent placement, and was 10 and 5.5% respectively. The key drawback were that of regrowth (38%) and rebleed (11%).⁶ Therefore, the concept of endoluminal reconstruction rather than endosaccular occlusion is most appealing to treat BLA and recently flow diverters (FDs) are being increasingly used to treat these aneurysms. Emerging data indicate that mid to long-term aneurysm occlusion rates are better and the need for repeat treatment lower with flow diversion.^{8,9}

FD placement harbingers the need for administering dual antiplatelet in the acute setting; the primary concern being the risk of rebleed as the aneurysm sac is not completely excluded from the circulation. Additionally, there is no unified consensus on when to administer antiplatelet and if one should defer treatment for a period to allow for the stabilization of the wall of the aneurysm sac. Intuitively, it may be safe to time the antiplatelet therapy in a way to have maximal platelet inhibition close to the time of delivery of the stent to reduce the possibility of rebleed prior to treatment. As regards to timing, the approach of deferring treatment may prove to be deleterious as BLA are notorious to grow and rebleed.⁶ Finally, due to the perceived risk of thrombo-embolism from resistance to clopidogrel in patients undergoing FD placement, platelet function assays (PFA) are being performed. These tests appear to have a strong negative predictive value.¹⁰ Contrary to this, the positive predictive value of these assays are low and there is no conclusive evidence to suggest a relationship between platelet function testing results and occurrence of target vessel thrombosis.^{10–12}

At our center, Prasugrel was used as first line antiplatelet as the incidence of platelet resistance appears to be lower with this newer thienopyridine drug.¹³ Treatment was not deferred and based on the pharmacodynamics properties of the drug, the loading dose was timed to achieve maximal platelet inhibition at the time of stent delivery.¹⁴ We report on angiographic and clinical outcomes, and the incidence of thrombo-embolism and hemorrhagic complications with this protocol for managing ruptured BLA in the acute setting without deferral of treatment using a single pipeline embolization device (PED). Furthermore, we have previously reported clinical outcomes in patients treated with non-FD reconstructive techniques.¹⁵

METHODS AND MATERIALS

Review of prospectively collected data from all consecutive patients treated between May 2014 and July 2015 for a ruptured BLA with a PED in the acute setting was undertaken. Treatment was offered within 24 h of admission and FD deployment was timed at 2 h following antiplatelet administration. All patients were loaded with Ecosprin (150 mg) and Prasugrel

(50 mg) 2 h prior to the procedure. The maintenance dose of Prasugrel was 10 mg. Clopidogrel was used in patients with age >75 years or a prior history of ischemic stroke as Prasugrel was associated with higher major bleed rates in this subset. Patients were screened for the need for external ventricular drain (EVD) and one was inserted if needed prior to loading with antiplatelet agents.

PED (ev3-Covidien, California) was used in all patients. Care was taken not to oversize the device and the shortest length that can be safely deployed was used. Aneurysm size, number and dimensions of the PED used, covered side branches, vasospasm, immediate and delayed thrombo-embolic and hemorrhagic complications, outcome at discharge and follow-up, and aneurysm occlusion rates were documented. Interval cerebral angiography (DSA) was done till complete occlusion was noted. The time points at which DSA was performed were 6 weeks, 6 months and 12 months. Institutional review board approved the use of human subjects for the study.

RESULTS

Nine patients with ruptured BLA treated with a PED were included. Most were females (55%) and the median age was 55 (43, 65). The median Fischer grade was 3 (2, 4) and the median Hunt & Hess grade was 2 (2, 3) (Table 1). EVD was not placed in any and all patients were treated within 24 h of the initial diagnostic angiography/admission. The median time from ictus to FD deployment was 4 days (2, 30); the majority was treated within 5 days of the ictus (66%). No CSF flow diversion procedures were performed prior to PED deployment. A single PED was used in all. Loading with antiplatelet was done approximately 2 h prior to device deployment in all patients. Technical difficulty was encountered in one (11%) patient; balloon angioplasty was performed in this case to achieve wall apposition of the proximal end of the stent. No periprocedural in-stent thrombosis, growth or rebleed was noted. Clinically symptomatic vasospasm needing single session of intra-arterial dilatation with Nimodipine (3 mg) followed by Milrinone (8 mg) was noted in one patient (11%; $n = 9$). This was followed with i.v. milrinone infusion at a dose of 0.5 mcg/Kg/min. No

Table 1. Patient characteristics

Patient	Age/Sex	Fisher grade	Hunt & Hess grade	Location	Size (mm)	EVD	Ictus to device deployment (days)
1	63/F	3	3	SC (R)	1.7 × 1.4	No	3
2	44/F	4	2	SC (L)	2.4 × 1.6	No	4
3	68/M	2	3	SC (R)	1.7 × 0.9	No	14
4	55/M	2	2	SC (R)	1.3 × 0.8	No	30
5	57/F	2	2	SC (L)	1.5 × 1.4	No	21
6	52/M	3	2	SC (R)	1.5 × 1.1	No	5
7	36/M	3	3	SC (R)	2.7 × 1.4	No	2
8	42/F	2	2	SC (R)	3 × 1.2	No	2
9	63/F	3	3	SC (L)	1.8 × 1.5	No	2

EVD, external ventricular drain; L, left; R, right; SC, supraclinoid segment of ICA ICA, internal carotid artery.

Figure 1. (a) Blister like aneurysm in the right dorsal supraclinoid ICA; (b) Pipeline embolization device deployed across the blister like aneurysm (Inset – FD lateral view); (c) partial filling of sac post stent deployment; (d) Complete occlusion of the sac at follow-up angiography in 6 months. FD, flow diverter; ICA, internal carotid artery.

ischemic complications were noted. Complete occlusion was noted on cerebral angiography in 2 (22.2%, $n = 9$) at 6 weeks, 4 (44.4%) at 6 months and 2 (22.2%) at 12 months (Figure 1). In one patient there was partial filling at last angiography at 6 months. This patient opted for contrast enhanced MRA at 12 months; there was no residual sac noted.

Patient 7 had a poor outcome with a modified Rankin Score (mRS) of 5 at follow-up. Admission NCCT brain revealed diffuse subarachnoid hemorrhage with focal clot in the right sylvian fissure. As there was no focal deficit, EVD was not inserted and FD placement was undertaken within 2 days of the ictus. The level of consciousness decreased on the sixth postoperative day and CT brain revealed perihematoma edema with mass effect leading to trans-tentorial herniation; there was no repeat bleed or hydrocephalus. He underwent emergency decompression under platelet cover. He had persistent left-sided weakness and dysarthria. Interval angiography at 6 months revealed partial filling of the aneurysm sac (Table 2).

DISCUSSION

The unfavorable geometry and the fragile wall of a BLA make both endovascular and surgical management of these aneurysms extremely challenging. In a meta-analysis examining endovascular management of ruptured BLA, immediate complete occlusion rates were significantly higher with endovascular PAO (77.3%) as compared to reconstructive techniques (33%).

Table 2. Procedural details, complication, outcome and follow-up data

Pt	PED size	SB covered	SB occluded	In stent thrombosis	Rebleed	Growth	Follow-up at which complete occlusion was noted on DSA	Technical complication	Outcome mRS
1	4 × 20	OA	–	–	–	–	6 months	–	<2
2	3.75 × 30	OA, A1 ACA, PCom, ACh	A1 ACA	–	–	–	12 months	–	<2
3	4 × 20	A1ACA, PCom, ACh	–	–	–	–	6 weeks	–	<2
4	3.5 × 18	OA	–	–	–	–	6 months	–	<2
5	3.5 × 20	OA	–	–	–	–	6 months	–	<2
6	3.75 × 25	OA, A1 ACA, PCom, ACh	–	–	–	–	12 months	–	<2
7	3.5 × 18	A1 ACA, PCom, ACh	–	–	–	–	Partial filling at 6 months ^a	–	5
8	3.25 × 20	A1 ACA, PCom, ACh	A1 ACA	–	–	–	6 weeks	–	<2
9	5 × 25	OA	–	–	–	–	6 months	Balloon angioplasty to achieve wall opposition of the proximal aspect of the stent	<2

ACA, anterior cerebral artery; ACh, anterior choroidal artery; DSA, digital subtraction angiography; mRS, modified Rankin Score; OA, ophthalmic artery; PCom, posterior communicating artery; PED, pipeline embolization device; SB, side branch.

^aContrast enhanced MR angiography at 1 year showed no residual aneurysm.

However, the perioperative stroke risk was higher with PAO (29.1%) than with reconstructive techniques (5%). Amongst reconstructive techniques, significantly better mid to long-term sac occlusion and lower retreatment rates were noted with FD) as compared to traditional reconstructive techniques. Occlusion and retreatment rates were 90.8 and 6.6% respectively with FD reconstruction; they were 69.7 and 27.7% respectively with traditional reconstructive techniques. Perioperative stroke risk was higher and rebleed rate lower with FD reconstruction in comparison to traditional reconstructive techniques.⁸ There is still considerable dilemma regarding timing of treatment and antiplatelet regime; a number of differing protocols have been reported in literature.

Yoon *et al*¹⁶ noted thrombo-embolic complication in 27% of patients with ruptured BLA treated predominantly within 48 h of symptom onset; this was despite pre-procedure aspirin and clopidogrel loading (timing not specified) and monitoring of platelet inhibition.¹⁶ There was no rebleeding and complete occlusion was observed in 72% of patients. Lin *et al*¹⁷ reported on a multicenter study of 26 patients treated with a PED for a ruptured BLA; the antiplatelet loading was done 12 h prior to procedure.¹⁷ They noted in stent thrombosis that resolved with eptifibatide/tissue plasminogen activator in 2 (7.6%) patients and brain stem ischemia resulting in death in one patient (3.8%). The timing of intervention from ictus was not specified and they noted complete occlusion without rebleed in all. Notably, when clopidogrel loading was performed at the time procedure, 63% (n=11) of patients treated in the setting of subarachnoid hemorrhage suffered thrombo-embolic complications that necessitated administration of abciximab.¹⁸ Conversely, favorable outcome with no incidence of thrombo-embolism or rebleed with an occlusion rate of 83% was reported by Chalouhi *et al*¹⁹ when treatment was deferred.¹⁹ Antiplatelet loading was done 8 h prior to procedure and only two patients were treated early (<7 days) in their cohort. Similarly, Aydin *et al*²⁰ intentionally delayed treatment for 5 days.²⁰ Antiplatelet was administered 12 h before procedure. PAO on follow-up was noted in one patient (9%). Mean duration between presentation and treatment was 9.6 days. No rebleed was observed. Therefore, there is no clear consensus on when to offer treatment and the timing of drug administration. Deferring treatment poses the risk of early rebleed, and therefore may be a questionable strategy. Further, one may attempt to time drug administration in such a fashion that the peak effect occurs close to the time of stent delivery with an effort to prevent thrombo-embolic complications without increasing the risk of bleeding. Here, it is worth noting that maximal inhibition of platelet function occurs at 4 to 8 h after loading with clopidogrel. Yet, timing of administration of the drug varied between centers and ranged from loading during to 12 h prior to procedure. Loading at the time of the procedure may lead to incomplete effect with increased incidence of thrombo-embolism. This may result in the need for administering a third antiplatelet agent (usually GpIIb/IIIa inhibitors) intra-arterially, which can theoretically increase the risk of rebleed from an aneurysm that is partly secured. On the other hand early (12 h or more) administration will theoretically increase the chance of rebleeding.

A critical issue to be addressed is that of resistance to clopidogrel. Clopidogrel hypo-responders on PFA ranged between 26.4 and 50.5%; they are at a higher risk of all-cause mortality, non-fatal myocardial infarction, in-stent thrombosis and stroke in a prospective study of patients undergoing percutaneous coronary intervention.^{21–23} Similarly, in neurovascular stent placement, adequate and in-range platelet inhibition is considered important to avoid major thrombo-embolic or hemorrhagic complication.²⁴ Thrombo-embolism occurred in 12.5% and hemorrhage in 10.4% of patients when platelet inhibition was not in the therapeutic range.²¹ Amongst the PFA, light transmittance aggregometry is considered to be the criterion standard and the verify-now test based on light transmittance is a fast and easy to perform point of care test.²⁵ Although these tests have a strong negative predictive value, they suffer from low sensitivity and specificity, poor correlation and importantly a low positive predictive value.¹⁰ Therefore, one may seek to use an alternate antiplatelet in which lack of platelet inhibition is less of an issue.

Prasugrel, a prodrug, requires a 1-step cytochrome P450 enzyme conversion into an active metabolite. Genetic polymorphism involving cytochrome enzyme reduces platelet inhibition by clopidogrel; whereas, this does not appear to affect responsiveness to Prasugrel.¹³ Similarly, drug interaction with proton pump inhibitor noted with clopidogrel is not seen with Prasugrel.²⁶ Experience with Prasugrel in patients undergoing neuro-interventional procedures is limited to retrospective review and prospective registry of patients undergoing elective intra and extracranial stent placement. Akbari *et al* (2013)²⁷ reported a high incidence (19.4%) of hemorrhagic complications with Prasugrel mostly due to wire perforation, clinically inconsequential parenchymal hemorrhage and extracranial bleed requiring blood transfusion.²⁷ Contrarily,²⁸ no thrombo-embolic or hemorrhagic complication with Prasugrel in patients treated for unruptured aneurysms was noted by Stetler *et al* (2013).²⁸ With little proof for or against Prasugrel from neurovascular literature, evidence relating to stent thrombosis and hemorrhagic complications comes predominantly from cardiac literature. Randomized trials have shown that death from any cause and non-fatal myocardial infarction was lower in the Prasugrel as compared to the clopidogrel arm. Importantly, the rate of stent thrombosis was significantly lower with Prasugrel. The main concern with prasugrel was the higher incidence of fatal hemorrhage. However, the risk of intracranial bleed did not differ between the two arms. Of note, a subgroup of patients with a prior history of transient ischemic attack/stroke had poor outcomes with Prasugrel.²² In this subgroup, Clopidogrel rather than Ticagrelor was used in our study. Ticagrelor was not used due to the higher incidence of fatal intracranial bleed.²³ Although questions can be raised as to whether the results from cardiac literature apply to neurovascular stenting procedures, the current best available evidence is from cardiac literature. Therefore we used Prasugrel in our patient cohort. PFA were not performed due to lack of evidence in favor of and the potential delay that this can introduce prior to treatment. Maximal inhibition of platelet function with Prasugrel occurs as early as 2 h; henceforth, the drug administration was timed in such a fashion that stent deployment will occur at

approximately 2 h following loading.¹⁴ To avoid risk of rebleed following treatment, we aimed to maximize diversion of flow away from the aneurysm sac.

The crucial factor to obtaining effective flow diversion with a single device is to select the most appropriate device dimension based on the arterial anatomy. Specific care was taken not to oversize the device to ensure that the porosity at the transitional zone at the distal end of the aneurysm sac, which acts as the inflow for the aneurysm is not high. Further, we avoided short or long distal landing zone to overcome fish mouthing or lipping at the distal end of the device that can result in endoleak.²⁹ More importantly a dynamic "push and pull" technique was employed to achieve a compact mesh that can effectively divert flow.³⁰ Similar to the experience of most authors, aneurysm sac filling was noted post stent deployment. However, none of the patients in our series suffered hemorrhagic complication. Our study is unique in that all patients with a ruptured BLA were loaded with Prasugrel without delay followed by deployment of a single PED within 24 h of admission; the majority of patients were treated within 5 days of the ictus. The patients treated in the delayed window were either due to delay in seeking medical attention or missed diagnosis at a peripheral center. Our experience indicates that loading dose of Prasugrel along with aspirin may be safe and effective for FD placement in setting of acutely ruptured BLA. This needs further confirmation in large-scale studies.

Other than rebleed, delayed ipsilateral parenchymal hemorrhage has infrequently been described in patients treated with FD in the anterior circulation.³¹ Many pathogenic mechanisms have been proposed; nonetheless, there is no agreement on any particular theory. In our series, none of the patients had delayed ipsilateral parenchymal hemorrhage. Another important concern is that of flow modification resulting in occlusion, reduction of caliber and reversal of flow in the side branches covered.³² This

is particularly pertinent in the acute phase after subarachnoid hemorrhage as flow diversion in the context of vasospasm can aggravate reduction in perfusion in the covered side branch. Immediate occlusion was not seen in any and none of the patients in our series developed clinically symptomatic vasospasm that resulted in cerebral infarction. On interval angiography flow reversal was noted in 40% of A1 anterior cerebral artery (ACA); whereas, good antegrade flow was demonstrated in the rest of the side branches that were covered. Finally, complete occlusion was noted in 89% of our patients treated with PED and is similar to that reported in the meta-analysis.

The key limitation to our study is the small sample size; therefore, no generalizations can be made. Secondly, none of our patients in our cohort needed EVD insertion. Therefore we are not able to conclude on the safety of Prasugrel in patients who need an EVD. Finally, none of the patients had a clinically symptomatic vasospasm. Therefore, in a patient with vasospasm the detrimental effect of flow diversion on covered side branches cannot be commented on.

CONCLUSION

Emergent loading with Prasugrel followed by FD deployment appeared to be safe and effective method to treat acutely ruptured blister aneurysms in our series. In addition, endovascular reconstruction with PED is more likely to achieve complete occlusion as compared to traditional reconstructive techniques. Further, our experience with managing blister aneurysms may indicate a lower morbidity and mortality with flow diversion; however, is limited by the small number of patients in the series. Further larger studies are required to confirm our findings.

ETHICS APPROVAL

Institutional review board has approved the use of human subjects for the study.

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