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ORIGINAL RESEARCH

Initial Experience with the Use of Intravenous Eptifibatide Bolus during Endovascular Treatment of Intracranial Aneurysms

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BACKGROUND AND PURPOSE: Despite systemic heparinization, thromboembolic complications remain a major concern related to endovascular treatment of intracranial aneurysms. We assessed the safety of intravenous eptifibatide administered during aneurysm coiling procedures to prevent such complications.

METHODS: From August 2001 to November 2004, 298 coil embolization procedures were performed to treat intracranial aneurysms; eptifibatide was used in 84 endovascular coil embolization procedures to treat 79 aneurysms in 74 patients. We retrospectively reviewed medical charts, radiographic images, and procedure notes to evaluate periprocedural complications related to eptifibatide.

RESULTS: The mean age of the 74 patients in our cohort was 55 ± 9 years (range, 31–84) harboring 79 aneurysms (32 ruptured/47 unruptured). Eptifibatide was given prophylactically in 77 procedures, whereas in 7 procedures, it was given for treatment of a thromboembolic event (visualization of an arterial branch occlusion). A total of 5 (5.9% [total cohort]) bleeding complications related to eptifibatide occurred during 84 procedures. Two patients (2.4% [total cohort]/6.3% [ruptured group]) developed intracerebral hemorrhagic complications exacerbated by eptifibatide. The other 3 (3.6% [total cohort]) patients had groin hematomas requiring blood transfusions but had no surgical intervention. One thromboembolic event occurred in the 77 patients receiving eptifibatide prophylactically.

CONCLUSIONS: Intravenous infusion of eptifibatide seems to be safe to administer in patients undergoing endovascular repair of an unruptured cerebral aneurysm. Caution must be used in patients harboring ruptured aneurysms as intracranial bleeding complications may occur. Further study is required to delineate the group of patients most likely to benefit from this therapy.

Endovascular treatment of an intracranial aneurysm with the use of detachable coils has become increasingly used in recent years. The International Subarachnoid Aneurysm Trial demonstrated that in selected patients with ruptured intracranial aneurysms, endovascular therapy may result in better outcomes compared with surgical treatment.[1] Despite technical improvement and accumulation of clinical experience, this procedure still carries a significant risk of stroke and death. Previous studies have shown that thromboembolic and ischemic complications are responsible for morbidity and mortality during and after intracranial endovascular procedures.[2] So far, numerous efforts have been aimed at reducing the incidence of thromboembolism; however, most studies addressing this issue were based on sporadic cases and on emergency treatment rather than prevention.[3-15] Abciximab has been described for urgently treating thromboembolism during the endovascular coiling of an intracranial aneurysm,[8-15] but its safety profile is unclear during these procedures. In addition, abciximab has a longer reversal time compared with other glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors that may be undesirable in patients harboring ruptured cerebral aneurysms. In this study, we present our preliminary results with the use of eptifibatide, a GP IIb/IIIa inhibitor with a shorter reversal time, during 84 intracranial aneurysm embolization procedures.

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Patients and Techniques

After obtaining approval from the Institutional Review Board of our hospital, a retrospective review of a data base of aneurysm patients was used to identify all patients who underwent endovascular treatment of intracranial aneurysms between August 2001 and November 2004. A total of 298 coil embolization procedures were performed; eptifibatide was used in 84 of them. The stroke and aneurysm rupture rates for all procedures was tabulated. All patients given eptifibatide intraprocedurally were reviewed. Of the 84 procedures in which eptifibatide was used, 74 patients harboring 79 aneurysms (32 ruptured/47 unruptured) were treated. All procedures were performed by 2 of the authors (M.H. and T.G.J.).

We retrospectively reviewed medical charts, including laboratory results and outpatient records, radiographic studies, and endovascular procedural records, of 74 patients meeting inclusion criteria. All periprocedural related complications, such as intraprocedural rupture of the aneurysm, changes noted on neurophysiologic monitoring, increasing hemorrhage on CT scan of the head, groin complications, and thromboembolic complications were recorded. Thromboembolism was defined as an absence of opacification of a previously seen vessel or the presence of an intra-arterial filling defect. In addition, a new area of ischemic injury on a CT scan in the territory of the aneurysm's parent vessel or a new focal neurologic deficit consistent with the aneurysm's location within 24 hours postprocedure was considered the result of a thromboembolism. This time window was selected because it is the most common timeframe for these events to occur and because, beyond this timeframe, the analysis may be confounded by the presence of vasospasm or hydrocephalus.

Table 1: Reason for infusion of eptifibatide

Description	No. of Cases ($N = 84$)
Neuroform stent placed	16
Broad neck (FNR < 2)	15
Operator's discretion	13
Aneurysm >10 mm	12
Branch occlusion	7
Coil prolapse	5
Retreatment of aneurysm	5
Multilobulated dome	4
ICA sacrifice	3
Coil fracture and retrieval	2
Interstitial filling	2

Note:—FNR indicates fundus-to-neck ratio; ICA, internal carotid artery.

Procedure

All procedures were performed with the patients under general anesthesia with intraoperative neurophysiologic monitoring (spectral electroencephalography, somatosensory evoked potential, and/or brain stem auditory evoked potential). A 6F guide catheter was placed in the cervical target artery proximal to the aneurysm. Systemic heparinization was routinely achieved before catheterization of all aneurysms to maintain activated clotting time at 250–300 seconds. A microcatheter and microwire were gently navigated into the aneurysm. All coils were introduced into the aneurysms using simultaneous biplane imaging with road-mapping until angiographically complete obliteration was achieved or until the risk of occluding a normal arterial branch adjacent to the aneurysm seemed imminent. Heparin was not reversed postprocedure, and when eptifibatide was given as a bolus, patients were not maintained on continuous intravenous heparin infusion for the usual 12–24 hours postprocedure. Eptifibatide was used during 84 procedures for various reasons (Table 1), with a bolus dose of 180 μg/kg administered intravenously. No patient received continuous infusions postprocedure.

The rationale for eptifibatide infusion in this cohort was as follows: (1) The rate of thromboembolic events in the literature based on small case series during placement of a Neuroform stent (Boston Scientific, Natick, Mass) is 7%–10%.[16,17] (2) Broad-necked and larger aneurysms have a higher likelihood of asymptomatic MR imaging/diffusion-weighted imaging hyperintensities[18] as a result of either longer procedure times, more sophisticated techniques (dual catheter technique, balloon remodeling), higher risk of coil protrusion in the parent vessel, or higher likelihood of unorganized thrombus formation.[19] (3) Coil prolapse into the parent vessel has been shown to be an independent risk of a postprocedural ischemic event.[6] This may be due to embolization of metal fragments or platelets from the protruding coil mass.[20,21] Likewise, coil fracture within the parent vessel is a risk of thromboembolic events. (4) Recoiling of a previously embolized aneurysm may carry higher rate of thromboembolic events[2] during deposition of coils into a coil mass with likely unorganized thrombus within the aneurysm. Recanalized aneurysms probably have early invasion of clot and are thus less likely to form a stable fibrin matrix.[22] During recoiling, some loose clot may theoretically dislodge into the parent vessel. (5) Multilobed aneurysms and aneurysms with interstitial filling were believed to be at higher risk for ischemic events as a result of the potential for thrombotic material to exit the coil mass because of incomplete stagnation of flow.

Eptifibatide was not reversed with platelet transfusion unless a bleeding complication was noted. The femoral artery puncture site was closed using a suture-mediated closure device (Perclose; Abbott Vascular Devices, Redwood City, Calif). Postprocedure, patients with ruptured aneurysms were managed in the neurosurgical intensive care unit. Patients with unruptured aneurysms treated without complication were observed in a neurosurgical stepdown unit for 24 hours before discharge. In cases of placement of a Neuroform stent, patients were loaded with 300 mg of clopidogrel and then placed on 75 mg/day clopidogrel and 325 mg/day aspirin postprocedurally for 30 days and then 325 mg/day aspirin indefinitely.

An external ventricular drainage (EVD) system was placed in patients with hydrocephalus preprocedure secondary to a ruptured cerebral aneurysm ($n = 14$). Only 1 patient required an EVD postprocedure. This was performed 14 hours after coil embolization.

Cases in which eptifibatide-related complications and procedure-related complications occurred were identified. Any bleeding or thromboembolic complication or change in neurologic status was recorded. In addition, any instances of thrombocytopenia (platelet count <100,000/mL) were recorded.

Table 2: Comparison of demographic and angiographic data between ruptured and unruptured groups ($N = 79$)

Variable	Ruptured	Unruptured	Total
Age (mean ± SD), y	55 ± 10	54 ± 11	55 ± 10
Female, *N* (%)	21 (66)	31 (66)	52 (66)
Aneurysm diameter (mean ± SD), mm	7.4 ± 3.1	7.1 ± 3.4	7.3 ± 3.3
Location of aneurysm			
Anterior circulation			
Cavernous ICA	1	1	2
Paraclinoid ICA*	2	11 (1)	13 (1)
Posterior communicating artery	4 (1)	3	7 (1)
ICA dorsal wall	0	2	2
ICA bifurcation	0	1	1
Anterior communicating artery	7	9	16
Pericallosal artery	0	3	3
MCA bifurcation	2	3	5
Posterior circulation			
Basilar artery tip	9 (3)	13	22 (3)
Superior cerebellar artery	1	1	2
Vertebrobasilar junction	2	0	2
Posterior inferior cerebellar artery	4	0	4
Total	32 (4)	47 (1)	79 (5)

Note:—Numbers in parentheses denote retreated aneurysms. ICA indicates internal carotid artery; MCA, middle cerebral artery; Paraclinoid ICA aneurysms included all aneurysms arising from the superior hypophyseal artery, ophthalmic artery, carotid cave, and clinoidal ICA segment.

Results

Eptifibatide was used in a total of 84 endovascular detachable coiling procedures to treat 79 aneurysms. In 77 procedures, eptifibatide was given prophylactically, whereas in 7 procedures, a branch occlusion was noted before administration (Table 1). The cohort's mean age was 55 ± 9 years (range, 31–84); 52 women (70%) and 22 men (30%) were treated. The clinical status of 32 patients with subarachnoid hemorrhage (SAH) was assessed using the Hunt and Hess scale: 1, grade I; 13, grade II; 10, grade III; 6, grade IV; and 2, grade V. In these 32 patients with SAH, 5 had additional aneurysms thought to be incidental based on the CT's blood pattern. When these 5 aneurysms are added to the 42 patients with unruptured aneurysms, 47 unruptured aneurysms were treated. Five aneurysms required retreatment with a second coil procedure.

Table 2 shows a comparison of demographic and angiographic data between the ruptured and unruptured groups. The most common location of the treated cerebral aneurysm

in our series was basilar tip followed by anterior communicating and then paraclinoid internal carotid artery (ICA). In 84 procedures, including 5 retreated ones, 28 aneurysms were less than 5 mm in size, 44 were between 6 and 10 mm, and 12 were between 11 and 25 mm.

Clinical Outcome

Overall, there were 4 deaths (4.7%) and 3 persistent neurologic deteriorations (3.6%). Of 4 patients who died, 2 patients were Hunt and Hess grade V, 1 was grade III, and 1 was grade 0. Two grade V patients died from diffuse cerebral edema on the 1st and 5th postoperative days, respectively. One grade III patient died from increased bleeding after an intraprocedural aneurysm rupture, and 1 grade 0 patient died 6 months later secondary to a contralateral middle cerebral artery (MCA) stroke and pneumonia. Only 1 of these deaths was felt to be partially attributable to the use of eptifibatide (patient with intraprocedural aneurysm rupture).

Three patients suffered persistent (>24 hour) clinical deterioration. The first patient became permanently hemiparetic after intentional ICA sacrifice for a ruptured paraclinoid aneurysm. The patient suffered an infarct as a result of hemodynamic impairment as seen on MR imaging perfusion/diffusion imaging. The second patient underwent unsuccessful clipping of a ruptured posterior communicating aneurysm but underwent craniectomy for a swollen brain. Endovascular coiling was then attempted, but the aneurysm was perforated during coiling and thus therapeutic carotid occlusion was performed. Eptifibatide was administered after successful sacrifice of the carotid was performed. The patient has remained hemiparetic from the hemorrhage secondary to the perforation of the aneurysm at 6-month follow-up. The third patient had a ruptured MCA bifurcation aneurysm that was coiled using Neuroform stent assistance. A subsequent thromboembolism to an MCA division occurred despite eptifibatide prophylaxis. Postprocedure head CT showed hemorrhagic conversion of the infarct that was probably caused or worsened by the eptifibatide. The patient underwent decompressive craniectomy and survived but has not regained independent function. This was the only patient with a thromboembolic complication despite eptifibatide prophylaxis and intracranial hemorrhage as a result of eptifibatide in combination with clopidogrel and aspirin.

Complications

During the 38-month period reviewed, of the 84 procedures performed with eptifibatide, 2 patients (2.4%) had an intraprocedural aneurysm rupture. In both of these patients, an EVD was inserted preprocedure. In the 77 procedures in which eptifibatide was given prophylactically, only 1 patient (1.3%) developed a thromboembolic event. There were 5 overall (5.9% [total cohort]) bleeding complications attributable to eptifibatide. Intracranial hemorrhages attributable to eptifibatide occurred in 2 patients (2.4% [total cohort]/6.3% [ruptured aneurysm group]) with ruptured aneurysms (Table 3). A third patient with an intraprocedural rupture of an aneurysm was given eptifibatide after sacrifice of the ICA as described above. In this patient, it is unlikely that eptifibatide contributed to the intracranial hemorrhage because the drug was administered after emergent sacrifice of the ICA as a result of aneurysm rerupture. In addition, no bleeding complications were noted along the catheter tract in the 14 patients receiving EVDs preprocedure. The 1 patient treated with an EVD after embolization also had no intracranial bleeding complications as a result of EVD placement.

Table 3: Complications following endovascular coiling with eptifibatide

Description	Patient No.	Rupture/Unrupture
Eptifibatide related		
Intracranial bleeding*	2	2/0
Groin hematoma	3	1/2
Thrombocytopenia†	2	2/0
Procedure related		
Arterial dissection	1	1/0
Intraprocedural rupture	2	1/0
Thromboembolic	1	1/0

* One patient with intraprocedural rupture was likely exacerbated with eptifibatide, and one patient had a hemorrorhagic transformation of a thromembolic infarction
† Both patients were on famotidine and one patient developed sepsis; thus, the etiology of the thrombocytopenia is unclear.

Vascular access site hematoma occurred in 3 (3.6% [total cohort]) procedures. All 3 patients were managed with conservative measures and blood transfusions.

Discussion

Despite improving operator skill and techniques, complications after endovascular embolization of cerebral aneurysms include thromboembolism, periprocedural aneurysm rupture, coil migration, vessel injury, vessel occlusion, and cranial nerve palsy.[2,23] Heparin is used routinely by many during endovascular treatment of intracranial aneurysms; nevertheless, periprocedural ischemic complications related to thrombus or embolus occur in 2.5%–28% of patients.[2,4,6,15,23]

The main finding of this retrospective study was that the rate of intracranial hemorrhage attributable to eptifibatide was 2.4% for the total cohort but 6.3% for patients harboring ruptured aneurysms. To our knowledge, this case series is the largest to demonstrate safety data on the use GP IIb/IIIa inhibitors during aneurysm coiling procedures.

Thromboembolic events during endovascular procedures are traditionally treated with intravascular volume expansion, blood pressure elevation, local infusion of fibrinolytics, maintenance of a therapeutic activated clotting time and local or systemic infusion of antiplatelet agents.[3-15] There are several reports of medications being used to treat thrombus that is detected at the time of angiography (Table 4), but little is known about the safety of using GP IIb/IIIa antagonists in this setting, especially in patients with ruptured cerebral artery aneurysms. Abciximab has been used in the emergency management of acute thromboembolic complications associated with endovascular aneurysm treatment. The use of such agents, however, has been advocated because acute thrombus is thought to be platelet rich and thus more likely to respond to GP IIb/IIIa inhibitors.[3,10,11,15]

Characteristics of GP IIb/IIIa Antagonists

GP IIb/IIIa inhibitors can potentially enhance thrombolysis via the following mechanisms: (1) prevention of platelet aggregation, leading to reduction both in thrombus mass and the platform for further thrombin generation; (2) inhibition of

Table 4: Review of emergency treatments of periprocedural thromboembolism

Study	No. of Patients	Treatment	Intracranial Bleeding Events	Recanalization
Cronqvist et al[3]	19	IA urokinase	3 (16%)	10 (53%)
Fourie and Duncan[5]	1	IV abciximab	0 (0%)	1 (100%)
Ng et al[8]	1	IV abciximab	0 (0%)	1 (100%)
Cloft et al[9]	4	IV abciximab	0 (0%)	2 (50%)
Kwon et al[10]	3	IA abciximab	0 (0%)	3 (100%)
Alexander et al[11]	1	IV abciximab	0 (0%)	1 (100%)
Mounayer et al[13]	13	IA abciximab	0 (0%)	12 (92%)
Bendok et al[14]	1	IV abciximab	0 (0%)	1 (100%)
Song et al[15]	7	IA abciximab	0 (0%)	5 (71%)

Note:—IA indicates intra-arterial; IV, intravenous.

Table 5: Comparison of the glycoprotein IIb/IIIa antagonists

	Abciximab	Tirofiban	Eptifibatide
Manufacturer	Eli Lilly	Merck	COR Therapeutics
Molecule size, datons	50,000	800	500
Receptor affinity (K_D)	High (5 nmol/L)	Low (15 nmol/L)	Low (120 nmol/L)
Plasma high-life, h	0.2	1.5–2	2–4
Biologic half-life, h	12–24	1.5–2	2–4
Excretion	Renal	Renal/hepatic	Renal
Method of reversal	Platelet transfusion	Fresh-frozen plasma, cryprecipitate, platelet transfusion	Fresh-frozen plasma, cryprecipitate, platelet transfusion

release of local thrombolysis inhibitors of by platelets; and (3) weakening of the clot structure by decreasing the binding of factor XIII, fibrin, and α-2 plasminogen inhibition.[24]

Currently, there are 3 FDA-approved GP IIb/IIIa receptor antagonists: abciximab, tirofiban, and eptifibatide (Table 5). Abciximab (ReoPro), a large compound, has a strong receptor affinity, long plasma half-life, and low plasma concentrations, making it difficult to reverse bleeding complications with platelet transfusions.[25] Eptifibatide (Integrilin) and tirofiban (Aggrastat) are small compounds that have lower receptor affinity and higher plasma levels and are shorter-acting than abciximab.[26]

Eptifibatide has theoretical advantages over abciximab in patients undergoing coil embolization procedures. First, it is less likely to induce thrombocytopenia because of its small molecular weight.[27] Second, it is less antigenic and thus has a lower probability of causing an adverse immune response such as that has been reported after abciximab administration.[28] Third, it has a low GP IIb/IIIa receptor affinity and is thus quickly reversible within 2–4 hours.[26] This factor is important in patients who harbor ruptured aneurysms and may require procedures in the intensive care unit including EVD systems. Despite its short half-life, the potential for significant hemorrhagic complications resulting from procedures performed within hours after its administration is of greatest concern and we currently administer eptifibatide in patients with ruptured cerebral aneurysms only if an EVD is already in place.

There are several limitations to this retrospective study and considerations to the use of eptifibatide in endovascular procedures: (1) We included 8 patients with poor Hunt-Hess grades in whom it may have been difficult to detect postcoiling focal neurologic deficits consistent with a thromboembolic event. In an attempt to account for this issue, all surviving patients with SAH had serial head CT scans that were used as a surrogate to determine whether new ischemic insults had occurred. (2) Small, clinically silent thromboembolic events can occur, and postprocedure MR imaging scans were not obtained; these would probably have been more sensitive in detecting such events. (3) Eptifibatide was ordered by the treating physician whenever it was thought that the drug was clinically indicated but without any prospectively established criteria. This makes an accurate assessment of who stands to benefit from this therapy difficult. Nonetheless, this study does provide a framework for a prospective randomized trial investigating the role of eptifibatide in reduction of morbidity associated with thromboembolic events after endovascular procedures both for unruptured and possibly for ruptured aneurysms.

Conclusions

This current report suggests that a bolus of intravenous eptifibatide may be safe in patients with unruptured cerebral aneurysms. Intracranial bleeding complications were noted in patients with ruptured aneurysms, and thus a larger number of patients need to be evaluated to make definitive safety claims. Further prospective studies are required to confirm these preliminary findings and identify the group of patients who stand most to benefit from this form of treatment.

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