In situ administration of abciximab for thrombus resolution during intracranial bypass surgery: case report

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Abciximab is a glycoprotein IIb/IIIa receptor antagonist that functions to prevent platelet aggregation, thus reducing thrombus initiation and propagation. It has been widely used during percutaneous endovascular interventions, such as aneurysm coil embolization, angioplasty, atherectomy, and stent placement, as both a preventative and a salvage therapy. The use of abciximab in cardiac and neurosurgical procedures has been associated with a reduced incidence of ischemic complications and a decreased need for repeated intervention. In these settings, abciximab has been delivered transarterially via a microcatheter or infused intravenously for systemic administration. The authors describe novel in situ delivery of abciximab as an agent to dissolve “white clots,” which are composed primarily of platelets, during an intracranial superficial temporal artery to middle cerebral artery bypass in a 28-year-old woman with severe intracranial occlusive disease. Abciximab was able to resolve multiple platelet-based clots after unsuccessful attempts with conventional clot dispersal techniques, such as heparinized saline, tissue plasminogen activator, mechanical passage of a wire through the vessel lumen, and multiple takedowns and re-anastomosis. After abciximab was administered, patency was demonstrated intraoperatively using indocyanine green dye and confirmed postoperatively at 1 and 10 months via CT angiography. The in situ use of abciximab as an agent to disperse a thrombus during intracranial bypass surgery is novel and has not previously been described in the literature, and serves as an additional tool during intracranial vessel bypass surgery.

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KEY WORDS  glycoprotein IIb/IIIa receptor antagonist; abciximab; cerebrovascular surgery; intracranial bypass surgery; EC-IC bypass; vascular disorders

Although the extracranial to intracranial (EC-IC) bypass has decreased in popularity since the publication of the EC/IC Bypass Study Group results that showed that EC-IC bypass failed to reduce the risk of ischemic stroke, this surgical technique remains an important tool in the treatment for a carefully selected patient population with cerebrovascular compromise. The EC-IC bypass technique has been used for several decades and the procedure has largely been unchanged. However, the development of new medications such as glycoprotein IIb/IIIa inhibitors, namely abciximab (Eli Lilly and Co.), has provided the neurosurgeon with an additional tool for addressing intraoperative thrombotic complications during EC-IC bypass.

We recently performed a superficial temporal artery (STA) to middle cerebral artery (MCA) bypass and encountered recurrent “white clots” (composed primarily of platelets) due to platelet aggregation that occluded the anastomosis. These clots were not treatable with conventional methods including irrigation with heparinized saline, local injection of tissue plasminogen activator (tPA), passage of a guidewire through the vessel lumen, and multiple takedowns and re-anastomosis. We were finally able to disperse the clot using in situ administration of abciximab. To our knowledge, this represents the first published report of using abciximab to resolve clot formation during intracranial bypass surgery.

Case Report

History and Presentation

A 28-year-old Caucasian woman presented with sudden onset of left upper-extremity greater than lower-extremity weakness. The patient was diagnosed with a right hemispheric stroke and further workup determined that she had moyamoya syndrome. MRI demonstrated an acute infarct in the right MCA territory including the corona radiata, centrum semiovale, and basal ganglia. A CT angiogram

ABBREVIATIONS  EC-IC = extracranial to intracranial; ICA = internal carotid artery; ICG = indocyanine green; ICH = intracerebral hemorrhage; MCA = middle cerebral artery; STA = superficial temporal artery; tPA = tissue plasminogen activator.

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showed extensive stenosis involving the supraclinoid segments of bilateral internal carotid arteries (ICAs) with near-complete occlusion of the left ICA and high-grade irregular stenosis of the right ICA (Fig. 1). The left side of the brain did show extensive collateral flow from the posterior circulation through the circle of Willis. Because the patient’s strokes were on the right side, a decision was made to perform an EC-IC bypass on the right side to preserve blood flow even though the vascular imaging showed greater stenosis on the left side.

Operation and Postoperative Course

Aspirin was administered preoperatively and continued throughout the postoperative period. During surgery, the right STA was identified and anastomosed to a posterior M_4 branch (Fig. 2A). Once completed, testing of the anastomosis for patency using Doppler ultrasonography was inconclusive. Subsequent, indocyanine green (ICG) dye administration demonstrated no flow through the anastomosis (Fig. 2B). The anastomosis was taken down and found to have multiple “sticky white clots” in both the STA and M_4 vessel segments. Multiple attempts were made to improve flow and dissipate the white clots, including repeated takedown and re-anastomosis, guidewire passage into the vessel lumen, heparinized saline, and direct tPA injection (Fig. 2C). During the takedown and re-anastomosis, white clots were visualized and removed from the vessel lumen (Fig. 2D). After each revascularization attempt, ICG dye was used to determine if flow had returned, and in each case, there was none across the anastomosis. As a last resort, we locally injected 2 mg of abciximab into the artery via a microsyringe and 27-gauge needle to restore patency (Fig. 2E). Subsequent ICG and Doppler ultrasonography demonstrated successful return of flow through the anastomosis with anterograde flow in the M_4 segment (Fig. 2F).

Postoperatively, the patient recovered uneventfully and the anastomosis was found to be patent on repeat CT angiography at 1 month (Fig. 3) and 10 months. At follow-up, the patient remained at her neurological baseline without development of any new neurological deficits.

Discussion

The clotting system can be divided into two major components, the platelet system and the thrombin system. The primary clotting mechanism in arteries relies on platelets while in veins clotting typically involves the thrombin system. On the arterial side, endothelial cell injury causes platelets to become exposed to von Willebrand factor and become activated. Activated platelets then adhere to and aggregate within the vessel, forming a viscous plug seen as a “white clot.” The final step of platelet aggregation and thrombus formation is mediated by the binding of platelet glycoprotein IIb/IIIa receptor to fibrinogen. This prevents further bleeding through a damaged vessel wall and is reinforced with a fibrin clot. These white clots often arise in arteries associated with myocardial infarction, stroke, and other ischemic conditions.8,10,17,19,30

On the venous side, the thrombin pathway leads to “red clot” formation. Through the intrinsic and extrinsic coagulation pathways, prothrombin is converted to thrombin, which in turn converts fibrinogen to fibrin. Fibrin strands stick to the exposed vessel wall and clump together. These
fibrin strands aggregate red blood cells into a cross-linked fibrin clot forming a “red clot.” Tissue plasminogen activator is a protein involved in the breakdown of these red clots. It is a serine protease found on endothelial cells that catalyzes the conversion of plasminogen to plasmin, the major enzyme responsible for red clot breakdown. Plasmin breaks the cross-linked fibrin mesh, making the clot soluble and subject to further proteolysis by other endogenous enzymes.

The need to preserve patency of a bypass graft must be balanced against the risk of hemorrhagic complications associated with anticoagulation. Single-agent antiplatelet therapy (aspirin or clopidogrel) has been shown in some instances to improve neurological outcome without a concomitant worsening of hemorrhage rates and is routinely used in EC-IC bypass surgery. Administration of in situ pharmacotherapy (e.g., heparinized saline, tPA) has also been used to reduce thrombosis within graft and recipient vessels. However, to our knowledge, there are no studies to date investigating in situ thrombolysis in intracranial bypass surgery or their impact on anastomotic patency.

Abciximab prevents thrombus formation by inhibiting platelet aggregation. Abciximab is an antagonist made from a chimeric mouse/human monoclonal antibody that targets the glycoprotein IIb/IIIa receptor on the platelet membrane responsible for binding fibrinogen; in doing so, platelet activation and endothelial adherence is precluded. As with other glycoprotein IIb/IIIa inhibitors, abciximab is not directly responsible for thrombolysis, but instead prevents aggregation of platelets. This prevents further growth and propagation of a thrombus and allows endogenous thrombolysis by the plasminogen/plasmin pathways. Abciximab has a plasma half-life of about 10 minutes; however, platelet aggregation returns to normal about 96–120 hours after discontinuation of the drug. Due to its strong affinity for the receptor on platelets, abciximab may occupy some receptors for weeks. The most common side effects are related to platelet dysfunction such as gastrointestinal bleeding.\(^6,22\)

Intravenous administration of abciximab is commonly used during cardiac interventions, such as angioplasty, atherectomy, and stent placement, to prevent platelets from aggregating and forming clots on intravascular devices. Abciximab has been associated with a decreased
incidence of ischemic complications and need for repeated coronary artery revascularization in the first month after the procedure. But, as with any medication that affects coagulation, intracranial hemorrhage complications are of the utmost concern. The hemorrhagic complication rates of abciximab have been studied extensively for coronary angioplasty and stenting and it appears that abciximab may have a safer profile than tPA with regard to intracranial hemorrhage. In a meta-analysis by Memon et al., the incidence of intracranial hemorrhage during percutaneous transluminal coronary angioplasty using abciximab was 0.12% compared with 0.3%–0.8% using conventional thrombolytics in several large, multicenter clinical studies, including the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial.

Successes with abciximab in the field of cardiology sparked interest for its use in other arenas. In neurosurgery, abciximab has been used to safely and effectively manage thromboembolic complications encountered during neuroendovascular procedures. It has been administered via intravenous and intraarterial routes, with some studies indicating no differences in efficacy and others indicating greater efficacy with intraarterial approaches. Intraarterial abciximab through directed microcatheter delivery has been used to successfully treat thrombotic complications during aneurysm coiling and also acute thrombus formation during Wingspan-Gateway (Boston Scientific) stent placement. In addition, abciximab has been used with good results in at least 1 case report to resolve an acute thrombus causing brain ischemia after carotid endarterectomy. A recent meta-analysis of intraoperative thromboembolic complications found that abciximab was associated with lower rates of short- and long-term morbidity when compared with fibrinolytics. Additionally, abciximab exhibited an increased trend toward higher recanalization rates.

Numerous studies have addressed the safety profile of abciximab in neuroendovascular interventions; some were case series with small cohort sizes. Nonetheless, many did not document a single event of periprocedural intracerebral hemorrhage (ICH). Others, however, have reported ICH rates ranging anywhere from 4% to 18%. The use of in situ thrombolytics after cerebral bypass could theoretically increase the likelihood for intracranial hemorrhage even though the dose administered in this case (2 mg) is substantially less than the standard intravenous loading dose of 0.25 mg/kg. While there is no data to support this presumption, the aforementioned instances of ICH and the premature termination of an international Phase III trial (AbESST-II study) involving abciximab use in acute ischemic stroke due to higher rates of fatal ICH serve as a cautionary reminder. Notwithstanding these risks, we believe that local in situ administration of abciximab is a useful addition to the surgical repertoire for addressing anastomotic occlusions during intracranial bypass surgery.

In our patient, in situ abciximab was used intraoperatively to restore flow across an STA-MCA bypass and was effective in contributing to a stable and patent anastomosis for at least 10 months after surgery. Fortunately, our patient did not suffer from some of the documented adverse risks of using abciximab, most worrisome of which is intracranial hemorrhage. Although we do not advocate the use of abciximab on a routine basis during intracranial bypass surgery, we believe that it is valuable as an adjunctive tool in restoring patency to an anastomosis in the bypass surgeon’s armamentarium.

References


Disclosures
The authors report no conflict of interest concerning the materi- als or methods used in this study or the findings specified in this paper.

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