Botulinum toxin to improve vessel graft patency in cerebral revascularization surgery: report of 3 cases

Ben A. Strickland, MD,¹ Robert C. Rennert, MD,² Joshua Bakhsheshian, MD,¹ Sebina Bulic, MD,³ Adrian J. Correa, MD,⁴ Arun Amar, MD,^{1,5} Joseph Carey, MD,⁶ and Jonathan J. Russin, MD⁷

Departments of ¹Neurosurgery, ³Neurology, ⁴Pathology, and ⁶Plastic Surgery; ⁵Zilkha Neurogenetic Institute; ⁷Neurorestoration Center, Department of Neurological Surgery, Keck School of Medicine, University of Southern California, Los Angeles; and ²Department of Neurosurgery, University of California at San Diego, California

Surgical revascularization continues to play an important role in the management of complex intracranial aneurysms and ischemic cerebrovascular disease. Graft spasm is a common complication of bypass procedures and can result in ischemia or graft thrombosis. The authors here report on the first clinical use of botulinum toxin to prevent graft spasm following extracranial-intracranial (EC-IC) bypass. This technique was used in 3 EC-IC bypass surgeries, 2 for symptomatic carotid artery occlusions and 1 for a ruptured basilar tip aneurysm. In all 3 cases, the harvested graft was treated *ex vivo* with botulinum toxin before the anastomosis was performed. Post-bypass vascular imaging demonstrated patency and the absence of spasm in all grafts. Histopathological analyses of treated vessels did not show any immediate endothelial or vessel wall damage. Postoperative angiograms were without graft spasm in all cases. Botulinum toxin may be a reasonable option for preventing graft spasm and maintaining patency in cerebral revascularization procedures.

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KEY WORDS botulinum toxin; revascularization; EC-IC bypass; graft patency; vascular disorders

FIRST described by Yasargil in 1967, extracranial-intracranial (EC-IC) bypass remains a valuable treatment modality for complex cerebral aneurysms and refractory symptomatic vessel occlusions.^{7,16,18} The maintenance of flow is critical to the success of bypass surgery, but it can be complicated by the need for interposition grafts connecting donor and recipient vessels due to the risk of vessel spasm and resultant thrombosis and/or ischemia.

While bypass grafts are typically selected based on flow capacity and size matching to recipient and donor vessels, the spasm risk and patency rates of different grafts are also considered.² Previous studies in the neurosurgical, plastic surgery, and cardiovascular literature have identified strategies to decrease the risk of graft spasm and/or thrombosis, including maintaining an elevated mean arterial pressure and using vasodilators in the immediate postoperative period, devoting attention to atraumatic graft harvests, and using antiplatelet agents.^{7,9,12,17,21,27–29} *Ex vivo* graft treatments with short-acting vasodilators prior to implantation have also been described,^{9,21} although no definitive spasm prevention strategy exists.

Botulinum toxin (BTX) is a powerful neurotoxin used safely in a multitude of clinical settings for muscle relaxation.²³ It has also been described for the prevention of arterial graft spasm in preclinical cardiovascular and plastic

surgery assessments,^{6,8,20,26} although no clinical data for this application exist. Herein, we report on the first clinical experience using BTX to prevent graft spasm in 3 patients who underwent EC-IC bypass. We also demonstrate, via histopathological analysis, the absence of any immediate endothelial or vessel wall damage from the BTX treatment.

Methods

Retrospective analysis of an IRB-approved, prospectively maintained database was performed to identify patients who had undergone EC-IC cerebral bypass surgery using grafts treated with BTX. Recorded information included patient demographics (age, sex), clinical presentation, and surgery performed, as well as imaging and neurological outcomes.

All procedures for vessel harvest and donor site anastomosis were performed by the senior author (J.J.R.) and a plastic surgeon (J.C.). Patients were considered for cerebral revascularization after conservative treatments had failed or if lesions were not amenable to traditional microsurgical or endovascular approaches. The revascularization strategy was planned through collaboration with the plastic surgery and neurosurgical teams. In all cases a descending branch of the lateral circumflex femoral artery

ABBREVIATIONS BTX = botulinum toxin; DLCFA = descending branch of the lateral circumflex femoral artery; EC-IC = extracranial-intracranial; ICA = internal carotid artery; MCA = middle cerebral artery; RA = radial artery; SAH = subarachnoid hemorrhage; STA = superficial temporal artery.

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FIG. 1. Case 1. Preoperative workup demonstrated left ICA occlusion with significant penumbral tissue. Lateral (A) and oblique (B) angiograms obtained in a 57-year-old man presenting with acute aphasia and hemiparesis, demonstrating a cervical left ICA occlusion. A CT angiography study (not shown) demonstrated vessel reconstitution beyond the ophthalmic segment. Axial diffusion-weighted (left, C) and perfusion-weighted (right, C) MRI studies demonstrated scattered anterior cerebral artery and MCA infarcts with a large ischemic penumbra in the left MCA distribution, as seen by (from left to right) increased mean transit times, decreased cerebral blood flow, and preserved cerebral blood volumes. Figure is available in color online only.

(DLCFA) graft was used as the bypass vessel, which was treated ex vivo with BTX before implantation. A small section of each treated (and untreated in 1 patient) DLCFA graft was collected and sent for histopathological analysis via standard H & E staining.

After the patient's right thigh was prepped and draped, a dissection plane between the rectus femoris and vastus lateralis muscles was developed. The DLCFA was dissected for approximately 10 cm using 3.0 nylon ties to ligate tributaries. The graft was ligated proximally and distally and then cut sharply and removed from the leg. The adventitia was removed, and the graft was flushed and then soaked using 100 U of BTX type A (Allergan Inc.) in 10 ml of normal saline for approximately 30 minutes. Before the graft was mobilized to the intracranial space, it was flushed with a heparin and milrinone solution, our standard graft irrigation solution consisting of 10,000 U of heparin with 10 mg of milrinone in 1 L of normal saline.

Results

Three patients, 2 for symptomatic carotid artery occlu-

sions and 1 for a ruptured basilar tip aneurysm, had undergone superficial temporal artery (STA) to middle cerebral artery (MCA) EC-IC bypass surgery utilizing DLCFA grafts treated ex vivo with BTX prior to implantation. The average patient age was 52.6 years, and all 3 patients were male. The bypass procedure was technically successful in all cases. None of the patients exhibited imaging or clinical signs of postoperative graft spasm. Histopathological analysis of the treated vessels demonstrated no endothelial or vessel wall injury.

Case Reports

Case 1

A 57-year-old man presented with the acute onset of dense mixed aphasia and right-sided paresis and was found to have a left internal carotid artery (ICA) occlusion. Preoperative CT angiography demonstrated occlusion of the cervical portion of the ICA with reconstitution beyond the ophthalmic segment (Fig. 1A and B). Perfusion-weighted MRI demonstrated scattered anterior cerebral artery and MCA infarcts with a large ischemic penumbra incorpo-

FIG. 2. Case 1. Postoperative imaging and histology demonstrated EC-IC graft health and the absence of spasm following ex vivo BTX treatment. Postoperative day 2 anteroposterior (A) and lateral (B) angiograms demonstrating a patent STA-MCA interposition graft (arrows) without evidence of spasm. Intrinsic left ICA flow is improved in these images because of partial endovascular treatment of the occlusion. A photomicrograph (C) of a portion of the DLCFA graft following BTX treatment demonstrated an intact endothelium and vessel muscular walls, with no structural deformities. H & E, original magnification $\times 100$. Figure is available in color online only.

rating the entire left MCA territory (Fig. 1C). An endovascular attempt to open the occluded vessel moderately improved ICA flow but was ultimately unsuccessful. An STA-MCA bypass with a BTX-treated DLCFA graft was performed. Postoperative MRI demonstrated no new ischemia, and angiography showed a patent graft without evidence of spasm (Fig. 2A and B). Histopathological analysis revealed no immediate effects of BTX treatment on the endothelium or vessel wall (Fig. 2C). The patient had an unremarkable postoperative hospital course before discharge to a rehabilitation facility. By the 4.5-month follow-up, he was residing at home, his speech was conversational, and his motor function had improved to being ambulatory without assistance (with stable right-sided upper extremity strength).

Case 2

A 45-year-old man presented with the acute onset of headaches and was found to have a subarachnoid hemorrhage (SAH) from a ruptured, broad-based, bilobed basilar tip aneurysm (Fig. 3). Angiography demonstrated bilateral carotid arteries that terminated in the ophthalmic arteries, and the intracranial circulation was entirely dependent on the basilar artery. Given the complicated morphology of the basilar tip aneurysm, we anticipated that he would

FIG. 3. Case 2. Preoperative vessel imaging demonstrated a large basilar tip aneurysm. CT angiography study obtained in a 45-year-old man following an SAH, demonstrating a broad-based, bilobed basilar tip aneurysm, with the patient's anterior circulation entirely dependent on the posterior communicating arteries. He was treated with an STA-MCA bypass with a BTX-treated DLCFA graft for revascularization of the anterior circulation in conjunction with clip ligation of the basilar tip aneurysm. Figure is available in color online only.

require temporary clipping of the basilar artery. He was, therefore, recommended for revascularization of the anterior circulation in conjunction with clip ligation of the basilar tip aneurysm. He underwent STA-MCA bypass with a BTX-treated DLCFA graft. Immediate postoperative CT angiography and postoperative day 11 angiography demonstrated a patent graft with no evidence of spasm (Fig. 4A and B). Graft histopathology demonstrated no immediate adverse effects of BTX treatment on the endothelium or vessel wall (Fig. 4C–F). The patient had an unremarkable postoperative recovery and was transferred to a rehabilitation facility once medically cleared. By the 2-month follow-up, he was living at home and remained neurologically intact.

Case 3

A 56-year-old man presented with acute left-sided weakness and was found to have a right ICA occlusion. His CT revealed perfusion deficits, and several attempts to wean him off of vasopressors failed with worsening left-sided weakness to the point of being barely antigravity. He underwent STA-MCA bypass with a BTX-treated DLCFA graft. His postoperative neurological exam was stable with blood pressure normalization. Postoperative CT angiography and conventional angiography demonstrated a patent bypass with no evidence of spasm (Fig. 5A and B) and improved right-sided perfusion. Graft histopathology demonstrated no evidence of endothelial or vessel wall injury

FIG. 4. Case 2. Postoperative angiography and histology demonstrated EC-IC graft health and the absence of spasm following BTX treatment. Postoperative day 11 anteroposterior (**A**) and lateral (**B**) angiograms demonstrating a patent STA-MCA with a DLCFA graft (arrows) that had been treated ex vivo with BTX. *Site of spasm on untreated distal STA at the clip site. Beginning of graft. A comparison of low-magnification and high-magnification images of untreated (**C** and **D**, respectively) and BTX-treated (**E** and **F**, respectively) portions of the DLCFA graft demonstrates integrity of the endothelium and vessel wall and no structural deformities after BTX treatment. Vasodilation was also noted in the treated sample. H & E, original magnification $\times 40$ (**C** and **E**), $\times 100$ (**D** and **F**). Figure is available in color online only.

(Fig. 5C and D). His remaining hospital course was unremarkable, and he had improving left-sided strength prior to discharge to a rehabilitation facility. By the 2-week follow-up, he was ambulatory in a rehabilitation facility with continued improvements in left-sided strength.

Discussion

Ensuring vessel patency is critical to the success of graft-based EC-IC bypass. Graft spasm represents a particularly challenging pathology given its potential to rapidly and severely alter blood flow. Historically, the 2 main options for cerebral bypass grafts have been the radial artery

(RA) and the saphenous vein.^{2,12,29} While there are advantages and disadvantages to both, RA grafts are generally preferred for EC-IC bypass given their higher overall patency rates and better donor-recipient vessel size matching. Nonetheless, RA grafts are at risk for spasm, an extreme smooth muscle-mediated vasoconstrictive response to mechanical or pharmacological stimuli, which can occur in up to 10% of cases.^{1,5,7,9} Other arterial grafts have also been described, such as the DLCFA graft that was used in the current series because of its closer size match to the donor STA, but are similarly susceptible to spasm.

When spasm occurs, treatment options include systemic anticoagulation, intraarterial injection of the cal-

FIG. 5. Case 3. Postoperative angiography and histology in a 56-year-old man treated using an STA-MCA bypass with a BTX-treated DLCFA graft for a progressively symptomatic, pressure-dependent right ICA occlusion. Day 4 postoperative anteroposterior (A) and lateral (B) angiograms demonstrated no spasm and graft patency. Arrows indicate the bypass graft. Site of STA-graft anastomosis. Low-magnification (C) and high-magnification (D) images of a portion of the BTX-treated DLCFA demonstrated no evidence of endothelial or vessel wall injury. H & E, original magnification $\times 40$ (C), $\times 100$ (D). Figure is available in color online only.

cium channel blocker verapamil and the antispasmodic papaverine, angioplasty, and local application of vasodilators.^{14,22} However, the prevention of graft spasm is the preferred strategy, and both mechanical and pharmacological prophylactic approaches have been described. As disruptions in the endothelium can lead to the release of spasmogenic agents, or spasmogens, such as endothelin and prostanoids, a meticulous surgical technique and preservation of the endothelium during graft harvest and implantation are important initial strategies for decreasing spasm risk.^{9,10} Preservation of the venae comitantes during harvest, along with both arterial and venous anastomoses, has also been suggested as a method of preserving the viability of tissues immediately surrounding the bypass graft,⁷ potentially decreasing spasm risk by reducing local oxidative stress.

Pharmacological prophylaxis of graft spasm is more robust in other surgical fields and typically involves treatment of the graft with a vasodilator prior to implantation,

along with postoperative systemic infusion of vasodilators. Protocols from the cardiovascular literature include ex vivo treatment with a verapamil plus nitroglycerin solution, often followed by the systemic administration of calcium channel blockers with or without long-acting nitrates.^{9,21} Other topical pharmacological agents, such as the synthetic prostacyclin iloprost and diltiazem, have also been explored.^{25,27} However, the half-lives of these therapies are minutes to hours, and efficacy data on these techniques are limited. A uniform ex vivo treatment and postoperative protocol for EC-IC bypass graft spasm prevention does not currently exist.

In this setting, BTX has been suggested as a potentially long-term spasmolytic for arterial grafts. This irreversible toxin, produced by the anaerobic, gram-positive bacterium *Clostridium botulinum*, consists of 7 distinct serotypes (A–G), with types A and B most often used in the clinical setting. While the primary mechanism of action of all BTX subtypes is through presynaptic cleavage of SNARE

FIG. 6. Angiograms (**A and B**) from previous cerebral bypass cases using DLCFA grafts, which were harvested in a manner similar to that in the featured cases, but without BTX treatment, demonstrating a susceptibility for postoperative vasospasm (arrows). When such vasospasm occurred, multiple rounds of intraarterial verapamil injections were typically needed for management. Figure is available in color online only.

(soluble NSF attachment protein receptor) proteins important for acetylcholine release into the synaptic terminal,⁴ the mechanism of its effects on arterial graft spasm is less clear, as neuronally mediated spasm of RA or DLCFA grafts is predominantly adrenergic.^{3,9,11} Secondary pathways are thus likely to contribute since the release of vasoconstricting catecholamines is also affected by BTX A–SNARE cleavage,¹⁹ and BTX A has been shown to

inhibit the presynaptic release of vasoconstricting agents like substance P, as well as to increase the concentration of vasodilating calcitonin-related peptides.^{13,30} Botulinum toxin C has also been shown to block the GTP-dependent phosphorylation of myosin light chains in vascular smooth muscle, inhibiting constriction.^{20,24} These mechanistic effects are probably occurring in the setting of neuronal hyperactivity proposed to result from surgical denervation.¹

To date, assessments of BTX for graft spasm prevention have been limited to preclinical cardiovascular and plastic surgery studies. In these works, in vivo rat perivascular pretreatments with BTX B augmented microvessel diameter prior to anastomosis,²⁶ and ex vivo treatment of rat aortas with BTX C resulted in the complete loss of adrenergic muscle contraction through the 2-hour study end point (significantly longer than the effect of papaverine).²⁰ In vivo perivascular pretreatment with BTX A was also shown to increase vessel diameter and decrease short-term thrombosis rates in rat and rabbit micro-anastomosis models.^{6,8} The arterial wall was not affected by the BTX treatment in any of these studies, and all in vivo treatments were well tolerated.

Thus, the present series represents the first clinical use of BTX for the prevention of arterial graft spasm and provides preliminary evidence for the safety and efficacy of this approach. The impetus for BTX use came from previous cases of severe spasm with DLCFA grafts at our institution, despite a meticulous surgical technique and postoperative blood flow optimization (Fig. 6). Following the ex vivo application of BTX A prior to DLCFA graft implantation in the featured cases, none of the patients exhibited either clinical or radiographic evidence of graft spasm over the short-term to midterm follow-up. As most severe arterial graft spasms occur within the first few days after implantation,^{10,15} delayed spasm in these patients is unlikely. Botulinum toxin A was chosen for application given its extensive clinical safety profile,²³ and histological analysis of the treated arteries revealed no short-term adverse effects on the endothelium or vessel wall. All 3 patients also had uneventful postoperative and outpatient courses. These data support the utility of BTX treatment for the prevention of arterial graft spasm for cerebral and other bypass applications.

Conclusions

Ex vivo BTX treatment represents an appealing method for the long-term prevention of bypass graft spasm. Initial cases have not revealed any clinical safety concerns, and radiographic appearances have been markedly improved compared with prior clinical experience. Further data are needed to elucidate the role of BTX treatment in revascularization procedures.

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Disclosures

The authors have no conflicts of interest.

Author Contributions

Conception and design: Strickland, Rennert, Bakhsheshian, Bulic, Correa, Russin. Acquisition of data: Strickland, Rennert, Bakhsheshian, Bulic, Russin. Analysis and interpretation of data: Strickland. Drafting the article: Strickland, Rennert, Bakhsheshian, Correa, Carey, Russin. Critically revising the article: Strickland, Rennert, Bakhsheshian, Correa, Amar, Carey, Russin. Reviewed submitted version of manuscript: Strickland, Rennert, Bakhsheshian, Bulic, Correa, Amar, Carey, Russin. Approved the final version of the manuscript on behalf of all authors: Strickland. Statistical analysis: Strickland. Administrative/technical/material support: Strickland. Study supervision: Strickland.

Correspondence

Ben A. Strickland: Keck School of Medicine of the University of Southern California, Los Angeles, CA. ben.strickland@med.usc.edu.