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Brief Insight about Botulinum toxin (BTX) and prevention of arterial spasm and post anastomotic thrombosis

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Abstract: Background: Botulinum toxin (BTX) presents a promising avenue for preventing arterial spasm and post-anastomotic thrombosis (PAT), significant complications following vascular surgery. Arterial spasm, characterized by involuntary constriction of arterial smooth muscle, impairs blood flow and can lead to ischemia and organ damage. PAT, the formation of a thrombus at the site of a vascular anastomosis, results in occlusion and potentially limb loss or death. Both complications share a common pathophysiological link: excessive smooth muscle contraction and platelet activation. BTX, a neurotoxin that inhibits acetylcholine release at neuromuscular junctions, effectively paralyzes smooth muscle by preventing its contraction. Preclinical studies demonstrate BTX's efficacy in reducing arterial spasm in various animal models by inhibiting vasoconstriction. Its application directly to the anastomotic site or regionally to surrounding tissues can prevent the spasm-induced reduction in blood flow crucial for successful healing. Moreover, BTX's impact extends beyond direct muscle paralysis. It modulates the inflammatory response, mitigating the release of pro-thrombotic factors and reducing platelet aggregation, thereby indirectly inhibiting PAT formation. The potential benefits of BTX extend to its ease of administration and localized effects, minimizing systemic side effects often associated with other antispasmodic agents. However, further research is crucial to optimize BTX's dosage, delivery method (e.g., direct injection versus regional block), and timing of administration for optimal efficacy. Large-scale clinical trials are needed to confirm its safety and efficacy in preventing arterial spasm and PAT in humans, particularly comparing its outcomes against established preventative strategies. Despite these necessary steps, BTX offers a novel and potentially transformative approach to improving outcomes in vascular surgery by mitigating these devastating complications. The targeted inhibition of smooth muscle contraction and its anti-inflammatory effects provide a compelling rationale for continued investigation into BTX as a preventative measure.

Keywords: *Botulinum toxin, arterial spasm, anastomotic thrombosis*

Introduction

Although vascular spasm is common, the causal mechanism is not completely understood [1]. Addressing vasospasm adequately is important clinically as it not only makes suture placement difficult but also causes a reduction in blood flow and an increased propensity for thrombus formation [1]. Both of which can result in tissue ischemia and flap failure [1]. Factors such as mechanical stretching of the vessel wall, endothelial damage, low ambient temperature, pH, anatomical location, and hematoma formation are thought to contribute to this phenomenon [1]. Spasm causes violent constriction of the vessels and also produces stasis; both factors are implicated in the thrombotic process [2]. Spasm can occur in sclerotic segments, and intimal tears and plaque ruptures in arteriosclerotic plaques are attributed to spasm [2]. The thrombus forms over the intimal disruption, abetted by the stasis of spasm, in arteries with mild to no intimal injury; continuing stasis over a period of time is considered the major factor in thrombus formation [2]. This ongoing stasis is attributed to an injury, as a spasm reaction to necrotic muscle and probably is equivalent to the no-reflow phenomenon of infarction [2].

Thrombosis in microsurgery can either totally or partially reduce perfusion to the free tissue transfer [3]. Total occlusion normally occurs at or near the microvascular anastomosis, while microscopic vasospasm in the distal microcirculation can account for malperfusion and wound healing problems [3]. The most common cause for failure of the free flap remains vascular thrombosis [4]. Its prevalence is evenly distributed among arterial, venous, and both [4]. Salvage rates decrease precipitously to 15 percent when both conduits thrombose [4]. Two factors contributing to a difficult anastomosis include vasospasm, traumatized recipient vessels within the zone of injury, radiation, scar, and infection [4]. Thrombosis, when it occurs, typically does so within the first 2 days in 80 percent of patients [4]. Techniques used to prevent vasospasm and thrombosis include abstinence from vasopressors during procedures, limited intraoperative manipulation of vessels, serosal stripping of sympathetic fibers from vessels, and warming protocols postoperatively [4].

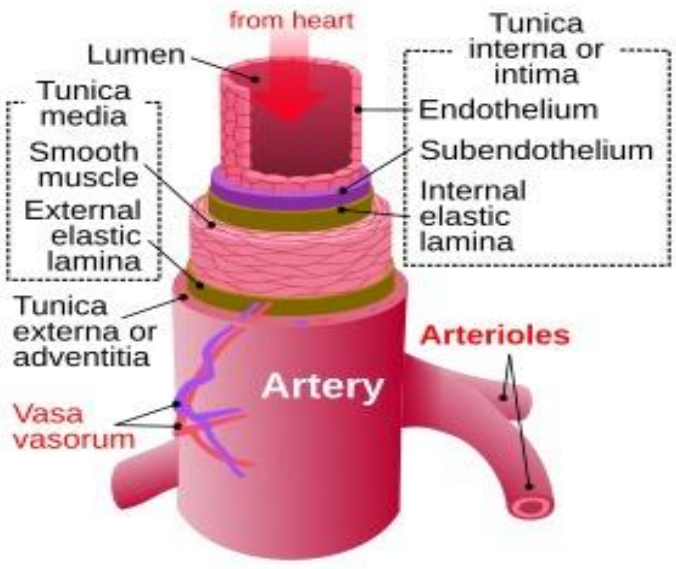

Fig. 1 : Artery layers [4].

Many of these techniques are used to prevent sympathetically mediated vasospasm [5]. The use of periarterial sympathectomy to manage chronic digital ischemia in Raynaud's phenomenon is well established [5]. Raynaud's phenomenon is marked by numbness, chronic pain, and extreme cold intolerance [5]. Conservative

therapies include cessation of smoking, avoidance of cold exposure, and avoidance of caffeinated beverages and chocolate [5].

There are different medications used to prevent or decrease the incidence of post-anastomotic thrombosis. These medications include:

Heparin: Heparin is an anticoagulant produced by basophils and mast cells that prevents the formation of new clots and the growth of existing clots in blood vessels [6]. Heparin prevents clot formation by binding to the enzyme inhibitor antithrombin III, which in turn inactivates thrombin and other proteases involved in blood clotting [6]. Clinically, heparin is used in its low-molecular-weight forms to prevent clot formation in a variety of different disease states [6]. Since heparin does not break down pre-existing clots but instead prevents new clots from forming, in microsurgery it is administered preoperatively to prevent clot formation at the site of vessel anastomosis [7]. In a rat model, the antithrombotic effect of heparin at an anastomosis by inserting a venous catheter proximal to the repaired vessel and found 100% of free flaps survived compared to 90% in controls [7]. Local irrigation for 10 min may enhance vessel patency or at least decrease side effects compared to systemic application, but high irrigation pressure (<100 mm Hg) must be avoided so as not to injure the endothelium [7]. Both UFH and LMWH are known to have antithrombin III-independent effects [8]. This may explain why study results differ in the debate of whether LMWH is as effective on arterial thrombosis as UFH [8]. Summarizing, heparin and LMWH have been shown to reduce the prevalence of venous and arterial thrombosis by approximately 50-60% when compared to no anticoagulation [8]. Compared to aspirin or dextran, the bleeding risk is highest among heparin, and overall LMWH shows fewer side effects than UFH [8].

Aspirin: Acetylsalicylic acid irreversibly blocks cyclooxygenase, which normally produces thromboxane and other procoagulatory factors that activate platelets [9]. We will focus on aspirin administration in microsurgery clinical studies here. Although aspirin inhibits platelet function more effectively than heparin, and preoperative administration has been shown to prevent both arterial and venous thrombosis, it is less effective than heparin in preventing clot formation at the site of vessel anastomosis [9].

Dextran/Hydroxyphenylacetate: Dextran is used as an antithrombotic (antiplatelet) to reduce blood viscosity and as a volume expander in anemia [10]. Dextran and hydroxyphenylacetate both are used for their antiplatelet and antifibrin effect, which occur via cell coating or their inhibition of α2-antiplasmin effects [10]. Dextran has not gained widespread use in microsurgery [10].

Thrombolytic or Fibrinolytic Drugs: Like heparin and aspirin, fibrinolytic drugs (streptokinase, alteplase, reteplase, and tenecteplase) are used to treat a variety of different disease states in which thrombosis is a risk [11]. However, different from heparin and aspirin, these agents are able to dissolve existing clots [11]. These drugs have been found to be most effective when administered within the first 60 min after a thrombotic event [11]. They are often administered in combination with other anticoagulant drugs, such as intravenous heparin or LMWH, for synergistic antithrombotic effects and secondary prevention [11]. Due to the limited number of well-controlled trials, there are no definitive conclusive results regarding efficacy and appropriate dosing [12].

Less Commonly Used Drugs: Pentoxifylline has been shown to improve microcirculatory perfusion and oxygenation in free flaps due to its effect of improving blood viscosity [13]. It has been described as being most effective when administration is begun 2 weeks prior to surgery [13]. Pentoxifylline has been shown to significantly improve arterial patency [13]. Other clinically available antithrombotic agents are iloprost, a synthetic analogue of prostacyclin (prostaglandin I2), hirudin, which is extracted from the saliva of leeches and

can inactivate thrombin antithrombin III, and ketorolac, a nonsteroidal anti-inflammatory drug in the family of heterocyclic acetic acid derivatives that acts by inhibiting the body's synthesis of prostaglandins [13].

Clopidogrel Use for Reducing the Rate of Thrombosis in a Rat Model of Microarterial Anastomosis: Clopidogrel bisulfate (Plavix) is a relatively new oral antiplatelet agent that inhibits adenosine diphosphate–induced platelet activation by irreversibly antagonizing the binding of this potent agonist to its receptor [14]. Clopidogrel has shown efficacy in preventing thrombosis in clinical settings [14]. Clopidogrel has also been shown to decrease the rate of thrombosis in an animal model [14]. Considering its improved efficacy over aspirin, which is routinely used by some microvascular surgeons in free tissue transfer, clopidogrel may be useful in the prevention of thrombosis in anastomotic vessels [14]. The four characteristics of the ideal animal model of microvascular anastomosis have been defined by Kersh et al. First, a permanent vascular modification should be made to provide a continued source of thrombogenesis. Second, the model should mimic clinical repair. Third, the diameter of the vessels should measure between 1 to 3 mm to allow for complete occlusion by a thrombus. Finally, thrombus formation should be gradual [15].

Topically used medications to reduce the incidence of arterial spasm and post-anastomotic thrombosis:

Papaverine: Early studies reported a traditional topical vasodilator, papaverine, with satisfactory results [16]. Papaverine is an opioid derivative and a non-specific vasodilator substance that relaxes blood vessels through several mechanisms, including inhibiting phosphodiesterase (PDE) and decreasing calcium influx or inhibiting the release of intracellularly stored calcium [16]. However, papaverine is not recommended for systemic use [16]. The major concern of the topical use of papaverine is its acidic nature, which may damage endothelial function [16]. A common clinical protocol to topically use papaverine is to mix papaverine with blood (intraluminal 1% papaverine in blood), which may reduce its acidity owing to the buffering effect of blood [16]. In addition, the onset of the vasodilation effect of papaverine is slower than with other vasodilators [16].

Lidocaine: Lidocaine is the most commonly used drug for local anesthesia; in addition to having analgesic properties, it is also considered to be a locally acting vasodilator at clinically relevant doses [17]. The vasodilator properties of lidocaine are believed to be due mainly to the inhibition of action potentials via sodium channel blocking in vasoconstrictor sympathetic nerves [17]. It is hypothesized that the vasodilator properties of lidocaine might also be mediated partly via another vascular pathway: by a direct effect on the β-adrenoreceptors of vascular smooth muscles, by modulating the release of adrenaline from vasodilator nerves and/or by stimulating the vascular endothelium to produce vasodilators such as nitric oxide or prostaglandins [11].

Physical methods used to reduce the incidence of arterial spasm and post-anastomotic thrombosis:

Warming: Vasodilation occurs naturally in the body in response to triggers such as low oxygen levels, a decrease in available nutrients, and an increase in temperature (warming) [8]. It causes widening of blood vessels, which in turn increases blood flow [8]. Warming/heating inhibits the tonic activity of the vasoconstrictor nerves through reflexes initiated by elevated temperature [8]. As heating increases in duration and internal temperature increases, the sympathetic cholinergic active vasodilator system is activated [8].

Botulinum toxin (BTX) and prevention of arterial spasm and post anastomotic thrombosis

Most clinicians are familiar with the blockade of acetylcholine release when botulinum toxin (BTX) is administered into skeletal muscle to treat spasticity [18]. In skeletal muscle, the effects of BTX are delayed in onset by 1 week and then last several months [18]. However, it is less well recognized that BTX also blocks the synaptic release of norepinephrine-containing vesicles [18]. The onset of action for norepinephrine-mediated vascular effects appears to be more rapid than for acetylcholine-mediated skeletal muscle effects [18]. The prevention of norepinephrine release acts as a sustained sympathetic blockade that can decrease pain as seen in complex regional pain syndrome type 2 [18]. Furthermore, BTX alters the expression of vascular mediators and promotes angiogenesis [18].

Botulinum toxin type A is vacuum-dried as a lyophilized powder that needs to be reconstituted in saline and has three available forms: Botox (onabotulinumtoxinA): Allergan, Madison, New Jersey; Xeomin (incobotulinumtoxinA): Merz Pharma, Raleigh, North Carolina; and Dysport (abobotulinumtoxinA): Ipsen, Cambridge, Massachusetts [19]. Botulinum toxin type B comes prepared as a pH-reduced liquid and has one form known as Myobloc (rimabotulinumtoxinB): Supernus Pharmaceuticals, Rockville, Maryland [19]. Botulinum toxin type A has been used in humans to treat ischemic pain and ulceration in severe peripheral artery vasospasm (Raynaud's) most commonly due to autoimmune diseases [19]. However, the use of subcutaneous perivascular injection of BTX-A to treat chronic vasospasm is often a last resort salvage technique rather than being considered as an early or potentially disease-modifying intervention [19]. This may be due to two major factors: (1) absence of a Food and Drug Administration (FDA)-approved indication for BTX administration to treat vasospasm; and (2) lack of awareness of its mechanism of action and vascular effects [19].

Perivascular BTX-A and BTX-B administration improves perfusion, increases arterial and venous dilation, reduces thrombosis, and improves both random pattern and pedicled flap survival in critical ischemic models [20]. In animal models when BTX is administered concurrently with the procedure or as pretreatment, the vascular benefits occur rapidly in as little as several minutes and can be sustained for several weeks [20]. This is substantially longer than other common vasoactive substances such as papaverine or local anesthetics that last for only a few hours [20]. During most vascular surgeries, vessel clamps are applied to control bleeding, permitting a "dry" repair with improved visualization [21]. Prior to clamp application, proximal and distal vessels are pharmacologically prepared by intraluminal heparinized saline to try reducing thrombosis and may be irrigated on their exterior surface with papaverine, lidocaine, or bupivacaine [21]. Additional pharmacologic augmentation with external vessel BTX irrigation could prevent subtle clamp-related endothelial injury that may increase the risk of vasospasm and thrombosis [21]. This was observed in a standard model for crush injury in the rat femoral artery that demonstrated the antithrombotic effect of perivascular BTX-A injection and maintenance of pulsatile bleeding [21].

One of the major reasons for thrombosis is sustained vasospasm [22]. There was a 62% absolute risk reduction of thrombosis within both arteries and veins following BTX administration when compared with saline control [22]. Botulinum toxin–mediated vasospasm and thrombosis prevention have been demonstrated in humans [22]. This has been observed clinically in a double-toe transplant that was complicated by repetitive

postoperative vasospasm and thrombosis where the toes were ultimately salvaged with the use of BTX at the time of a second revision vein grafting [22]. This case report demonstrates that administration of BTX concurrently with vascular repair in humans could be beneficial [22]. Botulinum toxin prevented vasospasm during clinical cerebral vascular bypass surgery in a small case series showing no graft vasospasm in postoperative angiograms [22]. Histopathologic examination of portions of the excess harvested vessels did not show any evidence of injury from BTX exposure [22]. Further evidence of beneficial vascular effects of BTX was resistance to thrombosis after vascular repair even when post-repair vessels are purposely subjected to extreme vasospastic challenge by ice water immersion and concomitant systemic phenylephrine administration [22].

Beneficial vascular effects of BTX have been demonstrated in human clinical trials [23]. Botulinum toxin has an FDA-approved indication for use in preventing and treating chronic migraine headaches, which have a vascular etiology [23]. Multiple studies have shown BTX-A reduces ischemic pain, improves ulcer healing, and reduces Raynaud's attack frequency and severity, demonstrating efficacy in the treatment of peripheral artery vasospasm [23]. Thus, based on this animal review and human studies, it is conceivable that BTX, like heparin or papaverine, may become standard in human clinical posttraumatic vessel repair, microvascular free flap anastomoses, and cardiac and peripheral artery bypass surgeries [23]. Topical BTX-A irrigation may make vessel repairs easier and protect the vessels and anastomoses from postoperative vasospasm and thrombosis [23]. This was demonstrated in a recent human radial artery graft study that determined BTX-A inhibits both endothelin-1– and 5-hydroxytryptamine–induced contractions [23]. Furthermore, the effectiveness of BTX-A, unlike papaverine, did not decrease over time [23]. Finally, a clinical study that compared six patients with one or more ischemic fingers managed without BTX showed an 83% amputation rate compared with five patients with ischemic fingers managed with BTX, which showed a 0% amputation rate [23].

Botulinum toxin type A has also been shown to prevent the release of norepinephrine at the neuromuscular junction and subsequently prevented sympathetic vasoconstriction of vascular smooth muscle [24]. Norepinephrine vesicles were blocked from release at the neuromuscular junction [24]. Vasoconstriction is also dependent on the recruitment of specific alpha 2 receptors (alpha 2c) involving a phospholipase D pathway that is completely blocked by botulinum toxin [24]. Consequently, it has been theorized that botulinum toxin type A may inhibit vasospasm by two mechanisms: by blocking sympathetically mediated cold-induced vasoconstriction and by preventing recruitment of alpha 2 receptors in vascular smooth muscle [24]. Further studies have shown increased blood flow, muscle perfusion, and glucose uptake after the administration of botulinum toxin [24]

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