Pharmacologic Optimization of Microsurgery in the New Millennium

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Learning Objectives: After studying this article, the participant should be able to: 1. Understand the mechanisms by which the three most common antithrombotic agents work. 2. Be familiar with accepted dosing levels for the three agents. 3. Understand the rationale for their use and formulate an algorithmic approach to microvascular thrombosis.

Microsurgical anastomoses are largely technically dependent; however, there exists a finite rate of failure, with often devastating consequences. Pharmacologic prophylaxis and intervention are used extensively in microsurgical cases, yet a unified algorithm does not exist among the various basic science and clinical studies in the literature. This results in a confusing and nonstandardized practice based on anecdotal experiences. The purpose of this article is to review the literature on this topic and synthesize a practical clinical management algorithm for pharmacologic therapy in microsurgery. (Plast. Reconstr. Surg. 108: 2088, 2001.)

The advent of microsurgery has opened new doors and hope for many plastic surgery patients. Microsurgical failure rates vary from 5 to 10 percent of free flaps and 15 to 30 percent of replants. Surgical technique is the single most important factor in patency1;2; however, various pharmacologic therapies have been proposed in an attempt to improve on anastomatic success. Along this theme, microvascular thrombosis has an alterable etiology for failure, addressing Virchow’s triad of stasis, hypercoagulability, and vessel injury. More than 21 pharmacological agents have been used; however, aspirin, heparin, and dextran remain the mainstays of treatment. Numerous animal studies and few prospective clinical studies characterize the literature, with no consensus on treatment guidelines. Despite the lack of unified science, pharmacologic therapy is often practiced on the basis of anecdotal experience, with often marked differences in agents, dosing, and timing. The purpose of this study was to review the literature and develop a tangible clinical management algorithm for pharmacological treatments in microsurgery.

LITERATURE REVIEW

Aspirin

Aspirin is an antiplatelet agent that acetylates cyclooxygenase and decreases the products of arachidonic acid metabolism, including thromboxane, a potent platelet aggregator and vasoconstrictor; and prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. Thromboxane is produced by platelet-derived cyclooxygenase, whereas prostacyclin is produced from endothelial cyclooxygenase. The minimal dose for complete suppression of thromboxane in humans is reported at 100 mg, although this is not on a per-weight basis.3-6 Aspirin decreases graft occlusion among patients who have had a range of vascular procedures, as seen in the Anti-Platelet Trialists Collaboration, with similar benefit if administered preoperatively or within 24 hours after surgery.7 Chewing produces the most rapid method for effective anticoagulation.8

The optimal dosing regimen of aspirin to selectively inhibit thromboxane while preserving prostacyclin function is debated; however, it is likely that low doses of enteric-coated aspirin (50 to 100 mg) inhibit platelet cyclooxygenase production of thromboxane, with minimal
inhibition of endothelial-derived production of prostacyclin. At higher doses, both thromboxane and prostacyclin are inhibited, and it is likely that the beneficial results at these high doses (up to 1300 mg a day) are seen because the benefits of inhibiting thromboxane outweigh the detriments of inhibiting prostacyclin. These data are not determined on a per-weight basis but are presumably based on a 70-kg adult. Lower-dose aspirin (81 and 325 mg) has shown to be more effective in reducing stroke, myocardial infarction, and death within 30 days and 3 months of endarterectomy than are higher doses (650 and 1300 mg). Although patency was not addressed in this study, this fact further supports the clinical efficacy of lower dosing of aspirin and may reflect less inhibition of prostacyclin levels relative to thromboxane at the molecular level.

The side effects of aspirin include bleeding, salicylate toxicity, gastritis, and renal failure.

**Heparin**

Heparin, originally discovered by McLean in 1916, is an antifibrin agent that targets the fibrin lattice that connects platelets together. Our present understanding of unfractionated heparin is that approximately one-third of it binds to antithrombin III (ATIII), which produces conformational changes converting ATIII from a slow inhibitor of coagulation enzymes to a more rapid one. The heparin/ATIII complex inactivates the coagulation factors XIIa, Xla, IXa, Xa, and IIa (thrombin). The inhibition of thrombin and, subsequently, the inhibition of thrombin-induced activation of factor V and factor VIII are primarily responsible for its anticoagulant effect.

Heparin is useful for both arterial and venous thrombi. Arterial thrombi, which usually form in areas of high or disturbed flow or at sites of plaque rupture, are formed primarily of platelet aggregates bound together by thin fibrin strands; thus both the coagulation cascade and platelet activation are important in its thrombogenesis. Venous thrombi, on the other hand, form in areas of stasis and are formed primarily by red cells and fibrin and less so by platelets; thus the coagulation cascade plays a much more prominent role than platelet activation in its etiology. Thus heparin possesses properties to prevent both platelet-induced (arterial) and coagulation-induced (venous) thrombi.

In the Heparin-Aspirin Reperfusion Trial, investigators compared heparin treatment to treatment with 80 mg of aspirin in 205 patients and concluded that heparin was more effective than aspirin in maintaining coronary artery patency, with 82 percent of heparin-treated vessels patent at 18 hours compared with only 52 percent using aspirin (p < 0.0002). These results have been challenged, and the aspirin dose may have been suboptimal, because 100 mg of aspirin maximally suppresses thromboxane A2 production and preserves prostacyclin. Bleich et al. compared subjects treated with heparin to control subjects, showing that treatment with heparin resulted in improved coronary artery patency after thrombolysis, with 71 percent patency at 48 hours in the heparin arm compared with just 44 percent in the controls (p < 0.023).

The relative contributions of platelet and fibrin to thrombus are speculative. Khouri et al. attempted to selectively inhibit the “platelet aggregation” pathway versus the coagulation cascade (fibrin formation) in a rat model to determine the relative contribution to anastomotic thrombosis. Inhibition of platelet aggregation had minimal effects in improving the patency rate, because fibrin alone could still form an occlusive thrombus in the absence of platelet aggregation. This is supported by other investigators’ findings and leads to fibrin formation via the coagulation cascade as a central figure in thrombus formation.

In the rabbit arterial inversion model, Greenberg et al. demonstrated that a 72-hour heparin infusion (with bolus) initiated before microvascular clamp release (with the APTT maintained at 2.5 to 3.75 times normal) resulted in a statistically significant increase in microvascular patency 7 days after surgery when compared with the results using normal saline infusion in control subjects (67 percent versus 19 percent, p < 0.05). Additionally, scanning electron microscopy revealed significantly less dense fibrin deposition and a decrease in the number of platelet aggregates in the heparin-perfused grafts. The hematoma rate in these grafts was 3 percent.

Khoury et al. compared antiplatelet agents versus heparin versus controls in the traumatized rat common femoral artery, and found that heparin effectively prevented both artery and vein occlusion (when therapeutic) compared with antiplatelet agents or controls.

Debate continues over the use of topical ver-
sus systemic heparin. Johnson and Barker reported that clot-bound thrombin is resistant to the systemic doses of heparin that may be safely used and thus the risks of bleeding do not warrant an intravenous bolus at the time of anastomosis completion. However, they submit a local irrigant dose of at least 50 U/ml does help prevent thrombosis without systemic side effects. Similar reports have described beneficial results with a topical irrigant solution of 100 U/ml, whereas topical solutions of 250 U/ml have been shown to alter the partial thromboplastin time.

A topical local irrigant of heparin 100 U/ml is advocated in Das and Miller’s review in 1994, who suggested that heparinized saline irrigation at a concentration of 100 U/ml has an effect on thrombus formation.

Conversely, Rumbolo et al. showed no patency benefit by topical agents, including heparin and urokinase, at 7 days. In the largest prospective review of free flaps and the determinants of success or failure by Khouri et al., topical heparin was not shown to have a significant effect on flap outcome.

Regarding systemic heparinization, the microvascular surgery literature recommends intraoperative anticoagulation with 100 to 150 U/kg of intravenous heparin before cross clamping, supplemented with 50 U/kg every 45 to 50 minutes until anastomosis and the reestablishment of flow. Use of intraoperative anticoagulation during microsurgery is supported by Vlastou and Earle, who found improved patency in the rabbit model with an intraoperative bolus of 1000 U of intravenous heparin before clamp removal. Anticoagulation with a single dose of 160 U/kg administered 10 minutes before clamp release is supported by improved patency in a rat crush/avulsion model, in which larger doses were associated with an unacceptable rate of hematoma formation.

Heparin is effective at preventing thrombosis. However, hematoma and bleeding are significant complications that preclude its routine clinical use other than as an intraoperative bolus and topical irrigating agent; Pugh et al. showed this to be true because of the high rate of hematoma formation (66 percent) reported in their retrospective study of lower-leg reconstruction when used alone or in combination with other drugs.

Dextran

Dextran, a heterogeneous polysaccharide synthesized from sucrose by the *Leuconostoc mesenteroides* bacterium, is produced as a 40,000 or 70,000 molecular weight polymer. Dextran has shown efficacy in bypass grafts and pancreatic transplants. Its five mechanisms of action include (1) increasing the electronegativity on platelets and endothelium, thus preventing platelet aggregation; (2) modifying the structure of fibrin, making it more susceptible to degradation; (3) inhibiting alpha-2 antiplasmin and subsequently activating plasminogen; (4) decreasing factor VIII and von Willebrand factor, thereby decreasing platelet function; and (5) altering the rheologic properties of blood and acting as a volume expander.

Because of the potential antigenicity of dextran, some authors recommend administering dextran 1 first as 20 ml of 150 mg/ml solution (or 0.3 ml/kg body weight in children) 1 to 2 minutes before an infusion of dextran 40 is administered, although this is not commonly practiced in our institution.

In microvascular anastomosis, a single preoperative bolus of dextran has shown improved patency in the immediate postoperative period; however, its long-term effect on patency is debatable, as determined from conflicting results in the literature. Salemark et al. used an arteriotomy and intimectomy system in the rabbit with clinically analogous doses of 0.7 ml/kg per hour, corresponding to a human dose of approximately 50 ml per hour in a 70-kg man, and found no long-term significant improvement in patency. In contrast, Rothkopf et al. used slightly more than 2 cc per hour of dextran 40 in rabbits for 5 days after performing arterial inversion grafts, resulting in improved patency and decreased platelet and fibrin deposits as shown in electron micrographs.

A retrospective clinical review of replants and revascularization by Pomerance et al. reveals a favorable experience with dextran (500 cc/24 hours) and aspirin (10 grains twice a day to approximately 648 mg twice a day) treatment initiated after anastomosis and continued for at least 3 days after surgery. However, the lack of controls or prospective data characterizes the clinical studies of dextran and other antithrombotic agents. Despite the experimental and retrospective clinical data, there are no prospective randomized clinical trials.
that document improved free-flap survival with dextran treatment.

**Thrombolytics**

Thrombolytic agents include tissue-type plasminogen activator, urokinase, and streptokinase. Tissue-type plasminogen activator, a locally active thrombolytic agent, has shown promising results in animal models and in clinical salvage therapy involving microsurgical anastomosis. Streptokinase and urokinase have been used as well, with good results in local thrombolytic therapy. Schubert et al. described the first use of intraoperative streptokinase to salvage a free flap, having used 7500 units of streptokinase and having drained the venous effluent to prevent systemic effects. For an established thrombus, urokinase delivered intraarterially has shown a statistically significant improvement in patency versus heparin or dextran. The risks of bleeding secondary to lytic agents must be carefully considered before their use but may be minimized by venting the venous effluent to prevent systemic exposure to the agent.

**Treatment Guidelines**

In the largest multicenter prospective study of free-tissue transfer, Khouri et al. reported that only postoperative subcutaneous heparin treatment had a statistically significant effect on preventing thrombosis. Although they recognize experimental evidence which shows that heparinized irrigation has a beneficial result in preventing thrombosis, the data from Khouri et al. have support no benefit to the use of heparin irrigation or other pharmacological interventions in the practices of 23 different surgeons. In 1982, in a world survey of anticoagulation practice used before, during and after surgery, Davies et al. revealed no consistent protocols and thus concluded that statistical analysis was impossible. In general, they that found free flaps had equal outcomes with and without pharmacological intervention, whereas replants had better outcomes without pharmacological intervention.

Johnson and Barker reviewed the mechanisms of coagulation and zones of the anastomosis and recommend prophylaxis to prevent thrombotic tendencies postoperatively in the event of a hypercoagulable or hypotensive state. They recommended dextran as the ideal prophylactic agent because it addresses both platelets and fibrin. Dextran is first given as a test dose (less than 5 ml of dilute dextran) with monitoring for a “rash or other adverse sequelae,” then as a 40-ml loading dose before the clamps are released, and then at a rate of 25 ml/hour for 5 days (no per-weight dosing was provided). If a white clot, which is indicative of platelet aggregation, is seen during the procedure, aspirin is administered (dose unspecified). An established thrombus is mechanically removed if possible or a fibrinolytic agent is used if the thrombus is more distal, with subsequent heparinization to twice the normal partial thromboplastin time. If systemic heparinization fails, local delivery of fibrinolytics is recommended. The authors did not provide guidelines for the duration of treatment.

Pugh et al. coincided with Johnson and Barker in recommending dextran prophylactically as a single intraoperative dose, with heparin reserved for complications. Similarly, Buckley et al. made treatment recommendations on the basis of a rat thrombosis model in which the best results were achieved with dextran and heparin, although heparin was associated with hematoma formation. The authors recommended treatment with 500 ml of dextran 40 over 3 hours before anastomosis, then 500 ml throughout each 24-hour period (approximately 21 ml per hour) for 3 days and heparinized saline 100 U/ml intraoperatively as a topical agent. In their study, poor results were achieved from treatment with aspirin, possibly because the relatively large dose used (30 mg/kg), which would correspond with a human equivalent of 2100 mg, inhibited prostacyclin and thromboxane.

In a study of 43 free flaps and replants, Vreotos and Tsavissis reported good results with a postoperative multidrug treatment regimen that included 330 mg of aspirin, 75 mg of dipyridamole, 440 ml of low molecular weight dextran in two doses, 60,000 IU streptokinase, 1500 IU streptodornase, and 100 mg of diclofenac.

In a retrospective study, Kroll et al. showed that low-dose heparin used clinically with an intraoperative bolus of 2000 to 3000 units followed by 100 to 400 units per hour for 5 to 7 days was not associated with increased rates of hematoma or transfusion requirements, whereas higher doses of 5000 to 10000 units per hour followed by 500 to 1200 units per hour resulted in higher rates of hematoma (6.7 percent versus 20 percent, respectively). Although they did not attempt to show beneficial
The diversity and frank discrepancy in the management and usage of pharmacologic agents in microsurgery is profound. Our recommendations are based on a critical review of the literature and our experience, which encompasses more than 300 replants and 500 free flaps performed during the period from 1991 to 2000. In this study, an algorithm is presented, with dosing performed on a per-kilogram basis. Adequate hydration is an important element of our treatment regimen to prevent vasoconstriction and lower blood viscosity. A number of untoward effects, including pulmonary edema, acute respiratory distress syndrome, and anaphylaxis are reported in the literature. Our experience with the use of dextran with free flaps has resulted in several cases of volume overload and pulmonary edema as well, particularly in patients over 50 years of age, and has thus limited our use of dextran with free flaps; however, in the young and otherwise healthy replant patient, we use dextran prophylactically with vigilance and caution. The theoretical advantages of selective inhibition of thromboxane over prostacyclin by low-dose aspirin (approximately 100 mg) is appealing and is a standard part of our regimen. Enteric-coated aspirin taken preoperatively theoretically allows the inhibition of platelets in the portal circulation because of the hepatic inactivation of aspirin, with minimal exposure to and thus inhibition of endothelial cyclooxygenase. A low dose is also appealing in terms of reduced side effects. Two weeks was chosen as the treatment time because it is the time period required for new endothelium to cover the anastomosis. We use heparin intraoperatively as a local topical agent at a dose of 100 U/ml and administer a single bolus of 80 U/kg before clamp removal. However, in the case of a complicated anastomosis or the presence of thrombi, systemic heparin is used postoperatively, with the goal of an activated partial thromboplastin time of 1.5 to 2 times normal. Other mechanisms for improved patency include the use of thorazine and lidocaine. Thorazine is reportedly a potent vasodilator and may have a role as an oral medication. Topical lidocaine has been shown to have a vasodilatory role without significant hemodynamic repercussions and is commonly used in our practice as a 20% solution on cotton pledgets. In a number of cases, we have also used an indwelling axillary or epidural catheter for analgesia, decreased muscle spasms, and decreased vasospasms as suggested by Berger et al. and Matsuda et al.

Microsurgery Algorithm

Replant. The following microsurgery algorithm is provided for replants (Fig. 1):

- Chewed loading dose of 1.4 mg/kg (100 mg in the 70-kg adult) of enteric-coated aspirin preoperatively followed by a dosage of 1.4 mg/kg per day for 2 weeks (aspirin is usually available as 325 mg; therefore, the pharmacist may be of assistance in providing an appropriate dose)
- Heparinized saline (100 U/ml) as a local irrigant
- Intravenous heparin bolus intraoperatively at 50 to 100 U/kg just before the release of microvascular clamps
- A test dose of dextran as per Johnson and Barker (<5 ml of a dilute solution) is recommended, with dextran 1 reserved for preventing allergic reactions in potential patients. Intraoperatively, dextran 40 is administered at a dose of 0.4 cc per kg per hour. The dose is cut in half on postoperative days 3 and 4, and weaned off on postoperative day 5.
- Lactated Ringer’s solution administered for 3 days at 125 to 150 percent of maintenance levels (as vigilance for clinical volume overload in patients older than 50 years of age)
- Continual warm local environment for the replant patient (by modified room temperature and/or the use of an air-warming blanket around the treated extremity)

Free flap. The following algorithm is provided for free flaps (Fig. 2):

- Chewed loading dose of 1.4 mg/kg of enteric-coated aspirin postoperatively followed by a dosage of 1.4 mg/kg per day for 2 weeks
- Heparinized saline (100 U/ml) as a local irrigant
- Intravenous heparin bolus intraoperatively at 50 to 100 U/kg just before the release of microvascular clamps
Chewed loading dose of enteric-coated aspirin 1.4 mg/kg preoperatively, then 1.4 mg/kg per day for 2 weeks

Heparinized saline as local irrigant 100U/ml

Heparin bolus intraoperatively 40U/kg just prior to release of clamps

Dextran: initial dose of Dextran 1 (see text) then Dextran 40

Lactated Ringer's for 3 days

Warm environment

Fig. 1. Algorithm for replant prophylaxis and failure protocol.

- Lactated Ringer's solution administered for 3 days at 125 to 150 percent of maintenance levels (as vigilance for clinical volume overload in patients older than 50 years of age)

The clinical examination is the mainstay of our postoperative monitoring regimen, with capillary refill, warmth, color, Doppler flow, and pin-prick examinations performed daily.

In replant patients, signs of venous insufficiency—including blue color, swelling, rapid capillary refill, or dark blood—warrant consideration for revision. If dressing removal, suture release, and elevation fail and the surgeon feels that the anastomosis may be implicated in the complications, revision of the venous anastomosis is then performed. The original preoperative regimen is then resumed, with the addition of heparin IV to prolong the partial thromboplastin time 1.5 to 2 times normal for 5 days. This dosage is gradually tapered over the subsequent 48-hour period. Otherwise, the following measures are taken: (1) dressing removal, suture release, optimized elevation; (2) nail-plate removal with heparin-soaked pledgets for the nail bed in finger replants; and (3) leech therapy, if there are still signs of venous insufficiency.

Conversely, in free-flap patients, venous insufficiency warrants immediate reexploration with the following: (1) division of venous anastomosis; (2) infusion of 500,000 to 750,000 units of streptokinase into the arterial pedicle;
(3) venous thrombectomy; (4) copious heparin (100 U/ml) irrigation; and (5) anastomotic revision once flow is reestablished, preferably to an alternate recipient vein.

In both replant and free-flap patients, arterial insufficiency warrants immediate reexploration, with subsequent heparinization for 5 days with a goal of a partial thromboplastin time 1.5 to 2 times that of normal.

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8. Feldman, M., and Cryer, B. Aspirin absorption rates and platelet inhibition times with 325 mg buffered aspirin tablets (chewed or swallowed intact) and with buffered aspirin solution. Am. J. Cardiol. 84: 404, 1999.


Self-Assessment Examination follows on the next page.
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1. ASPIRIN WORKS BY INHIBITING THE ENZYME:
   A) Cyclooxygenase
   B) Topoisomerase
   C) Reverse transcriptase
   D) None of the above

2. IN ADULTS, ASPIRIN LIKELY INHIBITS THROMBOXANE MAXIMALLY, WITH MINIMAL INHIBITION OF
   PROSTACYCLIN, AT A DOSE OF:
   A) 300 to 600 mg per day
   B) 50 to 100 mg per day
   C) 100 to 200 mg per day
   D) 200 to 300 mg per day

3. HEPARIN WORKS BY BINDING ANTITHROMBIN III AND SUBSEQUENTLY INHIBITS:
   A) Factor XII
   B) Factor XI
   C) Factor IX
   D) Factor X
   E) All of the above

4. RECOMMENDED CONCENTRATIONS OF INTRAOPERATIVE HEPARIN TOPICAL IRRIGATION INCLUDE:
   A) 50 to 100 U/ml
   B) 100 to 200 U/ml
   C) 25 to 50 U/ml
   D) More than 200 U/ml

5. BOTH THE MACROVASCULAR AND MICROVASCULAR LITERATURE SUPPORT THE USE OF AN
   INTRAOPERATIVE BOLUS OF HEPARIN OF:
   A) 100 to 160 U/kg
   B) 50 to 100 U/kg
   C) 150 to 200 U/kg
   D) 20 to 50 U/kg

6. DEXTRAN WORKS BY ALL OF THE FOLLOWING MECHANISMS, EXCEPT:
   A) Increasing the electronegativity on platelets and endothelium, thus preventing platelet aggregation
   B) Modification of the structure of fibrin, making it more susceptible to degradation
   C) Decreasing factor VIII and von Willebrand factor, which decreases platelet function
   D) Altering the red blood cell membrane proteins and increasing their permeability

7. ALL THE FOLLOWING CONDITIONS WARRANT IMMEDIATE REEXPLORATION, EXCEPT:
   A) Venous insufficiency in a replant
   B) Arterial insufficiency in a replant
   C) Arterial insufficiency in a free flap
   D) Venous insufficiency in a free flap

To complete the examination for CME credit, turn to page 2191 for instructions and the response form.