Anticoagulation Therapy in Microsurgery: A Review

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The advent of microsurgical tissue transfer including replantation greatly has expanded the scope of reconstructive surgery. There are few recent innovations in anticoagulation therapies for microsurgery, however, and anastomotic thrombosis remains an occasional cause of surgical failure. No consensus exists on the ideal anticoagulation protocol for microsurgery. This article reviews major pharmacologic modalities of anticoagulation, delineates the mechanism of action and study of efficacy of each agent, and compares the risks and benefits of popular anticoagulation therapies. Finally, it examines available human outcomes–based data and attempts to provide a glimpse of the future direction of microsurgical anticoagulation research. (J Hand Surg 2006;31A:836–846. Copyright © 2006 by the American Society for Surgery of the Hand.)

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Microvascular techniques are key components of reconstructive hand surgery to correct various congenital, ablative, and traumatic defects. Hand surgeons use microsurgical procedures to replant amputated digits or repair injured nerves and blood vessels. Intraoperative or postoperative anastomotic thrombosis necessitates re-operation and risks flap or replant failure. Surgical intervention for thrombosis generally involves anastomotic revision or interposition vein grafting. Despite these interventions vascular thrombosis is the leading cause of failure of microsurgeries.[1–5] With the incidence of flap failure reported to be as high as 10%, the primary prevention of thrombosis is of critical interest to microvascular surgeons.[6]

Although anticoagulation has been part of reconstructive surgery for 30 years, anticoagulation protocols vary widely among microsurgeons. Currently 96% of reconstructive surgeons use anticoagulants in free flap procedures.[6,7] Numerous studies evaluating prophylactic anticoagulation in microsurgery report efficacy in animal models, however, limited human data exist to support any clinician's preferred method. It is unknown whether the most efficacious protocol for human microsurgical anticoagulation has yet to be identified or whether no singular effective method exists.

This article reviews selected literature relating to anticoagulation for microsurgery and provides a summary of relevant basic science and clinical studies in animal and human models. We hope that this review will assist surgeons with informed decision making regarding the clinical use of anticoagulants in microsurgery.

Overview of Thrombosis in Microsurgery

The pathogenesis of venous thrombosis differs from arterial thrombosis.[8] Platelet aggregation is the underlying cause of arterial thrombosis whereas venous thrombosis is primarily the result of fibrin clotting.[8] Because venous thrombosis occurs more frequently than arterial thrombosis as the cause of free flap failure, fibrin strand development is a more significant factor in microvascular occlusion than platelet aggregation.[1,9,10]

The risk for thromboses is highest (80%) during the first 2 postoperative days and decreases to 10% after postoperative day 3.[2,9] In a study of the timing of pedicle thrombosis Ichinose et al[3] found that 90% of purely arterial thrombi occur on postoperative day 1 whereas 42% of purely venous thrombi occur after

postoperative day 1. This risk pattern is attributed to the initially low flow volume through the pedicle, which gradually increases in the postoperative period.

Several surgical factors are associated with free flap failure. The use of vein grafts in microsurgery and the presence of chronic wounds at recipient sites are associated with greater postoperative vascular thrombosis and failure.[4,11,12] Myocutaneous flaps and vein grafts are associated with increased thrombosis at the site of anastomosis and the free rectus abdominis and transverse rectus abdominis muscle flaps are associated with increased patency compared with other flaps.[4]

Despite the variety of reconstructive techniques and anticoagulation protocols used by microsurgeons, the reported failure rate among free flaps ranges from 4% to 10% and the reported failure rate among replants ranges from 15% to 30%.[4,5,13–15] Many flaps are salvaged successfully with thrombolytic treatment, indicating that the true rate of vascular thrombosis in microsurgery is higher.[16] Optimal prophylactic anticoagulation therapy promises significant reductions in morbidity.

Antithrombotic Therapy

The use of prophylactic antithrombotic agents is the most common strategy for avoiding vascular thrombosis after free flap surgery or vascular repair.[17–19] As early as 1978 Ketchman[20] proposed that to increase patency rates of microvascular repairs surgeons need agents that (1) decrease platelet function (eg, aspirin), (2) increase blood flow or decrease blood viscosity (eg, dextran), and (3) counteract the effects of thrombin on platelets and fibrinogen (eg, heparin). Today aspirin, dextran, and heparin are the mainstay of treatment. The use of these agents remains complicated by the challenge of providing optimal antithrombotic prophylaxis while minimizing adverse effects.

No consensus exists on the use of anticoagulation therapy after microsurgery. Many surgeons have their own particular protocols for perioperative anticoagulation that has been shaped by personal trials and errors. The following sections review and summarize experimental studies and clinical experiences reported in the current literature and provide an overview and comparison of popular anticoagulation therapies.

Heparin

Heparin, a polyglycosaminoglycan of varying lengths, has been used clinically for more than 50 years. It is currently the anticoagulant agent used most widely by surgeons to prevent both arterial and venous thrombosis.[21] Heparin binds to antithrombin III and enhances its antiprotease activity and accelerates its attachment to its substrate approximately 1,000-fold. As a result the active forms of coagulation factors II (thrombin), IX, X, XI, and XII are rendered inactive and the clotting cascade is impaired.[22] Through inhibition of thrombin generation heparin reduces the activation of coagulation factors V and VIII, recruitment of platelets, and formation of fibrin.[23,24] The antithrombotic effect of heparin is measured clinically by the increase in clotting time of blood and is expressed as prolonged activated partial thromboplastin time (APTT). A 2-fold increase in PTT is considered a therapeutic heparin level. In addition, large doses of heparin result in vasodilation that possibly is mediated by the release of nitric oxide from the endothelium.[25] The vasodilative effect of heparin may reduce thrombosis further by increasing the rate of blood flow.

Heparin prophylaxis is limited by an increased risk for hemorrhage from the surgical site and formation of hematoma.[26] Heparin therapy is associated with a greater incidence of hematoma than aspirin or dextran. In a retrospective study of lower-extremity reconstruction using free flaps Pugh et al[27] found a 66% rate of hematoma formation when heparin was used alone or in combination with other agents. This warrants discretion when administering unfractionated heparin because increased tissue pressures caused by the formation of a hematoma at the site of anastomosis can compromise perfusion and encourage thrombogenesis. In a recent retrospective review of 216 head and neck reconstruction patients given a combination of aspirin (325 mg every day) and subcutaneous heparin (5,000 U subcutaneously twice a day), Chien et al[6] reported a free-flap survival rate equivalent to other anticoagulation regimens without an increased incidence of hematoma.

Another important side effect of heparin therapy is heparin-induced thrombocytopenia (HIT).[28,29] Type I HIT is a rare (1%–3%) immune-mediated condition that results in a significant decrease in platelet count (30,000–55,000) 5 to 10 days after the initiation of heparin therapy. It is treated only by cessation of heparin therapy. Type II HIT is a nonimmune condition with a smaller decrease in platelet count (100,000), which occurs 1 to 2 days after the initiation of heparin therapy. Type II HIT usually improves spontaneously despite continuation of heparin therapy.[30] When given as a bolus heparin can result

in hypotension in patients having cardiac surgery or hemodialysis.[31–33] Disadvantages of heparin use include its low bioavailability and unpredictable dose-response relationship.[34] Subcutaneous administration to postoperative patients necessitates close monitoring of fluctuating coagulation levels, which extends the length and increases the cost of the hospital stay.[35]

The goal in heparin therapy is the efficient delivery of a minimal therapeutic dose to the site of vascular anastomosis. Maintaining low systemic heparin levels minimizes the adverse effects of anticoagulation. Rooks et al[36] reported no significant difference in the protective effect of intra-arterial and systemically administered intravenous heparin or dextran-40. In other studies systemic heparin provided greater protection against rethrombosis after the repair of a thrombosed anastomosis by vein graft repair than by simple re-anastomosis alone (82% vs 69% patency, respectively).[37] Stockmans et al[21] showed that heparin, when administered systemically to a therapeutic level (a 2-fold increase in PTT), reduces the rate of primary venous thrombosis by 60% whereas higher doses result in close to a 100% reduction. Higher plasma levels of heparin result in better protection against vascular thrombosis but increase the incidence of bleeding.[21] In an attempt to deliver high local doses of heparin while maintaining low systemic levels, Hudson et al[38] used an *in situ* venous catheter. The catheter was inserted proximal to the venous anastomosis in 83 free flaps to infuse 50 U/mL at 10 mL/h for 48 hours and then the dose was tapered over 5 days. They observed an increase of local APTT whereas the systemic APTT remained normal. Ultimately they reported zero re-explorations or flap failures in comparison with the usual re-exploration rate of 12% in the absence of local venous catheter anticoagulation.

Recently topical antithrombotic administration has been suggested as an alternate approach to local anticoagulation.[39] Fu et al[40] reported that topical administration of high-concentration heparin (750 μg/mL) results in 80% patency at the anastomosis sites at 7 days in the rabbit model. Ten minutes of intraoperative irrigation with high-dose heparin directly on the anastomosis optimizes endothelial binding of the drug and increases the local concentration of heparin.[41,42] In a multicenter prospective human clinical study, however, Khouri et al[14] did not observe a benefit to using intraluminal heparin irrigation, regardless of concentration, in reducing postoperative thrombosis. They did report a decrease in the occurrence of hematoma and hemorrhage in comparison with systemic heparin.

Topical heparin irrigation may increase vessel patency but the direct effect of the pressure can injure the vessel. Yan et al[43] reported that in the animal model lactated Ringer's solution pressures of 100 mm Hg or greater injures the endothelial cells and internal elastic lamina, which may have a detrimental effect on microvascular anastomoses. Therefore irrigation pressures less than 100 mm Hg minimize trauma to the delicate microvascular tissues and maximize vessel patency.

Low Molecular Weight Heparins

Low molecular weight heparin (LMWH) is a derivative of unfractionated heparin that is prepared through the deaminative hydrolysis of standard heparin into short polysaccharide fragments. These molecules are known to have the same inhibitory effect on active factor X but have a weaker antithrombin (factor II) activity. As a result LMWH is as efficacious as unfractionated heparin in preventing venous thrombosis with fewer adverse effects.[44,45] Malm et al[34] observed that LMWH (dalteparin) thrombin inhibition is sufficient to prevent thrombosis and does not cause a significant increase in bleeding. By using a rat model of deep arterial injury, doses of 180 U/kg LMWH or heparin caused a similar antithrombotic effect (close to 3-fold increase in patency at 30 minutes after surgery) but only the heparin group resulted in a statistically significant increase in bleeding.

The efficacy of LMWH to prevent arterial thrombosis is a point of debate. Although some studies clearly have found LMWH to be a less effective treatment than traditional heparin in reducing the frequency of arterial thrombosis,[46,47] others have reported better or equal results.[34,48] In a rabbit model Zhang et al[48] observed a 50% increase in the patency of arterial anastomoses with LMWH in comparison with no anticoagulation, but observed no difference in the patency of small venous anastomoses.

The side-effect profile of LMWH is superior to unfractionated heparin. In addition to causing fewer hematomas LMWH has higher bioavailability (85% compared with 10%), a longer plasma half-life, a steady dose-response relationship,[34,49] and causes fewer cases of thrombocytopenia compared with unfractionated heparin.[25,50,51] Thus LMWH produces reliable anticoagulation over a longer period of time without the need for monitoring.[49] After surgery LMWH can be administered on an outpatient basis, which reduces the length of hospitalization time.

Low molecular weight heparin has a lesser effect on APTT than does unfractionated heparin. This value was found to be 3-fold lower for the lowest dose of dalteparin with distinct antithrombotic effect (180 U/kg) compared with the same dose of unfractionated heparin.[34] Therefore the level of activity of LMWH is expressed best as units of anti–activated factor X (factor Xa) activity instead of APTT.[52] In a rat model Ritter et al[47] showed that a single injection of either unfractionated heparin or LMWH just before pedicle division results in a similar anastomotic patency and flap survival rate. Both increased APTT and anti–factor Xa levels but LMWH had a more prominent increase on anti–factor Xa, less of an increase in APTT, and no bleeding complications compared with unfractionated heparin. In addition the protective effects of LMWH include antithrombin-independent effects such as the release of tissue factor pathway inhibitor, interactions with heparin cofactor II, and platelet factor 4.[45] Therefore attempts to standardize LMWHs on the basis of anti-Xa activity have not been completely successful. This explains the inherent difficulty in determining equivalent doses of unfractionated heparin to LMWHs. The pharmacologic profiles and efficacies of LMWHs vary; therefore success with one LMWH at a certain dose does not generalize to the whole group.

Similar to unfractionated heparin the application of topical LMWH minimizes systemic side effects. Chen et al[100] examined the effects of topical heparin and topical LMWH (enoxaparin) on the patency of anastomosed vessels. The thrombosis rate for the first 7 days was reduced significantly after either treatment in comparison with saline irrigation. They did not find a statistical difference in patency or bleeding between unfractionated heparin and LMWH.[34] Lower doses (2 mg/kg) of subcutaneous LMWH (enoxaparin) were most effective at dilating capillaries (by 33%) without bleeding complications in an animal model.[53] Ertas et al[53] reported significant capillary dilation in rat cremaster muscle 5 hours after administration of 2 mg/kg and 4 mg/kg LMWH. The efficacy of higher LMWH doses (8 mg/kg) was no different than control, but caused markedly increased bleeding. Lower doses of LMWH increase functional capillary perfusion at the microcirculatory level of a rat cremaster muscle flap without increased propensity for bleeding in the predissection and postdissection period.

Dextran

Dextrans are a group of variously sized polysaccharides that are synthesized from sucrose by *Leuconostoc mesenteroides streptococcus* These agents are used commonly by microsurgeons to decrease vascular thrombosis. The antithrombotic effect of dextran is mediated through its binding to erythrocytes, platelets, and vascular endothelium, increasing their electronegativity and thus reducing erythrocyte aggregation and platelet adhesiveness. Dextrans decrease platelet adhesion by decreasing factor VIII-Ag (von Willebrand's factor). Platelets coated in dextran are distributed more evenly in a thrombus and are bound by coarser fibrin, which simplifies thrombolysis. By inhibiting α-2 antiplasmin, dextran also serves as a plasminogen activator in thrombolysis.[54,55] Larger dextrans that remain in blood vessels act as potent osmotic agents to reverse hypovolemia.[56,57] Volume expansion causes hemodilution, which improves blood flow and further increases patency of microanastomoses. No difference has been observed in the antithrombotic efficacy of intra-arterial versus intravenous dextran administration.[36]

The varying size of dextran, from 10 to 150 kd, results in prolonged antithrombotic and colloidal effects.[56] Larger dextrans are excreted poorly from the kidney and remain in the blood for weeks until they are metabolized.[58] Dextran-40 (molecular weight, 40 kd) is the most popular dextran for anticoagulation. Close to 70% of Dextran-40 is excreted in the urine within the first 24 hours after intravenous infusion and the remaining 30% is retained for several more days, prolonging its effects.[59,60]

Although there are relatively few side effects associated with dextran use, they can be very serious. These include anaphylaxis, volume overload, pulmonary edema, cerebral edema, or platelet dysfunction.[56,61,62] An uncommon but major complication of dextran's osmotic effect is acute renal failure.[63,64] A direct toxic effect on the tubules and glomeruli or intraluminal hyperviscosity are 2 proposed mechanisms.[65,66] Patients with a history of diabetes mellitus, renal insufficiency, or vascular disorders are at greatest risk. Brooks et al[64] recommended avoiding dextran therapy in patients with chronic renal insufficiency and a creatinine clearance rate of less than 40 mL/min. In a prospective randomized comparison of dextran- and aspirin-related complications in 100 patients undergoing microsurgical flap reconstruction for head and neck malignancy, aspirin and dextran were equally efficacious in preventing flap failure. Patients on dextran, however, had a 3.9- to 7.2-fold increased relative risk of systemic complications after 48 and 120 hours of dextran infusion, respectively. Because the benefits of dextran prophylaxis

do not outweigh the risks, dextran is a less commonly used anticoagulant therapy.[67]

Aspirin

Reconstructive surgeons frequently use aspirin (acetylsalicylic acid [ASA]) in the perioperative period to improve flap survival. Aspirin acetylates and inhibits the platelet enzyme cyclooxygenase, impeding arachidonic acid breakdown to thromboxane and prostacyclin. Thromboxane is a potent vasoconstrictor that induces platelet aggregation and prostacyclin is a vasodilator that inhibits platelet aggregation. There is evidence that aspirin impairs thrombin generation and reactions catalyzed by this enzyme at the site of anastomosis.[68] Perioperative administration of aspirin is known to prevent microvascular thrombosis at both anastomoses sites, although it is less effective than heparin.[69] Cooley et al[10] have shown that intravenous heparin yields higher patency compared with enterically delivered aspirin. Assessment with a scanning electron microscope proved that more fibrin accumulates in aspirin-treated vessels and more platelets aggregate in a heparin-treated group.[10]

The timing of aspirin administration relative to the time of surgery alters efficacy. Kort et al[37] did not find any protective effect of aspirin administered 30 minutes before surgery in rats. Similarly perioperative administration of oral aspirin at 30 mg/kg in a rat thrombosis model did not provide antithrombotic protection at 24 hours.[70] The administration of aspirin (4 mg/kg) 10 hours before surgery resulted in a significant increase in patency and decreased the rate of platelet aggregation.[71] In this study a single dose of ASA given before surgery resulted in a 2-fold increase in vessel patency at 1 week after anastomosis compared with control. Another study measured the protective effect of systemic aspirin (administered orally) in the maintenance of rat vein graft patency when administered for 1 week before surgery.[72]

The protective effect of aspirin doubles when coadministered during surgery with another antiplatelet agent, ticlopidine.[73] Similarly the combination of ASA with dipyridamole results in better venous patency than heparin alone (40% compared with 6.7%) and provides less arterial protection (6.7% compared with 73.3%) 1 day after surgery. The combination of the 3 provides the best arterial and venous antithrombotic protection.[8] In their search for the ideal aspirin dose Peter et al[74] found that low-dose aspirin (5 mg/kg, infused intra-arterially immediately after arterial and venous anastomosis in a rat model) reduces thrombus formation at both arterial and venous microanastomoses and results in better microcirculation through the muscle flap. Low-dose aspirin is preferred by many surgeons because it does not affect endothelial and smooth muscle cyclooxygenase. As a result prostaglandin I_2 (platelet antagonist and vasodilator) production is unaffected and there are fewer systemic side effects.[75]

The same mechanisms that make aspirin a powerful antithrombotic tool also can cause major problems. Platelet dysfunction results in increased blood loss during surgery, which increases transfusion and re-operation rates.[76] Experimentally desmopressin is helpful to reduce thrombus formation and increase overall platelet function after aspirin use.[77] Other aspirin side effects stem from its nonselective inhibition of cyclooxygenase. Cyclooxygenase-I has been referred to as the *housekeeping* enzyme because it is expressed in many normal tissues in the body and regulates functions such as blood flow to the kidney and protection of gastric mucosa.[78] By affecting the gastric mucosa and reducing platelet aggregation aspirin can cause serious gastrointestinal bleeding. This risk is dose dependent and a low-dose regimen (75 mg/d) minimizes the risk for bleeding.[79] Newer cyclooxygenase-II–selective inhibitors are associated with fewer renal and gastric side effects but do not prevent platelet aggregation, therefore they do not have a role in anticoagulation.[80]

Thrombolytics

Thrombolytic agents available for clinical use include streptokinase, urokinase, and tissue-type plasminogen activator. Their efficacy in reversing microvascular thrombosis is well documented in the animal model.[81,82] Human studies are available but scant. In a retrospective multi-institutional study Yii et al[83] reported no significant improvement in patency with the use of thrombolytic therapy in free-flap salvage; however, Rooks et al[36] reported that for an established thrombus, urokinase results in marked improvement in patency compared with heparin and dextran. They reported an advantage to intra-arterial over intravenous administration of thrombolytics because intra-arterially delivered urokinase results in significantly greater efficacy (100% for intra-arterial vs 40% intravenous). Because most human studies look at small study populations there are no definitive conclusions on the relative efficacy and appropriate dosing of thrombolytics; however, it is known that flap salvage is most successful on the first postoperative day compared with postoperative day 2 and

beyond.[83,84] Thrombolytic agents are associated with a risk for bleeding but this risk can be minimized by draining the venous effluent to prevent systemic exposure to the agent.[85]

Other Agents

Medical scientists continue to search for new antithrombotic and anticoagulant therapies that maximize benefits while minimizing adverse effects. The efficacy of these agents was tested primarily in the cardiovascular setting and only recently are these agents being investigated in microsurgery.

Hemorrheologic agents such as pentoxifylline (PTX) (Trental; Hoechst-Roussel Pharmaceutical, Inc., Somerville, NJ) typically are used to treat chronic occlusive arterial disease. They augment blood flow by vasodilating vessels, inhibiting platelet aggregation, and reducing fibrinogen levels. In addition PTX decreases blood viscosity by increasing erythrocyte deformability, which improves tissue survival.[86] The combination of these effects results in improved microcirculation and oxygenation in various flaps.[87] Because PTX requires a 2-week window before the drug is effective, a 2-week preoperative regimen is necessary. In a randomized blinded study to determine the efficacy of thromboprophylactic LMWH and pentoxifylline in the rat microvascular free groin flap model, Murthy et al[88] reported a statistically significant improvement in arterial patency with both LMWH and pentoxifylline, but not in combination. Inconsistent and insufficient human data make the prophylactic use of PTX in microsurgery experimental.

Recently recombinant hirudin, a compound originally isolated from medicinal leeches, has been used as an anticoagulant. A specific thrombin inhibitor, hirudin is more potent than heparin without adversely affecting platelets.[89] Hirudin can enter smaller spaces inside microthrombi because it does not require a cofactor, and therefore is smaller (7,000 d) than the bulky heparin–antithrombin III complex.[90] Similar to heparin, however, hirudin can cause significant bleeding when administered systemically.[89] Fu et al[40] reported that a high concentration of topical recombinant hirudin (750 μg/mL) results in significantly increased patency at 7 days (75% compared with 13.3% in the control group) with minimal bleeding in a rabbit microanastomosis model.

Tissue factor pathway inhibitor (TFPI), a naturally occurring protein, blocks the tissue factor pathway of coagulation. It forms complexes with tissue factor VIIa and Xa, thus inhibiting the coagulation cascade.[91] Recombinant human TFPI (SC-59735; Chiron Corp., Emeryville, CA) is more effective than heparin when added to irrigation solution used on thrombus-prone rabbit arteries.[92] In a multicenter, multinational, blinded, randomized, phase II study Khouri et al[14] found that intraluminal irrigation with low concentrations of SC-59735 (0.05 mg/mL) resulted in a flap failure rate similar to treatment with either high-dose SC-59735 (0.15 mg/mL) or heparin (100 U/mL). Irrigation with low-dose SC-59735, however, resulted in a marked incidence of hematoma formation compared with high-dose SC-59735 or heparin. Thus they suggested that a lower dose of recombinant human TFPI improves flap survival while minimizing the formation of postoperative hematomas.

Studies of Iloprost (CoTherix Inc., San Francisco, CA) report almost twice the rate of patency after resection, repair, and re-anastomosis of thrombosed anastomoses.[37,93] The difference is only statistically significant when vein grafts were used. Illoprost, however, is less effective than systemic heparin at maintaining patency at sites of vein graft re-anastomosis.[93]

In 1988 Nichter and Bindiger[94] found that treatment with ibuprofen and indomethacin markedly improved micrograft patency in a carotid rat model with no significant difference when compared with aspirin. Similarly the use of toradol (ketorolac) has been reported when aspirin was contraindicated.[95] Finally, perioperative oral ticlopidine, a known platelet inhibitor, has been shown to be more effective at maintaining patency at both 1 hour and 1 week in a rabbit model in comparison with aspirin (45% and 15% patency rates at 1 hour and 1 week, respectively, for ticlopidine compared with 35% and 10%, respectively, for aspirin).[73] The greatest increase in patency compared with control at 1 week occurred when aspirin and ticlopidine were administered concurrently, as opposed to when either agent was given individually (20% patency at 1 week).

Clinical Studies

Despite refined microsurgical skills and antithrombotic therapeutic options, 6% to 25% of microsurgical cases result in re-operation because of thrombosis at vascular anastomoses.[96,97] Research in this field has been performed primarily in animal models. Some researchers have suggested that the rodent model has a uniquely higher rate of recanalization in thrombosed veins, which calls for caution in extrapolating rodent data to human problems. There is a

paucity of data in the literature comparing anticoagulation options in human microsurgery. Therefore current recommendations for microsurgical anticoagulation therapy are based on extrapolations of conflicting animal data and scant human studies.

Recent literature examines the current state of the art in anticoagulation for microsurgery. A 2001 article by Conrad and Adams[98] reviewed the actions of dextran, aspirin, and heparin and recommended anticoagulation regimens for free flaps and replants. They recommended preoperative and postoperative chewed aspirin daily for 2 weeks, intraoperative heparinized saline irrigant, and a heparin bolus of 50 to 100 U/kg before releasing the clamps. For replants Conrad and Adams[98] also recommended Dextran-40 at 0.4 mL/kg/h, weaned off by postoperative day 5.

In 2001 Pederson[99] recommended for replants the use of an indwelling axillary catheter to deliver marcaine for 5 days to produce a chemical sympathectomy, the use of chlorpromazine as a peripheral vasodilator and sedative for 3 to 5 days, and the use of 325-mg aspirin for 3 weeks. His recommendations were not based on specific animal studies and were not the results of large outcomes studies of different methods of anticoagulation for microsurgery.

The only human study to look at this issue recently was the previously discussed study by Khouri et al.[14] This was a 6-month prospective study of 23 surgeons who performed 493 free flaps. This study looked at many variables and provided associations between different methods of anticoagulation and flap failure rates. Khouri et al[14] reported that only subcutaneous heparin significantly differs in its clinical effect, as subcutaneous heparin decreased the odds ratio for thrombosis by 27%. No other antithrombotic regimen had a statistically significant association with clinical outcomes.

Khouri[14] reported several other trends that were not statistically significant. There was flap failure in 2.2% of patients who were given preoperative systemic therapy such as heparin, aspirin, or dextran. Patients without preoperative systemic therapy experienced 4.6% flap failure. In addition, patients who received intraoperative systemic heparin as a part of a normal prophylactic anticoagulation protocol had a 5.6% flap failure rate versus 2.9% when no heparin was used in the normal protocol. There were no associations with outcomes reported for patients who received dextran, aspirin, or heparinized intraoperative irrigation.

It should be noted that Khouri's study[14] was not designed specifically to compare different methods of anticoagulation. One criticism of the study is that each surgeon used the anticoagulation protocol with which he or she was accustomed. Therefore each surgeon used an anticoagulation regimen appropriate to his or her specific technique. This confounding factor may invalidate conclusions drawn from this study.

Although no data clearly support any specific anticoagulant for microsurgery, this review provides a summary of current data to assist the clinician in designing a rational approach to anticoagulation for microsurgery. The timing of anticoagulation, route of anticoagulation, the use of combination therapy, and individualization of microsurgical anticoagulation to the surgical technique may improve future microsurgical outcomes.

The appropriate timing of anticoagulation therapy maximizes its effectiveness. The first 2 days after surgery are crucial in anticoagulation because the majority of clots form during this time. The best time to initiate anticoagulation treatment, however, may not necessarily be on those days. In their prospective outcomes study of free-flap surgeries, Khouri et al[4] reported a 2-fold decrease in flap failure (this was not statistically significant) with preoperative use of aspirin, dextran, or heparin. A significant antithrombotic effect is observed after a single dose of aspirin given several hours before surgery.[71] Anticoagulation is not popular secondary to an increased risk for intraoperative bleeding and most surgeons are inclined to initiate anticoagulation after the procedure. Khouri et al[4] concluded that the postoperative use of subcutaneous heparin is superior to any other perioperative administration. Similarly the route of anticoagulant delivery is a subject of interest. The effects of local delivery may differ from the systemic delivery of similar agents.

Another part of the solution may lie not in choosing the right antithrombotic therapy but in finding the best combination of agents. In the conclusion of their study Peter et al[74] suggested using systemic low-dose aspirin with heparin locally for irrigation of microvessels to maximize antithrombotic effect while minimizing side effects. Indeed future research may best be directed toward a combination of popularly used therapies rather than comparing single agents with each other.

The lack of progress in understanding how best to anticoagulate microsurgical patients may stem from the oversimplified attempt to apply a one-size-fits-all approach to microsurgical patients. A review of the diverse anticoagulation protocols used in various study

models and of the inconsistent outcomes reported for similar treatments indicates a need for individualized anticoagulation therapy. In an effort to elucidate individual risk Olsson et al[97] investigated coagulation and fibrinolysis during various microsurgical tissue transfers and found an association between specific plasma markers (thrombin-antithrombin III complex and prothrombin fragment-1.2) and flap failure. Preoperative hypercoagulability and excessive bleeding during surgery were predictors of re-operation.[97] By measuring each patient's coagulability before surgery using coagulation markers the surgeon could tailor the anticoagulation regimen. With close postoperative follow-up evaluation of the same markers it may be possible to reduce the need for re-operation.

In addition, anticoagulation regimens could be adapted to each surgical procedure. For example, TRAM flap surgery has a lower incidence of postoperative thrombosis (36%) whereas the use of vein grafts or transfer of a flap to a chronic wound bed increases the odds of the same event (2.5 and 2.9-fold, respectively).[9] The amount of bleeding during surgery is associated with an increased postoperative risk for thrombosis, likely owing to activation of coagulation pathways.[97] This observation underscores the importance of proper intraoperative hemostasis. A combination of patient status, surgical planning and approach, and up-to-date knowledge of anticoagulant agents and their efficacy is important in diminishing the incidence of thrombosis and postoperative flap failure.

The currently available data are not adequate to develop a rational evidence-based approach to anticoagulation for microsurgery. Animal studies exist to defend or refute the use of almost any pharmacologic means of anticoagulation for microsurgery. Insufficient human outcomes data exist to corroborate these animal studies. The data from Khouri et al[14] suggest that the only method of anticoagulation that is statistically significantly associated with a decreased odds of thrombosis is subcutaneous heparin. Based on published data no other single method has an obvious advantage. This indicates that an excellent microsurgical technique is the critical factor in consistently optimal microsurgical outcomes. Until reliable human outcomes data are available the choice of an anticoagulant to complement the surgical technique remains a matter of personal experience and interpretation of existing studies.

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