Review

A Review of Thrombosis and Antithrombotic Therapy in Microvascular Surgery

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Abstract

Despite a remarkable expansion of microsurgery, there is still no international consensus about routinely used prophylactic antithrombotic agents. Most treatment regimens still use aspirin, heparin (low-molecular-weight and unfractionated heparin) or colloids (hydroxyphenylacetate 6%/dextran); however, clear evidence for the clinical benefit of an ideal administration regimen or one agent over the other has not yet been established. Instead of searching for the one regime that fits all, an increasing number of reviews from different disciplines describe multistep approaches that optimize what has been shown to be most promising. This includes the use of antithrombotic agents, proper risk assessment, secondary prevention and professional training to optimize microsurgical skills. In this review, we describe factors included in traditional approaches and also emphasize the value of good surgical technique, which while recognized by all to be one of the most important factors for success, receives less emphasis in reviews describing thrombosis prophylaxis in microvascular surgery.

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Introduction

The number of microsurgical procedures performed each year has greatly expanded. This is due to the development of better and smaller instrumentation, widespread and standardized microsurgical training programs and a better understanding of the pathophysiology

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of manipulated tissues. The indications for free flap reconstruction have also been expanded in the last years due to a better and more refined understanding of flap anatomy and perfusion dynamics (perforator and free flaps).

When microsurgical technique is used to reconnect small blood vessels the threat of thrombotic occlusion is ever present, and is by far the leading cause of failure.

In our 1992 review ‘Thrombosis and antithrombotic therapy in microvascular surgery’ [1] we concluded that the best prophylaxis against thrombosis in microvascular surgery is ‘excellent surgical technique and proper patient selection’: this has not changed. In this review, 20 years hence, we provide the reader with a recapitulation of that which has not changed and an update on that which has, the latest antithrombotic approaches.

Because failure still occurs, even in the hands of the most technically skilled microsurgeon [2], antithrombotic medications continue to be used. The list of antithrombotic medications used is simple and has not changed in 20 years. The protocols used for administration of these drugs vary greatly, making it difficult to provide standard recommendations for the use of these agents in microvascular procedures.

When considering the use of antithrombotic medications in patients who will receive microvascular surgery it is important to take into consideration that some patients are already taking these drugs for general thrombosis prophylaxis. While heparin, specifically low-molecular-weight heparin (LMWH), is the antithrombotic drug of choice in surgical interventions, it is also administered chronically in patients with prothrombotic conditions and/or with poor vessel status.

Rather than providing the reader with specific recommendations, herein we list various recommendations published in recent reviews and let the reader decide which works best in his/her hands. We review basic science and pathophysiological evidence that supports successful antithrombotic strategies in microvascular surgery, including risk assessment, technical considerations and pharmacological intervention. These topics will be presented in the same order as they present in surgical practice, i.e. pre-, intra- and postoperatively.

The role of platelets in hemostasis and thrombosis is beyond the scope of this review and will be discussed in detail in an accompanying article in this issue.

Pathophysiology of Anastomotic Thrombosis

Thrombosis results from a predominance of procoagulatory factors described by the ‘Virchow Triad’: blood flow stasis, vessel wall injury and hypercoagulability. Animal studies demonstrate a close association between arterial thrombosis/platelet aggregation and venous thrombosis/fibrin clotting [3]. Arterial thrombosis typically (90%) manifests itself within the first 24 h postoperatively, whereas venous thrombosis occurs after 24 h [4]. While 80% of thrombotic occlusions occur in the first 48 h postoperatively [5], in most cases the pathophysiological cause can be traced back to the pre- and intraoperative phases.

Preoperative Causes

Preoperative causes of thrombosis are usually related to comorbidities like poor vessel status, posttraumatic vascular disease, smoking, diabetes, alcohol, immobilization, cancer, previous surgery, prior thrombosis and hereditary diseases [6]. Cofactors that can influence a patient’s coagulatory status include impaired perfusion, e.g. in hemorrhagic shock or poly-traumatized patients. Kwaan [7] concluded that ‘a therapeutic approach limited to a single target of the underlying pathogenic factor, such as the use of anticoagulants, is insufficient and often unsuccessful. Simultaneous management of all the contributory factors should therefore be considered’. Most of the literature describing preoperative factors contributing

Table 1. PubMed search

PubMed Central search conducted on 18.05.2012	
Search term used	Articles cited n
Thrombosis	171,131
Thrombosis and risk	37,353
Thrombosis and microvascular	1,606
Thrombosis and microvascular and microsurgery	367
Thrombosis and microvascular and microsurgery and risk	63

Table 2. Increased risk for thrombosis

Procedure	Increased risk for thrombosis	References
Use of vein graft	Yes	Miller et al. [69]
Chronic wound at recipient site	Yes	Kroll et al. [5]
Suture material	No	Acland [8]
Suture incision	Yes	Acland [8]

to thrombosis derives from clinical studies of patients with heart attacks, stroke or deep vein thrombosis, and only a few pertain to patients receiving microvascular surgery. This is evident in table 1 that shows the results of a Medline search on the topic.

Intraoperative Causes

In human vessels, exposure of subendothelial structures to blood flow has been shown to have a greater impact on anastomotic thrombosis than endothelial dysfunction, i.e. vasospasm [8]. While clamping small blood vessels causes endothelial dysfunction with enhanced thrombocyte aggregation, firm clot formation only occurs when blood flow in the vessel comes in contact with proteins like collagens I and III in the subendothelium [9]. Table 2 shows examples of microvascular procedures that present higher risks of exposing subendothelial structures to blood flow and in doing so increase the intraoperative risk for thrombosis.

The role of vasospasm seems less important in thrombus formation as spasm alone does not increase clot formation [10]. However, narrowing of the vessel lumen, by reducing blood flow, and reducing the number of thrombocytes necessary to occlude the vessel can synergize with prothrombotic factors [1]. Vasospasm can be minimized by local application of papaverine hydrochloride. Fathi et al. [11] showed in rabbit ear vessels that botulinum toxin enhances vessel diameter and consequently venous and arterial anastomosis patency.

Factors that compress or irritate the vessel anastomosis, e.g. hematoma, tightly closed wounds, drainage tubes positioned too close to an anastomosis or tendon, and joint or muscle movements, can all pose threats to vessel patency and lead to failure of a replant or a new flap.

Postoperative Causes

Traditional postoperative risk factors include venous congestion due to major trauma of the extremity (endothelial damage in arteries and/or veins), decreased movement and wound

infection [12, 13]. Kadota et al. [14] showed in their study of 24 patients that postoperative (day 5 or later) wound infection was the most common (54%) cause of anastomotic thrombosis. They concluded by emphasizing the importance of early detection and appropriate management of wound infection for avoiding postoperative thrombosis of the vascular anastomosis.

Another, less studied, factor that may play a role in replant and free flap failure is occlusion of the microcirculation downstream from the arterial anastomosis. This was demonstrated in a free flap model of the rat femoral artery in which, following a simulated poor vessel anastomosis, both the upstream arterial anastomosis and the downstream flap microcirculation were directly viewed using intravital microscopy [15–18]. Using this model system, both thrombus formation upstream at the arterial anastomosis and capillary perfusion in the downstream microcirculation were simultaneously viewed and measured. The authors found that emboli breaking off from the upstream thrombus flushed downstream and caused a significant decrease in capillary perfusion in the microcirculation [16]. These findings were confirmed by treating animals with antithrombotic agents like heparin and reversing thrombus and embolus formation, and decreased capillary perfusion [17]. In addition to obstructing the microcirculation in replanted tissues and free flaps, the presence of small platelet-rich emboli could also cause local vasospasm via thromboxane A₂ [18]. Together these – emboli occlusion and vasospasm – could be responsible for replant and free flap failures in the absence of thrombosis at the microvascular anastomosis.

Principles of Antithrombotic Therapy in Microvascular Surgery

The best antithrombotic therapy is thorough preoperative risk assessment and surgical planning, meticulous intraoperative microvascular technique and careful postoperative monitoring to enable early detection and intervention.

Preoperative Risk Assessment

Thorough preoperative risk assessment requires careful assessment of a patient's history, including questions to detect hereditary diseases, coagulopathies and vasculopathies, i.e. a history of deep vein thrombosis and abortions. In the case of positive findings, several clinical, laboratory and genetic tests are available. Depending on the time and resources available, assessments can include imaging tests like thrombelastography (testing the efficiency of coagulation in blood) or Multiplate (bedside platelet analysis), which are becoming more routine. In order to minimize the risks of failure in high-risk patients, there is also the possibility of using vein interposition grafts or arteriovenous loops [12].

Intraoperative Risk Assessment

Meticulous intraoperative microsurgical technique requires excellent microsurgical training. Soon after the pioneers of microvascular surgery implemented the first successful procedures on small vessels in rabbit ears [19], the first clinical finger replants [20] and free flaps [21] were performed. Teaching this new skill became an integral part of training programs in plastic and reconstructive, trauma and orthopedic surgery. In the early days, training consisted of *see one, do one* and *teach one*, but since then has evolved into well-structured courses with step-by-step instruction on the skills necessary to perform these technically challenging surgeries. Today, teaching basic microsurgical skills takes place typically in 3- to 14-day courses that provide a mix of didactic lectures and hands-on training in live animals. There are many microsurgery teaching courses available, most of which are part of or closely affiliated with university-based postgraduate reconstructive surgery training

Table 3. Recently published reviews

Review	Recommendations	
	important	to consider
Askari et al. [66]	Excellent technique	LMWH Risk-adaptive protocols
Schmitz et al. [67]	Excellent technique	LMWH (UFH), start preoperatively Bolus before reperfusion Risk-adaptive protocols
Brands et al. [68]	Excellent technique	Routine deep venous thrombosis prophylaxis Risk-adaptive protocols Smoking cessation
Conrad and Adams [43]	Excellent technique	Acetylsalicylic acid, start preoperatively, heparin/ dextran bolus (dextran administered for 5 days in replants only)

programs, such as the Frankfurt Microsurgery Teaching Course [22]. Over the years, standardized teaching methods together with improved microsurgical instruments, sutures and microscopes have led to the introduction of technically challenging procedures and to higher success rates.

As made evident in table 3, good microsurgical technique is recognized as the single most important factor for success. Veravuthipakorn and Veravuthipakorn [2] highlighted the importance of solid surgical technique by showing that even without antithrombotic intervention, near 100% success rates could be achieved in free flap and replant procedures when solid microsurgical technique was observed.

Postoperative Risk Assessment

Careful postoperative monitoring is essential as it allows early detection and intervention, and thus the possibility of salvaging a failing implant or free flap. In a retrospective review of 290 free flaps used for breast reconstruction, Vijan and Tran [23] showed a significant difference in salvage rates between flaps that were reexplored earlier versus later. They observed that flaps taken back to the operating room for reexploration within 128 min postoperatively were salvaged, while those taken back after 228 min failed. This emphasizes the importance of postoperative monitoring to enable early detection and intervention.

Most decisions to take patients back to the operating room for reexploration are based on clinical findings. In cases where these monitoring devices are not available, it is recommended to keep patients in intermediate care for observation for 48 h, the period when most complications occur. Also, it is essential to keep the hemoglobin levels above 7.5 g/dl and maintain body and room temperatures above 36 and 22°C, respectively. Care must be taken to keep partial thromboplastin time between 42 and 45 seconds. Finally, patients should be given antibiotics routinely in order to avoid postoperative infection and they should not consume nicotine, coffee or chocolate 6 weeks postoperatively.

Where monitoring devices are used, ultrasound Doppler is the most common (16.2%), followed by LICOX pO₂ monitor (5.9%) and finally thermosensors (4.4%). The most commonly used (43.1%) monitoring protocol described in the literature was hourly until day 3, followed by every 2 h until day 5 and finally at decreasing intervals until discharge from the hospital. In recent years, new approaches have been introduced. These include near-infrared indocyc-

anine green video angiography, which provides real-time information on arterial and venous patency [24], and thromboelastography, a test capable of detecting hypercoagulable states that can be used for predicting postoperative thromboembolic complications. These methods are still being tested in the clinical setting. Finally, in a recent report, Parker et al. [25] showed that a functional fibrinogen/platelet ratio above 42%, as measured by TEG[®], might be useful for identifying those patients most likely to develop thrombotic complications.

Pharmacological Intervention

In the absence of large-scale randomized clinical trials in microsurgery patients, guidelines for the use of antithrombotic therapy must be derived from clinical studies performed in patients with coronary disease or stroke. At present, most services performing microsurgery follow their own antithrombotic regime, based on a combination of aspirin, heparin and colloidal fluids, to decrease platelet function, counteract thrombin and increase blood rheology, respectively. Below we provide a brief description of each of these agents and their use in microsurgery.

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. Heparin prevents clot formation by binding to the enzyme inhibitor antithrombin III, which in turn inactivates thrombin and other proteases involved in blood clotting. Clinically, heparin is used in its low-molecular-weight forms (enoxaparin, dalteparin and tinzaparin) to prevent clot formation in a variety of different disease states (acute coronary syndrome, atrial fibrillation, deep venous thrombosis and pulmonary embolism), clinical interventions (cardiopulmonary bypass surgery, extracorporeal membrane oxygenation for extracorporeal life support, hemofiltration, indwelling central or peripheral venous catheters and vascular surgery) and to coat surfaces of different devices.

Since heparin does not break down preexisting clots, but instead prevents new clots from forming, in microsurgery it is administered preoperatively to prevent clot formation at the site of vessel anastomosis.

In a rat model, Hudson et al. [26] demonstrated 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. Local irrigation for 10 min may enhance vessel patency [27] or at least decrease side effects compared to systemic application [28], but high irrigation pressure (<100 mm Hg) [29] must be avoided so as not to injure the endothelium.

LMWH has some advantages over unfractionated heparin (UFH), such as bioavailability, lower risk of side effects like heparin-induced thrombocytopenia [30] and presumably lower risk of bleeding [31]. These benefits seem to justify disadvantages of LMWH like limited possibilities for drug monitoring by partial thromboplastin time [32]. The steady dose-response relationship of LMWH makes them safe even in high-risk diseases such as kidney deficiency, which has a risk of LMWH accumulation.

Both UFH and LMWH are known to have antithrombin III-independent effects in terms of their release of NO [33] or tissue factor pathway inhibitors [34]. This may also explain why study results differ in the debate of whether LMWH is as effective on arterial thrombosis as UFH.

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

[35, 36]. Compared to aspirin or dextran, the bleeding risk is highest among heparin [37] and overall LMWH shows fewer side effects than UFH [38].

Aspirin

Acetylsalicylic acid irreversibly blocks cyclooxygenase, which normally produces thromboxane and other procoagulatory factors that activate platelets. The mechanisms by which aspirin exerts this effect are discussed in detail in the accompanying manuscript; therefore, we will focus instead 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 [39]. The time of aspirin administration is important. Kort et al. [40] observed that when administered 30 min prior to surgery aspirin had no antithrombotic effect, while other authors describe a significant increase in vessel patency when administered 10 h preoperatively [41]. Low-dose (5 mg/kg) aspirin has been shown to be sufficient to irreversibly block platelet thromboxane production while at the same time preserving endothelial prostaglandin I₂ and other antithrombotic prostaglandin synthesis [42].

Dextran/Hydroxyphenylacetate

Dextran is a complex polysaccharide made of many glucose molecules and is composed of chains of varying lengths. It is used as an antithrombotic (antiplatelet) to reduce blood viscosity and as a volume expander in anemia. Dextran 40 is one of several groups of colloidal fluids that are preferred in the US whereas hydroxyphenylacetate (6%) is more commonly used in Europe. Both are used for their antiplatelet and antifibrin effect [43], which occur via cell coating or their inhibition of α_2 -antiplasmin effects [44]. When used as plasma expanders, dextran has been shown to provide additional benefits through hemodilution and the associated improvement in blood rheological properties [45]. Risks associated with the use of dextran, such as unwanted bleeding, allergic reactions, acute renal failure [46] and cerebral edema, have been proposed but not proven in well-controlled trials. At the same time, significant improvements in clinical outcomes have not been demonstrated [47]. Disa et al. [48] compared aspirin versus dextran in free flap procedures and found no difference, but did report an increase in side effects in the dextran group. Riva et al. [49] compared prostaglandin E₁ and dextran and showed no improvement. Because of these unremarkable results, their potential risks and alternative anticoagulation, dextran has not gained widespread use in microsurgery.

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 (myocardial infarction, thromboembolic strokes, deep venous thrombosis and pulmonary embolism) in which thrombosis is a risk. However, different from heparin and aspirin, these agents are able to dissolve existing clots. These drugs have been found to be most effective when administered within the first 60 min after a thrombotic event. They are often administered in combination with other anticoagulant drugs, such as intravenous heparin or LMWH, for synergistic antithrombotic effects and secondary prevention.

As it relates to microsurgery, thrombolytic drugs have been shown to be more effective than heparin or dextran in dissolving clots [50] and, in a limited number of clinical trials, have been reported to be able to ‘rescue’ vessel anastomoses postoperatively [51]. In spite of these reports, others have reported that their use did not significantly increase free flap salvage rates [52]. The reason for this could be that the observed poor flap perfusion might be caused

by factors other than thrombotic occlusion of the pedicle anastomosis, i.e. embolic occlusion of the downstream flap microcirculation (see above). Due to the limited number of well-controlled trials, there are no definitive conclusive results regarding efficacy and appropriate dosing [5]. The risk of bleeding can be minimized by drainage [53].

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 [54]. It has been described as being most effective when administration is begun 2 weeks prior to surgery. *Pentoxifylline* has been shown to significantly improve arterial patency, but it should not be used in combination with LMWH. While the mechanisms differ, when used together they might have an undetermined antagonistic effect, as animal experiments have shown decreased patency [55].

Other clinically available antithrombotic agents are *iloprost*, a synthetic analogue of prostacyclin (prostaglandin I₂) [56], *hirudin*, which is extracted from the saliva of leeches and can inactivate thrombin antithrombin III [27, 57], 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 [58].

Antithrombotic agents in development include, *rivaroxaban* [59], *glycoprotein II/III antagonists* [60], different *snake venoms* [61], *clopidogrel* [62] and *recombinant tissue factor pathway inhibitors* [33].

Current Recommendations for Therapy

Evidence from Clinical Trials

Recommendations for the use of anticoagulation therapy in microsurgery vary greatly. In a 6-month prospective clinical study, 23 surgeons operated 493 free flaps and compared dextran, aspirin and heparinized irrigation showing no significant differences [63].

Considering that most patients fit into the category of general recommendations for thrombosis prophylaxis, overall heparin seems to be the first choice. This is the recommendation made by the German Language Working Group for Microsurgery of the Peripheral Nerves and Vessels. LMWH (administered subcutaneously) is considered to be better than UFH; continuous UFH is preferred only in patients with complicating factors like renal insufficiency.

Initiation of Drug Administration

The time point when an agent is administered is of crucial interest. Khouri et al. [64] found a nonsignificant decrease in flap failure when preoperative aspirin, dextran or heparin was used. Several surgeons recommend the use of heparin administered preoperatively, especially in at-risk patients. No evidence is available indicating that intraoperative bolus administration of heparin is beneficial. When used as the only antithrombotic drug, aspirin must be administered several hours before surgery to be effective. However, since aspirin increases the risk of bleeding, in cases that cause large bleeding donor sites, surgeons in Europe generally avoid using it for prophylaxis. In contrast, in cases of finger replants or flaps in the lower extremities, aspirin is used more frequently [65].

The duration of postoperative anticoagulant treatment described in the literature varies greatly, ranging from 3 days to 2 months. If a patient is maintained on a combination of agents, such as aspirin and dextran or aspirin and heparin, typically one of the agents is used for 3–7 days and then discontinued leaving the patient on a single drug for an extended period. In many cases, both agents are discontinued simultaneously after 3–7 days.

Combination Therapy and Add-Ons

The reason for using drug combinations is to reduce the side effects and increase the efficacy. Li and Cooley [3] described arterial and venous patency rates that approached 100% when heparin, aspirin and dipyridamole were used together. Increased risk of bleeding limits the use of these combined therapies to high-risk groups, however precise specifications regarding their administration do not exist.

Implications for Future Research and Conclusion

As has been mentioned throughout this review, antithrombotic treatment and prophylaxis regimens in microsurgery vary greatly from surgeon to surgeon and from institution to institution. The reason for this is the lack of large, well-controlled, clinical trials that compare the multiple treatments being used. In the absence of these trials, treatments will continue to be mixed, and best practice recommendations will not be impossible.

Careful preoperative patient selection and risk analysis together with a well-planned surgical strategy continues to be the best approach. This will minimize the risks of intra- or postoperative thrombosis. The investigation, development and introduction of new, safer and more effective antithrombotic agents continue. However, without well-controlled studies that measure and compare their safety and effectiveness to existing treatments, it is possible that 20 years from now someone will write a follow-up review to this one and start by saying 'not much has changed'.

In conclusion, the best antithrombotic prophylaxis and treatment in microsurgery consists of a multistep approach, focusing on risk-adapted monitoring and intervention. Considering the undisputed importance of a good microsurgical technique, quality microsurgical training cannot be underemphasized.

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