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Postsurgical antithrombotic therapy in microsurgery: our protocol and literature review

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Abstract. – OBJECTIVE: Despite the improvements reached by microsurgeons in the last 30 years, postoperative complications still occur and most of them are the result of venous thrombosis at the pedicle anastomosis. Primary prevention of thrombosis is mandatory and anticoagulant therapy in the preoperative and postoperative period is widely used. Still, there is a lack of consensus in the literature about the best postoperative protocol for microsurgical reconstruction. The authors aimed to review the postoperative antithrombotic regimens described in literature focusing on their effects and risks, and moreover, share their experience.

MATERIALS AND METHODS: The authors performed a literature review of postsurgical antithrombotic protocols applied in reconstructive microsurgery. Research on PubMed server was performed typing the terms "antithrombotic", "postoperative", "microsurgery", "free flap pedicle", "anticlotting", "anticoagulant".

RESULTS: The authors described the postoperative standardized pro-weight pharmacological protocol applied in their unit: a combination of dextran and heparin. They inhibit more than one pattern of coagulation in order to stop platelet aggregation and thrombin action and, in the meantime, contending fluid loss with plasma expansion.

CONCLUSIONS: Nowadays, a non-standardized practice, based on experience, is applied by microsurgeons in postsurgical care; the authors performed a review of the combined antithrombotic therapies described in the literature. A standardized pro-weight pharmacological protocol is proposed; it allows to increase blood flow by volume expander action (Dextran) and thrombin inhibition (Heparin). Still, coagulation cascade and platelet function have a wide variability among humans, as well as the effect of drugs. Achieving an optimal antithrombotic effect and minimizing adverse reactions meantime remains a challenge.

Key Words:
Microsurgery, Postoperative therapy, Anticoagulation, Antithrombotic, Free flap.

Introduction

Reconstructive microsurgery had great improvements in the last 30 years and has reached a high success rate nowadays[1-3]. An experienced microsurgeon with its meticulous technique is considered fundamental to achieve a successful free flap transfer or replantation[4]. Nonetheless, postoperative complications still occur[5-7]; most of them are the result of venous thrombosis at the pedicle anastomosis[8,9].

A microsurgical failure often leads to multiple surgeries and prolonged hospital stay with increased costs and delays in recovery and rehabilitation[10]. Vasospasm, thrombosis, haemorrhage and venous congestion are all early complications that can cause reduction of perfusion in the transferred or re-implanted tissue[11]. Among these, thrombosis is the most dreaded one and it is the

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main reason for flap loss with an estimated risk of 2-6%[12], and it can be even higher if a vein graft is exploited[13]. Surgical manipulation of the endothelium, as well as the trauma, often leads to anastomosis patency problems due to the sub-intimal collagen exposure; moreover, it triggers coagulation and microthrombi appearance[14,15].

Primary prevention is mandatory because re-do anastomosis as well as new flap surgeries present higher failure's rates[16]. Furthermore, the lack of recipient vessels can represent a challenge to the surgeon that has to deal with planning an alternative reconstruction; while the patient has to face an additional surgery with further donor site morbidity, and both functional and aesthetic questionable outcomes.

Perioperative antithrombotic therapy is widely given in free tissue transfer and replantation. Administration of anticoagulant therapy in the preoperative and postoperative period is intended to improve outcomes: it mitigates thrombus formation and improves perfusion to the transferred tissue. Hypercoagulability, venous stasis, and endothelial injury, known as Virchow's triad, are all encountered during free flaps surgery or replantation[17]. Heparin, dextran and acetylsalicylic acid are the most used agents in this field, but some emerging drugs, such as thrombolytics, prostaglandin E1 and statins can help to prevent anastomosis failure[11].

Many antithrombotic options are available and there is no consensus on the best postoperative protocol. Currently its application, indications, timing and duration is based on personal experience and practice[18]: most surgeons rely on anecdotal evidence based upon prior use. It is evident that the need for routine use of anticoagulant or antiplatelet, in the early postoperative period after free flaps microsurgical reconstruction, lacks in clinical evidence[19]. We aimed to review the postoperative antithrombotic regimens described in literature focusing on their effects and risks, and moreover, share our experience.

Heparin

Heparin[20] (Heparin IV, Heparin SC) is an anticoagulant, and it prevents both arterial and venous thrombosis acting on various systems: it inactivates the coagulation factors II, IX, X, XI, and XII[21], reduces the activation of coagulation factors V and VIII, lowers the recruitment of platelets and fibrin deposition[22], and increases vasodilation[23]. The useful dose of heparin depends on multiple factors, but an intraoperative bolus heparin (5000 IU) and low dose intravenous heparin (2000-3000 IU bolus, continued by 100-400 IU/h) are considered commonly both safe and effective in preventing free flap failures[24]. Hematoma[25], haemorrhage from the surgical site[26] and heparin-induced thrombocytopenia (HIT)[27] are the main adverse effects that Heparin can cause; they can be minimized by maintaining systemic heparin levels low. Low Molecular Weight Heparin (LMWH) is a derivative of unfractionated heparin; it has the same inhibitory effect on factor X but has a weaker antithrombin activity. The result is effective in preventing venous thrombosis with fewer adverse effects[28]. Low molecular weight heparin is usually exploited after re-exploration and thrombectomy for vascular failure of the flap[29]. Anti-Xa concentrations are commonly used to monitor LMWH therapy and the recommended peak anti-Xa concentration is 0.5-1.0 IU/ml or 1.0-2.0 IU/ml for full anticoagulation and 0.2-0.4 IU/ml for prophylactic anticoagulation for venous thromboembolism[30]. Generally, 2.500 U dose of LMWH is considered useful to reach therapeutic concentrations[31].

Dextran

Dextrans[32] are considered plasma expanders; they can cause plasma volume expansion and consequent hemodilution that improves blood flow and patency of microanastomosis[33]. Dextrans are available in multiple molecular weights and the larger ones (>60,000 Da) remain in the blood for weeks, with prolonged antithrombotic and colloidal effects. Dextran-40 (40,000 Da) is the most used for anticoagulant therapy and it is usually given at a dose of 25 ml/h for 5 days post-operatively[34]. Moreover, dextrans present an antithrombotic effect; they bind vascular endothelium, erythrocytes and platelets reducing erythrocyte aggregation and platelet adhesion. Platelets coated in dextran are stored more equally in a thrombus, and are bound by raw fibrin; it simplifies thrombolysis and makes dextrans anticlotting agents[35,36]. However, their clinical effectiveness is still on study: Ridha et al[37] reviewed their application after free flap and replantation performances with poor results, while Pomerance et al[38] showed successful results using a combination of Dextrans (500 cc/24 h) and Aspirin (10 grains bid) for at least three days after finger replantation. Despite their efficacy, Dextrans present an increased risk of anaphylactoid reactions, adult respiratory distress syndrome, cardiac overload, hemorrhage, and renal damage[39].

Acetylsalicylic Acid

Acetylsalicylic acid (ASA) impairs thrombin generation and platelet aggregation. It is frequently used in the post-operative period by reconstructive surgeons as an anticlotting agent[40]. ASA can cause some important side effects as increased blood loss if used intra-operatively[41], and renal dysfunction or gastrointestinal bleeding for its non-selective cyclooxygenase inhibition[42]. Common ASA daily preventive dosage is 80-325 mg[43]. Some studies report low efficacy of ASA if used alone with low dose[44], however it is usually administered in combination with other drugs, such as heparin. Lee et al[45] showed off the efficacy of controlled continuous heparinization (CCH) over intermittent bolus heparinization (IBH) in distal digital replantation outcome. The IBH group patients received 300 mg of ASA, 10 μg of Prostaglandin E1 and intermittent intravenous bolus of 12.500 U of heparin daily. On the other hand, the CCH group was treated with a lower dose of ASA (100 mg per day) and the same amount of Prostaglandin E1, and heparin (12500 U) was administered continuously mixed in 500 mL of 5% dextrose at a rate of 20 mL per hour. In this study, CCH represented a statistically significant variable in replantation success rate; while neither major bleeding complications nor significant decrease in platelet levels were observed in both groups.

Thrombolytics

Thrombolytics (Streptokinase, Urokinase, Tissue-type Plasminogen Activator) can reverse microvascular thrombosis in animal models[46,47], but there are few studies that describe their effect on human models[48]. Intraoperative doses are 100,000-250,000 IU of urokinase/streptokinase or 15 mg of t-pa (Tissue-type Plasminogen Activator), that are infused over 30 minutes[49,50]. Postoperatively, thrombolytic agents can be injected through local intra-arterial and intravenous infusions as well as regional soft tissue injection[51].

Huang et al[52] employed Urokinase intraoperatively (600,000 U diluted in 30 ml saline) and postoperatively (200,000 U/12 h) managing limb or finger replantations. They showed off how urokinase could be used postoperatively in intermittent small doses to prevent thrombosis, and in high doses for vascular crisis management in the early stage. However, their use is associated to highly elevated risk of haemorrhagic complications[24].

Prostaglandin E1

The biological mechanism of Prostaglandin E1 (PGE1) action along with the reason for the long duration of its anti-ischemic and tissue-protective effects are still unknown. At the microcirculatory level, PGE1 presents vasodilating, antithrombotic and anti-ischemic properties. In addition, it has anti-inflammatory effects, inhibiting monocytes and neutrophils function[53]. As reported by the manufacturer, common side effects of PGE1 are headache, flushing and pain, reddening and edema along infusion vein. Less common events are allergic reactions, decrease in systolic blood pressure, tachycardia, angina pectoris, nausea, vomiting, diarrhoea, leukopenia, leukocytosis, thrombocytopenia, liver enzyme abnormalities and pulmonary edema. The preliminary study conducted by Rodríguez Vegas et al[54] showed the efficacy of PGE1 (40 μg/12 h) as an innovative therapy in intraoperative and postoperative care of free tissue transfers. It was associated to heparinized saline 100 U/ml, heparin (intraoperative bolus of 40 U/kg), LMWH (prophylactic doses until the adequate mobilization of the patient) and ASA (100-375 mg/24 h for 30 days).

Results

HMG-CoA reductase inhibitors

Recently, 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, better known as Statins, were presented as beneficial for free flap survival due to their vasoprotective and anti-inflammatory effect over endothelium[55]. Indeed, statins present the ability to reduce inflammation and thrombogenicity. Furthermore, they improve vasodilation and they are commonly used in the management of hyperlipidemia and prevention of coronary artery disease, stroke and ischemic events[56]. Well-known side effects are rhabdomyolysis[57] and adverse effects on liver with rare reports of liver failure[58]. In microsurgery, endothelium can be damaged during anastomosis and its inflammatory state and dysfunction can lead to reduction of anticoagulant factors and thrombi formation[59]. Statins can restore endothelial function, targeting inflammation, coagulation and vasoconstriction. Karsenti et al[60] described a preoperative 2-weeks treatment protocol with statins (40 mg of atorvastatin per day), continued after free flap surgery until complete stabilization of the patient. In their opinion, statins seem useful in free flap surgery for the reduction of perioperative morbidity and mortality and for limitation of the ischaemia-reperfusion damages on the free flap tissues.

Bloodletting and leech therapy

Bloodletting and the therapeutic use of medical leech (*Hirudo medicinalis)* date back to ancient Egypt and the beginnings of civilisation[61]. The first reported modern day use of leeches, alleviating venous engorgement following flap surgery, was published by Derganc and Zdravid in 1960[62].

Histological studies have shown that venous obstruction causes microcirculatory thrombosis, trapping of platelets and stasis. Even after successful reanastomosis, some changes in the microcirculation may persist; moreover, the re-establishment of normal circulation is prevented. The management of the congested flap may include application of leeches[63], usually 1 or 2 per session[64].

Without the proper treatment, the congested tissue becomes ischaemic, and such condition leads to tissue necrosis. A randomized control trial of leech-treated venous-compromised rodent epigastric skin flaps showed a significant increase in flap survival rate[65]. Furthermore, Riede et al[66] reported that the early application of medicinal leeches could improve local hemodynamic conditions in case of venous congestion and hematoma following plastic reconstructive surgery. The increased blood flow seems to result from a combination of bleeding, because it relieves obstruction and raises capillary pressure, and effects on the microcirculation caused by the leech's vasoactive secretions.

The main complication of leech therapy is infection. The reported incidence ranges from 2% to 36%[67]. It is due to the colonization of the leech gut with *Pseudomonas, Aeromonas hydrophila, Staphylococcus*, and other Gram-negative rods. Infection after leech therapy can cause septicemia, local tissue damage, flap failure, prolonged hospital stay, need for additional antibiotics, and even death[68]. Severe infections should be treated with aggressive debridement and high-dose antibiotics; reported flap survival in infected cases is less than 30%[69]. As an alternative to medicinal leeches "pin-pricking" of congested flaps is common. In our opinion this procedure is indicated only for slight venous congestion, as the inferior bleeding time makes it less effective than medicinal leech therapy.

The haematocrit "controversy"

Increased blood viscosity is an established risk factor for thrombosis[70]. Due to their discoid shape, deformability, intrinsic viscoelastic properties, and fibrinogen-binding ability, red blood cells (RBCs) are the primary determinants of blood viscosity[71,72]. RBCs likely contribute to arterial thrombosis and venous thromboembolism in unique ways[73].

The impact of hemodilution and the consequent effects of decreased haematocrit (HCT) on free flap microcirculation are highly controversial. Some small and medium retrospective studies investigated the effect of hemodilution on free flap survival in human subjects. Their results were absolutely conflicting, furthermore the cohort sizes and the retrospective nature of those studies limit conclusions[74-77]. For this reason, the use of hemodilution among microsurgeons in clinical practice is often various and not based on common scientific evidence, but rather on empirical unsystematic knowledge or personal experience. Furthermore, prospective human studies are hardly feasible; the randomization of human subjects would set an ethical matter, and the multifactorial nature of flap survival would make the results tough to understand.

Only few studies using a free flap animal model have been conducted[78-81]. They showed that hemodilution could improve the microcirculation, because of the change in blood viscosity associated with the anaemic state. Decreased viscosity would result in lower resistance, higher blood flow, and improved flap perfusion, thus leading to an increased ischemia tolerance and lower thrombosis rates. Moreover, hemodilution promotes reduction in platelet and erythrocytes aggregation, and dilution of coagulation factors.

Analysis of the problem and our algorithm

We strongly believe that a meticulous anastomotic technique has a dramatic importance to achieve a successful free flap or replantation. Furthermore, several factors affect the microvascular architecture: smoking history, alcohol abuse, radio- or chemotherapic treatment are considered threats to the patency of the vessels.

The postoperative antithrombotic regimens described above present their own mechanisms of action, ways of administration and risks, and they are resumed in Table I. All those agents could be combined to reach an optimal antithrombotic therapy. The targets are the coagulation cascade and the platelet aggregation as their mechanisms appear to be synergetic[11].

Vretos and Tsavissis[82] described the use of a combination of ASA, Dextran and two different thrombolytics as a successful post-operative antithrombotic protocol after replantation or free tissue transfer. Whereas Maeda et al[83] wrote about the benefits of

Table I. Postoperative antithrombotic agents for microsurgery practice.

Antithrombotic agent	Way of acting	Benefits	Dosages	Side effects/ Drawbacks
Heparin	Inhibition of thrombin generation, recruitment of platelets and formation of fibrin.	Efficient delivery of a minimal therapeutic dose to the site of vascular anastomosis.	2000-3000 IU bolus, continued by 100-400 IU/h.	Risk of hemorrhage, hematoma, heparin-induced thrombocytopenia.
Low Molecular Weight (LMWH)	Inhibition of factor X with a weaker antithrombin (factor II) activity than heparin.	Effective in preventing venous thrombosis with fewer adverse effects than heparin. It presents a more predictable dose–response relationship, greater bioavailability, and longer-half life.	Dose adjustment is performed using anti-Xa concentrations. 2500 U of LMWH are considered therapeutic.	Doubts about its efficacy in preventing arterial thrombosis.
Dextran	Lowering of erythrocyte aggregation and platelet adhesiveness. They are osmotic agents; they cause volume expansion and hemodilution that improve blood flow.	Same antithrombotic efficacy of intra-arterial versus intravenous dextran.	Dextran 40: 25 ml/h.	Risk of anaphylaxis, hemorrhage, cardiac volume overload, adult respiratory distress syndrome, pulmonary edema, cerebral edema, platelet dysfunction, acute renal failure.
Aspirin (ASA)	ASA inhibits the platelet enzyme cyclooxygenase and impairs platelet aggregation. It impairs thrombin generation too.	Effect increases when co-administered with another antiplatelet agent.	80-325 mg/day	ASA can increase transfusion and re-operation rates. Risk of renal dysfunction and gastrointestinal bleeding.
Thrombolytics	They act reversing microvascular thrombosis.	Useful in intermittent small doses to prevent thrombosis, and in high doses for vascular crisis management in the early stage.	200,000 U/12 h	High risk of haemorrhagic complications.
Prostaglandin E1	Vasodilating, antithrombotic anti-ischemic and anti-inflammatory properties.	Long duration of anti-ischemic and tissue-protective effects.	40 μg/12 h	Common side effects: headache, flushing, pain, edema. Less common: allergic reactions, decrease in systolic blood pressure, tachycardia, angina pectoris, nausea, vomiting, diarrhoea, leukopenia, leukocytosis, thrombocytopenia, liver enzyme abnormalities and pulmonary edema.
Leech therapy	Thanks to bleeding and anticoagulant effect (hirudin), they relieve congestion and vasodilate the micro circulation.	Powerful and localized anti-coagulant effect.	1-2 leeches per session	Risk of significant blood loss, infection.

Table II. Post-surgical antithrombotic combined therapies in microsurgery. The last line shows the standardized pro-weight pharmacological protocol applied in our unit in postoperative care of free flaps surgery or replantation.

Authors	I.V. Heparin/Low Molecular Weight Heparin (LMWH)	Dextran-40	Acetylsalicylic acid (ASA)	Thrombolytics	Prostaglandin E1 (PGE1)	Fluids	Others
Maeda et al. Br J Plast Surg. 1991	10,000 U heparin for 10 days			240,000 I.U. urokinase for 10 days	40 µg for 10 days		
Vretos and Tsavissis. Acta Orthop Scand Suppl. 1995		440 mL divided in 2 doses	330 mg + 75 mg dipyridamole	60,000 IU streptokinase and 15,000 IU streptodonase			100 mg diclofenac
Pomerance et al. J Reconstr Microsurg. 1997		500 cc/24 h for at least 3 days	10 grains bid for at least 3 days				
Rodríguez Vegas et al. Microsurgery 2007.	Prophylactic doses of LMWH until the adequate mobilization. Heparinization (100 U/ml) in selected cases		100-375 mg/24 h for 30 days		40 µg /12 h for 5-7 days		
Lee et al. Medicine (Baltimore). 2016	Group 1: intermittent intravenous bolus of 12.500 U of heparin daily Group 2: 12.500 U of heparin in 500 mL of 5% dextrose continuously 20 ml / h		Group 1: 300 mg/day Group 2: 100 mg/day		Group 1 and 2: 10 µg/day		
Authors' pro-weight protocol 2019	Day 1-5: I.V. heparin 50 U/kg/24h Day 6-7: LMWH 50 U/kg/24h	Day 1-5: 250 cc/24h if HCT: 27-30; 500 cc/24h if HCT: >30				Day 1-5: 40 cc/kg/24h if HCT: >30 Day 6-7: 20 cc/kg/24h if HCT: >30	Bloodletting up to 500 ml if HCT >36

local continuous intra-arterial infusion of urokinases, heparin and PGE1 associated for the same clinical use.

The European Society of Cardiology undertook a research on the best antithrombotic protocol that could be applied in various conditions[84]. After revascularization, in patients with lower extremity arterial disease (LEAD), the ones receiving a prosthetic graft were more likely to benefit from administration of platelet inhibitors; while patients treated with venous grafts reached better results with anticoagulant therapy, even if their risk of major bleeding was two-fold higher[85]. The Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial disease (CASPAR) randomized double-blind trial[86] compared the efficacy of aspirin plus clopidogrel *vs.* aspirin alone in below-knee venous or prosthetic bypass graft success. No significant difference was found in the primary outcome, but subgroup analysis was in favour of a beneficial effect of the double antiplatelet therapy in prosthetic grafts.

A similar investigation was conducted with the collaboration of the European Society for Vascular Surgery[87]: no difference in graft patency was found between ASA and vitamin K antagonist (VKA), but there were significantly fewer venous bypass occlusions under VKA, even if doubled bleeding risk was registered. Marginal benefit and more bleeding were found also comparing double antiplatelet therapy (DAPT) with VKA plus clopidogrel in femoro-popliteal bypass.

In conclusion, many studies were taken into account and no definitive indications could be found. Table II resume the various combinations of drugs described in literature for what concerns post-operative antithrombotic care in free flap surgery. We searched for a combination that inhibits various patterns of coagulation, in order to stop platelet aggregation and thrombin action, meantime contending fluid loss with plasma expansion.

In our unit, a standardized pro-weight pharmacological protocol with dextran and heparin is applied in all cases of free flaps transfer or replantation. This daily pharmacological protocol is carried out intravenously for seven days postoperatively. The full dose is administered until the fifth day, when the microanastomosis area get covered with pseudointima[88]. Lower dosages are given in the last two days. Additionally, when HCT is higher than 30%, intravenous fluids are administered; if the HCT gets higher than 36% in the second post-operative day we combine intravenous fluid with bloodletting therapy up to 500 ml. In our series we perform bloodletting through phlebotomy because it is easy to perform. Our prophylactic phlebotomy is performed only in selected patients. Future paths should include a multicentric randomized control trial evaluating the different therapies among reconstructing surgeons to establish a standardized protocol.

Conclusions

Achieving an optimal antithrombotic effect and minimizing adverse reactions meantime remains a challenge[89]. The literature does not contain adequate evidence to suggest an optimal postoperative anticoagulation regimen following free tissue reconstruction or replantation. Nowadays, microsurgeons apply a non-standardized practice based on experience. We offer a standardized pro-weight pharmacological protocol that allows to increase blood flow by volume expander action (Dextran) and thrombin inhibition (Heparin).

Conflict of Interests

The authors declare that there are no conflicts of interest.

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