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Prevention of Microsurgical Thrombosis

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1. Introduction

Free tissue transfer is a safe and reliable mode of tissue reconstruction. Though it is the highest rung on the reconstructive ladder, this method of reconstruction is utilized by a multitude of surgical specialties including: plastic and reconstructive, orthopaedic, otolaryngology, and oral maxillofacial. There are multiple indications for free tissue transfer. A few examples are: skeletal defects after debridement for osteomyelitis, breast reconstruction, various trunk and extremity defects, and most recently composite tissue allotransplantation – primarily face and hand transplantion. Despite employing perfect microsurgical technique, flap failure caused by anastomotic thrombosis continues to occurs in complicated and uncomplicated microvascular anastomosis. Many pharmacologic agents have been studied experimentally and clinically both in the treatment and prophylaxis of microvascular thrombosis; however, there still remains no consensus as to what the optimal pharmacologic regimen should be. In this chapter, we discuss the reported incidence of flap failure caused by microvascular thrombosis, review the pathophysiology of thrombus formation, review the anti-thrombotic pharmacologic agents commonly used for prophylaxis, and overview the current methods of flap monitoring.

2. Complications of free tissue transfer

The most common and feared complication of microvascular anastomosis is graft failure secondary to arterial or venous thrombosis. It is reported that this occurs in five to ten percent of cases[1]. Thrombosis is the body's natural defense mechanism to prevent blood loss. When a vascular insult occurs, the body employs platelets and fibrin to seal the defect. The physiologic process is initiated by the presence of tissue factor when injury to the vascular intima occurs. This results in the extrinsic pathway of the coagulation cascade to begin. Tissue factor activates factor X, which in turn activates thrombin, eventually leading to the activation of fibrinogen. When discussing free tissue transfer, the vascular intima has been injured as a result of the microsurgical anastomosis. It is imperative that the inherent process of coagulation be prevented. The use of pharmacologic anticoagulation has been a point of contention in free tissue transfer with no clinical study yielding conclusive evidence that it is the most effective means to prevent thrombosis.

In the vascular surgery literature, the use of pharmacologic anticoagulation has been shown to improve outcomes and patency rates. It has been described in the microvascular literature that three main pharmacologic agents exist and are used as an adjunct to preventing thrombosis. They are heparin, aspirin, and dextran. A multitude of pharmacologic protocols exist. Nearly all are based on anecdotal data Various doses of aspirin, heparin at subtherapeutic levels without titration to partial thromboplastin time, and intraluminal irrigation prior to completion of the anastomosis are a few examples. The authors explore the various pharmacologic agents and the evidence that exists in the literature. In addition, we review the methods for monitoring and protecting the fragile initial uncomplicated microsurgical anastomosis in order to prevent complication and reoperation.

3. Pharmacologic agents

ASPIRIN

Aspirin (acetylsalicylic acid) is part of the non-steroidal anti-inflammatory drug group (NSAIDs) and a well known medication for analgesia, antipyretic, and anti-inflammatory purposes. Its mechanism of action was described in 1971 by the British pharmacologist John Robert Vane[2] from the Royal College of Surgeons in London, and noted to prevent the production of thromboxanes and prostaglandins. It was shown that aspirin irreversibly inactivates the cyclooxygenase (COX) enzyme which is required for the synthesis of both thromboxane and prostaglandin. Aspirin functions differently when compared to other NSAIDs in that it acetylates the serine residue in the active site of the COX enzyme, whereas other NSAIDs bind reversibly. This property affords aspirin the ability to inhibit platelet aggregation, the primary role of thromboxane A_2, for the life of the platelet. Furthermore, aspirin decreases endothelial production of prostacyclin which acts as a vasodilator and inhibitor of platelet aggregation. It has been shown that low doses (40-80mg) selectively inhibit platelet-derived thromboxane by 95% while only slightly decreasing endothelial derived prostacyclin (35%). However, the aspirin dose of 325mg decreases prostacyclin production by 75%. The side effect profile for aspirin includes bronchospasm, peptic ulcers, gastritis, risk of gastric hemorrhage with concurrent use of alcohol of warfarin, hemolytic anemia in glucose-6-phosphate dehydrogenase deficiency[3], gout exacerbation, and Reye's syndrome[4](potentially fatal disease affecting the brain, liver, and other organs in children with concurrent viral illness). Despite the side effect profile, surgeons performing vascular anastomosis and free tissue transfer take advantage of the platelet aggregation inhibition properties of aspirin.

HEPARIN

Heparin was discovered in 1916 and noted to be a highly sulfated glycosaminoglycan with the highest negative charge density of any known biological molecule[5]. Heparin as well as enoxaparin (a low molecular weight derivative) has been shown to be effective in preventing deep venous thrombosis (DVT) and pulmonary embolism (PE) in at risk patients[6]. The primary function of heparin is the binding of antithrombin III (ATIII) which renders it active due to increased flexibility of the reactive site loop of the enzyme as a result of a conformational change[7]. Due to this, ATIII inactivates thrombin induced activation of factors V and VIII as well as factor Xa, which are all important factors in the coagulation cascade. Heparin can be administered as a once or multi daily dose for

prevention/prophylaxis of DVT and/or PE in at risk hospitalized patients. The dose depends on the formulation/preparation of heparin, patient renal function, and patient weight. The side effect profile of heparin most notably includes heparin-induced thrombocytopenia (HIT) with or without thrombosis (HITT). In this phenomenon, antibodies are produced against heparin when it is bound to a protein (platelet factor 4) which forms a complex that attaches to a receptor on the surface of a platelet resulting in activation of platelet microparticles leading to the formation of a thrombis[8]. As a result, thrombocytopenia ensues and the patient is also at risk of hemorrhage. Additionally, other side effects include elevation of serum aminotransferases which is not a result of liver dysfunction, but rather a drug effect, and hyperkalemia as a result of heparin-induced aldosterone suppression. As a result of heparin's mechanism and proven effects, systemic therapy has been employed by cardiothoracic and vascular surgeons to maintain patency of vascular anastomosis.

DEXTRAN

Dextran is a complex branched glucan with weights ranging from 3 to 2000 kilodaltons made from the polysaccharide fermentation of sucrose. The use of dextran in microsurgery revolves around its ability to decrease vascular thrombosis by reducing blood viscosity. This effect is hinged on dextran's binding of platelets, vascular endothelium, and erythrocytes which increases the overall negative charge thereby reducing aggregating properties. As a result, low molecular weight dextrans impair platelet function, prolong bleeding time, destabilize fibrin polymerization, act to expand blood volume by acting as potent osmotic agents, and decreased stability of platelet thrombus. The side effect profile of dextran is relatively small yet severe. The list includes anaphylaxis, pulmonary edema, cerebral edema, platelet dysfunction, and volume overload. Occasionally, acute renal failure has been described as a result of dextran

4. Anticoagulation use in free tissue transfer

In a study by Davies[9] in 1982, a questionnaire was dispersed to 73 microsurgery centers worldwide. In the responses, 825 free flaps were evaluated which showed that 691 surgeons used varying methods of anticoagulation, and 161 surgeons used no form of anticoagulation including no intraluminal heparin irrigation. In the anticoagulation group, it was found that there was an 89% success rate of free flap survival versus an 88% success rate in the non-anticoagulation group. This study was flawed by a lack of control for anticoagulation protocol which made inferences difficult to determine from the results.

In 1997, a study by Glicksman[10] surveyed microsurgeons' practices over a four year period and administered a retrospective questionnaire to investigate anticoagulation regimens. From these findings, 96% of respondents used some form of antithrombotic treatment. The various regimens employed by surgeons included: dextran, heparin, and aspirin. Of these surgeons who used dextran, 75% gave dextran intraoperatively and continued treatment for three to seven days. Other surgeons used heparin as an intraoperative bolus of 3000U to 5000U. Additionally, aspirin at a dose of 325mg once a day for up to fourteen days postoperatively was also documented. It is notable that this type of variety exists in that there is no empirical evidence in the literature to support these various protocols.

5. Evidence for aspirin

In 2005, a study by Chien[11] showed that in 216 head and neck reconstruction cases a post operative anticoagulation regimen of aspirin 325mg daily and administering heparin at 5000U subcutaneous twice a day showed similar flap survival and hematoma rates versus other anticoagulation protocols. This study however was limited by a lack of an internal control.

6. Evidence for heparin

A prospective multi-institutional study by Khouri[12] in 1998, which included 23 centers over a six month period, yielded 493 free tissue transfers to be evaluated. The results of the study showed a 4.1% flap failure rate, 8.3% intraoperative thrombosis, and 9.9% postoperative thrombosis requiring reexploration. It was found that administering only postoperative subcutaneous heparin therapy was responsible for a statistically significant decrease in the incidence of thrombosis. Further, it was concluded that intraluminal heparin, intraoperative systemic heparin, aspirin, and dextran had no impact on thrombosis rates and overall outcome. Unfortunately, this study was limited by the diversity of anticoagulation protocols used by each participating center.

In an animal model conducted by Ritter[13] in 1998, these authors investigated whether unfractionated heparin, low molecular weight heparin, could improve the patency of microvascular anastomoses. They concluded that due to the hematoma rate being present only in the unfractionated heparin group, that low molecular weight heparin is the anticoagulant of choice to both maintain vascular anastomotic patency and minimize hemorrhage.

7. Evidence against heparin

Pugh[14] in 1996 conducted a retrospective study evaluating the use of anticoagulants during surgery. It was determined that of the 15 patients who underwent microvascular free flap reconstruction for wound coverage, the use of heparin in addition to other anticoagulants had a higher associated hematoma rate versus the use of dextran and aspirin, both separately and together. This finding confirms the current regimen employed by most surgeons that the use of a single anticoagulant is necessary.

8. Evidence against dextran

While heparin, aspirin, and dextran all have pharmacologic properties making them wonderful agents to prevent anastomotic thrombosis and flap failure, they each have a side effect profile that is not benign. Many of the side effects are quite rare, and they each have the ability to cause bleeding and possibly overwhelming hemorrhage. Further, dextran has the ability to cause devastating systemic complications including anaphylaxis and volume overload leading to cerebral and/or pulmonary edema.

Disa[15] in 2003 found that patients receiving dextran had up to a 7.2 times increased rate of developing a systemic complication versus patients receiving aspirin. As a result, low molecular weight dextran was removed from use at that institution as an option for anticoagulation after head and neck reconstruction.

Further, in a study from 2003 by Sun[16], it was concluded that dextran was not necessary for microvascular anastomosis thrombosis prevention as the dextran free arm of their review had a 100% patency rate versus 96% in the dextran use group. Additionally, they mention the serious side effects of dextran and note that they can be prevented by not using this pharmacologic agent.

9. No evidence of efficacy

In a study from 1994, Kroll evaluated 517 free tissue transfers[17]. It was shown that the relationship between the use of anticoagulants and prevention of flap loss or prevention of thrombosis could not be established. Further, it was also concluded that low-dose (bolus heparin) in the perioperative period did not significantly increase the risk of hematoma.

Deutinger[18] in 1998 conducted a study evaluating the influence of dextran versus heparin as well as the technique of the anastomosis in free tissue transfer. In the study, 81 patients received dextran and heparin postoperatively, and 123 patients received heparin alone. It was found that there was no statistically significant difference in the rate of thrombosis in these two groups. However, an 8.9% ($p < 0.02$) higher rate of thrombosis was found with end-to-end anastomosis as compared with end-to-side.

In 2004, Veravuthipakorn[19] conducted a study to determine whether a pharmacologic agent is necessary to prevent anastomotic thrombosis and flap failure. They discussed 40 cases of free tissue transfer and replantation in which no antithrombotic agent was instituted intraoperatively or postoperatively. Their results showed one partial flap loss and two replantantion losses due to severe crush injuries. They state that technique is paramount in microvascular anastomosis. It was concluded that antithrombotic agents alone do not play a significant role in anastomotic patency.

Ashjian[20] in 2007 looked at 505 microvascular free tissue transfers to reconstruct oncologic defects, in which they allocated 260 patients to receive postoperative aspirin for five days whereas 245 patients received low molecular weight heparin. It was concluded that postoperative anticoagulation choice has no statistically significant effect on the incidence of free flap complications in terms of the following outcome variables: microvascular thrombosis, partial or total flap loss, hematoma, bleeding, deep venous thrombosis, pulmonary embolism, and death. They stated that aspirin and low molecular weight heparin therapy demonstrate equivalent outcomes when used as a single-agent in the posoperative period. The authors also concluded that intraoperative systemic heparin had no statistically significant effect on prevention of microvascular thrombosis, and a single dose of intraoperative heparin does not prevent thrombosis. They believe that intraoperative anticoagulation does not affect flap survival.

In 2010, Brands[21] conducted a review of the literature which showed that there is currently no consensus in the literature to prevent thrombosis after microvascular free flap reconstruction. Conclusions were drawn that non-pharmacologic means such as smoking cessation and meticulous microvascular surgery plays a crucial role in the outcome. The authors stated that it has not been determined as to which preoperative, intraoperative, or postoperative protocol for pharmacologic anticoagulation regimen is most effective to

prevent thrombosis, and that the decision should be made based on the individual patient and the risk profile for the development of thrombosis.

10. Conclusions

From these powerful studies in the current literature, it is evident that surgeons utilize preoperative, intraoperative, and postoperative anticoagulation to prevent the catastrophic negative outcome of vascular thrombosis leading to flap failure and necrosis. The specific method used by surgeons thus far is based upon operator preference. These highlighted studies provide evidence that there is no definitive protocol in microsurgery to prevent thrombosis; although there are some important insights that can be agreed upon after a careful review of the literature.

First and foremost, the rate of flap failure in microvascular surgery is very low, with success rates generally >95%. When flaps fail, it is not always a result of vascular thrombosis, but rather can be for a variety of other reasons as well, including improper flap inset, systemic hypotension, or perhaps even as a result of certain medications that causes severe vasoconstriction (which is certainly occasionally necessary as a life saving measure). When rates of flap failure are so low, and when they have multiple causes, it requires an extremely large study in order to show a statistically significant difference in any type of intervention. Thus far, such a study does not exist in regards to anticoagulation.

It is fair to say, based on one of the largest prospective studies (REF 12), that at the very least, subcutaneous heparin injections should be considered, if no other anticoagulant is to be used. Although this was certainly a flawed study, it was one of the largest studies, drawing upon the experiences of many of the most reputable microsurgery centers at that time. Because of the well established benefit of subcutaneous heparin in DVT prophylaxis, along with the long period of immobilization that these patients invariably experience at least during surgery, subcutaneous heparin does appear to be a prudent option. Currently, in our own institution, low molecular weight heparin injections has generally replaced regular heparin for DVT prophylaxis. It is also the opinion of the authors, that the risk of Dextran prophylaxis, as pointed out by the Disa study (REF 15), is enough evidence to preclude its use in our practice, particularly considering the lack of any other clinical data to support its use in preventing thrombosis in microvascular surgery. In summary, although anticoagulation may have a limited benefit in preventing thrombosis in microvascular surgery, it is far more important to perform a technically perfect operation, with painstaking attention to detail along every step of the procedure, including patient selection, pre-operative behavior modification (such as smoking cessation), flap selection and design, flap inset, and post-operative flap monitoring and care. The use of the venous coupling systems, as well as the recently available intra-operative fluoresence imaging system using indocyanine green dye are two technological advances that may prove to be quite beneficial in improving outcomes in microvascular surgery.

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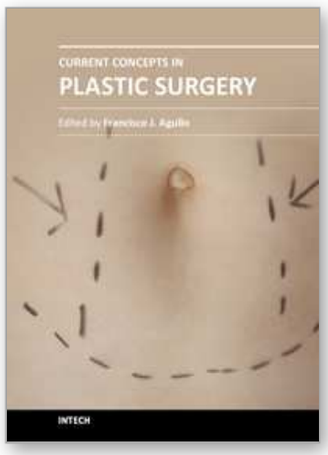

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Plastic surgery continues to be a rapidly growing field in medicine. There have been multiple recent advancements in the field. Specifically, there has been a continuously growing interest in fat grafting, body contouring, minimally invasive surgery, and plastic surgery education. At the same time, there have been continued advances and modifications in surgical techniques, which translate into better and improved results for our patients while increasing safety and efficacy. The title of the book is Current Concepts in Plastic Surgery and, as such, it highlights some of the "hot topics" in recent years. We have invited renowned specialists from around the world to share their valued expertise and experience. Most of the chapters will expose the reader to multiple techniques for achieving desired results, with emphasis on the author's preferred methodology.

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