



## EFFECTS OF POST-OPERATIVE ASPIRIN AND LOW MOLECULAR WEIGHT HEPARIN (LMWH) IN MICROVASCULAR FREE FLAPS IN LOWER LIMB RECONSTRUCTION AND THEIR OUTCOMES.

### Plastic Surgery

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### ABSTRACT

**Objective:** Examine if outcomes and complication rates for free flaps vary when postoperative aspirin and LMWH are used as pharmacologic thromboprophylaxis compared with only low dose heparin.

**Background:** Many protocols exist to prevent thrombosis after free-tissue transfer. Many surgeons advocate using low dose heparin and aspirin or other antiplatelet agents in the postoperative period, but little objective evidence supports this practice. This study evaluates the rate of microvascular thrombosis in patients undergoing free-tissue transfer treated with or without antiplatelet agents.

**Methods:** All consecutive free flaps for lower limb reconstruction from 2011–2017 at a single centre were reviewed retrospectively using a maintained database. Patients were divided in 2 groups based on postoperative anticoagulation administration. In group A, 5000 units of LMWH per day for 5 days with 325 mg of aspirin was administered daily for 30 days postoperatively. In group B, 5000 units of LMWH per day for 5 days. Patient demographics, diagnosis, procedure type were recorded. Outcome variables included microvascular thrombosis, partial or total flap loss, hematoma, bleeding, deep venous thrombosis (DVT), pulmonary embolism, and death.

**Results:** 634 patients underwent microvascular free flaps for lower limb reconstruction. 254 flaps (group A) received postoperative LMWH & aspirin therapy; 380 flaps (group B) received LMWH therapy only. Both groups were statistically similar in their composition. No statistically significant difference was noted between the 2 groups when comparing outcome variables including microvascular thrombosis, partial or total flap loss, hematoma, bleeding, DVT, pulmonary embolism, and death.

**Conclusions:** Postoperative aspirin administration has no statistically significant effect on the incidence of free flap complications, including bleeding, thromboembolism, and flap loss. We conclude LMWH with or without aspirin therapy demonstrates equivalent outcomes when used as postoperative anticoagulation in free flap reconstruction.

### KEYWORDS

#### INTRODUCTION:

Free flaps are considered to be a common and reliable surgical technique for covering large defects all over the body.<sup>1</sup> Microvascular free tissue transfer has revolutionized reconstructive surgery and a large number of surgical flaps are available to meet the needs of the recipient site.<sup>2</sup> The first clinical microvascular free tissue transfer was done in 1972.<sup>3,4</sup> With improvements in surgical techniques and devices, the reported overall rates of success of free flaps in the literature are as high as 95% to 97% in case of experienced surgeons. Antithrombotic prophylactic agents, such as low molecular weight heparin, aspirin and dextran have been routinely used for the prevention of microvascular thrombosis.<sup>5</sup> Despite of the above precautions 5 to 25% of transferred flaps require surgical revision due to circulatory compromise on the arterial or venous side.<sup>5</sup>

If the flap failure is due to thrombosis, arterial thrombus develops during the first 24 hours and venous thrombosis forms in the second postoperative day.<sup>1,6</sup> Currently there is no consensus as to what is the ideal anticoagulation regimen if any for patients undergoing free flap reconstruction.<sup>7</sup> In the present study we review outcomes and complication rates for free flaps for lower limb reconstructions when postoperative aspirin and LMWH were used compared with only LMWH in our tertiary care centre.

#### MATERIALS AND METHODS:

All consecutive free flaps from 2011–2017 at our centre were reviewed using a prospectively maintained database. The study included only patients undergoing lower limb reconstruction with free flaps. Head and neck surgeries were excluded from the study. Patients already on antithrombotic agents for prothrombotic conditions, atrial fibrillation, deep venous thrombosis were excluded from the study. Postoperatively, we monitored the perfusion status by tissue colour observation every 1 hour during the first day and then more widely apart and pin prick test every day or if any doubt was present regarding the blood flow.

Patients were divided in 2 groups based on postoperative anticoagulation administration. In group A, 5000 units of LMWH per day was given for 5 days while 325 mg of aspirin was administered orally daily for 30 days postoperatively. In group B, 5000 units of LMWH per day was given for 5 days only. Patient demographics, diagnosis, procedure type, anaesthesia duration were recorded. Outcome variables included microvascular thrombosis, partial or total flap loss, hematoma, bleeding, deep venous thrombosis (DVT), pulmonary embolism, and death.

Statistical analysis was performed using the Fisher exact test to detect differences in complication rates between group A and group B, with a null hypothesis that postoperative anticoagulation did not affect outcome. The sample size of 634 flaps (and greater than 245 flaps in each group) resulted in a power of 0.85. That is, using these numbers we have an 85% chance of finding a statistically significant difference between the 2 groups if one in fact exists. The study was approved by our institutional review board and ethics committee.

#### RESULTS:

634 free flaps for lower limb reconstruction were studied during the period 2011–2017. The mean age of patients was comparable in the two groups. Both male and female patients were equally distributed amongst group A and B. Out of 634 free flap patients 254 belonged to group A whereas 380 patients were in group B. Group A comprises of all the surgeries in the first three years of the study where both the anticoagulants were used whereas group B comprises of all the surgeries in the last four years where only LMWH was used. The operating surgeons and the standard of care remained the same throughout the study period.

Complications: In group A, 67 out of 254 patients had microvascular thrombosis postoperatively while 78 out of 380 patients had thrombosis in group B but this difference was not found to be statistically significant (Figure 1). 20% of patients in group A and 17% patients in group B had flap loss either partial or complete. This

difference was also not found to be statistically significant. The other complications like bleeding, hematoma, DVT, pulmonary embolism and death were comparable in the two groups. (Figure 2)

STATISTICS

Complications	Group A ( LMWH + Aspirin)	Group B ( LMWH )	Total	p Value
Total No Of Patients	254	380	634	
Microvascular Thrombosis	67 (26.37%)	78 (20.52%)	145	0.08
Haematoma	46 (18.11%)	65 (17.1%)	111	0.744
Bleeding	86 (33.85%)	94 (24.73%)	180	0.08
Flap Loss ( Partial / Complete )	51 (20.07%)	67 (17.63%)	118	0.437
DVT	24 (9.44%)	31 (8.15%)	55	0.571
Pulmonary Embolism	8 (3.14%)	11 (2.89%)	19	0.853
Death	6 (2.36%)	5 (1.31%)	11	0.322

Figure 1: Comparison of postoperative complications between group A and B

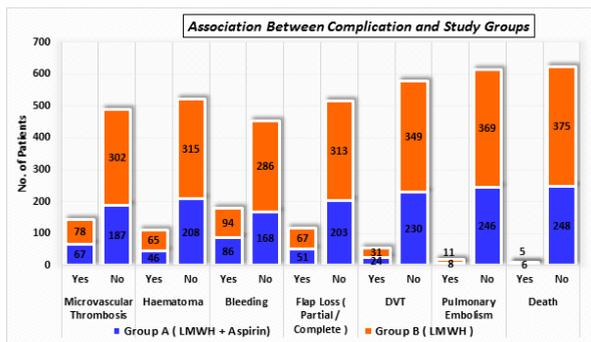


Figure 2: Graph showing comparison of postoperative complications between group A and B

DISCUSSION:

Although free-tissue transfer remains a safe and reliable mode of oncologic reconstruction, pedicle thrombosis continues to occur in up to 10% of cases despite refined microsurgical techniques.<sup>3</sup> Prophylactic anticoagulation is used to prevent pedicle thrombosis and flap failure. However, the choice of anticoagulation remains controversial. An ideal antithrombotic agent should have the following characteristics: 1) It should be effective in prevention of pedicle thrombosis 2) minimal side effects 3) low risk of bleeding 4) ease of administration.<sup>7</sup> Johnson PC, Barker JH in their review study on thrombosis and antithrombotic therapy in microvascular surgery concluded that the best prophylaxis against thrombosis in microvascular surgery is 'excellent surgical technique and proper patient selection.'<sup>8</sup> Khouri et al attempted to determine the relative contribution of platelets and fibrin to the thrombosis of microvascular anastomoses. Selectively blocking the thromboxane pathway and using heparin to block thrombin, they concluded that fibrin aggregation was more important to thrombosis than platelets. This would suggest that heparin anticoagulation rather than aspirin is the key to maintaining microanastomotic patency.<sup>9</sup>

Savoie et al,<sup>10</sup> studied thrombus composition using scanning electron microscopy. Their findings support the clinical use of 2 agents used simultaneously, one inhibiting fibrin strand formation and the other inhibiting platelet adherence aggregation, for the prevention of microarterial thrombosis. In another study Li and Cooley<sup>11</sup> showed that platelets play a major role in arterial thrombosis, whereas fibrin is central to venous thrombosis.

Due to the fact that both arterial and venous thrombi play a role in flap failure, it can be inferred from the above studies that a combination of antiplatelet and antifibrin agents must be employed. Davies DM in 1982 conducted a world survey of anticoagulation practice in clinical microvascular surgery, a total of 825 free flaps were studied. There were 161 cases of no anticoagulation use (including intraluminal heparin irrigation) and 691 cases of varying anticoagulation. This study showed no statistically significant difference between success rates between the 2 groups (88% no anticoagulation versus 89% anticoagulation). The lack of control for the anticoagulation protocol was a shortcoming of this investigation. Khouri et al<sup>9</sup> published the largest prospective multi-institutional trial on microvascular free flap surgery and outcome. They examined 23 centers over a 6-month

period, with a total of 493 free flaps. There was an overall 4.1% flap failure rate, 8.3% intraoperative thrombosis, and 9.9% post-operative thrombosis requiring re-exploration. They concluded that only postoperative subcutaneous heparin therapy had a statistically significant decrease in the incidence of thrombosis. Intraluminal heparin irrigation, intraoperative systemic heparin (bolus or infusion), aspirin, or dextran had no impact on thrombosis and outcome. This study is limited by the diversity of anticoagulation protocols used by each participating center.

Chien et al,<sup>7</sup> studied 216 head and neck reconstructions, they reported that a postoperative anticoagulation regimen of aspirin (325 mg daily) and subcutaneous heparin (5000 U SC twice a day) resulted in similar flap survival and hematoma rates as compared with other anticoagulation protocols. The limitation of this study was the lack of an internal control and faulty comparison of their results to published reports from other centres. This study was different from our study as we included only lower limb reconstruction with free flaps and not head and neck flaps. As a protocol at our centre aspirin as an anticoagulant is not given in head and neck flaps.

Brands M.T, Van den Bosch, published a review article on Prevention of thrombosis after microvascular tissue transfer in the head and neck in Dutch Head and Neck Cancer Centres. No consensus in the literature was found on how thrombosis could best be prevented. The Dutch Head and Neck Cancer Centers use routine deep venous thrombosis prophylaxis to prevent thrombosis in the anastomosis. It was also concluded that non-pharmacologic measures for preventing thrombosis, such as meticulous microvascular surgery and smoking cessation prior to the operation, are thought to play an important role in the prevention of thrombosis in microvascular free-flap reconstructions. A pharmacologic regimen to prevent thrombosis that is customized to the patient is suggested. This should be based on an individual risk profile for the development of thrombosis.<sup>13</sup> Jokuszies A, Herold C et al from the department of plastic, hand and reconstructive surgery, Germany conducted a review study on anticoagulation strategies in reconstructive surgery.

Antithrombotic measures are based on adequate microsurgical technique, patient selection, adequate recipient vessels, prevention of vessel spasm intraoperatively, prevention of external compression, pharmacological anticoagulation, optimized perioperative fluid management, early anastomotic revision in case of thrombosis. Undoubtedly however the lack of microsurgical experience and bad technique can never be compensated by any regimen of antithrombotic therapy. All the more, the development of consistent standards and algorithms in reconstructive microsurgery is absolutely essential to optimize clinical outcomes and increase multi-centric and international comparability of postoperative results and complications<sup>14</sup>. Enajat M, Mohammadi M, Debeij J, conducted a study on effect of acetylsalicylic acid on microvascular thrombosis in autologous breast reconstruction. The study included patients undergoing deep inferior epigastric artery perforator or free transverse rectus abdominis myocutaneous flap breast reconstruction at two academic centres in Netherland between 2005 and 2011. Patients at one centre received once daily 0.6ml of nadroparine and 40mg acetylsalicylic acid, while patients at the other centre received 0.6ml of nadroparine only. A total of 430 consecutive patients underwent 592 breast reconstructions. No statistically significant differences were found in the two groups in incidence of flap failure (2.8 and 2.5%), microvascular thromboembolic complications (2.6 and 3.8%), venous congestion (3.4 and 2.8%), or overall complications (28.0 and 32.3%). Hematoma tended to occur in the acetylsalicylic acid group (9.2 and 4.7%). So there was no protective effect of acetylsalicylic acid on microvascular complications. Hence its routine use was stopped.<sup>15</sup> Kearns M in their review article on standardization of training and practice of reconstructive microsurgery- recommendation for anastomosis thrombosis prophylaxis concluded that higher level studies are needed to investigate the clinical use of antithrombotic medications in microsurgery; however, given the small failure rates in modern practice, these will need to be large multicenter trials in order to reach sufficient power.<sup>16</sup>

Salgado et al<sup>17</sup> suggested aspirin and LMWH alone or a combination of them as anticoagulant medications. Dassonville et al<sup>18</sup> used LMWH as the anticoagulant agent and the result was 6.6% flap failure with 15% of cases being re-explored. Ebrahim karimi in their study concluded that the aspirin-enoxaparin short-term protocol may be a good choice

after free flap transfer in reconstruction of head and neck surgical defects.<sup>19</sup> Froemel D, in their review of thrombosis and antithrombotic therapy in microvascular Surgery concluded that 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.<sup>20</sup> Andreas M. Fichter in their study found that clopidogrel and hirudin are effective pharmacological agents that significantly increased the viability of perforator-based skin flaps in rats, but at a higher risk of postoperative bleeding.<sup>21</sup>

Limitations of our study: Our study is limited by the difference in the number of patients in the two groups, this difference was due to the choice of antithrombotic of the operating surgeon in the first three years and the later four years.

Conclusion: Postoperative aspirin administration has no statistically significant effect on the incidence of free flap complications, including bleeding, thromboembolism, and flap loss. We conclude LMWH with or without aspirin therapy demonstrates equivalent outcomes when used as postoperative anticoagulation in free flap reconstruction.

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