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# Low-molecular-weight heparin salvage in pedicled flap reconstruction in head and neck: a prospective cohort study

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## Main Article

Smriti Panda takes responsibility for the integrity of the content of the paper

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## Abstract

**Objective.** To determine if systemic administration of low-molecular-weight heparin impacts venous compromise in loco-regional flap reconstruction for head and neck subsites.
**Methods.** This prospective study was conducted on patients who had developed features of venous compromise of the flap. The case group received low-molecular-weight heparin (dalteparin).
**Results.** Of the 73 patients who developed venous congestion, low-molecular-weight heparin was administered in 47 patients. In the low-molecular-weight heparin subset, 23 patients had either reversal or non-progression of venous compromise (48.9 per cent). Of the patients who had no response to low-molecular-weight heparin rescue, complete necrosis was seen in 4 and partial flap necrosis was observed in 19. The corresponding numbers in the control group were 13 and 12, respectively (odds ratio 23.9, $p = 0.002$). Additionally, the low-molecular-weight heparin arm had a lower incidence of partial or complete flap necrosis ($p = 0.002$).
**Conclusion.** Low-molecular-weight heparin salvage, when instituted early, is likely to result in a significant reduction in flap-related morbidity.

## Introduction

Reconstructive options for complex head and neck defects that arise following resection of head and neck cancer range from microvascular free tissue transfer to loco-regional pedicled flaps. Although the former is considered the standard of care, loco-regional flaps, such as pectoralis major myocutaneous flaps, still account for the vast majority of flap procedures performed in resource-constrained high-volume oncology centres in Asia. Pedicled flaps are also relevant in the salvage setting following the failure of microvascular free tissue transfer.[1]

Although pedicled flaps such as pectoralis major myocutaneous flaps are robust and considered the workhorse of head and neck reconstruction even today, rates of flap necrosis range from 17 to 63 per cent.[2] Underlying factors responsible for the necrosis of a pedicled flap include compression of the pedicle, twisting of the pedicle, local oedema and vascular spasm.[3,4] Venous insufficiency has been found to outnumber arterial spasm following reconstruction due to either free tissue transfer or pedicled flaps.[4] The following reasons account for the greater vulnerability of venous channels: lower pressure in the venous system compared with the arterial system predisposing the former to compression injury, oedema and torsion, and insufficient venous outflow channels in some flaps, with concomitant high flow arterial influx.[4]

Venous insufficiency in a pedicled flap needs to be regarded with similar weightage as in the case of free tissue transfer. Once venous insufficiency is identified, the window period available for instituting salvage measures is crucial.[5] Unlike free tissue transfer, surgical re-exploration on account of venous insufficiency is not routinely undertaken for pedicled flaps.[4,5] Moreover, there are existing lacunae in the literature regarding successful salvage measures for early venous compromise in pedicled flaps. Hence, this study was undertaken to evaluate the role of low-molecular-weight heparin pedicled flaps showing signs of venous compromise.

## Methods

A prospective study was undertaken at a tertiary care oncology centre in India from January 2020 to July 2022. Patients who had undergone reconstruction for head and neck defects using loco-regional pedicled flaps and subsequently developed features of venous compromise were included. Patients receiving antiplatelet drugs (except low-dose

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aspirin) and warfarin were excluded. This study was conducted after obtaining institutional ethical approval (Institute Ethics Committee (IEC) PG-115/24.02.2022 and IEC PG-87/24). Informed written consent was obtained from all the participants.

### Intervention

The study population consisted of two groups with comparable baseline features. In Arm A, low-molecular-weight heparin (dalteparin) in a dose of 5000 Units was administered daily through the subcutaneous route for 5 days from the onset of venous insufficiency. Dalteparin belongs to the class of low-molecular-weight heparin. Unlike unfractionated heparin, dalteparin's mechanism of action involves more selective inhibition of factor Xa, thereby potentiating the antithrombin pathway.

In Arm B, no therapeutic intervention was undertaken following the onset of venous insufficiency.

The cases and controls were decided based on the treating unit to which the patient was admitted. Low-molecular-weight heparin was offered as salvage in one unit, whereas standard of care was followed for flap congestion in the other unit. Patient recruitment and data collection were done prospectively.

### Outcome

The primary outcome of this study was to determine the difference between the two arms in terms of the incidence of flap necrosis and the reversal of venous insufficiency. The secondary outcomes were to assess predictors of successful salvage with low-molecular-weight heparin. Adverse outcomes, especially bleeding-related complications, were also compared between the two arms. All patients were followed up for a minimum of four weeks post-operatively to determine the final outcome in terms of flap viability.

### Statistical analysis

All statistical analyses were performed using Medcal version 20.114. Comparison between the two groups was undertaken using the chi-square test. An unpaired *t*-test was used to identify the difference between the two means. Univariate analysis was performed using Fischer's exact test. Multivariable analysis was performed using logistic regression. A $p$ value less than 0.05 was taken to be statistically significant.

## Results

A total of 280 pedicled flap reconstructions were undertaken during the study time frame. Table 1 details the various flaps used for reconstruction. Of these, 73 flaps were included because of the presence of venous congestion. In addition, 47 out of 73 patients received low-molecular-weight heparin for venous congestion and were included in Arm A. The majority of the venous congestions were identified beyond 48 hours of surgery (71.4 per cent *vs* 28.5 per cent). The rest of the 26 patients were grouped under Arm B and did not receive any therapeutic intervention for venous congestion.

Table 2 summarises the baseline attributes of the two study populations. The groups were well balanced in terms of sex distribution, mean age, type of pedicled flap used and subsite reconstructed ($p > 0.05$). However, Arm B had a higher percentage of segmental mandibulectomy defects than Arm A ($p < 0.001$).

**Table 1.** Outcome following pedicled flap reconstruction

| Outcome | Cases (*n*) | Venous congestion (*n* (%)) | LMWH rescue (*n*) |
|---|---|---|---|
| PMMF | 213 | 43 (20.18) | 29 |
| IHMF | 33 | 13 (39.39) | 9 |
| SCAIF | 34 | 17 (50) | 9 |

LMWH = low-molecular-weight heparin; PMMF = pectoralis major myocutaneous flap; IHMF = infrahyoid myocutaneous flap; SCAIF = supraclavicular artery island flap

**Table 2.** Baseline characteristics of Arm A (LMWH arm) and Arm B (control arm)

| Characteristic | Arm A (*n* = 47) | Arm B (*n* = 26) | *p* |
|---|---|---|---|
| Sex (*n*) | | | 0.44 |
| – Male | 38 | 19 | |
| – Female | 9 | 7 | |
| Mean age ± SD (years) | 45.1 ± 11.80 | 48.5 ± 8.04 | 0.19 |
| Type of flap (*n*) | | | 0.5 |
| – PMMF | 29 | 14 | |
| – IHMF | 9 | 4 | |
| – SCAIF | 9 | 8 | |
| Subsite (*n*) | | | 0.19 |
| – Tongue | 18 | 6 | |
| – Buccal mucosa | 29 | 20 | |
| Procedure | | | |
| – Glossectomy (*n*) | | | |
| – STG/NTG | 9 | 3 | 1 |
| – CTG | 9 | 3 | |
| Mandibulectomy (*n*) | | | |
| – SM | 20 | 11 | <0.001 |
| – MM | 9 | 9 | |

LMWH = low molecular weight heparin; SD = standard deviation; PMMF = pectoralis major myocutaneous flap; IHMF = infrahyoid myocutaneous flap; SCAIF = supraclavicular artery island flap; STG = subtotal glossectomy; NTG = near-total glossectomy; SM = segmental mandibulectomy; MM = marginal mandibulectomy

### Primary outcome: Flap viability at four weeks

#### Arm A

Of the 47 patients who received LMWH, 23 flaps either did not show signs of progression or underwent complete resolution of congestion (Figures 1A and 2). On follow-up, 19 flaps underwent partial necrosis of the congested segment (Figures 1B) and complete flap necrosis due to the progression of congestion was noted in 4 patients.

#### Arm B

Of the 26 patients who did not receive any therapeutic intervention, spontaneous resolution of venous congestion was observed in only 1 patient (Figure 1). The other 25 flaps underwent various degrees of necrosis (partial necrosis in 12, complete necrosis in 13).

#### Comparison of Arm A and Arm B

The difference between the two arms in terms of reversal or non-progression of venous congestion was found to be statistically significant, with an odds ratio in favour of Arm A (odds

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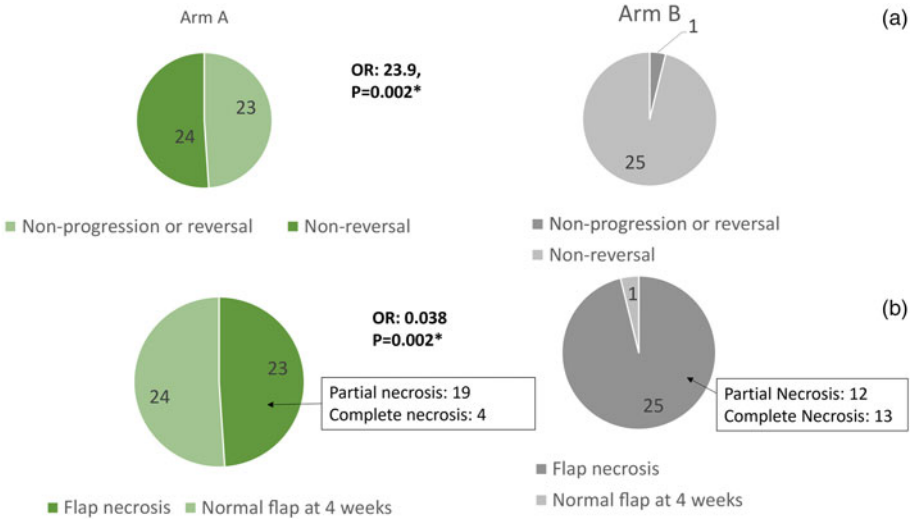


**Figure 1.** Pie chart depicting primary outcome analysis. (a) The difference between the two study arms in terms of reversal or non-progression of venous congestion. (b) The difference between the two study arms in terms of final flap viability at four weeks. Arrows are for showing a breakup of the number of cases depicted in the shaded area

ratio 23.9, $p = 0.002$). In terms of flap viability at 4 weeks, Arm B had a higher percentage of partial necrosis (46.15 per cent *vs* 40.42 per cent) and a higher incidence of complete necrosis (50 per cent *vs* 8.5 per cent). The latter difference was found to be statistically significant ( $p = 0.002$).

### *Secondary outcome: Predictors for successful salvage with low-molecular-weight heparin*

The variables considered in the univariate analysis were subsite reconstructed, type of flap and time of initiation of low-molecular-weight heparin (hours post-operatively) (Table 3). No statistically significant association could be demonstrated between subsite and type of flap with successful salvage. However, patients for whom low-molecular-weight heparin was initiated between 12 and 24 hours post-operatively ($n = 30$) demonstrated a 70 per cent salvage rate compared with a 13.3 per cent salvage rate in patients for whom low-molecular-weight heparin was initiated >24 hours post-operatively (odds ratio 15.6, $p = 0.005$).

### *Secondary outcome: Adverse effect analysis*

The incidence of surgical site hematoma was compared between Arm A and the remaining cohort of all patients (with or without venous congestion, $n = 233$). Arm A had a 12.76 per cent hematoma incidence while the rest of the cohort had a 2.57 per cent hematoma incidence (odds ratio 6.67, $p = 0.0017$). All patients ($n = 12$) who developed surgical site hematoma required a return to the operating theatre for evacuation of hematoma and clots. One patient in the non-low-molecular-weight heparin group required ligation of the external carotid artery. Hematoma formation did not prolong hospital stay, time to adjuvant treatment and time to oral feed initiation nor did it predispose to surgical site infection in any of the patients.

Multivariate analysis using logistic regression was performed to determine the predictors for secondary haemorrhage in the entire cohort of 280 patients. The factors considered were hypertension, chronic liver disease, coronary artery disease with a history of low-dose aspirin intake, abnormal coagulogram (defined as an international normalised ratio greater than 2) and low-molecular-weight heparin administration. The independent prognostic variables identified were hypertension (odds ratio 5.745, 95 per cent confidence interval (CI) = 1.40–23.5, $p = 0.01$) and low-molecular-weight heparin administration (odds ratio 7.7, 95 per cent CI = 2.04–29.15, $p = 0.002$). The study was limited in assessing the interaction between antiplatelet and low-molecular-weight heparin towards bleeding-related complications because only three patients were identified as receiving both antiplatelet and low-molecular-weight heparin.

## Discussion

This study prospectively evaluated the efficacy of low-molecular-weight heparin (dalteparin) in pedicled flaps used in head and neck reconstruction showing venous congestion ($n = 47$) compared to 26 patients who did not receive any therapeutic intervention for congestion and hence served as the control arm. In the intervention arm, 48.96 per cent of the flaps showed either reversal or non-progression of venous congestion. In the control arm (Arm B), only 1 patient showed signs of spontaneous reversal (3.8 per cent) ( $p = 0.002$). This translated to a significant difference between the two arms in terms of incidence of complete flap necrosis at 4 weeks (Arm A 8.5 per cent, Arm B 50 per cent) ( $p = 0.002$).

We also assessed the predictors for successful salvage and found higher salvage rates in the subset of patients where low-molecular-weight heparin was initiated in the early post-operative period (12–24 hours). The salvage rate documented in the early initiation subset was 70 per cent and the salvage rate in the subset where low-molecular-weight heparin was administered after a lapse of 24 hours was 13.3 per cent ( $p = 0.0015$).

The options available to increase flap viability in the context of microvascular free tissue transfer are myriad. Because of the paucity of evidence for the pedicled flap, this study was designed by extrapolating the available evidence in the field of microvascular reconstruction.[5] Although there is no uniform consensus even amongst microvascular surgeons, commonly employed agents targeting the coagulation pathway include heparin and its analogues, dextran, aspirin and statins.[6] An ideal antithrombotic agent in the setting of reconstruction should prolong flap viability and at the same time not cause unnecessary complications related to bleeding.[7] Because of the risk of post-operative haemorrhage, unfractionated heparin has been gradually replaced with low-molecular-weight heparin.[8]

Other reasons for favouring low-molecular-weight heparin over unfractionated heparin are the requirement for activated partial thromboplastin time (APTT) in the case of unfractionated heparin and the possibility of heparin-induced

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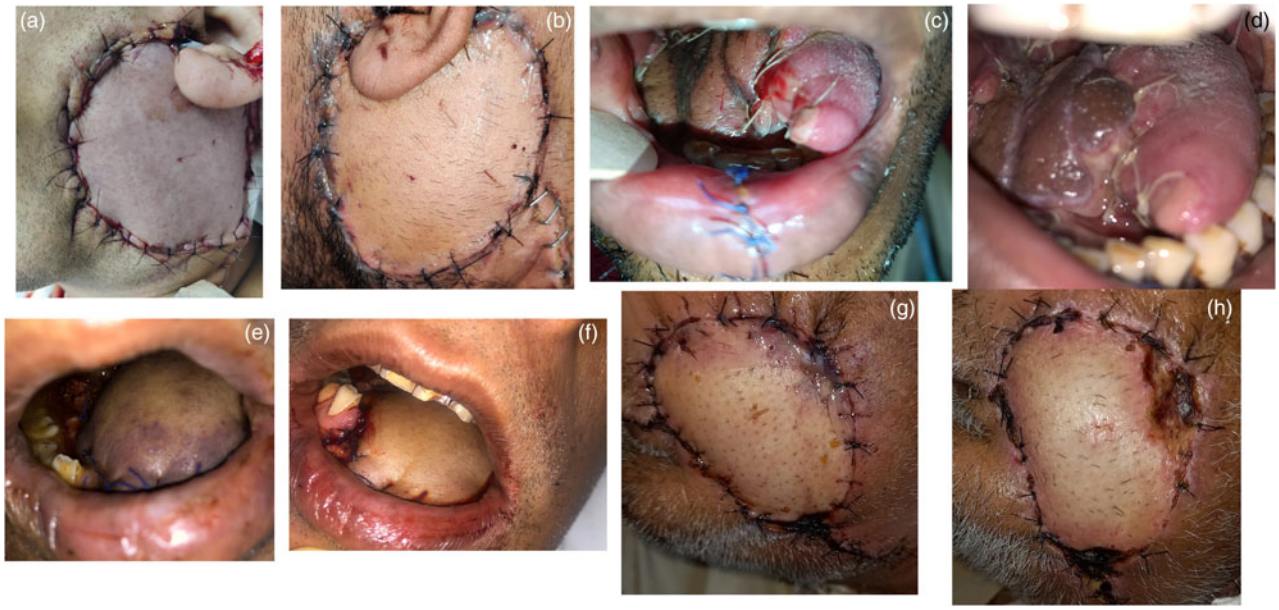


**Figure 2.** Before and after intervention images from Arm A. Before (a) and after (b) images of a congested pectoralis major myocutaneous flap used for skin coverage after radical parotidectomy showing complete reversal of congestion at 72 hours. Before (c) and after (d) images of an infrahyoid flap repair following compartment glossectomy showing non-progression of the congested area at four weeks post-operatively. Before (e) and after (f) images of a pectoralis major myocutaneous flap following subtotal glossectomy showing complete resolution of the congested area five days post-operatively. Before (g) and after (h) images of a bipaddle pectoralis major myocutaneous flap repair following full-thickness excision, segmental mandibulectomy and infratemporal fossa clearance showing the non-progression of congestion and partial necrosis of the congested area at four weeks

**Table 3.** Univariate analysis

| Factors influencing successful salvage with LMWH | | | | |
|---|---|---|---|---|
| Variable | Successful salvage (*n*) | Unsuccessful salvage (*n*) | Odds ratio | *p* value |
| Subsite | | | 1.07 | 0.90 |
| – Tongue | 9 | 9 | | |
| – Buccal mucosa | 14 | 15 | | |
| Time of administration | | | | 0.0015* |
| – 12–24 hours | 21 | 9 | 15.16 | |
| – >24 hours | 2 | 13 | | |
| Type of flap | | | | 0.65 |
| – Myocutaneous flap | 18 | 20 | 0.72 | |
| – Non-myocutaneous flap | 5 | 4 | | |
| Adverse effect analysis for entire cohort (*n* = 280) | | | | |
| Group | Secondary haemorrhage (*n*) | No secondary haemorrhage (*n*) | Odds ratio | *p* value |
| LMWH group (*n* = 47) | 6 | 34 | 6.67 | 0.0017* |
| Non-administration of LMWH complete group (*n* = 233) | 6 | 227 | | |

LMWH = low molecular weight heparin

thrombocytopenia.[6] Unlike heparin and its analogues, which target the coagulation pathway involved in venous thrombosis, aspirin, which is a cyclooxygenase inhibitor, functions by inhibiting platelet aggregation.[6] Studies performed by Khouri *et al.* on the fibrin and platelet content of anastomotic clots showed higher fibrin content than platelet content, thereby recommending heparin as the primary antithrombotic agent.[9] However, later studies utilising scanning electron microscopy have shown equal contents of fibrin and aspirin.[10] Thus, many microvascular surgeons have incorporated aspirin along with low molecular heparin in their antithrombotic armamentarium.[7] Nevertheless, the possible detrimental effects of combining two antithrombotic agents, as observed by Bahl *et al.* in their analysis involving a large database of otolaryngology patients receiving chemoprophylaxis for venous thromboembolism, should be noted.[11]

The role of statins is yet to be confirmed by larger studies.[6] Dextrans have also not been used in a widespread manner owing to possible side effects relating to volume overload, compromising the cardiovascular system in susceptible individuals and anaphylactic reactions.[6]

Our extensive literature search did not reveal studies performed on subcutaneous low-molecular-weight heparin salvage of compromised pedicled flaps. Thus, to the best of our knowledge, this is the only prospective study investigating the role of subcutaneous low-molecular-weight heparin in

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pedicled flap venous congestion. We did, however, identify one series of 9 compromised pedicled flaps where local injection of heparin showed a dramatic response, resulting in 100 per cent salvage rates.[5]

Unlike pedicled flaps, antithrombotic measures are routinely employed in microvascular free tissue transfer. However, the literature is conflicted over the efficacy of routine antithrombotic agent use in free flap surgery. In a meta-analysis conducted by Pan *et al.*, no statistically significant difference in terms of flap viability was noted amongst patients receiving either heparin or aspirin.[12] This study also found a higher rate of flap loss in the patient group receiving high-dose low-molecular-weight heparin. The only study skewing the results against high-dose low molecular weight heparin is that by Blackburn *et al.*, which reported higher flap loss with increasing dose of heparin, but without an increase in the incidence of bleeding-related complications.[13]

In the study by Numajiri *et al.* on unfractionated heparin, the heparin group was shown to cause significant prolongation of APTT and prothrombin time, causing an increase in bleeding-related complications while not resulting in a significant alteration in final flap viability.[8] Contrary to these studies, Eley *et al.* showed that high-dose dalteparin as used in our study did not increase bleeding risk.[8,12,13,14] In addition, it was found that lower doses of dalteparin caused an insufficient level of anti-factor Xa, which is a surrogate marker for low-molecular-weight heparin efficacy.[14]

The best evidence favouring subcutaneous heparin use following free flap surgery was reported by Khouri *et al.*[15] In their series of 493 free flaps, subcutaneous heparin use significantly reduced thrombotic complications in the flaps. Despite the literature being conflicted, real-world data, as revealed by a survey by Glicksman et al., showed that 96 per cent of reconstructive surgeons use some form of antithrombotic measure.[16]

There is little data regarding routine antithrombotic drug administration in otorhinolaryngology outside of a free flap reconstruction.[11] The Caprini risk assessment tool is commonly used to predict the predisposition of a patient for postoperative venous thromboembolism.[17] In the study by Bahl *et al.*, 30 per cent of patients with head and neck cancer and those undergoing reconstruction were found to have a Caprini score of 7 and higher compared to 16 per cent of non-oncology otolaryngology patients.[11] Although this study found subcutaneous low-molecular-weight heparin to be useful in the context of prevention of venous thromboembolism events in the above subset, results related to flap viability were not presented.

The study by Bahl *et al.* documented higher bleeding rates in patients receiving a combination of antiplatelet and low-molecular-weight heparin.[11] An 11.9 per cent incidence of bleeding complications was identified in patients post free flap reconstruction receiving thromboprophylaxis, which compares well with the 12.76 per cent incidence in our study.[11]

Kroll *et al.* performed a non-randomised prospective study on 517 free flap procedures, comparing no anticoagulation, low-dose heparin bolus and post-operative infusion, high-dose intra-operative bolus and dextran.[18] Hematoma rates were highest in the high-dose heparin group (20 per cent) and were 6.5 per cent in the low-dose group. However, flap survival and rates of pedicle thrombosis were lower than in patients who did not receive any form of anticoagulation ($p > 0.05$). Similar results were also observed in the study by Khouri *et al.*, in which hematoma rates were higher in the anticoagulation group and better results in terms of flap viability were also observed in these patients.[15]

As observed in our study, although hematoma rates were high compared with the rest of the cohort, we did not record the prolongation of hospital stay, delay in initiation of feeds or adjuvant treatment owing specifically to this complication. However, the sequelae associated with a compromised flap that goes on necrose to a significant extent can be disastrous in terms of treatment package time, quality of life and requirement of a second salvage flap.

Once venous congestion sets in, time to intervention is paramount. As noted in our study (Table 3), when the time to initiation exceeded 24 hours, only 2 flaps could be satisfactorily salvaged. Our results in pedicled flaps closely correspond to the findings observed in microvascular free tissue transfer.[6] In free flaps, 90 per cent of arterial thrombi and 42 per cent of venous thrombi occurred on the first post-operative day and 95 per cent of free flap re-explorations occurred in the first 72 hours.[6]

Although this study presents a novel idea to salvage pedicled flaps with early-onset venous congestion and results have been compared with a well-balanced control group, it was limited by the small sample size, especially of the control arm. The study also lacks a detailed analysis of surgical complications and other parameters of bleeding tendencies, such as the requirement for blood transfusion and the duration of surgical drain placement.

- It was found that 48.9 per cent of flaps could be effectively salvaged following the administration of low-molecular-weight heparin
- The low-molecular-weight heparin group had a significantly lower incidence of partial and complete flap loss compared with the control group
- Administration of low-molecular-weight heparin within 12–24 hours of flap congestion was associated with a higher salvage rate (odds ratio 16.6)
- The use of low-molecular-weight heparin was associated with a higher incidence of secondary haemorrhage rates

## Conclusion

Low-molecular-weight heparin (dalteparin) used in a dose of 5000 units subcutaneously once a day following venous congestion showed immense promise towards salvaging pedicled flaps which without any intervention have a remote chance of reversal, thereby drastically reducing the incidence of complete necrosis of the flaps.

**Competing interest.** None declared

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