JOURNAL OF PLASTIC SURGERY AND HAND SURGERY
2022, VOL. 56, NO. 5, 285–290
https://doi.org/10.1080/2000656X.2021.1968417

ARTICLE

Management of venous flap insufficiency: the role of low molecular weight heparin in salvage

İlknur Bayır[a], Cemal Alper Kemaloğlu[b] and Kemal Deniz[c]

[a]Department of Plastic, Reconstructive and Aesthetic Surgery, Amasya State Hospital, Amasya, Turkey; [b]Department of Plastic, Reconstructive and Aesthetic Surgery, Faculty of Medicine, Erciyes University, Kayseri, Turkey; [c]Department of Pathology, Erciyes University, Kayseri, Turkey

ABSTRACT

Flap loss resulting from venous insufficiency is a difficult issue, both with pedicled or free flaps. We examined the efficiency of low molecular weight heparin administration in various forms and dressing methods in venous insufficiency. Forty-five Sprague Dawley rats were included and inferior epigastric artery perforated island flaps were obtained from the abdominal skin of the animals. Nine animals were randomly allocated to each of five experimental groups: sham-control (Group 1), venous occlusion only (Group 2), occlusion with systemic enoxaparin (Group 3), occlusion with systemic enoxaparin + local enoxaparin infusion to the punctiform incisions (Group 4), and occlusion with systemic enoxaparin + local enoxaparin infusion to the punctiform incisions and enoxaparin-impregnated sponge dressing (Group 5). Group 5 had higher flap survival rates than the other groups. Groups 3 and 4 had numerically better vitality than the control group, but the difference was not significant. Low molecular weight heparin administration, with or without punctiform incisions, is not efficient in rescuing flaps with venous insufficiency. Specialised dressing methods are necessary to maintain bleeding.

ARTICLE HISTORY
Received 14 April 2021
Accepted 9 August 2021

KEYWORDS
Venous congestion; venous insufficiency; heparin; salvage therapy

Introduction

Flaps are critical instruments in reconstructive operations. Venous congestion continues to be a serious issue, both with pedicled and free flaps, that can be observed in the initial or later periods after surgery [1,2]. Venous congestion may result from mechanical pressure, venous thrombosis, or technical problems, as well as due to venous anatomy or uncertain causes [3–5]. Half or total flap loss is unavoidable if venous congestion is not immediately prevented.

Venous flap insufficiency can be managed surgically or medically. An operation is the gold standard method, particularly in the initial onset of venous issues due to mechanical or technical causes [6]. The later or unknown causes, or patients with inappropriate systemic states usually necessitate medical techniques. Medicinal leeches, hyperbaric oxygen therapy (HBOT), thrombolytic agents and low molecular weight heparin (LMWH) administration are the most commonly applied medical methods [7–11]. Medicinal leeches can improve venous flow considerably, but it has disadvantages, such as restricted accessibility, infection and significant iatrogenic blood loss [12]. Although HBOT greatly increases the survival of venous flap [9], this method is disputed and cannot be easily accessed [13]. Thrombolytic drugs may help with venous flap salvage [14]; however, their true potential and efficiency are uncertain [15].

Contrarily, LMWH is an accessible, safe and easy-to-apply method that can be used to manage venous congested flaps. It is usually utilised in subcutaneous injections with or without punctiform incisions [11,16]. Unfortunately, venous drainage cannot be maintained for a long time due to the short-acting local results of LMWH or blood clots on the punctiform incisions. Therefore, another method utilising LMWH should be used in treatment. We aimed to assess the efficiency of LMWH in different forms and dressing methods in the treatment of venous insufficiency.

Materials and methods

This study was conducted in line with the international regulations of Erciyes University Animal Experiments Laboratory after the approval (TTU-2018-8234) of the Ethics Committee was obtained. Forty-five male Sprague Dawley rats weighing 280–395 g were included in this study. Rats were randomly assigned to five groups, with nine animals in each. The process of the operation and planning of the experiment are thoroughly described.

Process of operation

Rats were anaesthetised by intraperitoneal administration of 10 mg/kg xylazine (Rompun; Bayer AG, Leverkusen, Germany) and 80 mg/kg ketamine hydrochloride (Ketalar; Pfizer, New York, USA) and the abdominal skin was shaved with electric scissors. The inferior superficial epigastric artery flaps were designed as 6 × 3 on one-half of the abdomen and elevated as island flaps, including the panniculus carnosus. The pedicle artery and vein were detected and isolated under the microscope and the vein was clamped for occlusion, depending on the experimental group. The flap was sutured into its initial site with a transcutaneous running suture (Figure 1).

CONTACT Cemal Alper Kemaloğlu dralperkemaloglu@yahoo.com Department of Plastic, Reconstructive and Aesthetic Surgery, Faculty of Medicine, Erciyes University, Köşk Mahallesi Prof. Dr. Turhan Feyzioğlu cad., No: 42, Melikgazi/Kayseri 38039, Turkey

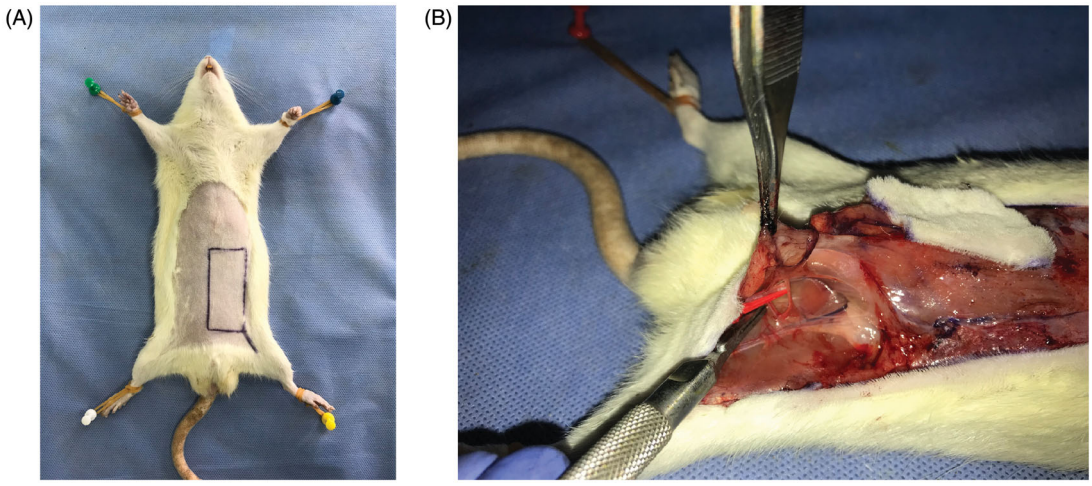


Figure 1. (A) Preparing the surgical area and drawing the flap (B) Detaching the flap and occluded vein.

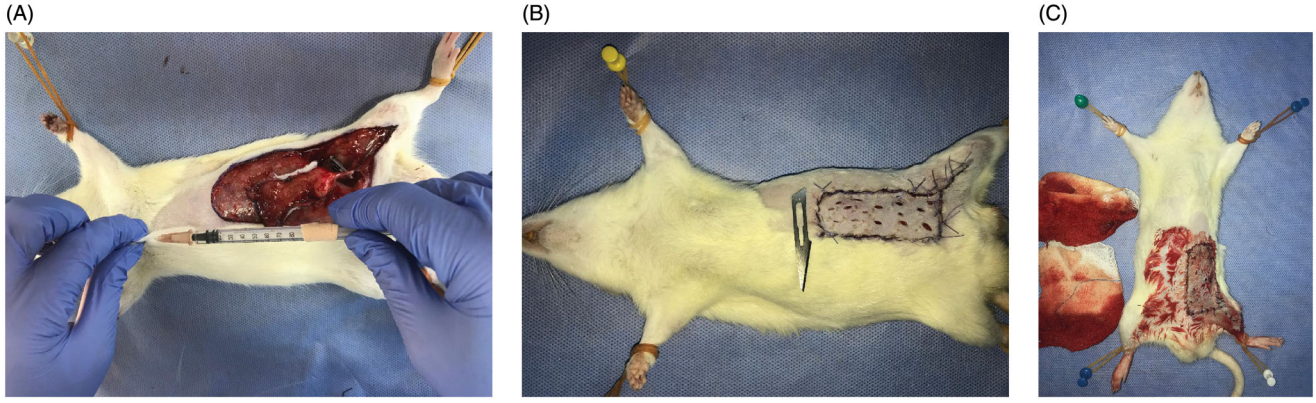


Figure 2. (A) Subcutaneous administration of enoxaparin following venous occlusion in Group 3 (B) Occlusion and punctiform incisions with local and systemic enoxaparin administration in Group 4 (C) Occlusion and punctiform incisions with local and systemic enoxaparin administration with enoxaparin-impregnated sponge dressing in Group 5. Note the active bleeding.

Planning of experiment

Group 1 (sham group): no further procedure was carried out on pedicles or flap.

Group 2 (control group): venous insufficiency was established by clamping the inferior epigastric vein for nine hours. The clamps were taken out under anaesthesia after nine hours. No further procedure was carried out.

Group 3: after venous insufficiency was established as those of Group 2, 5 mg/kg/day enoxaparin was systemically and subcutaneously administered once a day for five days.

Group 4: after venous insufficiency was established as those of Group 2, the flaps were divided into 18 boxes and each box was punctured with a no. 11 scalpel. Enoxaparin, 40 mg/0.4 ml, was administered into the punctured holes. This was repeated at 12-h intervals for five days.

Group 5: all procedures were the same as those of Group 4. but only a 40 mg/0.4 ml enoxaparin-impregnated sponge was placed on the flaps while the dressings were closed. This was repeated at 12-h intervals for five days (Figure 2).

All flaps were closed with a bundle dressing to prevent stepping on the flap. All animals were followed in separate cages. A daily 10 ml dose of 0.9% sodium chloride (NaCl) was provided intraperitoneally to avoid haemodynamic problems. The study was completed with the sacrificing of the animals at the end of the seventh day.

Measurement of the area of surviving skin in the flap

Flap viability was evaluated on the seventh day after surgery. Pictures of the flaps were taken (Canon EOS 2000 D; Canon Inc., Tokyo, Japan) and processed with an image analysis program (AutoCAD® 2013, Autodesk Inc., CA, USA) Flap viability was calculated as the ratio of viable area to the total area for each rat (percentage of skin flap survival = flap survival area/total flap area × 100).

Histopathological assessment

All flaps were histologically assessed with standard haematoxylin and eosin staining on the seventh day. All flaps were regarded as biopsy material and five micron sections were obtained from the samples embedded in paraffin blocks. The tissues were scored considering the presence of necrosis, inflammation and oedema as 0 = none, 1 = low, 2 = moderate and 3 = high. All histological assessments were carried out by the same pathologist who was blinded to the distribution of groups.

Data analysis

Data were analysed with the SPSS package software program for Windows, Version 24.0 (SPSS Inc., Chicago, IL, USA) and expressed in means and standard deviations, and minimum and maximum.

The flap survival rates of the groups were analysed with the *post hoc* Tukey test. The chi-square test was used in the comparison of necrosis, inflammation and oedema. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Two animals each in groups 2, 3, 4 and 5 expired due to anaesthesia and bleeding during the dressings. The study was performed with nine animals in group 1 and seven animals in each of the other groups.

Skin flap survival rates

The mean flap survival rate was 78.8 ± 32.3% in group 1, 11.8 ± 11.3% in group 2, 47.0 ± 27.8% in group 3, 27.8 ± 20.4% in group 4 and 66.8 ± 22.2% in group 5. The flap survival rate of group 5 increased significantly, as opposed to the control and fourth groups ($p = 0.02$ and $p = 0.04$, respectively). Groups 3 and 4 had clinically higher flap survivals than the control group, but the difference was not significant ($p = 0.08$ and $p = 0.74$, respectively). There was no difference in group 3 compared to groups 4 and 5 ($p = 0.59$ and $p = 0.56$, respectively) (Figures 3 and 4).

Histopathologic findings

The histopathological assessment findings on the seventh day are summarized in Figure 5.

Inflammation

The mean inflammation score was 1.4 ± 0.88 for group 1, 3 ± 0 for group 2, 2.2 ± 0.9 for group 3, 2.7 ± 0.7 for group 4 and 2.2 ± 0.4 for group 5.

Group 5 had significantly lower inflammation scores than group 2 ($p < 0.05$). There was no significant relationship between groups 2, 3 and 4 ($p > 0.05$) (Figure 6).

Necrosis

The mean necrosis score was 1.1 ± 1.1 for group 1, 3 ± 0 for group 2, 2.1 ± 1.0 for group 3, 2.5 ± 0.7 for group 4 and 1.7 ± 0.7 for group 5. Group 5 had significantly lower necrosis scores than group 2 ($p < 0.05$). Although groups 3 and 4 had higher macroscopic necrosis scores than in group 5, microscopic scores were not significant ($p > 0.05$). Groups 2, 3 and 4 did not have significant necrosis scores ($p > 0.05$).

Oedema

The mean oedema score was 1.5 ± 0.5 for group 1, 3 ± 0 for group 2, 2.1 ± 0.6 for group 3, 2.5 ± 0.5 for group 4 and 2.5 ± 0.5 for group 5. There was no difference between the groups in terms of oedema ($p > 0.05$).

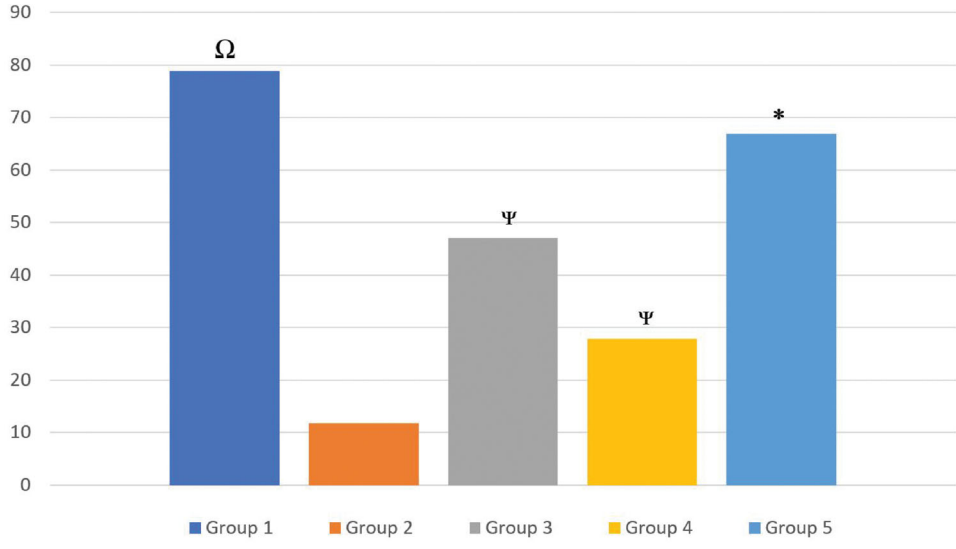
Discussion

Venous insufficiency is a more common and serious issue resulting in flap necrosis than arterial ischaemia. This might be caused by increased venous pressure, which directly causes venous thrombosis, stasis of flap microcirculation with unremovable free oxygen radicals and finally, arterial thrombus and flap necrosis [8,9].

Early diagnosis of venous insufficiency and appropriate treatment is necessary to recover venous congested flaps. Operational revision with exploration should be carried out immediately if venous congestion is observed in the initial period after surgery or the cause is clear. Late onset of venous insufficiency or unclear reasons usually require different medical therapies.

The primary aim of medical therapies is to deliver perfusion and diminish congestion by the time of neovascularisation (usually between the fifth and seventh postoperative day) [17]. This can be achieved with medicinal leeches [18], HBOT [13], thrombolytic agents [14,15] and subcutaneous LMWH administration with or without punctiform incisions [11,17,19]. All of these methods have particular benefits and drawbacks.

Leech therapy is highly common among reconstructive surgeons. Venous congestion has been effectively relieved in various



Ω $p<0.05$ when compared with groups 2, 3 and 4
Ψ $p>0.05$ when compared with group 2
* $p<0.05$ when compared with groups 2 and 4

Figure 3. Mean survival area (%) of flaps on the seventh day.

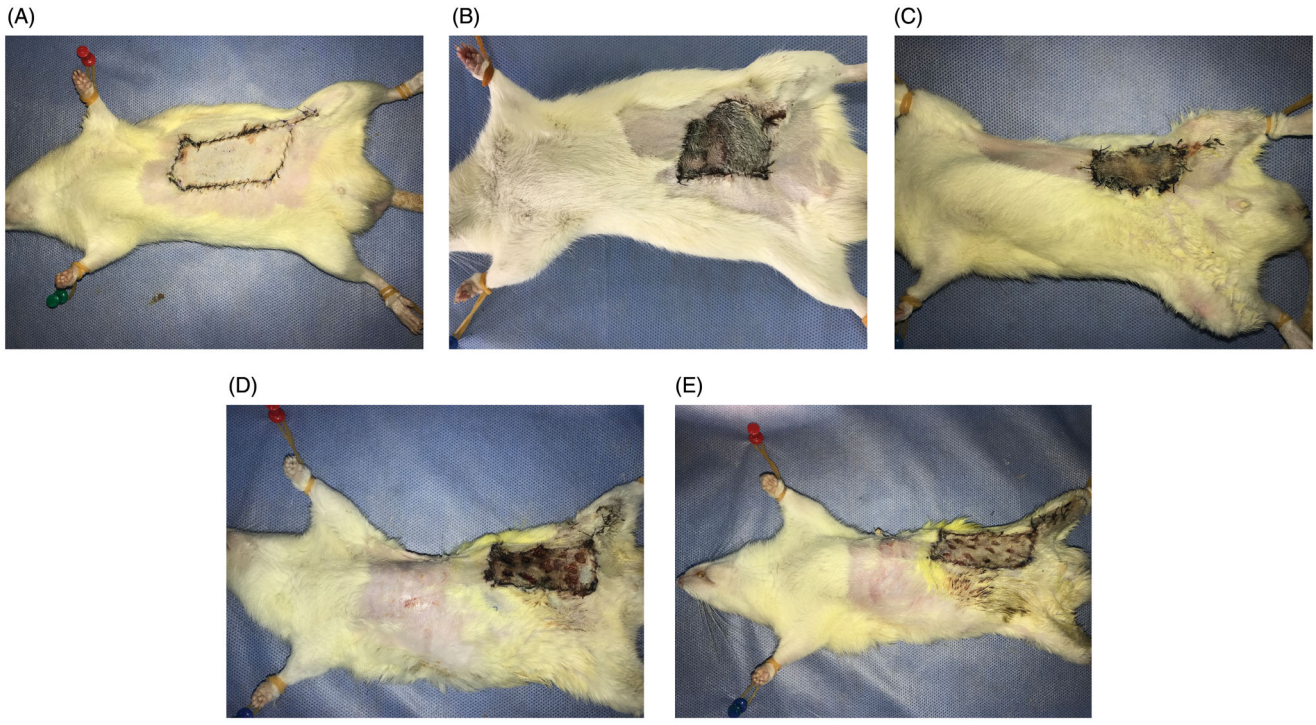
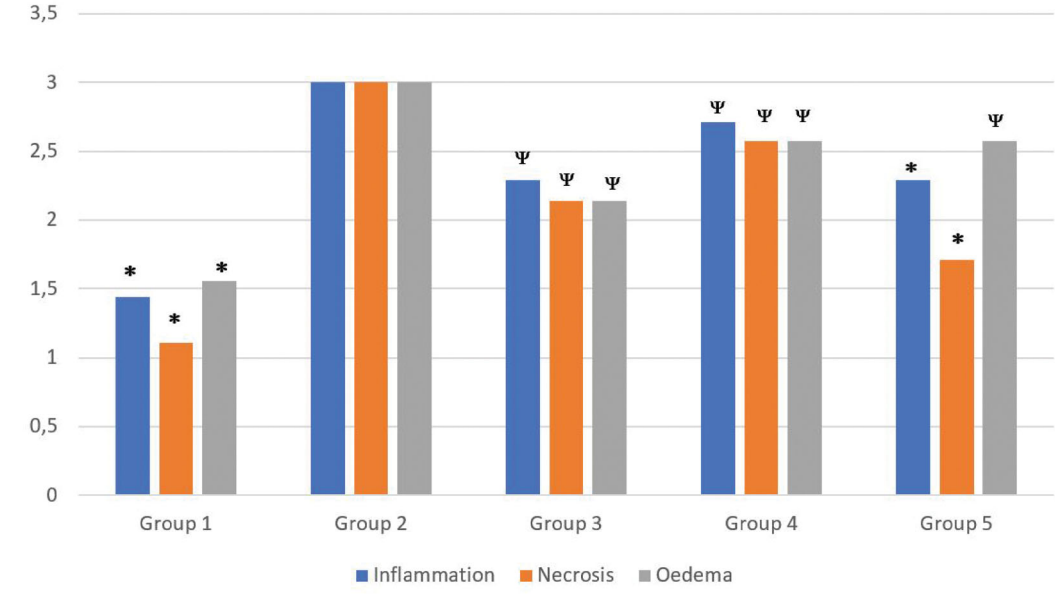


Figure 4. Flaps on the seventh day. (A) Sham (Group 1) (B) control (Group 2) (C) Group 3 (D) Group 4 (E) Group 5.



* $p<0.05$ when compared with group 2
Ψ $p>0.05$ when compared with group 2

Figure 5. Histopathologic scores on the seventh day.

damaged locoregional and free flaps and replanted appendages, such as the ear, nose, lip and digits [20–24]. Leech therapy, however, might result in serious complications, such as Aeromonas infection and the need for blood transfusions [25,26]. Additionally, this therapy may fail in high-volume flaps, in which the rate of success declines to nearly 30% [7,27].

Few studies have investigated the effect of HBOT on venous insufficiency. HBOT alone is not efficient and does not increase the survival rate of venous congested flaps [13,28]. Thrombolytic drugs are usually administered in free flap surgery to stop vascular thrombosis, but the advantages of these fibrinolytic agents in venous occlusion are still uncertain and they generally are beneficial in cases of isolated arterial thrombosis [29].

Heparin was also utilised in a case of treatment of a venous congested flap and named 'chemical leeching' [30], as it activates plasma antithrombin III and neutralises clotting. Heparin was

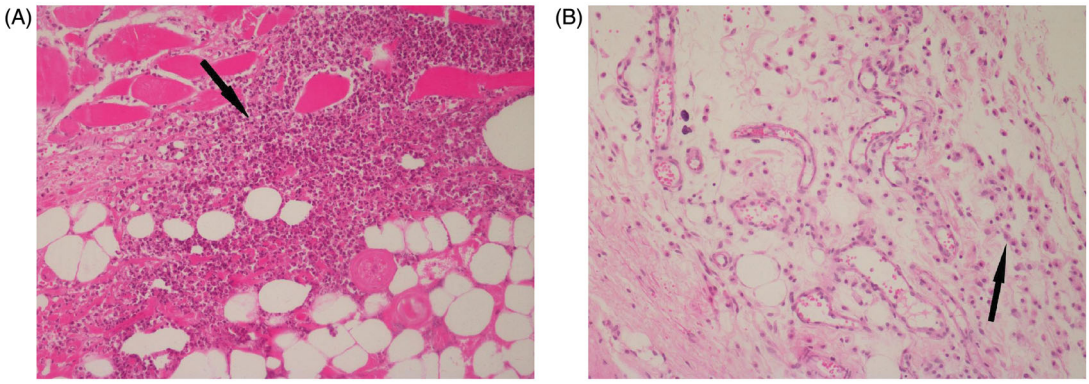


Figure 6. Histologic analysis of (A) control group and (B) Group 5. Black arrow shows increased and reduced inflammatory cell density in the control group and group 5, respectively (haematoxylin and eosin stain, original magnification: X 200).

slowly substituted by LMWH due to better pharmacokinetics (superior bioavailability and longer biologic half-life) and less tendency for bleeding [31].

There are few studies on LMWH for the management of venous insufficiency. Miyawaki and Chung found that subcutaneous injections of enoxaparin enhanced the survival of congested flaps in rabbits [16,32]. Perez et al. conducted the largest study on LMWH in humans, including 15 congested flaps that were injected with enoxaparin with multiform punctiform incisions [11]. These authors noted high success rates and emphasised that removing blood clots from punctiform incisions to preserve constant venous drainage is one of the most critical points of the treatment. However, this continuous process is time-consuming and uncomfortable for the patients and physicians.

We used LMWH in a single systemic or systemic + local injection with punctiform incisions, with or without anticoagulant dressing. Only using systemic LMWH could enhance flap survival rate, but would not be successful in preserving flap perfusion and properly relieving venous congestion. Interestingly, punctiform incisions on flaps with local and systemic LMWH therapy caused the group 4 animals to have worse flap survival than those in group 5. This might have resulted from multiple incisions, which decrease arterial perfusion and cause inefficient venous bleeding. Only punctiform incisions with local and systemic LMWH and enoxaparin-impregnated sponges were successful in the treatment of venous congestion. Thereby, coagulation of venous blood due to incisions should be prevented and accumulation should be continued, instead of only applying incision and LMWH injection.

Our study had some limitations. The metabolism of enoxaparin in humans and rats was divergent. Further clinical trials on humans should be conducted to confirm our methodology and findings. Systemic + local enoxaparin administration with absorbable dressing may cause excessive bleeding. Therefore, combined therapies should be used carefully in clinical practice.

Conclusion

LMWH therapy alone was not adequate to save venous congested flaps. Combining this method with anticoagulant dressing is critical in maintaining venous perfusion and rescuing the congested flap.

Disclosure statement

None of the authors has a financial interest in any of the products or devices mentioned in this article.

Funding

The study was supported by the research fund [#17/107] of Erciyes University.

ORCID

Cemal Alper Kemaloğlu http://orcid.org/0000-0001-7382-0702

References

[1] Largo RD, Selber JC, Garvey PB, et al. Outcome analysis of free flap salvage in outpatients presenting with microvascular compromise. Plast Reconstr Surg. 2018;141(1):20e–27e.
[2] Jose M, Varghese J, Babu A. Salvage of venous congestion using medicinal leeches for traumatic nasal flap. J Maxillofac Oral Surg. 2015;14(Suppl 1):251–254.
[3] Chang EI, Chang EI, Soto-Miranda MA, et al. Comprehensive evaluation of risk factors and management of impending flap loss in 2138 breast free flaps. Ann Plast Surg. 2016;77(1):67–71.
[4] Fujiwara M, Nagata T, Matsushita Y, et al. Delayed distally based sural flap with temporary venous supercharging. Microsurgery. 2013;33(7):534–538.
[5] Chang EI, Zhang H, Liu J, et al. Analysis of risk factors for flap loss and salvage in free flap head and neck reconstruction. Head Neck. 2016;38(S1):E771–E775.
[6] Akan IM, Yildirim S, GiderogŭLu K. Salvage of flaps with venous congestion. Ann Plast Surg. 2001;46:456.
[7] Nguyen MQ, Crosby MA, Skoracki RJ, et al. Outcomes of flap salvage with medicinal leech therapy. Microsurgery. 2012;32(5):351–357.
[8] Azzopardi EA, Whitaker IS, Rozen WM, et al. Chemical and mechanical alternatives to leech therapy: a systematic review and critical appraisal. J Reconstr Microsurg. 2011; 27(8):481–486.
[9] Gampper TJ, Zhang F, Mofakhami NF, et al. Beneficial effect of hyperbaric oxygen on island flaps subjected to secondary venous ischemia. Microsurgery. 2002;22(2):49–52.
[10] Casey WJ, Craft RO, Rebecca AM, et al. Intra-arterial tissue plasminogen activator: an effective adjunct following microsurgical venous thrombosis. Ann Plast Surg. 2007; 59(5):520–525.
[11] Pérez M, Sancho J, Ferrer C, et al. Management of flap venous congestion: the role of heparin local subcutaneous injection. J Plast Reconstr Aesthet Surg. 2014;67(1):48–55.

[12] Lineaweaver WC, Hill MK, Buncke GM, et al. Aeromonas hydrophila infections following use of medicinal leeches in replantation and flap surgery. Ann Plast Surg. 1992;29(3): 238–244.
[13] Lozano DD, Stephenson LL, Zamboni WA. Effect of hyperbaric oxygen and medicinal leeching on survival of axial skin flaps subjected to total venous occlusion. Plast Reconstr Surg. 1999;104(4):1029–1032.
[14] Serletti JM, Moran SL, Orland GS, et al. Urokinase protocol for free-flap salvage following prolonged venous thrombosis. Plast Reconstr Surg. 1998;102(6):1947–1953.
[15] Chang EI, Mehrara BJ, Festekjian JH, et al. Vascular complications and microvascular free flap salvage: the role of thrombolytic agents. Microsurgery. 2011;31(7):505–509.
[16] Miyawaki T, Jackson IT, Elmazar H, et al. The effect of low-molecular-weight heparin in the survival of a rabbit congested skin flap. Plast Reconstr Surg. 2002;109:1994–1999.
[17] Iglesias M, Butrón P. Local subcutaneous heparin as treatment for venous insufficiency in replanted digits. Plast Reconstr Surg. 1999;103(6):1719–1724.
[18] Whitaker IS, Oboumarzouk O, Rozen WM, et al. The efficacy of medicinal leeches in plastic and reconstructive surgery: a systematic review of 277 reported clinical cases. Microsurgery. 2012;32(3):240–250.
[19] Robinson C. Artificial leech technique. Plast Reconstr Surg. 1998;102(5):1787–1788.
[20] Cornejo A, Shammas RL, Poveromo LP, et al. Institutional outcomes of leech therapy for venous congestion in 87 patients. J Reconstr Microsurg. 2017;33(9):612–618.
[21] Zhao X, Higgins KM, Enepekides D, et al. Medicinal leech therapy for venous congested flaps: case series and review of the literature. J Otolaryngol Head Neck Surg. 2009;38(2): E61–E64.
[22] Ribuffo D, Chiummariello S, Cigna E, et al. Salvage of a free flap after late total thrombosis of the flap and revascularisation. Scand J Plast Reconstr Surg Hand Surg. 2004;38(1):50–52.
[23] Tuncali D, Terzioglu A, Cigsar B, et al. The value of medical leeches in the treatment of class IIC ring avulsion injuries: report of 2 cases. J Hand Surg Am. 2004;29(5):943–946.
[24] Frodel JL, Jr, Barth P, Wagner J. Salvage of partial facial soft tissue avulsions with medicinal leeches. Otolaryngol Head Neck Surg. 2004;131(6):934–939.
[25] Abbott SL, Cheung WK, Janda JM. The genus aeromonas: biochemical characteristics, atypical reactions, and phenotypic identification schemes. J Clin Microbiol. 2003;41(6): 2348–2357.
[26] Hermansdorfer J, Lineaweaver W, Follansbee S, et al. Antibiotic sensitivities of *Aeromonas hydrophila* cultured from medicinal leeches. Br J Plast Surg. 1988;41(6):649–651.
[27] Whitaker IS, Josty IC, Hawkins S, et al. Medicinal leeches and the microsurgeon: a four-year study, clinical series and risk benefit review. Microsurgery. 2011;31(4):281–287.
[28] Vishwanath G. Hyperbaric oxygen therapy in free flap surgery: is it meaningful? Med J Armed Forces India. 2011; 67(3):253–256.
[29] Yii NW, Evans GR, Miller MJ, et al. Thrombolytic therapy: what is its role in free flap salvage? Ann Plast Surg. 2001; 46(6):601–604.
[30] Barnett GR, Taylor GI, Mutimer KL. The "chemical leech": intra-replant subcutaneous heparin as an alternative to venous anastomosis. Report of three cases. Br J Plast Surg. 1989;42(5):556–558.
[31] Caplin DA, Nathan CR, Couper SG. Salvage of TRAM flaps with compromised venous outflow. Plas Reconstr Surg. 2000;106:400–401.
[32] Chung TL, Holton LH, 3rd, Silverman RP. The effect of fondaparinux versus enoxaparin in the survival of a congested skin flap in a rabbit model. Ann Plast Surg. 2006;56: 312–315.