EXPERIMENTAL STUDY

Effects of dabigatran and fondaparinux on degloving injuries: An experimental study

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ABSTRACT

BACKGROUND: Management of the skin degloving injuries is still a problematic issue, and the avulsed part of the skin may become necrotic. We hypothesized that the anticoagulant pharmacological agents, fondaparinux and dabigatran may be beneficial in the treatment of degloving injuries by enhancing the viability of the reattached flap.

METHODS: Twenty four Wistar rats were divided into three groups as follows: control group (Group 1), fondaparinux group (Group 2) and dabigatran group (Group 3). A model of a degloving injury on the tail of rats was developed in all groups. After 15 minutes, the avulsed flaps were sutured back. Group 1 received 1ml/day saline intraperitoneally for 10 days. Group 2 received 0.3 ml/kg/day fondaparinux intraperitoneally for 10 days. Group 3 received 30 mg/kg/day dabigatran orally for 10 days. At the end of the treatments, gross morphological and histopathological tail tissue survivals were evaluated.

RESULTS: Histopathological examination of the fondaparinux and dabigatran groups revealed that the tail skin was mostly viable with mild inflammation. The mean necrotic length in tails and severity of inflammation was significantly higher in the control group compared to the fondaparinux and dabigatran groups ($p<0.05$). No statistically significant differences were noted between the fondaparinux and dabigatran groups in histopathologic evaluations. There was no significant difference in necrosis lengths and the other histopathological parameters between dabigatran and fondaparinux groups.

CONCLUSION: Dabigatran and fondaparinux improved tissue survival in skin degloving injuries concerning gross morphological and histopathological findings. However, the findings of this study should be supported and improved by new experimental and especially clinical studies.

Keywords: Avulsion; degloving injury; flap; lower extremity reconstruction.

INTRODUCTION

A degloving injury is a soft tissue injury defined as a traumatic avulsion of the skin and subcutaneous tissue, together with the underlying deep fascia. Dermal vascular plexus is included in the skin, and it is damaged due to the separation of vessels from the skin in degloving injuries. A degloving injury mostly occurs due to shear forces as a result of contact of the extremity with circling objects forming a high speed of friction, such as vehicle wheels or motorcycle accidents.[1]

These injuries are divided into three patterns. Pattern 1 describes a pure degloving injury in which the underlying deep soft tissues are preserved. In pattern 2, deep soft tissues such as muscles and fascia, are also involved. Pattern 3 is the most severe type. It causes a degloving injury in the superficial skin

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and then continuously transfers into the deep soft tissues and even the bones, resulting in varying damages of soft tissue and different types of fractures.[2] The most common sites of degloving injuries are the extremities, especially the lower extremities, but these injuries may also occur in other regions of the body, such as the trunk and the cephalic region.[3] Mismanagement of such injuries results in delayed full-thickness necrosis of the avulsed skin flap and loss of the limb, or even worse, death.[4] Many strategies for management of degloving injuries have been proposed, including re-adaption of the flap, converting the avulsed flap into a graft, revascularizations or re-plantations as salvage, as well as the reconstruction with grafts, local flaps and free flaps.[5–7]

Most studies related to degloving injuries in humans are composed of cross-sectional studies, descriptive studies or case reports. The use of pharmacological agents that are involved in coagulation may enhance the viability of the reattached flap with or without vascular anastomosis and may have beneficial effects on patients with degloving injuries. Dabigatran etexilate mesylate is an orally administered novel anticoagulant, which is a direct thrombin inhibitor.[8] Dabigatran prevents the conversion of fibrinogen to fibrin and thus inhibits thrombus formation.[9] Fondaparinux sodium is a new class of synthetic anticoagulant drugs that selectively bind and potentiate antithrombin III, thereby specifically inhibiting the factor Xa in the coagulation cascade.[10]

We hypothesized that fondaparinux and the oral drug dabigatran, which have a similar mechanism of action in the coagulation cascade, may have beneficial effects on wound healing and improve the survival of avulsed skin in rat tails by facilitating microcirculation and preventing microthrombus formation. To our knowledge, there is no study that evaluated the effectiveness of these novel anticoagulants on degloving injuries. Hence, in this experimental study, we aimed to evaluate the efficiency of fondaparinux and dabigatran, novel antithrombotic agents, on degloving injuries in rats.

MATERIALS AND METHODS

All experiments were conducted in strict accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals. The experimental procedures were performed in the Practice and Research Laboratory of Kahramanmaraş Sütçü Imam University. The protocols in this study were approved by the Local Committee on Animal Research Ethics (Ethics Committee File No: 2018/04, Approval date: 20.03.2018).

Drugs and Chemicals

Fondaparinux (Aspen, France) 0.3 mg/kg/day was dissolved in 0.9% saline and administered intraperitoneally in 1 ml/kg of volume. Dabigatran (Boehringer Ingelheim, Germany) was mixed with drinking water and given orally to the rats by 30 mg/kg/day in 1 ml of volume by oral gavage. The rats were anaesthetised by an intramuscular injection of 50 mg/kg of ketamine hydrochloride (Ketalar®; Pfizer, Istanbul, Turkey).

Study Groups

Twenty-four male Wistar-albino rats with a body weight of 260–300 g each were equally and randomly divided into three groups (n=8 per group). The animals were kept in separate cages at an ambient temperature of 22°C and 60±5% humidity with a 12-hour light/dark cycle and ad libitum access to rat chow and water.

The first group was the control group and administered 0.5 ml of saline once a day intraperitoneally (i.p.). In the second group, 0.3 mg/kg of fondaparinux was administered once a day i.p. for 10 days. In the third group, 30 mg/kg of dabigatran was administered daily by gastric gavage for 10 days. A model of a degloving injury on the tail of rats was developed in all groups. After 15 minutes, the avulsed tissues were sutured back. The colour of the skin and the status of the wound were examined daily for 10 days. During the studied period, no rats were excluded due to death or self-mutilation. At the end of the treatments, the rats were sacrificed by cervical dislocation.

Induction of Degloving Injury in Rats' Tails

The surgical method was based on the degloving injury model reported by Oztuna et al.[11] The skin and subcutaneous tissues were incised circumferentially 5 cm distal to the base of the tail. Subsequently, a moderate manual force was applied to the tail at the distal end of the incision using the thumb and index fingers. When a 4-cm-long avulsion of the skin and subcutaneous tissue from the underlying tendon and vascular tissue was achieved, the traction was ceased (Fig. 1). Fifteen minutes after the injury, the avulsed tissue was reapproximated and sutured back to its original position using 4/0 vicryl.

Evaluation of the Gross Morphologic and Histopathological Changes

The lengths of the necrotic tail regions were measured in millimetres using a ruler. The circumferential lengths of necrosis

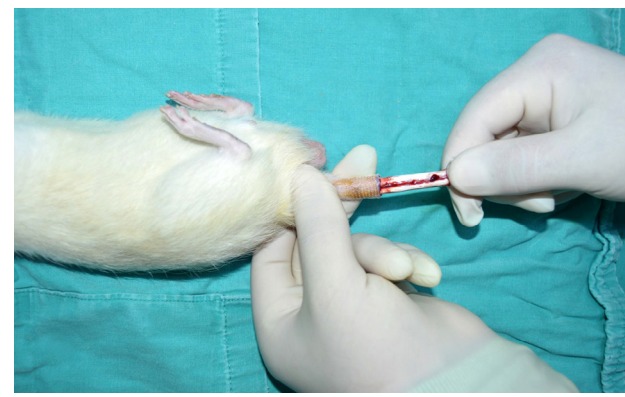

Figure 1. Creation of a degloving injury site in the tail of the rats.

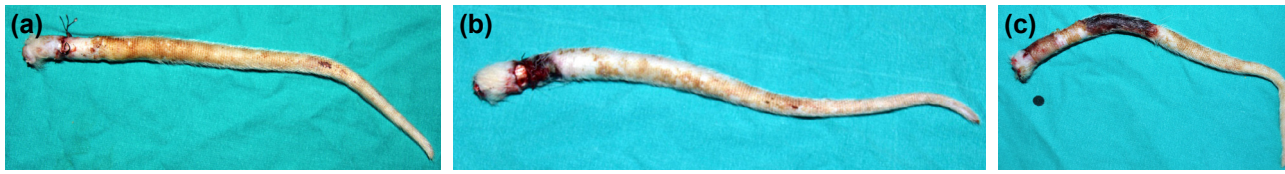

Figure 2. (a) Intact epidermis in the dabigatran group. **(b)** Limited necrosis of the tail in the fondaparinux group. **(c)** Severe necrotic skin of the tail in the control group.

at the proximal and distal boundaries were measured. Warm, pink-white and pliable tissue was evaluated as viable skin, and brown-black, cold and hardened tissue was considered to be necrotic skin. For the histopathological examinations, the tissue samples were embedded in paraffin and sectioned in a longitudinal orientation, fixed in 10% neutral buffered formalin and stored in 5% formic acid. The tissues were followed by a Leica ASP 300 tissue processor device and sectioned at a thickness of 3 µm on a microtome (Leica RM 2145). The samples were stained with Haematoxylin-Eosin and examined via light microscopy by an experienced pathologist.

Data Analysis

All data were recorded and analysed using SPSS for Windows v.15.0 (SPSS Inc., Chicago, IL, USA). Kruskal-Wallis H test was used for the statistical analysis of gross morphological and histopathological differences among the groups. Bonferroni correction was applied to correct for comparative differences. Comparisons in the 95% confidence interval and those that were found to have p-values of smaller than 0.05 were considered significant.

RESULTS

Gross Morphologic Changes

The avulsed tail flaps were cyanotic, and distal tail segments were oedematous in all animals on the postoperative day 2. We observed surgical wound infection in one rat in the saline group. Haematoma occurred only in one rat in the fondaparinux group. We also observed partial wound dehiscence of 3 mm in the tails of three rats, secondary to full-thickness necrosis in two rats in the control group, as well as one rat in the fondaparinux group. Skin necrosis was on a measurable level at the end of day 10.

In the dabigatran and fondaparinux groups, six tails of each group healed well and showed limited necrosis (Fig. 2a, b), whereas a clear length of necrotic tails was observed in almost all of the rats in the control group (Fig. 2c). The mean length of the necrotic area was significantly higher in the saline group than the other groups (p=0.013). There were no statistically significant differences in the lengths of the necrotic area between the dabigatran and fondaparinux groups (Table 1).

Histopathological Results

The clinical findings, histopathological findings and results of the statistical analysis demonstrated that the differences between the dabigatran and fondaparinux groups were not significant. There was a significant difference between the results of the control group and both the fondaparinux and dabigatran groups (Fig. 3).

Kruskal Wallis test was used to determine whether the necrotic tissue length values changed for the three groups. According to the results of the test, there was a statistically significant difference between the mean values of necrotic tissue length among the three groups (p<0.05). Multiple comparison tests were performed to see the difference between the groups. According to the results of Bonferroni multiple comparisons, the necrotic tissue length in the saline group was significantly higher in comparison to the dabigatran and fondaparinux groups (p<0.05). The lowest necrotic tissue length was determined in the dabigatran group. While the p-value was 0.013 for the necrotic tissue length for the dabigatran and saline groups, there was no statistically significant difference between the fondaparinux and dabigatran groups.

The severity of inflammation was evaluated using the Kruskal Wallis test for the three types of drugs. According to the results of the test, there was a statistically significant difference between the mean values of inflammation among the three groups (p<0.05). According to the results of the Bonferroni test, the severity of inflammation was significantly higher in the saline group in comparison to the fondaparinux and dabigatran groups (p<0.001). While the severity of inflammation

Table 1. The length of the necrosis (mean±SD) in the tails of rats

	Group 1 (Saline)	Group2 (Fondaparinux)	Group 3 (Dabigatran)
	Mean±SD	Mean±SD	Mean±SD
Length of necrosis (mm)	48.5±6	23.5±8.03	16.75±8.74

SD: Standard deviation.

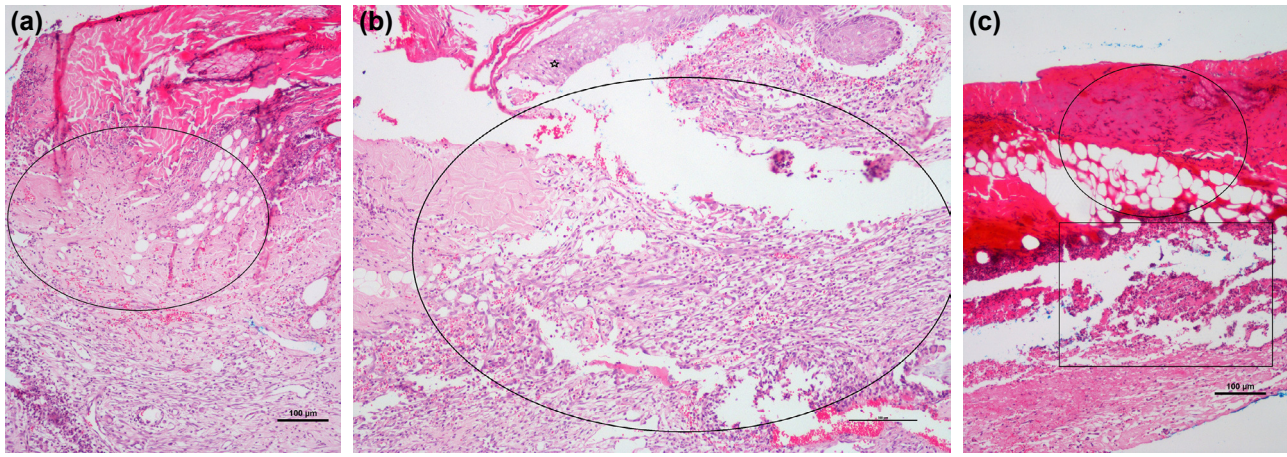

Figure 3. (a) In the dabigatran group, the epidermis was thinner than normal but not necrotic (marked with a star), and in the dermis, significant neovascularization and mild chronic active inflammatory infiltrate were observed (in the circle). **(b)** In the fondaparinux group, dermoepidermal blisters were seen on the surface, but no necrosis was observed, and the epidermis was intact (marked with a star). There were significant neovascularization and mild chronic inflammatory infiltrate in the dermis (in the circle). **(c)** In the control group, both the epidermis and papillary dermis were completely necrotic (in circle), and severe inflammation was also observed in the reticular dermis (inside the rectangle).

was determined in the saline group as the maximum, there was no statistically significant difference between the dabigatran and fondaparinux groups.

To determine the neovascularization values, the Kruskal Wallis test was used. According to the results of the test, both fondaparinux and dabigatran groups showed significantly higher neovascularization in comparison to the saline group (p=0.011). There was no statistically significant difference between the fondaparinux and dabigatran groups.

Although a better granulation tissue formation was seen in the dabigatran and fondaparinux groups in comparison to the saline group, the difference among the groups was not statistically significant (Figs. 4, 5).

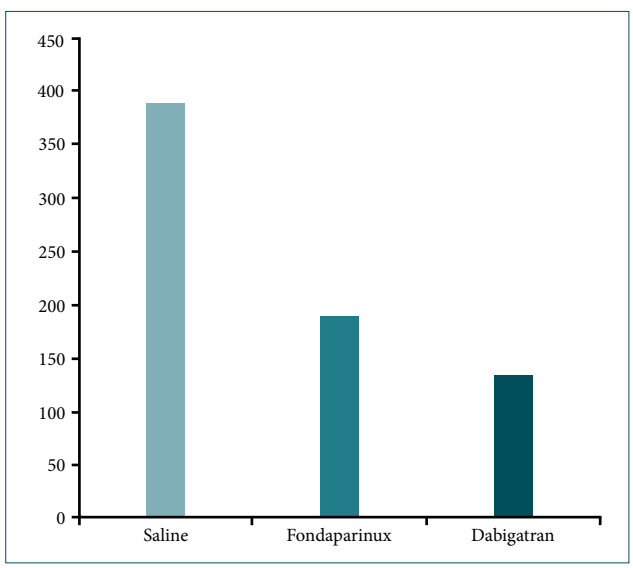

Figure 4. Total necrotic lengths in the tails (mm).

DISCUSSION

Degloving injuries are distinguished from other injuries by the damage in neurovascular structures that occurs together with trauma mechanisms. Vascular avulsion in the degloved skin results in necrosis due to impaired blood supply. A pure degloving injury is an avulsion with intact underlying anatomic structures, such as tendons, bones and joints. The skin and subcutaneous tissues are severely damaged and they are separated from the underlying fascia and muscles.

Management of degloving injuries is challenging in both the upper and lower extremities. Degloving injury treatment is based on the viability of the avulsed skin flap and the site of the injury area. Depending on the type and severity of the degloving injury, various treatments may be performed including re-attachment of the flap, converting the avulsed flap into a full-thickness skin graft, reconstruction with split-thickness skin grafts, local or free flaps, revascularization and re-plantation.[6] There are several studies that provided satisfactory results in degloving injuries of the upper extremities thanks to microsurgical treatments like revascularization, venous anastomosis, arterial anastomosis or arterialisation by arteriovenous shunts.[12–17] Although there are no established guidelines or a consensus for the management of degloving injuries, the general treatment principles include preservation

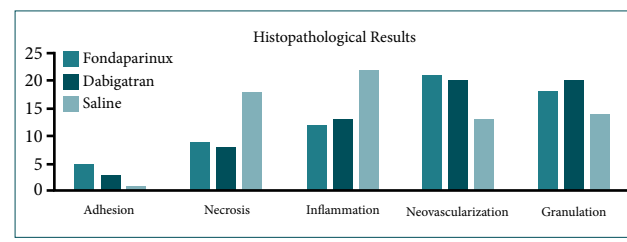

Figure 5. Histopathological results in the groups.

of as much tissue as possible, early primary definitive wound coverage, good-quality skin envelope and early functional recovery.[18]

In fact, what makes management of degloving injuries so complex and involved is that the treatment options strictly change depending on the specific anatomy of the injury site, as well as its unique features. Hence, as a necessity, these cases must be evaluated with their own characteristics based on the trauma region. Latifi et al.[19] reported on the treatment options of degloving injuries by anatomical locations. The principal and best surgical treatment option in hand and finger degloving injuries is always replantation or revascularisation. Since avulsion of the blood vessels, consequently, the intimal damage may extend beyond the visible injury level; tissue viability should be examined meticulously. Nonetheless, the existence of other life-threatening injuries or crush injury of the degloved flap may not allow replantation.[18] When direct microsurgical anastomosis is not possible, the crossed arterial anastomosis technique and vein grafts, either for arterial repair or venous repair may be helpful in obtaining successful results. Because of the lack of an artery in degloved skin, repair of the hand using distally based skin flaps has been reported using arteriovenous shunting.[20] In such cases of hand degloving injuries, when a suitable artery could not be defined in the degloved flap for direct physiological revascularisation, radial artery to cephalic vein and/or superficial vein to digital artery arteriovenous anastomoses, in other words, arterialisation by creating arteriovenous fistulas, have been reported as reasonable salvage procedures in some cases.[21,22]

Zhang et al.[23] recommended giving a survival chance for degloved hands and fingers by replantation or revascularization when the degloved skin is not severely damaged. However, they reported both the fingers and degloved flap following microsurgical repair were completely salvaged in only one of their patients. They suggested that, in the presence of diabetes mellitus, vascular diseases or heavy smoking history, microsurgical procedures require serious consideration.

Lower limb and foot degloving injury management differs from upper extremity management with its complexity, since it requires different specialties.[19] Repositioning and suturing the flap back with or without microsurgical anastomosis, split-thickness skin grafting obtained from degloved flaps by defatting, dermal matrices, VAC (vacuum-assisted closure) or reconstruction with either flaps or grafts are the basic treatment modalities.

Some authors agree that full-thickness skin graft conversion of the avulsed flap is the most appropriate choice in lower extremity degloving injuries since it is mostly not possible to identify a proper artery for anastomoses, or a proper artery in the degloved limb is often absent or traumatized. Moreover, vascular anastomoses are rarely successful for damaged skin flaps and contraindicated in most degloving injuries, especially when degloved flaps are contused. When microsurgical repair is not feasible, replacement of avulsed skin flaps as full-thickness skin grafts may consistently provide satisfactory results in the treatment of degloving injuries in the lower extremities.[24] Hence, recently, the most frequently used technique in degloving injuries of the lower extremities is defatting the avulsed part and converting it into a full-thickness skin graft to cover the defect when revascularization is not possible.[2] Thereto, Chen and Liu[25] noted that preservation of the subcutaneous vascular network and adequate drainage might provide a better effect than split-thickness skin meshing and grafting alone. It is assumed that the golden time for degloving injury treatment is eight hours after injury because the initially avulsed flap has perfusion, but it then develops ischemia and necrosis due to circulation disorders as time goes by. The coagulation cascade reaction of damaged vascular endothelial cells alters the biological effects and blood coagulability. Since the inner walls of the blood vessels are very conducive to thrombosis, skin microcirculation worsens even further. As pointed out, in addition to the importance of anticoagulants after degloving injuries with or without microsurgical repair, they also play a major role in the survival of degloved flaps by decreasing the risk of thrombosis.[10,23] Herein, we utilized fondaparinux and dabigatran, since anticoagulation may have beneficial effects on wound healing and improve the survival of avulsed skin by facilitating microcirculation, preventing microthrombus formation and inhibition of coagulation cascade. Fondaparinux is a synthetic and selective inhibitor of the factor Xa that has proven efficacy and safety for preventing venous thromboembolism in orthopaedic surgery. In several recent studies, fondaparinux has been shown to be effective in preventing postoperative venous thromboembolism and venous congestion-associated flap failure.[25–27]

Dabigatran, a novel anticoagulant, is a direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin and thus inhibits thrombus formation. Dabigatran has been approved by the FDA for the treatment of deep venous thrombosis and/or pulmonary embolism and venous thromboembolism prophylaxis. It has predictable pharmacokinetic and pharmacodynamic profiles, no known food interactions and no genetic metabolism variations.[28]

The first rat model for degloving injuries was described by Oztuna et al.[11] in 2006. The authors induced a 3-cm-long avulsion injury in the tails of rats and examined the effects of pentoxifylline on the viability of avulsed flaps. In 2012, Milcheski et al.[29] described another degloving injury model in rat hindlimbs. They described four different types of hindlimb degloving injuries, including proximal flow pedicled flap, distal flow pedicled flap, lateral flow pedicled flap and medial flow pedicled flap. This animal model was used in a subsequent study to examine the effects of pentoxifylline and allopurinol on the viability of avulsed hindlimb flaps.[30] Although a hindlimb degloving injury model may seem to be more clinically relevant, it may be misleading while evaluating the re-

sults. Once, during wound healing, plasmatic imbibition is expected to occur more in avulsed hindlimb flaps because of the relatively vascular nature of the underlying muscles. This condition may cause some part of the avulsed flap to be taken up as a graft by the underlying healthy vascular tissue. Compared to hindlimbs, the tissue underlying the avulsed flap in the tail is relatively more avascular, and hence, the probability of graft uptake is lower. Moreover, in a hindlimb degloving injury model, the avulsion of the flap is caused solely by traction using a towel clamp, and there is almost no crushing force applied to the tissues. However, while creating an avulsed flap in the tail degloving injury model, some force is also applied to the tissues by the thumb and the index finger. Therefore, while hindlimb and tail degloving injury models are both applicable to evaluate the avulsed skin as a defatted flap or a full-thickness graft, the tail degloving model mimics the clinical facts better concerning the trauma mechanism, and it is more reliable in determining the efficacy of drugs.

We observed significant variability in the extent of flap necrosis in the tail degloving injury model when we compared our results with the results of the relevant studies in the literature. Demirtas et al.[31] examined the efficiency of hyperbaric oxygen therapy on healing in an experimental model of degloving injury in the tails of nicotine-treated rats and reported a necrosis length of 7.87±3.31 mm. Cebesoy et al.[32] encountered positive effects of both heparin and enoxaparin on the treatment of degloving injuries in rat tails, and they reported necrotic length as 10.2 mm. Azboy[33] evaluated the effects of the antithrombotic agents, enoxaparin and rivaroxaban, on tissue survival following skin degloving injury in an experimental rat tail model, and they reported a necrosis length of 14±5 mm in their control group.

Altun et al.[34] compared the tail and hindlimb models in degloving injuries. They observed that the tail degloving injury model was a more reliable animal model for degloving injuries although the hindlimb degloving injury model may seem as if it was more clinically relevant. The extent of necrosis of tails in their study was higher with a length of 28.42±3.04 mm in comparison to those in previous studies. They explained this difference by the variability in the magnitude of the degloving force. We also observed a higher extent of necrosis in tails with a length of 16.75±8 mm in the dabigatran group and 48.5±6 mm in the saline group. In this study, even in the dabigatran group whose results were the best, the necrotic tail length measurements were longer than the results reported in similar studies in the literature. The most important reason that caused this difference is probably the length of the degloved tail. Although we implemented the model with a repeatable and standard force with the help of the preliminary studies before the experiment, another minor reason to encounter this difference may perhaps have been the variation in the magnitude of the force while leading to the degloving damage, as previously stated by Altun. Nonetheless, more importantly, the method in our study differed from the aforementioned studies concerning the avulsion length created in the tail. The main reason for finding longer necrotic lengths was probably the creation of the degloving injury by avulsing the skin and subcutaneous tissue by 4 cm of length in the experimental model. The longer amount of avulsion while creating the degloving injury very likely caused us to obtain increased lengths of necrotic tails in all groups. This minor modification of the degloving injury model in the rat tail may be considered as a form of a mildly increased type 1 ring injury model, and it may also have caused the range of the numeric results of the treatments in this study to be broader. In our opinion, this minor modification in the experimental degloving model may also contribute to obtaining more comparable results with clinical practice.

This study had some limitations. First of all, we did not use different doses of dabigatran and fondaparinux. We administered the doses based on previous experimental studies in the literature. Secondly, it is difficult to reproduce the same magnitude of manual force each time while leading to a skin degloving injury. However, preliminary experiments served us well to apply a more applicable and standard magnitude of the manual force in the experimental procedures. Nevertheless, it will be more beneficial to form a system or a device producing a standard magnitude of degloving force to avoid the variability in the groups. Since there were not any perforators of adequate calibre to repair the rat tail veins, we were not able to evaluate the effects of the drugs on perforasomes or a revascularized degloved flap. In a recent study by Kabakaş et al.,[35] although arterial perforator repair has been achieved, neighboring perforasomes have survived partially; however, the results of their study on degloving injuries seem promising for future studies. Therefore, to have a better understanding of this particular injury type and its effects on perforasomes, it will be necessary to develop new experimental degloving injury models allowing perforator repair and investigate the efficiency of pharmacological agents that can increase survival on these models. In our opinion, future experimental studies to focus on these recommendations will definitely make valuable contributions to degloving injury management. Moreover, we investigated the efficiency of dabigatran and fondaparinux only for the pattern 1 degloving injury model, which did not include deep soft tissues, bone fractures or any crush injury just like those without a completely diminished circulation. Therefore, the findings obtained in this experiment should not be considered valid for pattern 2 and pattern 3 degloving injuries. Finally, one should consider that the pharmacological agents used in this experiment showed significant efficacy in degloving injury, but these are not an alternative to replantation or revascularization. Depending on the findings of this experiment, these agents show beneficial effects and provide improvement in pattern 1 degloving injuries with adequate circulation in cases where any perforator repair is unavailable, or microsurgical revascularization cannot be performed.

In conclusion, our findings suggest that fondaparinux and dabigatran had positive effects on preserving the viability of degloved rat tail skin flaps and contributed to limiting the progression of ischemia and necrosis. Fondaparinux and dabigatran significantly improved the survival rate in skin degloving injuries in a rat tail model. Based on the promising results obtained in this study, even in the absence of microsurgical repair, we believe that fondaparinux and dabigatran administration may be used as a supplementary treatment and provide beneficial effects for skin flap survival in degloving injuries. Further studies with different drug doses and study designs are required to assess whether or not these results may be applicable in humans, especially following arterial or venous repairs after degloving injuries.

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REFERENCES

1. Hudson DA, Knottenbelt JD, Krige JE. Closed degloving injuries: results following conservative surgery. Plast Reconstr Surg 1992;89:853–5.
2. Yan H, Gao W, Li Z, Wang C, Liu S, Zhang F, et al. The management of degloving injury of lower extremities: technical refinement and classification. J Trauma Acute Care Surg 2013;74:604–10. [CrossRef]
3. Hakim S, Ahmed K, El-Menyar A, Jabbour G, Peralta R, Nabir S, et al. Patterns and management of degloving injuries: a single national level 1 trauma center experience. World J Emerg Surg 2016;11:35. [CrossRef]
4. Mandel MA. The management of lower extremity degloving injuries. Ann Plast Surg 1981;6:1–5. [CrossRef]
5. Pilancı O, Aköz Saydam F, Başaran K, Datlı A, Güven E. Management of soft tissue extremity degloving injuries with full-thickness grafts obtained from the avulsed flap. Ulus Travma Acil Cerrahi Derg 2013;19:516–20.
6. Waikakul S. Revascularization of degloving injuries of the limbs. Injury 1997;28:271–4. [CrossRef]
7. Jeng SF, Hsieh CH, Kuo YR, Wei FC. Technical refinement in the management of circumferentially avulsed skin of the leg. Plast Reconstr Surg 2004;114:1225–7. [CrossRef]
8. Callahan S, Goldsberry A, Kim G, Yoo S. The management of antithrombotic medication in skin surgery. Dermatol Surg 2012;38:1417–26.
9. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. Clin Appl Thromb Hemost 2009;15:9S–16S. [CrossRef]
10. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al; Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med 2004;140:867–73. [CrossRef]
11. Oztuna V, Eskandari MM, Unal S, Colak M, Karabacak T. The effect of pentoxifylline in treatment of skin degloving injuries: an experimental study. Injury 2006;37:638–41. [CrossRef]
12. Lo S, Lin YT, Lin CH, Wei FC. A new classification to aid the selection of revascularization techniques in major degloving injuries of the upper limb. Injury 2013;44:331–5. [CrossRef]
13. Rodríguez-Lorenzo A, Lin CH, Lin CH, Ching WC, Lin YT. Replantation of a degloved hand with added arteriovenous anastomoses: report of two cases. J Hand Surg Am 2009;34:1864–7. [CrossRef]
14. Boernert K, Ganot G, Ulrich MK, Iselin LD. Preserving the lower extremity after severe devolving injuries to meet the patient's demand in two cases: (Limb salvage after degloving injury). Trauma Case Rep 2018;15:8–15. [CrossRef]
15. Weinand C. Degloving Injuries of Upper Extremity: A Strategy with Full Thickness Skin Mesh. World J Plast Surg 2018;7:372–6. [CrossRef]
16. Lin YH, Jeng CH, Hsieh CH, Lin HC. Salvage of the skin envelope in complex incomplete avulsion injury of thumb with venous arterializaiton: a case report. Microsurgery 2010;30:469–71. [CrossRef]
17. Ju J, Li J, Hou R. Microsurgery in 46 cases with total hand degloving injury. Asian J Surg 2015;38:205–9. [CrossRef]
18. Krishnamoorthy R, Karthikeyan G. Degloving injuries of the hand. Indian J Plast Surg 2011;44:227–36. [CrossRef]
19. Latifi R, El-Hennawy H, El-Menyar A, Peralta R, Asim M, Consunji R, et al. The therapeutic challenges of degloving soft-tissue injuries. J Emerg Trauma Shock 2014;7:228–32. [CrossRef]
20. Slattery P, Leung M, Slattery D. Microsurgical arterialization of degloving injuries of the upper limb. J Hand Surg Am 2012;37:825–31. [CrossRef]
21. Chin T, Ono S, Hyakusoku H. Successful repair of flayed tissue in a degloving injury of the hand by arteriovenous anastomosis. J Plast Surg Hand Surg 2014;48:423–5. [CrossRef]
22. Wang Y, Rui Y, Zhou J, Li F, Wu Y, Liu J. Successful repair of total hand degloving injury by avulsed skin in situ replantation through vascular transplantation: a case report. Ther Clin Risk Manag 2018;14:1429–33. [CrossRef]
23. Zhang G, Ju J, Jin G, Tang L, Fu Y, Hou R. Replantation or revascularization for the treatment of hand degloving injuries. J Plast Reconstr Aesthet Surg 2016;69:1669–75. [CrossRef]
24. Sakai G, Suzuki T, Hishikawa T, Shirai Y, Kurozumi T, Shindo M. Primary reattachment of avulsed skin flaps with negative pressure wound therapy in degloving injuries of the lower extremity. Injury 2017;48:137–41. [CrossRef]
25. Chen Y, Liu L. Clinical analysis of 54 cases of large area soft tissue avulsion in the lower limb. Chin J Traumatol 2016;19:337–41. [CrossRef]
26. Reynolds NA, Perry CM, Scott LJ. Fondaparinux sodium: a review of its use in the prevention of venous thromboembolism following major orthopaedic surgery. Drugs 2004;64:1575–96. [CrossRef]
27. 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;56:312–5. [CrossRef]
28. Schmitt AR, Zender CA, Bordeaux JS. A new oral anticoagulant in the setting of dermatologic surgery. J Am Acad Dermatol 2013;68:869–70.
29. Milcheski DA, Ferreira MC, Nakamoto HA, Tuma Jr P. Development of

an experimental model of degloving injury in rats. [Article in Portuguese]. Rev Bras Cir Plast 2012;27:514–7. [CrossRef]
30. Milcheski DA, Nakamoto HA, Tuma P Jr, Nóbrega L, Ferreira MC. Experimental model of degloving injury in rats: effect of allopurinol and pentoxifylline in improving viability of avulsed flaps. Ann Plast Surg 2013;70:366–9.
31. Demirtas A, Azboy I, Bulut M, Ucar BY, Alabalik U, Ilgezdi S. Effect of hyperbaric oxygen therapy on healing in an experimental model of degloving injury in tails of nicotine-treated rats. J Hand Surg Eur Vol 2013;38:405–11. [CrossRef]
32. Cebesoy O, Isik M, Erzincan T, Pamukcu U, Bilgin F, Subasi M. Analysis of the effects of heparin and enoxaparin on degloving injuries. Bratisl Lek Listy 2014;115:550–3. [CrossRef]
33. Azboy I, Demirtaş A, Bulut M, Alabalik U, Uçar Y, Alemdar C. Effects of enoxaparin and rivaroxaban on tissue survival in skin degloving injury: an experimental study. Acta Orthop Traumatol Turc 2014;48:212–6.
34. Altun S, Orbay H, Ekinci M, Cetinbas A, Bal A, Arpaci E, et al. A comparison of rat degloving injury models. Acta Orthop Traumatol Turc 2017;51:308–12. [CrossRef]
35. Kabakaş F, Özçelik İB, Mersa B, Dağdelen D, Aksakal İA, Özalp T. Perforator artery repair in revascularization of extremity degloving injuries. Injury 2019;50:S99–104. [CrossRef]

DENEYSEL ÇALIŞMA - *ÖZET*

Avülsiyon yaralanmalarında fondaparinuks ve dabigatranın etkileri: Deneysel bir çalışma

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AMAÇ: Avülsiyon yaralanmalarının yönetimi hala zorlayıcı bir konudur ve avülsiye olan deri flepleri nekroza uğrayabilmektedir. Antikoagülan ajanlar olan fondaparinuks ve dabigatran ile tedavi edilen avülsiyon yaralanmalarında tekrar yerine sütüre edilen fleplerin sağkalımını artırması hedeflenerek avülsiyon yaralanmalarının tedavisinde faydalı olabileceğini düşündük.
GEREÇ VE YÖNTEM: Yirmi dört adet Wistar sıçanı üç gruba ayrıldı: Kontrol grubu (Grup 1), fondaparinuks grubu (Grup 2) ve dabigatran grubu (Grup 3). Tüm sıçanların kuyruğunda bir avülsiyon yaralanma oluşturulduktan 15 dakika sonra, avülsiyonlu dokular geri yerine sütüre edildi. Grup 1, 10 gün boyunca periton içine 1 ml/gün serum fizyolojik aldı. Grup 2, 10 gün boyunca periton içine 0.3 ml/kg/gün fondaparinuks aldı. Grup 3, 10 gün boyunca oral olarak 30 mg/kg/gün dabigatran aldı. Tedavilerin sonunda, morfolojik ve histopatolojik parametreler ve kuyruk doku sağkalımları değerlendirildi.
BULGULAR: Histopatolojik incelemede fondaparinuks ve dabigatran gruplarında kuyruklarının çoğunluğunun sağlam kaldığı ve enflamasyonun ise hafif düzeyde olduğu gözlendi. Fondaparinuks ve dabigatran gruplarına göre kontrol grubunda ortalama kuyruk nekroz uzunluğu ve inflamasyonun şiddeti istatistiksel olarak daha yüksek bulundu ($p<0.05$). Dabigatran ve fondaparinuks grupları arasında nekrotik alanın uzunluğu ve diğer histopatolojik parametreler açısından anlamlı bir fark saptanmadı ($p>0.05$).
TARTIŞMA: Dabigatran ve fondaparinuks, avülsiyon yaralanmasında morfolojik ve histopatolojik bulgular ile doku sağkalımını artırmıştır. Bununla birlikte, bu çalışmanın bulguları yeni deneysel çalışmalar ve özellikle klinik çalışmalar ile desteklenmeli ve geliştirilmelidir.
Anahtar sözcükler: Alt ekstremite rekonstrüksiyonu; avülsiyon; flep.

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