Comparing the Effect of Eutectic Mixture of Lidocaine and Prilocaine and Capsaicin on Improving Ischemic Random Skin Flaps: An Animal Model

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Abstract

Background: Ischemia of skin flaps is an important complication in reconstructive surgery. This study evaluated the effectiveness of eutectic mixture of lidocaine and prilocaine (EMLA) and capsaicin on improving flap survival.

Methods: A number of 39 white-albino male rats were divided randomly into three groups: EMLA, capsaicin, and control groups. A standard rectangular, distally based dorsal random pattern skin flap was elevated on each rat. Intraperitoneal cefazolin was administered to prevent infection. No pharmaceutical agent was administered for the control group except for pure Vaseline cream. In EMLA group, EMLA cream was administrated daily after surgery for 10 days. In capsaicin group, capsaicin cream was rubbed on the flap surface daily. The rats were evaluated 10 days after the operation for viable and necrotic portions of flaps.

Results: The mean values of necrosis in the flaps were 603.33 ± 116.00 mm^2, 665.00 ± 220.26 mm^2, and 920.00 ± 247.31 mm^2 in the EMLA, capsaicin and control groups, respectively. Both EMLA and capsaicin were effective on flap survival significantly (P = 0.002 and P = 0.011, respectively). Despite advantages, EMLA was not significantly better than capsaicin (P = 0.739).

Conclusions: EMLA and capsaicin are effective pharmaceutical agents that significantly increase the viability of random skin flaps in rats. They can be added to other vasoactive topical agents to reach better results and be used as a medical workhorse in reconstructive wards.

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Introduction

In plastic surgery, flaps are routinely used for covering tissue defects from trauma, ablative surgery or congenital malformation. Despite tremendous progress in the past two decades, flap surgery still has a considerable morbidity (1). Among local skin flap procedures, random pattern skin flaps are a reliable and convenient procedure. However, after a random pattern skin flap surgery, partial or complete distal flap necrosis is a common problem (2).

Factors involved in distal skin flap necrosis are categorized as either extrinsic or intrinsic. The extrinsic category consists of systemic or local causes such as malnutrition, hypotension, infection, compression, thrombosis, and kinking. The only intrinsic factor has been arterial insufficiency (3). These patients frequently need multiple operations and experience severe scar formation. These outcomes are associated with more hospital stay, longer work-off periods, unsatisfied results and increased medical costs (4). The clinical use of random pattern flaps may be limited by the development of necrosis in the distal area due to ischemia-reperfusion injury (5).

Surgical techniques such as flap delay procedures have been used to improve flap survival, and many

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drugs have been tested in the search for decreasing ischemic damage (6). In an attempt to search for alternatives to reduce or even prevent tissue necrosis; studies are being conducted using experimental models with the application of different kinds of drugs such as vasodilators, anticoagulants, antioxidants, prostaglandin inhibitors, calcium channel blockers, and antiadrenergic agents (7).

Capsaicin with various formulations can relief pain and also cause vasodilation by releasing vasodilator mediators. Topical eutectic mixture of lidocaine and prilocaine (EMLA) has clinical benefits in office procedures. It seems to release vasodilator factors and is a kind of vasoactive agent, besides local anesthesia. This study sought to compare the effect of two commonly used topical agents, i.e., EMLA and capsaicin, on improvement of distal ischemia of random skin flap in animal models.

Materials and Methods

A number of 39 white-albino male rats weighing 280-350 g living in the animal lab of a hospital in Tehran were housed separately under the same conditions in summer 2014. They were divided randomly into three groups with 13 rats in each group. All animals were anesthetized using 30-40 mg/kg Na thiopental intraperitoneally. They received 40 mg/kg Keflin intraperitoneally. Their backs were shaved, and a 2 cm × 9 cm caudally pedicle dorsal random flap was prepared according to an adaptation described by McFarlane et al. (8). The flaps contained skin and panniculus carnosus. Sacral pedicles were saved at the flap base. No special effort was taken for hemostasis, and the free edges of the flap were loosely sutured in place with 4-0 nylon (Figure 1).

Figure 1. Caudally based skin random flap

To protect the animals from harming themselves, dressings were used on the operative site. Animals received their treatments every day according to their groups by a different researcher as drugs A (cream EMLA), B (cream capsaicin), and C (cream Vaseline as placebo which used to moist wounds as traditional care) (Figure 2).

Figure 2. Topical agents used in the study

The topical agents were rubbed on the surface of the flaps. After 10 days, the animals were examined by another examiner. The amount of necrotic segment of the flap in contrast to the healthy segment was measured with a metric ruler (Figure 3). The results were presented as percentages of skin necrosis area (mean and standard deviation). The difference in the mean percentage of flap necrosis between the three groups was analyzed using SPSS software (version 16, SPSS Inc., Chicago, IL, USA).

Figure 3. Measuring necrotic area

Results

A number of 39 animals underwent surgery. Three rats died during the study (one from each group). Hence, the study ended with 36 rats. The mean values of necrosis area in the flaps were 603.33 ±116.56 mm^2, 665.00 ± 220.26 mm^2, and 920.00 ± 247.31 mm^2 in the EMLA, capsaicin, and control groups, respectively (Figure 4).

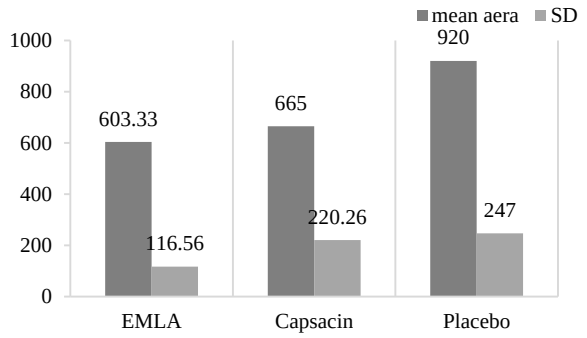

Figure 4. Necrotic area in 3 groups

In the control group (n = 12), the mean area of the flaps was 1800 ± 20 mm^2, and the mean necrotic area of flap was 920 ± 247 mm^2 (51%). In the EMLA group (n = 12), the mean area of the flap was 1800 ± 20 mm^2, and the mean necrotic area of flap was 603.33 ± 116.56 mm^2 (33%). In the capsaicin group (n = 12), the mean area of the flap was 1800 ± 20 mm^2, and the mean necrotic area of flap was 665.00 ± 220.26 mm^2 (37%). Using the ANOVA test, the difference between the three groups showed that both EMLA and capsaicin have significant differences with control group in decreasing flap ischemia and necrosis (P = 0.002 and P = 0.011, respectively). However, the difference was not significant among these agents (P = 0.739).

Discussion

Random pattern skin flaps are frequent reconstructive procedures. However, skin flap necrosis is usually concerning. Surgical delay and systemic pharmaceuticals are known solutions with their own costs. Harder et al. (1) compared different preconditioning tools in the improvement of flap survival.

Machado et al. (9) compared the effects of transcutaneous electrical nerve stimulation on wound healing. In 2016, Sharifi et al. (10) showed that parenteral pentoxifylline improves flap condition in rats. In 2016 Kashefi et al. (11) compared topical phenytoin and capsaicin and arrived at better results with capsaicin on necrotic flaps of rats. However, Moradi et al. (12) in 2016 had another idea and reported that survival of experimental critical flaps in rats after sensory denervation with capsaicin decreased. As a topical anesthetic agent, EMLA was shown to enhance flap survival percentage in rats about 81.2% ± 1.2% (13). Fatemi et al. (4) compared the effect of enoxaparin and clopidogrel on survival of random skin flap in rats. They found clopidogrel to be more effective. Livaoglu et al. (14), Hayden et al. (15), Rohrich et al. (16), and Kim et al. (17) found improved random skin flap survival by nitroglycerin ointment, glutathione and Vitamins A, C, botulinum toxin A and E and Hirudoid, respectively.

All these mentioned studies sought solutions to overcome flap failure through surgical or medical treatments. Different drugs examined with various results and side effects. We chose capsaicin and EMLA due to their availability and feasibility and being cost benefit and used standard operations and post-operative treatments to present these topical agents as lifeboats in ischemic challenges.

According to the studied reports and our results, topical agents have advantages to the others according to cost benefit, feasibility, easy to use and reproducibility. In our study, flap survival increased in animals treated with topical EMLA and capsaicin (P = 0.002 and P = 0.011, respectively). This can be because of their role as vasoactive agents that modulate releasing of vasodilator mediators to the reconstructed tissues. There was no significant difference between both groups (P = 0.739), although EMLA had better results. Maybe another study with more number of animals can have different results.

In this study influencing factors controlled to lower unwanted sequel, but we suggest studies among more than one topical agent to obtain and make a mixture including effective drugs.

Distal ischemia is a common complication in most random skin flaps, and it seems that EMLA and capsaicin are effective pharmaceutical agents that significantly increase the viability of random skin flaps in rats.

Conflict of Interests

Authors have no conflict of interests.

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