The efficacy of topical phenytoin and capsaicin on random pattern dorsal skin flaps in rats

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AIM: *We investigated the efficacy of topical phenytoin and capsaicin on random pattern dorsal skin flaps in rats.*
MATERIAL AND METHOD: *Twenty one Wistar rats were used in the study. Random-pattern McFarlane dorsal flaps 3 cm x 10 cm were raised in all the rats .A plastic barrier was placed between the flap and its donor site The flaps were sutured back to the original position with 4/0 nylon sutures. The rats were randomly divided into three groups (n=7). Group I was given only gel, Group II was given 2 gr gel with % 1 phenytoin and Group III was given 2gr gel with %0.1 capsaicin and pure gel. Capsaicin application were used twice a day on 2 consecutive days,subsequently Group III was given only gel on 5 consecutive days. Phenytoin and placebo application were used twice a day on 7 consecutive days. Images were transferred to a computer and ratio of flap necrosis area to total flap area was calculated*
RESULT: *The mean percentage of necrosis in the flaps were 37.27±3.86%, 36.3±6.2%, 23.4±5.9 % in the control, phenytoin and capsaicin groups, respectively. The percentage of flap necrosis was significantly lower in the Capsaicin Group compared to the control group (37.27% vs 23.4%, p<0.01). Although phenytoin had a lower mean percentage of flap necrosins than the control group, this difference was not significant (37.27 vs 36.3 , p>0.05).*
CONCLUSION: *We showed topical capsaicin increased the random pattern skin flap survival in rats whereas topical phenytoin had no positive effect. We believe that further studies are required to investigate the efficiency of topical phenytoin applications.*

KEY WORDS: Capsaicin, Phenytoin, Skin flaps.

Introduction

Although it is not common, necrosis is one of the major complications in random pattern flap applications.
Up to date, there have been studies questioning the effects of surgical and chemical delays [1-3] systemic drug therapy [4-6], topical medical therapy [7-9] and TENS [10,11]. (transcutaneous electrical nerve stimulation) on flap necrosis. Topical medical therapy has been shown to be advantageous due to its minimized side effects regarding direct target organ sensitivity, easy applicability and cost effectiveness [16,17].
The 2 drugs selected for this study, capsaicin and phenytoin, have widely differing mechanisms of action.
To our knowledge this is the first study investigating the effects of topically administered phenytoin ointment on flap necrosis.
Phenytoin (sodium diphenylhydantoin) is a well-known antiepileptic drug.Kimball first noted that gingival hyperplasia occurred in some patients treated with phenytoin [13]. In 1958, Shapiro published the first clinical study to examine the effects of phenytoin on the healing of gingival wounds [14]. Subsequent in vivo and clinical studies

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with topical phenytoin suggest acceleration in wound healing, granulation tissue formation [15-17], reduction in oedema, inflammation, wound transudate and exudate [18,19], and decrease in bacterial contamination [18,19]. Possible facilitation of nerve regeneration [18].
Biopsies of phenytoin-treated open wounds show neovascularization and collagenisation [15].
There is evidence that phenytoin has a positive healing effect on various types of wounds [16,17]. Studies have shown topical phenytoin to promote healing of decubitus ulcers [20], venous stasis ulcers [16], diabetic ulcers [21,22], traumatic wounds [18,19], burns [23,24], leprosy trophic ulcers [16], large gluteal abscess [25] and peridontal diseases [26].
Phenytoin may also be useful in enhancing the healing of clean surgical wounds [27-29].
Topical capsaicin formulations are widely used to manage pain [30,31]. Clinical studies of these medications, in general, suggest modest beneficial effects against various pain syndromes, including post-herpetic neuralgia (PHN), diabetic neuropathy, and chronic musculoskeletal pain [32].
Topical application of capsaicin causes marked vasodilation by the release of vasodilator neuropeptides, such as substance P (SP) and calcitonin gene-related peptid(CGRP)[33-35], inhibits platelet aggregation [36] and increases angiogenesis [37,38]. These findings suggest capsaicin a role in diminished flap necrosis.
In this study we investigated the effects of topical phenytoin and capsaicin application on flap necrosis in postoperative salvage of failing flaps in an animal model.

Material method

Twenty one Wistar rats, weighing between 250 - 350 g, were used in the study. Animals were fed standard rat chow and water *ad libitum* throughout the study period. All animals received humane care in accordance with the Guide for the Care and Use of Laboratory Animals. Kobay Deney Hayvanları San. Tic.A Animal Ethics Committee permission was taken. The rats were anesthetized intraperitoneally with thiopental (30mg/kg) and intramusculer with ketamin+xylazine (80mg/kg+10mg/kg) for surgery. Following anesthesia, animals were immobilized in the prone position. The dorsal skin of the rats was outlined and the surgical area was prepared under sterile conditions. Subsequently, random-pattern McFarlane dorsal flaps 3 cm x 10 cm were raised in all the rats (Fig. 1). Panniculus carnosus was included in the flap. A plastic barrier was placed between the flap and its donor site [30]. The flaps were sutured back to the original position with 4/0 nylon sutures. The rats were randomly divided into three groups (n=7). Randomization process was performed using a lottery. 1 g hydroxypropylmethyl cellulose (4000 cPs, Sigma, USA) was wetted with 25 g deionized water for 24 h. 0.1 g capsicum oleoresin was dissolved in a mixture of deionized water/tween 80/propylene glycol (18.9 g /1 g/ 4 g) and added to the gel base by gently mixing. The gel formulation contained 0.1% capsicum oleoresin. 1 g Hydroxypropylmethyl cellulose (4000 cPs, Sigma, USA) was wetted with 40 g deionized water for 24 h. 0.5 g phenytoin sodium was dissolved in 8.5 g deionized water and added to the gel base by gently mixing. The gel formulation contained 1% phenytoin sodium.

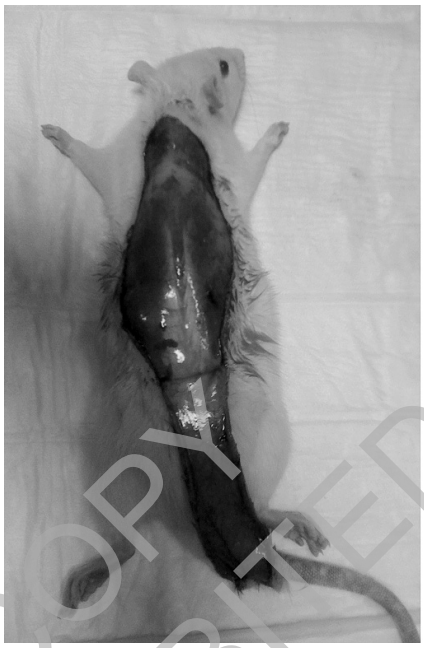

Fig. 1: McFarlane dorsal flaps.

After surgery, Group I was given only gel, Group II was given 2 gr gel with % 1 phenytoin and Group III was given 2gr gel with %0.1 capsaicin and pure gel. To prevent cannibalism, the rats were housed individually after surgery. Capsaicin application were used twice a day on 2 consecutive days,subsequently Group III was given only gel on 5 consecutive days. Phenytoin and placebo application were used twice a day on 7 consecutive days. Capsaicin was applied only to the flap while phenytoin and placebo was applied both to the flap and incision line. Photographs of flap areas in each animal were taken from 25cm distance using a digital camera (Sony Cyber-Shot Carl Zeiss) and a tripod on day 7 after operation. Images were transferred to a computer and ratio of flap necrosis area to total flap area was calculated using Auto Cad 2006 programme.
The results were presented as percentages of skin necrosis areas (mean _ SD). The difference in the mean percentage of flap necrosis between the three groups were analysed using a one-way ANOVA test, which is a parametric variance technique. . The difference in the mean percentage of flap necrosis between the two individual groups were analysed using Mann-Whitney U-test. Probabilities of less than 0.05 were accepted as significant.

Results

Twentyone animals underwent surgery and no animals died during or after the operation.The mean percentage of necrosis in the flaps were 37.27± 3.86%, 36.3±6.2%, 23.4±5.9 % in the control, phenytoin and capsaicin groups, respectively. The Capsaicin Group had a significantly lower percentage of flap necrosis than either the control or Phenytoin groups(Table 1. p <0 .0001) The percentage of flap necrosis was significantly lower in the Capsaicin Group compared to the control group (37.27% vs 23.4%, p<0.01). Although phenytoin had a lower mean percentage of flap necrosis than the control group, this difference was not significant (37.27 vs 36.3, p>0.05). Figure 2 shows a comparison of the mean percentages of the necrosis area among all three groups.

Discussion

In surgical procedures random patterned skin flaps are frequently used in repair of skin defects. A major complication of this application is however, skin flap necrosis.

Although there have been studies showing the effects of surgical delay, chemical delay [1-3], systemic drug therapy [4-6], topical medical therapy [7-9] and TENS [10,11] transcutaneous electrical nerve stimulation) on flap necrosis prevention and treatment of flap necrosis are still a challenge to the surgeons.

Regardless of the method chosen the decrease the risk of flap necrosis, it should have clinical availability, easy administration, a high therapeutic index (safety), reproducibility of effective results, feasibility of only postoperative treatment, cost-effectiveness, known mechanism of action, established bioavailability, and protective effects on flap necrosis as defined by Rohrich et al [12]. Topical applications of both phenytoin and capsaicin are to full fill a great number of these conditions.

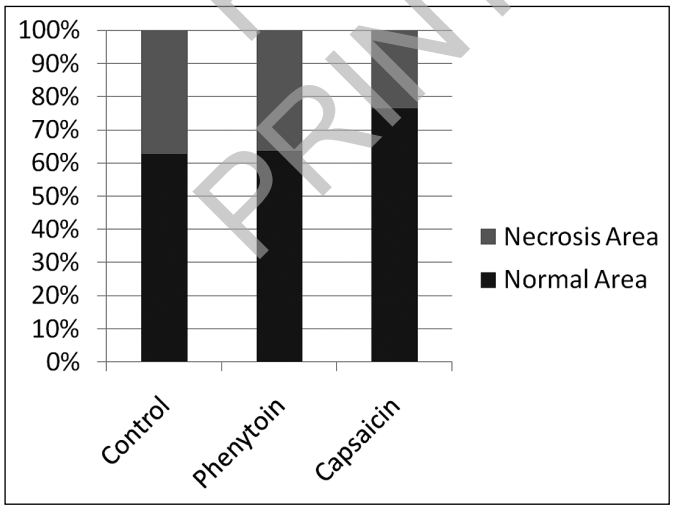

Fig. 2: Distribution of the percentage of necrotic area per group

Topical application of capsaicin causes marked vasodilation [33-35], inhibits platelet aggregation [36] and increases angiogenesis [37,38]. Via these effects capsaicin increases the survival of random pattern skin flaps [9,39,40]. In agreement with literature we showed that topical capsaicin application to increase survival of random pattern skin flaps in rats compared to the placebo controls.

As Godoy and his friends [9] also indicated, we determined that 2 days of capsaicin application is effective for saving flap. Group that Capsaicin is applied in this work, has become a second control group within the group that topical phenytoin is used for salvaging flap necrosis for the first time.

Capsaicin inhibits flap necrosis in a manner as Transcutaneous Electrical Nerve Stimulation (TENS). Both applications cause vasodilation in flap by increasing neuropeptide secretion. Liebano et al. reported that application of TENS in two consecutive days to be efficient to increase the random skin flap viability. In the light of this report we decided to use topical capsaicin only for two days which was easily applicable [9-11].

There has been no previous report about using topically administered phenytoin ointment on flap necrosis. However, there is evidence in literature suggesting that phenytoin has positive healing effects on various types of wounds [16,17].

Suwalsky et al. showed that low (micro molar) concentrations of the antiepileptic agent applied to the outside surface of the toad epithelium increased the electrical parameters (short-circuit current and potential difference) by over 40%, reflecting stimulation of Na+ transport [41]. The hypothesis of this study was to see whether this electrical parameter increase might cause an increase in secretion of neurotransmitters with vasodilatatory effects. We decided to investigate the role of phenytoin in random patern flap healing due to its abilities to reduce oedema and inflammation, wound transudate and exudate [18,19], to decrease bacterial contamination [18,19], to increase neovascularization [15], to might cause an increase in secretion of neurotransmitters with vasodilatatory effects [41] and to cause positive effect in rapid pain relief [18].

Unfortunately, we could not detect any beneficial effects of phenytoin application on random pattern skin flap survival when compared to placebo controls. The effect that mostly makes think that phenytoin will be useful for preventing flap necrosis is the increasing of neovascularisation and warning epithelial electrical activity. We think that the failure of phenytoin to prevent necrosis connects that it cannot show these mentioned effects over flap sufficiently. We think that failure of phenytoin to prevent necrosis can be related to the application dose, concentration, duration, frequency and applied area of the medicine.

In conclusion, we showed topical capsaicin increased the

random pattern skin flap survival in rats whereas topical phenytoin had no positive effect. We believe that further studies are required to investigate the efficiency of topical phenytoin applications.

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Commento e Commentary

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Defect coverage using local skin flaps remains a pillar of plastic reconstructive surgery. For this purpose, random-pattern skin flaps provide a reproducible and relatively safe method for the reconstruction of congenital, traumatic or neoplastic defec [1-3]. However, distal flap necrosis remains a serious complication in all random skin flaps.

A number of pharmacological experimental treatment modalities designed to reduce flap necrosis have been explored, including the use of vascular endothelium growth factor (VEGF), ketorolac, topical lidocaine and prilocaine (EMLA), dexamethasone and carnitine, topical oleic acid, and nitric oxide ($NO^{)}$ [5-7]. Other agents such as sympatholytics, hemorheologic agents, free radical scavengers and vasodilators have also been tested. To date, however, there is no clinically approved, reliable, or widely accepted pharmacological treatment for the failing flap [8-9].

Studies have investigated the effects of systemic [10-11], local [12-13] and combined [14] pharmaceutical applications on flap survival. Many studies have tested drugs such as antiadrenergics [15-16], vasodilators [17-18], antispasmodics [19], anticoagulants and calcium-channel blockers [20] to improve flap viability. However, undesirable side effects, high drug prices, limited availability or the need for long-term treatment during the pre-operative period make some drugs impractical for clinical use [20]. In yet other studies, researchers have tried to improve the viability of skin flaps by topically applying medicines, in an attempt to enhance local action and minimize systemic action, thereby reducing side effects [18-21]. These drugs include capsaicin [21,23], a substance that promotes vasodilatation and inhibits platelet aggregation (24-25). As demonstrated in the paper by Bilgen et al., capsaicin increases random pattern skin flap survival in rats. In view of the physiological mechanisms of ischemia that lead to flap necrosis and the reported effects of capsaicin, further studies on this substance are warranted to improve the viability of ischemic random pattern skin flaps. Iinuma and Sawada [22] attributed the improvement in skin flap viability after topical application of capsaicin to platelet disaggregation. By contrast, Miyawaki et al. [21] concluded that the beneficial effect of capsaicin on skin flap viability is due to vasodilation caused by the release of vasodilator neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), as well as to increased neovascularization [16,26-27].

Sildenafil, a PDE 5 inhibitor, was found to effectively reduce skin necrosis, is able to prolong the vasodilating effects of nitric oxide. Really previous experiments identified the vasodilating action of nitric oxide as an important factor in the reduction of distal skin flap necrosis. Further refinement and testing of the effects of PDE 5 inhibitors on flap necrosis may lead to the development of pharmacological therapies for the enhancement of skin flap viability [4].

Further investigations on both animal and human models are warranted to better understand the effectiveness of the therapies available as well as their potential clinical uses. Any instruments that may reduce the incidence of necrosis in flap surgery would be welcomed by plastic reconstructive surgeons.

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La copertura dei difetti cutanei mediante lembi locali è ancora una delle basi in chirurgia plastica ricostruttiva. Per questo scopo, i lembi cutanei random forniscono un metodo riproducibile e relativamente sicuro per la ricostruzione di difetti congeniti, traumatici, o neoplastici [1-3]. Tuttavia, in tutti i lembi cutanei random, la necrosi della porzione distale del lembo con conseguente deficit ricostruttivo rimane una grave complicanza.
Numerosi trattamenti farmacologici sperimentali sono stati esplorati per diminuire necrosi del lembo, quali il fattore di crescita vascolare endoteliale (VEGF), il ketorolac, la lidocaina e la prilocaina a uso topico (EMLA), il desametasone e la carnitina, l'acido oleico topico, e l'ossido nitrico (NO) [5-7]. Altri agenti come simpaticolitici, agenti emoreologici, radicali liberi, e vasodilatatori sono stati testati. Ad oggi, tuttavia, non vi è alcun trattamento clinicamente approvato, affidabile, o farmacologicamente accettato per il fallimento dei lembi [6,7].
Alcuni studi hanno studiato l'effetto sistemico [10-11], locale [12-13], e combinato [14] di tali applicazioni farmaceutiche sulla sopravvivenza dei lembi. In molti studi, farmaci come antiadrenergici [15-16], vasodilatatori [17,18], antispastici [19], anticoagulanti e calcio-antagonisti [20] sono stati utilizzati per migliorare la vitalità dei lembi. Tuttavia, gli effetti collaterali indesiderati, l'alto costo, la limitata disponibilità o la necessità di un trattamento a lungo termine nel periodo preoperatorio rende impraticabile l'utilizzo di alcuni farmaci per uso clinico [20]. In altri studi, i ricercatori hanno cercato di migliorare la vitalità dei lembi cutanei mediante applicazione topica di farmaci, cercando di aumentare l'azione locale e di ridurre al minimo l'azione sistemica, diminuendo, così, gli effetti collaterali [18-21]. Tra questi farmaci c'è la capsaicina [21-23], una sostanza che, in generale, promuove la vasodilatazione e inibisce l'aggregazione piastrinica [24,25]. Come dimostrato dal lavoro di Bilgen et al. la capsaicina ha aumentato la sopravvivenza dei lembi random nei ratti. In considerazione dei meccanismi fisiologici dell'ischemia che portano alla necrosi e degli effetti della capsaicina, è importante studiare questa sostanza allo scopo di migliorare la vitalità lembi cutanei random ischemici. Iinuma e Sawada [22] hanno attribuito il miglioramento della vitalità dei lembi cutanei dopo l'applicazione topica di capsaicina alla disaggregazione piastrinica. D'altra parte, Miyawaki et al. [21] hanno concluso che l'effetto benefico della capsaicina nella vitalità del lembo cutaneo è dovuto alla vasodilatazione causata dal rilascio di neuropeptidi vasodilatatori, come sostanza P (SP) e calcitonina gene-related peptide (CGRP), e a un aumento della neovascolarizzazione [16,26-49].
Il sildenafil, un inibitore del PDE 5, è stato trovato efficace nella riduzione della necrosi cutanea, in grado di prolungare gli effetti vasodilatatori dell'ossido nitrico. Infatti esperimenti precedenti avevano individuato nell'azione vasodilatatrice dell'ossido nitrico un fattore importante nella riduzione della necrosi distale dei lembi cutanei. Un ulteriore affinamento e la sperimentazione degli effetti di inibitori della PDE-5 su necrosi del lembo potrebbero portare allo sviluppo di terapie farmacologiche per il miglioramento della vitalità del lembo cutaneo[4].
Ulteriori indagini con modelli animali e modelli umani sono necessarie per meglio l'efficacia delle terapie così come la possibilità di un loro uso clinico. Certamente la possibilità di poter disporre di strumenti che riducano l'incidenza della necrosi è auspicabile negli interventi chirurgici che necessitano l'utilizzo di lembi.

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