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Comparison of Topical Sucralfate and Silver Sulfadiazine Cream in Second Degree Burns in Rats*

Porównanie skuteczności miejscowego sukralfatu i soli srebrowej sulfadiazyny w kremie w leczeniu oparzeń drugiego stopnia u szczurów

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. The most prevalent topical treatment for partial thickness burns is silver sulfadiazine 1% (SSD). Recent studies have shown that the healing of partial thickness burns is delayed with the use of SSD. One of the potential burn dressings is sucralfate.
Objectives. With this study the authors have aimed to analyze comparatively the effects of sucralfate and SSD on second degree burn wounds in rats.
Material and Methods. Forty-eight male rats were divided into three equal groups. A burn model was constituted on the back of all rats. The burned areas in the first, second and third groups were covered daily with sucralfate, SSD and cold cream (control), respectively. At the end of the 7th, 14th, 21st and 28th day, the rats were anesthetized and the burned skin tissue samples were collected for histopathological examination.
Results. At the end of the study, the epidermis and horny layer was completely formed in the SSD and sucralfate group; however the appendix of skin was just formed in the sucralfate group. Also the percentage of wound healing was calculated at 76%, 91% and 100% respectively in the control, silver sulfadiazine and sucralfate groups.
Conclusions. Sucralfate is known to have multiple beneficial effects on wound healing. Using topical sucralfate accelerates the burn wound healing process in comparison with both the control and SSD groups and can be used as an adjunctive or alternative agent in the future (**Adv Clin Exp Med 2013, 22, 4, 481–487**).

Key words: sucralfate, silver sulfadiazine, second degree burns, rat.

Streszczenie

Wprowadzenie. Najbardziej rozpowszechnionym sposobem miejscowego leczenia oparzeń II stopnia jest sól srebrowa sulfadiazyny 1% (SSD). Ostatnie badania wykazały, że leczenie oparzeń II stopnia jest opóźnione z wykorzystaniem SSD. Jednym z możliwych opatrunków oparzeniowych jest sukralfat.
Cel pracy. Analiza porównawcza wpływu sukralfatu i SSD na oparzenia drugiego stopnia u szczurów.
Materiał i metody. Czterdzieści osiem samców szczurów podzielono na trzy równe grupy. Model oparzenia utworzono na grzbiecie wszystkich szczurów. Spalone obszary w grupach pierwszej, drugiej i trzeciej codziennie pokrywano odpowiednio sukralfatem, SSD i zimną śmietaną (grupa kontrolna). Na koniec dnia 7, 14, 21 i 28 szczury usypiano i spalone próbki tkanki skóry zebrano do badań histopatologicznych.
Wyniki. Na koniec badania naskórek i warstwa rogowa skóry były całkowicie uformowane w grupie SSD i sukralfatu, jednak skóra właściwa została wytworzona w grupie z sukralfatem. Skuteczność gojenia ran obliczono na 76%, 91% i 100% w grupie kontrolnej, z solą srebrową sulfadiazyny i z sukralfatem.
Wnioski. Sukralfat wywiera korzystny wpływ na gojenie ran. Przy zastosowaniu miejscowym sukralfat przyspieszał

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proces gojenia ran po oparzeniu w porównaniu z grupą kontrolną i SSD oraz może być stosowany jako alternatywa lub środek wspomagający leczenie w przyszłości (**Adv Clin Exp Med 2013, 22, 4, 481–487**).

Słowa kluczowe: sukralfat, sól srebrowa sulfadiazyny, drugi stopień oparzenia, szczur.

Burns are one of the most widespread injuries all over the world. In the United States, more than 1 million burn victims need medical attention every year, but only 45,000 of them require hospitalization [1]. A similar situation exists in the United Kingdom, where burns comprise 1% of the workload in emergency wards as well as 0.014% of hospital admissions [2]. Thus, most burns are not severe and could be managed outside the hospital.

The most prevalent topical treatment for partial thickness burns is silver sulfadiazine 1% (SSD) [1, 3]. SSD is the topical agent of choice for severe burns and is used almost universally today in preference to compounds such as silver nitrate and mafenide acetate. SSD cream, in spite of being effective, causes some systemic side effects consisting of neutropenia, erythema multiforme, crystalluria and methemoglobinemia [4–6]. Topical agents which are used only as antimicrobials include silver nitrate, sulfamylon and a combination of a sulfonamide and SSD. Sulfamylon has broad spectrum activities, but it is easily absorbed systemically and can lead to toxic complications. SSD has become the standard topical treatment for burn wounds [4]. More recent studies have shown that the healing of partial thickness burns is delayed with the use of SSD [7, 8], indicating the need for a better burn dressing.

One of the potential burn dressings is sucralfate. Sucralfate is a basic aluminum complex of sucrose sulfate and a cytoprotective agent. The sporadic studies and case reports available in the literature are all consistent, indicating the favorable effect of topical sucralfate in wound repair and skin protection. Almost all studies have indicated the safe and effective behavior of this compound [9–17]. Sucralfate has also been shown to have antibacterial activity [18, 19] and has been successfully studied in decreasing pain and improving healing after hemorrhoidectomy [20], in peristomal and perineal dermatoses, in moist desquamation during radiotherapy, in erosion and ulceration of the perineal area, in vaginal ulceration, in dystrophic epidermolysis bullosa, in second and third degree burns, and in a pilot trial with nonhealing, full-thickness venous stasis ulcers refractory to 8 weeks of conventional therapy [9–17].

With this study the authors aimed to analyze comparatively the effects of sucralfate and SSD on wound healing in a burn wound that has been made in rats.

Material and Methods

Animals

Forty-eight male Wistar rats (200 to 250 g each) were obtained from the Razi Institute (Karaj, Iran) and housed in groups of three per cage under standard laboratory conditions. All animals were kept at a constant room temperature (21 ± 2°C) under a normal 12-h light/12-h dark cycle with free access to food and water. All animal experiments were carried out in accordance with the European Union's Council Directive of November 24th, 1986 (86/609/EEC) to minimize their suffering.

Chemicals

Sucralfate cream (Avene Cicalfate Restorative Skin Cream, purchased from Avene Co., France), silver sulfadiazine 1% (topical cream, purchased from Sobhan Pharmaceutical Co., Tehran, Iran), cold cream (Botafarma, 12.5% spermaceti + 12% white wax + 56% liquid paraffin + 0.5% borate of soda + 19% distilled water) [21], ketamine (Rotexmedica, GmbH, Germany), and xylazine (Loughrea Co., Galway, Ireland) were used in this study.

Method

All animals were administered general anesthesia through peritoneal injection of xylazine (5 mg/kg) and ketamine (40 mg/kg) and the back hair of them was shaved. Then a round iron plate (heated to 80°C) was placed on each animal's skin for 1 second in order to create a 1.75 cm^2 second-degree burn injury [22]. Then the animals received an intraperitoneal injection of saline (0.1 l/kg) and were placed in individual cages for recovery. To confirm the degree of burns, histopathological samples were taken randomly from eight rats. Then all animals were randomly divided into three groups (n = 16 in each group). The first group was treated with sucralfate cream, the second group was treated with the silver sulfadiazine 1% and the third group was treated with cold cream.

By considering the day that the authors caused burn in rats as zero, the punch biopsies with disposable punch were taken of the large diameter wound burn and surrounding skin of 12 animals (n = 4 in each group) at the end of the 7th, 14th, 21st and 28th day (needle size = 8 mm). Skin sections were fixed in 10% formaldehyde, dehydrated in ethanol (50% to 100%), cleared in xylene and embedded in

paraffin. Sections (4 to 5 μm thick) were prepared and stained with hematoxylin and eosin (HE) dyed for histopathological examination and observed under a microscope at a high magnification. The thickness of granulation tissue at the center of each wound was examined and recorded. Also, to determine the percentage of wound healing, the wound surface was measured by tracing the margins of the open wound on digital images of the wounds that were scanned into the computer. The open wound area was then later calculated using Scion Image version beta 4.0.2 (Scion, Frederick, Md) on the aforementioned days (7^{th}, 14^{th}, 21^{st} and 28^{th}). After that, the following formulas were used to determine the percentage of wound and healing:

Area of wound = Open wound area was calculated using Scion Image (details above)

Percentage of wound = (Area of wound on particular day × 100) ÷ the area of wound on the first day

Percentage of healing = (100 – percentage of wound)

Ethical Approval

The study was approved by the ethics committee of the Qazvin University of Medical Science before its initiation, and the protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Statistical Analysis

The collected data was analyzed using SPSS software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Ill, USA). One-way ANOVA tests were used, where appropriate, for comparing data between all groups. Continuous data was demonstrated as mean ± standard deviation. *P* – values less than 0.05 were considered significant.

Results

At the End of the First Week

In all groups, no epidermis existed in the burn site and fibrino-leukocytic exudate was seen with edema and transudates in the wound and surrounding tissue. A necrotic layer with predominant inflammatory PMN cells and granulation tissue with angiogenesis were seen in all groups (Fig. 1).

At the End of the Second Week

In the sucralfate group, the thickness of the fibrino-leukocytic layer was decreased in comparison with the control and SSD groups, although granulation tissue had increased. Fibroblast density was increased in the dermal layer in all groups, in addition to this increase; angiogenesis was also greatest in the sucralfate group. The percentage of inflammatory PMN cells was reduced while the number of mononuclear inflammatory cells had started to increase (Fig. 2).

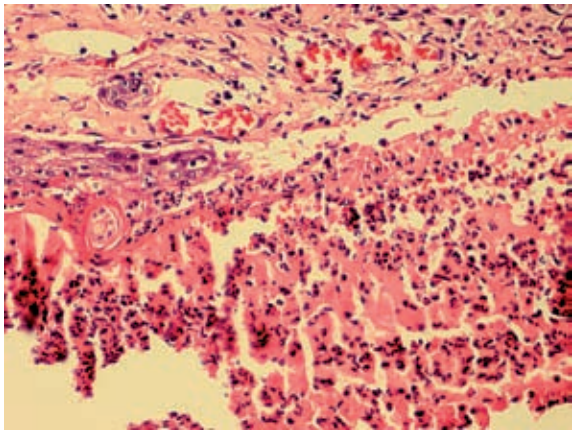

Fig. 1. The first week in the third group (high magnification ×400): Exudative and necrotic layer at first week. The predominant inflammatory cells are PMN

Ryc. 1. Stan w pierwszym tygodniu w trzeciej grupie. (duże powiększenie 400×): wysiękowe i martwicze warstwy w pierwszym tygodniu. Dominujące komórki zapalne to granulocyty obojętnochłonne

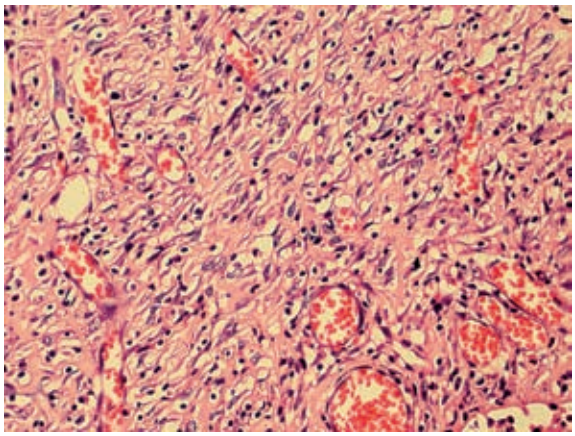

Fig. 2. The second week in the first group (high magnification ×400): The granulation tissue is present. There is more vascular proliferation than in the first week. There is a decrease in the percentage of PMN inflammatory cells and the mononuclear inflammatory cells begin to increase in numbers

Ryc. 2. Drugi tydzień w pierwszej grupie (duże powiększenie 400×): są obecne wysiękowe, martwicze i zianinowe warstwy. Istnieje więcej proliferacji niż w pierwszym tygodniu. Zmniejszył się odsetek komórek zapalnych granulocytów obojętnochłonnych i jest coraz więcej jednojądrzastych komórek zapalnych

At the End of the Third Week

In the control group, the cells in the wound bed were more organized. The epidermis layer was not formed and fibroblast density had increased in this layer. In the silver sulfadiazine group, despite forming an epidermis layer, the horny layer hadn't formed and in the sucralfate group, the epidermis layer as well as a thin horny layer were seen. Like new parallel blood vessels in the silver sulfadiazine group were also seen on the wound surface in this group. The granulation tissue was more organized than other groups. In this week, the percentage of inflammatory PMN cells was reduced and density of fibroblast and macrophage was increased (Fig. 3).

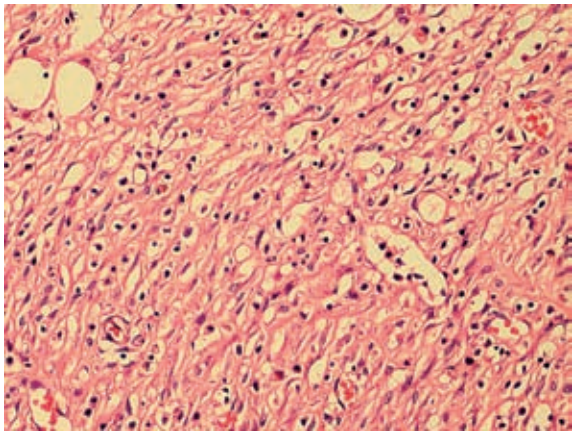

Fig. 3. The third week in the first group (High magnification ×400): There is decrease in the number of inflammatory cells, particularly PMNs, and an increase in the number of macrophages and fibroblasts. A fine deposit of collagen matrix is also present

Ryc. 3. Stan w trzecim tygodniu w pierwszej grupie (duże powiększenie 400×). Zmniejszyła się liczba komórek zapalnych, w szczególności granulocytów obojętnochłonnych i zwiększyła się liczba makrofagów i fibroblastów. Cienka warstwa macierzy kolagenowej jest również obecna

At the End of the Forth Week

In the control group, the epidermis layer had formed in spite of the fact that some areas showed lack of epidermis in the center of the wound. The horny layer was created in the middle of the wound, otherwise there wasn't any in the center of the wound. In this week in the silver sulfadiazine group, the epidermis and horny layer was completely formed, however the appendix of skin was not formed.

In the sucralfate group, the epidermis and horny layer was completely formed at the end of the 4th week. There was fibrous tissue in the central part of the lesion. The inflammatory cells' content was reduced and a low number of mononuclear inflammatory cells was seen (Fig. 4).

At the end of the fourth week, the percentage of wound healing was calculated at 76%, 91% and 100%, respectively, in the control, silver sulfadiazine and sucralfate groups. This result was significantly different between all groups ($p < 0.05$). The percentage of wound healing in this study is summarized in Table 1 and Fig. 5. Also, present results in this study have shown that the thickness of granulation tissue was significantly different between each group ($p < 0.05$). The mean values of thickness of granulation tissue in the center of the wounds for sucralfate cream, SSD and control groups are shown in Table 2.

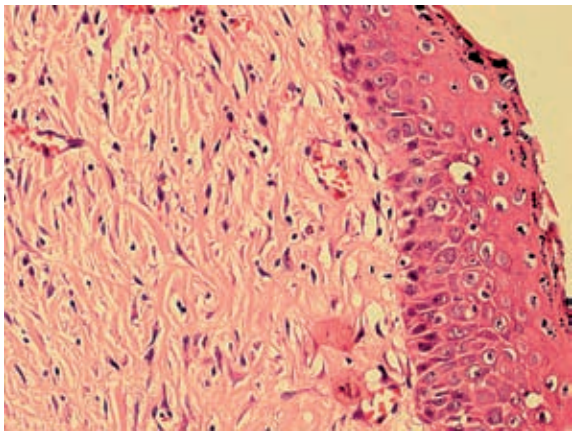

Fig. 4. The fourth week in the first group (high magnification ×400): The inflammatory cells are scattered and are mostly mononuclear. Vascularity is also decreased. There is a higher number of fibroblasts than normal and more deposits of collagenous matrix (scar tissue formation)

Ryc. 4. Stan w czwartym tygodniu w pierwszej grupie (duże powiększenie 400×): komórki zapalne są rozproszone, w większości jednojądrzaste. Unaczynienie również zmniejszyło się. Istnieje większa liczba fibroblastów niż normalnie i więcej warstw macierzy kolagenowej (powstawanie blizn)

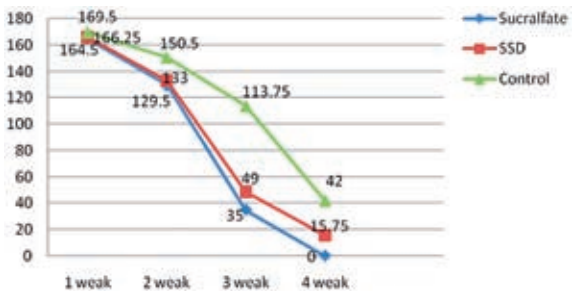

Fig. 5. Wound area (mm^2) over 4-week treatment

Ryc. 5. Obszar rany (mm^2) podczas 4-tygodniowego leczenia

Table 1. The percentages of wound healing

Tabela 1. Odsetek wyleczonych ran

	1st week (Tydzień 1)	2nd week (Tydzień 2)	3rd week (Tydzień 3)	4th week (Tydzień 4)
Sucralfate group	6	26	80	100
SSD group	5	24	72	91
Control group	3	14	35	76
P-Value	P > 0.05	P < 0.05*	P < 0.05*	P < 0.05*

Table 2. Thickness (mm) of granulation tissue in the center of the wound

Tabela 2. Grubość (mm) tkanki ziarninowej na środku rany

	1st week (Tydzień 1)	2nd week (Tydzień 2)	3rd week (Tydzień 3)	4th week (Tydzień 4)
Sucralfate group	0.985 ± 0.01	1.856 ± 0.03	2.580 ± 0.01	3.200 ± 0.02
SSD group	0.736 ± 0.02	1.214 ± 0.03	2.010 ± 0.03	2.765 ± 0.01
Control group	0.380 ± 0.05	0.896 ± 0.01	1.520 ± 0.03	2.000 ± 0.01
P-Value	P < 0.05*	P < 0.05*	P < 0.05*	P < 0.05*

Discussion

Wound repair depends on neoangiogenesis, the activation of local immune response, and in the presence of growth factors including epidermal growth factor (EGF), transforming growth factor β (TGF-β), and basic fibroblast growth factor (bFGF) [23–27].

Sucralfate is known to have multiple beneficial effects on wound healing. This drug induces the proliferation of dermal fibroblasts and keratinocytes in vitro, and inhibits the release of interleukin-2 and interferon-γ from damaged skin cells [28]. The physical barrier feature of sucralfate is to diminish inflammatory reaction and improve mucosal healing [17, 29–31]. Limiting the inflammation might decrease fibrosis and stricture formation and EGF expression as well as the expression of other factors involved in tissue repair processes [32]. Stimulating effects on vascular factors, such as angiogenesis, which play important roles in tissue repair, have been demonstrated by sucralfate [33, 34]. Sucralfate does not have any adverse effects [35] thus it is widely employed in clinical practice to prevent or treat recurrent aphthous stomatitis and several gastrointestinal diseases [36, 37].

Unfortunately not many in vivo or in vitro histopathological studies about this drug have been carried out in the world. Because of that, the main objective of this study was to determine the effectiveness of the local treatment of burn wounds with sucralfate and compare it to SSD.

According to the results that were obtained in this study, using topical sucralfate accelerates the burn wound healing process in comparison to both the control and SSD groups, so that at the end of the fourth week, thickness of granulation tissue was significantly higher in the sucralfate group. Also, the percentage of wound healing was calculated at 76%, 91% and 100%, respectively, in the control, silver sulfadiazine and sucralfate groups. These results confirm another study about the role of granulation tissue in wound healing [38] and demonstrate the power of sucralfate in neoangiogenesis, proliferation of dermal fibroblasts, EGF expression and the expression of other factors involved in tissue repair processes. This is in concurrence with other studies, which have shown that sucralfate stimulates epithelial cell proliferation by causing accumulation of epidermal growth factor in the ulcerated areas [39, 40]. Burch et al. [28] showed, in animal studies, that sucralfate cream accelerates cell proliferation in the superficial skin layer, leading to a clear thickening of the epidermis the same as in dermis experimental studies by Szabo et al. [34] that have shown that sucralfate stimulates angiogenesis, which increases granulation tissue. Moreover, sucralfate induced PGE2 synthesis and IL-6 release from cultured skin cells in the study by Burch et al. [28], which was responsible for the healing process.

Limitations

Unfortunately present study has several limitations. The small sample size may have led to an important error. Furthermore, the current study was limited to 28 days only, during which time, all the wounds did not heal completely. On the other

hand, the burned areas in this study were covered daily, while 2 or 3 dressing per day probably would have a better outcome in wound healing. Finally, this study is limited to rats with second degree burns and may not generalize to humans.

The authors concluded that in a burn wound model in rats, sucralfate was found to expedite the healing process both histopathologically and statistically as compared to SSD and the control group. Sucralfate powder is a very cheap, safe and well-tolerated drug in addition having a lack of side effects**.** In the usage of oral medication, aluminum is poorly absorbed and this drug is excreted through the kidneys [41] and in patients with renal disease should be prescribed with caution. However topical medication, due to its low concentration and lack of absorption through the skin, doesn't have any such complications [42]. SSD ointment in patients with allergy to sulfonamides can have severe complications. Another advantage of these drugs is the ability to be used in children and in all parts of the skin. Through its antimicrobial, antioxidant, anti-inflammatory and immunomodulatory effects, sucralfate can be used as an adjunctive or alternative agent in wound healing therapies in the future. However, further studies are certainly needed to shed more light on the healing mechanism of sucralfate.

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