A Comparative Study of the Burn Wound Healing Properties of Saline-Soaked Dressing and Silver Sulfadiazine in Rats

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Abstract The purpose of this study was to further investigate that phenomenon and to explore the effect silver sulfadiazine on wound healing. Full-thickness burn wounds were created on the dorsum of Wistar albino rats under anesthesia. The wounds were treated with silver sulfadiazine and saline-soaked dressing for fourteen days, and then observed until healed. Wound surface area was measured each three days. Time to 50% and 90% healing was compared. No clinical infections occurred. Wound half-life and healing times were shortest in the saline-soaked group ($P < 0.0001$) in full-thickness burns. Wound contraction was delayed by silver sulfadiazine. These data suggest that silver sulfadiazine retard burn wound healing. Infection control without delay of burn wound healing is most appealing and clinical trials are planned.

Keywords Silver sulfadiazine · Saline-soaked dressing · Burn wounds care

Introduction

The final aim of burn management and therapy is wound healing and epithelization as soon as possible in order to prevent infection and to reduce functional and aesthetic

effects [1]. The use of topical chemotherapy has been fundamental in that regard and has helped to improve the survival of patients with major burns and to minimize the incidence of burn wound sepsis, a leading cause of mortality and morbidity in these patients [2]. The overriding objective of acute burn care is closure of the burn wound with the patient's own epidermis. Sometimes that happens spontaneously, and sometimes it requires an operation to excise the burned tissue and ultimately cover the wound with an autologous skin graft. When it becomes clinically apparent that the burn is a full-thickness injury or third-degree burn, common, current practice is to proceed with operation as expeditiously as possible. The gold standard in topical burn treatment is silver sulfadiazine, a useful antibacterial agent for burn wound treatment, recent finding, however, indicate that the compound delays the wound healing process [3]. And that silver may have serious cytotoxic activity on various host cells [2, 4–6]. This study compares the efficacy of silver sulfadiazine with that of saline-soaked dressing in full-thickness burn wounds in rats.

Material and Methods

Adult Wistar albino rats (220–250 g) were used. The animals were obtained from Experimental Research Center of Tabriz University of medical sciences; they were housed in a room with a 12:12-hour light/dark cycle and provided standard rat chow and water ad libitum. Eighty animals were randomly divided into 4 groups. The rats were housed individually. All equipment was modified to prevent the risk of infection to the personnel and all cages were kept in a separate room to prevent laboratory contamination. The use of anesthesia during the operative procedure and

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subsequent postoperative care were consistent with the guidelines in the National Institutes of Health's Guide for the Care and Use of Laboratory Animals (NIH publication No. 86-23, revised 1985; Bethesda, Md) and also approved by the experimental animal committee at Tabriz University of Medical sciences.

Full-thickness burn wounds (2 by 2 cm) were created on a shaved area of the animals' dorsal skin in forty rats and partial thickness burn wounds (2-2 cm) in other forty rats. Briefly, the animals were anaesthetized with intraperitoneal ketamine hydrochloride (40 mg/kg) and shaved. They received a full-thickness and partial-thickness dorsal scald burn in boiling water by a standard method [7].

Group 1 (partial thickness burn) and group 2 (full-thickness burn) animals were treated with saline-soaked dressing only, every 8 h. Group 3 (partial thickness burn) and group 4 (full-thickness burn) animals were treated with silver sulfadiazine (Flamazine (Smith and Nephew Healthcare, Hull, UK) only, every 12 h. Animals were weighed and margins traced on acetate film every days. Wound surface area was measured by radial planimetry.

All wound area measurements were expressed as a percentage of the initial wound size. These serial area measurements were plotted against time and an exponential decay curve fitted to data by a non-linear, least squares technique. From this continuous function, the time taken for each animal's wound to reach 50 and 90% of its initial size was calculated. Ninety percent healing was chosen as our endpoint as the healing of the remainder of the wound to completion is generally variable and dependent upon other factors such as animal interference. These rats were not given any oral or parenteral antibiotics. The wound half-lives were compared using the Kruskal-Wallis one way analysis of variance and by Scheffé's technique for multiple comparisons. All analyses were performed using a SPSS 15 on a personal computer. Analysis of absolute area measurements by simple linear regression showed that initial wound area made no significant difference to half-life calculations.

Results

All animals survived for the full length experiment. All animals gained weight equally throughout the experiment. No clinical infection was recorded. Wound half-life and healing times were shortest in the saline-soaked dressing in full-thickness burn groups ($P<0.0001$) (Fig. 1). Wound half-life and healing times were equal in partial-thickness burn groups.

The mean diameter of the wound was comparable on day 3 (1.9 ± 0.1 mm vs. 1.9 ± 0.08 mm in NS and SSD

Fig. 1 Effect of saline-soaked dressing and silver sulfadiazine on time to achieve 50 and 90% full-thickness burn wound healing. Mean time in days is shown with significant difference. Wound healing time significantly shortest in the saline-soaked group ($P<0.0001$), Kruskal-Wallis multiple comparison analysis

groups, respectively; $p=0.089$). The mean diameter of the wound was significantly lower in NS group on day 7 (1.7 ± 0.08 mm vs. 1.900 ± 0.045 mm; $p<0.001$) in full-thickness groups. The mean diameter of the wound was significantly lower in NS group on day 14 (1.3 ± 0.08 mm vs. 1.500 ± 0.45 mm; $p<0.001$) in full-thickness groups ($p<0.001$). The mean diameter of the wound was comparable on day 7 (1.7 ± 1.66 mm vs. 1.7 ± 2.40 mm in NS and SSD groups, respectively; $p=0.495$) in partial-thickness burn groups. The mean diameter of the wound was comparable on day 14 (1.4 ± 1.66 mm vs. 1.49 ± 2.40 mm in NS and SSD groups, respectively; $p=0.495$) in partial-thickness burn groups (Fig. 2).

Normal saline accelerated contraction rate of full-thickness burn wounds more quickly comparing with silver sulfadiazine. There is no significant difference between partial-thickness burn groups regarding half-life and final healing rate.

Discussion

Burn wounds, even of partial depth, can present challenging clinical problems if the surface involved is sufficiently extensive. Excision and early wound closure are the recommended treatment at the present time. However, topical treatment is required in most burn patients with superficial burns. It is also needed in deep burns pending more definitive closure modalities

Fig. 2 Variation of mean burn wound size according to time and groups in partial and full-thickness burns

because it plays a vital role in preventing microbial invasion.

Silver compounds have been the mainstay of topical burn care since the early 1960s [8]. Silver ion, which is released from silver sulfadiazine, kills virtually all known microbes, including yeasts. It kills on contact by blocking their cellular respiratory pathways [9].

Silver sulfadiazine has beneficial and adverse effects. The beneficial effects include: 1-antimicrobial activity 2-beneficial effects on the wound bed [10–12]. Silver-based technologies added benefits by down-regulating tissue inhibitors of metalloproteinase to levels that facilitate wound healing [10]. the results of several studies suggest that nanocrystalline silver specifically may play a role in altering or compressing the inflammatory events in wounds and facilitating the early phases of wound healing. These benefits are associated with reduced local matrix metalloproteinase levels and enhanced cellular apoptosis [12, 13]. 3- Zinc metabolism was up regulated, implying increases epithelialization [14, 15]. 4-increased calcium level have also been observed in experimental wounds treated with silver. The implication of this are unclear at the moment, but we do know that calcium is an essential

component of hemostasis as factor IV, and that increase in calcium in the wound margin are a normal feature of healing in acute skin wounds [16]. 5- Potent anti-inflammatory properties [17].

Adverse effects of silver sulfadiazine includes: 1-delayed wound healing is often observed clinically following the use of silver-containing topical antimicrobial agents [18, 19]. Silver sulfadiazine cream might also slow down the proper healing mechanisms of the wound [20]. Mean healing times were significantly ($P, 0.0001$) shorter in saline-soaked dressing than silver sulfadiazine. This finding identical to other studies [3, 18–21]. Healing time was normal when silver sulfadiazine was used in spit-thickness donor sites but significantly slower in deeper wounds [3, 21]. The mechanism by which this unique effect of delayed healing occurs is not yet clear. 2- Delay in eschar separation in deep burns is due to the low bacterial load of the burn wounds. 3-prolonged conservative treatment with silver sulfadiazine, especially in the early years even longer than three weeks, usually results in healing with hypertrophic or atrophic scars [22, 23]. 4-prolonged topical application of silver sulfadiazine cream can induce argyria [24]. Argyria, a permanent disorder caused by silver deposition in the skin's micro-vessels in patients who are exposed to chronic silver toxicity [25, 26], is only seen following large oral or inhaled intakes of silver dust or colloidal silver over extended period of time and has never been reported as a result of topical application [27]. 5-direct silver induced renal toxicity. Kidney function improved on withdrawal of the topical cream [24]. 6- Transient leucopenia which occurs within several days of the initiation of therapy. This is associated with a disproportionate decrease in circulating neutrophils. The incidence is from 5–15% of patients treated [28], and it has been proposed that there is a direct toxic effect of silver sulfadiazine on bone marrow [29]. Despite these observations, however, no increase in the incidence of infectious complications has been identified, and the leucopenia recovers spontaneously, whether or not the agent has been discontinued [29]. 7- cytotoxicity in vitro [21]. In vivo studies have found no evidence for cytotoxicity [23]. Despite the fact that after decades of use, the evidence for cytotoxicity is not clear and silver sulfadiazine remains the main topical product used in burn units [27, 29]. Various observer toxic effects confirm that this topical cream should not be used for long periods on extensive wounds [24]. High concentration of nano-silver base inorganic antibacterial agents had cytotoxic effects on rat fibroblasts. Cytotoxicity was directly proportional to the silver concentration. Low silver ion release rate may prevent interference with wound-healing mechanisms [24]. No cytotoxic effects were observed at or below the concentration of 25 g/L [25]. Significant absorption of silver from large burn wounds (40% body surface area or greater) treated topically with

silver sulfadiazine, so there is the possibility of silver toxicity occurring [26]. 8-no evidence has been provided so far to show that silver influence the immuno-suppressed state commonly seen in burns [16]. 9-allergic reactions may prove a contraindication for their use in some patients. Cutaneous sensitivity reactions, typically in the form of a maculopapular rash, occur in less than 5% of patients and rarely require discontinuing the drug. Acute hemolytic anemia has been reported in a burn patient treated with silver sulfadiazine who lacked the enzyme glucose-6 phosphatase [27]. 10-hepatic damage due to silver deposition. 11-crystalluria and methemoglobinemia [28].

It is clear that effects of the various silver products available on wound infection and wound healing are variable. Understanding the characteristics of these products and dressings may enable them to be targeted more appropriately according to the specific requirements [29]. A word of caution, however, about extrapolating too directly from laboratory studies to clinical application, nevertheless, based on available evidence it is recommend at present that silver-based products should be avoided if possible as a topical antimicrobial strategy where rapidly proliferating keratinocytes are exposed as in donor sites, superficial partial thickness wounds and undifferentiated cultured keratinocyte applications [18, 29]. The ultimate goal remains the choice of a product with superior profile of antimicrobial activity over cellular toxicity [28, 29].the search for suitable topical burn therapy will continue to focus on preparations that can kill microbes and promote tissue regeneration while limiting tissue damage. Concern about the toxicity of purified chemicals will continue to make people turn to complementary and alternative medicines. Low toxicity, cheaper costs, easier handling and availability are all factors that may promote the use of complementary and alternative medicine. Our study shows that silver sulfadiazine may be retard burn wound healing and has demonstrable deleterious effects on burn wound healing in full-thickness burn wounds.

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