

ORIGINAL ARTICLE

SILVER SULPHADIAZINE AND FUNDERMOL IN THE TOPICAL TREATMENT OF BURN WOUNDS: AN EXPERIMENTAL COMPARATIVE STUDY IN RATS

Abdolaziz Rastegar Lari, PhD*, Reza Alaghehbandan, MD**

*Department of Microbiology and Immunology, Iran University of Medical Sciences, Tehran;

**Kurdistan University of Medical Sciences, Sanandaj, Kurdistan, Iran

Background– Fundermol is a topical agent for partial-thickness burns. Silver sulphadiazine is a topical agent for treatment of burn wounds. The aim of this study was to compare the efficacy of silver sulphadiazine dressing versus fundermol for burn healing and consequently prevention of infection in rats.

Methods– Eighty-four Albino NMRI rats were scalded with boiling water for 6 seconds, resulting in second degree burns involving 10% total body surface area (TBSA). The rats were randomly divided into groups A and B; each group was further divided into three subgroups (A1, A2, A3, B1, B2, B3) of 14 rats each. The burned skin of group A rats was swabbed with *Pseudomonas aeruginosa* culture 1 day after burn induction; group B rats were not exposed to the bacteria. As *P. aeruginosa* is the most common and important bacteria in our epidemiological setting, we chose *P. aeruginosa* for this study. Rats in subgroups A1 and B1 were treated with silver sulphadiazine, and those in subgroups A2 and B2 with fundermol. Subgroups A3 and B3 received no treatment. All the rats were observed for 30 days and then sacrificed by Ether. Infection/contamination was determined by the culture of burn wound; looking for microorganisms such as *P. aeruginosa* and *S. aureus*. During histologic examinations, healing was evaluated by the following factors: surface vessel density, numerical vessel density, and surface epithelial density.

Results– Silver sulphadiazine decreased the incidence of burn-wound infection by up to 85% in contaminated rats during the 30-day study period, while fundermol were effective in 58%. There were statistically significant differences between mean surface vessel density of burn wound in groups A1 and A2 with control group ($P < 0.01$) on 15th day. Mean numerical vessel density in groups A1 and A2 was significantly higher than control group on 15th and 30th day ($p < 0.01$). There was statistically significant association between mean surface epithelial density of burn wounds in group A1 with groups A2 and control on 15th day post burns ($p < 0.01$).

Conclusion– Treatment of partial-thickness burn wounds with fundermol was not superior to silver sulphadiazine. We measured healing process by histological examinations and culture of the burn wounds. It could be considered as a hypothesis, because fundermol as a new topical agent was clinically comparable to silver sulphadiazine in treatment of burn wounds.

Keywords • experimental • fundermol • rat • silver sulphadiazine

Introduction

Burn and effective burn therapy have been considered one of the major public health problems in the world.¹⁻⁶

Although infection is one of the most common

•Correspondence: Dr. Abdolaziz Rastegar Lari, PhD, Department of Microbiology and Immunology, Iran University of Medical Sciences, Tehran, Iran. P.O. Box: 14515-717, Fax: +98-21-8054355, E-mail: lari@iums.ac.ir.

causes of death after thermal injury, limited information is available on the association between bacterial colonization of burn wounds and survival outcomes of burn patients.⁶⁻⁸ Although modern antimicrobial therapy has improved the outcome of serious burn injuries,⁹ infections remain a major cause of morbidity and mortality in patients surviving the shock phase of thermal injury.

Much progress has been made in recent years in

the field of topical burn therapy. At present, available preparations meet the majority of characteristics of an ideal topical agent.¹⁰ However, much effort must be put into finding better and more cost-effective products, especially for developing countries that experience burn accidents more frequently than developed nations.

Effective local treatment is very important in preventing wound infection and ensures successful skin grafting.^{11,12} On the basis of both *in vitro* and *in vivo* studies, Moyar in 1965 concluded that a 0.5% solution of silver nitrate is the lowest concentration at which antibacterial action against *Staphylococcus aureus*, hemolytic Streptococci, *Pseudomonas aeruginosa* and *Escherichia coli* could be exerted.^{11,12} Mafenid acetate was introduced a short time after the reintroduction of silver nitrate, followed a few years later by silver sulphadiazine. Thus, in a short period of time three medications appeared on the market, representing a radical change in the topical treatment of burns.^{11,12}

The action of silver sulphadiazine has been intensively studied.^{11,13,17} Although various attempts have been made to develop more effective silver compounds, so far silver sulphadiazine remains the most widely used substance of this type.¹¹⁻¹⁷

Fundermol, a topical agent derived from the *Lavsonia* plant, has been applied by clinicians in the treatment of partial-thickness burns for the last few years, based entirely on clinical and experimental experience. Unfortunately, there are no published studies comparing the efficacy of fundermol, a new topical agent, with other common topical agents in the treatment of burns. Therefore, we conducted this comparative efficacy study of silver sulphadiazine dressing versus fundermol in the healing of burn wounds in the rat.

Materials and Methods

Eighty-four albino NMRI rats weighing between

280 and 350 g, obtained from Razi Institute, Karaj, Iran were used in these experiments. All animals were provided with water and food *ad libitum* throughout the study. Standard guidelines on the care and management of laboratory animals were applied.¹⁸

Rats were anesthetized using 40 mg/kg intraperitoneal thiopental 2%, (generously supplied by Specia Rhone-Poulenc Rorer, France) and their backs were shaved with electric clippers. They were placed in a mold in such a way that approximately 10% of their body surface area remained exposed.¹⁹ The exposed skin surface of each rat was immersed in 90°C water for 6 seconds, resulting in a grade II burned wound of 10% total body surface area (TBSA). To prevent shock, the animals were resuscitated with intraperitoneal injection of 3-5 mL saline solution. The rats were randomly assigned to two groups, A and B, with 42 rats in each group. Groups A and B were subdivided subgroups 1, 2 and 3, with 14 rats in each subgroup. Using a swab, the bare area of the skin in rats of group A was inoculated with *P. aeruginosa* (ATCC27853) overnight culture suspension in brain heart infusion 1 day after burn induction. Rats in group B were not inoculated (Table 1). Rats in subgroups A1 and B1 were treated with silver sulphadiazine dressing daily for 30 days, and those in groups A2 and B2 with fundermol daily for 30 days. Rats in subgroups A3 and B3 received no medication. A2 rats were observed for 30 days and then sacrificed with an overdose of anesthetic Ether.

Culture samples from the burn wound were taken with a sterile cotton swab on days 15 and 30. All culture samples from naturally expired or sacrificed rats were used to inoculate blood and MacConkey agar, and then incubated overnight at 37°C. Presence of *P. aeruginosa* was determined by pyocyanin (blue-green) pigments and fruity smell. Also, *S. aureus* was not considered as a control in this study. Tissue specimens were also

Table 1. Experimental status of different rat study groups

Group	N	Burn treatment	<i>P. aeruginosa</i> exposure
A	42		
1	14	Silver sulphadiazine	5 x 10 ⁷
2	14	Fundermol	5 x 10 ⁷
3	14	None	5 x 10 ⁷
B	42		
1	14	Silver sulphadiazine	None
2	14	Fundermol	None
3	14	None	None

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Table 2. Frequency of positive *P. aeruginosa* culture testing and mortality rate of rat study groups

Group	<i>P. aeruginosa</i> positive (%)		Mortality rate (%)
	Day 15	Day 30	
A			
1 (n = 14)	14.3	—	28.6
2 (n = 14)	42.8	14.3	28.6
3 (n = 14)	100	100	42.8
B			
1 (n = 14)	—	—	0
2 (n = 14)	—	—	0
3 (n = 14)	—	—	14.3

obtained for histopathologic examination for surface vessel density, numerical vessel density, and surface epithelial density on days 15 and 30. Comparisons between the groups were performed using the *t* test, A *p* value less than 0.05 was considered statistically significant.

Results

P. aeruginosa and *S. aureus* were cultured from burn wounds of all the rats in subgroup A3 on days 15 and 30. Six rats (42.8%) in this subgroup died during the 30-day study period. In subgroup B3, no microorganisms were isolated but two rats (14.3%) died (Table 2).

In subgroup A1, two of the 14 burn-wound cultures yielded *P. aeruginosa* and *S. aureus* on day 15; after 30 days, four of the 14 cultures were positive for *S. aureus*. The mortality rate in subgroup A2 was 28.6% (4/14). In this subgroup, six of 14 burn wound cultures were positive for *P. aeruginosa* and *S. aureus* on day 15; after 30 days, four of 10 cultures were positive for *S. aureus* and two of 10 for *P. aeruginosa*.

No microorganisms were found in subgroups B1 and B2 during the period of study, and no

deaths occurred.

Mean surface and vessel density of burn wounds in subgroups A1 and A2 and A3 are shown in Figures 1 and 2. There were statistically significant differences between mean surface vessel density of burn wound in subgroups A1/A2 and those of subgroup A3 ($p < 0.01$) on day 15. Also, there were significant associations between mean surface vessel density of burn wounds in subgroup A1 and subgroup A3 ($p < 0.01$), as well as between subgroup A1/A2 and the subgroup A3 ($p < 0.05$) on day 30. However, no statistically significant differences were found between mean surface vessel density in subgroups A1 and A2 on days 15 and 30.

Mean vessel density of burn wounds in subgroups A1 and A2 as shown in Figure 2 were significantly higher than those of the subgroup A3 on days 15 and 30 ($p < 0.01$). However, no statistically significant differences were found between mean vessel density in subgroups A1 and A2 on days 15 and 30.

Mean surface epithelial density of burn wounds in A3, A1 and A2 subgroups on days 15 and 30 are presented in Figure 3. A significant association between mean surface epithelial density of burn

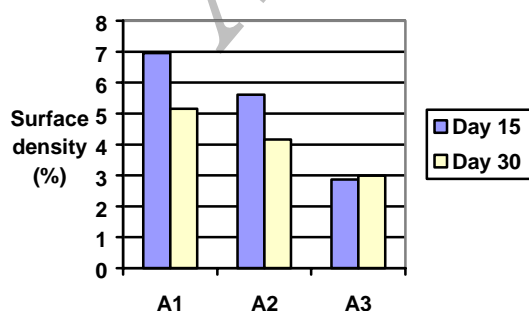


Figure 1. Surface Vessel density in subgroups (A1: Silver Sulphadiazine, A2: Fundermol, A3: Control)

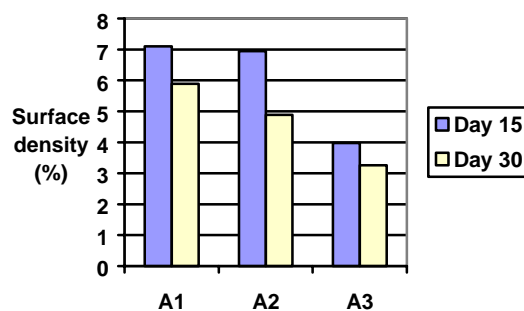


Figure 2. Numerical Vessel density in subgroups (A1: Silver Sulphadiazine, A2: Fundermol, A3: Control)

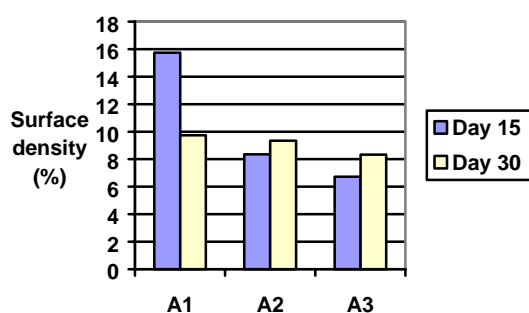


Figure 3. Surface epithelial density in subgroups (A1: Silver Sulphadiazine, A2: Fundermol, A3: Control).

wounds between subgroups A1 and both subgroups A2 and A3 was found on day 15 ($p < 0.01$). This finding was not true for association of mean surface epithelial density of burn wound between the three A subgroups on day 30 ($p > 0.05$). Also there were no significant differences between mean surface epithelial density of burn wound of A3 and A2 subgroups ($p > 0.05$).

Discussion

Infection remains the major cause of morbidity and mortality following the shock phase in burn patients. Measures to reduce the risk of wound infection and subsequent sepsis include early excision wherever possible, and the use of topical antimicrobial agents such as silver sulphadiazine. The advantages of this medication are that it is easy and painless to apply and remove, turning the necrotic skin into a yellow, leathery crust with good resistance to infection, which enables the caregiver to excise the wound stage by stage where early massive excision is not possible. Using newer topical agents, which are more effective and have less side effects, is challenging. Fundermol, a new topical agent deemed to be very effective in the treatment of burn wounds, was compared with silver sulphadiazine in terms of effectiveness in the treatment of partial-thickness burn. The results show that silver sulphadiazine decreased burn wound infection/contamination by up to 85% in inoculated rats for 30 days, while fundermol was effective only in 58% of infected rats. Although the bactericidal activity of silver sulphadiazine measured by frequency of positive *P. aeruginosa* culture testing and mortality rate in study groups was more effective than fundermol, there was no

statistically significant difference between the two ($p = 0.493$).

The mortality rate in group A was around 29%, which was significantly higher than the 14.3% rate in group B ($p = 0.005$). This can be explained by the occurrence of infection/septicemia after *P. aeruginosa* exposure of the rats of group A. In subgroup A3, the presence of *P. aeruginosa* in burn wound and proteolytic activity of the burn process justifies the 42% mortality rate. Mortality rates in the A1 and A2 subgroups were lower than that of subgroup A3 at 28.6%, probably due to the bactericidal activity of silver sulphadiazine and fundermol.

The results of mean surface and vessel density suggest that silver sulphadiazine promotes wound healing during the first 15 days after burn in inoculated rats. The probable mechanism is stimulation of revascularization.²⁰

Referring to the results regarding mean surface epithelial density, it seems that silver sulphadiazine induces faster epithelialization activity compared to fundermol.

Considering that there were no statistically significant differences between fundermol and silver sulphadiazine in terms of mortality rate, bactericidal activity, and wound healing, one can conclude that treatment of partial-thickness burn wounds with the newer agent fundermol has no benefit over the established agent silver sulphadiazine.

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References

- 1 Rastegar Lari A, Bahrami Honar H, Alaghebandan R. *Pseudomonas* infections in Tohid Burn Center, Iran. *Burns*. 1998; **24**: 637–41.
- 2 Rastegar Lari A, Alaghebandan R. Experimental study of *Pseudomonas aeruginosa* infection in burn rats. *Arch Iranian Med*. 1999; **2**: 191–4.
- 3 Rastegar Lari A, Alaghebandan R, Nikui R. Epidemiological study of 3341 burns patients during three years in Tehran, Iran. *Burns*. 2000; **26**: 49–53.
- 4 Alaghebandan, R. MacKay Rossignol AM., Rastegar Lari A. Pediatric burn injuries in Tehran, Iran. *Burns*. 2001; **27**: 28–32.
- 5 Panjeshahin MR, Rastegar Lari A, Talei AR, et al. Epidemiology and mortality of burns in the South West

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- of Iran. *Burns*. 2001; **27**: 219–26.
- 6 Rastegar Lari A, Alaghebandan R. Nosocomial infections in an Iranian burn care center. *Burns*. 2000; **26**: 737–40.
 - 7 Mason AD, McManus AT, Pruitt BA. Association of burn mortality and bacteremia. *Arch Surg*. 1986; **121**: 1027–31.
 - 8 McManus AT, Mason AD, McManus WF, et al. Twenty-five-years review of *Pseudomonas aeruginosa* bacteremia in a burn center. *Eur J Clin Microbiol*. 1985; **4**: 219–33.
 - 9 Clark WR, Fromm BS. Burn mortality. Experience at a regional burn unit. Literature review. *Acta Chir Scand Suppl*. 1987; **537**: 1–126.
 - 10 Ross DA, Phipps AJ, Clarke JA. The use of cerium nitrate-silver sulphadiazine as a topical burns dressing. *Br J Plast Surg*. 1993; **46**: 582–4.
 - 11 Klasen HJ. A historical review of the use of silver in the treatment of burns. II. Renewed interest for silver. *Burns*. 2000; **26**: 131–8.
 - 12 Klasen HJ. Historical review of the use of silver in the treatment of burns. I. Early uses. *Burns*. 2000; **26**: 117–30.
 - 13 Munster AM, Helvig E, Rowland S. Cerium nitrate-silver sulfadiazine cream in the treatment of burns: a prospective evaluation. *Surgery*. 1980; **88**: 658–60.
 - 14 Fox CL, Monafo WW, Ayvazian VH, et al. Topical chemotherapy for burns using cerium salts and silver sulfadiazine. *Surg Gynecol Obstet*. 1977; **144**: 668–72.
 - 15 Saffer LD, Rodeheaver GT, Hiebert JM, et al. *In vivo* and *in vitro* antimicrobial activity of silver sulfadiazine and cerium nitrate. *Surg Gynecol Obstet*. 1980; **151**: 232–6.
 - 16 De Gracia CG. An open study comparing topical silver sulfadiazine and topical silver sulfadiazine-cerium nitrate in the treatment of moderate and severe burns. *Burns*. 2001; **27**: 67–74.
 - 17 Ross DA, Phipps AJ, Clarke JA. The use of cerium nitrate-silver sulphadiazine as a topical burns dressing. *Br J Plast Surg*. 1993; **46**: 582–4.
 - 18 UFAW. *The UFAW Handbook on the Care and Management of Laboratory Animals*. 5th ed. Edinburgh: Churchill Livingstone; 1976.
 - 19 Walker HL, Mason AD. A standard animal burn. *J Trauma*. 1968; **8**: 1049–51.