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Original Article

Evaluation of silver sulfadiazine 1%-cerium nitrate 2.2% cream efficacy and safety in moderate to severe burn patients: a single-blind randomized clinical trial

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Abstract: Background: Burn injury is a major global health crisis. Topical antimicrobials such as silver sulfadiazine (SSD) are commonly used for superficial burn wounds. SSD has a broad-spectrum antimicrobial activity and also anti-inflammatory property, but also suffers from some limitations. Therefore, some studies suggest to add cerium nitrate (CN) to SSD, as an immunomodulatory and tanning agent with antitoxic properties, but its effect on patients' mortality, length of hospital stay, and bacterial colonization is contraversial. Objectives: In this research, we evaluated the efficacy and safety of SSD 1%+CN 2.2% cream in patients with moderate to severe burn. Material and Methods: Twenty-two patients who fulfilled the inclusion criteria randomly were assigned to the intervention (n=7) or control (n=15) group and received SSD 1%+CN 2.2% or SSD cream 1% respectively, once daily until the complete re-epithelization or prepration of the burned skin for grafting. Intesity of pain, re-epithelialization time, required interventions, laboratory and clinical findings and final outcome were recorded. Results: There was no significant difference in re-epithelialization time between the treatment and control groups (P>0.05). The same findings were reported about the required interventions and laboratory and clinical parameters. However, the final outcome and the pain score on third day were significantly better in the treatment group (P=0.017). On the other hand, all patients in the treatment group needed graft surgery. Conclusion: Use of SSD 1%+CN 2.2% cream did not significantly improve re-epithelization time or infection occurrence and patients' pain, but also increased graft surgery rate in comparison with SDD 1% cream in moderate to severe burns.

Keywords: Silver sulfadiazine, cerium nitrate, flammacerium, moderate-severe burn, infections

Introduction

Burn is a specialized form of trauma and a major global health crisis which mostly occurrs in countries with poor economic conditions [1, 2]. Therefore, Management of burn injury could be a major treatment challenge that can lead to disability and death [3]. Infection as a complication of burns plays a key role in morbidity and mortality of the patients [4, 5]. A multidisciplinary approach including surgery and chemoprophylaxis can reduce wound infection and consequently mortality [6, 7]. Early excision of burn wounds and their temporary or permanent coverage is the standard of the care for burns [7]. However, early excision and grafting are not always possible for various reasons. For example, in extensive burns involving more than 50% of the total body surface area (TBSA), the lack of donor areas can lead to delayed wound healing for weeks, unless biological or synthetic dressings are used after removal of the burned tissues [8, 9]. Therefore, it is very important for patients to receive prophylaxis for wound infec-

tion until the excision of the burn wound [5, 9]. Topical antibiotics are valuable agents in a prophylatic manner [6, 10]. Silver sulfadiazine (SSD) is the topical sulfonamide of choice in severe burns and is widely used [11]. Unfortunately, SSD certainly does not inhibit the growth of some gram-negative (e.g. *Pseudomonas aeruginosa)* and gram-positive (e.g. *Staphylococcus aureus)* bacteria [11, 12]. It also creates a damp matrix scar with loose edges which allows the proliferation of bacteria; so scar debridement will be difficult [8, 13]. This formulation is not actually very successful in inhibiting bacterial growth in burns over 50-60% of the TBSA [12, 13].

Cerium nitrate (CN) is a salt of the rare earth element lanthanide, which has low absorption and solubility in the form of phosphate salts, so it has limited toxicity to mammals [14]. It can improve the immune activity which is suppressed by a burn injury by binding to the protein-lipid complex as a tanning agent, in contrast to SSD and mafenide [15-18]. But it has limited antibacterial activity, particlurlay against common pathogens in burns [8, 13]. Therefore, it seems that the antitoxic effect of CN is more effective than its antimicrobial activity in wound healing and consequently improving survival. Its hardening effect on the eschar is generally accepted for prevention of bacterial entrance and maintaining a moist wound environment, which aids wound healing [19].

Various studies on CN have been performed in adult and pediatric burn populations and conflicting results were reported. In a clinical trial, patients treated with CN and SSD had lower mortality rate compared with SSD alone. It has also been reported that the CN use reduces the incidence of delayed death by about 50% compared to SSD, especially in high-risk patients with extensive burns [20]. In another open label study, a cream containing CN 0.05 M and SSD 0.03 M reduced mortality in patients suffering from burns covering over 50% of TBSA (mean total burn size of 75%) from 66% to 27% in comparison with patients who treated by SSD and also re-epithelization rate was 8 days faster. They mentioned that dry sell-like eschar of SSD-CN allowed planned excisions and instant autologous grafting about 11 days earlier than SSD group; which resulted in shorter hospital stay and cost saving. However, wound infection did not differ considerably between two groups and patients complained from stinging pain more commonly in the SSD-CN group, which was manageable with analgesics [14]. In another study on 64 patients with a burn extent between 30 to 90%, 0.04 M CN solution beside routine treatment measures reduced mortality from 80% to 10% in comparison with patients who treated just with routine measures such as SSD [21]. However, a multicenter, randomized, controlled trial has shown that CN with SSD was not effective in reducing burn wound infection and did not improve median time to wound healing compared to SSD [22]. Another clinical study on 31 children with burns [15] found no benefit of using cerium-enhanced SSD over SSD alone.

Moreover, the combined formulation of SSD 1%+CN 2.2% under the *Flammacerium* brand is available in the UK pharmaceutical market and only European approval for this product has been reported [19, 23].

In Iran, the high cost and shortage of synthetic, biosynthetic, and biological dressings, as well as cultured autograft epithelium, have limited their use in the treatment of enormous open wounds. The topical formulation of SSD is available in Iran as 1% cream, but a combined formulation with CN is not available and it costs too high to import the available foreign products.

Therefore, in this study, we decided to assess the efficacy and safety of a topical formulation of SSD 1%+CN 2.2% for the management of moderate-severe burns in a teaching burn center, in Mashhad, Iran.

Material and methods

Study design

This study was a single-blind, randomized, controlled clinical trial that was conducted from August 2019 to September 2021 in the Burn ward of Imam Reza Hospital, the main burn center in the east of Iran, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran.

Study population

Burn extent were measured based on the Lund-Browder chart. Burn patients were included in the trial in the first 24 hours of hospitalization if

they had met the subsequent criteria: (1) age range 18-70 years old; (2) deep partial or full thickness burns; (3) burn extent between 10% and 50%; according to Lund & Browder chart; (4) willingness to participate in the study and sign a written informed consent. Participants were not included if they had at least one of the following conditions: (1) inhalation burns; (2) electrical and chemical burns; (3) burns in the face, hands and perineum; (4) history of known allergies to sulfonamides; (5) history of methemoglobinemia; (6) pregnancy & lactation; (7) G6PD deficiency; (8) oliguria and anuria; (9) liver dysfunction (liver transaminases >5 upper limit normal). Unwillingness of patients to continue the study was considered as exclusion criteria.

Ethics

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1398.172) and was registered at the Iranian Registry of Clinical Trials (IRCT20190927044902N1, Registration date: 2020-01-05). Undersigned written informed consent form was obtained from all patients.

Study protocol

The patients were randomly allocated to the SSD 1%-CN 2.2% (intervention) or routine burn dressing (control) group. SSD-CN cream was made within the Industrial Pharmacy Laboratory of Mashhad School of Pharmacy under sterile conditions from April 2019 to March 2021 and was packed in 0.5 kg containers. In control group SSD 1% cream (produced by Sobhan Darou Company, Rasht, Iran) was used which was also packed in 0.5 kg containers. Topical formulations were applied directly to the wound once daily after cleansing with normal saline and plain gauze dressings and a tubular widely woven fixation dressing were used and continued until complete re-epithelialization or preparation of the skin for a graft.

All patients received appropriate fluids and electrolytes according to the standard protocols after the initial evaluation, washing the wound with soap and water and normal saline. The bandage was changed daily, in the absence of the infection signs. If infections occurred, appropriate empiric and targeted antibiotic therapy were offered to the patients.

Sample size

According to the results of Gracia et al. study [14], the duration of re-epithelialization in two groups of SSD and SSD+CN was 25.1±19.4 days and 17.2±8.3 days, respectively. Considering α=5% and β=20% using the following formula, the sample size in each group was 56. However, after inclusion of 7 patients in the treatment group, as all of them underwent skin graft surgery, disproportionately to the severity of the burn, we terminated the study based on the ethical committee recommendation.

$$n_1 = n_2 = \frac{(S_1^2 + S_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(\bar{X}_1 - \bar{X}_2)^2}$$

Outcomes

Patients' demographic data, past medical and drug history, type, mechanism, anatomical location and the extent of the burn according to Lund & Browder criteria and physical findings of patients were recorded at the beginning of the study.

The primary outcome of the study was the re-epithelialization time (calculated in days between the time of burn occurrence and the time when epithelialization reaches 90%) which defines the overall response of the patient to the treatment (**Table 1**). Moreover, pain severity was assessed one hour after changing the dressing based on visual pain scale at baseline and after 3, 7, 14 and 21 days, as the secondary outcome. Pain assessment tools include the continuous visual analog scale (VAS) where the patient makes a mark anywhere along a line from no pain to a maximum that represents the worst possible pain, the numeric rating scale (NRS) where the patient selects a discrete number on the line between 0 and 10.

Patients' need to systemic antibiotic therapy and graft was also defined beside sepsis and wound infection rate, in both treatment and control group.

Patients' vital signs (body temperature, blood pressure (BP), respiration rate (RR), and heart rate (HR) and laboratory data including complete blood cell differentiation (CBC diff), blood sugar level, serum creatinine, sodium, potassium, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and albumin level)

Table 1. Treatment response rate scale

Overall Response To Treatment	Epithelialization Time	Bacterial Growth
Excellent	Under 7 days	Lack of bacterial growth (-)
Good	7-14 days	Bacterial eradication in 7 days
Medium	14-21 days	Bacterial eradication in 14 days
Bad	More than 21 days	Bacterial eradication over 14 days

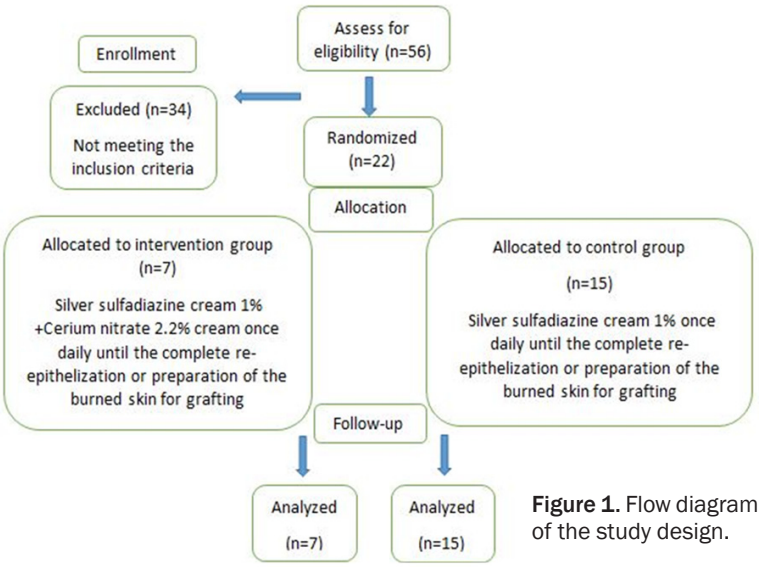

Figure 1. Flow diagram of the study design.

were assessed at baseline and then after 3, 7, 14, and 21 days.

The duration of hospital stay and the patients' final outcome (death or complete or partial recovery) were also recorded. It should be mentioned that partial recovery means that the patient discharged with personal consent from the hospital.

Randomization and blinding

A computer-generated random allocation sequence was developed by using randomization.com site. Patients were enrolled by burn physicians and were assessed by them and also the pharmacy student. Neither patients nor clinicians could be blind to treatment assignment, as the appearance of SSD and SSD+CN was very different. The data analysts (S.E. and M. KR.) were blinded.

Statistical methods

Data were analyzed by SPSS software version 26 (IBM Corp., Armonk, NY). Results have been reported as mean ± standard deviation or median (range) for continuous variables with normally and non-normally distributed, respectively and numbers or percentages for nominal parameters. Comparisons between two groups were performed by independent sample t-test for quantitative variables and fisher's exact test for qualitative variables. Kolmogorov-Smirnov test was used to assess the normality of the variable's distribution. In case of abnormal distribution of data, the proportional non-parametric test was used. In this study, *P*-value <0.05 was considered significant.

Results

Baseline characteristics

In this clinical trial, 56 burn patients were screened and 22 eligible patients were enrolled in the study according to the inclusion criteria (n=7 in the intervention group and n=15 in the control group) (**Figure 1**). The mean (±SD) age of participants in the study was 39.68±16.63 years old, the mean weight was 68.23±16.04 kg, and 59.1% of them were men. Baseline characteristics were not significantly different between the control and intervention groups. Moreover, most of patients in both groups did not have past medical and drug history. Baseline characteristics of patients are summarized in **Table 2**.

Comparison of burn characteristics between the intervention and control groups

The most common burn mechanism in the intervention and control groups was fire. The

Table 2. Comparison of demographic characteristics between two groups

		Group		*P*-value[1]
		Intervention	Control	
Gender	Male n (%)	2 (28.6)	11 (73.3)	0.074
	Female n (%)	5 (71.4)	4 (26.7)	
Age (mean ± sd)[2]	Years	59±12.58	62.93±12.58	0.068
Weight (mean ± sd)	Kilogram	68.85±13.78	67.93±17.44	0.061

[1]Independent sample T-test; [2]Fisher's exact test.

Table 3. Comparison of burn characteristics and medical and disease records between two groups

		Group		*P*-value
		Intervention n (%)	Control n (%)	
PMH	No	6 (85.7)	9 (60)	0.248[1]
	Cardiovascular	1 (14.3)	0 (0)	
	Hypertension	0 (0)	1 (6.7)	
	Neuropsychiatric diseases	0 (0)	4 (26.7)	
	Diabetes	0 (0)	1 (6.7)	
DH	No	5 (71.4)	11 (73.3)	0.462[1]
	Opioid use	2 (28.6)	2 (13.3)	
	Neuropsychiatric medications	0 (0)	2 (13.3)	
Mechanism	Gas	3 (42.9)	7 (46.7)	0.61[1]
	Flame	1 (14.3)	7 (46.7)	
	Scald	3 (42.9)	1 (6.7)	
Burn site	Head	2 (28.6)	7 (46.7)	0.712[2]
	Neck	2 (28.6)	7 (46.7)	
	Trunk	1 (14.3)	1 (6.7)	
	Upper Arm	4 (57.1)	5 (33.3)	
	Forearm	4 (57.1)	5 (33.3)	
	Hand	4 (57.1)	5 (33.3)	
	Thigh	0 (0)	2 (13.3)	
	Leg	4 (57.1)	5 (33.3)	
	Foot	4 (57.1)	5 (33.3)	
	Buttock	0 (0)	0 (0)	
	Genitalia	0 (0)	0 (0)	
Degree of the burn	Deep partial thickness	4 (57.14)	3 (42.86)	0.5[1]
	Full thickness	6 (40)	9 (60)	
Extent of the burn (mean ± SD)		19.14±11.8	23.4±9.94	0.33[1]

[1]Fisher's exact test; [2]independent sample T-test.

site of burn in the SSD-CN and SSD groups were mostly the extremities and upper parts of trunk, respectively. The median (range) degree of burn and the average extent of burn measured were 2 (1) and 19.14±11.8% in the intervention group and 3 (2) and 23.4±9.94% in the control group, respectively. There was no significant difference between two groups in terms of the abovementioned parameters (**Table 3**).

Comparison of the epithelialization rate, treatment final outcome and duration of hospitalization between two groups

Analysis of the final outcomes showed that in the intervention group all patients had complete recovery; while in the control group just 40% of patients had complete recovery and the others experienced partial recovery (P=0.016). The mortality rate was zero in both groups.

Table 4. Comparison of epithelialization rate and treatment outcome between two groups

		Group		*P*-value
		Interventionn (%)	Control n (%)	
Epithelialization rate	Fast (about 10 days)	5 (71.4)	5 (33.3)	0.247[1]
	Medium (2 to 3 weeks)	1 (14.3)	7 (46.7)	
	Slow (about 4 weeks)	1 (14.3)	1 (6.7)	
	Very slow (5 to 6 weeks)	0 (0)	2 (13.3)	
Treatment outcome	Complete recovery	7 (100)	6 (40)	*0.017[1]
	Partial recovery	0 (0)	9 (60)	
	Death	0 (0)	0 (0)	
Duration of hospitalization (mean ± SD)		12.28±6.34	14.86±8.52	0.486[2]

[1]Fisher's exact test; [2]independent sample T-test. *P<0.05.

Table 5. Comparison of therapeutic response rate between two groups

		Group		*P*-value
		Intervention n (%)	Control n (%)	
Overall Response to Treatment	Excellent	0 (0)	0 (0)	0.225[1]
	Good	5 (71.4)	5 (33.3)	
	Medium	1 (14.3)	7 (46.7)	
	Bad	1 (14.3)	3 (20)	

[1]Chi-square test.

Moreover, evaluating the rate of epithelialization, 71.4% of patients receiving the combined formulation had a healing rate of less than 10 days (rapid epithelialization rate), while 46.7% of patients in the control group had a healing rate of between 2 and 3 weeks (moderate epithelialization rate). There was no significant difference between the rate of re-epithelialization between the two groups (P=0.247). Besides, regarding the duration of hospitalization, the difference was not meaningful between two groups (P=0.486) (**Table 4**).

In the evaluation of patients based on the Therapeutic Response Rate Scale, in the control group, most of patient experienced moderate response to the treatment (46.67%) but most of cases in the intervention group had good response (71.43%), which was not significantly different (P=0.225) (**Table 5**).

In the following pictures, 2 cases who received SSD 1%-CN 2.2% cream are presented (**Figures 2** and **3**).

Comparison of infection rate, systemic antibiotic use and graft surgery between the treatment and control groups

All patients receiving SSD+CN cream and 80% of patients in the control group required graft surgery, which was not significantly different (P=0.523), but it was worrisome in the intervention group as all patients underwent surgery. Wound infection rate was also a little bit higher in the intervention group (57.1 vs. 46.7%, P=1). On the other hand, the sepsis rate and also the systemic antibiotic use was higher in the control group, but the difference was insignificant (P=1 & 0.09, respectively) (**Table 6**).

Comparison of vital signs between two groups

Comparing the vital signs of patients receiving the combined formulation with the control group, no significant difference was observed except for diastolic pressure on the 7th day of hospitalization, which was meaningfully lower in the intervention group (**Table 7**).

Comparison of the laboratory data between two groups

No significant difference between two groups was found during the three weeks follow-up regarding laboratory data including WBC, serum blood sugar, creatinine, ESR, CRP and albumin levels. Just baseline sodium level was meaningfully higher in the intervention group (**Table 8**).

Comparison of pain score between two groups

The pain score was significantly lower at third day (P=0.045) and also near to significant after

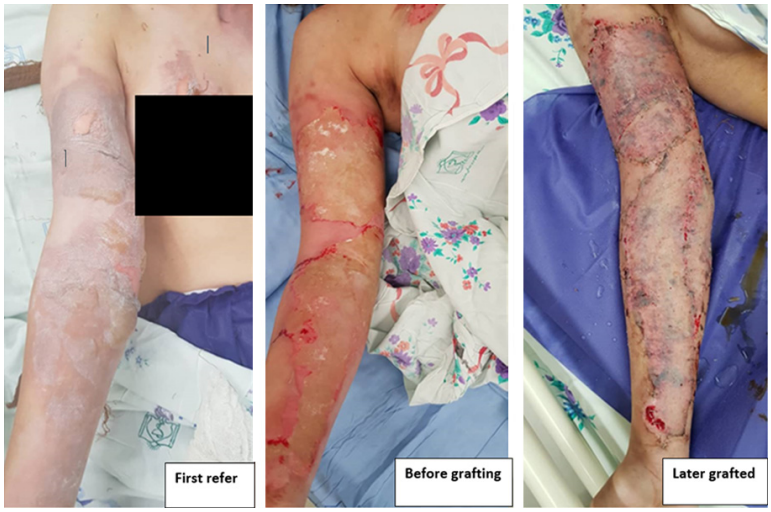

Figure 2. The patient had a 20% burn and the mechanism of the burn was boiling water receiving a 1% silver sulfadiazine (SSD) cream with 2.2% cerium nitrate (CN).

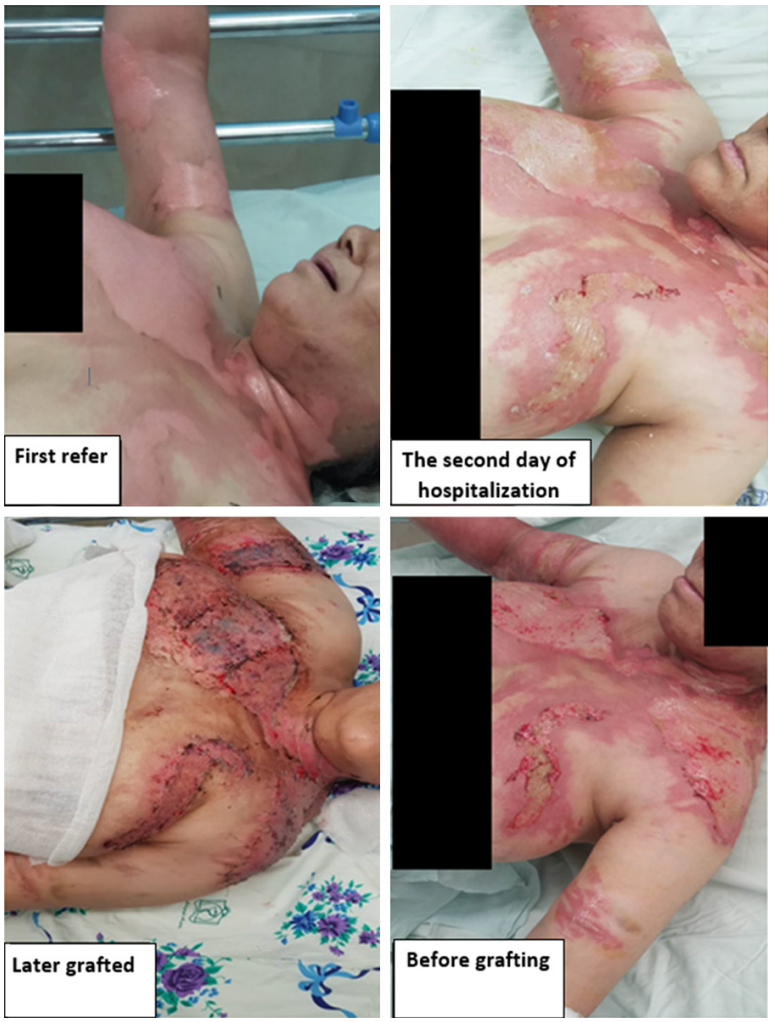

Figure 3. The patient with 12% burn and the mechanism of burn of boiling water who received 1% silver sulfadiazine (SSD) cream with 2.2% cerium nitrate (CN).

one week (P=0.067) in the treatment group, but in other time points of assessment despite lower score in treatment group the difference was insignificant (**Table 9**).

Safety of treatment

In the present study, both creams were well tolerated and there were no major complaints. However, four patients felt warmth on the wound (on day 3) and 1 patient reported burning sensation on first day (**Figure 4**) in the treatment group and just one patient in SSD group complained warmth on the wound. Of course, full distinction of drug adverse reaction from burn complications is not possible.

Discussion

Burn injuries are among the top fifteen most common causes of illness worldwide with considerable physical or mental consequences and can even lead to death [24, 25]. Infection remains the most common cause of morbidity and mortality in burn patients [26].

The major direct effect of burns on health is secondary to impaired normal skin function; as the first line of the body's defense system against the invasion of various pathogens [26].

SSD is a topical antibiotic approved by the US Food and Drug Administration (FDA) and is widely used for more than 50 years as a chemoprophylaxis for partial thickness burns [8, 27]. However, treatment failure is considerable in burns exceed 60% of the body, which may be due to the improper activity against

Table 6. Comparison of systemic antibiotic use, incidence of sepsis and wound infection between two groups

	Group		*P*-value[1]
	Intervention %	Control %	
Graft	100	80	0.523
Systemic Antibiotic	71.4	100	0.091
Sepsis	85.7	93.3	1.00
Wound Infection	57.1	46.7	1.00

[1]Fisher's exact test.

gram-negative and some gram-positive bacteria [12].

Adding cerium nitrate 2.2% to sulphadiazine 1% is proposed to improve its wound healing properties and patients' ultimate survival [8, 28]. This combined formulation can produce a yellow-green, leathery, dry appearance of the full skin thickness eschars and a similar, thinner crust-like layer covering deep dermal bums.

Therefore, limited studies were performed to evaluate the safety and efficacy of this formulation and contradictory results were reported [8, 29, 30]. Some studies have mentioned CN as a safe and effective substance in the management of moderate to severe burns along with SSD [31]. However, limited number of well-designed clinical trials is available in this area.

So, in this clinical trial, the effectiveness of SSD 1%+CN 2.2% cream was evaluated in 2nd and 3rd degree burn wounds. Based on our results, there was no significant difference between the intervention and control groups regarding re-epithelization and therapeutic response rate, duration of hospitalization, infection and sepsis occurrence and systemic antibiotic use, laboratory data and vital signs and also the pain scores. The graft surgery rate also did not show considerable difference but all patients in the intervention group underwent surgery.

An *in vitro* evaluation showed that the MIC of *Pseudomonas aeruginosa* was greater for 100 mcg of CN+100 mcg SSD+CN than for 100 mcg of SSD alone (100% & 40% vs. 19%), which means that similar to our findings, adding CN to SSD may not improve its efficacy particularly against Pseudomonas aeruginosa infection [13].

Ten years after Hager's experimental study, Wasserman et al. performed a clinical study and showed that CN 0.05 M+SSD 0.03 M cream significantly improved survival rate in patients with major burn despite not being too much efficient in preventing wound colonization and septic complications. It is proposed to be due to the protective action of the yellow-green eschar formed by CN+SSD cream [14]. Gracia et al. evaluated the efficacy of SSD+CN topical formulation in burn management in a clinical trial for the first time in 2001. Sixty patients with moderate to severe burns were randomly divided into two equal groups. Patients received burn dressings containing the drug (SSD+CN or SSD alone) daily unless the presence of wound infection signs, and it was changed 2-3 times a day. The results showed that in the SSD+CN group, fewer patients died (1 vs. 4). However, the rate of wound infection was not significantly different between two groups. The re-epithelialization rate of relative skin thickness was 8 days faster in the combined group (P=0.03). The hospitalization period was also significantly shorter (P=0.03) (23.3 days vs. 30.7 days). However, the rate of transient tingling at the wound site was higher in the intervention group, which was well controlled with analgesia. As a result, this study suggested the superiority of SSD+CN to SSD lone [8].

Comparing this study with our clinical trial can propose some key points: (1) In both studies, most of cases in SSD+CN group are classified as "rapid" healing (wound re-epithelialization ≤10 days). (2) Sepsis was more common in SSD in both studies, however the sepsis rate was much higher in our study in both groups (about 10 times higher) which needs special attention. (3) The length of hospital stay in the intervention group was shorter in both study but in our study the difference was insignificant and it is also noteworthy that the average hospital stay was much longer in the Gracia study (23.39±11.4 vs. 12.28±6.34). (4) The mortality rate was much higher in Gracia et al. study but no patient died in our study despite high rate of sepsis occurrence and graft surgery. (5) The wound infection and need for interventions (skin graft and systemic antibiotic

Table 7. Comparison of vital signs between two groups during the study

		Temperature °C					Heart rate beats/min				
		Refer first	Day 3	Day 7	Day 14	Day 21	Refer first	Day 3	Day 7	Day 14	Day 21
Group	Intervention (mean ± SD)	37.13±0.36	37.51±0.6	37.4±0.3	37.1±0.28	37.51±0	100.28±9.7	101.57±4.8	96.28±12.5	102.5±19.0	90±0
	Control (mean ± SD)	37.19±0.29	37.44±0.19	37.4±0.19	37.94±0.66	37.44±0.2	102.4±10.33	97.93±11.7	98.3±13.27	104.4±16.5	113.7±14.6
	P-value[1]	0.882	0.39	0.946	0.16	0.478	0.655	0.444	0.745	0.899	0.296
		Systolic pressure mmHg					Diastolic pressure mmHg				
		Refer first	Day 3	Day 7	Day 14	Day 21	Refer first	Day 3	Day 7	Day 14	Day 21
Group	Intervention (mean ± SD)	124.57±20.1	126±17.9	118±8.2	124±5.6	120 ±0	78.42±13.0	76.78±11.9	65.71±7.9	86±4.2	80±0
	Control (mean ± SD)	121.53±10.4	126.53±8.4	123.53±10.4	127.2±6.8	127.2±9.2	73.73±9.8	74.4±7.5	76.61±9.9	78±4.8	88±19.0
	P-value[1]	0.642	0.925	0.241	0.588	0.827	0.358	0.563	*0.023	0.099	0.751

		Respiratory rate beats/min				
		Refer first	Day 3	Day 7	Day 14	Day 21
Group	Intervention (mean ± SD)	18.42±1.3	19.14±0.69	19.28±3.45	21.5±2.12	17±0
	Control (mean ± SD)	17.73±1.2	18±1.69	18±5.65	19.5±2.07	22±3.6
	P-value[1]	0.262	0.104	0.593	0.284	0.353

[1]Independent sample T-test. *P<0.05.

Table 8. Comparison of laboratory data between two groups during the study

		Blood sugar levels mg/dL					Serum creatinine level mg/dL				
		Refer first	Day 3	Day 7	Day 14	Day 21	Refer first	Day 3	Day 7	Day 14	Day 21
Group	Intervention (mean ± SD)	134.71±14.2	101±8.8	85±0	81±0	105±0	0.9±0.24	0.92±0.14	0.7±0	0.8±0	1.5±0
	Control Group (mean ± SD)	128±48.1	123±19.9	119.42±30.3	109.16±20.8	70.5±27.6	0.92±0.20	0.78±0.14	0.71±0.15	0.66±0.13	0.7±0.1
P-value[1]		0.724	0.087	0.329	0.266	0.346	0.844	0.052	0.951	0.408	0.2
		Blood sodium levels mEq/L					Blood potassium levels mEq/L				
		Refer first	Day 3	Day 7	Day 14	Day 21	Refer first	Day 3	Day 7	Day 14	Day 21
Group	Intervention (mean ± SD)	139.28±1.4	135.85±4.9	132±1.4	129±0	137±0	3.88±0.5	3.75±0.7	3.35±0.07	4.7±0	4.1±0
	Control Group (mean ± SD)	136.73±2.6	135.3±2.4	133.6±2.01	134.66±4.1	137.33±2.3	4.026±0.5	3.69±0.3	3.43±0.58	3.83±0.48	3.83±0.35
P-value[1]		0.029*	0.742	0.317	0.26	0.912	0.58	0.786	0.857	0.159	0.578
		Blood urea level mg/dL					WBC[4] Blood levels 10^9/L				
		Refer first	Day 3	Day 7	Day 14	Day 21	Refer first	Day 3	Day 7	Day 14	Day 21
Group	Intervention (mean ± SD)	26.28±8.2	17.57±7.9	31±0	27±0	24±0	14.8±7.3	9.34±3.8	7±2.6	10.4±0	7.6±0
	Control Group (mean ± SD)	33.26±12.7	21.53±10.7	19.4±9.3	21.16±11.2	12.66±10.7	16.56±5.1	8.07±3.0	10.33±4.5	9.08±2.8	6.43±2.1
P-value[1]		0.203	0.404	0.267	0.652	0.459	0.525	0.439	0.262	0.698	0.678
		Blood albumin levels g/dL					CRP[2] mg/dL		ESR[3] mm/h		
		Refer first	Day 3	Day 7	Day 14	Day 21	Refer first	Day 3	Refer first	Day 3	
Group	Intervention (mean ± SD)	.	2.7±0.62	2.3±0	2.5±0	2.9±0	2.46±4.6	10±0	11±11.35	6±0	
	Control Group (mean ± SD)	3.2±0.14	3.2±0.58	2.75±3.8	2.52±3.9	2.5±0.28	60.85±69.12	.	7.22±12.9	12±0	
P-value[1]		0	0.158	0.297	0.958	0.454	0.085	.	0.663	.	

[1]Independent sample T-test; [2]C-reactive protein; [3]Erythrocyte sedimentation rate; [4]White blood cell. *P<0.05.

Table 9. Comparison of visual pain manual scores between two groups

		Group		*P*-value[1]
		Intervention n (%)	Control n (%)	
Pain Score (median (range))	Admission day	4 (7)	7 (6)	0.106
	Day 3	4 (4)	6 (6)	0.045*
	Day 7	2 (4)	4 (6)	0.067
	Day 14	3 (3)	3 (7)	0.72
	Day 21	3 (1)	4 (1)	0.083

[1]Mann-Whitney test. *P<0.05.

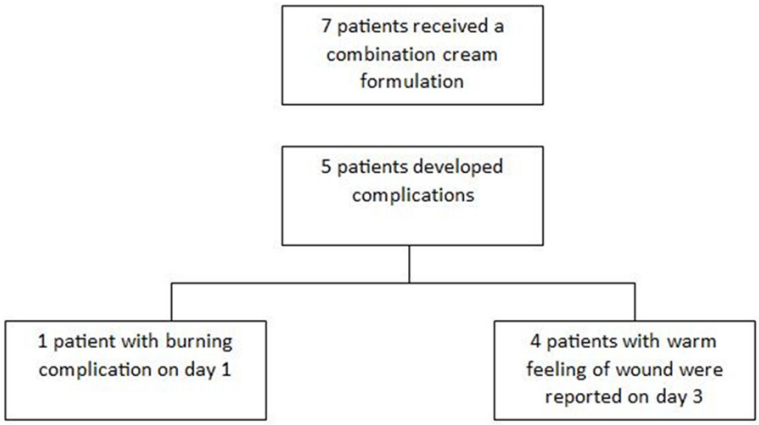

Figure 4. Flowchart side effects.

therapy) were significantly higher in our study, and contrary to expectations, more wound infections and graft occurred in SSD+CN group cases.

There are several explanations for the discrepancies between our findings and Gracia et al. study which could be considered; (1) Our evaluation was performed on a smaller population, which was inevitable because of the Ethics committee opinion. (2) In considerable number of patients' systemic antibiotics were administered empirically just based on clinical assessment in our study, while in the study of Gracia et al., systemic antibiotics were prescribed in case of culture confirmed wound infection or sepsis. (3) The mean age of the patients in the present study was at least 10 years older than that of Gracia study and extremes in age (very old or very young) are risk factors of burn infection. (4) More than 70% of patients in our intervention group were female, while in former study, 46.6% of patients were female. (5) The cases of our intervention group mostly had burns caused by boiling water and gas, while the Gracia study did not provide accurate information about the burn mechanism, which can be effective in different findings. However, our patients were almost identical to the previous study in terms of the average extent of the burn which is another proposed risk factor and patients with a TBSA burn >20% are more at risk of infection.

Another trial by Oen et al. showed that use of SSD+CN in hospitalized patients with acute burns could not be effective in prevention of infection and wound healing. In that study 152 patients with new burns were randomly assigned to the study groups (SSD 1%+CN 2.2% (flammacerium®) group, n=78; SSD 1% group, n=76). During the study, one patient in the intervention group and three patients in the control group died. Surgery was required in 13 and 15 patients, respectively in SSD+CN and SSD groups (P=0.57). The mean wound healing time was 9 versus 11 days in SSD and SSD+CN groups, respectively (P=0.17). In general, no significant difference was seen between two groups which are in consistent with our findings [22]. There are some differences between the abovementioned study and the current one: (1) Oen et al. study had a larger population. (2) Most of patients in the intervention group was male (80%) in Oen study, but in our study the sexual distribution of patients was comparable between two groups. (3) The average age of the patients in our study was about 20 years higher than the abovementioned study, in other words, our cases were older. (4) Regarding the burn mechanism, in the above study, most of the cases were fire burn, while in our study most of patients were hospitalized with gas burns. (5) The assessment scales were different between two studies and also longer follow-up period in Oen study may be effective in study findings.

The main strength of the present study was evaluation of various factors as primary and secondary outcomes. But this study suffered from some limitations. First, the sample size was small because of the strict inclusion criteria and also stopping the project in the middle of the way. Second, the lack of wound culture in most of patients resulted in empiric systemic antibiotic use in most of cases which distorted the results. Moreover, early excision is very important in patients' outcome which is delayed in most of cases in our study.

Conclusion

Based on our findings, topical formulation of SSD 1% and CN 2.2%, may not have significant superiority to the SSD 1% alone in prevention of wound infection and sepsis and also acceleration of burn healing defined by re-epithalization rate and therapeutic response rate scale scores, duration of hospitalization, survival and pain scores (except on third day of admission), in patients with moderate to severe burns. Moreover all patients in this group underwent graft surgery which was not a promising finding. Further well-designed clinical trials on large sample size with use of various formulations of SSD-CN are recommended for better judgment.

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Undersigned written informed consent form was obtained from all patients.

Disclosure of conflict of interest

None.

Abbreviations

ABG, Arterial blood gas; BP, Blood pressure; CN, Cerium nitrate; CXR, Chest X-ray; CBC diff, Complete blood cell differentiation; DH, Drug history; ECG, Electrocardiogram; HR, Heart rate; PMH, Past medical history; RR, Respiration rate; SSD, Silver sulfadiazine; TBSA, Total body surface area; U/A, Urine analysis.

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