

Comparative Effects of Recove[®] and Nitrofurazone 0.2% on the Treatment of First and Second-Degree Burns: a Double-Blind Randomized Clinical Trial

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ABSTRACT

Background: Burns are among the major health challenges of all societies and more than any other trauma incur physical, mental, social, and economic burdens on the patient and society. This study was conducted to assess whether Recove[®] burn ointment is capable of alleviating the pain, preventing the formation of new blisters and controlling the microbial contamination of the wound.

Methods: We, therefore, compared its efficacy to *nitrofurazone 0.2%* cream. This randomized clinical trial was conducted on individuals who had two burn injuries in their body at the same time in the Motahari Burn Hospital, Tehran Province, from June to October 2016. Sampling was carried out with a non-random method using available samples. The intervention in experimental and control groups was Recove[®] and *nitrofurazone*, respectively. The effect of interventions on pain relief, the formation of new blisters and prevention of infection at the burn wound were evaluated. In our double-blind study, blindness was applied to the patients and the person evaluating the outcomes.

Results: Both Recove[®] and nitrofurazone interventions significantly alleviated pain ($P < 0.01$), but Recove[®] showed more effectiveness ($P=0.01$). Similarly, in terms of new blister formation, the experimental group receiving Recove[®] showed less new blister formation over 24 hours after treatment compared to nitrofurazone group ($P=0.03$) and with respect to antimicrobial activity, there was no significant difference between Recove[®] and nitrofurazone ($P=0.12$).

Conclusion: Recove[®] was effective on pain reduction, prevention of new blisters formation as well as infection. Therefore, it seems that Recove[®] could be considered as a new and efficient treatment for burn.

KEYWORDS

Burn; Recove[®] burn ointment; *Nitrofurazone* cream; Pain; Blister

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INTRODUCTION

A burn injury is defined as damage to the skin or other tissues, mostly caused by heat (e.g., fire, hot liquid) and to a less extent by electricity, chemicals, friction, and radiation¹. Based on the thickness and severity



of the damaged tissue, burns are classified into three degrees. The first-degree burn is a superficial burn, meaning that only the outermost layer of skin, the epidermis, is involved. The injured area is erythematous and painful, but blisters are not present. It heals with no scars. In second-degree burn, not only the epidermis but also parts of the dermis, the second layer of skin, are involved. In this stage, in addition to pain and erythema, secretions from the injured area and blisters might develop. In third-degree burns, the epidermis, the full thickness of the dermis and potentially deeper tissues such as muscle, tendons, or bone are involved. The area may be almost painless due to nerve damage²⁻⁴.

Burns and their related injuries are one of the most important causes of death and life-long disability all over the world, with a mortality rate of 180 thousand cases per year. Most of these deaths occur in low and middle-income countries and approximately two-thirds of these cases relate to the African and South-East Asian countries. In addition, the rate of death of children following burning in low and middle-income countries is more than seven times higher than high-income countries⁵. Non-lethal burns usually cause long-term hospitalization, disfigurement, and disability; resulting in individual life difficulties, quality of life decrement, and eventually social isolation. Annually, one million people suffer from moderate to severe burns in India. In the United States, as a developed country, about 1.2 million people suffer from fire injuries annually, about 100,000 of them are hospitalized and about 5,000 die from complications of burn⁶. In Bangladesh, Colombia, Egypt, and Pakistan, about 17% of childhood burns result in temporary disability and in 18% of cases, permanent disability is caused^{5, 7}. In accordance with the Central Emergency Committee of Iran, among the 150 most common causes of death, burns are ranked sixth⁸.

Due to the high incidence of infection in burn wounds, which is a critical challenge in the treatment of burn patients, its care should be given special attention. According to the characteristics of the burn wound, it requires different treatment modalities, including systemic drug administration, topical product usage and surgical treatment such as skin grafting. After assessing the depth and extent of the burn, if needed and possible, it should be debrided thoroughly. Topical treatments in burn wounds are of great importance and various

medications are used for this purpose^{4,9}.

We aimed to compare the effect of two topical treatments of Recove[®] ointment and nitrofurazone 0.2% cream on pain relief, prevention of new blisters formation and control of the infection of burn wounds.

MATERIALS AND METHODS

Patient selection

This randomized, double-blind and with before and after design clinical trial was conducted on patients with burn incidents in the Motahari Burn Hospital, Tehran Province, from June to October 2016. Non-random sampling was performed using available individuals from wounded patients referring to the Motahari Hospital Emergency Department.

The following criteria were used to include the patients in the trial: participants aged 12 to 70 years, having first or second-degree burns, less than 6 hours since the burn incident, any burned area of the body except the head, face and perineum, having two burns on the body which could be divided into right or left or those were proximal and distal in one limb. The exclusion criteria included lack of tendency to continue and cooperate in research, burns of more than 10%, patients requiring hospitalization, burns on the head, face or perineum, electrical or chemical burns, those needing injectable pain relief agents, suffering from diseases such as diabetes, uncontrolled hypertension, immunodeficiency or any illnesses that may be worsened by participation in this trial.

Randomization

To eliminate individual factors, an intra-individual comparison of two treatments of Recove[®] and nitrofurazone was performed. Overall, 30 qualified patients with two right or left burns on their body or two proximal-distal burns on one limb were selected. To determine which patient's burn undergoes treatment with intervention or control therapy, the simple random allocation was applied using a random numbers table.

Trial design

The control group received routine treatment consisting of irrigation with normal saline (sodium chloride 0.9%), topical nitrofurazone 0.2% (a broad-spectrum antibiotic) followed by a bandage.

Acetaminophen was used as an analgesic. In the experimental group, routine treatment was performed with the exception of nitrofurazone 0.2% cream, and instead, a relatively thick layer of Recove® burn ointment (Containing zinc oxide, sesame oil, and camphor) was applied to the burn wounds. Each patient's bandage was changed daily and treatment continued up to 4 days.

Outcome measurement

The effects of topical treatment (Recove® or nitrofurazone) on pain relief, prevention of new blisters formation and infection control were investigated. The level of pain relief was quantitatively measured by numerical criteria (0: painless and 10: the highest level of pain) based on the patient's response, one hour after treatment initiation. The scores of 6-8 were considered as moderate pain and those more than 8 as severe pain. The formation of a new blister was assumed as a qualitative two-state variable (existence and absence) and measured by visual observation over the next 24 hours after treatment, using imaging and subsequent evaluation by the assessor. In terms of infection, a culture of the injured area was performed on the fourth day after treatment initiation on blood agar medium. The outcome was considered as a qualitative two-state variable (positive and negative culture).

Blinding

The participants, outcome assessors, data managers, study monitors, and statisticians were all blinded to the allocation to avoid information bias. Patients were advised not to compare the characteristics of drug and procedure of the treatment with other patients. Blinding was maintained until all patients completed the study. Since the outcome of the pain was measured by the patient's response, it was of great importance. In the case of appearance of a new blister, the evaluation was performed by recorded images over the next 24 hours after treatment. After the preparation of the microbial cultures, those were analyzed by clinical evaluators in the laboratory of the medical center, who did not know about their allocation.

Ethics Approval

Participants were informed of the trial and its purpose then received the printed study information and had the opportunity to ask questions. All subjects

provided written informed consent before their enrollment in the study. This study was reviewed by the Ethics Committee of Iran University of Medical Sciences and approved by IR.IUMS.REC.1395-26742. In addition, the study protocol with the IRCT ID number: IRCT201606148177N15 was registered in the Iranian Registry of Clinical Trials.

Statistical analysis

To analyze the data distribution, descriptive statistical methods such as mean and standard deviation were used for quantitative variables. Furthermore, percentages and numbers were applied to qualitative items. To evaluate the normality of quantitative variables, one-sample Kolmogorov-Smirnov test was used. To determine the significant difference between therapeutic groups, tests such as Mann-Whitney and chi-square were used. The Wilcoxon test was also used to compare the results of before and after treatment in both study groups. All statistical analyses were performed with SPSS version 22 (IBM Corp., Armonk, NY, USA) considering a significant level of 0.05.

RESULTS

Based on the patients' characteristics presented in Table 1, a total of 30 people with first or second-degree burns, with an average age of 36 years (57% of which were men), and with an average of 82 min after the burn incident were enrolled in the study. The most common underlying cause of burns was hot liquids (57%).

The results of the Kolmogorov-Smirnov test to determine the normality of the average pain score showed that the distribution of this variable is not normal ($P=0.01$). Therefore, non-parametric tests were used to analyze them. With respect to pain score at the beginning of the trial, the results of the Mann-Whitney U test exerted that there was no significant difference between groups treated with Recove® and nitrofurazone 0.2% (6.27, 6.31, $P=0.31$, respectively) (Table 2). To evaluate the effectiveness of each treatment in pain reduction, the Wilcoxon test was performed on the average pain score, which demonstrated that one hour after treatment the level of pain diminished significantly to 2.88 ± 1.17 from 6.27 ± 1.18 at the beginning of the intervention in the Recove® group ($P < 0.01$). Similarly, in the nitrofurazone 0.2% group, in one

Table 1: Characteristics of included patients.

Characteristic		Number of patients	Average	Percentage
Age, year (SD)		30	36 (13.2)	-
Gender	Male	17	-	56.7
	Female	13	-	43.3
Time past after burn incident, min, (SD)		26	82.5 (58.1)	-
Cause of burn	Hot liquids	17	-	56.7
	Fire	5	-	16.7
	Hot food	3	-	10
	Others	1	-	3.3
Missing		4	-	13.3

Table 2: The results of average pain score at the beginning and 1 h after treatment (n=26).

Variable	Recove ^o treatment	Nitrofurazone treatment	*P
Average Pain score at the beginning (SD)	6.27 (1.18)	6.31 (1.22)	0.31
Average Pain score 1 hour after (SD)	2.88 (1.17)	3.96 (1.56)	0.01
**P	P < 0.01	P < 0.01	

* P expressed for comparison of two different groups (Recove^o and nitrofurazone) for every single time. Data were analyzed by Mann-Whitney U test.

** P expressed for comparison of two different times (at the beginning and 1 h after) for each group. Data were analyzed by Wilcoxon test.

Table 3: The percentage of the suffering from moderate to severe pain 1 h after treatment (n=26). Data are expressed as percentage and analyzed by chi-square test.

Groups	Number of patients suffering from moderate to severe pain 1 h after treatment	Percentage	P
Recove ^o treatment	1	3.8	0.01
Nitrofurazone treatment	8	30.8	

Table 4: The results of percentage of blister appearance at the beginning and 24 h after treatment in each group (n=26). Data are expressed as the percentage of blister and analyzed by chi-square test

Groups	Presence of blister at the beginning of the study		Blister formation 24 h after treatment	
	Number of patients suffering from blisters	Percentage	Number of patients suffering from new blisters	Percentage
Recove ^o treatment	15	57.7	4	15.4
Nitrofurazone treatment	14	53.8	12	46.2
P	1		0.03	

hour after the treatment, the average pain value decreased significantly and reached 3.96 ± 1.56 from 6.31 ± 1.22 at the beginning of the study ($P < 0.01$). The results of the Mann-Whitney U test to compare the effect of two treatments of Recove^o and nitrofurazone 0.2% on relieving pain within one hour after treatment illustrated that despite the remarkable effect of both treatments on pain relief, Recove^o compared to nitrofurazone 0.2% was more

effective; with a significant difference (2.88, 3.96, $P=0.01$, respectively) (Table 2). Also, the results of the chi-square test indicated that there was a significant difference in the percentage of cases with moderate to severe pain (score above 6) between the two groups of Recove^o and nitrofurazone 0.2% one hour after treatment (3.8%, 30.8%, $P=0.01$, respectively) (Table 3). In the case of blistering, there was no significant



Figure 1: The burn wounds of patients; at the beginning and 1 h after treatment by Recove® or nitrofurazone.

Table 5: The results of positive microbial culture four days after treatment in each group (n=26). Data are expressed as percentage and analyzed by chi-square test

Groups	Number of patient with positive microbial culture	Percentage	P
Recove® treatment	11	42.3	0.12
Nitrofurazone treatment	6	23	

difference between Recove® and nitrofurazone 0.2% groups at the beginning of the treatment (57.7%, 53.8%, $P=1.00$, respectively) (Table 4 and Figure 1). Moreover, comparing the two groups of Recove® and nitrofurazone 0.2%, in terms of the percentage of the burned patient that new blisters were formed in their wounds within 24 hours after treatment, the chi-square test showed that although there was no significant difference in this regard at the beginning of the study, Recove® was significantly more effective and further reduced the occurrence of new blister during this period (15.4% compared to 46.2%, $P=0.03$) (Table 4 and Figure 1).

In the case of infection, based on the percentage of patients whose wounds were infected during 4 days after treatment, the analysis of results using chi-square test revealed that there was no statistically significant difference between antibacterial effects of Recove® and nitrofurazone ($P=0.12$) (Table 5).

DISCUSSION

The present study suggests that, although both Recove® and nitrofurazone 0.2% treatments were effective in relieving pain of burned patients, Recove® ointment displayed a greater impact versus nitrofurazone 0.2%. In addition, in terms of new blisters formation, Recove® exhibited a more pronounced effect, and with respect to antimicrobial activity, a significant difference was not observed between them.

Recove® burn ointment, which its effectiveness was studied in this trial, is comprised of zinc oxide (20%), sesame oil (58.5%) and camphor (2.5%). The potential of zinc, an essential trace element, in the wound treatment has been accepted at the World Union of Wound Healing Societies meeting held in France in 2004^{10, 11}. The wound healing properties of zinc oxide have been investigated by

researchers. Arslan et al. showed that the application of zinc oxide (20%) to partial-thickness burn wounds of rabbits diminished debris and necrotic tissues as well as raises epithelialization. They also demonstrated that local utilization of zinc oxide is more effective than topical silver sulfadiazine in accelerating re-epithelialization of burn wounds. In addition, by measurement of the thickness of skin layers (epidermis and dermis) at the burned area and scar tissue during six weeks post-burn, they concluded that zinc oxide had better function than silver sulfadiazine in wound healing¹⁰. Using not zinc-deficient domestic pigs, topical application of zinc oxide enhanced re-epithelialization of partial-thickness skin wounds¹².

The sesame oil, another component of Recove[®] ointment, has many pharmacological activities. It is used in various skin and hair products. There are many lignans in the oil and seeds of sesame. For example, a large group of secondary metabolites in plants that have numerous biological effects, such as sesamin, sesamol, and sesamol. Besides, the oil and seed of sesame contain tocopherols and fatty acids. Sesamin and its related derivatives contribute to the antioxidant properties of sesame¹³⁻¹⁵. Thanks to the antioxidant activity, sesame oil is able to decrease lipid peroxide, which elevated in burn wounds and subsequently reduce the duration of epithelialization. Sesame oil and seed had healing properties on different types of wound such as burn, excision and incision wounds, besides, all formulations containing sesame decreased the period of epithelialization as well as wound contraction¹⁶.

In the case of prevention of new blister formation, Recove[®] had a better function than nitrofurazone. The thermal damage to the skin causes the activation of immune system and subsequently the production of pro-inflammatory cytokines, which lead to increase of vascular permeability and fluid leakage. On the other hand, xanthine oxidase, an enzyme with catalytic properties, increases the histamine activity and leads to progressive local enhancement in the vascular permeability of the burn wound. Finally, by edema and then fluid accumulation in one place, blister is formed¹⁷⁻¹⁹. The more ability of Recove[®] ointment to prevent of new blisters might be attributed to the anti-inflammatory and antioxidant effects of sesame

oil. Sesame oil could reduce the level of pro-inflammatory cytokines such as TNF- α and IL-6, induce antioxidative enzymes and diminish reactive oxygen species¹⁵. The camphor also has some anti-inflammatory activities. In a study conducted on atopic dermatitis-induced mice, camphor leaves extract has been shown to be able to inhibit the macrophage-derived chemokine production and alleviate allergic inflammation²⁰.

As explained earlier, the effectiveness of Recove[®] on pain reduction was more than that of nitrofurazone. This property could be attributed to camphor, another composition of Recove[®] ointment, which is a terpenoid and known as a local pain reliever. This substance is a common component of various topical products. The analgesic characteristics of camphor are due to its modulatory effects on transient receptor potential channels (TRP channels). TRP channels are a group of ion channels mediating a variety of sensations like pain, warmth or coldness, different kinds of tastes, pressure, etc.²¹⁻²³.

In terms of infection rate, a statistically significant difference was not observed between Recove[®] and nitrofurazone groups. Nitrofurazone is applied as a topical adjuvant therapy in patients suffered from different degrees of burns. Due to its good penetration in the eschar, it can be used to treat invasive infections. Its antimicrobial properties are suspected to be via the interference of DNA synthesis in the microorganism and inhibiting certain enzymes in the carbohydrate metabolism. The spectrum of antimicrobial activity of nitrofurazone is widespread and is effective against gram-positive and gram-negative bacteria. However, it is ineffective against most *Pseudomonas aeruginosa* species and not active against fungi or viruses. In addition, some pathogenic microorganisms such as *Staphylococcus aureus* and *Escherichia coli* are able to acquire resistance against nitrofurazone, which is a serious global concern^{24, 25}. The antimicrobial effects of Recove[®] could be attributed to the presence of sesame oil and to some extent zinc oxide. The sesame seed oil contains natural antimicrobial substances, which are active against bacteria (e.g. *Staphylococcus* and *Streptococcus*) and fungi²⁶. Some bacterial species involved in infections of the endocardium were sensitive to zinc oxide. In addition, the growth and attachment of *Staphylococcus aureus* were inhibited by zinc oxide^{11, 27}.

CONCLUSION

Our investigation demonstrated that the Recove® treated group experienced better and more efficient pain relief as well as better prevention of the new blister formation. On the other hand, in terms of microbial control of the burned wound, there was no significant difference between Recove® and nitrofurazone 0.2%. Eventually, it seems that an ointment containing zinc oxide, sesame oil, and camphor is a good choice to treat first and second-degree burns. Of course, to provide more comprehensive results about Recove®'s efficacy, and to assess its benefits over other agents, further studies are required.

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CONFLICT OF INTEREST

Toasan Darou Pharmaceutical Company, Qom, Iran manufactures Recove® ointments.

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