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Comparing the Effects of Topical Application of Honey and Nitrofurazone Ointment on the Treatment of Second-degree Burns with Limited Area: a randomized clinical trial

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ABSTRACT

Background: Burn is among the problems, which leads to numerous health and financial side effects for the patients and their families. The high costs of new dressings and burn rehabilitation have resulted in the increased tendency of researchers toward using complementary therapies and cost-effective ingredients such as honey with natural origin. Regarding this, the aim of this study was to compare the effect of topical use of honey and Nitrofurazone ointment on superficial second-degree burn healing.

Methods: This clinical trial was conducted on 50 patients with superficial second-degree burns referring to Yaftabad Hospital, Tehran, Iran, during 2013-2015. The participants were selected using the convenience sampling method, and then randomly assigned into two groups. The wounds were dressed daily until complete wound healing, with organic honey in one group and Nitrofurazone ointment and sterile gauze in the other group. For the purpose of the study, the two groups were compared in terms of such factors as pain intensity (for the first week), antibacterial activity (for the first week), histopathological parameters (14 days later), wound healing, and wound scar (6-12 months later). The comparisons were made through the visual analogue scale, laboratory culture results, pathologist's ratings, daily photographs, and Vancouver Scar Scale, respectively. The data were analyzed using the SPSS software version 21 by the t-test and Chi-square test.

Results: According to the results, the patients' pain intensity gradually decreased in both groups of honey (P<0.001) and Nitrofurazone (P<0.001) treatments and the pain intensity results showed better improvement in the honey group. Nevertheless, there was no significant difference between the two groups in this regard (P>0.05). Furthermore, the two groups showed no significant differences in terms of the epithelialization rate (P=0.52), inflammatory cells (P=0.71), vascularization (P=0.79), repair duration (P=0.43), and scar score (P=0.28).

Conclusion: As the findings of the present study indicated, honey and Nitrofurazoneon had comparable effects on the healing of second-degree burns (i.e., partial thickness) with less extended area. However, further studies are needed for the replacement of Nitrofurazone with honey.

1. Introduction

Burn has been introduced as one of the major problems by the World Health Organization (WHO). According to the WHO statistics, 265,000 deaths annually occur due to burn, most of which happen in the countries with poor and moderate financial conditions, especially in Southeast Asia.[1]

Burn damage is usually accompanied by mortality, inability, several surgeries, hospitalization,

long rehabilitation period, and high therapeutic costs.[2] Burn wound results in disturbed structural integrity of tissue, loss of blood vessels, and oxygen deficiency. This condition may also cause infection due to the loss of skin protective function against the microorganisms.[3]

Wound healing is a really complicated process, including three stages of inflammation, proliferation, and regeneration.[4] Healing process is the result of interaction between cytokines, growth factors, cellular and blood components, and extracellular matrix.[2- 4]

Despite the advances in antiseptics, medications, and surgical procedures, burn injuries are still considered as a health issue.[4- 6] In the developing countries, burn wounds are mostly covered by temporary coverings, such as allografts and different engineered dressings. Yet, in some developing countries like Iran, these dressings are costly and less accessible. Therefore, there is always tendency for cheap and available dressings, which control infection and accelerate wound repair process.[7]

In Ayurveda medicine (i.e., the ancient science of India), honey has been utilized since 2500 BC by the Egyptians, Greeks, and Romans. Hippocrates has used honey for the treatment of wounds and gastritis, and it is still considered as a non-stimulating, nontoxic, cheap, and available material in medicine.[7- 10]

Generally, honey components include fructose, glucose, sucrose, minerals, vitamins, flavonoids, antioxidants, amino acids, and other unknown materials, which vary in different honey types based on the used herbal coverage.[4, 9] Different studies have noted numerous properties for honey, the most important of which are anti-bacterial,[11] anti-inflammatory, immunogenesis,[12] and wound repair features. The anti-bacterial properties of honey could mainly be attributed to hydrogen peroxide resulting from the reducing sugar present in honey, and also high osmolarity, high acidity, and nitric oxide. Moreover, honey reduces the inflammation by decreasing prostaglandins. It also stimulates the production of lymphocytes as well as antibodies and accelerates the activity of macrophages and growth factors.[4, 9, 13]

In a clinical trial performed by Malik et al. (2010), it was demonstrated that honey accelerates burn wound healing (partial thickness) in comparison with silver sulfadiazine.[5]

Mashood et al. (2011) also compared the impact of honey and silver sulfadiazine on superficial partial thickness burns wound and indicated that honey could improve wound healing and reduce infection and pain.[14]

Nitrofurazone as the most common treatment for the second-degree burns has side effects such as sensitivity, itching, contact dermatitis, and slow repair process. The majority of the studies have compared honey with silver sulfadiazine ointment. Regarding this, the current study was performed with the aim of comparing the influence of topical honey and Nitrofurazone ointment on the healing of second-degree burn wounds with limited area.

2. Methods

2.1. Design

This clinical trial was conducted on the patients with second-degree burn referring to the burn emergency of Yaftabad Hospital, Tehran, Iran, within December, 2013-August, 2015.

2.2. Participants and setting

Following a study by Mashhoud et al (2006),[14] the sample size was calculated as 50 by the sample size formula (using G*Power 3.1.3, $\alpha=0.05$, $\beta=0.2$, effect ratio=0.17). The patients were selected through simple convenience sampling method. Subsequently, they were divided into two groups of 25 people by random assignment method through the Random Allocation V.1.0.0 software.

To this aim, 50 random numbers were entitled as the first (i.e., organic honey) and the second groups (i.e., 0.2% Nitrofurazone ointment); subsequently, each patient was assigned a number and entered the study groups. The inclusion criteria were: 1) age group of 18-60 years, 2) referring in the first 24 h after burn, 3) having second-degree burn covering less than 10%, and 4) lack of concurrent diseases that disturb the healing procedure (e.g., diabetes, chronic renal failure, malignancy, and corticosteroid consumption), 5) electrical, chemical, and respiratory burns, and 6) burns in the face, fingers, and perineal region. On the other hand, the exclusion criteria included infection occurrence during the study, lack of response to therapy, and need for graft surgery.

2.3. Instruments

The data were collected using the demographic form, Visual Analog Scale (VAS), Vancouver Scar Scale (VSS), and a form for recording the results of culture, epithelialization process (superficial tissue repair), angiogenesis, inflammatory cells, and also the wound healing time. The demographic form included information such as age, gender, burn type, burn cause, and the mean of burn percentage.

The VAS is a 10-centimeter scale, which is graded from 0-10, and the patients determine their

pain intensity on the lines. In this tool, zero score signifies a painless condition, and score of ten is indicative of the most severe possible pain. This tool has been applied in different studies as a standard tool.[15- 17]

The VSS was used by Salivan et al. in 1990 for the first time.[18] This scale evaluates the burn scars based on four variables, including vascularity, height/thickness, pliability, and pigmentation within a range of 0-13 (Table 1). The VSS has been utilized in various studies as a standard tool, and has the required validity and reliability.[19, 20]

2.4. Data Collection

The patients were examined for the inclusion criteria by the emergency department doctor immediately after referring to the Burn Emergency Unit. Therefore, the patients who met the inclusion criteria were randomly invited to participate in the study with all the ethical considerations.

In both groups, first, the burn wound was flushed with 0.9% normal saline. Then, the daily dressing in the first group was performed by a thin layer of organic honey and dry gauze. On the other hand, in the second group, the daily dressing was covered with a thin layer of 0.2% Nitrofurazone ointment (Iran _ Najo medical company) and dry gauze. The dressings were daily changed by the nurse of the burn until the complete healing of the wound.

The honey used in this study was taken from the mountainous regions of Taleghan, Iran, the plant cover of which is mainly thyme and locoweed. Additionally, all the chemical, physical, and microbial tests and also spore count were performed on honey samples by the Behesht Ayin Laboratory (specialized in food, medication, and hygienic-cosmetic materials quality control). This laboratory is granted the approval from the Ministry of Health and Medical Education. The samples were used after checking their agreement with the Iranian national standard number 92.

In order to evaluate the patients' pain intensity on days 1-7 of hospitalization, the patients were asked to report the intensity of pain resulting from dressing change by VAS. In order to perform microbial culture, the samples were taken through culture swabs from all the patients by the same nurse and immediately transferred to the laboratory.

According to the literature, 14-21 days are scientifically required for the healing of the partial thickness wounds.[21] Therefore, the samples were taken by a surgeon using a 2-millimeter punch biopsy (kai medical, 1110 Oyana, Seki City, Gifu Pref., 501-3992, Japan) on the fourteenth day after burn in order to assess the epithelialization process (superficial tissue repair), angiogenesis, and inflammatory cells in each group (The samples were immediately sent to the laboratory in 10% formalin solution for histopathological evaluations.

Afterwards, sections of about 2 μm were prepared from the samples, and the H&E stained slides were evaluated by light microscope with HPF40 for the measurement of epithelialization rate (superficial tissue repair). In this process, scores of zero, one, two, and three were given to the lack of epithelialization, epithelialization of one third of the area, two third of the area, and complete epithelialization, respectively.

Regarding the angiogenesis process and inflammatory cells, scores of zero, one, two, and three were assigned to the lack of angiogenesis, and poor, moderate, and extensive angiogenesis, respectively. Then, the results of the evaluation were compared between the two groups. In order to investigate the wound healing duration in the study groups, daily photographs by digital camera (Nikon, 4.3-180mm 1:3-5.9) were used.

Afterwards, two surgeons (i.e., plastic and burn surgeons), who were not involved in the treatment, evaluated and graded the respective changes. The time for wound healing was reported by the surgeons in different days, and the means the two groups was compared in this regard. It is worth mentioning that the numerical results of the surgeons' evaluations were so close (Diagram 1).

Finally, for checking the remained scar, the patients were asked to refer to the hospital 6-12 months after the first dressing. This evaluation was performed by the same surgeon for all the patients using the VSS.

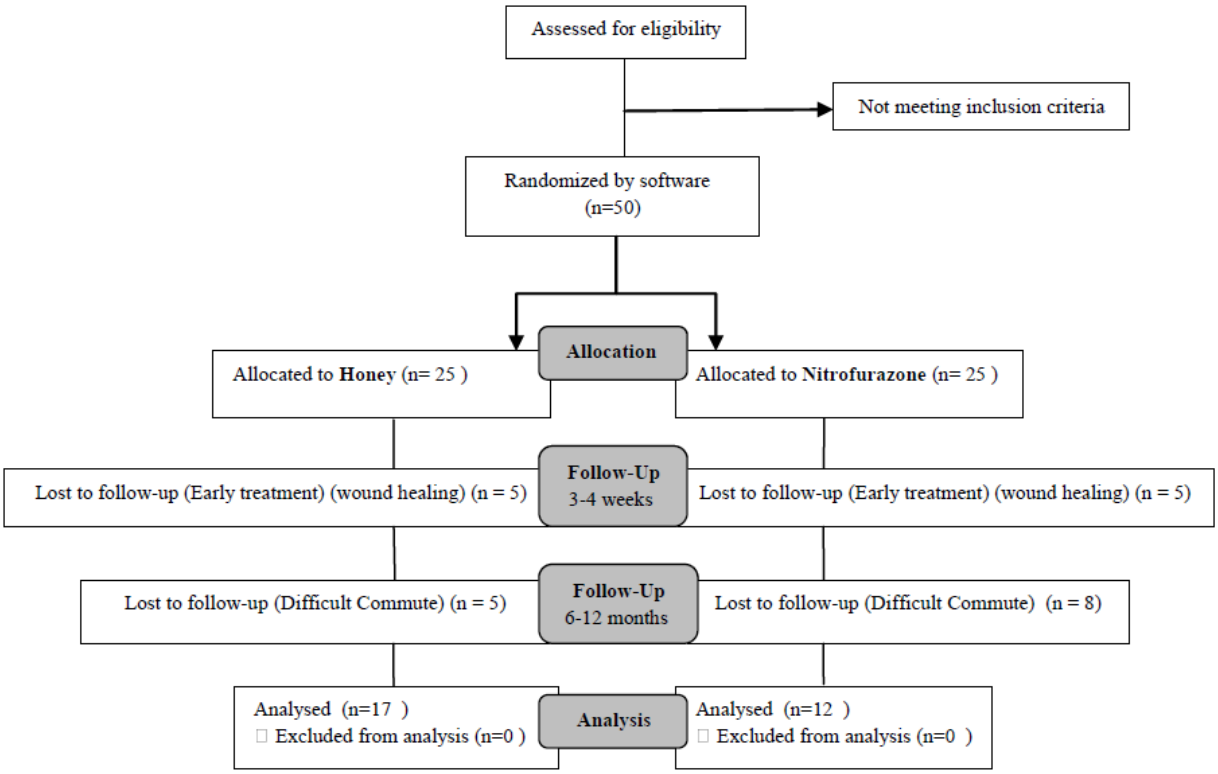

Diagram 1. Stages of conducting the study

2.5. Ethical considerations

Consent was taken from all the participants before the intervention according to the 91-03-129-19146-82523 regulations of Ethics Committee of Research in Iran-Tehran University of Medical Sciences, Tehran, Iran. The patients were provided with sufficient information about the aims of the study and the confidentiality of the data.

2.6. Statistical analysis

Data analysis was performed using the descriptive statistics. The Chi-square test was also employed to compare the two groups in terms of gender, burn cause, and wound culture results. Furthermore, the independent t-test was also used for comparing the two groups regarding the age, mean of burn percentage, mean intensity of the pain caused by dressing change, histological evaluation results, mean of wound healing duration, and mean of the remaining scar. Additionally, the intra-group comparison of the mean intensity of the pain resulting from dressing change within days 1-7 was performed by the repeated measure analysis. All these statistical analysis were performed using the SPSS version 21.

Table 1. Vancouver Scar Scale

Scar characteristics		Score
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pigmentation	Normal	0
	Hypopigmentation	1
	Hyperpigmentation	2
Pliability	Normal	0
	Supple	1
	Yielding	2
	Firm	3
	Ropes	4
	Contracture	5
Height	Flat	0
	<2 mm	1
	mm	2
	>5 mm	3
Total score		13

3. Results

During the process of this study, 8 and 13 cases were excluded from the honey dressing and Nitrofurazone group, respectively. These exclusions were mainly due to the healing of the wounds and not referring to the hospital anymore. Therefore, the study was continued with 17 participants in the honey group and 12 patients in the Nitrofurazone treatment group. (Diagram 1).

Regarding the burn type, all the participants had thermal burns. Other personal characteristics are demonstrated in Table 2. According to this table, no statistically significant difference was observed between the two groups regarding the personal characteristics of the participants.

The pain intensity of the patients gradually reduced in both groups of honey treatment ($P<0.001$) and Nitrofurazone ($P<0.001$); however, the difference between the two groups was not significant (Table 3).

The results of the Chi-square test indicated that the difference between the two groups was not significant considering the positive and negative cultures of the patients on the first ($P=1$) and third days ($P=0.26$). In addition, there was no case of positive culture in neither of the groups on day seven (Diagram 2). The isolated microorganism in all the positive cultures was *Staphylococcus aureus*.

Based on the independent samples t-test, the difference for epithelialization was not statistically significant between the honey (2 ± 1.5) and Nitrofurazone (2.25 ± 1.5) groups ($P=0.52$). Furthermore, the number of inflammatory cells in the honey treatment group (0.75 ± 0.88) was so close to that of the Nitrofurazone group (1 ± 1.15) ($P=0.71$). The mean of angiogenesis score was not significantly different between the honey (2.25 ± 0.46) and Nitrofurazone groups (2.33 ± 0.57)($P=0.79$) (Figure 1).

The mean repair durations were 6.38 ± 3.24 (95% CI: 4.64-8.1 days) and 5.45 ± 2.38 days (95% CI: 3.85-7.05 days) in the honey and Nitrofurazone groups, respectively. Nonetheless, this difference was not significant ($P=0.43$) according to the independent t-test (Figure 2).

The mean of scar scores were reported as 1.59 ± 2.87 (95% CI: 0.12-3.25) and 0.63 ± 1.5 (95% CI: -0.37-1.64) for the honey and Nitrofurazone groups, respectively. However, based on the results of the independent sample t-test, this difference between the two groups was not statistically significant ($P=0.28$).

Table 2. Demographic characteristics of the participants

Variables / Groups	Gender N(%)		Burn cause N(%)			Age (years) M±SD	Total Burn Surface area(TBSA) M±SD
	Male	Female	Scald	Flame	Contact		
Honey	9(53)	8(47)	14(82)	2(12)	1(6)	39±13.61	4.88±2.42
Nitrofurazone	9(75)	3(25)	10(83)	2(17)	0(0)	40.42±14.29	4.25±1.81
P-value	0.27*		0.66*			0.79**	0.47**

*Chi-square test, **Independent sample test

Table 3. Comparison of pain intensity between in the two treatment groups from the first day until the seventh day of intervention

Groups	Honey	Nitrofurazone	P-value
Days of pain intensity evaluation	**M± SD**	**M±SD**	
First	9±1.69	9.17±0.93	0.69**
Second	8.65±1.76	9.17±0.93	0.67***
Third	8.06±2.13	8.58±1.67	0.59***
Fourth	7.44±2.15	7.72±1.95	0.72***
Fifth	6.80±2.04	7.50±1.84	0.39***
Sixth	6.60±2.16	7.50±1.84	0.29***
Seventh	5.93±2.81	6.67±1.58	0.48***
***P-value**	<0.001	<0.001	

*Repeated measurement ANOVA, **Mann-Whitney U test, ***Independent sample t-test

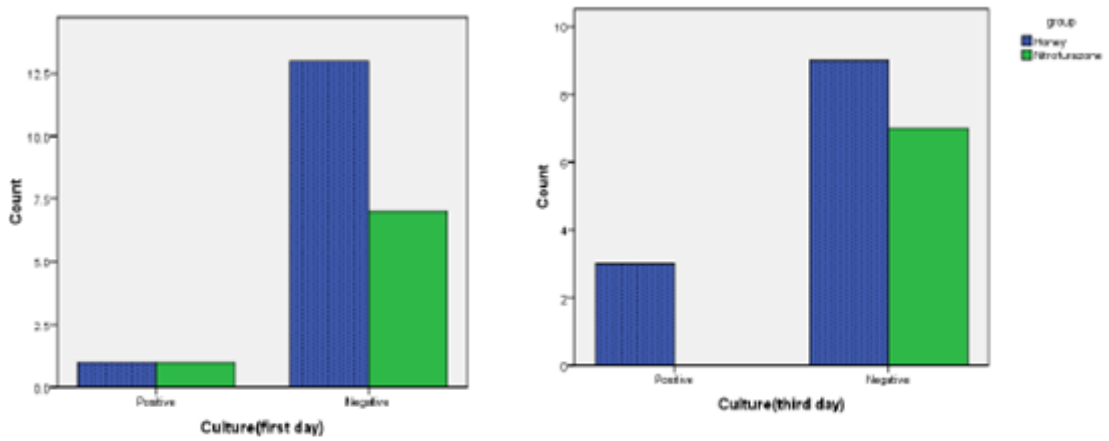

Diagram 2. Results of culture on days one and three in the honey and Nitrofurazone groups

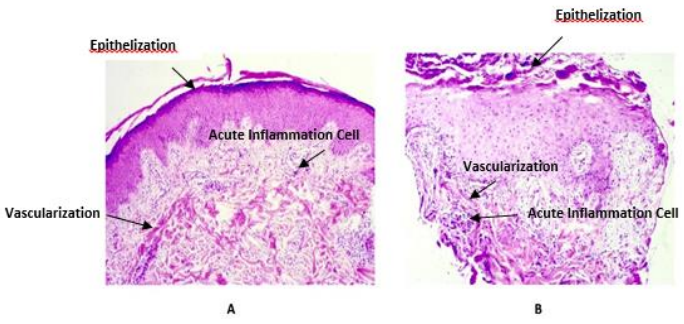

Figure 1. Comparison of epithelialization, angiogenesis, and inflammatory cells between honey (A) and Nitrofurazone groups (B) using the HPF40

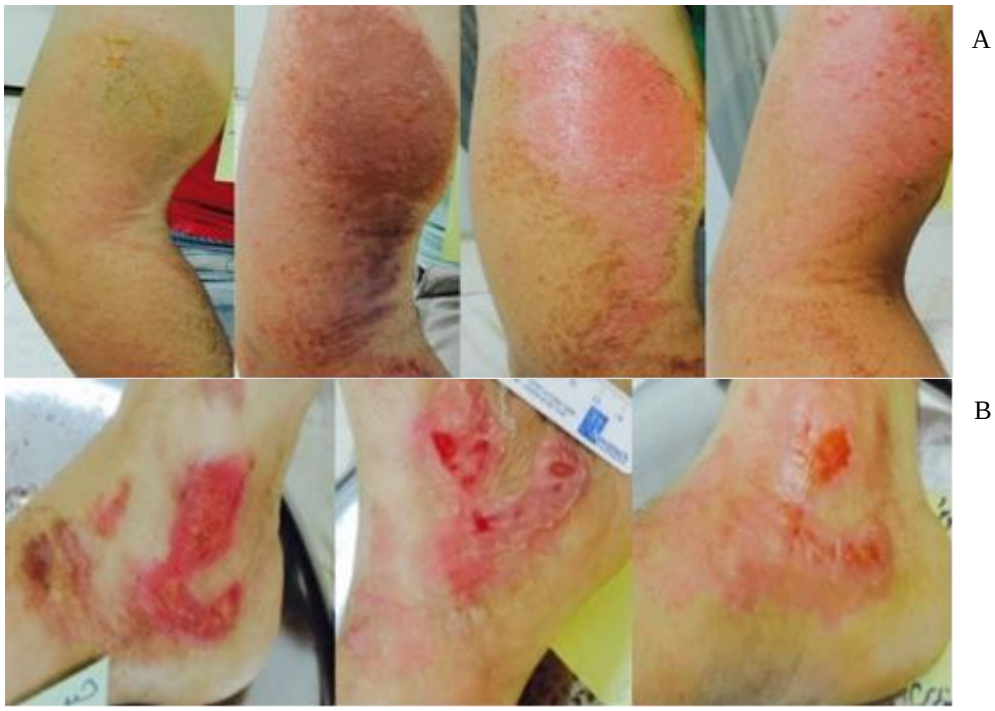

Figure 2. Wound healing process in the honey (A) and Nitrofurazone (B) groups

4. Discussion

The results obtained from this study demonstrated that topical honey and Nitrofurazone ointment did not have significant differences regarding several aspects of burn wound healing, such as pain intensity, bacterial culture results, histopathology results, wound healing duration, and the scar scores . Therefore, the current study demonstrated the antimicrobial and repairing properties of honey, which were indicated in various studies.

Subrahmanyam et al. (2001) first showed in a laboratory study that the concentration of 30% is the minimum required concentration for the antibacterial activity of honey against different microorganisms isolated from infected burn wounds.[22] Khoo et al. (2010) also noted the impact of honey (i.e., Tualang honey) on the complete control of Pseudomonas aeruginosa and wound closure, compared to hydrofiber dressing.[23]

Taslim et al. (2013)[11] also showed the antibacterial activity of honey against the same microorganism. Overall, most studies have confirmed the antibacterial effect of honey on Pseudomonas aeruginosa.[24, 25] However, in a study performed by Nasir et al. (2010),[24] Tualang honey of Malaysia was not effective against the gram-positive bacteria in comparison with silver sulfadiazine and medical honey dressings.

On the other hand, on the third day of the intervention, Nitrofurazone was observed to have more satisfying outcomes, compared to honey. Nonetheless, on the seventh day, no positive culture was found in the group under honey treatment. This difference in findings could be due to the prolongation of the study and the reduction of the antibacterial properties of honey. Therefore, it is essential to use the same type of honey with similar conditions for all patients.

Hashemi et al. evaluated the properties of honey and Mafenide for the treatment of full-thickness burn in rabbit ear. They reported that the pathologic score of the honey group was higher than that of the Mafenide acetate group on both days of 14 and 21 after burn. However, this difference was not significant between the two groups. In the mentioned study, the results of the pathologic tests did not demonstrate a significant difference regarding epithelialization and angiogenesis in spite of the lower severity of inflammation in the honey group. In a study conducted by Hashemi, deep-tissue (e.g., cartilage) side effects of burn in Mafenide acetate group were significantly less than those in the honey group. Therefore, despite the reported curative effects and antibacterial activity of honey, no positive evidence was observed considering its role in the prevention of deep bacterial side effects (e.g., cartilage inflammation). Similar to the current study, in the mentioned study, honey was not recommended as dressing for deep wounds, and just accelerated the repair of the partial-thickness burns.[9]

In a a clinical trial conducted in Pakistan, Malik et al. (2010) evaluated the influence of honey and silver sulfadiazine on 150 patients with superficial

burn wound (i.e., partial thickness) covering less than 40%. The evidences of this study showed that honey was more effective in repairing the partial-thickness superficial burn wound in comparison with silver. In consistent with the findings of the present study, this difference was reported to be significant. It could be noted that enhanced healing in the honey group, compared to the silver sulfadiazine group was more related to the delayed epithelialization in the silver group.[5]

In a review study conducted by Jull et al. (2015) investigating the effect of honey on wound healing, out of the 26 trials, 11 cases examined the burn wound. In the mentioned study, out of the reviewed articles, two studies that had investigated the superficial burn wound for comparing the honey dressing with the traditional ones had high quality evidences. The findings of the mentioned study were indicative of the superior effects of honey in the treatment of burn with partial thickness, compared to the traditional treatments. In the present study, the effects of honey and Nitrofurazone on the healing of second-degree burn wounds were found to be comparable. Nonetheless, honey was also concluded to be effective in the healing of partial-thickness burn wounds in the current study.[8]

In another study, Mashhood et al. (2006) investigated the impact of honey and silver sulfadiazine on the superficial and partial-thickness burn wounds on 50 patients with burns covering less than 15%. They reported honey to be more beneficial regarding all the three parameters of pain, healing duration, and culture, compared to silver sulfadiazine. In line with the present study, honey was demonstrated to improve the healing of superficial wounds and reduce the dressing change pain compared to silver; however, the results were not significant in comparison with Nitrofurazone group.[14]

In another study carried out by Baghel et al. (2009) in India, the impact of honey and silver sulfadiazine on first- and second-degree burns with areas of less than 50% was investigated. The mentioned study showed that honey led to improved outcomes regarding the healing time, infection control, and scar prevention.[26] These findings are consistent with those of the current study indicating the positive effect of honey on the healing of superficial second-degree burn wounds.

In the few studies investigated the scar condition, honey was reported to show better results in this regard. However, these studies employed short follow-up period and did not standardize the utilized scale.[26, 27] Nevertheless, in the current study the remained scars were evaluated 6-12 months post-treatment by the VSS and the difference between the results of the two groups was not significant.

5. Conclusion

As the findings of the present study indicated, honey and Nitrofurazone ointment had comparable effects on the second-degree burn wound healing. Therefore, it could be applied for the treatment of the partial-thickness burn wounds with limited area. Further studies are needed for investigating the effect of honey on deep and extensive burns.

One of the limitations of this study was that most of the patients did not refer for research evaluations when their wounds healed in the first week of the treatment. This let to the reduction of the samples and continuation of study duration. In addition, since the used honey was tested, and given that it was essential to use one type of honey with the same conditions for all the patients, the study could not be extended.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

Tooran Bagheri: Design and conduct of the research, preparation and confirmation of the article, Mohammadjavad Fatemi: Scientific consult and final confirmation of the article, Seyed Abouzar Hosseini: Pathological evaluations and cooperation in writing the article, Mohsen Saberi: Statistical analysis and cooperation in writing the article, Mitra Niazi: Edition and cooperation in writing the article, Mahnoush Momeni: Scientific consult for performing the study and cooperation in writing the article, Zahra Masoumi: Cooperation in performing the study and writing the article.

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