The effect of propolis and honey lotion on improving diabetic foot ulcers

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ABSTRACT

Background and objective: Diabetic foot ulcer, as one of the most important complications of diabetes, is a major problem in the management of patients with diabetes. In many cases, diabetic wounds do not respond to the usual treatments and lead to amputation. In addition, it imposes a high cost on the patient and the community. Propolis is a product that produced by bees to protect the hive from pathogens. Propolis is a resin material processed using salivary glands from the gums of various plants (some species are more commonly used) by worker bees. Propolis has multiple properties that are useful in the treatment of wounds, including diabetic wounds, due to its anti-inflammatory, antioxidant and antimicrobial properties. The authors have performed a study in order to evaluate the efficacy of propolis on improving diabetic foot ulcers. The comparison between the control group and the intervention group shows that the treatment effect of the intervention group (Propolis) is better. Stusies have been shown that the medicinal properties of honey and propolis. Therefore, the aim of this study was to determine the effect of Propolis and honey lotion on the healing of diabetic foot ulcers.

Materials and methods: In this study, the clinical trials of 60 patients with diabetic foot ulcers were randomly assigned into the study based on the Wenger criteria. Wound swab was done for culture in the both group and antibiotics were given accordingly. Both group had daily dressings. Patients were evaluated for 4 weeks. Wound area measurements were performed on the first day and four weeks after the intervention.

Results: Differences in mean wound size in control and intervention groups prior to intervention were not significant using the Mann-Whitney test (P=0.068). However, changes in the mean wound size before and after the intervention was statistically significant in the two intervention and control groups using the Mann-Whitney test (p. Less than 0.001). This indicates the effectiveness of the intervention in reducing the size of the wound in patients with diabetes. This showed remarkable signs of improvement at the end of the 30th days.

Conclusion: It is expected that using propolis and honey lotion could better improve diabetic foot ulcers and accelerate wound healing.

Introduction

Foot ulcers are major heatlh problems in patients with diabetes mellitus (DM) and more than 60% non-traumatic lower extremity amputations are performed in diabetics, with about 80% due to ulcers [1]. About 10% of people with diabetes have at least one or two causes of foot ulcerations when they are diagnosed with the disease. 41.5% of people with diabetes in Iran have amputations [2]. The incidence of diabetic foot ulcers increases over time, so that in the first year the diagnosis of diabetes it is 27.3%, and after five years of diagnosis, the rate increases to 74.6 [3].

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KEYWORDS

- propolis
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- diabetes
- diabetic foot ulcers

Diabetic foot ulceration (DFU) and DM-related amputations are one of the main causes of infection and disability, which besides its costly nature, is responsible for substantial emotional and physical distress for patients, which reduces the quality of life and care for these individual [4].

In developed countries, up to 22% of all health care resources are spent on diabetic foot care, however, this amount is 40 % in developing countries, where are experiencing more common episodes of DFU [5].

Several factors, such as peripheral arterial disease, peripheral neuropathy, foot deformity, and secondary bacterial infection, play a role in delaying the healing of diabetic foot ulcers. Foot ulcers in diabetic patients are frequently infected and could potentially progress to cellulitis, and if not treated quickly and appropriately, can lead to infection of the blood, gangrene and sometimes amputation [6]. The mortality rate due to amputation is high, ranging from 13-40 % at 1 year to 35-65% at 3 years. Also a 5-year mortality rate of 39–80 % indicates that the total death rate is equal to that of the most life-threatening malignancies [7].

A study by Omsterming et al., in 2007 on patients with limb amputations showed a higher mortality rate compared to deaths caused by colorectal cancer and Hodgkin's lymphoma [8]. Despite standard therapies, the wound often does not heal with standard treatments. Infections around the ulcers can be caused by different organisms and needs to be covered by more types of pathogens. Also, many pathogens are resistant to a variety of antibiotics, so the use of non-antibiotic treatments can be effective in preventing antibiotic resistance and will be more acceptable to the patient [9].

All treatments used to treat foot ulcers have a relative effect on wound healing or preventing amputation. Therefore, it is necessary to evaluate and analyse new non-invasive drugs that have the most therapeutic effect on wound care. In a study conducted by Sobhanian et al. in 2006 with the aim of determining the effect of honey on the treatment of diabetic wounds in people with diabetes, in Jahrom city, the ulcers on the feet of those treated with honey dressings healed faster than those treated with regular dressings [7]. Studies show that propolis contains flavonoids, cinnamic acid, phenolic acids, caffeic acid and several esters are very useful and behaves as free radical propolis has been used for treatment such as viral, bacterial and fungal infection, as anti hyperalgesic [10].

The results of a 2015 study by Ragab et al. on the effect of propolis on diabetic foot ulcers showed that the test group who used propolis dressings had a significant reduction in wound size and depth compared to the control group and 76.6% of patients with foot ulcers healed completely [11]. Studies conducted in Iran have been mostly case reports. In one study, Haghighian et al. used a mixture of heated honey and olive oil and reported a case of healing of diabetic ulcers [1]. In Iran, no large scale study in this area has been carried out so far. In the present research, we are seeking to propose a low-cost wound treatment for the patient to heal aulcers in the shortest possible time, and efforts are being made to reduce the complications of diabetic foot ulcers. Therefore, we sought to investigate the effect of propolis and honey lotion on improving diabetic foot ulcers in a cost-effective manner.

Materials and Methods

This research has been registered in the Iranian Clinical Trial Registration Center with the code IRCT20200113046120N1. This study was a Randomized Open Label Study conducted on 60 patients meeting the inclusion criteria visiting the Wound Care Center, Yara Insitite, ACECR, from August 2019 for 7 months. In this study, we chose the open labeled randomized controlled trial due to some problem such as lack of acceptable topical placebo. So, we lost a number of patients enrolled in control groups. Additionally, there were a few subjects with a great wound area which screwed the mean of wound area in control group. However, our Biostatistician confirmed that there was no statistical difference between two groups significantly.

The inclusion criteria for entering into the study were as follows: having type 1 or type 2 diabetes, aged above 18 years, non-healing single or multiple neuropathic ulcers of at least 6 weeks in duration corresponding to the Wagner's grades 1 and 2 wound classification, HbA1C ≤ 9 and no allergy to propolis or honey. Exclusion criteria for this study were active wound infection with obvious purulent discharge, fever and chills requiring intravenous antibiotics, and clinical or radiographic evidence of osteomyelitis or gangrene, strong clinical evidence of severe circulatory failure of the lower extremities, Ankel Brachial Index ≤ 0.7, drug abuse, and sensitivity to propolis and honey at

the beginning of treatment. The overall aims and objectives of the study were provided to patients and a questionnaire was completed by the researcher to exploit demoghraphic data and wound characteristics. In order to observe ethical considerations after obtaining permission from the ethics committee of Shahid Beheshti University of Medical Sciences, (approval code is IR.SBMU.PGARMACY.REC.1398.031), all patients were informed to participate in the study and during the completion of the questionnaires patients were also assured of confidentiality and anonymity. Eligible individuals after routine testing (including ALP, AST, ALT, K, Na, Cr, Urea, HbA1C, FBS, PT, PTT, ESR, CRP, and CBC), determining-degree of wound grade based on Wagner's classification ,measurement of wound size and depth, and digital photography were entered into the study and were assigned into two randomized control and intervention groups through a quadruple random block.

General therapies, including blood sugar control, antibiotic therapy. In the both group the wounds were initially debrided and treated till there was no sepsis or cellulitis. A normal dressing was covered with sterile gauze in the control group following debridement and cleansing the wound with normal saline and the patient were taught by the researcher how to change the dressing daily. In the intervention group, the layer of lotion that containing Propolis and honey paste was applied and wounds covered by the same way. This lotion was prepared by the medbee in the form of 25 cc lotion. Honey lotion was mixed with propolis in the ratio of one to three.

For the local treatment in intervention group (Propolis), topical application of propolis ointment was used. The ulcers were rinsed with physiological normal saline (sodium chloride solution), and then the propolis ointment was applied. Then gauze pads were placed on the ulcer.

The nessesary instructions were given to patients or their caregivers on how to change the dressing and care the wound by the researcher. The patients were asked to change the dressing routinely every 24-hours and a lotion was given to the patients, and local wound care was provided by the research team during visits to the medical center and by the patients or their caregivers at home on other days.

After the first referral and treatment onset in both intervention and control groups, each patient was referred to the wound center for taking history and accurate examination of the wound; and debridement take place early and completely according on different condition of patient. The average time between visits was 10 days.

The wound was examined and wound size was measured and recorded four weeks before the intervention and four weeks after the intervention. Therefore, the intervention was performed once a day for 4 weeks. Feeding the photography image into the computer, the wound surface area was calculated by Auto CAD software. The data were then analyzed using SPSS software version 22. The the Kolmogorov–Smirnov test was used to determine the normal distribution of all quantitative data. If the data were not normal, non-parametric Mann-Whitney test was used. To test the relationship between the two qualitative variables, the Chi-square Pearson test was used. The data obtained from the study were described as descriptive statistical methods (frequency, percentage and ± mean standard deviation).

Results

We recruited 70 patients (40 men and 30 women) with grade I and II ulcers in the study, and 10 patients were excluded from the study due to ischemia of the foot, active wound infection, osteomyelitis, and living long distances from the research center. The remaining 60 (34 males and 26 females) were divided into two control and intervention groups (30 in each group).

The mean age, duration of the wound, and the duration of diabetes did not differ significantly between the two controls and intervention groups. The two groups were similar in terms of gender frequency, age, previous history wound healing and amputation, blood sugar control, wound, hemoglobin A1C, marital status, level of education, and smoking.

In the control group, 40% were female and 60% were male, and in the intervention group, 46.7% were female and 53.3% were male (P=0.602). The frequency distribution of blood sugar control in the control group was 53.3 insulin and the 63.3 oral drug and in the intervention group was 36.7 insulin and 80 oral drug, which did not differ significantly (P=0.152). The quantitative demographic data and wound characteristics of patients are given in **TABLE 1**. No significant differences were observed between the two groups before the intervention. The effectiveness of Propolis and honey lotion on the healing of

diabetic foot ulcers and reduction in the wound area was investigated in two groups of cases and control before and after the intervention.

Prior to the intervention, the wound area was 5.26 ± 6.17 in the control group and 4.39 ± 4.37 in the intervention group and the area of the wound after the intervention was 4.64 ± 4.86 in the control group and 1.50 ± 2.10 in the intervention group. The results show that in the intervention group, the difference between the mean dimensions of the wound prior to and after the intervention is significant using the Wilcoxon test with a P value ≤ 0.001. But in the control group, the difference between the mean dimensions of the wound size before and after the intervention using the Wilcoxon test with a P value ≤ 0.001 is also significant. The difference in mean wound size between control and intervention groups before the intervention was not significant using Mann-Whitney test (P=0.068). However, after the intervention, the difference between the mean wound dimensions in the control and intervention groups was significant using the Mann-Whitney test with a P value ≤ 0.001. The above results confirm the effect of intervention on the use of propolis and honey lotion on wound dimensions in patients with diabetes (**TABLE 2**). Also, the mean variations in wound size before and after the intervention have a statistically significant difference between the two groups of intervention and control. This indicates the effectiveness of the intervention in reducing the size of the wound in patients with diabetes (**TABLE 3**). Proportion of patients with wound area reduction greater than or equal to 50% at the last assessment.

TABLE 1: Demographic and wound characteristics.

Variable	Study group	Control group	p-value
Mean age	8.68 yr ± 56.73	6.85 yr ± 54.20	p=0.215
Gender%	53.3% male	60 male%	p=0.602
	46.7% female	40 female%	
Marital status%	Married %76.7	Married 70.60%	p=0.836
	Single=23.3%	Single=29.4%	
Smoker%	56.70%	52.30%	p=1.00
Blood sugar control Drugs%	36.7% Insulin	53.3 Insulin	p=0.152
	80% oral medication	63.3% oral medications	
Wagner1	1	1	P=1.00
Wagner 2	29	29	P=1.00
Diabetes duration (year) Previous wound healing	5.1 ± 11.83	5.8 ± 11.56	P=0.381 p=0.519
	76.7% yes	83.3% yes	P=0.381 p=0.519
Previous amputation	36.7% yes	23.3% yes	p=0.399

TABLE 2: Mean and standard deviation of wound area.

	Study group		**P-value**
	Control	**Intervention**	
Prior to intervention	5.26 ± 6.17	4.19 ± 4.73	0.068
After intervention	4.64 ± 4.86	2.10 ± 1.50	P<0.001

TABLE 3: Wound dimensions difference (Reduction ulcer size) before and after the intervention in two intervention and control groups.

Study group		P-value
Intervantion	Control	
2.69 ± 2.77	0.76 ± 1.27	0.029

Discussion

One of the most important findings of the present study was the improvement of diabetic foot ulcers using Propolis and honey lotion, which showed a positive effect of propolis and honey lotion in the intervention group compared to the control group. In other words, after four weeks of intervention, the size of the wound in the intervention group significantly reduced compared to the control group.

In 2016, Atman et al. conducted a clinical trial at Jabir Diabetes Center in Sudan on diabetic patients. In this study, 86 patients with type 1 and type 2 diabetic foot ulcers were divided into two groups, of which 43 patients were in the experimental group and 43 patients were in the control group. The lotion containing propolis and honey was applied to the wound as a dressing. The dressing was applied daily for up to a week or more depending on the status of the wound. The results of the study showed that the wound healed in the experimental group after 11.5 weeks and the healing was attained in the control group after 15 weeks. The difference between the above study with that of ours is that in the present study, patients were followed only in 8 weeks and the sample size was less and also wounds in the intervention group improved more than the control group, while in the study of Atman et al. the duration of treatment was reduced (11). A similar study in Australia by Hansha et al. in 2014 examined the effect of propolis (alone) on diabetic foot ulcers, with wound healing in the propolis group 1 to 3 weeks and overall improvement4 weeks later.

The results of this study showed that the use of propolis compared to routine wound care was associated with a significant improvement in diabetic foot ulcers. In this study, patients were classified into two groups of control and intervention, and for each group, two subcategories of antibiotic and antibiotic-free treatment (4 groups in total) were considered (control group and antibiotic group 66 patients, antibiotic-free control group 18 patients, Propolis group with antibiotics(16 patients), antibiotic-free propolis group (8 patients) (6). Our study is different from the so called research in that 4 groups were considered for comparison and propolis was used alone for dressing in the Australian study, while in the present study, both propolis and honey lotion was were used. A study in Iran by Haghighian et al. entitled "treatment of diabetic foot ulcer with propolis and olive oil: a case report"was conducted in the Endocrinology and Diabetes Clinic of Tabriz with on a toe ulcer with 2 cm^2 wound size and a depth of 1 cm and the patient's dressing was changed every 12 hours. After one week of treatment, new tissue was seen in the wound and the ulcer wound was completely lealed within two weeks [12].

In 2014, one study carried out in Greece by Karamatos et al. where patients with diabetic ulcers were divided into two groups: honey treatment and traditional medicine therapy. The group of patients treated with honey did not need antibiotic treatment, while patients in the traditional medicine treatment group underwent antibiotic therapy [13]. The findings showed that there was no significant difference between the two groups in terms of wound healing, which contradicts with the findings of the present study. The reason for the discrepancies may be attributed to the lack of antibiotic use in both groups. The limitation of this study was the lack of cooperation of patients to refer the clinic on time in order to the ulcers be visited and examined and the lack of complete care of the wound by patients and ignoring the recommendations for wound healing. Based on the findings of this study, nurses can use this dressing to treat patients' diabetic wounds in the internal medicine and orthopedics departments and diabetes units. It is recommended that a study with the same subject be performed on wounds of other grades, and that a similar study be performed with a longer follow-up period.

Conclusion

The present study was conducted as a clinical trial. According to the study, the effect of Propolis and honey lotion on the healing of diabetic foot ulcers was greater than that of sterile gauze dressings. Due to the effect of modern dressings in reducing the healing time of wounds and the need to use these dressings by experienced and trained staff, the use of Propolis and honey lotion dressing is recommended.

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wounds were initially debrided and treated till there was no sepsis or cellulitis then a thick layer of propolis and honey paste was applied. Wounds were covered with sterile gauze and wrapped with non-elastic crepe bandage. In the control group after debridement dressing done using tap water and wounds covered by the same way.

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