ORIGINAL ARTICLE

A Randomized, Controlled Clinical Trial of Honey-Impregnated Dressing for Treating Diabetic Foot Ulcer

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Abstract

Objective: To investigate the effect of Beri-honey-impregnated dressing on diabetic foot ulcer and compare it with normal saline dressing.

Study Design: A randomized, controlled trial.

Place and Duration of Study: Sughra Shafi Medical Complex, Narowal, Pakistan and Bhatti International Trust (BIT) Hospital, Affiliated with Central Park Medical College, Lahore, from February 2006 to February 2010.

Methodology: Patients with Wagner's grade 1 and 2 ulcers were enrolled. Those patients were divided in two groups; group A (n=179) treated with honey dressing and group B (n=169) treated with normal saline dressing. Outcome measures were calculated in terms of proportion of wounds completely healed (primary outcome), wound healing time, and deterioration of wounds. Patients were followed-up for a maximum of 120 days.

Results: One hundred and thirty six wounds (75.97%) out of 179 were completely healed with honey dressing and 97 (57.39%) out of 169 wtih saline dressing (p=0.001). The median wound healing time was 18.00 (6 - 120) days (Median with IQR) in group A and 29.00 (7 - 120) days (Median with IQR) in group B (p < 0.001).

Conclusion: The present results showed that honey is an effective dressing agent instead of conventional dressings, in treating patients of diabetic foot ulcer.

Key Words: *Wound dressing. Beri honey. Diabetic foot ulcer. Wound healing time.*

INTRODUCTION

Diabetic foot ulcer is one of the main reasons of morbidity in diabetic patients, and it accounts for about 50% of non-traumatic amputations throughout the world.[1] Wound dressing is an integral part in the management of diabetic foot ulcer.

Honey dressing is one of the emerging options in this context, because there is growing body of literature which reflects increasing evidence to explain the multiple effects of honey originating from variety of bioactive compounds found in honey.[2] In addition to its broad spectrum bactericidal effect, honey also promotes debridement and reduces inflammation. Activation of immune cells and reduction of malodour are also attributed to honey dressing.[3,4] Presently, a range of approved honey dressings are available from several manufacturers.[4] It has been shown that out of 109 evidence-based conclusions, topical application of honey was effective in reducing wound healing time as compared to film or gauze-based dressings in superficial and partial thickness burns.[5] Manuka honey-impregnated dressings were effective even in recalcitrant cases, which had already undergone continuous dressing changes, local debridement therapy, maggot treatment, use of vacuum assisted dressings, and systemic antibacterial therapy.[6]

Although, there are some clinical trials reported previously which evaluated the effects of honey in diabetic ulcer but the number of patients enrolled and the study design were questionable.[7-9] Large and better designed Randomized Controlled Trials (RCTs) are awaited in order to provide appropriate levels of evidence of clinical efficacy of honey in treating diabetic foot ulcer. Therefore, this trial was conducted to evaluate the role of honey-impregnated dressing in treating diabetic foot ulcer of Wagner grade1 or 2 in comparison with normal saline dressing.

METHODOLOGY

This study was conducted in the Department of General Surgery, Sughra Shafi Medical Complex, Narowal, Pakistan and Bhatti International Trust (BIT) Hospital, affiliated with Central Park Medical College, Lahore, Pakistan. It was a 4-year, prospective, parallel-group, RCT which was started from 15 February, 2006 to 15 February, 2010. Each patient was briefed about the study protocol and a written consent was taken. A proforma was filled either by the patient or his/her caretaker. Six hundred and ten patients were assessed for eligibility for the study. All patients ≥ 18 years of age with diabetic foot ulcer (Wagner's grade 1 or 2) were

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selected for the study. Patients with diabetic foot ulcer of Wagner's grade 3 - 5, Ankle Brachial Pressure Index (ABPI) < 0.7, venous ulcers or malignant ulcers, uncontrolled diabetes i.e. HbA1c > 7%, patients with > 1 ulcers, patients with haemoglobin < 10 g/dl and patients with local signs of infection (presence of pus, initial culture positive) in the wound were excluded from the study.

Three hundred and seventy five patients, with Wagner's grade 1 and 2 ulcers, met the eligibility criteria and were enrolled in the study. These patients were divided in two groups; group A (n=195) treated with honey dressing and group B (n=180) treated with normal saline dressing and grouping was done by simple randomization method (computer-generated random numbers). In present study, principal investigator generated the random allocation sequence with the help of information technology person and enrolled the participants. The patients were assigned to intervention by any member of surgery department; which might be the principal investigator himself or any other team-member (consultant/ registrar / sister in-charge). They could only select patient for eligibility criteria or intervention, but the selection of patient as to whether he/ she will receive honey dressing or normal saline dressing, was decided on computer-generated random number.

A sample size of 258 diabetic foot ulcer patients was required, 129 in each group, to detect a clinically important difference of 17% between groups in treating diabetic foot ulcer between two groups with 80% power and a 5% level of significance. This 17% difference represents a 52% successful treatment rate using honey impregnated dressing and 35% successful treatment rate using normal saline dressing.

Table I: Baseline characteristics of all patients .

Characteristics	Honey treated group (n=179)	Saline treated group (n=169)	p-value
Age (years), Median (IQR)	54 (47-64)	54 (47-63)	0.05*
Gender			
Male, n (%)	103 (57.54)	85 (50.29)	0.17**
Female, n (%)	76 (42.46)	84 (49.71)	
Wound size			
≤ 5 x 5 x 2 cm, n (%)	92 (51.3)	90 (53.2)	0.73**
> 5 x 5 x 2 cm, n (%)	87 (48.6)	79 (46.7)	

*# Values are expressed as Median (IQR); * Mann-Whitney U test, **Chi-square test.*

We used the following formula for calculating sample size.

$$n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \{(p1\ (1-p1) + (p2\ (1-p2))\}] / (p1 - p2)^2$$

Based on above formula, the calculated sample size was 129 for each group. Therefore, total sample size required was 258. By assuming 10% dropout rate, recalculated sample size was 143 in each group, by using the formula: N1 = n / (1-d).

Where, N = adjusted sample size, d = dropout rate, n = calculated sample size.

However, more subjects were enrolled than the calculated number (195 subjects in experimental and 180 subjects in control group) for considering potential dropouts.

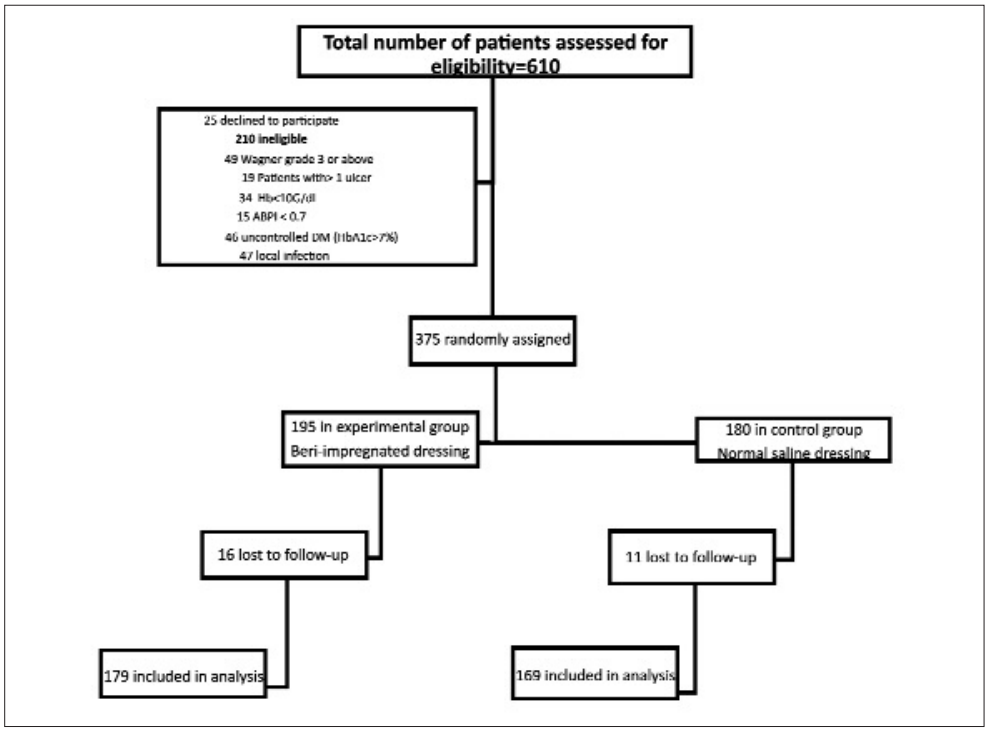

Figure 1: Enrolled patients and their follow-up.
ABPI = Ankle brachial pressure index; DM = Diabetes mellitus; HbA1c = Glycated haemoglobin; Hb = Haemoglobin.

Three hundred and forty eight patients (n=179 in group A, n=169 in group B) completed the study; therefore, data was analysed for only those patients who completed the study. Their gender distribution is shown in Table I. Beri (*Ziziphus jujuba*) honey was used in the study that was provided by the Department of Microbiology, University of Health Sciences, Lahore, Pakistan. The honey was collected from district Karak, Pakistan. The honey was kept in dark, at room temperature (20 - 30°C). All honey samples were gamma irradiated before clinical application from Pakistan Radiation Services (PARAS), Lahore, Pakistan. The honey samples were checked for antibacterial efficacy by Agar well diffusion

assay and only those samples were used in the trial which showed zone of inhibition ≥ 18 mm at 50% w/v dilution against ATCC 25923 *Staphylococcus aureus*.

All patients were admitted in surgical ward for at least first 2 dressings. Enrolled patients and their follow-up are summarized in Figure 1, while baseline characteristics are summarized in Table I. Twenty seven patients (10 males, 17 females) could not continue the study at various stages due to different reasons.

Wound was washed before dressing with normal saline to remove debris and was measured by using ruler technique.[10,11] The measurement was performed in centimetres (cm) and in three dimensions i.e. length (L), width (W) and depth (D) of wounds (Table I). Length was measured while considering heel at 12 O' clock and toes at 6 O'clock position. The wound measurement was repeated every 7 days, if it was not healed completely. Wound sizes ranged from 2 x 1 x 0.3 cm to 10 x 8 x 5 cm and these patients were divided according to their wound sizes, for comparing baseline characteristics, into two groups; patients having wound size > 5 x 5 x 2 cm and having wound size ≤ 5 x 5 x 2 cm.

Wound dressing was sealed with 2nd layer for protection. Dressing was performed twice daily for three days and then, depending on the wound condition, either once/ twice daily or after 48 hours. Dressing was performed in the hospital by doctor on duty or nursing staff, properly trained in dressing protocol. Dressing was performed, after the discharge of patient, by nursing staff if patient could walk in easily or by the attendant of the patient who was trained to perform dressing and, in that case, material was provided to the patient. Off-loading was done by using full-boot cast, special shoes or crutches according to the situation. Debridement of wound was done when required and most of the time it was performed in outpatient department under local anaesthesia or without anaesthesia, if patient was not feeling pain.

Primary outcome was defined as complete healing of the wound. Secondary outcomes were wound healing time, side effects of dressing methods, patients' satisfaction and deterioration of wound. Deterioration of wound was defined as any wound which shifted to Wagner grade 3 or above, signs of local or systemic infection and the wounds necessitating some kind of amputation. All patients were followed for a maximum of 120 days or earlier if wound was healed. Wound healing was considered when there was closure of the wound with complete epithelialization and no discharge.

The study protocol was approved by the institutional review boards and ethical committees of both institutes.

Statistical analysis was carried out on Minitab 16. Normal distribution of the data was checked by Kolmogorov-Smirnov test and if p-value was ≤ 0.05, the data was considered to be non-normally distributed. Median with Interquartile Range (IQR) was given for non-normally distributed quantitative variables. Qualitative variables like success and failure rates of both types of dressing were represented by frequencies and percentages. Chi-square test was used for comparing number of subjects completely healed, not completely healed and deteriorated in both study groups.

To examine age differences and differences in duration of wound healing in honey and saline-treated dressing, Mann-Whitney U-test was used, and p-value ≤ 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the study subjects are shown in Table I. Out of 375, 27 patients, 16 from honey treated and 11 from saline treated group, were lost to follow-up (Figure 1). In each group, patients were followed-up for a maximum 120 days.

One hundred and thirty six (75.97%) wounds were completely healed with honey dressing and 97 (57.39%) with saline dressing, while the number of incompletely healed wounds, was significantly less in honey treated group as compared to saline treated group, 32 (17.87%) vs. 53 (31.36%), respectively (p = 0.001, Figure 2). Mean wound healing time was 18.00 (6 - 120) days in group A and 29.00 (7 - 120) days in group B (p < 0.001, Table II).

No serious side effect was observed in both groups. Three patients from group A complained of mild itching at the start of the treatment and those symptoms

Table II: Differences in healing time of wounds among the two groups.

	Wound healing in honey treated patients (n=136)	Wound healing in saline treated patients (n=97)	p-value
# Duration (days), median (IQR)	18.00 (6-120)	29.00 (7-120)	< 0.001*

*# Values are expressed as Median (IQR), *Mann-Whitney U test, p-value < 0.05 was considered as significant.*

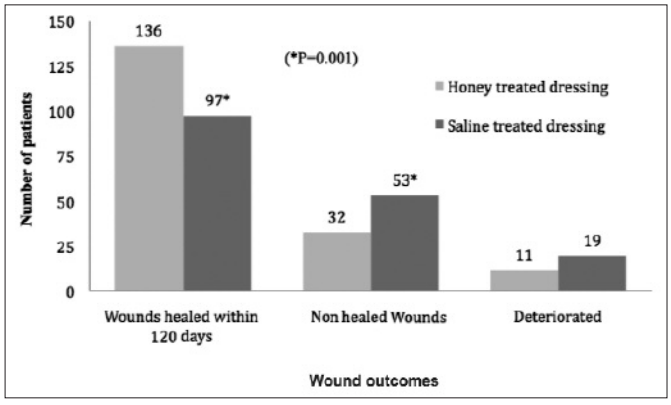

Figure 2: Comparison of honey and saline treated dressing in both study groups. *Chi-Square test, p-value ≤ 0.05 was considered as significant.

subsided after 48 hours. No patient left the study on account of side effects. Most of the patients, of both groups, showed satisfaction regarding their management of foot ulcer, whether treated by honey dressing or conventional dressing.

DISCUSSION

The present trial shows that honey-impregnated dressing significantly reduced the duration of wound healing in diabetic foot ulcer patients. The reasons of this outcome could be the potent anti-inflammatory, anti-bacterial activity and increase in growth factor release and debriding effects of honey.[12,13] Honey also increases lymph flow in wound which is helpful for removal of toxins.[13] Previously, a clinical study showed the benefits of honey dressing in diabetic foot ulcer in terms of easy application, better outcome and patients' satisfaction.[14] Another study (n=30) found that honey dressing was more effective as compared to povidone-iodine dressing regarding mean healing time.[7] The number of patients in the later study were few.[7] Honey was not gamma irradiated and honey's anti-bacterial activity was not determined *in vitro*. A study in Egypt also showed clinical and cost effectiveness of clover honey in the treatment of diabetic foot ulcer.[8] However, the number of patients enrolled in that study was small (n=30) and honey's anti-bacterial activity was not standardized before clinical application. In a prospective pilot study, Pedyphar (ointment containing natural royal jelly honey and panthenol) was found to be effective in treating diabetic wounds.[9] Similarly, Hammouri found that honey dressing was more effective in the management of diabetic foot ulcer in comparison with normal saline and povidone-iodine dressing.[15] Beneficial effects of honey on diabetic foot were also observed in a study conducted at Ayub Medical College, Abbottabad, Pakistan.[16] Molan in his review article, had shown the effectiveness of honey in the management of wounds.[12] In a recent randomized double-blinded study, mean wound healing time was less in manuka-impregnated dressing as compared to traditional dressing (31 ± 4 vs. 43 ± 3 days).[17] Most of the previous studies were not well-designed and small number of patients were enrolled in the studies.

In the current study, the number of enrolled-patients was good enough and the study continued for 4 years. The patients' basic characteristics were almost identical and the study was conducted in two centres. We could not identify the cause(s) of delayed wound healing and deterioration of wound in certain patients of both groups.

There were some limitations in the study. Firstly, the study subjects mostly belonged to lower socioeconomic class. Secondly, the wound healing was observed only clinically, and we neither isolated the microorganisms nor studied for histopathological aspects of wounds frequently due to lack of facilities. Thirdly, the study could not be blinded because honey has specific odour and colour. Moreover, honey stains the wound margins.

Although, several studies have shown the effectiveness of honey dressing in diabetic foot ulcer, still many clinicians are reluctant to use it in their clinical practice. The reason may be lack of strong level one evidence of the beneficial effect of honey on diabetic foot ulcer (although no dressing method has level one evidence), personal bias, lack of knowledge about the full spectrum of honey's anti-bacterial and wound healing potential.

CONCLUSION

Honey dressing was more effective in terms of number of ulcers healed and time to healing, in comparison with traditional normal saline dressing in diabetic foot. However, there is still a need for more well-designed, large and double blinded RCTs for corroborating the findings of the present study.

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