COMPARISON BETWEEN TOPICAL HONEY AND MAFENIDE ACETATE IN TREATMENT OF BURN WOUNDS

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SUMMARY. Histological and clinical studies of wound healing were performed in comparable cases of fresh partial-thickness burns treated with honey dressing or mafenide acetate in two groups of 50 randomly allocated patients. Of the patients with honey-treated wounds, 84% showed satisfactory epithelialization by day 7 and 100% by day 21. In wounds treated with mafenide acetate, epithelialization occurred by day 7 in 72% of cases and in 84% by day 21. Histological evidence of reparative activity was observed in 80% of wounds treated with honey dressing by day 7 with minimal inflammation. Fifty-two per cent of the mafenide acetate treated wounds showed reparative activity with inflammatory changes by day 7. Reparative activity reached 100% by day 21 with the honey dressing and 84% with mafenide acetate. Thus, in honey-dressed wounds, early subsidence of acute inflammatory changes, better control of infection, and quicker wound healing were observed, while in mafenide acetate treated wounds a sustained inflammatory reaction was noted even on epithelialization.

Keywords: burn wounds, mafenide acetate, honey

Introduction

In the developed world, burn wounds are often covered temporarily with xenograft or preserved homografts. These are not available and too costly for use in developing countries such as Iran. Hence, the continuing need of a local application for wound treatment - one that is cheap, easily available, and effective in preventing infection, decreasing fluid loss, and enhancing epithelialization - is commonly perceived by surgeons treating burns in the developing world.

One such application is honey, which has been used for medical purposes since ancient times. Topical application of honey to burns and other wounds has been found to be effective in controlling infection and producing a clean granulating bed.[1-4]

Honey was used topically in Ayurvedic medicine in 2500 BC, and the Egyptians, Greeks, and Romans used it as well. Hippocrates prescribed honey for various purposes, including the management of wounds and gastritis. Honey is non-irritant, non-toxic, easily available, and cheap. Honey's wound-healing properties are also mentioned in the Koran and the Bible.[5]

Mafenide acetate is a topical agent with a broad spectrum of activity because of its sulpha moiety. It is particularly useful against resistant *Pseudomonas* and *Enterococcus* species. All topical antibacterials appear to be equally effective in controlling burn wound infection when applied early, before heavy colonization has occurred. Only mafenide acetate is able to penetrate the eschar, and it is the only agent capable of suppressing dense bacterial proliferation beneath the eschar surface. Mafenide acetate is especially effective against *Clostridia*. The main disadvantage of mafenide acetate is its strong carbonic anhydrase inhibition, which interferes with renal buffering mechanisms. Bicarbonate is wasted, chloride is retained, and the resulting hyperchloraemia is compensated for by an increase in ventilation and subsequent respiratory alkalosis. It can also cause an allergic rash, with painful application on the skin, for example in second-degree wounds. The primary disadvantages of silver sulphadiazine are its lack of eschar penetration and the development of bacterial resistance to its antibacterial action. If bacterial density in the wound increases while silver sulphadiazine is being used, the agent must be discontinued and mafenide acetate, which penetrates the eschar, substituted instead. Of greater concern is the increasing development of Gram-negative bacterial resistance to this agent. Mafenide acetate is the most effective agent in its ability to penetrate burn eschar, but silver sulphadiazine penetrates thick es-

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char less readily than some other agents, including mafenide acetate. Mafenide acetate also possesses very potent antibacterial properties and is particularly effective against Gram-negative organisms. The agent also possesses certain antifungal properties.

For these reasons, mafenide acetate is typically reserved for small full-thickness injuries.[6,7] This agent is used primarily as a second line of defence or as a primary treatment for small and infected wounds. We chose mafenide acetate for comparison with honey because of its penetration to the eschar and its more potent antibacterial properties, and in order to make a better evaluation of these properties. An easily available, cheap dressing material that is able to limit infection still remains an enigma. This study reports a prospective randomized trial carried out to make a clinical and histochemical comparison of burns treated with honey dressing and with mafenide acetate in order to assess their wound healing rates.

Materials and methods

A total number of 100 cases of superficial thermal burns involving less than 40% of the total body surface area (TBSA) treated in our unit over the period 20 March 2010 to 20 March 2011 provided the material for this study. The prospective randomized protocol had been previously approved by the Tabriz University of Medical Sciences Ethical committee. Informed consent was obtained from the patients or from the patients' parents in the case of children. After initial management, patients were allocated at random to two groups. In group I (n = 50) pure, unprocessed, undiluted honey obtained from hives was applied in quantities of 16-30 ml, depending on the size of the burn, to the burn surface after this had been washed with normal saline. In group II (n =50) the wounds were covered with pieces of gauze impregnated with mafenide acetate after being washed with normal saline. These were replaced every day. The wounds were inspected every two days until healing.

In group I, after spreading of the honey, the wound was covered with dry sterile gauze and bandaged. Honey was applied on alternate days and, at the time of dressing, the amount of discharge, any foul smell, the type of granulation tissue and signs of healing, and the time taken for healing were noted. The wounds were observed for evidence of infection, excessive exudate, or leakage until healing. The time taken for healing was recorded in both groups. Bacterial cultures and sensitivity determinations were made from the swabs taken from the surface of the wounds and blood cultures on admission and on days 7 and 21 in all cases or until the wounds healed. Biopsies were collected from the wounds in both groups on admission and on days 7 and 21. After inducing local anaesthesia with 1% lidocaine infiltrated using a 26-gauge needle, biopsies were taken from the wound surface to include 3 mm depth of the wound and a 3 mm area of normal skin. The biopsies were transferred to 10% normal saline and then fixed, sectioned, and stained with haematoxylin, eosin, and fungi by periodic acid-Schiff stain. The sections were viewed and photographed at 40x and 70x magnification. The definitive diagnosis of burn wound infection was made only by wound biopsy, the single important sign of burn wound infection being the presence of microbial organisms in unburned viable tissue. The remainder of the biopsy sample was sent to the microbiology laboratory for quantitative culture and antibacterial sensitivity tests.

The recovery of more than 10^5 organisms per gram of tissue is highly suggestive of burn wound infection and a bacterial density greater than 10^5 organisms per gram tissue with a concomitant positive blood culture with the same organism is a relatively reliable indicator of wound sepsis. The results with regard to clinical assessment, bacteriological studies, and histology on the day of administration and on days 7 and 21 in both groups were analysed using the chi-square test. The level of significance was set at 0.05.

Results

Of the 100 patients, 52 were female and 48 male. The youngest was 3 years old and the oldest was 70. Eighty patients were in the age group 21-30 years. The burn surface area ranged from 10 to 40% TBSA. The mechanism of injury was flame burn in 85 patients and scalds in 15 patients (*Table I*). The wounds in both groups were observed clinically every two days. Among the 50 patients treated with honey dressing, exudative fluid was present from the raw areas on day 7 in four wounds, while the remainder presented healthy granulation. In group II

Table I - Patient data

Variable	Group I (patients treated with honey dressing)	Group II (patients treated with mafenide acetate dressing)
Number of patients	50	50
Male	23	25
Female	27	25
Age (yr)		
Mean	25.2	26.4
Range	3-68	5-70
Causes of injury		
Flame	43	39
Scald	7	11
Burn surface area (%)		
Mean	14.5	15.6
Range	10-40	10.5-40

(mafenide acetate), the wounds presented exudation of fluid from the raw areas in 8 cases and were dry in the other 42, with eschar formation in 40 patients. The eschar had to be removed and dressing was continued until granulating surfaces were obtained In honey-treated wounds, there was no eschar and the margins of the wounds were free of oedema. On day 21, in the honey-treated group, only one patient had fluid exudate, compared to eight in wounds treated with mafenide acetate. Clinical signs of wound infection and the presence of pus and slough in the wounds were observed in two patients on day 7 in each group and by day 21 in 0 and 10 patients respectively in the honey and the mafenide acetate groups. Clinical evidence of granulation tissue formation and epithelialization of raw areas were observed in 42 patients in group I and 36 patients in group II by day 7. In honey-treated patients, all the wounds healed by day 21 (100%) compared to 42 patients (84%) ($p < 0.001$) in the mafenide acetate treated group (*Table II*).

Table II - Time required for healing in patients with burns

Time required for healing (days)	Group I (honey dressing)	Group II (mafenide acetate dressing)
0-7	42	36
8-10	4	2
11-15	2	2
16-21	2	2
22-30	0	8
Total	50	50
Chi-square test: $p < 0.001$		

On the day of admission, wound histology in both groups showed necrotic changes both in the epidermis and the dermis, with the formation of blisters, coagulation necrosis, and, in places, dermo-epidermal disruption. In 40 of the honey-treated patients (80%), the changes reverted by day 7 with diminution of acute inflammatory changes, control of microbial infection, and early reparative signs, such as reactive changes with slight epithelial hyperplasia covering the granulation tissue with little perivascular inflammation). Six patients (12%) presented no evidence of granulation tissue and a lack of reactive changes in the epidermis. In four cases (8%), histological evidence of infection in the form of inflammatory cells, bacterial colonies, and abscesses in the subcutis were observed. By day 21 all the patients in the honey-treated group showed epithelialization and granulation tissue formation.

In comparison, in the mafenide acetate treated group, 26 wounds showed reparative changes, such as normal maturation, normal honey layer, and intact basal pigmentation) and granulation formation (52%, no evidence of granulation and reactive changes in two (4% per cent) and in 22 wounds evidence of infection was present on day 7. By day 21, 42 patients showed epithelialization of wounds and eight had wound infection, which subsequently healed between 25 and 30 days (*Table III*). Pathological examination showed reactive changes with slight epithelial hyperplasia covering the granulation tissue, with little perivascular inflammation, as observed on day 7 in honey-treated wounds, and a lack of reactive changes in the epidermis, with normal maturation, a normal horny layer, and intact basal pigmentation, coupled with an absence of granulation tissue in the dermis in the mafenide acetate treated groups. Thus, in the honey-treated group, reparative activity was found in 40 wounds by day 7 and in all 50 wounds by day 21, while in the mafenide acetate treated group, reparative activity was noted in 26 patients by day 7 and in 42 patients by day 21 ($p < 0.005$, significant). Eight patients showed no reparative changes and these patients presented infections.

Table III - Burn wound healing with honey and with mafenide acetate

Number of patients	Group I		Group II	
	Day 7	Day 21	Day 7	Day 21
Clinical evidence of wound healing	42 (84%)	50 (100%)	36 (72%)	42 (84%)
Histopathological evidence of wound healing	40 (80%)	50 (100%)	26 (52%)	42 (84%)
Chi-square test: $p < 0.005$				

The acceleration of epithelialization in the honey-treated group appeared to occur between days 6 and 9, both clinically and histologically. The bacterial cultures from the wound swabs collected on admission showed a positive swab culture in 46 wounds, with four sterile, in group I (the honey-treated group), while blood cultures and tissue biopsies were negative. By day 7 the blood culture and tissue biopsies were negative in 34 wounds and by day 21 the culture swab was positive in only one patient. In the mafenide acetate treated group, 44 patients showed positive swab cultures at the time of admission, six were sterile, and blood cultures and tissue biopsies were negative in all patients. The wounds became sterile in 38 wounds by day 7, twelve continuing to be positive and with one positive blood culture and tissue biopsy, treated with antibiotics and wound excision. By day 21, only six wounds showed positive swab cultures and 44 were negative ($p < 0.001$), and blood cultures and tissue biopsies were negative in all patients. The organisms isolated in positive swab cultures in both the groups were *Staphylococcus* coagulase positive, *Streptococci*, *Klebsiella*, *Pseudomonas*, and *B.*

proteus. All the wounds of patients treated with honey healed by day 21 and no skin grafting was needed by any patient. In the mafenide acetate treated group, eight patients' wounds converted to deep wounds and required skin grafting ($p < 0.05$, significant).

No irritation, allergy, or other side effects were observed in any patient in either group. The subjective relief of pain was better in the honey-treated group. Hospital stay in the honey-treated group was 22 ± 1.2 days versus 32.3 ± 2 days in the other group ($p < 0.005$, significant). At three-month follow-up, there was one contracture in group I (neck) and five in group II, which responded to physiotherapy (this difference is significant). *Figs. 1* and *2* show the clinical appearance of burns in mafenide acetate and honey-treated wounds on day 7.

Discussion

Epidermal regeneration of a wound is a complex process in which residual epithelial cells proliferate in an integrated manner to form an intact epidermis. In first- and second-degree burns, there are still a number of epithelial cells which survive in hair follicles and sweat glands. Prevention of infection is the primary aim of burn wound treatment so that there is optimal regeneration of these cells, and a moist environment is best suited for epithelialization and wound healing.

It has been held that honey's healing effect could be due to various physical and chemical properties. Honey's high osmolality and acidity are among the physical characteristics that contribute to its antibacterial activity. Hydrogen peroxide, volatiles, organic acids, flavonoids, beeswax, nectar, pollen, and propolis are important chemical factors that give honey its antibacterial properties[6] and these properties have been confirmed in numerous studies.[5,8,9] In addition, honey contains catalase, which originates from pollen. The level of hydrogen peroxide in a given honey is determined by its relative levels of glucose oxidase and catalase.[10] Likewise, most phytochemical factors withstand dilution in wound fluids. Overall, honey has a restraining influence on the growth of most bacteria, including some methicillin-resistant *Staphylococcus aureus* strains and this makes honey attractive for the prevention and treatment of infection both in chronic wounds[11,12] and in acute wounds. Unlike most conventional local chemotherapeutics, honey does not lead to the development of antibiotic-resistant bacteria, and it may be used continuously.[5,12] Rapid clearance of infections, rapid suppression of inflammation, minimization of scarring, and stimulation of angiogenesis as also of tissue granulation and epithelium growth have been reported with honey dressing.[6,7,11,12]

All these physical and chemical factors give honey unique properties as a wound dressing. Topical application of honey has long been recognized as effective in controlling infection and producing a clean granulating wound bed. Because of its high viscosity it forms a physical barrier, creating a moist environment which appears to be helpful and accelerates wound healing. Its antibacterial effects are attributed to an inhibine factor which seems to be effective through hydrogen peroxide.[13] The enzyme catalase present in honey has an antioxidant property[14] and honey may therefore have a role as an anti-oxidant in thermal injury.[15] Honey's nutrient contents, such as laevulose and fructose, improve local substrate supply and may help promote epithelialization. All these factors contribute to honey's antibacterial activity.

Finally, several phytochemical factors for antibacterial activity have been identified in honey.[11,16] In the present study, wounds treated with honey showed early control of infection, and the wound-healing process was accordingly accelerated. Clinically, this was found to be taking place between days 6 and 9. By day 4, in the honey-treated group, the wound margins showed no oedema; the exudate was reduced by day 7, and the wounds were showing epithelialization in 84% of the patients.

In the present study, honey of multifloral origin was used after confirmation of its sterility. Although measurement of the inhibine count[17] and a check whether the honey passed through filter paper[18] had been advised, we did not find this necessary because bacterial cultures (before and after treatment) showed that honey inhibited the growth of organisms. Some studies reported that honey had a better epithelialization effect than other topical antimicrobial agents in burn wounds.[19] In our study, the pathological score[20] of the honey group was better than that of the mafenide acetate group both 14 and 21 days after burn ($p < 0.05$, significant). Rapid desloughing, the early appearance of healthy granulation tissue, early epithelialization, and accelerated wound healing have all been reported with use of the honey dressing. Honey also contains a thermoliable factor, inhibine, related to honey's plant source.

Mafenide acetate is a sulphonamide with quick and deep penetration into burn eschar and excellent antibiotic properties.[7,21] These characteristics make it ideal for areas of deep burns. Its antibiotic cover includes both Gram-positives and Gram-negatives, with minimal antifungal activity.[22] In the patients treated with mafenide acetate, fluid exudation lasted longer, and 60% of the wounds presented eschar formation which needed escharectomy. When granulation appeared the wounds healed but in eight patients split-thickness skin grafts were needed. Histologically, early attenuation of acute inflammatory changes, control of infection, and early reparative activities were seen more in the honey-treated group than in that treated with mafenide acetate. The bacteriological studies confirmed that by day 21 none of the honey-treated patients, except for one case, showed any bacterial growth, compared to

the mafenide acetate treated group, in which six patients showed positive culture. Surface cultures of the burn wound may be helpful as regards epidemiological information but are not always useful in making the diagnosis of invasive infection. The histological examination of burn wound biopsies is the most rapid and reliable means of detecting invasive burn wound infection as compared to surface cultures of the burn wound including qualitative counts. The surface cultures of burn wounds correlate poorly with the presence of invasive burn wound infection as detected by histopathology.[3,24]

Conclusion

In conclusion, honey, as a topical agent, does not adhere to the burn surface. Compared to mafenide acetate, honey appears to have better results as a topical treatment for superficial burns because it favours fast re-epithelialization and decreases inflammatory reaction. In addition, treating superficial burns with honey is cost-effective because it shortens the duration of treatment.

This prospective study shows that honey caused wounds to heal earlier than those treated with mafenide acetate by making the wounds sterile thanks to its antibacterial effect. There were no side effects such as allergy, irritation, or toxicity. It was also noted that residual scarring and depigmentation were reduced with honey dressing. This study demonstrated that honey may lead to better healing effects and epithelialization of the superficial wound than some other topical antibiotics, such as mafenide acetate. More *in vivo* studies are however required.

COMPARAISON ENTRE LE MIEL ET L'ACÉTATE DE MAFENIDE EN APPLICATION TOPIQUE DANS LE TRAITEMENT DES BRÛLURES. RÉSUMÉ. Les auteurs ont effectué des études histologiques et cliniques sur la cicatrisation des lésions dans des cas comparables de brûlures récentes d'épaisseur variable traitées avec un pansement composé ou de miel ou d'acétate de Mafenide, divisés en deux groupes de 50 patients répartis aléatoirement. Parmi les patients dont les lésions ont été traitées avec du miel, 84% ont démontré une épithélialisation satisfaisante au jour 7 et 100% au jour 21. Pour ce qui concerne les lésions traitées avec l'acétate de Mafenide, l'épithélialisation s'est produite au jour 7 dans 72% des cas et au jour 21 dans 84% des cas. Des signes histologiques d'activité réparatrice ont été observés dans 80% des lésions traitées avec le pansement de miel au jour 7 avec une inflammation minime. Cinquante-deux pour cent des lésions traitées avec l'acétate de Mafenide ont montré une activité réparatrice avec des modifications inflammatoires au jour 7. L'activité réparatrice touchait 100% au jour 21 dans le cas du pansement de miel et 84% avec l'acétate de Mafenide. Les lésions traitées avec le pansement de miel ont été donc caractérisées par une réduction plus précoce des réactions inflammatoires aiguës, un meilleur contrôle de l'infection et une guérison plus rapide des lésions, tandis que, pour ce qui concerne les lésions traitées avec l'acétate de Mafenide, une réaction inflammatoire soutenue a été notée, même après l'épithélialisation.

Mots-clés: brûlures, acétate de Mafenide, miel

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