# Wound healing with honey – a randomised controlled trial

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*Objectives.* To compare honey and IntraSite Gel as wound-healing agents, to record side-effects, gauge patient satisfaction and calculate the cost-effectiveness of the honey used.

*Design and setting.* A prospective, randomised, double-blind controlled trial was carried out among goldmine workers.

*Outcome measures.* Outcome measures were healing times of shallow wounds and abrasions; side-effects; patient satisfaction with treatment; and amount of honey and IntraSite Gel used.

*Results.* The mean healing times of shallow wounds treated with honey or with IntraSite Gel did not differ significantly ($p = 0.75$, 95% confidence interval (CI): -5.41; 7.49 days). When adjusted for wound size, the 2.8-day difference in favour of honey was not significant ($p = 0.21$, 95% CI: -2.41; 8.09). In the case of abrasions there was also no significant difference ($p = 0.83$, 95% CI: -4.98; 6.19 days). When adjusted for wound size, the difference of 0.22 days in favour of IntraSite Gel was not significant ($p = 0.94$, 95% CI: -5.72; 6.15.4). Of patients treated with honey, 27% and 10% respectively experienced itching and pain, and 2 experienced burning for a short time after application. Of patients treated with IntraSite Gel, 31% experienced itching. All patients in both treatment groups were either satisfied or extremely satisfied with treatment. The average cost of treatment per patient was R0.49 with honey and R12.03 with with IntraSite Gel.

*Conclusions.* A distinction should be made between shallow wounds and abrasions when wound healing is being measured. There was no evidence of a real difference between honey and IntraSite Gel as healing agents. Honey is a safe, satisfying and effective healing agent. Natural honey is extremely cost-effective.

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The study was conducted in 1996. Since then great advances have been made with regard to understanding the healing properties of honey, how to use it, and the development and availability of honey products. 'Honey, the most ancient of wound treatments, is taking its place in modern wound care ... it is easy to apply, painless and comfortable, harmless to tissues, creates a moist healing environment, is antibacterial and stimulates healing and epithelialisation.'[1] Some of honey's antibacterial activity is due to the high osmolarity created by its sugar content, some is due to hydrogen peroxide released by exudate, and some is due to phytochemicals that come from the nectar of plants.[1] The latter are so important a factor in Manuka honey (from *Leptospermum scoparium*) that this activity is measured as the 'Unique Manuka Factor' (UMF number).[1]

*In vitro* and animal studies[2-4] have also advanced our knowledge of honey's properties of moisture retention, antimicrobial and angiogenetic activity, and granulation tissue formation and epithelialisation.

As honey becomes accepted in mainline wound care, concerns about potency, sterility, and contamination from its natural sources have led to standardisation, regulation and licensing. It is unfortunate in some ways that such stringency means that honey 'off the shelf' may not be acceptable. The European Union requires honey products sold in Europe to meet essential health and safety requirements and to be CE (Conformité Européenne)-marked.[5]

The way in which honey is applied and the materials used as wound dressings make a difference. Wound exudates can either activate or dilute some of the healing properties. This has led to commercial products that incorporate honey in substrates such as hydrocolloids and hydrogels.[1]

Finally, honey scores in terms of the 'aesthetics' and prejudices of wound care! Honey-impregnated dressings deal with its perceived 'messiness', and honey 'cleans' and deodorises offensive wounds.[1,6]

In the developing world a reluctance to stay with simple and still effective methods, treatments and equipment, in order to 'catch up' with the developed world, comes at a cost. Postmes and Vandeputte[7] suggest that honey be used instead of high-tech products such as the new recombinant growth factors. As far as we can tell, no literature refers to the cost-effectiveness of honey in wound management. This may receive low priority in modern protocols, but should rate highly in resource-based health delivery.

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## Methods

### Objectives

The study aimed: (*i*) to compare wound healing using natural honey and IntraSite Gel as healing agents; (*ii*) to record side-

effects; (*iii*) to gauge patient satisfaction; and (*iv*) to calculate the cost-effectiveness of the honey used.

## Design and setting

A prospective, randomised, double-blind controlled trial was carried out by one of the authors (KP) at Randfontein Estates Gold Mining and Westonaria Gold Mining from September 1995 to July 1996. Patients were mineworkers.

## Eligible patients

Those with shallow wounds not deeper than 2 cm and not larger than 100 $cm^2$ or with abrasions between 10 and 100 $cm^2$ in size, which included donor sites for skin grafting and partial-thickness burns, were included in the study. The presence of slough (which term will hereafter include descriptions of necrosis) was recorded.

## Excluded patients

Those unwilling to be tested for HIV or with underlying or surrounding wound infection, genital or malignant ulcers, wounds of the legs, perineum, fingers or toes (making wound measurement difficult), systemic disease or chronic alcoholism were excluded from the study.

## Estimation of study group size

The required size calculated for each group to detect a difference between mean healing times of 5 days was at least 40 patients, using an $\alpha$–value of 0.05, power of 80%, and a standard deviation (SD) of 8 days.

## Stratified randomisation

Enrolled subjects were stratified by wound type, HIV status and the presence of slough, then randomised (using random permuted blocks of size 10) to treatment with either honey or IntraSite Gel to produce approximately equal numbers in each treatment group and an approximate balance of the 3 possible prognostic factors (Table I).

## Other characteristics recorded

Other characteristics recorded were initial wound size, age, body mass index, systolic and diastolic blood pressure, and smoking history.

## Outcome measures

**Healing time.** Healing time was considered to be the number of days elapsed before the predetermined endpoint was reached of 3 $cm^2$ for shallow wounds, or full epithelialisation for abrasions. The 3 $cm^2$ endpoint was chosen so that inpatient care was not prolonged only for the sake of reliable study supervision.

**Side-effects.** Side-effects measured were pain, burning sensation, itching, allergic reaction, or any other reaction specifically mentioned.

**Patient satisfaction with treatment.** On the 7th day of treatment, or earlier if healing time was less, the patient was asked to say whether he was very dissatisfied, dissatisfied, satisfied, or very satisfied with treatment, or whether he could not say.

**Amount of honey and IntraSite Gel used.** This was measured per patient in grams.

## Healing agents

The two agents evaluated were natural monofloral aloe honey, creamed by crushing and not heated, and IntraSite Gel, a hydrogel wound-care product manufactured by Smith and Nephew Ltd. consisting of propylene glycol 20%, starch copolymer 2% and water 78%.

## Wound management

All wounds were cleaned once daily with normal saline. Honey was then applied with a prepacked wooden spatula, using a fresh spatula for each application. IntraSite Gel was expressed from sterile sachets. The amounts applied depended on the size of the wound. All wounds were covered with Opsite to keep the agent in place. Patients did not know which agent was being used. All patients' diets were supplemented with zinc sulphate and vitamins A, B and C.

## Wound evaluation

KP evaluated each wound on the day of entry to the trial, without knowing which agent would be applied. When the healing endpoint was approaching he measured the surface area daily, still blinded, the applied agent from the previous day having been washed off with normal saline.

**Table I. Wound types randomised by block for treatment with honey or IntraSite Gel (withdrawn from analysis)***

| | HIV-negative | | | | HIV-positive | | | |
|---|---|---|---|---|---|---|---|---|
| | Slough† + | | Slough - | | Slough + | | Slough - | |
| Wound type | Honey | IntraSite Gel | Honey | IntraSite Gel | Honey | IntraSite Gel | Honey | IntraSite Gel |
| Shallow wound | 10 | 7 (1) | 10 (3) | 10 | 3 | 4 | 2 | 4 |
| Abrasion | 5 (1) | 6 | 6 | 5 | 0 | 1 | 4 | 5 |
| Subjects enrolled | 16 | 14 | 19 | 15 | 3 | 5 | 6 | 9 |
| Final study group | 15 | 13 | 16 | 15 | 3 | 5 | 6 | 9 |

* Total number of enrolled subjects = 87 (honey group $N$ = 44, IntraSite Gel group $N$ = 43).
Total number in final study group = 82 (honey group $N$ = 40, IntraSite Gel group $N$ = 42).
† The term 'slough' here includes recorded descriptions of necrosis.

### Wound measurement

Transparent Opsite Flexigrid films (Smith and Nephew Ltd.) with 5 mm squares were used to trace the wound outlines. Squares were counted, and quarters of squares estimated as 6 $mm^2$. Partial-thickness burns and abrasions were not measured again because full epithelialisation was their healing endpoint.

### Ethics

It was known that both agents were without serious side-effects and that neither was absolutely superior as treatment. With the help of an interpreter, KP did his best to explain randomisation and blinding to the patients. Consent to take part in the trial and to be tested for HIV were recorded on a consent form.

### Analysis

Analysis of covariance was used to compare the healing times of the treatment agents in order to allow adjustment for wound size, wound type, HIV status and the presence of slough. This showed overwhelming evidence of a wound type/wound size interaction (effect modification), but no evidence of any other interaction. Hence comparison of healing times between treatment groups was carried out separately for each wound type and analysis of covariance again used to make the above adjustments.

Cost-effectiveness was calculated as the average cost per patient of all the honey used divided by the average cost of all the IntraSite Gel used, expressed as a percentage.

## Results

Of 87 patients enrolled, 5 were excluded from the analysis: 1 wound was misjudged as being an abrasion but there was complete skin loss, 1 was misjudged as being a shallow wound but there were islands of healing, 1 patient withdrew after 2 days for personal reasons, and 2 wounds were dressed with both agents in error. Forty wounds were treated with honey, of which 25 were shallow wounds and 15 were abrasions or partial-thickness burns. Forty-two wounds were treated with IntraSite Gel, of which 25 were shallow wounds and 17 were abrasions, donor sites or partial-thickness burns. The composition of the groups did not differ significantly in terms of recorded characteristics (Table II).

The mean healing times for all shallow wounds and all abrasions were 16.6 days (SD 11.23) and 16.81 days (SD 7.67) respectively.

The mean wound sizes for all shallow wounds and all abrasions were 786 $mm^2$ and 3 868 $mm^2$ respectively. The difference of 3 082 $mm^2$ was significant (95% confidence interval (CI): -3 873; -2 292). The difference in the range of wound sizes (shallow wounds 1 450 $mm^2$, abrasions 8 920 $mm^2$) was considerable (Fig. 1).

Analysis of covariance showed that in the case of shallow wounds there was a highly significant effect of wound size on healing time ($p < 0.001$), but in the case of abrasions there was no such significant effect ($p = 0.24$).

### Shallow wounds

Analysis by 2-sample *t*-test found no significant difference in mean healing time between those treated with honey ($N = 25$, 16.08 days) and with IntraSite Gel ($N = 25$, 17.12 days) ($p = 0.75$, 95% CI: -5.41; 7.49) (Fig. 2 and Table III). Analysis of covariance, adjusting for wound size, HIV status and slough, also showed no evidence of a significant difference ($p = 0.28$). The estimated difference was 2.84 days in favour of honey (95% CI: -2.41; 8.09).

### Abrasions

Analysis by 2-sample *t*-test found no significant difference in mean healing time between those treated with honey ($N = 15$; 17.13 days) and with IntraSite Gel ($N = 17$, 16.53 days) ($p = 0.83$, 95% CI: -4.98; 6.19) (Fig. 3 and Table III). Analysis of covariance, adjusting for wound size, HIV status and presence of slough, also showed no evidence of a significant difference ($p = 0.94$). The estimated difference was 0.22 days in favour of the gel (95% CI: -5.72; 6.15).

There was evidence that the distribution of healing times was skewed to the right (slower healing), particularly in the case of shallow wounds. However the 2-sample *t*-test is robust to moderate departures from normality. To test the effect of this assumption separate analyses, using log transformations of healing times and also non-parametric (Mann-Whitney) tests, gave similar results.

The side-effect of itching was mentioned by 27% of the honey group and 31% of the IntraSite Gel group. In the honey group 10% of patients complained of pain and 2 patients experienced

**Table II. Treatment groups compared (standard deviation)**

| | Honey group ($N = 42$) | IntraSite Gel group ($N = 40$) |
|---|---|---|
| Mean age (years) | 39.1 (8.0) | 39.0 (7.2) |
| Mean body mass index | 23.6 (3.1) | 23.1 (2.9) |
| Mean systolic BP | 121.2 (13.5) | 118.9 (13.1) |
| Means diastolic BP | 78.7 (11.8) | 77.0 (9.9) |
| Never smoked (*N* (%)) | 26 (61.9) | 20 (50.0) |
| HIV-positive (*N* (%)) | 9 (21.4) | 14 (35.0) |

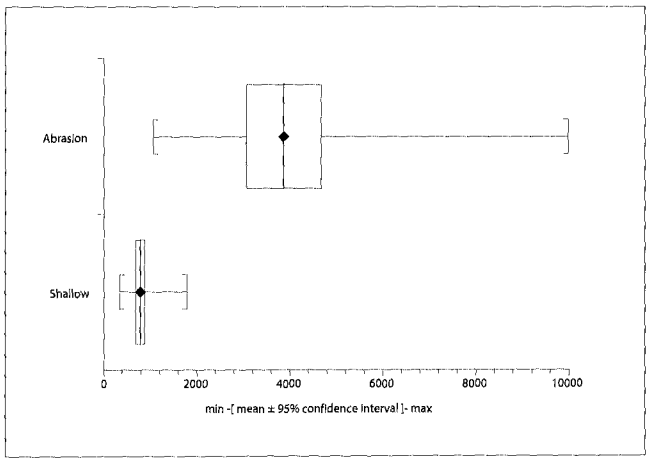


*Fig. 1. Box plot of wound size ($mm^2$) by wound type.*

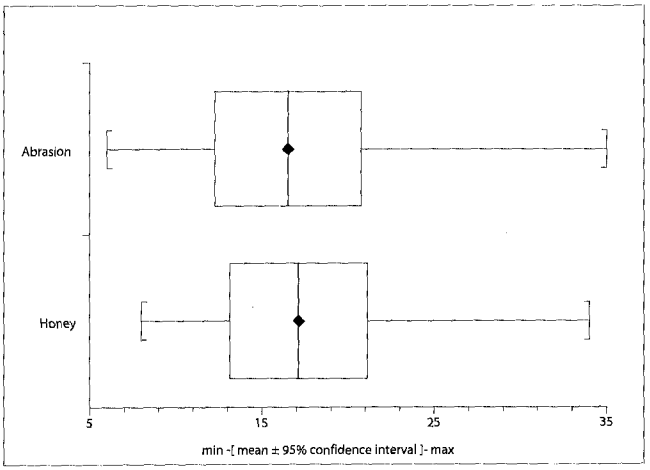


*Fig. 3. Box plot of healing time (days) of abrasions by agent.*

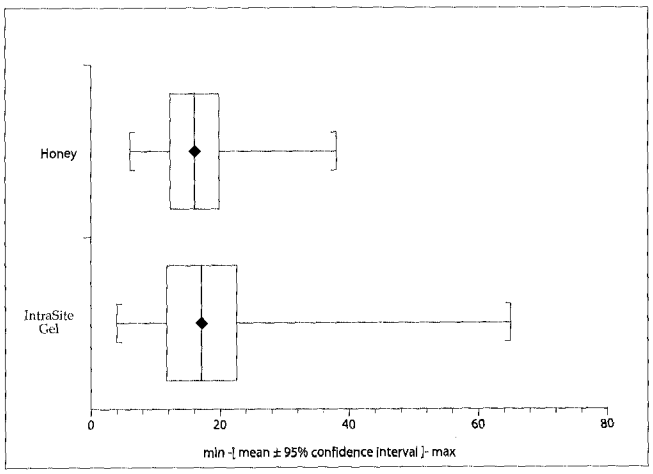


*Fig. 2. Box plot of healing time (days) for shallow wounds by agent.*

a burning sensation for a short time after application. No patient asked for treatment with either agent to be stopped.

There was no significant difference between patient satisfaction in the 2 treatment groups. Twenty-two per cent and 78% of patients in the honey group were satisfied or very satisfied respectively. The proportions in the IntraSite Gel group were 29% and 71%.

The average cost of the use of honey was 4% that of Intrasite Gel (Table IV).

## Discussion

Most studies of honey's healing effects have been observational. There are few randomised controlled trials in a clinical setting. Subrahmanyam's several studies[8-11] were of patients with burns of varying degrees, among whom the measurement in days of 'complete healing' was often complicated by overgranulation. Sometimes 'signs of healing' were compared.

We suggest that it is a strength of this study of comparative healing powers that the wounds studied were small enough to

**Table III. Mean healing times (days) with honey or IntraSite Gel (95% CI)**

| Agent | Shallow wounds | Abrasions |
|---|---|---|
| Honey | 16.08 (12.3 - 19.9) | 17.13 (13.1 - 21.1) |
| IntraSite Gel | 17.12 (11.7 - 22.5) | 16.53 (12.3 - 20.8) |

dress in a standard way, were primarily uninfected and did not include chronic, non-healing wounds.

The antibacterial potency of different natural honeys can vary up to a 100-fold.[12] Monofloral aloe honey was used. To justify this identification we relied on the advice of an experienced beekeeper that bees focus on abundantly flowering aloes at a time when other species are scarcely flowering.

The antimicrobial and healing properties of honey are distinguishable. Healing was therefore compared in non-infected wounds. Apart from ethical considerations, we did not include an untreated control group because the positive healing properties of honey have been demonstrated in animal studies.[2]

Diets of both groups were supplemented with zinc sulphate and vitamins A, B and C to obviate the possibility of compromising deficiencies. Since then no evidence of benefit has been found in studies of zinc and the healing of leg ulcers, but inadequate zinc intakes are prevalent in southern Africa.[13,14]

No evidence has been found for the effectiveness of oral multivitamin supplementation, including vitamin C, on ulcer healing.[15]

The only references we found in the literature of clinical trials to the measurement of healing refer to 'signs of healing' or 'complete healing'. A statistical analysis reported to compare the rates of wound healing, in fact compared healing time in days.[10] We abandoned healing rate (wound size/healing time) as a comparative measure.

While the healing process involves many tissues, the only observable part is epithelialisation and its completion. The

**Table IV. Cost of agents used**

| | Average used per patient (g) | Purchase price (R/g) | Cost/g (R) | Average cost per patient (R) |
|---|---|---|---|---|
| Honey | 35.17 | 7.00/500 | 0.014 | 0.49 |
| IntraSite Gel | 27.83 | 6.50/15 | 0.433 | 12.06 |

study measured the time in days to reach defined endpoints of such wound closure. Abrasions or partial-thickness burns may include islets of epithelial cells, so that epithelialisation might proceed 'multi-marginally' from many margins within the boundary of the lesion, compared with 'uni-marginal' healing from the one boundary of a shallow wound. Initial wound size, more obviously, affects the duration of epithelialisation and, although measured, was not allowed for by stratification. The argument on which our analysis is based was as follows.

Preliminary analyses showed correlation between the size and healing time of shallow wounds, but no such correlation for abrasions. This seemed to support the thesis that abrasions heal 'multi-marginally' whereas shallow wounds heal 'uni-marginally'. Because their healing processes were in some way different, we decided to separate the wound types for comparative purposes.

It is important to recall that the study was designed with a discriminating difference in healing time of 5 days. Non-inferiority study designs were generally not used at the time of the study.

## Conclusions

When analysing wound healing, shallow wounds and abrasions should be separated. The worst-case scenario for honey, considering confidence intervals, was inferiority by 2.4 days for shallow wounds, and 6.2 days for abrasions. Best-case scenarios favour honey by 8.1 days for shallow wounds and 5.7 days for abrasions. This is not evidence of a real difference between honey and IntraSite Gel as healing agents.

That honey is a safe, satisfying and effective healing agent is confirmed. That it was comparably effective in the study allows the important conclusion that, in a natural form, honey is extremely cost-effective.

This research comprised K Polinder's dissertation for the MFamMed degree at the Medical University of Southern Africa.

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