Standardized antibacterial honey (Medihoney™) with standard therapy in wound care: randomized clinical trial

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Abstract

Title. Standardized antibacterial honey (Medihoney™) with standard therapy in wound care: randomized clinical trial.

Aim. This paper is a report of a study to compare a medical grade honey with conventional treatments on the healing rates of wounds healing by secondary intention.

Background. There is an increasing body of evidence to support the use of honey to treat wounds, but there is a lack of robust randomized trials on which clinicians can base their clinical judgement.

Method. A sample of 105 patients were involved in a single centre, open-label randomized controlled trial in which patients received either a conventional wound dressing or honey. Data were collected between September 2004 and May 2007.

Results. The median time to healing in the honey group was 100 days compared with 140 days in the control group. The healing rate at 12 weeks was equal to 46.2% in the honey group compared with 34.0% in the conventional group, and the difference in the healing rates (95% confidence interval, CI) at 12 weeks between the two groups was 12.2% (−13.6%, 37.9%). The unadjusted hazard ratio (95% CI) from a Cox regression was equal to 1.30 (0.77, 2.19), P = 0.321. When the treatment effect was adjusted for confounding factors (sex, wound type, age and wound area at start of treatment), the hazard ratio increased to 1.51 but was again not statistically significant.

Conclusion. Wound area at start of treatment and sex are both highly statistically significant predictors of time to healing. These results support the proposition that there are clinical benefits from using honey in wound care, but further research is needed.

Keywords: Medihoney™, nursing, randomized clinical trial, standard therapy, standardized antibacterial honey, wound care
Introduction

It is known that honey has been used to treat wounds for at least 4000 years by civilizations as diverse as the Sumerians, Chinese, ancient Greeks, eastern African tribes and American Indians. In the 1960s and 1970s, a few authors described the clinical use of honey, including one report on the treatment of surgical wounds following carcinoma of the vulva (Cavanagh et al. 1970); however, it was not until the late 1980s and early 1990s that honey became more widely used in mainstream wound care when scientific papers published around that period described its antimicrobial properties, suggesting that it offered an attractive alternative to the use of antibiotics and other chemotherapeutic agents for the treatment of wound infections. This was opportune at a time when the emergence of antibiotic resistant strains of bacteria was beginning to cause real concern (Law et al. 1988, Boyce 1989) following an outbreak of methicillin-resistant Staphylococcus aureus (MRSA) in London in 1980/1981 (Townsend et al. 1984). Furthermore, formal small-scale studies, which were later comprehensively summarized by Molan (1999), suggested that honey appeared to offer real benefits in wound healing.

Background

Composition of honey

Honey is essentially a super-saturated solution principally comprising a mixture of sugars together with small quantities of enzymes and amino acids, vitamins, minerals, organic acids and aromatics responsible for its flavour and odour, although the exact composition varies widely, according to the geographical source and the plants on which the bees have been feeding.

An analysis of 490 samples of American floral honey showed that the average concentrations of the principal components were as follows: moisture 17.2%, fructose 38.2%, glucose 31%, maltose 7.35% and sucrose 1.3%. Small quantities of other higher sugars and oligosaccharides were also present (White & Doner 1980).

In addition to the carbohydrate components, honey also contains the enzymes invertase, which converts sucrose to glucose and fructose; amylase, which breaks down starch; glucose oxidase, which converts glucose to gluconolactone, which in turn yields gluconic acid and hydrogen peroxide; catalase, which breaks down the peroxide formed by glucose oxidase to water and oxygen; and acid phosphorylase, which removes inorganic phosphate from organic phosphates.

Other minor components include trace amounts of B vitamins, calcium, iron, zinc, potassium, phosphorous, magnesium, selenium, chromium and manganese and antioxidants such as the flavonoids ascorbic acid, catalase and selenium. Organic acids such as acetic, butanoic, formic, citric, succinic, lactic, malic, pyrogulutamic and gluconic acids are also present, which together are responsible for the low pH (3.5–6). The main acid present is gluconic acid, formed in the breakdown of glucose by glucose oxidase (White & Doner 1980).

Antibacterial properties of honey

The antibacterial activity of honey was first reported in 1882 (Cooper 2005). Initially thought to be an osmotic pressure effect, it was subsequently found that activity increased on dilution because of the production of hydrogen peroxide by the enzyme glucose oxidase.

Allen et al. 1991 compared the potency of 345 samples of honey at different dilutions and identified that, for all but two types of honey tested – Leptospermum scoparium (Manuka honey) and Echium vulgare (Viper’s Bugloss), activity was eliminated by the addition of catalase. This is important when choosing an appropriate medical grade honey for the management of bioburden as catalase is present in wound fluid, tissue, blood and other bodily fluids (Gaetani et al. 1996).

The antimicrobial activity of honey has been described in numerous early studies reviewed by Molan (1992a,b). Later studies also demonstrated that antibacterial Leptospermum honey successfully inhibited the growth of antibiotic-resistant strains of micro-organisms both in vitro (Cooper et al. 1999, 2002) and in vivo (Blaser et al. 2007).

Lusby et al. (2005) compared the antimicrobial activity of local honey with ‘therapeutic’ honeys at different concentrations and reported that 12 of the 13 bacteria were inhibited by all the honey samples, with only Serratia marcescens and the yeast Candida albicans remaining unaffected. Little or no antibacterial activity was seen at honey concentrations <1%, with minimal inhibition at 5%. Medihoney™ (Medihoney Pty Ltd, Richlands, Australia) and Leptospermum scoparium (manuka) had the overall best activity, but the locally produced honeys had equivalent inhibitory activity for some, but not all, bacteria. It should be noted that this in vitro study did not include the addition of catalase, which would have more accurately mimicked a wound environment and would potentially have reduced the antimicrobial activity of those honeys that relied mostly on hydrogen peroxide as their key antimicrobial component.
Using a well diffusion method, Wilkinson and Cavanagh (2005) compared the activity of 13 honeys at four concentrations (10%, 5%, 2.5%, and 1% w/v) with corresponding dilutions of an ‘artificial’ honey, a solution containing the principal sugars found in honey and using Escherichia coli and Pseudomonas aeruginosa as the test organisms. All samples were also tested in the presence of catalase to eliminate the antibacterial effects of hydrogen peroxide. Statistical analysis confirmed that artificial honey had no measurable effect on E. coli but inhibited the growth of P. aeruginosa at 10% and 5%. All honeys tested had an inhibitory effect on the growth of E. coli and P. aeruginosa, but the results were variable although all were more effective than the artificial honey at 5% and 10%. Only one (Patterson’s honey) demonstrated statistically significant activity against E. coli at 2.5%.

George and Cutting (2007) compared the sensitivity of 130 clinical isolates to a proprietary leptospermum honey (MedihoneyTM). They reported that the growth of S. aureus and MRSA was inhibited by 4% honey but the Gram negative enterobacter, including vancomycin-resistant organisms, required 6–8% honey to inhibit growth. Pseudomonas aeruginosa was the most resistant organism examined, requiring 12–14% honey to inhibit bacterial development (George & Cutting 2007).

All these laboratory studies actually provide a very conservative assessment of the antimicrobial properties of honey as a wound dressing. When used clinically, honey is generally applied directly to the surface of a wound in much higher concentrations than those used in the laboratory studies, and therefore its ability to kill micro-organisms is much greater than the studies suggest. At the highest concentrations, although the production of hydrogen peroxide is initially inhibited as the honey becomes diluted at the wound surface by the production of exudate, the hydrogen peroxide concentration will increase and the antibacterial activity of the honey will be maximized.

Current status of honey treatment

Studies suggest that honey reduces inflammation, swelling, pain and odour and promotes debridement, granulation and epithelialization, resulting in healing with minimal scarring (Molan 1998, 2005, Cooper et al. 2005, White & Molan 2005). As a result, honey has increased in usage and has been evaluated in a number of studies. In 2006 Molan (2006) identified 17 randomized controlled honey trials involving a total of 1965 participants, and five clinical trials of other forms involving 97 participants.

In 2008 the results of a community-based open-label randomized trial were published, comparing the healing rates of venous leg ulcers dressed with a calcium alginate dressings impregnated with manuka honey with standard treatment (Jull et al. 2008). All participants in the study also had compression bandaging. The primary treatment outcome was the proportion of ulcers healed after 12 weeks, but secondary outcomes included time to healing, change in ulcer area, incidence of infection, costs per healed ulcer, and quality of life. A total of 368 patients were treated, 187 of whom were randomized to honey and 181 to alternative treatment. At 12 weeks, there was a 5·9% absolute increase in healing in favour of honey, although this failed to reach statistical significance (absolute increase 5·9 (95% confidence interval (CI) −4·3 to 15·7) per cent; P = 0·258). Wounds treated with honey also achieved a 9·6% greater reduction from baseline and 23% fewer episodes of infection, although neither parameter achieved statistical significance. The application of honey was found to result in increased pain compared with traditional treatments, but it is noteworthy that the level of pain was not assessed and that only four participants gave pain as the rationale for withdrawing from treatment, suggesting that the reported pain was transient and/or tolerable. In the honey-treated group, the wounds of 19 patients deteriorated compared with nine patients in the standard therapy, but this difference was not statistically significant. Patients allocated to honey treatment spent a total of 10 patient-days in hospital compared with 40 patient-days for those treated conventionally. There was a financial advantage in favour of honey if the cost of hospitalization was included in the calculation, but this was reversed if the hospital costs were omitted. Although the results of this study suggested that the use of honey had some beneficial effects on healing and infection rates, the authors considered that these were insufficiently robust to support the proposition that honey-impregnated dressings significantly improved venous ulcer healing at 12 weeks compared with usual care.

The study

Aim

The aim of the study was to compare a medical grade honey with conventional treatments on the healing rates of wounds healing by secondary intention.

Design

The study was designed as a single centre, open-label, randomized controlled trial, involved the participation of community
nursing staff and was co-ordinated by the first author (VR). The study was undertaken between September 2004 and May 2007. The honey used was Medihoney™ Antibacterial Honey, a standardized, widely used medical honey that is predominantly sourced from Leptospermum species. The honey is sterilized by gamma irradiation to eliminate bacterial spores which are known to be present in raw honey.

Participants

The study was conducted at a large district general hospital in the United Kingdom. Patients were invited to take part in the project either at their attendance at an outpatient clinic or during an episode of inpatient care.

All patients with a wound healing by secondary intention were eligible for inclusion in the study unless they had:

- Diabetes
- History of neuroses, psychoses or dementia
- Known allergy to bee/honey products
- Venous ulcers of < 12 weeks duration
- Grade 1 or Grade 4 pressure ulcers (European Pressure Ulcer Advisory Panel grading system)
- Wounds containing exposed tendon, muscle or bone, or wounds where malignancy was present or suspected.

Patients with an existing wound infection requiring systemic antibiotics were also excluded, as were those who had received antibiotic therapy in the preceding 2 weeks.

Power calculation

It was estimated that 50% of patients treated with conventional dressings would achieve healing by 24 weeks. To detect a 20% greater healing rate in the honey treated group with 80% power and at the 5% statistical significance level, each group required 93 patients. A target recruitment of 200 patients was therefore needed to allow for potential dropouts.

Interventions

For patients randomized to treatment with honey, the wound was covered with a layer of honey to a depth of approximately 3 mm, followed by a low-adherent dressing and an absorbent dressing held in place with tape or a bandage as appropriate. Patients randomized to the control group were treated with a dressing (or dressing system) selected from the first author’s employing hospital’s wound care formulary in accordance with standard local practice. The dressing selected was therefore, in the professional opinion of the practitioner, the most appropriate treatment available, given the aetiology and condition of the wound at that time.

As honey is regarded as an effective debriding agent, the presence of slough or necrosis did not necessitate any change in the treatment of wounds in the intervention group, but when slough or necrosis were encountered in the control group the protocol dictated that they should be treated with a hydrogel to facilitate autolytic debridement. Where clinically indicated, compression bandaging was used for patients in both groups in accordance with the hospital’s leg ulcer policy.

Randomization

Prior to randomization, the study research nurse assessed patient eligibility and obtained written informed consent from eligible patients. Allocation to treatment was determined using blocked randomization (with sequences produced using computer software (STATA version 8.2; StataCorp, College Station, TX, USA) with randomly varying block sizes), stratified by two factors, age (< 40 and ≥40 years old) and size of wound (< 10 and ≥10 cm²). Stratification was used in conjunction with blocked randomization to ensure a balanced distribution of the stratifying factors across the two treatment groups. Sealed, opaque, serially numbered envelopes were produced from the randomization sequence for each stratum separately, and an independent third party with access to the envelopes was contacted by telephone to determine treatment allocation as patients were recruited.

Data collection

All randomized patients were subject to full assessment at baseline, and a clinical history was undertaken using case report forms prepared specifically for the study. As part of this process, the characteristics and appearance of the wound were recorded. For wounds on the lower leg, ankle brachial pressure index was measured to establish whether the patient was suitable for compression therapy. Wound photographs and measurements for the trial were held on the Leg Ulcer Telemedicine System (LUTMS), designed by Good Hope Hospital, West Midlands, UK, which is a dedicated, secure, electronic patient recording system. The LUTMS allows incorporation of colour digital images in the electronic patient record and inclusion of ulcer measurements, and automatically plots ulcer healing rates.

A full wound assessment was repeated every 2 weeks (until 12 weeks) and then every 4 weeks until the patient had received 24 weeks of treatment. Between these assessments, dressings were applied by ward nurses (if the patients were in hospital) or community nurses, who were informed of the patient’s entry into the trial and were given written information and details of the dressing regime. A contact telephone
number was provided should any changes of treatment or cause for concern arise.

Ethical considerations

The study approved by the appropriate ethics committee and medical officer responsible for the care of each patient recruited. Informed consent was obtained from each patient after fully explaining the aims and procedures of the study. Patients were also informed that they could withdraw from the project at any time and assurances of confidentiality were given.

Data analysis

The trial was analysed and reported following the ‘CONSORT’ guidelines (Moher et al. 2001). Statistical analysis was carried out on an intention to treat (ITT) basis, retaining patients in their randomized treatment groups regardless of the actual treatment received and including protocol violators and ineligible patients. Two sensitivity analyses were also carried out to assess the impact of protocol violators on the conclusions drawn from the ITT analysis.

The first sensitivity analysis (per protocol, PP) only included patients who received the treatment to which they were randomized and censored patients at the time point of any deviation from randomized treatment. The second sensitivity analysis (as treated, AT) analysed patients according to the treatment they actually received.

Continuous variables were summarized for each treatment group separately, using mean (standard deviation) for normally distributed outcomes and median (interquartile range) for non-normally distributed outcomes. Frequency tables (with percentages) were produced for categorical data, stratified by treatment arm in all cases.

The primary outcome, time to healing, was calculated as the number of days between the date of randomization and the date of complete healing of the wound (or date of last follow-up for individuals whose wounds had not healed by the end of their follow-up period). For the purpose of this study, complete healing was defined as a continuous layer of epithelium. Survival analysis was carried out when all patients had a minimum of 24 weeks follow-up after randomization. Survival curves were estimated by the method of Kaplan and Meier (1958) and compared across treatment groups with the log-rank test at a two sided statistical significance level of 5%. The unadjusted hazard ratio and respective 95% confidence interval was computed using the Cox proportional hazards regression model (Cox 1972). In a secondary analysis, the stratification factors (age and wound area at the time of randomization) and other potential confounding factors (sex and wound type) were adjusted for by including them in the Cox model. The proportional hazards assumption of the Cox regression models was ascertained by inspection of plots of $-\ln(-\ln (\text{survival}))$ vs. ln (time), and by using a formal hypothesis test based on Schoenfeld residuals.

The secondary outcome measures were time to 50% reduction in wound area, calculated as the number of days between the date of randomization and the date when 50% of the original wound area was covered with epithelium (or date of last follow-up for individuals whose wound had not achieved 50% reduction in wound area by the end of their follow-up period), healing rate at 12 weeks and incidence of 50% reduction in wound area at 12 weeks. The incidence of adverse events and withdrawal from treatment in each treatment group was also recorded.

For each treatment group, the median time to healing (and time to 50% reduction in wound area) along with the healing rate (and rate of 50% reduction in wound area) and standard error at 12 weeks and at 24 weeks, were estimated from the Kaplan–Meier survival curves. The difference in healing rates between treatment groups at 12 weeks (and at 24 weeks) and difference in rates of 50% reduction in wound areas between treatment groups at 12 weeks (and at 24 weeks) were analysed by 95% confidence intervals. The incidence of withdrawal from treatment and adverse events in each treatment group were also calculated.

Results

Although it was originally intended that 200 patients would be recruited to the study, for reasons discussed later only 114 eligible patients were identified, and 105 (92.1%) consented to be randomized to honey or conventional treatment (see Figure 1). Fifty-two patients were randomized to receive honey and 53 to receive conventional treatment. Two patients randomized to the honey group (3.8%) did not receive honey (one as a result of the patient’s decision, the other as a result of a clinical decision), and six allocated to the conventional treatment group (11.3%) received honey (all but one as a result of a clinician’s decision). The reasons for this serious deviation from protocol are discussed later. The baseline demographics of the randomized treatment groups are presented in Table 1.

Time to healing

The median time to healing in the honey group was 100 days compared with 140 days in the control group (see Figure 2). The unadjusted hazard ratio (95% CI) from the Cox regression was 1.30 (0.77, 2.19), $P = 0.321$. Thus, wounds of patients in
the honey group were on average 30% more likely to heal at any particular time than those in the control group, but the wide confidence interval for the hazard ratio, which passes through the null effect of 1, indicates that this difference was not statistically significant; the 95% CI suggests that, in reality, the wounds of those in the honey group might have been more than two times more likely to heal than those in the control group (2.19), but might also have been 23% less likely to heal at any particular time (0.77).

The healing rate (95% CI) at 12 weeks was 46.2% (32.9%, 61.7%) in the honey group compared with 34.0% (22.3%, 49.5%) in the conventional group, and thus the difference in the healing rates (95% CI) between the two groups was 9.4% (−36.3%, 55.0%).

When the treatment effect was adjusted for confounding factors (sex, wound type, age and wound area at start of treatment), the hazard ratio increased to 1.51 (meaning that the wounds of patients in the honey group were on average 50% more likely to heal at any particular time than those in the control group) but was again not statistically significantly different from 1 (see Table 2). Wound area at start of treatment and sex are both highly statistically significant predictors of time to healing. Men are on average 77% less likely to have healing of wounds compared with women, and with each cm² increase in wound area the likelihood of the wound healing decreases by an average of 2% at any particular time point.

The conclusions from the PP and AT analyses were similar to those from the ITT analysis. The median time to healing

Figure 1 Consort flow diagram showing course of patients through trial.
Table 1 Demographics at baseline. All values are numbers (%) unless otherwise stated

<table>
<thead>
<tr>
<th></th>
<th>Conventional treatment (n = 53)</th>
<th>Honey (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): mean (SD)</td>
<td>68.2 (15.5)</td>
<td>66.4 (16.1)</td>
</tr>
<tr>
<td>Wound area at start median (IQR)</td>
<td>51 (2.0, 15.6)</td>
<td>47 (1.5, 20.8)</td>
</tr>
<tr>
<td>Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>42 (79.3)</td>
<td>37 (71.2)</td>
</tr>
<tr>
<td>Hospital</td>
<td>5 (9.4)</td>
<td>7 (13.5)</td>
</tr>
<tr>
<td>Community and hospital</td>
<td>5 (7.6)</td>
<td>8 (15.4)</td>
</tr>
<tr>
<td>Self</td>
<td>2 (3.8)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Table 2 Multivariable Cox Regression of time to healing

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start</td>
<td>1.00 (0.98, 1.01)</td>
<td>0.674</td>
</tr>
<tr>
<td>Wound area at start</td>
<td>0.98 (0.96, 0.99)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sex: (baseline female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.23 (0.11, 0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wound type: (baseline leg ulcer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast wound</td>
<td>1.26 (0.58, 2.77)</td>
<td>0.479</td>
</tr>
<tr>
<td>Other</td>
<td>1.74 (0.67, 4.50)</td>
<td></td>
</tr>
<tr>
<td>Treatment: (baseline conventional)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honey</td>
<td>1.51 (0.88, 2.58)</td>
<td>0.134</td>
</tr>
</tbody>
</table>

Time to 50% reduction in wound area

The median time to 50% reduction in wound area was 32 days in the honey group compared with 46 days in the control group (see Figure 3). The unadjusted hazard ratio (95% CI) from the Cox regression was 1.29 (0.82, 2.03); P = 0.266. The rate of 50% reduction (95% CI) at 12 weeks was 68.2% (54.4%, 81.2%) in the honey group compared with 70.5% (57.1%, 82.8%) in the conventional group, and the difference in rates (95% CI) between the groups was −2.3% (−37.0%, 32.3%). The rate of 50% reduction (95% CI) at 24 weeks was 94.0% (79.1%, 99.4%) in the honey group compared with 80.1% (66.4%, 90.9%) in the conventional group, and the difference in rates (95% CI) between the groups was 13.9% (−61.5%, 89.4%).

When the treatment effect was adjusted for confounding factors (sex, wound type, age and wound area at start of treatment), the hazard ratio remained virtually unchanged and was not statistically significant (see Table 3). In this adjusted analysis, sex was a statistically significant predictor of time to 50% reduction in wound area (as with time to healing), and age decreased slightly in the honey group (91 days) in the PP analysis but remained the same otherwise. The unadjusted and adjusted hazard ratios for treatment remained non-statistically significant, although they did increase slightly compared to the ITT analysis.
was just statistically significant. Men appear to be approximately 60% less likely to experience 50% reduction of wound area compared with women at any particular time point, and with each year increase in age, the likelihood of 50% reduction of wound area decreases by an average of 2%.

As with the analysis of time to healing, the conclusions from the ‘per protocol’ and ‘as treated’ analyses were similar to those from the ITT analysis. The median time to 50% reduction remained virtually the same in these sensitivity analyses, and the unadjusted and adjusted hazard ratios increased slightly compared to the ITT analysis but remained statistically non-significant.

**Patient withdrawals**

One patient in the honey group (1.9%) was lost to follow up (as they moved to an alternative hospital) and one patient died in each group (1.9% in each group); these patients were included in the analysis until the point at which they were lost to follow up or died. Two patients (3.8%) from each group discontinued treatment prematurely (see Figure 1).

**Adverse events**

One patient (1.9%) in each treatment group died, and one patient in the honey group experienced pain. The leg ulcers of two patients (3.8%) in the honey group and one (1.9%) in the control group deteriorated during the study. Three patients (5.8%) from each group discontinued intervention as radiotherapy or further surgery was indicated.

**Discussion**

**Study limitations**

Although we originally intended to include 200 patients, because of recruitment problems the study was actually terminated prematurely when only 105 patients had been enrolled because, as commonly happens, the number of patients with suitable wounds who were able or willing to enter the study was lower than expected. However, on this occasion the problem was greatly exacerbated by the considerable amount of publicity that had been generated about the use of honey as a topical treatment. Initially this publicity attracted patients to volunteer to take part in the study as they regarded honey as an established natural treatment. All these patients understood that there was a possibility that they would be randomized to the control arm, and most were prepared to take that risk and duly accepted the alternative form of treatment if they were so allocated. Unfortunately, however, because of the lack of blinding, a small number of patients allocated to conventional treatment did not adhere to treatment and received honey as a result of either patient pressure or external clinical decision.

Part-way through the study, the recruitment problem was made very much worse when honey products were added to the list of reimbursable items that can be supplied against an NHS prescription, with further associated publicity in the press. This meant that those patients who specifically wished to receive the treatment, or nursing staff who wished to administer it, could obtain it on prescription without having to take part in a clinical study with all the extra issues that involved and the possible risk that randomization would result in inclusion in the control arm. This reduced the number of patients enrolling in the study, and greatly increased the timeframe in which we would be able to fully enrol our target number. It was therefore decided that for practical reasons the study should be closed prematurely.

With hindsight, it is possible to identify ways in which the study might have been improved. According to the protocol, wounds of all types could be included, and it might be argued that mixing wounds in this way could have an impact on the validity of the analysis. It might, therefore, have been preferable to stratify by wound type rather than by age, but fortuitously the proportion of leg ulcers in two treatment groups was very similar, as these are arguably the most difficult wound types to heal.

**Discussion of results**

Wound care is often complex, frequently time-consuming, sometimes confusing, and nearly always expensive. A plethora of dressing products is available to nursing and medical profession, and these vary widely in construction and composition. Very few of these products have been subjected to formal assessment by means of randomized control trials, which are generally regarded as the ‘gold standard’ method of
What is already known about this topic

- Wound care is often complex, frequently time-consuming, sometimes confusing and nearly always expensive.
- The antibacterial activity of honey is well-documented, along with the publications of numerous case studies and trials reporting improved healing rates following the application of honey to wounds.
- Honey is easy to use by clinicians and is readily accepted by patients.

What this paper adds

- Healing times after treatment with honey are reduced compared with conventional treatment and, although not reaching statistical significance, the results are of clinical significance.
- It was interesting to note that males were statistically significantly less likely to achieve healing or 50% reduction in wound size ($P < 0.001$ and $P = 0.001$ respectively) compared with females when the survival analysis was adjusted for age, wound area, wound type and treatment.
- The management of randomized controlled trials, especially when unblinded, can be arduous and demanding, even with careful planning and attention to protocol.

Implications for practice and/or policy

- Honey is suitable for wounds at all stages of healing.
- Stratifying by wound type rather than age could improve the validity of further research in this field.

making comparisons between similar products or products used for a similar indication. In addition, for many reasons these studies do not always reflect normal clinical practice, not least because the eligibility criteria eliminate some of the most difficult-to-heal wounds or the patients are treated as hospital inpatients despite most wounds being managed in the community.

The difficulties faced by staff responsible for wound care may best be illustrated by reference to the treatment of leg ulcers, which probably represents one of the greatest challenges faced by community nursing staff. Graduated external compression is frequently recommended as the principal treatment for ulcers caused by venous insufficiency, and it has been stated that if this is administered correctly then the choice of primary dressing is irrelevant. Whilst there can be no doubt that appropriate levels of compression are a major factor in the treatment of these ulcers; however, there are still a proportion of wounds which fail to respond appropriately and therefore adjunct treatment is necessary in addition to compression.

A very basic Medline search using the search terms ‘leg ulcer(s)’ ‘trial’ and ‘randomized’ identified 380 publications, but a more carefully constructed search would doubtless have identified many more. Few systematic reviews have been published in this area, and those that are available are of little practical value for determining treatment. In the absence of unequivocal advice supported by meaningful clinical data, leg ulcer care in the community is therefore generally largely determined by the knowledge and experience of the primary healthcare team, and the community nursing staff in particular. Such local knowledge and experience may also be supported by national guidelines, such as those produced by the Royal College of Nursing, (National Institute for Health and Clinical Excellence 2005, Royal College of Nursing 2006), National Institute for Health and Clinical Excellence, (National Institute for Health Clinical Excellence 2001, 2005), Scottish Intercollegiate Guidelines Network, (Scottish Intercollegiate Guidelines Network 1998).

Most clinical studies involve the use of a carefully selected patient population and are limited to two dressings or forms of treatment, one the material provided by the sponsor and the other a product chosen to act as a control. Both products are applied to all wounds in accordance with the randomization schedule, regardless of whether the use of the comparator would normally be considered to represent ‘best practice’ in that particular situation. Consequently, although such a study, if conducted appropriately, may be considered to fulfil all the requirements of a randomized control trial and therefore be suitable for inclusion in a systematic review, it does not always reflect clinical practice and therefore may sometimes be of limited practical value. In this study, an alternative approach was adopted. By not imposing a potentially inappropriate product on patients in the control group, honey was effectively being tested against ‘best practice’ as it was understood at the time.

Conclusion

Whilst our data strongly suggest that healing times after treatment with honey are reduced compared with conventional treatment, and the results are of clinical significance (median of 100 compared with 140 days respectively), as with the Jull et al. (2008) study, insufficient patients were included for this to reach statistical significance. Nevertheless
we believe that our results give further support to the proposition that there are clinical benefits associated with the use of honey in the management of wounds in clinical practice. Although not specifically addressed in this study, it is possible that the reduction in healing times also had implications for treatment costs (consumables and nursing time) and improved the quality of life of the patients concerned. These elements should be considered in future research on the topic.

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Author contributions

VR and SD were responsible for the study conception and design. VR performed the data collection. SD performed the data analysis. ST, SD and VR were responsible for the drafting of the manuscript. SD provided statistical expertise. VR obtained funding.

References


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