The use of honey in chronic leg ulcers: a literature review

Mwipatayi BP • Angel D • Norrish J • Hamilton MJ • Scott A • Sieunarine K

Abstract

The purpose of this study was to investigate the clinical effects of topical honey on chronic leg ulcers, through a systematic review of published trials – randomised (RCTs) and non-RCTs – and to clarify its role in our daily practice. The Pubmed, MEDLINE, EMBASE, CINAHL database and the Cochrane Library were searched for relevant publications on the efficacy of honey as an antibacterial agent and in the promotion of wound healing in chronic leg ulcers 1980-2004. We found 13 publications concerning the use of honey in chronic leg ulcers, but only two were clinical trials of relevance to our study. The studies analysed were influenced by different sources of bias, especially lack of blinding, poor reporting quality and poor sample size. None of those studies was a RCT. In order to elucidate the evidence for the use of honey as a first line treatment in chronic leg ulcers, RCTs and laboratory studies on cellular effects are urgently needed.

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BP Mwipatayi *
FCS (SA), MMed (Surg)

D Angel
RN, BN, MRCN

J Norrish
RN, BSc

MJ Hamilton
BHB, MBChB

A Scott
FRACS

K Sieunarine
DDU, FRACS

Department of Vascular Surgery
Royal Perth Hospital
Perth, WA 6000
Tel: (08) 9224 2191
Fax: (08) 9224 2625
E-mail: bibombe@iinet.net.au

* *Correspondence to BP Mwipatayi*

Introduction

For thousands of years, honey has served as a natural remedy for numerous ailments. The early Egyptians were the first to use honey as a component in the topical treatment of wounds, as evidenced from their writings in the Smith papyrus (1650BC). In recent times, it has been 'rediscovered', with numerous reports of clinical studies, case reports and randomised controlled trials (RCTs) showing it rates favourably alongside modern dressings materials in its effectiveness in managing wounds [1].

Honey has numerous properties: a natural anti-inflammatory effect, a stimulatory effect on granulation tissue and an antibacterial effect (against many strains of bacteria: Staphylococcus, Streptococcus and *Helicobacter pylori*) [2]. The high osmolarity of honey has been considered a valuable tool in the management of sloughy and septic wounds. It produces a cleansing effect and naturally debrides non-viable tissue. Honey dressings (HDs) have also been shown to reduce odours from infected wounds.

However, despite its numerous properties, scepticism still exists among the medical and nursing fraternity in the use of honey in the treatment of legs ulcers. Partially because there is a lack of level I and IIa evidence to support the fact that this type of dressing and topical agent will have a definitive bearing on ulcer healing [3].

Venous ulcers occur in 0.3% of the adult population in Western countries [4]. Although limb loss and death are unusual, chronic venous ulceration is associated with a marked reduction in quality of life. It occurs commonly above the medial malleolus and is a characteristic sign in the post-thrombotic limb and chronic venous hypertension.

Non-operative therapy has been shown to be highly effective in controlling the symptoms of chronic venous insufficiency and promoting the healing of venous ulcers [5]. Compression therapy with multi-layer, graduated, high grade (30-40mmHg at the ankle) bandaging has been shown in clinical trials beyond doubt to heal venous ulcers [6]. However, there is a perceived confusion about what is the best primary dressing for a chronic leg ulcer, which is not responding to conventional therapies.

The aim of this review is to investigate the clinical effects of topical honey on chronic leg ulcers, through a systematic review of published trials – RCTs and non-RCTs – and to clarify its role in our daily practice. The key outcomes measured are wound healing rate and eradication of infection.

Properties of honey

Curative properties of honey

Carbohydrates comprise the major portion of honey – about 82%; these are monosaccharides and disaccharides (about 9%) [7]. There are also some oligosaccharides (4.2%) formed from incomplete breakdown of the higher saccharides present in nectar and honeydew. A number of enzymes, including invertase, are found in honey – amylase (breaks starch down into smaller units), glucose oxidase (converts glucose to gluconolactone and result in the formation of gluconic acid and hydrogen peroxide), catalase (breaks down the peroxide formed by glucose oxidase to water and oxygen) and acid phosphorylase (removes inorganic phosphate from organic phosphates) [8].

Honey also contains 18 free amino acids, of which the most abundant is proline, and other compounds (organic acids and a number of aromatic acids). It is quite characteristically acidic, with a ph of between 3.2 and 4.5, which is low enough to be inhibitory to many animal pathogens.

Antimicrobial properties of honey

The antibacterial effects of honey are both physical and chemical. It exerts a very high osmotic pressure, which results in dehydration of organisms and inhibition of microbial growth [2]. However, when used as a wound contact dressing, the dilution of honey by the wound exudate reduces the osmolarity to a lower level, resulting in the neutralisation of the antibacterial effect, although it has been observed that *in vitro* the antibacterial action of honey is increased when diluted. This paradox can be explained by the fact that honey contains enzymes which are probably entirely responsible for the antimicrobial action of honey.

The main antibacterial component is hydrogen peroxide, formed in a slow-release by the enzyme glucose oxidase present in honey, which varies widely in potency [2, 9]. The glucose oxidase enzyme is secreted from the hypopharyngeal gland of the bee into the nectar to assist in the formation of honey from the nectar. The glucose oxidase enzyme has been found to be practically inactive in full-strength honey. It gives rise to hydrogen peroxide only when the honey is diluted [9, 10].

One of the non-peroxide ingredients, 'propolis', a material used by bees to repair their hives, contains an antibacterial substance called galangine, which is used as a food preservative. Several chemicals with antibacterial activity have been identified in honey by various researchers but their quantities were far too low to account for any significant amount of activity.

The chemical compositions and antibacterial effects of honey will depend on the type of flowers from which it is made. Studies using a wider range of dilutions report the minimum inhibitory concentrations of the honeys tested to range from 25-0.25%, >50-1.5%, 20-0.6% and 50-1.5% [11-13].

Honey is not sterile and there is a perceived risk of wound contamination from the presence of *Clostridium botulinium* spores and *Bacillus* spp. in honey [15]. Heating will easily deactivate the enzyme responsible for the antibacterial action; thus processed honey often has a low activity. Therefore, it should be used only when treated by gamma irradiation that kills clostridium spores without loss of any of the antibacterial activity [14].

Recent research shows that the proliferation of peripheral blood B-lymphocytes in cell culture is stimulated by honey at concentrations as low as 0.1%; phagocytes are activated by honey at concentrations as low as 0.1%. Honey stimulates monocytes in cell culture to release cytokines, tumour necrosis factor-alpha, interleukin-1 and interleukin-6, which activate the immune response to infection [15].

Various brands of honey with standardised antibacterial activity, sterilised by gamma-irradiation, are available commercially. New Zealand 'Manuka' honey, leptospermum honey, has an unusually high level of plant-derived non-peroxide antibacterial activity [16]. It contains an additional antibacterial component found only in leptospermum honey, 'unique Manuka factor' (UMF) that is not destroyed by

exposure to heating and light. There is evidence that the two antibacterial components may have synergistic action. The honey with UMF is more effective than that with hydrogen peroxide against some types of bacteria. It is twice as effective as other honey against *Escherichia coli* and *Staphylococcus aureus*, with the UMF number being the equivalent concentration of phenol antibacterial activity. The Australian leptospermum honey, Medihoney®, has been listed with the Therapeutic Goods Administration (TGA) in Australia for use clinically [17].

Honey and wound healing

Honey provides a moist healing dressing that prevents bacterial growth even if the wound is heavily infected. The benefits of a moist wound environment are well established – it protects the wound, reduces infection rates, reduces pain, debrides necrotic tissue, and promotes granulation tissue formation [18]. It will enable epithelialisation to occur along the top surface of the wound.

Honey prevents and decreases the malodour in wounds. Anaerobes such as Bacteroides and Clostridium species, and Gram-negative rods such as Pseudomonas and Proteus species, which are inhibited by honey, generate foul smells. The deodorisation effects can also be explained by the formation of lactic acid by honey rather than the ammonia, amines and sulphur compounds produced from serum and dead cells that are metabolised by bacteria.

Honey produces rapid tissue regeneration and suppresses inflammation (the mechanisms of which is not fully elucidated), oedema and exudation. Its high viscosity, which varies from floral source to floral source, provides a protective barrier to prevent wounds from becoming infected, effectively sealing the wound [19].

The presence of a layer of diluted honey and fluid prevents the dressing from adhering to the wound, enabling the dressing to be changed without disrupting the partially healed wound or causing pain. Honey provides a chemical debridement action, which is partially explained by the generation of hydrogen peroxide in the 'Fenton' reaction, where H_20_2 reacts with ferrous ions, yielding the hydroxyl radicals (Figure 1). The acid pH does contribute to the ideal environment for fibroblastic activity – migration, proliferation and organisation of collagen, which results in stimulation of wound healing.

Mode of application of honey

It is recommended to clean the wound first (preferentially with saline) both before dressing it with honey and when dressings are changed [20]. Honey, in a gel form, should be applied liberally either directly to the wound or to the dressing with the aid of a sterile spatula, where appropriate. A thin absorbent dressing with a non/low adhering surface should be used to cover the wound gel, with additional absorbent secondary dressing applied as required [20].

The frequency of dressing changes required depends on how rapidly the wound gel is being diluted by exudate. Daily dressing changes are usual during the initial stages of wound healing; more frequent changes may be needed if the wound gel is being diluted by a heavily exudating wound. When exudation is reduced, dressing changes can be less regular (2-3 days) [21].

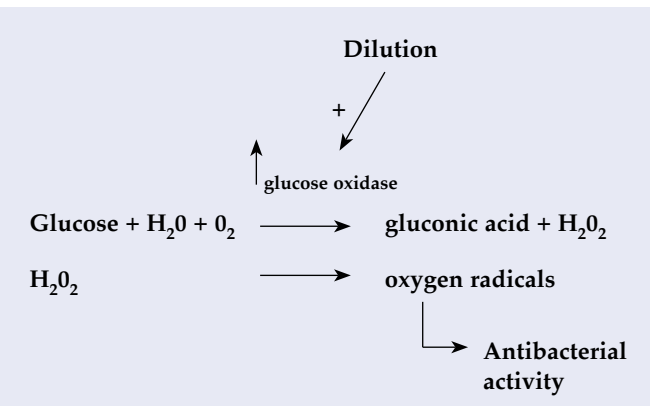
The effectiveness of honey in reducing inflammation and exudation should lead to less frequent changes being required later. Therefore, there should be no need to change a dressing frequently to prevent bacterial growth underneath, as the antibacterial activity of honey will prevent this if there is not excessive dilution by exudate; this is especially true if a honey with a high level of activity is selected.

Methods

The Pubmed, MEDLINE, EMBASE, CINAHL database and the Cochrane library were searched for relevant publications on the efficacy of honey as an antibacterial agent and in the promotion of wound healing in chronic leg ulcers 1980-2004. Search terms were honey, Manuka honey, chronic leg ulcers and wound dressing. Only publications on the use of honey for treatment of chronic leg ulcers were selected.

The Internet was searched, particularly the University of Waikato [22]; the date of the last search was 20 February 2004. Authors were not contacted for original data to avoid bias in the analysis of data. All RCTs and non-RCTs that compare the use of HDs with other dressing agents in leg ulcers were reviewed for analysis. Only RCTs and non-RCTs

Figure 1. Chemical debridement action.



were analysed and validated. The simple approach to assess validity of studies as described in the *Cochrane Reviewers' Handbook 4.2.1* was applied on the studies that were selected (Table 1) [23]. The main outcomes were the wounds' healing time and the number of wounds, initially with bacterial growth, which were rendered sterile by honey use.

Results

We found 13 publications in the use of honey in chronic leg ulcers but only two were clinical trials, non-RCT.

Oluwatosin *et al.* compared topical honey to phenytoin in the treatment of chronic leg ulcers [24]. Fifty cases of chronic leg ulceration were studied, each for a period of 4 weeks. They were assigned into three groups: the first group of patients were managed with honey, the second with phenytoin/honey mixture, and the last received phenytoin topical treatment. He found that phenytoin was superior to honey as a topical agent in the treatment of chronic ulcers but not statistically significant.

In this study, there is a moderate risk of bias that raises some doubt about the results. Firstly, there is a lack of central randomisation and allocation concealment was unclear. Secondly, there was inadequate blinding to the treatments given. Lastly, the study compares three small groups of patients with different wound management, which weakens the overall validity of results.

The second study from the Netherlands evaluated the use and safety of a honey-medicated dressing in 60 patients with chronic (n=21), complicated surgical (n=23), or acute traumatic (n=16) wounds [1]. In all but one patient, it was found easy to apply, helpful in cleaning the wounds, and without side effects. There was also a wide range of dressing agents used in the initial group of 13 patients with chronically non-responding wounds. Unfortunately, in this study, the patient population was not limited to leg ulcers alone, and honey was not compared to any other wound dressing agents.

One retrospective analysis was conducted in patients with sickle cell disease [25] but did not fulfil review criteria and was not included in this review analysis.

Additional results

The studies analysed have been influenced by different sources of bias, especially lack of blinding, poor reporting quality and poor sample size. Due to the small number of studies, we analysed RCTs conducted on the use of honey in the dressing of wounds other than leg ulcers.

Seven RCTs were found during the same MEDLINE search; five performed in India by the same researcher [26], one preliminary report from Malaysia [27] and the last one from Istanbul, Turkey [28]. Four non-RCTs were published up to date from different authors. A total of 14 review articles have been published to date, four from the same authors looking at the role of honey in the management of wounds [19].

Efem conducted one of the first clinical trials of honey as a wound a dressing in 59 patients with recalcitrant wounds and ulcers, 47 of them treated for more than a 1 month period with conventional treatments of commercial wound dressings or systemic and topical antibiotics [9]. He observed that honey debrided wounds rapidly, replacing sloughed, gangrenous, and necrotic tissue with granulation tissue. In addition, surrounding oedema subsided and offensive-smelling wounds were rendered odourless within 1 week.

Subrahmanyam has conducted a number of studies comparing honey to conventional treatments in treating burns. In a prospective trial, 50 burn patients were randomised to be treated either with early tangential excision (TE) and skin grafting or by the application of HDs, with delayed skin grafting as necessary.

He found that in the TE group, the skin grafting take rate was 99±3% while in the HD group, the graft take rate was 74±18% ($p<0.01$). Only one TE patient died due to status asthmaticus, while there were three deaths, all from sepsis, in the HD patients. At 3 month follow-up, 92% of the TE patients had good functional and cosmetic results versus 55% in HT patients (three of whom had significant contractures). He concluded that early TE and skin grafting was clearly superior to expectant treatment using topical honey in patients with moderate burns [29].

Table 1. Validity of studies.

Risk of bias	Interpretation	Relationship to individual criteria
A: Low risk of bias	Plausible bias unlikely to seriously alter the results	All of the criteria met
B: Moderate risk of bias	Plausible bias that raises some doubt about the results	One or more criteria partly met
C: High risk of bias	Plausible bias that seriously weakens confidence in the results	One or more criteria not met

Subrahmanyam conducted another RCT, where he compared honey and silver sulfadiazine (SSD). He found that in HD wounds there was early subsidence of acute inflammatory changes, better control of infection and quicker wound healing than that observed in the SSD treated wounds. The conclusion of the study was that honey was as effective as, or more effective than, SSD [18].

Those prospective studies were well conducted, with a large numbers of patients providing statistically significant results and demonstrating that dressing of burn wounds with honey is safe and effective. However, those clinical findings in isolation provide insufficient evidence on which to base a clinical practice and a decision about which dressing to use.

Cooper and Molan conducted a study looking at the sensitivity of 58 clinical isolates of *S. aureus* to the antibacterial activity of either honey of mixed pasture source or Manuka honey [11]. They found that there was little variation between the isolates in their sensitivity to honey – minimum inhibitory concentrations were all between 2-3% for the Manuka honey and between 3-4% for the pasture honey. They concluded that honey would prevent growth of *S. aureus* if diluted by body fluids a further 7-14-fold beyond the point where their osmolarity ceased to be completely inhibitory.

Conclusion

There is increasing evidence to support the therapeutic use of honey, mostly in burns and post-operative wounds. Different research has supported that honey have several important properties – a natural anti-inflammatory effect, stimulatory effect on granulation tissue and antibacterial effect that make it a dressing agent that facilitates wound healing. The high osmolarity of honey has been considered a valuable tool in the management of sloughy and septic wounds.

However, the paucity of clinical trials on the use of honey in leg ulcers has been the downfall to its use as a first line wound dressing agent. Therefore, there is a need for RCTs to support the use of honey as a cost-effective and better alternative therapy to conventional dressing agent for chronic leg ulcers. Until then, modern clinicians will remain sceptical.

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