Evidence Summary: Wound management: medical-grade honey

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QUESTION

What is the best available evidence regarding the use of medical-grade honey for wound management?

BACKGROUND

Medical-grade honey refers to honey that has been sterilised by gamma radiation, provides an indicator of the level of the honey's antibacterial activity, is registered for medical purposes and meets national requirements for medical product labelling.[1] Medical-grade honey can be used as an ointment or gel, or impregnated into wound dressings.[2]

The antibacterial activity of medical-grade honey differs according to the floral plant source from which the nectar is derived. Honeys from different species can vary by as much as 100-fold in their level of antibacterial activity.[3] (Level 5c) Honeys with very high levels of antimicrobial activity can be sourced from New Zealand and Australian bees feeding on varieties of *Leptospermum e.g.* manuka and jellybush (*Leptospermum scoparium and polygalifolium*), and marri (*Corymbia calophylla)*and jarrah (*Eucalyptus marginata)*. Referencing antibacterial activity to phenol has become the *defacto* standard for testing honey and is used to assign the Unique Manuka Factor value to medicinal honey products (e.g. UMF® 16+).[4]

Honeys are also differentiated into two categories based on the major source of their antibacterial activity: hydrogen-peroxide dependent (e.g. marri and jarrah) and non-peroxide (*Leptospermum).* The antibacterial activity in the *Leptospermum* species honey derives from phytochemicals, primarily methylglyoxal (MGO),[4, 5] and is more stable than the hydrogen-peroxide dependent honeys which can vary significantly over time. However, the latter may be more effective as an antifungal agent.[6] (Level 5c) Commercially the MGO content is expressed as a number e.g. '500+MGO' indicating a minimum methylglyoxal concentration of 500mg per kg of honey. A direct comparison cannot be drawn between the UM and MGO factors in terms of the value of the antibacterial activity[4] but a high rating in either indicates a high level of antibacterial activity.

Honey can be significantly diluted by wound exudate or by other factors and still prevent bacterial growth. The minimum inhibitory concentration (MIC) is the lowest concentration to which honey can be diluted and still remain effective. The MIC will vary with the level of antibacterial activity of the honey used and/or the sensitivity of the various strains of the organism. Consequently there are variances reported in the MIC in the various laboratory studies that have been undertaken. For example one review reported the MIC of *Leptospermum* honey for *Staphylococcus aureus* to be 2% to 3%. In contrast, in a honey sourced in India the reported MIC for *S. aureus* was 20 to 25%. The reported MIC of *Leptospermum* honey for pseudomonads ranges from 5.5% to 9%.[3, 7] (Level 5c)

In addition to honey's topical antimicrobial properties, it has been used as an autolytic debriding agent, an anti-inflammatory, a deodoriser for malodorous wounds and for maintenance of a moist wound environment.

CLINICAL BOTTOM LINE

Effectiveness in reducing infection

There is a sizable number of laboratory studies indicating the broad spectrum of honey's antibacterial activity[7] (Level 5c) but the number of randomised control trials (RCTs) (Level 1c) on the effectiveness of medical grade honey is still limited.

A RCT (n=49) explored the feasibility of using *Leptospermum* honey, compared to conventional dressings, to reduce the incidence of wound infection after microvascular free tissue reconstruction for cancer of the head and neck. There was no significant statistical difference between the two groups in terms of positive wound swabs (p>0.09) or positive wound swabs for methicillin –resistant *S.aureus* (MRSA) (p>0.09). There was, however, a significant difference in length of hospital stay in favour of the honey group (p= 0.047), with the 95% confidence interval (CI) for the mean difference representing a saving of between 2.2 and 11.2 days.[8] (Level 1c)

In a RCT (n=368) the incidence of clinically determined infection when honey-impregnated alginate dressings were compared to 'usual care' (a variety of dressings selected as most appropriate by the district nurse) was not statistically significant between groups (p=0.228). Thirty two (17.1%) of the honey treated group experienced episodes of infection compared to 40 (22.1%) of the control group.[9] (Level 1c)

A prospective observational study of 20 spinal-cord injured (SCI) patients with chronic pressure ulcers/injuries (Grades III and IV), colonised with a variety of organisms including MRSA, found that after one week of treatment all wound swabs were void of bacterial growth.[10] (Level 4b) The use of honey in combination with systemic antibiotics to treat 15 clinically infected wounds of various types in paediatric haematology-oncology patients resulted in all wounds becoming bacteria free over the varying treatment periods with no adverse effects.[11] (Level 4c)

Of the numerous case series or case study reports using honey to treat long-standing chronic wounds that had failed to respond to other wound management strategies, only two[12, 13] found the honey did not eliminate bacteria from the wound (Levels 4c & 4d respectively). In one, [12] despite an initial improvement, the clinical infection reactivated. In the other case,[13] pre-discharge wound swabs indicated four types of bacteria with heavy growth of *Pseudomonas spp*. The authors did query whether this was colonisation as the clinical signs of infection had subsided. Failure to use a honey with a sufficient level of antibacterial activity might also have been a factor.

Of the case studies and case series that reported success in eliminating bacteria from the wounds, the majority employed honey only,[14-19] while two others[20, 21] used honey in conjunction with negative pressure wound therapy. (Levels 4c & 4d)

The potential for bacteria to develop resistance to honey derived from the *Leptospermum* bush was tested under experimental conditions. A temporary resistance was observed under long-term stepwise resistance testing but no lasting mutations were detected. The study concluded that the risk of bacteria acquiring resistance to medical grade honey will be low if honey with a high level of antibacterial activity is used consistently in clinical care.[22] (Level 5c)

Effectiveness in promoting healing

In a prospective RCT (n=42)[23] comparing honey with povidone iodine dressings in the treatment of chronic wounds (≥ 6 weeks), 32% of the honey group achieved complete healing in six weeks compared to none in the comparator group. The median surface area in the povidone iodine group reduced from 4.25cm^2 to 1.95cm^2 at week six while in the honey group reduction was from 4.35cm^2 to 0.55cm^2 (p=0.05). (Level 1c)

In Jull's[9] RCT 55.6% (104/187) of the venous leg ulcers in the honey treated group had healed completely at 12 weeks compared to 49.7% (90/181) in the usual care group, a result that was not statistically significant (p=0.258). The mean time to healing was 63.5 days for those receiving topical honey and 65.3days in the comparator group (p=0.553). (Level 1c) Likewise, an RCT[24] comparing honey to standard therapy, the median healing time between the two groups was not statistically significant (p=0.134) nor was the time to 50% reduction in wound area (p=0.287). However the authors noted that both complete healing time and time to 50% reduction in wound area were quicker for the honey group (median 100 days compared to 140 days and 32 days compared to 46 days respectively) which were of clinical significance. It should be noted that this study was underpowered due to recruitment difficulties. (24) (Level 1c) Similar results were found in a RCT[25] comparing honey versus silver coated bandages for malignant wounds. There was no significant statistical difference between the groups in either median decrease in wound size (p=0.563) or in wound cleanliness (p=0.145). However from a clinical perspective the median decrease in wound size in the honey group (15cm^2 vs 8cm^2) was significant.[25] (Level 1c)

In the observational study using honey to treat chronic pressure ulcers/injuries in patients with SCI, in four weeks 18 (90%) of the wounds had completely healed and the scars were soft and elastic.[10] (Level 4b) Another observational study of 11 patients (10 of whom had a tissue defect resulting from trauma) who required spilt skin grafting had honey applied to the graft site. Dressings were done at day 5 post-operatively and then alternate days thereafter until complete healing. There were no cases of graft loss, mobilisation of the graft, hematoma, infection or allergic reactions over an average of 17 months follow up.[26] (Level 4b) In evaluating honey-impregnated tulle dressings 80% (16/20) of the wounds showed improvement with less slough and movement along the healing continuum (duration of follow-up not specified).[27] (Level 4b)

In the case series and case studies (Levels 4c & 4d) on the use of honey primarily in wounds which had not responded to other treatments, six reported on successful wound closures over varying periods of time (2 to 28weeks).[11, 15, 17, 19, 28, 29] Five reported progress on granulation and epithelisation at the time of reporting. [6, 18, 20, 21] Only one study reported two cases in which there was no progress in healing; in both these wounds honey was not effective in eradicating infection.[12]

Effectiveness in reducing wound malodour

The RCT comparing honey and silver coated dressings for the treatment of malignant wounds over a period of four weeks found both treatments demonstrated a statistically significant reduction in malodour over the intervention period (p=0.007) with no significant difference between groups (p=0.862).[25] (Level 1c)

In the RCT comparing honey with conventional dressings in reconstruction surgery for patients with head and neck cancer, the percentages of patients in both groups who were satisfied/very satisfied with control of odour were almost the same: honey 17 (81%) and conventional dressings 14 (82%).[8] (Level 1c)

Four case studies also reported on the rapid reduction and elimination of odour when using honey dressings,[12, 13, 21, 29] in the first case[12] despite the resurgence of infection in the wound. (Level 4d)

Effectiveness in relation to pain and patient comfort

A number of studies reported on pain, including general wound pain (in particular those studies focusing on patients with chronic wounds) and /or pain associated with the dressing procedure. One RCT,[23] using an eleven point (0 to 10) Visual Analogue Scale (VAS), found the median pain score for the honey group reduced from 7 to 1 by the sixth week of treatment while the povidone iodine group only reduced to 5 in the same time period. The overall VAS comfort scores for the honey group increased from 4 to 9 while the povidone iodine group only increased from 4 to 6 in the same period. (Level 1c) In Robson, et. al.'s[24] RCT involving patients with wounds healing by secondary intention, only one patient out of 52 in the honey treated group experienced pain. (Level 1c) Another RCT[9] indicated that there were significantly more reports of ulcer pain in the honey treated group than the usual care group [47 vs 18, p = 0.00, relative risk (RR) 2.5 (95% CI 1.5 to 4.2)] but pain intensity was not recorded. Only four of the 31 participants who withdrew from the study gave pain as their reason for withdrawing. A third RCT[25] found there was no significant difference in VAS scores for wound pain (p=0.733) between the honey versus silver coated dressing groups. (Level 1c) A fourth RCT[30] also found no difference between the mean VAS pain values of honey and paraffin tulle gras dressing groups, with the scores in both groups being low [1.6 standard deviation (SD) 1.22 vs 1.57, SD 1.3: p=0.37]. (Level 1c)

An observational study and two case studies reported positive responses in terms of wound pain to honey dressings. Of the 40 patients in the observational study,[31] (Level 4b) 18 (72%) reported a decrease in pain while in five (20%) the level of pain remained the same and the remaining two patients withdrew from the study due to continuous pain. In one case study[18] over a 16 day period the patient's severe pain on admission had reduced. In the other[16] in one month the patient's VAS pain score had diminished from 9 to 2 then, after a further month, the score was zero. (Level 4d)

In relation to pain associated with dressing the wound, the study[8] comparing honey with conventional dressings for the head and neck microvascular tissue reconstruction found that 62% (13/21) of the honey group and 69% (11/16) of the comparison group always/ sometimes experienced pain on removal of the dressing (with three in each group indicating it was always painful). Eighty six percent (18/21) of the honey group rated the comfort of the dressing as satisfactory/very satisfactory compared to 76% (13/17) of the conventional dressing group. Neither of these results was statistically significant. (Level 1c) In the RCT[30] comparing honey and tulle-gras dressings following toenail surgery the mean VAS pain scores experienced during dressing changes were 1.26 (SD 1.09) and 1.23 (SD 0.84) (p=0.56) respectively. (Level 1c)

In an observational study[27] involving the use of a honey-impregnated tulle dressing for 20 patients, only four (20%) found the dressing uncomfortable. Pain was found to subside after the first dressing. (Level 4b) Another observational study[32] of 40 patients with recalcitrant leg ulcers reported that no patients found the honey dressing removal painful. Two case studies and two case series reported either no pain,[15] reduction or no increase.[16, 18, 29] In another case series only one patient experienced severe pain (which was opioid resistant) on application of honey.[14] In a fourth case series slight pain eased after 20-30 minutes post application. (Level 4d) (Level 5c)

Storage

Factors such as temperature and exposure to light can affect the stability of the antibacterial activity of honey. Storage at 4^0C has been found to mitigate loss of activity to some extent.[6] (Level 5c)

ADVERSE EFFECTS

- Honey dressings should be avoided in patients with a known history of allergy to honey.[2] Individuals who have bee or bee sting allergies are usually not allergic to properly irradiated honey products.[33]
- Due to honey's osmotic effect drawing fluid from surrounding tissues, increased levels of exudate may increase the risk of maceration of the surrounding skin.[16,32] (Levels 4d & 4B respectively)

CHARACTERISTICS OF THE EVIDENCE

This evidence summary is based on a structured search of the literature and selected evidence-based health care databases using the search terms honey and medical grade honey. The evidence in this summary comes from:

- Six randomised control trials[8, 9, 23-25, 30] *(Level of evidence 1c)*
- Five observational studies[10, 26, 27, 31, 32] *(Level of evidence 4b)*
- Six case series[11, 12, 14, 18, 28, 29] *(Level of evidence 4c)*
- Seven case reports[13, 15-17, 19-21] *(Level of evidence 4d)*
- Three in-vitro studies [3, 6, 22] *(Level of evidence 5d)*
- Three review articles[1, 2, 7] *(included studies of various levels of evidence)*

[Note: The following systematic reviews were not included as the analyses did not differentiate between included studies using medical grade or non-treated honeys.

Vanamme L, Heyneman A, Hoeksema J, Monstrey S. Honey in modern wound care: A systematic review. Burns 2013; 39(8): 1514 – 1525

Jull AB, Cullum N, Dumville J, Wetsby M, Despande S, Walker N. Honey as a topical treatment for wounds. Cochrane Database Syst Rev. 2015:6.

Wijesinghe M, Weatherall M, Perrin k, Beasley R. Honey in the treatment of burns: a systematic review and meta-analysis of its efficacy. NZ Med J 2009: 122 (1295):47-60.]

BEST PRACTICE RECOMMENDATIONS

- There is evidence to support the use of medical-grade honey for chronic wounds that are not responding to conventional treatments. (Grade B)
- Honey is effective in eliminating wound malodour. (Grade B)
- Before applying a honey dressing, ensure the patient is not allergic to honey. (Grade A)
- Assess for both general wound pain and pain associated

with dressing changes, and administer analgesics as appropriate (Grade A)

- Given honey's osmotic effect, excessive exudate may occur. This could require superabsorbent dressings and more frequent dressing changes. (Grade B)
- To avoid the potential of microbial resistance developing, only use honey products that have a high level of antimicrobial activity e.g. UMF15+, >500+MGO, and change the dressing regularly particularly in heavily exuding wounds.(Grade B)
- Ensure honey products are stored in accordance with the manufacturer's instructions and adhere to the 'use-by-date'. (Grade A)

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