An observational study of the use of a honey impregnated dressing (MelMax®) in the treatment of wounds

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Background to the use of honey in wounds

The historical and current literature reports the successful use of honey to manage a diversity of wound aetiologies. However, only in the last 40 years is research on its mode of action and contribution to wound healing being investigated. Gethin G, Cowman S. (2005).

Honey has been shown to reduce *Pseudomonas* in wounds (Cooper and Molan 1999) and has antiseptic properties, possibly with the same osmotic action as sugar. Honey, placed cutaneous on wounds, accelerates the healing process (Gethin and Cowman 2005: Oryan and Zaker 1998). In fact, Positive findings on honey in wound care have been reported from 17 randomized controlled trials involving a total of 1965 participants, and 5 clinical trials of other forms involving 97 participants treated with honey. The effectiveness of honey in assisting wound healing has also been demonstrated in 16 trials on a total of 533 wounds on experimental animals (Molan 2006).

In one case study a patient with dystrophic epidermolysis bullosa of 20 years' duration had received many treatments such as dressings and creams and on occasions the wound began to heal but never progressed to closure. A honey impregnated dressing was used and the wound healed successfully in 15 weeks (Hon 2005). Clinical observations suggest that honey holds significant promise particularly in the management of non-healing wounds (Dunford 2005).

The antibacterial property of honey was first recognised in 1892 by van Ketel (Dustmann 1979). Honey is a supersaturated sugar solution with a low water activity which means that there is little water available to support the growth of bacteria and yeast (Molan 1992). Also, honey, like other saturated sugar
syrups and sugar pastes, has an osmolarity sufficient to inhibit microbial growth (Chirife et al. 1983).

Hydrogen peroxide is a well-known antimicrobial agent, initially hailed for its antibacterial and cleansing properties when it was first introduced into clinical practice (Turner 1983). In more recent times it has lost favour because of inflammation and damage to tissue (Saissy et al. 1995; Salahudeen et al. 1991; Halliwell and Cross 1994). However, the hydrogen peroxide concentration produced in honey activated by dilution is typically around 1 mmol/l (Molan 1992), about 1000 times less than in the 3% solution commonly used as an antiseptic. The harmful effects of hydrogen peroxide are further reduced because honey sequesters and inactivates the free iron which catalyses the formation of oxygen free radicals produced by hydrogen peroxide (Bunting 2001) and its antioxidant components help to mop up oxygen free radicals (Frankel et al. 1998).

Studies in animal models have demonstrated that honey reduces inflammation (seen histologically), compared with various controls, in deep (Postmes et al. 1997) and superficial burns and in full-thickness wounds. In addition, the glucose content of honey and the acid pH (typically between pH3 and pH4) may assist in the bacteria-destroying action of macrophages (Ryan and Majno 1977).

pH is the acronym for "Potential Hydrogen". In definition, it is the degree of concentration of hydrogen ions in a substance or solution. It is measured on a logarithmic scale from 0 to 14. The body pH is very important because pH controls the speed of biochemical reactions. There appears to be very little
written about the state of pH in wounds and its effect on wound healing. Nevertheless, the pH of a wound is known to influence healing (Dissemond et al. 2004) and it is also known that bacteria and dressings will change the wound pH. This article will examine the acidic/alkaline balance within a wound and will provide a background to the importance of wound pH and how changing that pH can, in part, control wound healing (Kaufman and Berger, 1988).

The acid / alkaline balance

As early as the seventeenth century, an amateur chemist, Robert Boyle, labelled substances as either acids or bases (alkalies) (Figure 1) and claimed acids to be sour in taste, (acid comes from the Latin term acere, which means sour) corrosive to metals, will change litmus red, and will become less acidic when mixed with bases. Bases (he claimed) were slippery, changes litmus paper blue, and become less basic when mixed with acids.

In the late 1800's, a Swedish scientist, Arrhenius, claimed that water dissolves many different compounds by separating them into their individual ions. He
suggested that acids are compounds that contain hydrogen that dissolve in water to acids such as Hydrochloric acid. At the same time, bases can be defined as substances that dissolve in water to release hydroxide ions such as sodium hydroxide. Mixing these acids and bases can cancel out or neutralize their extreme effects and a substance that is neither acidic nor basic is known as 'neutral'. The acid to alkaline balance (pH scale) is from 0 - 14 with 0 1 2 3 4 5 6 (7 healthy) 8 9 10 11 12 13 14

Oxygen deprivation in a wound will lead to lower fluid pH whereas the more oxygen rich the wound fluid the higher the pH. The pH range is from 0 to 14, with 7.0 being neutral and related to health with anything above 7.0 being alkaline, anything below 7.0 considered acidic.

The ideal pH balance for blood is 7.4 and human blood stays in a very narrow pH range of 7.35 - 7.45 and above or below this range means symptoms and disease (Majno, and Joris 1996) and this nominal value of pH is regulated very accurately by the body. If the pH of the blood gets outside the range of 7.35 to 7.45 the results can be serious and even fatal as at a value of 7.8, cells stop functioning and the patient dies.

While the interstitial fluid exhibits a pH near neutral, the pH of intact skin ranges from about 4.8 to 6.0 and this low pH of the skin is attributed mainly to the presence of the so-called "acid mantle," a natural skin barrier to the external environment (Dikstein and Zlotogorsky 1989). An acidic balance will decrease the ability of the body to absorb minerals and other nutrients, as well as decreasing the energy production in the cells and the ability to repair damaged cells. The low pH will also decrease the body’s ability to detoxify
heavy metals while it provides an environment in which tumor cells thrive, and will make it more susceptible to fatigue and illness (Majno, and Joris 1996).

**Wound pH and the relationship to healing**

The role of wound bed pH has proven to be of fundamental importance during the healing of chronic wounds, and prolonged chemical acidification of the wound bed has been shown to increase the healing rate in chronic venous leg ulcers (Wilson et al. 1979).

Hypoxia within the tissues is one of the major signals that induces angiogenesis (growth of new blood vessels) and, at the same time, the hypoxic condition will lead to reduced extracellular pH (Goerges, and Nugent 2004). This development of new vessels (angiogenesis) is essential to wound healing and when the hypoxic gradient is destroyed capillary growth ceases (Knighton et al. 1981).

Wound beds have been shown to have a natural extracellular pH ~6 (Goerges, and Nugent 2004) and it could be expected that the acidic pH would have detrimental effects on endothelial cells. However, endothelial cells survive fairly well under these conditions (Burbridge, et al. 1999). Indeed, it was found that the rate of microvessel growth is increased at acidic pH in an endothelial cell culture model system and, therefore, local changes in the extracellular environment, such as acidification, might actually stimulate microvessel growth (Burbridge et al. 1999). Extracellular pH could also have an impact on extracellular protein structure and interactions, which may ultimately also have an influence on cell activity (Goerges and Nugent 2004).
Dressings and wound pH

The centre of a wound space is usually hypoxic (Phillips et al. 1995), hence the acidic tendency in the wound bed as hypoxia induces an acidic response. Hydrocolloids, which have an occlusive effect, generate a further temporary oxygen depletion in the site of the injury (Knighton et al. 1981; Varghese et al. 1986), reducing the pH balance even further. Scientific experiments revealed that this oxygen depletion in the damaged area will stimulate angiogenesis and sprouting of the vessels into the wound site (Knighton et al. 1981). The oxygen tension (pO2) in wounds dressed with hydrocolloid dressings is usually very low and the pH is in the acid region (Varghese et al., 1986). This environment is also thought to have an inhibiting effect on the growth of some bacterial species (Thomas 2002).

In normal wound healing, in the acute phase, protease levels rise in response to the wounding and, when present in appropriate concentrations, proteases promote cell migration and activate growth factors and then decrease as the wound heals. A consistent feature of chronic wound is chronic inflammation which is associated with a rise in neutrophils. These neutrophils and their proteases are implicated in tissue damage in chronic wounds (Yager and Nwomeh, 1999) and, in chronic wounds, protease levels remain elevated and this prolongs the inflammatory phase and reduces fibroblast proliferation (Phillips et al. 1998).

Proteolytic activity is sensitive to the environmental pH and decreasing the pH level could thus be a simple and effective way of reducing protease activity and promoting healing (Greener et al. 2005). Prager (1999) found that
Investigation of MelMax®

Proteolytic activity is greatest at a pH of 8.4. Collagen dressings will bind excess proteases and other inflammatory proteins to its structure and lowers the wound pH to around pH5 which, in turn, helps to reduce the harmful protease activity.

The relationship of bacteria to wound pH

The optimal pH of granulation wound for the take of skin graft is 7.2-7.5 (Chai 1992), and this neutral to alkaline level will prevent the growth of bacteria within the graft site. Chai identified that the pH of granulation of a burn wound is directly related to quantity and species of bacteria in the granulation tissue. Chai also found that the wound pH is 6.7 or lower when the number of *Escherichia coli* or *Staphylococcus aureus* is over 10(7)/gm of granulation tissue. Conversely, the wound pH is 8.0 when the number of *Pseudomonas aeruginosa* (Figure 2) is 10(8)/gm of granulation tissue (Chai 1992). What Chai did not explain was why certain dressings can lower the pH without actually encouraging *Escherichia coli* or *Staphylococcus aureus*. This may indicate that the bacteria are responsible for lowering the pH when they are present, but are not actually encouraged into the wound by the acidic / alkaline balance of the wound bed. *Pseudomonas aeruginosa* is very damaging to the skin surrounding the wound containing...
Pseudomonas aeruginosa. As Pseudomonas aeruginosa functions in an environment of pH 8 and proteolytic activity is greatest at pH 8, then, perhaps, this could provide an explanation for why the periwound area is often affected. Also, if the environment is already at pH 8 when proteolytic activity is at its greatest, then Pseudomonas aeruginosa will find the wound bed an optimum place to be.

An old and very out-dated method of treating Pseudomonas aeruginosa was to soak the wound in acetic acid. This is a little like soaking open wounds in vinegar and could be extremely painful for the patient. Nevertheless, the rational was always sound as Pseudomonas aeruginosa creates a pH of 8.0 and the acetic acid would reduce that pH dramatically so that the bacteria could not survive. Perhaps a recommendation for future research would be the effect that changing the pH has on bacterial contamination. For instance, would lowering the pH of a wound reduce Pseudomonas aeruginosa colonisation and how that could be achieved without causing the patient pain.

The action of honey creates an acidic environment and promotes an enzyme that produces the small amounts of hydrogen peroxide previously described. This will prevent bacterial growth through its acidic pH. At the same time, the low pH could be responsible for lowering proteases within the wound and this would also promote healing.
Purpose of Study

The purpose of this study is to evaluate the efficacy and potential of MelMax®, honey impregnated dressing in achieving wound closure in common types of wounds found in patients in the community.

Methods

Wound healing prognosis is difficult to predict. However, Cukjati et al. (2001) arranged in order of decreasing prediction capability, prognostic factors as follows:

- Wound size
- Patient's age
- Elapsed time from wound appearance to the beginning of the treatment
- Width-to-length ratio
- Location and type of treatment.

Added to this is the knowledge that wounds colonised by bacteria will be slow to heal or completely intractable. Therefore, the patient’s age, wound size, duration of wound and width to length measurements were all recorded.

The wounds were chronic and greater than 3 months and in a deteriorating or static phase.

Study aims

1. To gain real world learning of the dressing to provide guidance to clinicians
2. Utilise results from the study (assuming positive) to market product
**Study objectives**

To evaluate the effectiveness of MelMax® in non-healing chronic wounds of longer duration than 3 months. The parameters being measured were pain levels during wear time, pH status, rate of healing and ease of use.

Assessment included:

- The Verbal Descriptor Pain Scale 1-10
- The subjects’ self-report
- Nurses reported experience of using the dressing during the study
- Evidence of healing with photography and planimetry measurements
- pH strip test.

**Investigator/site**

Principal investigator:

Sylvie Hampton. Tissue Viability Consultant

Eastbourne

**Study design**

This was a prospective, descriptive, evaluative, non-blinded clinical study using individual case studies with a sample size of 31 patients with recalcitrant wounds (non-healing wounds present for more than 3 months). The study duration was officially 6 weeks for each patient, but decisions to continue beyond the study time was based on clinician assessment of patient need.
The selected patients were those with chronic, non-healing wounds and the status of ‘non-healing’ was established by the investigator. The assessment was undertaken by research nurses, trained to undertake the assessment, and the subjects were carefully selected to provide a cross section of the wound population. Those with established arterial disease considered detrimental to healing were excluded from the study.

The patients were screened, consented and enrolled to the study by the research nurse. After granting informed consent, each patient was allocated a unique ID for identification. The frequency of dressing change and type of compression used was according to individual assessed need and local protocol.

A case report form was administered on entry, weekly for 6 weeks and at the patient exit point from the study. Measurements were undertaken on week 1 and week 6 as well as photographs being taken.

- Each subject was provided with a full written and verbal explanation of the evaluation
- Each subject was given time to discuss their problems with the research nurse and assisted with developing realistic aims for their problem wounds
- If any patient was unable to provide informed consent, then nurses and patient’s relatives discussed the benefits to the patient and made a decision away from TVCS Consultants
- Photographs are very powerful evidence of wound healing rates and therefore, visits and photographs were undertaken (with the subject’s permission) weekly by the evaluating team.
- Any wound care required during the interim period (between the weekly visits by the evaluating team) was provided by the responsible primary
nurse or the patient themselves. The nurses were provided with education in how to use and apply the MelMax® dressing.

- MelMax® dressings were provided so that care could be continuous.
- Pain was assessed on a recognised scale of 1-10 with 10 being the worst pain to possibly experience and 1 = no pain.
- Each patient with a leg ulcer wound was assessed for venous/arterial insufficiency with Doppler ultrasound by the research nurse. If the outcome of the assessment indicates venous disease, then orthopaedic wool and short-stretch compression was used as an adjunct to MelMax® and applied over the dressing. This was used at least 2 weeks prior to any patient being included in the study.
- Healing rates were established through wound measurements.

Subject selection

Patients were recruited from NHS clinic, nursing homes, primary care trusts and from TVCS clinic.

Inclusion criteria:

- Signed informed consent
- Adult patients over the age of 18 years
- Patients with non-healing wounds of > 3 months duration
- Patients (or their advocate) able to demonstrate understanding through verbalisation and performance, information about the study and the study dressing
- Patients (or their advocate) able to articulate information about their leg ulcer/pressure ulcer management

Exclusion criteria:

- Patients who in the judgement of the nurse are not appropriate for the study
- Patients who refuse to take part in the evaluation
- Patients without an advocate
Patients not undergoing compression therapy for venous leg ulceration

Patients who have existing neurological disorders that would alter pain perception (i.e. Guillain-Barre syndrome, multiple sclerosis and myasthenia gravis)

Patients with pre-existing wound infection (confirmed by presence of cellulitis, positive wound swab) or other unrelated pain conditions

Patients with uncontrolled diabetes

Patients who are active alcohol and/or drug abusers

Patients who are currently taking immunosuppressants or any medication that would impair/influence wound healing. This may include steroids, antibiotics, specifically for treating a wound infection, radiation treatments and chemotherapy agents

Patients who have a known sensitivity or allergy to the dressing

Patients who are moribund

Patients with arterial disease of the lower limbs

Study supplies

The Sponsor supplied adequate supplies of MelMax® dressings in order to complete the study.

Methodology

The study was a prospective, descriptive, non-blinded clinical study to evaluate the effectiveness of MelMax® dressing in improving healing in recalcitrant wounds. Each wound was examined weekly where possible. Each wound was photographed and measured.

MelMax® often required a secondary dressing. TVCS were careful to apply the same dressing as secondary dressing in order to reduce the variable that could potentially occur if another dressing type was used.
Results

Figure 3. At the start of the case studies, (prior to application of MelMax®) 31 wounds were non-healing.

<table>
<thead>
<tr>
<th>Healing status prior to Melmax</th>
<th>Non-healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing status prior to Melmax</td>
<td>0</td>
</tr>
<tr>
<td>Non-healing</td>
<td>31</td>
</tr>
</tbody>
</table>

Figure 4. Although 5 were lost to follow up these 5 wounds were healing on day of discharge. 1 was discontinued as another dressing had been applied for one week. This means that 51% are in a healing status and 19% healed within the 6 week period of commencing the case studies.

Figure 4. There was a difference in cost of £2.84, per dressing change, between dressings used prior to MelMax® and post MelMax®.
Figure 5. Prior to MelMax®, there was a total average cost of £426 dressings per day, for all 31 patients. Once Melmax was commenced, this cost lowered to £339 (21% reduction in costs). This was an average, which lowered further as 6 patients healed and no longer required dressings.
Investigation of MelMax®

Average surface area (of all wounds) in squared cms

Figure 6. The pie chart demonstrates an average, healing that occurred in each wound. There is an average loss of surface area of 17 cms$^2$ in each wound.

Total square cm surface area of all wounds pre and post Melmax

Figure 7 When all wounds of those completing the study were measured, the total surface area was 689 cms$^2$. This reduced to 303 cms$^2$ on the final day (44% reduction). A total surface area loss of 235 cms$^2$ over all wounds when Melmax was applied.
Very few patients experienced pain either before or during Melmax. Those who did have pain had ALL reduced pain by day 42 apart from one patient who discontinued Melmax after 3 weeks. When she was followed up, her wound had deteriorated and the pain had returned. This had an affect on the final score. Nevertheless, the pain level on day 42 was 62.5% lower than on day 1. The reasons for this drop in level is partly due to the healing that had occurred and potentially due to the reduction in bacterial colonisation.

The exudate type of serous/haemoserous/purulent
Figure 10. On day 42, the % of purulent is 0%, the haemoserous has reduced from 46.6% to 19% and serous exudate, which demonstrates a clean wound, is up to 81%.

Figure 11. Exudate levels have significantly reduced over the 42 days.
Figure 12. This chart demonstrates how odour has significantly reduced over the 42 day period. 100% reduction in significant malodour, a 27% increase in some malodour as the significant malodour reduced and a 61% increase of no odour on day 42. This demonstrates a shift from malodour to no odour.

Figure 13. Daily dressing changes are extremely costly in nurse time and cost of dressings. This chart demonstrates how this cost is lowered from the majority on day 1 being dressed daily to every 3 days (67%) to day 42 when the majority is dressed every 4 to 7 days (77%).

Discussion

Bacteria causes odour, vaso permeability (and increased fluid loss) and pain. During a 42 day period of each case study, exudate levels reduced, pain levels reduced and fluid loss reduced significantly. Each one of these parameters can be directly related to a reduction of bacteria in the wounds.
Linked with the reduction of pH in each wound tested, we can be confident that MelMax® is responsible for an overall reduction of colonisation in these wounds. This would lower the potential for clinical infection.

The cost reduction in the 42 day period is also significant with a 44% reduction in costs of dressings per dressing change. This is without the cost of the nurse visits which range from £22 per 15 minutes for practice nurses and £80 per visit for district nurses (average of £51). Added on to the cost of an average dressing this would make the average dressing cost prior to Melmax £68.74. Therefore, the swing shown in figure 13, from the majority being dressed daily to every 3 days prior to MelMax®, to the majority being dressed 4 days to weekly, has a very large cost implication for the NHS.

Conclusion
The purpose of this series of case studies was to evaluate the efficacy and potential of MelMax®, honey impregnated dressing in achieving wound closure in common types of wounds found in patients in the community. This was fully achieved as shown in the photographs and the graphs which all demonstrate a high healing potential and a reduction in bacteria and pH levels.

The MelMax®, dressing was simple to use, promoted an optimum wound healing environment and has a high cost saving implication. It also appeared to reduce pain in painful wounds, although this may be related to the reduction of bacterial colonisation.
References


