DOUG NESTJONES  
Consultant specialist in woundcare, University of Reading

JAN VANDEPUTTE  
Wound care expert, RENVA bvba, Belgium

References

Laboratory evidence suggests that honey has antibacterial properties that are due partly to its acidity and partly to phytochemicals from the nectar of particular plants (Molan, 2004). More recent research, however, shows that the phytochemicals do not play such a major role, as discussed later in this article (Nisbet et al, 2010). Honey can remove *Enterococcus* species and *Pseudomonas aeruginosa* from multiple, infected, non-healing leg ulcers caused by meningococcal septicaemia (Dunford et al, 2000), with simultaneous loss of malodour, as well as a reduction in pain.

The most noticeable effect of using honey on a wound is the rapid formation of granulation tissue, which marks the transition from chronic inflammation to wound repair, followed by the clearance of infection (Efem, 1988; Hejase et al, 1996; Baghel et al, 2009). (For a complete overview of the benefits of honey in wound care, the authors refer to Molan [2002]).
It is clear that honey can be considered as nature’s high-tech dressing, but honey itself is not user-friendly. Nor is the use of honey in wound care a new phenomenon — the ancient Egyptians mixed honey with fat and other ingredients (Jones, 2001).

Honey does not always kill fungi to the same extent as it kills bacteria (Will* et al, 1992), and the concentration of honey needed to kill Candida albicans is usually 100%, whereas most bacteria are killed at concentrations of 20% and even 10%. The main reason for honey’s antibacterial qualities is its osmotic effect (high concentration of molecules) and the presence of glucose, which produces hydrogen peroxide in small amounts, but enough to kill microorganisms.

Schmidt et al (1993) have demonstrated that hydrogen peroxide (H\(_2\)O\(_2\)) stimulates fibroblast growth in cell culture at micro- and nanomolar concentrations. The hydrogen peroxide production of any wound technology is, in the authors’ experience quite important, but is often clouded by other factors, such as the honey source.

Nisbet et al (2010), evaluated three different types of honey to check the phytochemical effect on the healing of full-thickness wounds in rabbits. Their aim was to see a difference associated with the flower source of the honeys. They wrongly assumed that, currently, only two (Medihoney™[Derma Sciences] and Manuka honey) are approved for use in wounds (this is not the case and many honeys are actually approved by CE legislation to be used in wounds), and therefore, they expected to see a difference in healing between the different honeys.

More specifically, Nisbet et al (2010) wanted to discover whether unifloral honey was better than multifloral honey, as had been suggested in some publications, such as Subrahmanyam et al (2001). Nisbet et al (2010), could find no statistical difference between the honeys. This is consistent with the authors’ experience, that the origin of the honey used in a wound care preparation is not the major factor in obtaining a functional product. The key, then, is how the honey is treated during the production/sterilisation process.

In some commercially available gels, certain ingredients can create allergies or can destroy the benefits of the honey. For instance, when honey is heated above 40°C, glucose oxidase will be destroyed and will fail to produce H\(_2\)O\(_2\) when in contact with water/wound fluid. When honey hydrogels (mixture of honey and monomers) are manufactured, they are heavily diluted with water, and irradiated to achieve maximum cross-linking, which destroys all of the benefits of the honey. Some honeys, such as Manuka honey, do not generate H\(_2\)O\(_2\) as they naturally contain vitamin C, which destroys the H\(_2\)O\(_2\) as soon as it is produced.

In some commercially available honey gels, vitamin C is an ingredient (displayed on the product packaging), which implies that these gels do not produce H\(_2\)O\(_2\) at all. It is also important to check the pH of the honey gels to evaluate whether the pH is still in the range of 3.2–4.5. As explained later in this article, the pH level of the product used on wounds with a low pH (3–5) can have a very positive effect on the healing (Melladerm Plus has a pH level of 4.3).

Honey has a pH of between 3.2 to 4.5, but when mixed with other components, the end product can have a pH of 7 and above, thus losing the benefits of acidity. In other words, it is very difficult for a clinician to evaluate the difference of the commercially available honey products because most companies tend to advertise the honey source and the benefits that this brings, but fail to explain the consequences of the production process used to manufacture/sterilise the end product.

A new honey-based gel, Melladerm Plus, was developed by SanoMed Manufacturing. Melladerm Plus consists of honey, PEG 4000, propylene glycol and glycerine. This gel is patented (Europe and USA), CE marked and has been on the market for around four years. In this article, the authors will elaborate on some tests involving this product and the clinical outcomes.

ZONE OF INHIBITION TEST

To evaluate the long-term effects of H\(_2\)O\(_2\) production, a zone of inhibition test was performed, showing that honey gel could be diluted 30 times before losing its antibacterial activity against Staphylococcus aureus. To execute the

References


Wounds UK 2012, Vol 8, No 2 107
actual assay, the authors chose an LMG-reference culture, i.e. *S. aureus subsp. aureus*. The test strain is cultivated in triple sugar broth (TBS) and then incubated at 35°C for 24 hours. By means of pour plate method, the concentration of the overnight culture is determined (1x10^9 cfu/ml).

A 1,000-fold dilution of this overnight culture in sterile physiological water provides a homogeneous suspension with a concentration of 1x10^6 cfu/ml. Then 1.0ml of this suspension is added to 100ml of an appropriate medium (Colombia-agar +5% sheep blood) and gives an end concentration of 1x10^4 cfu/ml. The inoculated medium is now ready to be poured into glass petri-dishes (19cm in diameter, per 100ml).

When the medium is solid, the authors pierced five holes (Ø — 13.8mm) on each plate. A serial dilution of the honey gel was prepared in sterile distilled water. A 20% (m/v%) stock solution of the gel was prepared in sterile distilled water. Starting from this solution, the following dilutions were made — 20% down to 1% m/v, with every whole percentage in between. From each dilution, 200µl is transferred into the prepared wells in the plates. As mentioned before, at five dilutions per plate.

Due to the β-haemolytic activity (haemolytic activity leads to a colour forming in the agar gel and allows an easy detection of where the bacteria are) of the used strand of *S. aureus*, it is relatively easy to detect the inhibition zones (the darker, brownish circles around the pierced wells, (see Figures 1 and 2).

The authors concluded that Melladerm Plus inhibits the growth of *S. aureus* when the concentration of the product is higher than 4% mass/volume (m/v).

This clearly demonstrates the effect of the H₂O₂ activity of the honey. Honey or honey-based products that fail to produce H₂O₂ must have another mechanism to achieve the same antibacterial effect when diluted.

Oxyhemoglobin releases its oxygen more readily in an acidic environment

In 1973, Leveen et al published an article showing that when the release of oxygen from oxyhemoglobin is impeded, oxygen transport to the tissues is impaired sufficiently to interfere with wound healing and also to cause tissue necrosis.

Oxyhemoglobin releases its oxygen more readily in an acidic environment. As ascertained by the Bohr effect, when there are excess protons in the solution (blood), the state of deoxyhemoglobin is more likely to exist than oxyhemoglobin. Even small changes in pH could induce wide changes in the standard oxygen dissociation curve (Naeraa et al, 1963).

Leveen et al (1973) tested 137 wounds and found that 89.9% had a pH of 7.4–9. The higher the pH, the longer it took to heal the wounds. Leveen demonstrated that a five-fold increase of oxygen released from the oxyhemoglobin was obtained by a shift of only 0.9 pH units. Any factor that causes even a small change in the pH of the healing wound might appreciably alter the available supply of oxygen to the tissue. Conversely, even mild acidification of a wound might substantially hasten healing by enriching the supply of oxygen to the tissues (Kaufman et al, 1985).

The authors believe that using a gel containing high molecular weight water soluble particles, such as PEG 4000, with a low pH can change the local pH in a wound — resulting in a significantly higher oxygen perfusion in the wound. The pH

Figure 1 (above) shows dilutions 11% to 15% m/v while Figure 2 (below) shows dilutions 1% to 5% m/v.

References


Jones HR (2001) Honey and healing through the ages. In Munn, PA (ed) *Honey and healing*. IBRA; Cardiff, 1-4


of Melladerm Plus is 5. Faster healing was seen when using Melladerm Plus in acute and chronic wounds.

More research should reveal if this is due to the acidification of the wound. A low pH will also stop proteases from working in the wound. Most metalloproteases are active (dissolving proteins) in a pH range of 7–9. Lowering the pH will stop the proteases from breaking down the wound tissue.

**METHOD**

Some 147 patients with chronic wounds were treated with the test dressing until complete wound closure was achieved. The clinical data were obtained in accordance with Medical Device Directive (MDD), annex X and harmonised standard ISO 14155. Community nurses treated the majority of the patients at home, while the rest were treated at hospital or in a care home setting. Where possible, photographs were dated and a label was placed next to the wound. None of the nurses were paid or compensated for taking part in the study and a computer programme was used to collect the data in a standardised way. The size of the ulcers and the degree of pathology was important in order to effectively interpret the healing time.

Next to healing time, other parameters were also taken into account. The honey gel was found to be very user-friendly and usually the nurse applied the gel on to gauze or a non-adherent dressing (Melolin®). Most nurses reported that a thin layer of gel applied once a day gave better results than large amounts of gel. Honey-based products are often known for a stinging effect during the first hours and the authors discovered that in the study group, complaints about a pain sensation almost always related to patients with arterial insufficiency.

In the other pathology group, complaints about pain were not often reported. In some cases, a red inflammatory ring around the wound was evident, especially in wounds with lots of necrotic tissue, which is quickly dissolved by the honey gel. The authors believe that this is due to the acidic environment bringing more blood into the wound area.

**Performance compared with other dressings**

In order to get some kind of perspective, the authors looked at older data (from 1998–2002), as well as other photo-documented case reports that used high-tech dressings. They also used an existing database of 74 patients (nine skin tears, 18 burns, 24 venous ulcers and 22 pressure ulcers) to compare the healing rates with the honey gel (see Table 1 for a comparison of healing times). The dressings employed in the study were all moist healing and were all considered high-tech dressings. Examples include: DuoDerm® (Convatec), Comfeel® (Coloplast), Kaltostat® (Convatec), OpSite® (Smith & Nephew), Intra Site Gel® (Smith & Nephew), Alevyn® (Smith & Nephew), Elasto-Gel® (Southwest Technologies), Betadine® (Purdue Products) and Flamazine® (Sinclair IS Pharma).

The healing time and all other relevant parameters were also collected. The overall difference in healing time was in favour of the honey gel, with an average of 26% faster healing for all wound types.

**ANALYSIS PER WOUND TYPE**

**Burns results**

In the comparison group (those patients from the older database), there were 12 burn wounds, mainly treated with

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean healing time comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healing time with other products (days)</td>
</tr>
<tr>
<td>Skin tears</td>
<td>24</td>
</tr>
<tr>
<td>Burns</td>
<td>22</td>
</tr>
<tr>
<td>Venous ulcers</td>
<td>62</td>
</tr>
<tr>
<td>Pressure ulcers</td>
<td>93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48</td>
</tr>
</tbody>
</table>

---

**References**


Wounds UK 2012, Vol 8, No 2 109
Flamazine and Betadine. In the test dressing group, there were also 12 burns. Most of the
burns were first or superficial second-degree burns (which will heal without
surgical debridement in 21 days), and in both groups, there were two patients with
deep second-degree burns. In two cases, the authors could compare treatments for just
one patient (they had two arms burned). In these two cases the authors could see a 30%
difference in healing time in favour of the
honey gel treatment.

The average healing time for the honey
gel-treated burns was 16 days and in the
other group it was 22 days. The average
healing time difference was, therefore, 27%
faster for the honey gel group.

In both groups, the age range of the
patients encompassed infants through to
older people. The average size of the burns
was 52cm² for the honey gel group and
51cm² for the comparison group.

The difference in healing time was
statistically (unpaired t-test) significant
(the two-tailed P value = 0.0451). The
difference in healing time might be
explained by the antibacterial activity of
the honey gel and the quick debridement
of dead tissue and slough.

Skin tears
In the comparison group, there were 13
patients with skin tears, compared with 17
in the honey gel group, but four patients
were referred to the venous ulcer group,
since this was the dominant underlying
pathology. There was a variety of lesions from superficial flaps to deeper wounds.

The average size of the skin tears was
18cm² in the honey gel group and 16.2cm²
in the comparison group. The average
healing time — 18 days versus 24 days
for honey gel group and comparison
group respectively — was not statistically
significant (the two-tailed P value equals
0.4965). The difference in healing time was
significant (the two-tailed P value = 0.0011). The
average ulcer size in the honey gel group
was 21.5cm², while in the comparison
average healing time was 62 days.

The difference was not statistically
significant (the two-tailed P value
= 0.2605). The difference in healing
time was mainly attributed to a better
debridement and a more controlled
bioburden pattern in the honey gel group,
while the comparison group treated with
Betadine suffered from a lack of adequate
debridement leading to a delay in healing.

Venous ulcer
There were a total of 50 patients falling
within this category and treated with the
test dressing. The average age was 76.
Meanwhile, there were 24 patients in the
comparison group. The average healing
time for the honey gel group was 38 days
(the range being five to 90 days, with a
median of 34), whereas the comparison
group's average healing time was 62 days.
This equated to a healing time difference
of 39%, which was statistically significant
(the two-tailed P value = 0.0011). The
average ulcer size in the honey gel group
was 16cm², while in the comparison
group it was 18cm².

The first striking fact was that the healing
time of the venous ulcers was very diverse
and not related to the ulcer size. In some
cases, rather large, superficial ulcers (for
e.g., 20cm²) healed in 20 days, while
several ulcers with a size of between 1cm² to
3cm² required 90 days to complete healing.

It was discovered that a key factor is
the degree of venous insufficiency and
whether the patient is receiving the
correct compression therapy. In four cases
where different products were used for
months without healing taking place, the
wound was found to heal completely with
the honey gel. Some ulcers (for instance,
small ones on top of the inner ankle
bone) needed considerably more time
Figures 3-6 (above from top) relate to case study 1: 1) Wound before Melladerm Plus was applied. Wound had been treated with Betadine gel. 2) Wound after three days’ honey gel treatment. 3) Wound after 20 days’ honey gel treatment. Wound is debrided, while granulation and epithelialisation is commencing. 4) After 40 days, the wound is completely healed.

Figures 7-9 (above left to right) relate to case study 2: Figures 5 and 6 both show the wound after seven days of honey gel treatment — most of the crust has dissolved. Figure 7 shows the wound after 15 days of honey gel treatment and compression therapy.

Pressure ulcers

The number of patients in the honey gel test dressing group was 15, with an average age of 81.7, while in the comparison group, there were 22 patients. The extent of the ulcers varied, but in most of the cases, the patients were bedridden. The mean ulcer size was 41.6cm² in the honey gel group and 56cm² in the comparison group. The honey gel removed large amounts of necrotic tissue and due to the osmotic power of the honey granulation tissue is growing quickly.

The average healing time was 78 days for the honey gel group and 93 days for the comparison group (the two-tailed P value equalled 0.2737) and was not statistically significant; equating to an average healing time difference of 17%. The larger pressure ulcers that used to be seen in the 1990s are rarely seen now, due mainly to improved mattresses and better nursing care.

Infected ulcers

In terms of infected ulcers, there was no comparison group to compare with, but the test dressing group comprised 25 patients. The average size of the ulcers was 7.98cm², while the average healing time with the honey gel was 18 days. In those cases, the better healing rate was seen. Looking at the origin of the infected wounds the authors mainly found surgical wounds that discharged pus for a couple of days postoperatively.

In some cases, the patient was in a physically bad condition, but there were also younger, healthy patients who required surgery after road accidents. Again all the wounds did heal and the infection cleared very quickly after the application of the honey gel. The results with honey gel for the treatment of infected ulcers are very promising and can be explained by its antimicrobial activity.

DISCUSSION

To get an overview of the entire database, all of the pictures from the case reports were placed on a large table for our perusal. Various statistical tests were then performed, and 147 fully documented cases proved to be enough to draw a clear scientific conclusion.

The main positives of using honey gel are the quick debridement of necrotic tissue, its antibacterial properties and the acidification of the wound environment, which releases more oxygen into the tissue. It is clear that the honey gel has benefits in the treatment of infected wounds and in wounds with large amounts of necrotic tissue. The authors will continue to build-up the wound database in the same standardised way.

CASE STUDIES

Case study 1

A 69-year-old female with a skin tear presented with an ulcer that was 34cm² (Figures 3–6). She had previously been treated with Betadine and was not receiving any compression therapy. The new treatment plan involved applying Melladerm - WITHOUT AD.indd   7
0x0 10/06/2012 15:03
Melladerm Plus, while cleansing involved SanoSkin® Cleanser (SanoMed Manufacturing).

**Case study 2**
A 76-year-old female developed a venous ulcer on her left leg, but due to excess amounts of exudate, the whole leg became one large wound over a period of 18 months (Figures 7–9). Prior to honey gel treatment, the leg was treated by being washed in water twice a week — emollient and compression bandaging were then applied. The honey gel treatment comprised 10 minutes of rubbing over the entire wound area. Over 80% of the necrotic tissue was removed at this point with gentle pressure from the handle of disposable forceps. The remaining crust dissolved over the next few days.

**Case study 3**
This case involves a 70-year-old female with venous insufficiency and an ulcer of 1cm² (Figures 10–12). She had been treated for six months with Betadine gel, while compression therapy took place both before and after the honey gel treatment. Honey gel was prescribed by the vascular surgeon and the wound was fully healed after 51 days.

**Case study 4**
The patient was a 30-year-old male with an infected (surgical) trauma wound (Figures 13–16). The ulcer size was 12cm² and before honey-based gel the wound had been treated with Betadine. The revised treatment plan involved Melladerm Plus Tulle, as well as cleansing with SanoSkin Cleanser.

**CONCLUSION**
The honey-based gel used here appears to perform at least on a par with other high tech dressings. The clinical results are consistent with the reports of the effect of honey in wound care in other studies. Further research is, however, needed to determine the effect of the acidification of the wound and the differences in the honey products that are currently available.