Nursing Practice

Review

Wound care

In vitro and clinical studies of a new bioengineered medical-grade honey suggest it has a broad-spectrum antimicrobial effect in healing wounds

The role of bioengineered honey in wound care

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Honey has been used to treat wounds for centuries but, although published studies show the effectiveness of medical-grade honeys, a recent review judged the evidence to be of variable quality. In vitro and clinical studies of a new bioengineered medical-grade honey suggest it has a broad-spectrum antimicrobial effect.

In the UK, an ageing population, alongside a rise in long-term conditions such as obesity and diabetes, are exerting greater demands on wound care management. For example, Morgan (2015) notes a greater prevalence of acute wounds, such as minor tibial injuries in the elderly, with an age-related dimension influencing the prevalence of chronic wounds, such as diabetic foot ulcers, pressure ulcers and leg ulcers. According to Guest et al (2015), in 2012-13:

- There were around 2.2 million wounds managed by the NHS;
- Wounds accounted for 18.6 million practice nurse visits, 10.9 million community nurse visits and 3.4 million hospital outpatient visits;
- The annual cost for the NHS of managing these wounds and associated comorbidities was £5.3 billion.

Dowsett et al (2014) expect the cost of wound dressings and other materials to rise from £420m in 2014 to £461m in 2019. There is a further complication with the rise of antimicrobial resistance (AMR). A review of AMR (O'Neill, 2014) states that in Europe and the United States there are at least 50,000 deaths annually from antimicrobial-resistant infections, with a predicted global death toll of 10 million people by 2050, which would make AMR the biggest cause of death before cancer.

One way to address the challenge of wound care in the age of AMR is to consider wound therapies that limit the unnecessary use of antimicrobials, while maximising patient outcomes. Medical-grade honey, whose usage dates back to the ancient Egyptians, is one such therapy.

Honey and wound care

Honey is a viscous, super-saturated, acidic solution (pH 3.2 to 4.5) comprising around 80% sugar (such as fructose, glucose, maltose, sucrose) and 20% water, antioxidants (such as flavonoids) and proteins (such as the enzyme glucose oxidase) (Stephen-Haynes and Callaghan, 2011). The relative concentrations of ingredients vary according to plant age, origin, location, season and mode of processing (Van-damme et al, 2013; Stephen-Haynes and Callaghan, 2011). Honey's antimicrobial effect is achieved through a range of factors, outlined in Box 1.

Depending on the wound condition, in addition to its antimicrobial properties, honey can influence wound healing by:

- Deodorising, debriding and providing a moist wound environment;
- Influencing cell migration and proliferation, and collagen production to speed up wound closure;
- Stimulating or inhibiting cytokines, such as tumour necrosis factor-α and interleukin-6 from human monocytes and macrophages, which have a role in the inflammation process;
- Dehydrating and providing a microbial barrier that prevents the growth of pathogens and promotes the healing of wounds (Guest et al, 2015).

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» Increasing or decreasing the production of reactive oxygen species from neutrophils, depending on the particular wound micro-environment. The immunomodulatory activity of honey is complex because of the involvement of multiple, quantitatively variable compounds in honeys of different origins. (Majtan, 2014)

Clinical applications

Active manuka honey was the first medical-grade honey to be registered as a medical device in the UK in 2004. Medical-grade honey differs from supermarket honey in terms of its proven antimicrobial activity, traceability of source and lack of contaminants, with gamma irradiation ensuring sterility (Cooper and Gray, 2012).

Medihoney, which is also derived from manuka honey, is one of the most widely studied and used medical-grade honeys. Its antimicrobial action relies mainly on the presence of methylglyoxal (MGO), which is derived from nectar in the flowers of the Leptospermum scoparium tree. It is not only effective against wound-associated organisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *E. coli*, but also against antibiotic-resistant bacteria (Stephen-Haynes and Callaghan, 2011).

Secondary-intention healing

In a randomised controlled trial of 105 patients with wounds healing by secondary intention (where a wound is left open to heal by itself), Robson et al (2009) compared manuka honey (Medihoney) with standard wound care. They found that, although differences in healing times with manuka honey compared with standard treatment were clinically significant (100 days and 140 days, respectively), they were not statistically significant.

Diabetic ulcers

Majtan (2011) suggested that MGO is a potential risk factor in the healing of diabetic ulcers, stating that "the scope of MGO damage in diabetes is huge, because MGO is able to form adducts on protein, lipoproteins and DNAs at any site where its concentration is high". However, this was not supported by Kamaratos et al (2012) in their study of 63 patients with type 2 diabetes. They concluded that manuka honey-impregnated dressings were an effective treatment for neuropathic diabetic foot ulcers, "leading to a significant reduction in the time of healing and rapid disinfection of ulcers".

Biofilms

Cooper et al (2011) cited evidence that bacterial biofilms (a community of microbes adhering to a surface) are associated with persistent infections and linked to chronic wounds. Cooper et al used Actifon manuka honey in laboratory studies and found that biofilms of methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant *Enterococcus* were inhibited at concentrations of manuka honey that could be used clinically. They concluded that the efficacy of the product in inhibiting biofilms in vivo needs to be tested.

Manuka honey and silver

Cooper and Gray (2012) highlighted that the popularity of silver in the prevention of wound infection has been challenged by concerns over its efficacy, cost-effectiveness and safety, as well as the silver resistance of some organisms. But, while they suggested that "manuka honey is an effective alternative antibacterial product to silver for the prevention and management of wound infection", they also acknowledged that "medical devices containing either inhibitor vary in their formulations and delivery mechanisms, making generalisations unwise".

Limitations

Despite the future promise of antimicrobial honey as a novel and cheap means of treating wounds without compounding the problem of AMR, it may not necessarily be an appropriate treatment for all wound-related conditions.

A major, 26-centre trial in Australia and New Zealand involving 371 participants aimed to find the best way to stop peritoneal-dialysis-related infections (Johnson et al, 2014). The researchers assessed whether the daily application of manuka honey (Medihoney) at the exit site would prolong the time for developing peritoneal-dialysis-related infections compared with standard exit-site care plus intranasal mupirocin for nasal carriers of *S aureus*. The manuka honey was found not to be superior to nasal mupirocin for nasal carriers of *S aureus*, and the findings did not support a role for the product in the prevention of peritoneal-dialysis-associated infections.

Although evidence has accumulated in support of honey’s role in accelerating wound healing, a recent Cochrane review based on evidence published up to October 2014 deemed some of it to be of variable quality. When Jull et al (2015) assessed the effects of honey compared with alternative wound dressings and topical treatments for the healing of acute and/or chronic wounds, they identified 26 trials with a total of 3,011 participants in which honey was compared with a range of different treatments for acute and chronic wounds. Two of the trials (992 participants) were judged to provide high-quality evidence showing that honey dressings healed partial thickness burns quicker than standard treatments. One trial (50 participants) provided moderate-quality evidence suggesting that honey dressings healed postoperative wounds quicker than povidone iodine antiseptic washes followed by gauze, resulting in fewer adverse events.

The reviewers concluded, “It is not clear if honey is better or worse than other treatments for burns, mixed acute and chronic wounds, pressure ulcers, Fournier’s gangrene, venous leg ulcers, minor acute wounds, diabetic foot ulcers and Leishmaniasis as most of the evidence that exists is of low or very low quality.”

Bioengineered honey

Jull et al’s Cochrane review (2015) did not include evidence on the use of Surgihoney RO (SHRO), a bioengineered medical-grade honey that was recently placed on drug tariff. This bioengineered honey, the only one of its kind so far, has undergone a unique proprietary process that ensures high antimicrobial potency through the

**Box 1. Antimicrobial effect of honey**

The antimicrobial effect of honey is achieved through a range of factors:

- A low moisture content depletes bacteria of water and therefore prevents growth
- A high sugar content extracts water from bacteria by osmosis
- A low pH inhibits bacterial growth
- Production of hydrogen peroxide by the action of the enzyme glucose oxidase, when honey is diluted with wound exudate; the hydrogen peroxide breaks down, releasing low concentrations of reactive oxygen, destroying invading microbes and promoting healing
- The presence of bee defensin 1, an antimicrobial peptide passed to the honey from the bee’s immune system, is thought to disrupt the bacterial cell membrane
- The presence of the antimicrobial methylglyoxal – manuka honey contains up to 100 times higher concentrations of methylglyoxal than other honeys
prolonged release of hydrogen peroxide. As hydrogen peroxide breaks down, it produces reactive oxygen, exerting antimicrobial activity against both Gram positive and Gram negative bacteria, including multidrug-resistant strains, such as MRSA, *E. coli* and *P. aeruginosa* (Cooke et al., 2015).

Unlike manuka honey, which is sourced solely from the *Leptospermum scoparium* tree, SHRO can be made from any honey that meets a European standard of being independent of floral source, and free of contaminants, antibiotics and pesticides. Also, whereas manuka honey’s antimicrobial activity comes mainly from MGO, the bioengineered product’s antimicrobial activity depends on the controlled release of reactive oxygen. Its antimicrobial action is based on an ability to deliver safe, low concentrations of reactive oxygen via the formation of hydrogen peroxide over a sustained period. The breakdown of hydrogen peroxide results in the release of reactive oxygen, which attacks invading microorganisms and promotes healing. Given the bioengineered aspect of the product, the honey component can be regarded as the ‘delivery vehicle’ for the reactive oxygen.

Halstead et al. (2016) have shown that SHRO is more effective in vitro than manuka honey in destroying bacteria and biofilms. SHRO is also more cost-effective, largely because it does not depend on a single, specific floral source, as manuka honey does.

**Evidence base**

A non-comparative, observational study of SHRO was carried out in 104 patients with 114 non-healing and clinically infected wounds in England (84 patients), Ethiopia (10 patients), Uganda (six patients) and Tonga (four patients) (Dryden et al., 2016). The study population included 33 patients with leg ulcers, 20 with traumatic and surgical wounds, 18 with pressure ulcers, 14 with surgical wounds and five with diabetic ulcers. Wounds were treated with SHRO dressings. Twenty-four (21%) of the wounds healed and 90 (79%) improved. There was a reduction in wound pain, exudate, dead tissue and bacterial load.

**Use in Caesarean section**

Caesarean wound infection is a major cause of prolonged hospital stay, comorbidities and mortality, with wound infection rates of around 10% (Dryden et al., 2014a). Dryden et al conducted a prospective follow-on trial looking at surgical site infection rates in healthy women undergoing Caesarean section who were given prophylactic antibiotics. They found that SHRO dressings were effective when used on Caesarean section wounds to prevent infection, showing a 60% reduction in infection rates from 5.42% before intervention to 2.15% when using the product.

**Biofilms**

In a laboratory study funded by the National Institute for Health Research, Halstead et al. (2016) compared the bioengineered honey SHRO with two medical-grade manuka honeys (Activon and Medi-honey) and five antimicrobial dressings (AMDs) – Aquadel Ag (silver), Aquadel Ag+ Extra (silver), Actilite (honey), L-Mesitran Net (honey) and L-Mesitran Hydro (honey) – to stop biofilm formation by 16 bacterial strains, including *P. aeruginosa*, *Acinetobacter baumannii* and MRSA. All the honeys prevented biofilm formation, but SHRO was the most potent, and was superior to the medical honeys and AMDs in vitro.

**Long vascular lines**

Dryden et al. (2014b) conducted a prospective evaluation to assess the effects of SHRO on the bacterial colonisation of intravenous long lines in 60 oncology patients receiving outpatient chemotherapy; all patients were offered line dressing, with 30 receiving SHRO dressings and 30 receiving non-antimicrobial dressings. The authors concluded that the bioengineered honey is “an effective antimicrobial line-site dressing, significantly reducing line site colonisation and eradicating existing colonisation”.

**The future**

In recent years evidence around the potential benefits of medical-grade honey in clinical practice has been critically evaluated. Existing medical-grade honeys continue to be refined, but it appears that the application of bioengineering techniques can enhance the inherent antimicrobial activity of honey. NT

**References**


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