Does honey have a role in paediatric wound management?

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Abstract

Topical honey treatment has been shown to possess antimicrobial properties, promote autolytic debridement, stimulate growth of wound tissues to hasten healing, and to start the healing process in dormant wounds, stimulating anti-inflammatory activity that rapidly reduces pain, oedema and exudate production. This article provides an overview of the use of honey as a medicinal substance, particularly its use in wound treatment, and reviews the published data concerning honey as a form of complementary and alternative medicine in paediatric wound management. The literature reviewed was found by searching the PubMed, BIOSIS, and ISI Web of Science databases for the term honey. Exclusion criteria were articles where honey was used in a mixture with other therapeutic substances.

Key words: Honey ■ Paediatric ■ Child ■ Wound ■ Infection

Honey has a long history of use as a medicinal substance. Stone-age paintings dating to 6000 BC or earlier depict people gathering honey. References to the use of honey as a medicine are found in ancient scrolls (e.g. Egyptian papyri dated from 1900–1250 BC and veda (Hindu scripture) approximately 5000 years old), tablets (e.g. Sumerian clay tablets estimated to 6200 BC), and books (e.g. the Holy Koran, the Talmud, and both the Old and New Testaments of the Bible) (Molan, 1995). The ancient Egyptians used honey to treat wounds and gut conditions. Hippocrates recommended the use of honey to treat ulcers and relieve pain and thirst, and used a mixture of honey, water and other substances to treat acute fevers (Zumla and Lulat, 1989). The Bible mentions the use of honey in treating eye problems (Becks and Smedley, 1944). However, it was not until 1892 when the antibacterial property of honey was first recognized by Van Keetal (Dustman, 1979). Since then, topical honey treatment has been shown to possess antimicrobial properties, promote autolytic debridement, stimulate growth of wound tissues to hasten healing, and to start the healing process in dormant wounds, stimulating anti-inflammatory activity that rapidly reduces pain, oedema and exudate production.

What is in honey?

Honey is a carbohydrate-rich syrup produced by bees from plant nectars and from the excretions of plant-sucking insects (White et al, 1962; Siddiqui and Furgala, 1968). The exact chemical composition of honey varies depending on plant source, season and production methods; however, its major components are fructose and glucose, with lesser amounts of sucrose, other disaccharides and oligosaccharides (Siddiqui and Furgala, 1968; Thomas, 1990; Lawrence, 1999). A large number of other chemical compounds are present in small quantities, for example, potassium, syringic acid, 3,4,5-trimethoxybenzoic acid, 2-hydroxy-3-phenylpropionic acid and the flavonoid pinocembrin (Tan et al, 1989).

Medical honey can be defined as gamma-irradiated purified honey, obtained by purification of the honey from the comb of the bee *Apis mellifera* and all its subspecies.

Antibacterial, anti-inflammatory, and antiviral activity

Antibacterial activity

Honey has been shown to have antibacterial effects owing to its high osmolarity and low pH (Thomas, 1990; Ambrose et al, 1991; Molan, 1992; Booth, 2004; Marshall et al, 2005):

- Its low water activity inhibits microbial growth, particularly bacterial growth. When applied topically to wounds, water is drawn away from the wound by osmosis, helping to dry the infected tissue and inhibiting bacterial growth
- It has a low pH (typical range between 3.4 and 5.5) as a result of the formation of gluconic acid. When honey is diluted with water, glucose oxidase catalyses glucose to form gluconic acid and hydrogen peroxide. Hydrogen peroxide kills bacteria without having cytotoxic side-effects. In addition, wound healing situations are often accompanied by pH values of 7.3 from wound exudates, which is also the optimum pH range for protease activity; reducing the pH of the wound environment through the application of honey may reduce the activity of proteases, thereby facilitating tissue regeneration.

Kwakman et al (2010) have reported on the role of sugar, hydrogen peroxide, methylglyoxal, and bee defensin-1 in the antibacterial properties of honey. In their study they show that the antibacterial effects of honey are reduced after the

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combined neutralization of these factors. Similarly, Baghel et al (2009) argue that the antibacterial activity of honey is mainly a result of the presence of 'inhibins' in honey. They conclude that these inhibins consists of hydrogen peroxide, flavinoids, and phenolic acids.

White et al (1962) tested the antibacterial effects of undiluted Sudanese honey against the pathogens *Bacillus subtilis, S. aureus, E.coli, Klebsiella aerogenes* and *Pseudomonas aeruginosa*, and then repeated the experiment with with five antibiotics: ampicillin, cefradine, chloramphenicol, gentamicin and oxytetracycline. The results showed that the honey used were inhibitory against all these bacteria; however, they found that gentamicin was the only antibiotic effective against *P. aeruginosa (Table 1).*

Anti-inflammatory activity

Although the mechanisms by which honey speeds up the healing process have not been determined, there have been attempts at providing an explanation: one way in which honey may work is through the stimulation of an inflammatory response in leukocytes (Abubarfeil et al, 1999; Tonks et al, 2001, 2007). Inflammation is the mechanism which triggers the cascade of cellular events that give rise to the production of growth factors which control angiogenesis and the proliferation of fibroblasts and epithelial cells.

Tonks et al (2007) have discovered a 5.8 kDa component of manuka honey which stimulates production of tumour necrosis factor-alpha (TNF-α) via TLR4 (toll-like receptor 4). These findings reveal mechanisms and components involved in honey stimulation of cytokine induction and could potentially lead to the development of novel therapeutics to improve wound healing for patients with acute and chronic wounds.

Antiviral activity

Nitric oxide metabolites, nitrite and nitrate, have been identified in honey from Yemen, the United Arab Emirates, Germany, and India (Al-Waili, 2003a). Nitric oxide has antiviral effects against the DNA and RNA of a number of viruses, and there is some evidence of nitric oxide activity blocking HIV-1 replication (Torre et al, 2002). The presence of nitric oxide metabolites in honey and the ability of honey to increase nitric oxide production in a range of biological fluids may also explain the potent biological effects of honey (Al-Waili, 2003b, Al-Waili and Boni, 2003). Al-Waili (2004) and Holzgreve (2005) have demonstrated that honey treatment results in shorter healing times of herpes labialis lesions when compared to treatment with aciclovir.

Table 1. Manuka honey

Allen at al (1991) found that destroying the peroxide-generating ability of honey through the use of catalase was associated with a loss of antibacterial activity. Manuka honey (derived from the plant Leptospermum scoparium, and vipers bugloss (derived from the plant Echium vulgare were the only honeys tested that retained significant antibacterial activity. Willix et al (1992) showed that complete inhibition of growth of Staphyloccoccus aureus was achieved at a manuka honey concentration of only 1.8% compared with 4.9% for other honeys.

Animal studies

Animal studies allow histological examination of the healing wounds, providing additional data besides the usual measurements of decrease in wound size and time to heal. These allow us to study the effectiveness of honey in promoting the healing of standardized wounds created on experimental animals.

Bauer et al (1996) studied 24 male mice which had a surgical skin excision in the neck region. Fifty percent (n=12) of the animals had pure honey applied in a thin layer to the wounds twice daily, while the control group (n=12) had saline applied at the same frequency and time of day. They found that the mice treated with honey had a greater thickness of granulation tissue in the centre of the wounds compared to the control mice.

Postmes et al (1997) studied pigs which had deep skin burns applied on their flanks. The study compared the efficacy of honey, sugar solutions, and silver sulfadiazine of similar concentrations in wound healing. The honey and the sugar both produced more rapid healing than silver sulfadiazine, with wounds closing within 21 days for honey and sugar, but requiring between 28 and 35 days for silver sulfadiazine. The mechanism by which honey produced a more rapid and effective healing than silver sulfadiazine was not identified; however, the researchers found that the tissue treated with sugar showed more myofibroblasts than with the honey.

Medicinal honey products

There is a lot of interest within the area of chronic wound management for products with an antibacterial and anti-inflammatory quality such as honey (*Table 2*).

Medihoney has been one of the first medically certified honeys licensed as medical devices for professional wound care in Europe, the United States (FDA approval), and Australia (Molan, 2004; 2006).

Many comparative studies have been set up on the new generation of medical device grade 'honey products' (Sofka et al, 2004; Bangroo et al, 2005; Marshall et al, 2005; Simon et al, 2006). Although gamma-irradiated medical honey is available, most of the cases in the medical literature have used raw honey (Sofka et al, 2004; Simon et al, 2006; Blaser et al, 2007).

Statistical significance in comparative trials of wound dressings is rarely obtained. Many studies show beneficial effects when treating viral diseases and meticillin-resistant *S. aureus* (MRSA) infections with honey (Cooper et al, 1999; Natarajan et al, 2001; Cooper et al, 2002; Dilber et al, 2002; Torre et al, 2002; Al-Waili, 2003a, 2004; Holzgreve, 2005; Lusby et al, 2005; Blaser et al, 2007). However, in these studies, most often only case studies are reported and statistical significance is lacking.

According to a meta-analysis review by Wijesinghe et al (2009), the available evidence indicates a markedly greater efficacy of honey compared with alternative dressing treatments for superficial or partial thickness burns, although the limitations of the studies included in the meta-analysis restrict the clinical application of these findings.

Gethin (2004) concludes that there is a lack of high quality comparative evidence for unconventional treatments (such as honey) for wound healing; a systematic review of the use of honey as a wound dressing suggested that although time to healing was significantly shorter in studies using honey, study quality was poor. The review suggests that confidence in the conclusion that honey is a useful treatment for superficial wounds or burns is low, and that the evidence available from comparative studies on patients is limited by lack of blinding, poor reporting and poor validity.

Mirsirlioglu et al (2003) evaluated the effectiveness of a honey-impregnated gauze, a hydrocolloid dressing, a paraffin gauze, and a saline-soaked gauze in the treatment of skin graft donor sites. They found that honey impregnated gauzes showed faster epithelization time and a low sense of pain than paraffin gauzes and saline-soaked gauzes. However, there was no significant difference between honey-impregnated gauzes and hydrocolloid dressings with regard to epithelization time and sense of pain. They conclude that the use of honey-impregnated gauzes is effective, safe and practical.

In a randomized controlled trial, calcium alginate dressings impregnated with manuka honey did not significantly improve venous ulcer healing at 12 weeks compared with usual care (Jull, 2007).

Robson and Cooper (2005) report that radiation-induced tissue injury and wounds with radiation-impaired healing are traumatic for patients and challenging for their caregivers. The effect of leptospermum honey as a primary dressing for managing these wounds was assessed in four patients (age range 63–93 years) who had previously undergone radiotherapy that left them with fragile friable areas of damaged skin that did not respond to conventional treatment. Compromised areas involved the neck, cheek, groin/perineum, and chest. In patients 1 and 2, after topical application of honey via hydrofibre rope and nonadhesive foam, respectively, improvements in the size and condition of wound/periwound area and a reduction in pain were noted. After including honey in the treatment regimen of patients 3 and 4, complete healing was noted in two and a half weeks (with honey and paraffin) and 6 weeks (with honey-soaked hydrofiber rope), respectively. No adverse events were reported. The researchers conclude that honey, as an adjunct to conventional wound/skin care post radiation therapy, is promising.

A number of authors have argued that there is a need for more than one robust randomized controlled trial to support the use of honey (Cooper et al, 2001; Dixon, 2003; Gethin, 2004; Simon et al, 2006).

Use of honey in paediatric wound management

The scientific evidence for using conventional wound care products, especially in paediatric patients, is poor and no prospective randomized studies have been performed in this particular population. There is little information on treating paediatric patients with honey for wound management. Only a few case reports exist for the paediatric population (Sofka et al, 2004; Simon et al, 2006).

Simon et al (2006) have reported that a paediatric patient with acute myeloic leukaemia and wound infection with meticillin-resistant coagulase-negative *Staphylococci* received topical medical honey application (Medihoney), leading to successful healing without local or systemic complications. They also report on 15 paediatric oncology patients with different oncologic diseases who were successfully treated with Medihoney (Simon et al, 2006).

Table 2. Criteria for the ideal wound antiseptic

- Fast onset of bactericidal action
- Enhancement and acceleration of the physiologic process of wound healing
- No side-effects
- Cost-effective

Simon et al (2006) also report on an internet-based documentation system with standardized items for the documentation of Medihoney and wound healing. The main objective of this database was the cumulative analysis of prospectively documented treatment experiences from participating centres, including paediatric and adult patients. Supplemented with exemplary clinical data from paediatric oncology patients receiving chemotherapy, their article reviews the scientific background and promising experience with Medihoney in wound care issues. Simon et al's (2006) study showed promising results in treating immunocompromised paediatric patients with medical honey in an oncologic and haematologic centre at the University of Bonn (Germany), where Medihoney is used in wound care by the Department of Pediatric Oncology, Children's Hospital.

Potential safety risks of honey in children

Honey poisoning, allergy to honey, infant botulism and pain are the most known complications following honey intake.

Mad honey poisoning

Honey derived from the Black Sea region has been found to contain grayanotoxin I, which is thought to be responsible for honey poisoning. Different forms of grayanotoxins have been isolated from the leaves and flowers of the rhododendron and some other plants (Dilber et al, 2002). Animal studies have showed that grayanotoxin I increases the membrane permeability to sodium in sodium-dependent excitable membranes and maintains those cells in a state of depolarization. Cardial rhythm disturbances such as bradycardia or atrioventricular block, convulsions, vomiting, sweating, blurred vision, chills and cyanosis have been described in cases of honey poisoning (Semaya and Narahishi, 1981; Dilber et al, 2002; Akinci et al, 2010).

Allergy to honey

Allergy is not common, but is well recognized and can result in anaphylaxis. Allergy may be due to both plant and bee proteins and pollen found in the honey.

Infant botulism

Infant botulism is a rare condition caused by contamination of honey with spores of *Clostridia*. Infant botulism affects mainly infants aged under 12 months, and nearly 95% of reported cases are found in the first 6 months of life. No cases of infant botulism have been linked to topical medical honey application. Concerns about wound infection from *Clostridium* spores appear unfounded (Molan, 2004).

Pain

Some patients experience pain on application of honey to the wound. In these cases a correlation between the concentration of honey and the level of pain seems to be present; higher concentrations of honey seem to induce a higher level of pain (Ozlugedik et al, 2006; Mphande et al, 2007), and it is thought that the high osmotic potential (drawing pain) and/or low pH may be the cause. While pain does do not appear to exert a negative effect on healing, it can influence the patient's quality of life.

Conclusions

This article has aimed to show that honey has much to offer in the field of paediatric wound care. Its low cost, antibacterial and antiviral effects, and the absence of antibiotic resistance as found in conventional antibiotics, are important advantages in treating paediatric patients with honey, and offers a cost-effective therapy for treating paediatric wound infections. Disadvantages to topical honey application may appear in children with a known allergy to honey, although these instances are rare.

To date, guidelines for the use of honey in paediatric wound care do not exist. The authors recommend that extensive randomized controlled trials should be performed. The studies reporting the use of honey and paediatric wound management show promising results, and further intensive research in this interesting field of wound management is necessary. BJN

Conflict of interest: none

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KEY POINTS

- Topical honey treatment has been shown to possess antimicrobial properties, promote autolytic debridement, stimulate growth of wound tissue, and reduce pain, oedema and exudate production
- There is little information regarding the use of honey for wound management in paediatric patients
- Its low cost, antibacterial and antiviral effects and the absence of antibiotic resistance development as found in conventional antibiotics are important advantages in treating paediatric patients with honey
- Studies reporting the use of honey and paediatric wound management show promising results. Further intensive research in this interesting field of wound management is necessary

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