

CHAPTER 9

A SUMMARY OF PUBLISHED CLINICAL RESEARCH ON HONEY IN WOUND MANAGEMENT

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This chapter is intended to provide a broad overview of the current clinical data published on honey in wound management. It is not presented as a review, systematic or otherwise. Whilst honey and honey-based treatments have been used on wounds for millennia, it is only recently that we have seen any attempt to provide meaningful clinical data on medical grade honey products. This is not to discount all previous data, as that does have a role in guidance. According to Molan (2002):

Dressing wounds with honey, a standard practice in past times, went out of fashion when antibiotics came into use. Because antibiotic-resistant bacteria have become a widespread clinical problem, a renaissance in honey use has occurred.

In the past two decades, numerous laboratory studies and clinical trials have shown that honey is an effective broad-spectrum antibacterial agent that has no known adverse effects on wound tissues.

Clinically, topical honey treatment has been shown to have many key actions:

- antibacterial and antimicrobial
- autolytic debridement
- deodorises wounds
- stimulates growth of wound tissues to hasten healing and to start the healing process in dormant wounds
- anti-inflammatory activity rapidly reduces pain, oedema, and exudate and minimises hypertrophic scarring
- moist wound healing.

When looking at clinical evidence it is important to rank the available information according to current standards, thus a randomised clinical trial (RCT) is recognised as the highest level of clinical evidence. Such trials are very expensive in terms of time to plan, conduct, analyse and report, and, in terms of financial costs. However, this should not, and does not, discount all other evidence (Rolfe, 1999). A systematic review has been conducted on the published evidence on honey in wound care (Moore *et al*, 2001). This concluded that the evidence available (at that time) from seven comparative studies on 264 patients was limited by lack of 'blinding', poor reporting and poor validity. Much has changed since the Moore review; quality comparative studies have been set up and preliminary data reported on the new generation of 'Medical Device grade' honey products.

Until very recently, the honey used in wound management has been generic, non-sterile material, sourced from supplies intended for nutritional rather than medical use. However, in recent years, we have seen a number of honey-based wound treatments come to the UK market with the European Conformity (CE) mark and regulatory approval as sterile Medical Devices for use on full-thickness wounds (NZX, 2005).

Clinical reports

The topical application of honey has been reported to rapidly clear existing wound infection (Cavanagh *et al*, 1970; Efem, 1988 and 1993; Phuapradit and Saropala, 1992; Armon, 1980; Sofka *et al*, 2004): to facilitate healing of deeply infected surgical wounds (McInerey, 1990; Vardi *et al*, 1998; Al-Waili and Saloom, 1999; Cooper *et al*, 2001; Ahmed *et al*, 2003): and, halt spreading necrotising fasciitis (Hejase *et al*, 1996). In some cases, the application of honey has promoted healing in infected wounds that were not responding to conventional therapy (such as antibiotics and antiseptics: Wood *et al*, 1997; Harris, 1994; Dunford *et al*, 2000a,b; Ahmed *et al*, 2003) including wounds infected with antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (Natarajan *et al*, 2001; Dunford *et al*, 2000; see Chapter 2 for details of antibacterial activity). Honey rapidly deodorises wounds (Molan, 2002; Subrahmanyam, 1991; Kingsley, 2001; van der Weyden, 2003; Stephen-Haynes, 2004) and promotes autolytic debridement to facilitate the

rapid development of a clean, granulating wound bed (Subhramanyam, 1998; Stephen-Haynes, 2004). A rapid rate of healing has been reported in wounds treated with honey (Hejase *et al*, 1996; Blomfield, 1973; Ahmed *et al*, 2003); this also serves to kick-start the healing process in otherwise 'dormant' wounds (Efem, 1988; Wood *et al*, 1997; Somerfield, 1991; Bloomfield, 1976; Stephen-Haynes, 2004). Also, honey has been reported to stimulate the growth of epithelium (Efem, 1993; Hejase *et al*, 1996; Subhramanyam, 1994 and 1998), thus occasionally making plastic surgery unnecessary (Molan, 2001). It also is reported to minimise scarring (Efem 1993; Dunford *et al*, 2000a; Subhramanyam, 1993 and 1994; Molan, 2001).

Honey reduces inflammation (Subhramanyam 1998), oedema and exudate levels (Efem, 1993 and 1988; Hejase, *et al* 1996) and can have a 'soothing' effect when applied to wounds, including burns (Subhramanyam 1993; Keast-Butler 1980) and donor sites (Misirlioglu *et al* 2003). However, some patients report a stinging sensation upon application (Vandeputte and Van Waeyenberge, 2003: see *Chapter 1*, and *Table 10.1*).

Table 10.1: Reported pain on application of honey in a study of eighty-nine patients (from Vandeputte, 2003)

Wound type	No pain	Mild pain	Severe pain
Venous ulcers	31	4	1
Burns*	5	2	0
DFU	5	1	0
Mixed	9	2	3
Pressure ulcers	15	3	0
Skin tears	8	0	0

*Note: not all medical honey dressings are advocated for the treatment of full-thickness burns, always read the manufacturer's instructions before use.

In addition, honey has been used successfully on skin grafts, infected skin graft donor sites (Misirlioglu *et al*, 2003), infected traumatic wounds (Green 1988) and paediatric oncological lesions (Sofka *et al* 2004), necrotising fasciitis (or Fournier's gangrene: Hejase *et al*, 1996) abscesses, pilonidal sinuses, pressure ulcers, leg ulcers, diabetic ulcers (Tovey, 1991), tropical ulcers, sickle cell ulcers, and malignant ulcers (Efem, 1988).

Honey is also claimed to be a reliable alternative to conventional dressing for managing skin excoriation around stomas (ileostomy and colostomy), and facilitating epithelialisation of the damaged surface (Aminu *et al*, 2000). This aspect of skin care is supported by reports of the beneficial effects of honey on paediatric (napkin/diaper) dermatitis (Al-Waili, 2005), and on atopic eczema and psoriasis (Al-Waili, 2003).

Comparative effectiveness

In three prospective, randomised, controlled clinical trials, honey was found to help heal superficial burns quicker than polyurethane film (OpSite™, Smith and Nephew), a dressing commonly used for providing a moist healing environment; and quicker than silver sulfadiazine (SSD) 1% ointment, the current 'gold standard' dressing for preventing infection in burn wounds (Pruitt, 1987). In a study comparing honey-impregnated gauze with the polyurethane film, the mean times to healing in each group ($n = 46$) were 10.8 days and 15.3 days respectively ($p < 0.001$). In addition, significantly fewer honey-dressed wounds became infected ($p < 0.001$; Subrahmanyam, 1993). In the first of the two studies that compared honey-impregnated gauze with silver sulfadiazine-impregnated gauze ($n = 52$ patients in each group), 87% of the wounds treated with honey healed within fifteen days, compared with 10% of those treated with SSD ($p < 0.001$; Subrahmanyam 1991). In this study, a statistically significant difference ($p < 0.001$) was found in the clearance of bacteria from the burns. In the forty-three out of fifty-two cases that presented positive swab cultures on admission in the group treated with honey, thirty-nine (91%) became sterile within seven days. In the comparison (SSD) group, only three (7%) of forty-one wounds with positive swab cultures became sterile: evidence of the antibacterial effect of honey *in vivo*.

In the second burns trial (twenty-five patients in each group), 100% of the wounds treated with honey healed within twenty-one days, compared to twenty-one (84%) of those treated with SSD ($p < 0.001$; Subrahmanyam, 1998). In addition to the significant difference found in burn wound healing, biopsies of the treated areas showed greater histopathological evidence of reparative activity. This was seen in 80% of wounds treated with honey dressing compared to 52% of the wounds treated with SSD ($p < 0.005$; noted in biopsy samples from the wound

margins after seven days of treatment). Regarding the clearance of bacteria from burns, in twenty-three of the twenty-five cases treated with honey that had positive swab cultures on admission in the group, fifteen (65%) of the wounds became sterile in seven days and twenty-two (96%) in twenty-one days. By comparison, of the twenty-two wounds with positive cultures treated with SSD, sixteen (73%) became sterile in seven days, and nineteen (86%) in twenty-one days ($p < 0.001$). This is further evidence of the antibacterial effect of honey *in vivo*.

Although these trials showed that honey offered better control of infection than standard treatment, a trial on moderate burns where half of the total burn area was full-thickness showed that control of infection was better with early tangential excision followed with autologous skin grafting than with honey treatment (Subrahmanyam, 1999). In two groups ($n = 25$) of young adults, 34% of swab cultures were positive for the group treated with honey, compared with 10% of the group treated with early tangential excision ($p < 0.05$). Antibiotics were needed for 32 ± 18 days in the honey-treated group compared with 16 ± 3 days in the excision group ($p < 0.001$). These findings relate to the need to debride eschar as it serves as a 'reservoir' of potential pathogens in the burn. The mean blood volume replaced was less with the honey treatment ($21\% \pm 15\%$, compared with $35\% \pm 12\%$, $p < 0.01$) and skin grafting was required on only eleven patients of the group treated with honey.

In recent reports where selected honey was used on an infected wound following surgical treatment of hidradenitis suppurativa (Cooper *et al*, 2001) and infected skin lesions from meningococcal septicaemia (Dunford, 2000a), the antibacterial activity gave rise to rapid clearance of infection and healing of the wounds. In both of these studies, it had not been possible to achieve healing with the many systemic antibiotics and modern dressing materials previously tried over a long period of time. Good infection control was reported in a crossover study of nine infants with large infected surgical wounds (Vardi, 1998). Honey was used on the wounds after they failed to heal following at least fourteen days of treatments with intravenous antibiotics (a combination of vancomycin and cefotaxime, subsequently changed according to bacterial sensitivity), fusidic acid ointment, and wound cleaning with aqueous 0.05% chlorhexidine solution. Marked clinical improvement was seen in all cases after five days of treatment; all wounds were closed, clean, and sterile after twenty-one days of honey application. A prospective, randomised controlled trial on severe post-operative wound infections following caesarean section or abdominal hysterectomy was conducted to compare dressing with honey ($n = 26$) to washing wounds with 70%

ethanol and applying povidone-iodine ($n = 24$). Both groups received systemic antibiotics according to culture and sensitivity. In the group treated with honey, infection was rapidly eradicated (6 ± 1.9 days vs 14.8 ± 4.2 days), wounds healed faster (10.7 ± 2.5 days vs 22 ± 7.3 days), post-operative scars were less than half the size, and the period of hospitalisation was less than half of that for the patients in the control group (9.4 ± 1.8 days vs 19.9 ± 7.4 days: $p < 0.05$ for each parameter: Al-Waili and Saloom, 1999). This study was of particular interest as all patients were treated with appropriate antibiotics, yet the topical application of honey still proved to be effective in reducing bioburden. This might be due to low local tissue levels of antibiotic from poor perfusion of the wound. It is of interest that *in vitro* studies have shown a synergy between honey and common antibiotics in multidrug resistant *Pseudomonas spp* (Karayil *et al*, 1998). It would, therefore, appear to justify the combination of systemic antibiotics with use of topical antibacterials (such as honey) in wounds where poor perfusion and drug resistance might compromise healing.

A trial on patients with dehiscent abdominal wounds following caesarean section, showed healing in less than half the time (mean length of stay in hospital 4.5 days, range two to seven days) when the wound was dressed with honey, compared retrospectively with the usual treatment of wound care (cleansing with hydrogen peroxide solution, Dakin's solution, and packing with saline-soaked gauze) and subsequent re-suturing (mean length of stay in hospital 11.5 days, range nine to eighteen days: Phuapradit and Saropala, 1992).

Wound deodorising

Malodour is a common feature of chronic wounds; it is attributed to the presence of anaerobic bacterial species such as *Bacteroides spp*, *Peptostreptococci* and *Prevotella spp* (Bowler *et al*, 1999). It is probably more than just the antibacterial action that is responsible for the rapid deodorising of wounds observed when honey dressings are used. The malodorous substances produced by bacteria are short-chain fatty acids, ammonia, amines, and sulphur compounds. These are formed by the metabolism of amino acids from decomposed serum and tissue proteins. Honey provides a copious quantity of glucose, a substrate metabolised by bacteria in preference to amino acids.

Immune system activity

The clearance of infection may not only be the result of the antibacterial action of honey. Recent research indicates that honey may work by stimulating the activity of the immune system. Honey at concentrations as low as 0.1% has been found to stimulate proliferation of peripheral blood β -lymphocytes and T-lymphocytes in cell culture and activate phagocytes from blood. Also, honey at a concentration of 1% has been reported to stimulate monocytes in cell culture to release the cytokines TNF-1, IL-1, and IL-6, which are intermediates in the immune response. In addition to the reported stimulation of leukocytes, honey has the potential to augment further the immune response by supplying glucose. This is essential for the 'respiratory burst' in macrophages that generates hydrogen peroxide, the dominant component of the bacteria-destroying activity of these cells (see Molan, 2002).

Wound debridement

Like any other moist wound dressing, honey facilitates the debridement of wounds by the autolytic action of tissue proteases. Unlike other wound dressings, honey creates a moist environment by drawing out lymph fluid from the wound tissues through its strong osmotic action. This provides a constantly replenished supply of proteases at the interface of the wound bed and the overlying necrotic tissue, which may, in part, explain the rapid debridement brought about by honey. This osmotic action also washes the surface of the wound bed from beneath. This explains the frequent observation of honey dressings removing debris such as foreign bodies (eg. dirt, grit) with the dressing (Molan, 2002). It also helps explain the painless lifting off of slough and necrotic tissue that is observed (Efem, 1988 and 1993; Hejase *et al*, 1996; Subrahmanyam, 1993 and 1998). Another possible explanation for the observed rapid debridement is activation of the proteases by hydrogen peroxide liberated by honey. The proteases in wound tissues are normally in an inactive state but can be activated by oxidation. The matrix metalloproteases of connective tissue, normally present in a catalytically inactive conformation, may be activated by the hydrogen peroxide (Peppin and Weiss, 1986; Weiss *et al*, 1985). High

protease activity is strongly associated with impaired wound healing, which may suggest that activation of proteases by honey would be harmful rather than beneficial. However, a causal effect has never been proved (Ashcroft *et al*, 2000); possibly, the association is the result of both impaired healing and high protease activity together caused by the same factor — excessive, uncontrolled inflammation (Agren *et al*, 2000). Excessive inflammation prevents healing and the attraction of inflammatory leukocytes gives rise to high levels of proteolytic enzyme activity at the site of the inflammation (Ashcroft *et al*, 2000; Agren *et al*, 2000). The potent anti-inflammatory action of honey (see below) would resolve such a situation and prevent excessive proteolytic activity. It also has been suggested that high levels of proteolytic activity and high levels of inflammation are both caused by a lack of secretory leukocyte protease inhibitor, which is an inhibitor both of serine proteases and the production of TGF- β , a potent chemoattractant of inflammatory cells. Yet, proteolysis in wound tissues is a normal part of the healing process and responsible for autolytic debridement.

Anti-inflammatory action

Clinical observations of reduced inflammation following application of honey to a wound are substantiated by the results of *in vivo* studies that have shown that honey, when compared to various controls, reduces inflammation. Histological evidence of reduced numbers of inflammatory cells present in wounds dressed with honey exists from studies of deep (Postmes *et al*, 1997) and superficial burns, as well as full-thickness wounds. These effects were due to components other than the sugar in honey (Postmes *et al*, 1997). Evidence also has come from similar findings in biopsy samples from burn wound tissue of hospital patients (Subrahmanyam, 1998). Although it is a vital part of the normal response to infection or injury, excessive or prolonged inflammation can prevent healing or even cause further damage to tissues (Agren *et al*, 2000). Suppressing inflammation, as well as reducing pain for the patient, reduces the opening of blood vessels, thus reducing oedema and exudate. Pressure in tissues secondary to oedema restricts the flow of blood through the capillaries, starving the tissues of the oxygen and the nutrients vital for leukocytes to fight infection and for fibroblasts to multiply for wound healing. Finally, healing may be impaired because

swelling increases the distance for diffusion of oxygen and nutrients from the capillaries to the cells.

Stimulation of tissue growth

The evidence provided supports the following statements:

- ⌘ Honey is a bioactive wound dressing that provides rapid wound healing.
- ⌘ Honey promotes the formation of clean healthy granulation tissue and re-epithelialisation.
- ⌘ The stimulation of cell growth seen with honey is probably also responsible for 'kick-starting' the healing process in chronic wounds that have remained non-healing for long periods.

Conclusions

The clinical evidence for the use of honey in wound management is steadily accumulating and, with the advent of various forms of manufactured honey dressings currently commercially available or being developed for marketing, the flow of evidence will continue. Whilst the evidence pre-2000 was on generic honeys, more recent research has been focused on the sterile medical grade honey products intended specifically for wound management. These products have been designed to overcome many of the problems of messiness and difficulty of handling, making honey-based products as convenient to use as the more familiar modern wound dressings. Some involve the combination of honey with a modern dressing such as alginate or sheet hydrogel. Others present honey as a tubed formulation of amorphous gel or of ointment. This brings the most ancient form of wound dressing known into the realms of the most modern — an easy-to-use, bioactive dressing that provides a moist healing environment, with the advantage of having within a single product a range of actions (debriding, deodorising, antibacterial, growth-promoting, anti-inflammatory, and scar-minimising), usually available only individually in a range of

products. These attributes will, no doubt, be shown to be cost-effective in future clinical research.

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