

Randomized clinical trial of honey-impregnated dressings for venous leg ulcers

Andrew Jull¹, N. Walker¹, V. Parag¹, P. Molan² and A. Rodgers¹, on behalf of the Honey as Adjuvant Leg Ulcer Therapy trial collaborators

¹Clinical Trials Research Unit, University of Auckland, Auckland and ²Honey Research Unit, University of Waikato, Hamilton, New Zealand
Correspondence to: Mr Andrew Jull, Clinical Trials Research Unit, School of Population Health, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand (e-mail: a.jull@ctr.u.auckland.ac.nz)

Background: The efficacy of honey as a treatment for venous ulcers has not been evaluated, despite widespread interest. This trial aimed to evaluate the safety and effectiveness of honey as a dressing for venous ulcers.

Methods: This community-based open-label randomized trial allocated people with a venous ulcer to calcium alginate dressings impregnated with manuka honey or usual care. All participants received compression bandaging. The primary outcome was the proportion of ulcers healed after 12 weeks. Secondary outcomes were: time to healing, change in ulcer area, incidence of infection, costs per healed ulcer, adverse events and quality of life. Analysis was by intention to treat.

Results: Of 368 participants, 187 were randomized to honey and 181 to usual care. At 12 weeks, 104 ulcers (55.6 per cent) in the honey-treated group and 90 (49.7 per cent) in the usual care group had healed (absolute increase 5.9 (95 per cent confidence interval (c.i.) -4.3 to 15.7) per cent; $P = 0.258$). Treatment with honey was probably more expensive and associated with more adverse events (relative risk 1.3 (95 per cent c.i. 1.1 to 1.6); $P = 0.013$). There were no significant differences between the groups for other outcomes.

Conclusion: Honey-impregnated dressings did not significantly improve venous ulcer healing at 12 weeks compared with usual care. Registration number: ISRCTN 06161544 (<http://www.controlled-trials.com>).

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Introduction

Leg ulcers are defects in the epidermis, below the knee, which are present for more than 4–6 weeks¹. Typically, leg ulceration is a chronic, relapsing condition; venous insufficiency is the most common cause, accounting for most leg ulcers^{2,3}.

The standard treatment of venous ulcers is compression of the lower leg by tight bandaging or hosiery to reduce hydrostatic pressure in the leg⁴. This treatment has been known since the 17th century, and few other adjuvant treatments have been found to be effective^{5,6}. Lack of evidence for other treatment options has not stopped both patients and health workers advocating a cornucopia of interventions; one currently gaining popularity is honey.

Honey has been used in wound healing for thousands of years, with the first record of it in the Edwin Smith papyrus

(2600–2200 BCE)⁷. Interest is undergoing a revival⁸, with an eightfold growth in the number of studies, reports and letters on the therapeutic potential of honey for treating wounds in the past decade. *In vitro* and animal studies indicate that honey has antibacterial properties, stimulates cytokine release and may stimulate cell growth, thereby facilitating wound healing⁹. Animal model evidence and case reports on chronic wounds suggest honey has a beneficial effect, but they do not offer reliable evidence on which to base treatment decisions.

A systematic review found seven randomized trials of honey in wound care, six of which were in patients with moderate burns¹⁰. The review could not assess whether honey was beneficial in wound healing, largely because of the poor quality of the reports. In addition, findings from acute wounds may not usefully be extrapolated to chronic wounds¹¹.

Given the lack of trial information to guide decisions on the use of honey for treating venous ulcers, the increasing use of honey by patients and practitioners, and the evidence from *in vitro* and animal studies suggesting plausible mechanisms of action, the Honey as Adjuvant Leg Ulcer Therapy (HALT) trial was undertaken to evaluate the effectiveness of honey in the management of venous leg ulcers.

Methods

This open-label, multicentre randomized controlled trial was conducted between May 2004 and September 2005. Patients were eligible if they were 18 years or older, had been diagnosed with venous ulceration (clinical presentation and ankle:brachial pressure index greater than 0.8) or mixed venous and arterial ulceration (clinical presentation and ankle:brachial pressure index greater than 0.7), were able to tolerate compression and were able to give informed consent. Patients were excluded if they had a history of diabetes, rheumatoid arthritis or peripheral arterial disease, had an allergy to calcium alginate or manuka honey, or were already using honey to treat their leg ulcer. Participants were recruited from four community-based district nursing services in the Auckland, South Auckland, Waikato and Christchurch regions of New Zealand. The study was approved by the Northern Regional Health and Disability Ethics Committee.

Randomization

Eligibility was assessed and consent obtained by the study research nurses. Participants were randomly assigned to one of two groups by an independent central telephone service. The allocation sequence was stratified by study centre and the Margolis index¹² using minimization. The Margolis index is a prognostic score for venous ulcer healing derived from dichotomous categorizations of ulcer area and duration of the current ulcer (Table 1). Where more than one leg ulcer was present, the largest ulcer was used as the reference ulcer and all ulcers were treated with the allocated treatment.

Interventions

Participants in the treatment group received manuka honey dressings (ApiNate™ UMF® 12+; Comvita New Zealand, Te Puke, New Zealand) that were changed each time the compression bandaging was changed, with frequency determined by clinical need. All the honey was from the same batch, and it was impregnated into calcium alginate

dressings. Participants in the usual care group received dressings that the district nurse deemed appropriate at the time of each visit. The dressing choices reflected the normal range of choices available to nursing services at each study centre (alginate, hydrofibre, hydrocolloid, foam, hydrogel, non-adherent, iodine or silver dressings).

All participants received compression bandaging as standard background therapy. The range of compression bandaging reflected what was normally available in the study centres, with the choice determined by participant or district nurse preference.

Outcome measures

The primary outcome measure was the proportion of participants with a completely healed reference ulcer at 12 weeks, as determined by the research nurse. The research nurse was not blind to allocation. Healing was defined as complete epithelialization of the ulcer with no scab. Secondary outcome measures included time to healing (determined from forms returned weekly by the district nurse), change in ulcer area from baseline (calculated by a blinded reviewer from a digital photograph obtained at baseline and at 12 weeks by the research nurse)¹³, incidence of clinically determined infection (defined as the presence of signs and symptoms of infection or a wound swab being obtained, and treatment with antibiotics), adverse events, health-related quality of life (HRQoL) and cost effectiveness. HRQoL was measured at 12 weeks using the Short Form 36 health survey (SF-36®)¹⁴, the Charing Cross Venous Ulcer Questionnaire (CXVUQ)¹⁵ and the EuroQol 5D (EQ-5D)¹⁶. A health services perspective was used for determining cost effectiveness.

Statistical analysis

A sample size of 360 people was calculated as necessary to detect a 30 per cent relative increase (relative risk (RR) 1.30) in the proportion of healed ulcers in the intervention group at 12 weeks, with 90 per cent power and an α of 5 per cent. The sample size was inflated to 400 to allow for 10 per cent loss to follow-up. The relative increase equated to an absolute increase in healed ulcers from 55 to approximately 71 per cent at 12 weeks, a benefit that had been suggested by the most conservative of the honey for burns trials¹⁷.

All statistical analyses were specified *a priori* and were two-tailed; $P < 0.050$ was considered significant.

The primary analysis was by intention to treat, with all participants included, and participants lost to follow-up deemed treatment failures. Adjusted analyses were

conducted using logistic regression for dichotomous outcomes or linear regression for continuous outcomes. Correlations between co-variables were checked to prevent highly correlated variables being included in the adjusted models.

Three sensitivity analyses for the primary outcome were specified *a priori*. First, healing state identified by blinded review was used to test whether the level of agreement between the research nurses and a blinded reviewer had an impact on the outcome. Second, the last healing state reported by the district nurse was carried forward to test the assumption that participants lost to follow-up were treatment failures. Third, crossovers between treatment groups and loss to follow-up were excluded to test the effect of participant withdrawals from treatment.

Time to healing was analysed using Kaplan–Meier curves, the log rank test and Cox proportional hazards regression analysis. The assumption of proportionality for each co-variate was reviewed using formal testing and visual assessment of scaled Schoenfeld residuals plots. Change in ulcer area was analysed using linear regression.

Incidence of infection was compared using Fisher's exact test for comparison of episodes between groups. Quality of life scores were compared using the Student's *t* test and adjusted for baseline imbalance using linear regression. RRs and 95 per cent confidence intervals (c.i.) were calculated for adverse events. The incremental cost-effectiveness ratio (ICER), the ratio of the difference in the mean total costs and the difference in proportion healed in each group were calculated by the standard method¹⁸.

Results

Recruitment achieved 92.0 per cent of the planned target. Of 392 people approached, 368 agreed to be randomized to honey or usual care (Fig. 1). The baseline characteristics of those randomized did not differ from those of patients registered but not eligible. Baseline data were similar for both study groups. Ulcer area and duration were highly correlated with the Margolis index (results for ulcer area and mean ulcer respectively: Spearman $r_s = 0.6$,

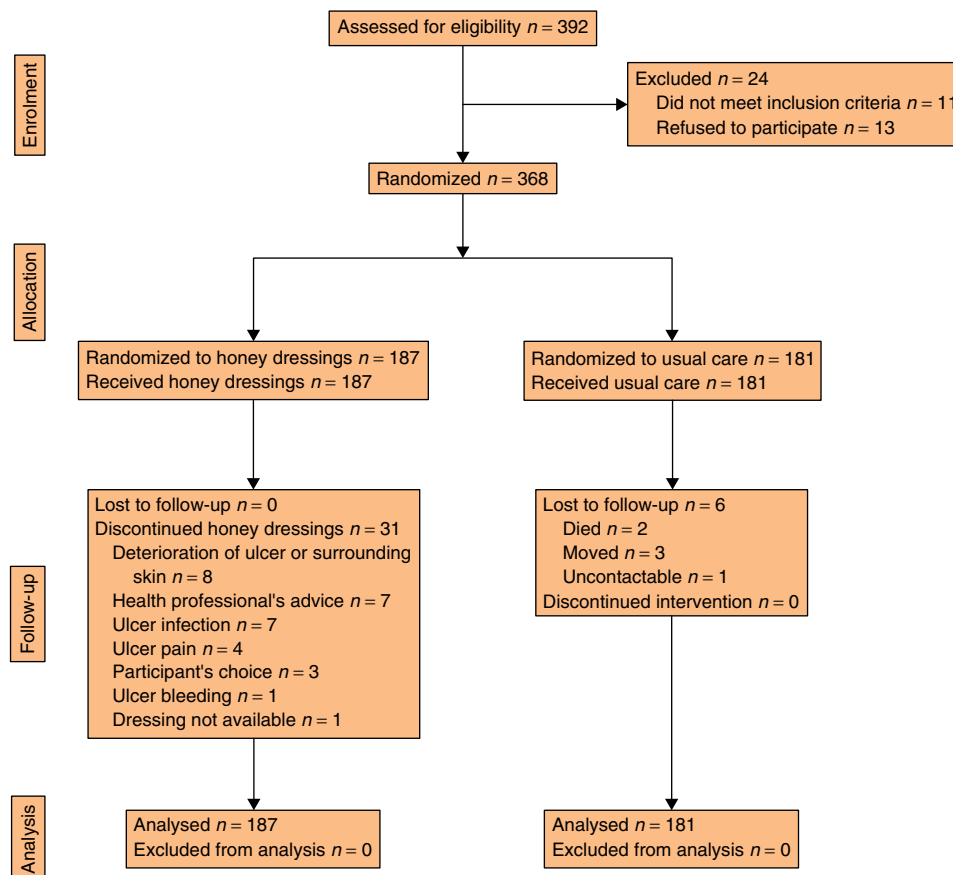


Fig. 1 Flow of participants in the Honey as Adjuvant Leg Ulcer Therapy trial

Table 1 Characteristics of participants by treatment group

Characteristic	Honey (n = 187)	Usual care (n = 181)
Age (years)*	66.9(17.5)	68.3(17.1)
Sex ratio (M : F)	91 : 96 (48.7 : 51.3)	89 : 92 (49.2 : 50.8)
Current smokers	37 (19.8)	32 (17.6)
Ethnicity		
New Zealand European	146 (78.1)	137 (75.7)
New Zealand Maori	23 (12.3)	30 (16.6)
Pacific Island	16 (8.6)	13 (7.2)
Asian	2 (1.1)	1 (0.6)
ABPI*	1.1(0.2)	1.1(0.2)
≥0.8	184 (98.4)	175 (96.7)
>0.7, <0.8	2 (1.1)	5 (2.8)
Ulcer area (cm ²)†	2.7 (0.1–193)	2.6 (0.2–81)
Ulcer duration (weeks)†	20 (3–688)	16 (2–999)
Venous Clinical Severity Score*	14.3(3.8)	15.0(3.9)
Margolis index		
0 (ulcer size ≤ 5 cm ² and ≤ 6 months)	85 (45.5)	84 (46.4)
1 (ulcer size > 5 cm ² or > 6 months)	69 (36.9)	68 (37.6)
2 (ulcer size > 5 cm ² and > 6 months)	33 (17.6)	29 (16.0)
Compression system		
Short stretch	2 (1.1)	5 (2.8)
Long stretch	5 (2.7)	5 (2.8)
Three layer	74 (39.6)	65 (35.9)
Four layer	106 (56.7)	106 (58.6)
SF-36® summary component score		
Physical component score*	36.7(10.1)	34.0(9.8)
Mental component score*	48.7(11.6)	50.5(12.4)

Values in parentheses are percentages unless otherwise indicated. Values are *mean(s.d.) or †median (range). ABPI, ankle : brachial pressure index; SF-36®, Short Form 36 health survey.

$P < 0.001$; Spearman $r_s = 0.8$, $P < 0.001$) and thus only the Margolis index was retained in adjusted analyses.

Loss to follow-up was similar between the two groups, although withdrawal from the study differed significantly (31 participants in the honey-treated group compared with none in the usual care group). In almost two-thirds of those withdrawing (20 of 31), it was because of problems at the ulcer site, including pain, infection, bleeding and wound deterioration. The other main reason was practitioner or patient choice, although details were not recorded. All participants who withdrew were followed up at 12 weeks.

Complete healing at 12 weeks

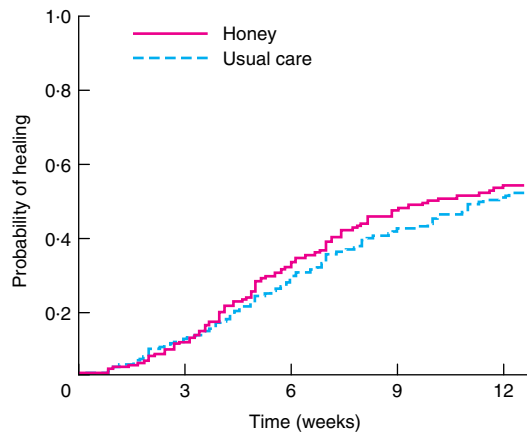
At 12 weeks, 104 ulcers (55.6 per cent) in the honey-treated group had healed compared with 90 (49.7 per cent) in the usual care group, giving a 5.9 (95 per cent c.i. -4.3 to 15.7) per cent absolute increase in healing at 12 weeks with honey ($P = 0.258$). The findings were similar when adjusted for stratification factors (study centre, Margolis index) and in the sensitivity analyses.

Time to healing

Mean time to healing was 63.5 days in the honey-treated group and 65.3 days in the usual care group (mean difference -1.8 (95 per cent c.i. -7.7 to 4.1) days, $P = 0.553$). Time to healing (hazard ratio 1.1 (95 per cent c.i. 0.8 to 1.5); $P = 0.451$) did not change when adjusted for stratification factors (*Fig. 2*).

Change in ulcer area

There was no significant difference between the treatment groups for percentage change in ulcer area from baseline. The mean reduction from baseline ulcer area was 74.1 per cent in the honey-treated group and 65.5 per cent in the usual care group, giving a mean difference in percentage reduction of ulcer area between the groups of 8.6 (95 per cent c.i. 23.9 to -4.7) per cent; $P = 0.186$. The findings were similar when adjusted for stratification factors.



No. at risk					
Honey	187	171	129	101	57
Usual care	181	164	131	106	63

Fig. 2 Kaplan–Meier plot for time to ulcer healing for patients receiving honey dressings or usual care

Incidence of clinically determined infection

In the honey-treated group, 32 participants (17.1 per cent) had episodes of infection compared with 40 (22.1 per cent) in the usual care group. The difference was not significant (absolute decrease 5.0 (95 per cent c.i. -3.1 to 13.1) per cent; *P* = 0.228). The difference in the number of episodes

of infection between the two groups was also not significant (37 versus 49 respectively; *P* = 0.449).

Adverse events

In the honey-treated group, 111 participants reported one or more adverse events compared with 84 in the usual care group (RR 1.3 (95 per cent c.i. 1.1 to 1.6); *P* = 0.013). There were significantly more reports of ulcer pain in the honey-treated group (Table 2), although pain intensity was not recorded.

Health-related quality of life

At 12 weeks, 360 participants (97.8 per cent) completed all three HRQoL questionnaires (186 in the honey-treated group and 174 in the usual care group). There were no significant differences between the groups in the summary component scores for the SF-36®, the overall scores for the CXVUQ, or the visual analogue scores for the EQ-5D (Table 3).

Cost effectiveness

The ICER was (in New Zealand dollars) -\$9.45 (95 per cent c.i. -\$39.63 to \$16.07) in favour of honey when all costs were considered (Table 4). This finding was driven by the difference in hospitalization rates for a very small number of participants (three were hospitalized

Table 2 Number of participants reporting one or more adverse events (excluding infection)

Event type	Honey (n = 187)	Usual care (n = 181)	Relative risk	<i>P</i> *
Local				
Pain	47	18	2.5 (1.5, 4.2)	0.001
Bleeding	3	3	1.0 (0.2, 4.7)	0.968
Dermatitis	8	8	1.0 (0.4, 2.5)	0.947
Deterioration of ulcer	19	9	2.0 (1.0, 4.4)	0.061
Erythema	6	4	1.5 (0.4, 5.1)	0.556
Oedema	4	1	3.9 (0.4, 34)	0.189
Increased exudate	5	1	4.8 (0.6, 41)	0.108
Deterioration of surrounding skin	5	3	1.6 (0.4, 6.7)	0.504
New ulceration	16	15	1.0 (0.5, 2.0)	0.926
Other	6	3	1.9 (0.5, 7.6)	0.336
Systemic				
Cardiovascular	4	3	1.3 (0.3, 5.7)	0.735
Cancer	2	2	1.0 (0.1, 6.8)	0.974
Neurological	4	1	3.8 (0.4, 34.3)	0.189
Gastrointestinal	4	2	1.9 (0.4, 10)	0.434
Injury	10	9	1.1 (0.5, 2.6)	0.871
Musculoskeletal	13	9	1.4 (0.6, 3.2)	0.423
Respiratory	6	3	1.9 (0.5, 7.6)	0.336
Other	3	7	0.4 (0.1, 1.6)	0.182

Values in parentheses are 95 per cent confidence intervals. * χ^2 test.

Table 3 Quality of life scores

Instrument	Honey (n = 187)	Usual care (n = 181)	Mean difference	P*
SF-36® PCS	39.0	37.9	1.1 (−0.8, 3.0)	0.256
SF-36® MCS	51.1	50.4	0.7 (−1.1, 2.4)	0.437
CXVUQ (overall)	33.5	35.1	−1.6 (−4.2, 0.9)	0.204
EQ-5D VAS	75.1	73.5	1.6 (−1.5, 4.7)	0.313

Values in parentheses are 95 per cent confidence intervals. SF-36® PCS, Short Form 36 questionnaire, physical component summary; SF-36® MCS, Short Form 36 questionnaire, mental component summary; CXVUQ, Charing Cross Venous Ulcer Questionnaire; EQ-5D VAS, EuroQol 5D questionnaire, visual analogue scale. *Student's *t* test.

Table 4 Base case of mean health service costs per participant

Item	Honey			Usual care		
	Healed (n = 104)	Not healed (n = 83)	Mean total cost (n = 187)	Healed (n = 90)	Not healed (n = 91)	Mean total cost (n = 181)
Drug	0.93	3.58	2.11	1.03	4.91	2.98
District nursing	581.15	1214.79	862.39	513.19	1072.88	794.58
Nursing	224.78	517.68	354.78	212.44	434.38	324.02
Dressings	92.16	216.19	147.21	36.39	148.28	94.28
Bandages	259.39	460.70	348.74	258.28	471.37	365.41
Swab	4.81	20.23	11.66	2.78	18.85	10.86
Outpatient appointment*	2.47	7.46	4.68	2.36	5.83	4.10
Community care†	4.08	14.55	8.72	2.38	16.45	9.45
Hospitalization	56.24	17.62	39.09	16.25	305.28	161.56
Total mean cost	644.86	1258.00	917.00	535.20	1405.35	972.68

Values are given in New Zealand dollars. *Visits to any outpatient hospital clinic. †Visits to community-based health worker (general practitioner, practice nurse or others).

for a total of 10 days in the honey group compared with six hospitalized for a total of 40 days in the usual care group). The difference was probably attributable to random variation, and exclusion of these costs reversed the ICER to \$11.34 (95 per cent c.i. −\$2.24 to \$26.25) in favour of usual care.

Discussion

In this trial, honey-impregnated dressings did not improve venous ulcer healing at 12 weeks. They were sometimes painful and probably more expensive. Furthermore, these dressings did not significantly improve time to healing, change in ulcer area, incidence of infection or quality of life.

A large number of adverse events were observed, as participating centres were required to report any untoward event, whether considered related to the treatment or not. Significantly more events were reported in the honey-treated group, as would be expected in an open-label trial. Pain is a known side-effect of using honey; 35 per cent of patients in the largest case series reported transient

or continuous pain associated with honey¹⁹. The pain is reportedly due to the acidity of honey²⁰. In the HALT trial, 25 per cent of the honey-treated group reported one or more episodes of pain as an adverse event, but only four participants gave pain as the reason for withdrawing from treatment, suggesting that the pain was short-lived or tolerable. Any further trials of honey in wounds should record detailed information on ulcer pain, including intensity and duration.

The HALT trial had a number of strengths. To date, it remains the only one to have investigated the effect of honey on venous leg ulcer healing as the primary outcome. Healing is a hard outcome of direct relevance to patients and clinicians. Participants were randomly allocated, and balanced for key prognostic indicators ensured by minimization. Allocation was concealed up to the point of randomization by using a central telephone service. Intention-to-treat analysis was undertaken with the inclusion of all participants randomized, and follow-up was virtually complete, with less than 2 per cent of participants lost. With almost 400 people recruited, this study had the

power to conclude that honey did not have a large enough effect for the authors to consider it clinically relevant. Some may argue that the trial should have been powered to detect a more modest difference, but at the time of designing the study the most conservative estimate from previous honey for wound trials suggested a 16 per cent absolute difference was plausible. Furthermore, powering the study for a smaller difference would have required a much larger sample size (for a 10 per cent difference, a sample size of 1030 would have been necessary).

There were, however, some limitations. First, the trial recruited fewer participants than anticipated, despite extending the recruitment period. It did recruit enough participants to retain 90 per cent power, as the anticipated loss to follow-up did not occur. Second, funding limitations precluded longer follow-up. Although the 12-week outcome has been standard in previous trials^{5,21–24}, longer follow-up would have been ideal to assess the possibility of a delayed effect. Third, outcome assessment could not be blinded as honey stains wound margins and leaves an odour. However, re-analysis of the primary outcome using healing state determined from blinded review of ulcer photographs did not affect the study findings.

A usual care comparison was the most pragmatic trial design. A calcium alginate control was considered, but alginate dressings are absorptive and adhere to the wound bed, producing less exudate. Ulcer size could therefore be influenced by the removal of adherent dressings. It is possible that a treatment effect may have been diluted by allowing a range of dressings in the control comparison. However, such an effect appears unlikely, as three systematic reviews have found little evidence to support the view that dressings have an impact on venous leg ulcer healing^{25–27}. Similarly, a Cochrane review of compression systems did not find one type of multilayer system to be more effective than any other²³. In the HALT trial, 95 per cent of participants had multilayer compression, with balance between the remainder with respect to type of compression. Compliance with compression was also similar across both groups.

Honey-impregnated dressings are a moist wound dressing marketed without specific indication and therefore were used to treat all venous ulcers in this trial, irrespective of clinical presentation. The results should therefore be considered as generalizable to all venous ulcers, regardless of wound bed appearance, until further evidence suggests otherwise. Similarly, the results should be considered as applying to all types of honey. The effect of different honeys on healing has not been compared *in vivo* in either the animal or the human model. However, the activity of jelly bush honey, manuka honey and New Zealand pasture

honey on cytokine expression has been compared with that of artificial honey²⁸. Although jelly bush honey did produce significantly greater cytokine expression, all three honeys increased tumour necrosis factor (TNF) α , interleukin (IL) 1 β and IL-6 expression compared with artificial honey.

The results of this trial conflict with the generally positive results of previous trials. This discrepancy is possibly due to publication bias. Of 18 trials identified in a systematic review, 13 reported findings in favour of honey, despite having small sample sizes. A funnel plot found no positive and few negative studies scattered around the base of the funnel when chance effects should have produced such results in underpowered trials. Another possible explanation is that almost three-quarters of previous trials have focused on the use of honey for acute wounds, in particular burns. Although the cytokines TNF- α and IL-1 β are necessary for the inflammatory response, levels are significantly increased in chronic wounds²⁹, with greater levels in non-healing venous ulcers compared to healing venous ulcers^{30,31}. These cytokines cause imbalance in favour of the proteinases normally responsible for tissue degradation²⁹. Manuka honey has been found to increase TNF- α and IL-1 β expression in cell lines^{28,32}, and it is possible that this feature of manuka honey could delay healing in venous ulceration where the cytokines are already overexpressed.

There was no additional benefit from using honey-impregnated dressings for venous ulceration. The focus of venous ulcer management should remain on high compression and treatments that have demonstrated efficacy as adjuvants to compression.

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