

Effectiveness of Honey Dressing in Wound Healing: Systematic Review and Metaanalysis

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ABSTRACT

Objective: The objective of this research is to evaluate the effectiveness of honey in promoting wound healing.

Method: The MEDLINE/PubMed electronic database, Cochrane library, ClinicalTrials.gov, EBSCO, Scopus, ProQuest, Cambridge Core, reference lists, conference proceedings, and researchers in fields of eligible studies were searched. Six studies (n = 682 subjects) were included in qualitative analysis of which three studies (n = 174 subjects) were included in meta-analysis. Several parameters are used to assess the effectiveness of honey in wound healing, including average time for the wound to heal, percentage of wound reduction, eradication of infection, pain score, healing index, and the amount of patient healed during observation time. Articles with normal saline as control are chosen for the study.

Result: From the systematic-review perspective, Honey dressing application can promote wound healing faster than normal saline, including better in eradication of infection, pain score, healing index, and the amount of patient healed during observation time, but from meta-analysis study, honey dressing application is not proven to promote wound healing faster than normal saline.

Conclusion: Application of honey dressing is superior in promoting wound healing compared to normal saline from systematic-review study, but not proven with meta-analysis study.

Keywords

Honey, Normal saline, Wound healing.

Introduction

Wound can be a massive burden in health cost. Data collected from Medicare, A conservative estimate of the annual cost is \$28 billion when the wound is the primary diagnosis on the claim. When the analysis included wounds as a secondary diagnosis, the cost for wounds is conservatively estimated at \$31.7 billion [1].

The ancient Egyptians used honey as a wound treatment since at least 3000 BC. Honey was an integral part of the "Three Steps of Medicine" used by the ancient Egyptians. This included the

use of "plasters" (made from honey, animal fat, and vegetable fiber), and dressing wounds – not much different from modern wound management. This ancient Egyptian "wound ointment" method showed very strong bactericidal characteristics against Staphylococcus aureus, Escherichia coli, and coliform bacteria. Honey has continued to develop and be used as a treatment of wound healing ever since [2].

Subrahmanyam evaluated the honey as a biologic dressing for burns. Honey is also proven for its anti-oxidative effect, bactericidal, anti-nociceptive and wound healing properties [3].

Normal saline is an isotonic liquid that is physiological, non-toxic and does not cause hypersensitivity so it is safe to use under

any conditions. Normal saline protects granulation tissue from dryness, maintains moisture around the wound and helps wounds undergo the healing process. Giving normal saline dressing to wounds can reduce edema. Saline can draw fluid from the wound through the process of osmosis. In addition, normal saline has an anti-inflammatory response so that it can reduce pain and erythema symptoms that arise in the wound, and increase blood flow to the wound area, so that the wound healing process speeds up [4].

This study aims to assess effectiveness of honey in promoting wound healing compared to conventional dressing normal saline.

Methods

Literature Search

The MEDLINE/PubMed electronic database, Cochrane library, ClinicalTrials.gov, EBSCO, Scopus, ProQuest, and Cambridge Core. Reference lists, conference proceedings, researchers in fields of eligible studies were searched. The following Mesh terms were used for searching: ("honey" AND "trials"). Three reviewers independently using PRISMA flow diagram 2009 performed a literature search [5].

Differences in opinion were resolved between all reviewers to reach a consensus.

Inclusion criteria include observational studies regarding the comparison of honey and normal saline in promoting wound healing until October 2020. Studies were excluded if they were written neither in Indonesian nor in English, were case reports, serial cases, letters, literature reviews, or systematic reviews.

Study Selection

Three reviewers conducted the study selection independently. Duplicate articles were removed. Using the predefined inclusion and exclusion criteria, title/abstract reviews and full-text reviews were assessed for eligibility. To reach a consensus, differences in opinion were resolved between all reviewers.

Data Extraction

Data were extracted independently by three reviewers using a modified The Cochrane Collaboration data collection form [6]. Differences in opinion during data extraction were resolved between all reviewers and consensus was reached.

Data Synthesis

Meta-analysis difference in weighted mean was conducted using Review Manager 5.4. A descriptive synthesis was performed where data were not available to enable pooling.

Result

Initial database searches identified 125 no duplicate records, of which 109 and 10 were excluded during the title/abstract and full-text review assessment. Six studies were included in this review, of which three were included for meta-analysis. Figure 1 gives details of the study selection process.

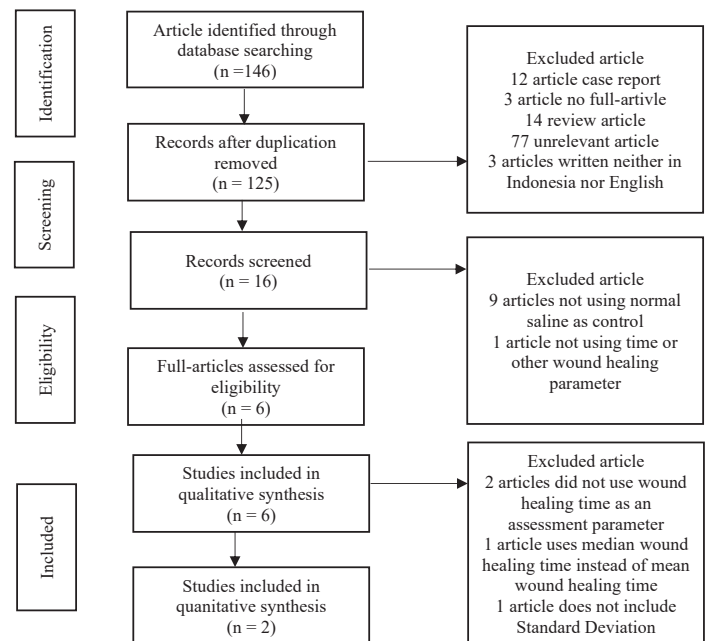


Figure 1: PRISMA flow diagram.

Study Characteristics

In the 6 studies included in the qualitative review, it was found that the study was conducted in India, Turkey, Greece, Pakistan, Malaysia and Iran. All of those studies were conducted between 1999. - 2015. Four studies used a double-blind RCT, one study used a single-blinded RCT and one was an open-label trial. The total sample from 6 studies is 682 people with an average age of 50.26 years. The wound characteristics used in these 6 studies included infected wounds, trophic ulcers, diabetic ulcers, venous ulcers, pressure ulcers, split-thickness-skin-graft donor wounds, and surgical wounds due to Modified Widman Flap (MWF), and intentionally made wounds on experimental animals.

The baseline characteristics of the 6 studies included in the systematic review and meta-analysis are summarized in Table 1.

Quality of Study in Included Studies

Table 2 shows that 6 studies that were included in the systematic review found 1 study with a high risk of bias, namely the Misirlioglu study (2003). Kamaratos (2012) and Tan (2012) studies were low risk of bias, while the other 3 studies included a medium risk of bias. Misirlioglu (2003) research used non-randomized research, so blinding was not carried out. Kamaratos (2012) study used a double-blinded randomized controlled trial. There is blinding from both the patient and the therapist, but there is no known blinding (outcome assessment). In the research conducted by Tan (2012), it was conducted on experimental animals, there was randomization in the selection of research subjects, and there was blinding of those who gave treatment and had complete data. Based on this, there is only 1 study that has a high risk of bias, 2 studies that have a low risk of bias, and 3 other studies with moderate bias.

Table 1: Study Characteristic.

No	Publication	Average Age	Methodology	Subjects	Experimental Treatment	Control Treatment	Result
1	Dubhasi, 2015 [130] (India)	50,5 year	double-blinded RCT	50/50	Patients were treated with commercially available sterile honey. This honey is melted by stirring/light heating. This honey is applied to the gauze and cover the wound surface. For moderate to severe wounds, dressing changes are done once daily and a secondary dressing is used to absorb it watery honey seeping from the main dressing.	The patient was treated with a normal saline dressing. Dressing change was done once a day	<p>1. The appearance of granulation tissue The appearance of granulation tissue was faster in the Honey and Phenytoin group than in the Normal Saline group ($p < 0.0001$)</p> <p>2. Wound area reduction A significant reduction in wound area was found at the end of 3 weeks of treatment in the honey and phenytoin group compared to the normal saline group ($p < 0.0001$).</p> <p>3. Eradication of infection Eradication of infection was shown to be faster in the honey-treated group (mean 8.4 days \pm 1.71) and the phenytoin-treated group (mean 9.28 days \pm 2.03) compared to the normal saline-treated group. (mean 14.94 days \pm 2.56). ($p < 0.0001$)</p> <p>4. Pain reduction Pain relief was found to be significant in patients treated with honey and phenytoin compared with normal saline dressings. ($p < 0.0001$)</p> <p>5. Length of hospitalization required The hospital stay was less in patients in the honey group compared with those treated with phenytoin and normal saline group. ($p < 0.0001$)</p>
2	Misirlioglu 2003 [131] (Turki)	32 years	open-label-trial	14/15	This study involved patients who underwent a split-thickness skin graft donor. All donor skin is removed with an electric dermatome, to a depth of no more than 0.014 inches. The donor site is the skin in the thigh area. The skin taken from each patient was about 16 cm long and 5 cm wide (an average of 98 cm ²). Patients were treated using gauze moistened with honey and covered with sterile dry gauze	The patient was treated with a normal saline dressing. Dressing change was done once daily	<p>1. Wound healing time Donors treated with honey were epithelialized about 3 days faster than donor sites treated with paraffin gauze (9.4 vs 12.4 days, ($p < 0.05$ statistically significant). The mean healing time was 9.6 days in the honey-treated donor area and 9.4 days in the hydrocolloid-coated donor area; there was no statistical difference between these groups. Donors treated with epithelialized honey were about 4.1 days faster than donor sites treated with normal saline-soaked gauze (9.1 vs 13.2 days, ($p < 0.001$ statistically significant).</p> <p>2. Pain score Less pain was observed with the honey-soaked gauze compared to the paraffin and normal saline-soaked gauze ($P < 0.05$).</p>
3	Kamaratos 2012 [117] (Yunani)	56 year	double-blinded RCT	32/31	This study involved patients with lower extremity neuropathic ulcers with severity grades of Wagner 1 and 2. Patients were treated with Medihoney Tulle Dressing which was changed daily. Dressing changes are carried out by trained nurses who do not know the contents of the ingredients used to treat them	The patient was treated with a normal saline dressing. Dressing change was done once daily	<p>1. Wound healing time. The mean duration of healing was 31 ± 4 days in the honey group compared to 43 ± 3 days in the normal saline group ($P = 0.02$)</p> <p>2. Eradication of infection In the honey group, 25 (78.13%) patients had sterile wounds in the first week, 5 (15.62%) in the 2nd week and the remaining 2 (6.25%) in 4 weeks. In group II patients, 11 (35.5%) patients presented with sterile ulcers within 1 week, 12 (38.7%) patients within 2 weeks, 4 (12.9%) patients within 4 weeks and the remaining 4 (12, 9%)</p>
4	Imran 2015 [119] (Pakistan)	54 years	double-blinded RCT	179/169	The Honey Berry (<i>Ziziphus jujuba</i>) used in this study was provided by the Department of Microbiology, University of Health Sciences, Lahore, Pakistan. This honey is collected from Karak district, Pakistan. The honey was stored in a dark room, at room temperature (20 - 30°C). All honey samples were given gamma rays before being given to the patient. The honey sample was investigated for its antibacterial effect by agar well diffusion test and only that sample was used in the experiment which showed an inhibition zone of 18 mm at 50% w/v dilution against ATCC 25923 <i>Staphylococcus aureus</i> . The wound dressing is covered with a 2nd layer for protection. Dressings were performed twice daily for three days and then, depending on the condition of the wound, either once/twice daily or once every 48 hours.	The patient was treated with a normal saline dressing. Dressing change was done once daily	One hundred and thirty-six (75.97%) wounds were completely healed with honey dressing and 97 (57.39%) with normal saline dressing, while the number of wounds that did not heal completely, was significantly less in the honey-treated group compared to the non-healed group. given normal saline, 32 (17.87%) vs. 53 (31.36%), respectively ($p = 0.001$). The median wound healing time was 18.00 (6 - 120) days in honey group and 29.00 (7 - 120) days in saline group ($p < 0.001$).

5	Samani 2011 [118] (Iran)	36 years	Single blinded RCT	5/5	<p>This study involved patients with surgical wounds due to Modified Widman Flap (MWF). The patient were treated with topical Thymus Vulgaris honey at the surgery site. Patients wer asked to apply honey with a sterile brush which were given to them in the package and rinse with normal saline.</p> <p>Subjects were also instructed to hold the lips up in the treated area and held for 5 minutes. Patients were instructed to gargle 30 minutes after administration of topical honey with 15 cc of normal saline to prevent possible triggering of dental caries.</p>	Package given to control contains normal saline	<p>1. Healing index There was a significant improvement in wound healing in terms of time and treatment effect in both groups although faster wound healing was observed in the Honey treated group. (p< 0.001)</p> <p>2. Gingival index The trend of changes in the gingival index in phase I of this study was significant in the experimental and control groups (p = 0.001)</p> <p>3. Plaque index The plaque index in the experimental and control groups increased towards day 1 which continued to worsen until day 3, then was followed by plaque repair in both groups. (p=0,1)</p>
6	Tan 2012 [129] (Malaysia)	Rats 180 - 250 gr	RCT	6/6	<p>This study used adult male Sprague-Dawley rats weighing between 180 and 250g. An incision was made with a full thickness of 4 cm², and without infection, the excision wound was used in this study. Therapy were started 24 hours after wound creation, the wound is exposed to air, and a dressing is applied once a day. Mice were randomly divided into four experimental groups with 24 animals per group. The untreated group was left without any treatment to serve as the untreated control group. The saline group was treated topically with normal saline (negative control), the Intrasite group was treated with Intrasite Gel (positive control), while the Gelam group (experimental group) was given Gelam honey. Six rats from each group were sacrificed on day 1, 5, 10, and 15 of treatment. The entire area of wound tissue was carefully removed from each mouse and immediately fixed for histological processing. All samples were properly labeled with a unique number prior to storage and measurements were performed randomly to overcome experimental bias.</p>	No treatment	<p>The use of Intrasite Gel and Gelam honey showed a significant reduction in wound healing (P < 0.05) compared to no treatment and saline treatment. There was no significant difference in the duration of wound healing between the groups treated with Intrasite Gel and Gelam honey: both healed in about 13 days. However, untreated wounds take about 16 days to heal: about three days longer than the wound healing time required for Intrasite Gel and Gelam honey treatments.</p>

Table 2: Study Characteristic.

	Random sequence generation	Allocation concealment	Blinding (participants personnel)	Blinding (outcome assessment)	Selective reporting	Incomplete outcome data	Other bias	Overall
Kamaratos <i>et al.</i> , 2012	?	+	+	?	+	+	?	+
Misirlioglu <i>et al.</i> , 2003	-	-	-	-	?	-	?	-
Dubhashi <i>et al.</i> , 2014	?	+	?	?	?	?	?	?
Imran <i>et al.</i> , 2015	+	+	?	?	?	?	?	?
Samani <i>et al.</i> , 2011	+	+	?	?	?	?	?	?
Tan <i>et al.</i> , 2012	+	+	+	?	?	+	?	+

Circle symbol with a positive sign indicates a low risk of bias, circle with a question mark the risk of bias cannot be assessed, circle with a negative sign indicates a high risk of bias.

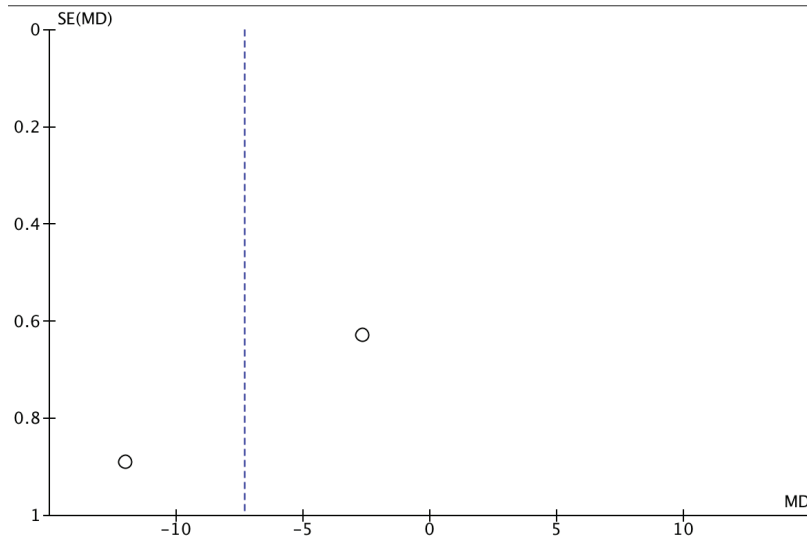


Figure 2: Funnel plot meta-analysis of Kamaratos (2012) and Tan (2012).

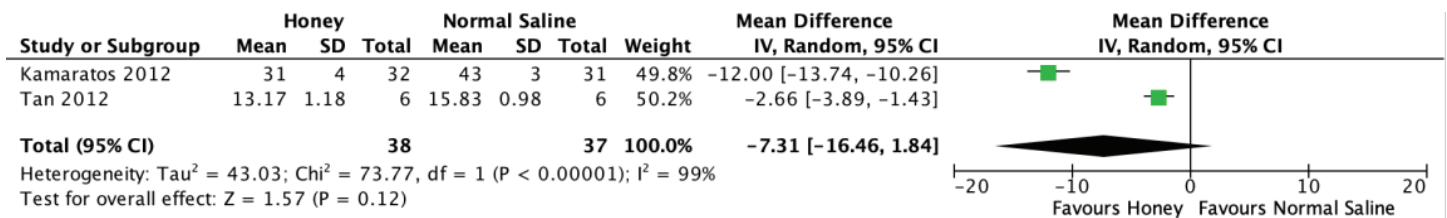


Figure 3: Forest plot.

Figure 2 shows the Funnel plot meta-analysis using Revision Manager 5.4. If there is no publication bias, the research will be distributed symmetrically regarding the summary effect. In this meta-analysis, publication bias cannot be ruled out, because the funnel plot depicts an asymmetrical picture [13].

Meta-analysis

Meta-analysis means difference of healing time required between wound treated with honey compared with normal saline is explained as Forest plot (Figure 3). The overall effect of mean difference healing time is -7.31 (95% CI = -16.46 to 1.84), a negative value indicating that the healing time required for honey treated group is lower than that in controls. But the p value is $p=0.12$ so test for overall effect is not significant statistically. This is due to only 2 trials available for quantitative study, because other studies were excluded.

Heterogeneity is variation between studies. In this meta-analysis, the p value for chi square is less than 0.05%, i.e. 0.00001, so this analysis is heterogeneous. The heterogeneous value is enormous, because the difference in healing time between studies is quite wide, because this study uses different wound characteristics. The research used by Kamaratos (2012) subjects are chronic wounds that are difficult to heal, while Tan (2012) subjects are wounds that can heal secondarily, then the subject of Kamaratos (2012) requires a longer healing time than the subject research from Tan (2012). In addition, different honeys also play a role in influencing this enormous heterogeneity [13].

Discussion

This is a systematic review and meta-analysis to compare the effectiveness of honey to normal saline dressing in promoting wound healing. The overall study have moderate bias risk and from the funnel plot it depicts that bias cannot be excluded from this study. The use of honey to treat wound has been used since the ancient Egyptians [2].

The age range of the sample varied among the studies included in the systematic review and meta- analysis. Dubhashi's research (2014) has research subjects with an age range of 20-80 years. Misirlioglu's research (2003) has research subjects with a range between 14-64 years. Imran research (2015) has research subjects with a range between 47-64 years. Kamaratos research (2012) had research subjects ranging from 42-72 years. Samani research (2011) has research subjects with a range between 35-40 years. Tan et al research has research subject's rats weighing 180 - 250 gr.

Based on the literature, age affects wound healing. Although the elderly can heal most wounds, they have a slower healing process, and all phases of wound healing are affected. The inflammatory response is decreased or delayed, as is proliferative response. Remodeling occurs, but to a lesser extent, and the collagen formed is qualitatively different. So, especially in the elderly, the accompanying medical problems must be addressed to allow maximum healing. Recent trials of new therapies to improve wound healing show, however, that much can be done to improve the prognosis of elderly patients with risk factors known to influence wound healing [14].

All of the study conducted in a study shows that honey promotes wound healing better than normal saline. Dubhashi's study (2014) the results of statistical analysis of the appearance of granulation in the wound return $p < 0.001$, very statistically significant. Imran (2015) who measured the median healing time showed that honey provided a faster wound healing time than normal saline, with $p < 0.001$, very significant statistically. Misirlioglu's study (2003) wound area treated with epithelialized honey was about 4.1 days faster than the donor site covered with normal saline-soaked gauze, providing statistical analysis with a P value of < 0.001 , very significant statistically. Samani's research (2011) showed that faster wound healing was observed in patients treated with honey ($P < 0.001$), statistically significant. Research in this systematic review showed that honey is superior to normal saline in wound healing, showing significant and very significant statistical results [7-9,11,15].

Based on the literature, Honey exerts its effects on wound healing through its antimicrobial properties and the alteration of physiologic and immunologic functions. Honey is proven to have a good antibacterial effect, so it can inhibit and kill both aerobic and anaerobic bacteria. The antibacterial effectiveness of honey is obtained from the phenolic content and hydrogen peroxide it contains, in addition to the high levels of flavonoids, polyphenols, and osmolarity levels, which also have an effect against bacteria. Antibacterial effect has anti-resistant properties against bacteria that are sensitive to it. The antibacterial effect of this honey can help speed up wound healing [16].

Honey has a low pH. This low pH manifests by inhibiting the action of proteases, which further increases the rate of epithelialization of the wound. It was proven that wounds that received honey had a faster epithelialization rate than controls. This increase in the rate of epithelialization can help speed up wound healing [17].

Keeping the wound moist is the expected physiological effect of wound management. Honey has a high osmolarity so that it can maintain wound moisture so that adequate physiological conditions are achieved for wound healing. Properly maintained wound moisture can help the accelerate wound healing [16].

Removal of necrotic tissue is one way to ensure oxygenation and vascularity of the wound tissue. Honey has an inhibitory effect on the production of Plasminogen Activator Inhibitor so that honey has an autolytic debridement effect. This autolytic debridement effect can help accelerate wound healing [18].

Honey has an antioxidant effect, which is mediated by the levels of flavonoids, polyphenols and levels of vitamin C it contains [19].

Our study have limitations in the form of the number of research subjects regarding comparison of the effectiveness of honey to normal saline dressing in promoting wound healing. Some studies were excluded from the meta-analysis because no same assessment parameters or incomplete results.

Some study do not do blinding, and the risk of bias if very high. The wound treated in this journal also very different, some study using acute wound such as skin graft donor, and the other study treats chronic wound such as diabetic ulcer. This variability creates very high heterogeneity.

Conclusion

This study demonstrated the efficacy of honey in wound healing compared to normal saline dressing. From the systematic review point of view, all of the study conducted in a study shows that honey promotes wound healing better than normal saline. But from the meta-analysis or quantitative study shows that honey is not proven to promote wound healing better than normal saline. More research and study are needed to justify the use of honey to treat acute and chronic wound.

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