Review

The effects of honey compared to silver sulfadiazine for the treatment of burns: A systematic review of randomized controlled trials

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A R T I C L E   I N F O

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A B S T R A C T

Evidence from animal studies and trials suggests that honey may accelerate wound healing. The objective of this review was to assess the effects of honey compared with silver dressings on the healing of burn wounds. Relevant databases for randomized controlled trials (RCTs) of honey compared with silver sulfadiazine (SSD) were searched. The quality of the selected trials was assessed using the Cochrane Risk of Bias Assessment Tool. The primary endpoints considered were wound healing time and the number of infected wounds rendered sterile. Nine RCTs met the inclusion criteria. Based on moderate quality evidence there was a statistically significant difference between the two groups, favoring honey in healing time (MD – 5.76 days, 95% CI – 8.14 to – 3.39) and the proportions of infected wounds rendered sterile (RR 2.59; 95% CI 1.58–2.88). The available evidence suggests that honey dressings promote better wound healing than silver sulfadiazine for burns.

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1. Introduction

Burn injuries are common. The definition of burns by the World Health Organization [1] is “an injury to the skin or other organic tissue primarily caused by heat, radiation, radioactivity, electricity, friction or contact with chemicals”. The severity of burn injuries depends on the depth of the wound injury and the extent of the body area affected. As a result of burn injuries, the skin loses its protective function against microorganisms leading to a high risk of infection. Burn wounds are also susceptible to infection because their moist environment provides an ideal situation for bacteria to multiply [2]. Infection by microorganisms is a major cause of morbidity associated with extended hospital stay and high medical costs [3], impairment in work and quality of life and can lead to social rejection due to disfigurement [1]. The prevention of infection, therefore, is an important factor in the acceleration of healing and reduction of morbidity [1].

Recently, topical dressings containing honey as well as silver sulfadiazine (SSD) have re-emerged as a treatment option for burn wound management [4]. Honey is postulated to facilitate wound healing by its chemical debridement and anti-inflammatory action [5], and its ability to create a viscous barrier on the wound surface thus preventing the invasion of microorganisms [5–8]. Meanwhile, SSD may be considered as the gold standard for topical burn treatment [9]. In contrast to honey, silver-containing dressings are capable of absorbing the burn exudates and releasing silver which has been recognized as an effective antimicrobial agent against a broad range of bacteria, yeast, and viruses [3,10]. However, recent findings have shown that topical silver delays rather than promotes wound healing and is associated with potentially severe adverse effects [11–13].

Several systematic reviews have examined the effectiveness of both silver and honey for acute and chronic wounds including burn injuries [14–17]. However, none of these reviews specifically compared the efficacy of honey versus SSD in burn wounds. Thus, the aim of this systematic review was to determine the efficacy of honey compared to SSD in burn wound healing.

2. Materials and methods

The following databases were searched; MEDLINE (1966–2014), Cumulative Index of Nursing & Allied Health Literature; CINAHL (1982–2014), Cochrane Database of Systematic Reviews (1996–2014), Cochrane Central Register of Controlled Trials (1991–2014), and Database of Abstract of Reviews of Effects; DARE (2001–2014). The search of MEDLINE was limited to humans and a filter was applied to identify Randomized Controlled Trials (RCTs) in all databases as described elsewhere [18]. For the search strategy, the Medical Subject Headings “Silver” and “Honey” AND “burn” OR “burn wound” were used. To ensure that the search was comprehensive, the reference lists of the retrieved articles and any identified review articles were reviewed. In addition, the corresponding authors of identified studies were contacted, and experts working in the field of burn therapy or honey, were asked for further studies. RCTs involving silver compared with honey for burn wound healing were included. No restriction on the language, date, and publication type of the studies was applied. The relevant data were extracted by two reviewers and methodological quality was assessed using the Cochrane Criteria for Risk of Bias assessment [19]. Any disagreements between the two reviewers were resolved through discussion.

3. Data analysis

Trials were only included if they used time for burn healing or infection rate as primary outcomes. Measures such as pain and adverse events were the secondary outcomes. The outcome measure used for statistical pooling was burn healing reported either as dichotomous or continuous outcomes. For dichotomous outcomes, relative risk (RR) was calculated and the results were reported as RR with 95% confidence intervals (CI) while for healing time, results were collected on the reported mean difference (MD), the weighted mean difference (WMD), or standardized mean difference (SMD) with 95% CI as appropriate between the silver and honey groups. In some studies where data required for meta-analysis was missing, attempts were made to contact the original authors for detailed information. If standard deviation could not be obtained, equal variance and normal distribution of the data were assumed, and standard deviations based on the p-value provided in the articles were calculated.

Statistical heterogeneity was analyzed using the Index, I² test as recommended by The Cochrane Collaboration. If the I² statistic was deemed high (over 75%) we explored the heterogeneity [20].

4. Results

The flow of searches, and number of trials identified and included in this study are shown in Fig. 1. Of the 5150 records identified, 17 full text articles were assessed and 7 studies were excluded for reasons as stated in Fig. 1. Only ten trials met the inclusion criteria and of these, nine trials provided quantitative data and were therefore included in the quantitative analysis.

5. Description of studies

A total of ten trials were included with a total of 717 patients with a variety of burn wounds (Table 1). Four trials [8,21–23]
included patients with superficial thickness wounds; three trials [24–26] included patients with partial thickness wounds, while the other three trials [27–29] included patients with superficial thickness and partial thickness wounds.

Undiluted honey was used in all of the trials except one [23]. Topical honey + dressings were used in all trials; seven trials compared it with topical silver agents + dressings [23–29] while three trials compared it with silver-containing dressings [8,21,22].

Primary outcome measures such as time taken to complete wound healing and number of wounds rendered sterile were reported in most of the studies. Secondary outcome measures such as pain were only reported in two trials [25,27] and the adverse effect of interventions were not reported in any of the studies.

6. Risk of bias assessment in included trials

The risk of bias of the included studies is summarized in Fig. 2. The majority of the trials had unclear risk of bias for sequence generation, concealment of allocation, and blinding of participants and outcome assessor. However one trial [25] was judged to have high risk of bias for randomization as the trial used a consecutive sampling method which was a type of non-probability sampling [30] that could cause selection bias. There was no loss to follow up in any of the included studies.

Trials were determined as having low risk of bias for the domain “selective outcome reporting” when outcomes measures specified in the methods section were also reported in the results. Except for two trials, [22,26] all other trials were judged to have low risk of bias. For other potential bias, the focus was on baseline comparability between honey and silver treated groups. All the trials reported comparable baseline characteristics between the intervention and control groups.

7. Effects of intervention

Out of 10 included trials; quantitative data were only available for 9 trials. The results were based on outcome measures, which were commonly reported among the included trials. These outcomes were also presented in previous systematic reviews looking at different interventions for burn wounds.

7.1. Complete wound healing time

Results for only four trials involving superficial and partial thickness burns were suitable for pooling [8,21–23]. The pooled effect using the random-effect model ($I^2 = 93\%$) showed a statistically significant effect favoring honey for superficial thickness wounds (MD $-4.62; 95\%$ CI $-7.37$ to $-1.88$) (Fig. 3). Two other trials [26,27] just reported that the duration of wound healing was shorter in the group treated with honey compared to the group treated with silver.

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<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Participants</th>
<th>Age in years (mean (SD)/range)</th>
<th>Intervention: (No. of subjects)</th>
<th>Control: (No. of subjects)</th>
<th>Duration of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baghel et al. [28] (India)</td>
<td>78 patients with first and second degree burns</td>
<td>H: 34.5 (NR)</td>
<td></td>
<td>SSD cream (n = 41)</td>
<td>2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: 28.5 (NR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sami et al. [25] (Pakistan)</td>
<td>50 patients with partial thickness thermal burns</td>
<td>1.5–50</td>
<td>Pure, unprocessed, and undiluted topical honey (n = 25)</td>
<td>1% SSD cream (n = 25)</td>
<td>2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangroo et al. [23] (India)</td>
<td>64 patients with superficial thermal burns</td>
<td>Less than 12 years old</td>
<td>Honey (n = 32)</td>
<td>SSD (n = 32)</td>
<td>Until wound healed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>Shah et al. [29] (Pakistan)</td>
<td>84 Patients with first and second degree burns</td>
<td>25.95 (16.7)</td>
<td>Pure and undiluted honey (n = 42)</td>
<td>SSD cream (n = 42)</td>
<td>2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mashhood et al. [27] (Pakistan)</td>
<td>50 patients with superficial and partial thickness burns</td>
<td>27.4 (NR)</td>
<td>Honey-added (pure, unprocessed, and undiluted) dressings (n = 25)</td>
<td>1% SSD cream (n = 25)</td>
<td>Until wound healed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mujalde et al. [26] (India)</td>
<td>110 patients with partial thickness burns less than 50% of total body surface area</td>
<td>10–50</td>
<td>Undiluted pure honey with sterile gauge, cotton pad, roller bandage (n = 55)</td>
<td>SSD cream with sterile gauge, cotton pad, roller bandage (n = 55)</td>
<td>Until wound epithelialized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21 days</td>
</tr>
<tr>
<td>Okeniyi et al. [24] (Nigeria)</td>
<td>27 children with partial thickness burns</td>
<td>5.5 (3.4)</td>
<td>Crude undiluted honey dressing (n = 15)</td>
<td>SSD (Dermazine) dressing (n = 12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam [8] (India)</td>
<td>104 patients with superficial thermal burns</td>
<td>1–65</td>
<td>Honey (pure, unprocessed, undiluted) dressing (n = 52)</td>
<td>Silver sulfadiazine impregnated gauze (n = 52)</td>
<td>2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 month</td>
</tr>
<tr>
<td>Subrahmanyam [21] (India)</td>
<td>50 patients with superficial thermal burns</td>
<td>H: 25.2 (NR)</td>
<td>Honey-added (pure, unprocessed) dressings (n = 25)</td>
<td>SSD impregnated gauze (n = 25)</td>
<td>Until wound healed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: 26.4 (NR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subrahmanyam et al. [22] (India)</td>
<td>100 patients with superficial burns</td>
<td>H: 26.5 (1.0)</td>
<td>Honey-added (pure, unprocessed) dressings (n = 50)</td>
<td>SSD impregnated gauze (n = 50)</td>
<td>Until wound healed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: 25.2 (2.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: n = number of participants; SSD = silver sulfadiazine, NR = not reported, H = Honey, C = Control.
7.2. Wounds healed (proportion)

Only three trials [24,28,29] provided data for the proportion of patients with completely healed wounds. Pooling of data (Fig. 4) shows that there is a statistically significant difference between the two groups in the proportion of patients with wounds healed favoring the honey group (RR 2.13; 95% CI 1.61–2.80).

7.3. Number of infected wounds rendered sterile

Seven trials reported the number of infected wounds rendered sterile [8,21–23,25,28,29]. As shown in Fig. 5, the pooled results for the three subgroups (superficial thickness, partial thickness, and superficial and partial thickness wounds) shows a statistically significant beneficial effect favoring honey (RR 9.08; 95% CI 1.69–48.81).

7.4. Pain

Two trials [25,27] reported the proportion of patients with complete pain relief at 3 weeks and the pooled analysis showed that there was no significant difference between the two groups (RR 1.00; 95% CI 0.41–2.44).

7.5. Adverse events

None of the studies reported adverse events.

8. Discussion

Based on the evidence, for superficial or partial thickness wounds, honey was found to have statistically significant beneficial effects compared to SSD for the outcomes time to complete wound healing, proportion of wounds completely healed, and proportion of infected wounds rendered sterile. However, it should be noted that the heterogeneity among the included studies for the meta-analysis of complete wound healing time and number of infected wounds rendered sterile was high (more than 90%) due to variations in the age of included participants, duration of follow up, and the types of outcomes reported.

Data from animal studies and human trials suggests that silver delays wound healing as it is toxic to regenerating keratinocytes [31–35]. Additionally, in a systematic review published in 2012, Aziz et al. [11] reported that when silver was compared to non-silver dressings, silver was shown to worsen healing time. However, silver is still used as a comparator or control in many burn trials because it is considered as the gold standard in the treatment of burn wounds [9,35,36]. Thus, it seems that when honey is compared to silver, the effect of honey on wound healing may be amplified rather than honey being truly effective.

It is difficult to judge the quality of the evidence as the majority of the domains in the risk of bias assessment were inadequately described. Additionally, about half of the included studies were open trials. Although binding of participants and care providers was difficult, the trial investigators could have blinded the outcome assessors to reduce the risk of outcome bias. If information on group assignment is not concealed from participants, their

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### Fig. 4 – Comparison: Honey versus silver; Outcome: Wound healed (proportion).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Honey Events</th>
<th>SSD Total</th>
<th>Risk Ratio M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okenyi et al., (24)</td>
<td>13</td>
<td>15</td>
<td>2.08 [1.03, 4.18]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>15</td>
<td>12</td>
<td>2.08 [1.03, 4.18]</td>
</tr>
<tr>
<td>Total events</td>
<td>13</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 2.06$ ($P = 0.04$)

### Fig. 5 – Comparison: Honey versus silver; Outcome: Number of infected wounds rendered sterile.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Honey Events</th>
<th>SSD Total</th>
<th>Risk Ratio M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baghel et al., (28)</td>
<td>30</td>
<td>37</td>
<td>2.22 [1.44, 3.41]</td>
</tr>
<tr>
<td>Shah et al., (29)</td>
<td>33</td>
<td>42</td>
<td>2.06 [1.36, 3.13]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>79</td>
<td>83</td>
<td>2.13 [1.56, 2.88]</td>
</tr>
<tr>
<td>Total events</td>
<td>63</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $Chi^2 = 0.06, df = 1$ ($P = 0.81$); $I^2 = 0$
Test for overall effect: $Z = 4.96$ ($P < 0.00001$)
Test for subgroup differences: $Chi^2 = 0.00, df = 1$ ($P = 0.95$), $I^2 = 0$

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Honey Events</th>
<th>SSD Total</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangroo et al., (23)</td>
<td>23</td>
<td>25</td>
<td>7.36 [2.54, 21.35]</td>
</tr>
<tr>
<td>Subrahmanyam (21)</td>
<td>17</td>
<td>23</td>
<td>0.86 [0.64, 1.15]</td>
</tr>
<tr>
<td>Subrahmanyam (8)</td>
<td>39</td>
<td>43</td>
<td>12.40 [4.15, 37.00]</td>
</tr>
<tr>
<td>Subrahmanyam et al., (22)</td>
<td>40</td>
<td>44</td>
<td>11.6%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>135</td>
<td>129</td>
<td>8.01 [0.33, 192.24]</td>
</tr>
<tr>
<td>Total events</td>
<td>119</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $Tau^2 = 9.92, Chi^2 = 129.95, df = 3$ ($P < 0.00001$); $I^2 = 98$
Test for overall effect: $Z = 1.28$ ($P = 0.20$)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Honey Events</th>
<th>SSD Total</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sami et al., (25)</td>
<td>17</td>
<td>20</td>
<td>1.70 [1.08, 2.68]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>20</td>
<td>22</td>
<td>1.70 [1.08, 2.68]</td>
</tr>
<tr>
<td>Total events</td>
<td>17</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 2.28$ ($P = 0.02$)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Honey Events</th>
<th>SSD Total</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baghel et al., (28)</td>
<td>24</td>
<td>37</td>
<td>5.46 [1.41, 860.28]</td>
</tr>
<tr>
<td>Shah et al., (29)</td>
<td>26</td>
<td>42</td>
<td>11.6%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>79</td>
<td>83</td>
<td>11.6%</td>
</tr>
<tr>
<td>Total events</td>
<td>50</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 0.00, df = 1$ ($P = 0.99$); $I^2 = 0$
Test for overall effect: $Z = 3.99$ ($P < 0.00001$)

Total (95% CI) | 234 | 100.0% | 9.08 [1.69, 48.81] |
Total events | 186 | 36         |                               |

Heterogeneity: $Tau^2 = 4.35$, $Chi^2 = 171.65, df = 6$ ($P < 0.00001$); $I^2 = 97$
Test for overall effect: $Z = 2.57$ ($P = 0.01$)
Test for subgroup differences: $Chi^2 = 12.04, df = 2$ ($P = 0.002$); $I^2 = 83.4$

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responses to the intervention are most likely to be affected [37]. Likewise, investigators who are not blinded can affect the participants’ attitude towards the intervention received, as well as the participants’ compliance throughout the length of study [38]. Another limitation of this review is that the outcome assessment for wound healing is not consistent among studies as most of the trial authors did not explicitly state the definition of wound healing and how it was measured.

In the light of all these limitations, the findings of this review should be interpreted with caution. The results of this review are in agreement with other reviews examining evidence of effectiveness of honey for wound healing [16,17] where the quality of evidence in the included trials limits the drawing of a firm conclusion regarding the beneficial effects of honey for burn wound management.

9. Conclusion

Despite a positive finding favoring honey when compared to silver, the scarcity of high quality evidence to justify routine use of honey for burn wound healing in clinical practice is highlighted in this review. Authors of future trials should use common and clinically relevant end-points to assess the effectiveness of honey, and to use the Consolidated Standards of Reporting Trial (CONSORT) statement to improve the quality of reporting of trials.

Given the evidence that silver delays re-epithelialization, its use as a control or comparator should also be reassessed in future trials as any intervention would almost always be found more effective than silver.

Acknowledgements

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