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Topical honey for the treatment of diabetic foot ulcer: A systematic review

Ramya Kateel [a], Prabha Adhikari [a, *], Alfred J. Augustine [b], Sheetal Ullal [c]

[a] Department of Medicine, Kasturba Medical College Mangalore, Manipal University, India
[b] Department of Surgery, Kasturba Medical College Mangalore, Manipal University, India
[c] Department of Pharmacology, Kasturba Medical College Mangalore, Manipal University, India

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ABSTRACT

Topical honey has been used for the treatment of wound since ancient time. But the medical evidence proving it is limited. Hence a systematic review was planned. An exhaustive literature search was done in PUBMED, COCHRANE, GOOGLE using 'topical honey', 'diabetic foot ulcer', 'chronic wounds' as key words. Literature search showed total of five clinical trials and about ten observational studies in various part of world. Out of five clinical trials three concluded that honey dressing is better than conventional dressing, all the clinical trials proved safety of honey for the treatment of diabetic foot ulcer. Observational studies included total of 320 patients which also showed safety of honey but efficacy cannot be considered from observational studies. This review showed that honey dressing is safer for treatment of diabetic foot ulcer but there is insufficient good quality data to realistically conclude on the efficacy of honey on diabetic foot ulcers.

Contents

1. Introduction

Honey is a commonly used natural bee product which is available in most parts of the world. It has been used for the treatment of various infected wounds since ancient times because of its antimicrobial properties [1]. The introduction of effective antibiotics in the 20th century led to a decline in the use of topical honey for wounds. However the recent medical literature has shown a change in the trend with several studies reporting its efficacy in treating different types of wounds, including burns and infected wounds [2–6]. Honey has multiple properties which attribute to its wound healing capacity. These include antibacterial [7] property by releasing hydrogen peroxide in a quantity which causes auto debridement of necrotic tissue without harming granular tissue [8], acidity and osmotic effect which minimizes the growth of pathogens [9], an increase in the rate of healing by stimulating release of growth factors [10] an antioxidant and anti-inflammatory action which contributes to wound healing [11].

Ulceration of the foot is common in diabetes and may lead to amputation of the leg. It is one of the common causes of morbidity

* Corresponding author.
E-mail addresses: ramyakateel@gmail.com (R. Kateel), prabha.raghuveer@gmail.com (P. Adhikari), alfred.augustine@manipal.edu (A.J. Augustine), sheetal.ullal@manipal.edu (S. Ullal).

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Table 1
Randomized controlled clinical trials on topical honey for treatment of diabetic foot ulcer.

Authors study design	Sample size and patient selection	Comparator and follow up duration	Outcome measured	Conclusion
Shukrimiaetal 2008 [13] Randomized controlled open label clinical trial	Sample size: 30 Inclusion criteria: age 31–65 with Wagner type II diabetic foot ulcer	Povidone iodine dressing. First post-operative day till surgical closure of wound or further debridement.	Mean duration for surgical closure Control-15.4 (9–36) days Topical honey-14.4 (7–26) days $p < 0.005$ No adverse effect observed	Honey can be a safe alternative dressing for Wagner type II diabetic foot ulcer
Kamaratos A V et al., 2014 [14] Randomized controlled open label clinical trial	Sample size: 63 Inclusion criteria: patients with neuropathic diabetic foot ulcer.	Conventional dressing. 16 weeks.	Mean healing time Control 41 ± 3 days Manuka honey- 31 ± 4days $p < 0.05$ Percentage of ulcer healed- Control–90% Honey–97% $P > 0.05$ Percentage of disinfected ulcer control–35.5%, 12.9%, 0%, 12.9% for I, II, IV, VI week respectively Manuka honey-78.13%, 15.62%, 38.7%, 6.25% for I, II, IV, VI week respectively $P < 0.05$ No adverse effect observed	Manuka honey impregnated dressing represents an effective treatment for neuropathic diabetic foot ulcer
Jan W A, etal 2012 [15] Randomized controlled open label clinical trial	Sample size: 100 Inclusion criteria: Patients with Wagner grade I to IV.	Pyoidone iodine dressing. 10 weeks.	Percentage of ulcer recovered 2–4 week-30%, 60% 5–7 week-26%, 34% 8–10 week-44%, 6% for control and topical honey group respectively $P < 0.0001$ amputation rate control–34% Honey-28% Recovery rate Control-66% Honey-72% $p = 0.658$ No adverse effect data available	Honey dressing was more effective than conventional Pyodine dressing in terms of recovery time for diabetic foot ulcer
Rehman E U etal, 2013 [16] Randomized controlled open label clinical trial	Sample size: 60 Inclusion criteria: Wagner's grade I &II diabetic foot ulcer.	Povidone iodine/normal saline dressing 2 weeks	Percentage reduction in ulcer size Control-54.63 ± 3.42%, Honey-80.81 ± 17.27% $p < 0.001$ Less complication in honey group.	Wound healing was better with honey dressing compared to povidone iodine dressing
SiavashMetal2015 [17] Randomized placebo controlled open label clinical trial	Sample size: 60 Inclusion criteria: diabetic foot ulcer patients with infection control	Placebo 3 months	Control v/s topical royal jelly There was no significant difference between two groups in terms of reduction in ulcer depth, width, length, incidence of complete healing and duration of complete healing with p values 0.69,0,95,0,7,0.74 and 0.6respectively	5% topical royal jelly did not show any superiority over placebo

in diabetic patients and has a negative impact on quality of life [12]. Topical honey is used as one of treatment options by many clinicians to treat diabetic foot ulcer mainly because of its wound healing properties and cost effectiveness. There are several randomized controlled clinical trials and observational studies reporting the use of honey for treating diabetic foot ulcers. But there is a lack of a systematic review on the use of topical honey for the treatment of diabetic foot ulcers. Hence this review was planned.

2. Materials and methods

An exhaustive literature search was performed using PUBMED, COCHRANE, GOOGLE using 'topical honey', 'diabetic foot ulcer', and 'chronic wounds' as key words. Articles published in English language were included. All clinical trials with or without control, blinded or open, placebo or active drug control which included at least one diabetic foot ulcer patient treated with honey were included. Observational studies, case reports and case series were also included. All studies assessing the efficacy of honey were included due to the paucity of randomized controlled trials.

3. Results

A total of five randomized controlled trials and 10 observational studies were included. All the studies were between 2008 and 2015. Out of five randomized trials, one was a placebo controlled, double blind study, whereas other 4 were open label active control studies. Details of randomized control trials are given in Table 1.

The literature survey showed a total of 10 observational studies out of which three were case reports, two case series, two experimental studies and three observational prospective studies. Their details are given in Table 2.

4. Discussion

Studies on the use of honey for different types of diseases are increasing. It has been used for treatment of wound since ancient time. Honey because of its antibiotic, antioxidant, anti-inflammatory, auto debridement, growth factor stimulation and

Table 2
Case reports, Case series and Prospective observational studies on topical honey for diabetic foot ulcer.

Authors type of study	Sample size investigational product	Outcome	Conclusion
Makhdoom a et al., 2009 [18] Experimental Case series	12 (14 feet) Topical honey	75% (9) of patient underwent amputation out of which 66.67% (8) were toe amputation and 8.3% (1) was below the knee amputation.	Honey showed an excellent result decreasing rate of leg or foot amputation.
Mansour S et al., 2011 [19] Case series	8 Topical royal jelly	Mean healing time-41 days No adverse effect	Royal Jelly dressing may be an effective method for treating diabetic foot ulcers besides standard treatments.
SurahioARetal, 2014 [20] Prospective observational study	172 Topical honey	Healing rate was 7–35 days Amputation rate-5 patients Below knee-1.16% Big toe-1.75%	Honey can be successfully used for treatment of diabetic foot ulcer as it reduced amputation rate
Moghazy AMetal, 2010 [21] Prospective observational study	30 Topical honey	Complete healing in 43.3% Decrease in size and healthy granular tissue-43.3% Treatment failure 6.7%	Honey is clinical and cost effective alternative for diabetic foot ulcer
TasleemSeatl, 2011 [22] Experimental study	4 Honey ointment containing 20% active antimicrobial honey	Healing-95% Mean healing time-20 (8–40)	Effective and alternative low-cost product for the treatment of wound infections.
Tehemton Eetal, 2011 [23] Observational study	29 Ghee and honey combination	Ulcer healing-21 days Granular tissue appearance-16 days Amputation-7 cases	Efficacious and safer for treatment of diabetic foot ulcer
Abdelatif et al., 2008 [24] Prospective pilot study	60 Further grouped based on Wagner ulcer grade PEDYPHAR (topical royal jelly)	Complete healing-9weeks for 96% Patients of grade I, II and III	PEDYPHAR ointment may be a promising, safe conservative local treatment
Lofty M et al., 2006 [25] Case report	1 Mixture of bee Propolis and myrrh mixed with honey	Complete healing-4 weeks	Resulted in the clean odor free wound which healed well.
Mohamed H et al., 2014 [26] Case report	1 Honey in combination with hydroalginate and off loading	10 × 15 cm ulcer healed after 16 weeks	Effective in managing diabetic Foot ulcer at primary care level.
Jennifer J, 2005 [27] Case report	1 Topical honey	Granular tissue appeared-2 weeks Complete healing-after 6 weeks No recurrence of ulcer up to 2 years	Honey is clinical and cost effective treatment for diabetic foot ulcer

osmolality property has been recommended for treatment of various types of wound infections [5–11]. There are several studies conducted to compare efficacy of topical honey with conventional dressing. There are reviews available for the use of honey on burn and other chronic infections [28–30] but there is no systematic review available for the use of honey for treatment of diabetic foot ulcer. Few studies have tested the efficacy of honey dressing on diabetic foot ulcer.

In this systematic review, we found five randomized clinical trials conducted on diabetic foot ulcer. A total of 310 patients was included in randomized clinical trials out of which 50% of patients were treated with topical honey. Out of five clinical trials, three concluded that honey dressing was better than conventional dressing. Two trials concluded that there was no significant difference between the two groups. There was no adverse event reported in any of the clinical trials. None of the studies were blinded. One study included diabetic foot ulcer of all grades, but results were not discussed based on the ulcer characteristics. One study used a placebo as a control comparator group. There was no uniformity in efficacy parameters, type or grade of ulcer included or follow up period. Hence the results cannot be pooled. So we conclude that there is insufficient data on efficacy of honey dressing for diabetic foot ulcer. However, none of the studies reported any adverse events. Hence we conclude that honey dressing is safe and can be an alternate dressing for diabetic foot ulcer. To prove its superiority over conventional dressing, properly designed randomized controlled clinical trials with adequate sample size, uniform inclusion criteria and outcome measures are necessary. Follow up period has to be optimized from at least 6 weeks to 3 months, which is necessary for complete healing.

There were three case reports, two case series, two experimental studies and three observational prospective studies reported which involved total of 320 diabetic foot ulcer patients. There was no case control study conducted. All the observational studies reported higher efficacy of honey, decrease in amputation rate and the patient compliance was better. Few studies reported earlier microorganism clearance proving honey's antibacterial property. But all the observational studies are of low evidence. In a case series by Makhdoom A et al. [18] reported that honey showed excellent results even though more than 3/4th of patients in the study underwent amputation. The studies included in the review are heterogeneous to a great extent. Most of observational studies and case reports have low evidence because of poor study design and therefore their results are inconclusive. However, observational studies and case reports would have been of value if they had reported safety data although there are reports about amputation. Honey's superiority as reported by these case reports and observational studies based on amputation rate can be justified if the

amputation rate improved especially in patients who were scheduled for amputation or. Even if one fourth of them avoided amputation it would be worthwhile to try honey dressing before amputation. But these details were not provided by the authors.

Many of studies have not reported the source, type or composition of honey. SiavashM et al. in a randomized clinical trial and case series [17,19] used topical royal jelly and its composition was water (50–60%), protients (18%), carbohydrates (15%), lipids (3–6%), mineral salts (1.5%), vitamins, 10-hydroxyl-2-decenoic acid, insulin like peptide. Manuka honey was used by Kamaratos A V et al. in a randomized clinical trial [14]. Combination of ghee and honey was used in one observation study source of both were not mentioned [23]. Different ingredients of honey, which help with wound healing and granulation were not discussed in any of the studies. Honey produces hydrogen peroxide when it comes in contact with the wound. It is released in an amount enough for debridement and antibacterial property and dilute enough not to affect the host [31]. Mauka honey releases a non peroxide substance called Unique Manuka Factor, which is responsible for its antibacterial property [4]. Recent study showed it to be methylglyoxal [32]. Honey has Osmolarity property providing nutrition, Low pH and high glucose content which stimulates macrophages and thus help in wound healing [33]. The contradictory data shown in this study may be because of different type and composition of honey used.

Hence, in this review we are not able to draw a conclusion on clinical application of honey for diabetic foot ulcer because of low evidence due to poorly designed studies. The Cochrane review [5] on the use of honey as topical treatment was also not able to draw an overall conclusion because of the heterogeneous nature of patients included and comparator studied. Most of the studies included in the Cochrane review were inferior. It included twenty six trials in which three trials were on acute wound, eleven on burns, two trials on venous leg ulcer, two trials on diabetic foot ulcer and one with a postoperative wound.

5. Conclusion

There is insufficient good quality data to realistically conclude on the efficacy of honey on diabetic foot ulcers. This review showed that honey dressing is safer for treatment of diabetic foot ulcer. Also, it shortens the total treatment period, micro-organism clearance time and rate of amputation. But further qualitative and quantitative double blind clinical trials with uniform inclusion criteria, efficacy parameters such as time for complete healing, percentage reduction in ulcer size and microbiological clearance along with sufficient follow up period up to complete healing are required to obtain better evidence.

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