

*Original Article***The efficacy of topical Royal Jelly on diabetic foot ulcers healing: A case series***

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Abstract

BACKGROUND: Foot ulcers and infections are the major sources of morbidity in individuals with diabetes mellitus. This study aimed to evaluate the efficacy of topical Royal Jelly (a worker honey bee product) on healing diabetic foot ulcers.

METHODS: Diabetic patients with foot ulcers that were referred to our clinic at Khorshid Hospital, Isfahan, Iran; were evaluated three times a week and treated according to standard treatments consisted of offloading, infection control, vascular improvement and debridement if required. In addition, all ulcers were measured and then topical sterile 5% Royal Jelly was applied on the total surface area of the wounds. Eventually, they were covered with sterile dressings. Each patient was followed for a period of three months or until the complete healing.

RESULTS: A total of eight patients were enrolled in this study. Of these, two had two ulcers and, therefore, ten ulcers were evaluated. Two ulcers were excluded. Seven of the remained eight ulcers healed. Mean duration of complete healing was 41 days. One ulcer did not completely heal but improved to 40% smaller in length, 32% in width and 28% in depth. The mean length, width and depth reduction rates were 0.35 mm/day, 0.28 mm/day and 0.11 mm/day, respectively.

CONCLUSIONS: Royal Jelly dressing may be an effective method for treating diabetic foot ulcers besides standard treatments.

KEYWORDS: Diabetic foot ulcer ;Royal Jelly; Offloading; Debridement.

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Foot ulcers and infections are the major sources of morbidity in individuals with Diabetes Mellitus (DM). Approximately 15% of individuals with DM develop a foot ulcer and a significant subset will ultimately undergo amputation (14% to 24% risk with that ulcer or subsequent ulceration).¹ It has been estimated worldwide that every 30 seconds a lower limb is lost because of diabetes and its incidence will increase due to the expected rise in type 2 diabetes in future.²

Wound dressing is an intervention with demonstrated efficacy in diabetic foot ulcers. Dressings promote wound healing by creating a moist environment and protecting the

wound. It is increasingly important to identify and use low-cost and effective dressings for diabetic foot ulcers as medical costs and rates of DM continue to rise.

Royal jelly (RJ) is the exclusive food of queen honey bee (*Apis Mellifera*) larva, and is secreted from the hypopharyngeal and mandibular glands of the worker honey bee.³ RJ consists of water (50% to 60%), proteins (18%), carbohydrates (15%), lipids (3% to 6%), mineral salts (1.5%) and vitamins⁴ together with a large number of bioactive substances such as 10-hydroxyl-2-decenoic acid (1.7%)⁵ and several Insulin like peptides.⁶ RJ contains phenolic compounds with anti oxidant activity⁷ as well

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as a potent antibacterial protein (royalysin) and 10-hydroxy decenoic acid possessing strong antimicrobial properties.⁸

RJ has been demonstrated to possess several pharmacological activities including anti-inflammatory properties.⁹ Researches showed that Royal Jelly is a vasodilative and hypotensive product using animal models. Therefore, it can dilate vascular system in lower limbs and facilitate blood flow in vascular bed.¹⁰ This honeybee product can increase the growth rate of cells and has antitumor activity that may be used for killing tumor cells in the future.¹¹⁻¹³ Two major problems in diabetic patients are hypercholesterolemia and insulin resistance which may be improved by RJ.^{14, 15} Considering the pathogenesis of diabetic foot ulcers and mechanisms based on which the current management has been designed, application of RJ dressing on diabetic foot ulcers may be effective and RJ may be a moist dressing with antibacterial and tissue-healing properties. The side effects of RJ use are limited to some case reports which have been caused by oral ingestion.¹⁶⁻¹⁹

This case series reports our experience in treatment of 10 diabetic foot ulcers with topical Royal Jelly and is a part of an ongoing large double blind clinical trial.

Methods

This was a pilot study as a prelude to a clinical trial on patients with diabetic foot ulcers referred to diabetic clinic of Khorshid Hospital, Isfahan, Iran from July 1st through November 30th, 2010. All patients suffered from Type 2 Diabetes mellitus with one or multiple ulcers on their feet were entered into this study. Patients with foot gangrene, osteomyelitis, severe sepsis, alcohol and history of drug abuse, cancer, congestive heart failure, end stage renal disease, liver failure, use of drugs which may interact with wound healing (Glucocorticoids, Immunosuppressive drugs and cytotoxic drugs) and those who preferred to receive the treatment out of the study were not included. Drug side effects (hypersensitivity to RJ), inappropriate follow up by the patient, and the

patient's desire to withdraw in each phase of the study were considered as exclusion criteria.

After filling and signing the consent form by the patients or their family member, they were educated on wound care and management of the ulcer. The plan of this study was explained to them. Complete information including age, sex, duration of being affected by DM and ulcer, history of recurrent wounding, previous wound healing problems, prior therapies and response, functional impact of wound on the patient, sufficient social history to define potential adverse impact on diabetic foot care, risk factors for diabetic foot ulcers, condition of glycemic control, oral hypoglycemic agents or insulin usage and their dosages were obtained and the patient's general health condition was examined systematically by an endocrinologist.

The diabetic foot ulcers were assessed with regard to number, position, length, width (measured by digital caliper), depth (measured by means of a sterile probe placed in the ulcer) of the ulcer and the presence of infection, callus, necrotic tissue or ischemia. Dorsalis pedis and tibialis posterior pulses were evaluated by palpation. Ankle Brachial index (ABI) was determined as a comprehensive physical examination for assessing vascular setting in patients. Normal values of ABI were considered from 0.91 to 1.30 and ratio <0.91 or >1.30 determined as indicative of peripheral arterial disease (PAD).²⁰ The ulcer condition was categorized according to the Texas University Wound Classification System (table 1).

Standard treatments (i.e., offloading, infection control, vascular improvement and debridement if required) were applied for all patients. The glycemic values of patients were evaluated at the beginning of the study and then, in regular periods of time. We advised special fitting shoes and total contact cast (TCC) for each patient based on the position of the ulcer for offloading the wounds. Antibiotics were used when needed. Everyone with suspected arterial insufficiency in physical examination (lack of tibialis posterior and dorsalis pedis pulses, ABI <0.91 or >1.30) was

Table 1. Texas University Wound Classification System for diabetic foot ulcers

Stage	Grade 0	Grade 1	Grade 2	Grade 3
A	Preulcer or postulcer lesion No skin break	Superficial ulcer	Deep ulcer to tendon or capsule	Wound penetrating bone or joint
B	+ Infection	+ Infection	+ Infection	+ Infection
C	+ Ischemia	+ Ischemia	+ Ischemia	+ Ischemia
D	+ Infection and ischemia	+ Infection and ischemia	+ Infection and ischemia	+ Infection and ischemia

referred to a cardiologist for further evaluation (e.g. color doppler or angiography if needed) and treatment (e.g. angioplasty or bypass grafting based on the condition). Wound debridement has been proposed to be performed as often as needed based upon the presence of necrotic or fibrinous tissue.

Every patient was visited three times a week. In each visit, photography of the ulcers was taken at a distance of 20 to 30 cm and in the same light. The wound condition, length, width, depth, healing progression, presence of infection and the need for debridement were assessed and all of these data were recorded in patient's information card. After all, the total area of the wound was washed and cleaned with normal saline without use of chlorhexidine on the surface of it and then, was treated with sterile 5% Royal Jelly and finally was covered with layers of sterile gauze. As mentioned before, all other routine treatments and evaluations were applied for all the patients and they did not use any other drugs on their wound during the study.

Our Royal Jelly is composed of sterile natural Royal Jelly (5%) in a sterile base which is pharmacologically ineffective (95%) and was prepared in School of Pharmacy and Pharmaceutical Sciences of Isfahan, Department of Pharmaceutics.

Each patient was followed for 3 months or until complete healing, the one occurred first. Complete ulcer healing was considered as complete epithelialization of the wound so that it would not need cleaning and dressing in any part. Duration of complete healing and reduction in wound length, width and depth were also calculated.

Results

Eight patients were enrolled in this study (3 females and 5 males) aged 62±6 years (mean ±SD). Two patients were excluded, one for inappropriate follow-up and another for personal desire to withdraw. Two patients had two ulcers, so the total number of ulcers was 8 (Table 2). Amongst these patients, 3 had ischemic and the remaining 5 patients had neuropathic ulcers. Seven ulcers completely healed with a mean duration of 41 days. One of the ulcers did not completely heal during a three-month study period but became 40 % smaller in length, 32 % in width and 28 % in depth. We did not observe any side effect after using topical Royal Jelly on diabetic foot ulcers.

Discussion

Our pilot study showed that Royal Jelly dressing may be an effective and safe method for treating diabetic foot ulcers. Diabetic foot ulcers usually occur on a background of neuropathy (motor, sensory or autonomic) with or without vascular insufficiency and infection, leading to neuropathic, ischemic or neuroischemic manifestations with superimposed infection. Royal Jelly possesses some characteristics which can interfere with above mentioned pathogenic factors. It has vasodilative activity that can affect local vasculature around the wound and dilate the vessels to facilitate blood flow.¹⁰ On the other hand, antibacterial activity is one of the major properties of this drug that may be useful for infectious wounds. In vitro studies have confirmed that 10-hydroxydecanoic acid in Royal Jelly has antibiotic activity.⁵ The antibiotic effectiveness is thermostable, i.e. is not destroyed by moderate heating, but it decreases

Table 2. Characteristics of the patients

age	sex	Duration of being affected by the ulcer	Position of the ulcer	First measurements			Last measurements			Type of the ulcer	grading	Duration of complete healing	
				Length (mm)	Width (mm)	Depth (mm)	Length (mm)	Width (mm)	Depth (mm)				
1	57	male	20 days	Plantar surface of the first left toe	8.28	6.22	8.27	0	0	0	neuropathic	II-B	39 days
2	58	female	6 months	Medial surface of the first right toe	6.78	5.45	5.9	0	0	0	Ischemic	I-C	30 days
3	58	female	14 days	Dorsal surface of the first left toe	6.5	6	0	0	0	0	neuropathic	I-A	14 days
4	70	female	5 months	Tip of the first right toe	8.7	8	2.1	0	0	0	neuropathic	I-A	33 days
5	71	male	3 months	Dorsal surface of the first left toe	25.9	17.86	0	0	0	0	Ischemic	I-C	25 days
6	71	male	3 months	Extensive ischemic ulcer in total plantar surface of left foot*	25.9	17.86	0	0	0	0	Ischemic	I-C	70
7	58	male	9 months	Plantar surface of right first toe	9.47	7.95	2.6	0	0	0	neuropathic	II-A	77 days
8	53	female	4 years	Plantar surface of left foot	26.6	25.8	8.4	10.8	8.4	2.4	neuropathic	I-A	Did not completely heal in 90 days
9	60	male	2.5 years	Plantar surface of left foot	21.7	18.99	4.54	19.5	15.9	1.5	neuropathic	I-A	Excluded after 42 days
10	70	male	2 years	Right heel	9.2	3.29	8.14	7.1	2.4	6.4	neuropathic	II-A	Excluded after 25 days

*the ulcer was too extensive to be measured at first, but after 36 days of treatment a measurable ulcer remained and since that time the diameters were measured and recorded.

with improper or long-term storage. Antibiotic action has been proven to be effective against the following microorganisms: *Escherichia coli*, *Salmonella*, *Proteus*, *Bacillus subtilis* and *Staphylococcus aureus*.²¹⁻²² In addition, Royal Jelly has insulin-like activity that may be useful for local growth and improve wound healing.^{6, 11} As a matter of fact, increasing growth rate in normal cells is very helpful for wound closure. Other features of this drug include anti-inflammatory activity⁹ as well as anti hy-

percholesterolemia ameliorating insulin resistance activity that may be helpful in the treatment of diabetes.¹⁴⁻¹⁵

A limited number of studies have examined Royal Jelly application on wounds. One of them is Abdelatif et al study that was published in March 2008. They used PEDYPHAR ointment (Royal Jelly and panthenol in an ointment base) for dressing of diabetic foot ulcers and followed them based on the Wagner classification. They believed that this drug

can create alkaline environment in the wound, while antimicrobial, immunomodulating and nutritional properties of Royal Jelly eradicate infection and promote healing.²³ Fujii et al showed some anti-inflammatory activity by decreasing exudation and collagen formation in granulation tissue with Royal Jelly in their article in 1990.⁹ Royal Jelly also shortened the healing period of desquamated skin lesions. They concluded that Royal Jelly possessed an anti-inflammatory action and was able to augment wound healing, but did not have an insulin-like action in streptozotocin-diabetic rats. They recommended double blind placebo controlled clinical trials to confirm this conclusion.

Our study had some limitations. Firstly, measuring the length, width and depth of wounds with digital caliper may have some inaccuracies so this problem can be solved by using more precise methods and devices. Another

limitation of this pilot study was the number of patients, thus we intend to increase it for our large clinical trial to have more accuracy.

In conclusion, our pilot study showed that this ancient medicine (Royal Jelly) may help wound healing in patients with diabetic foot ulcers and it can be more effective when used along with other standard treatments. Optimal management of diabetic foot ulcers involves a multimodality approach directed at regular foot care, blood glucose control, and early recognition of foot problems. Appropriate surgical management, administration of systemic antibiotics, and offloading techniques are necessary to prevent the progression of these ulcers.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

MS, SSh and SH carried out the design, coordinated the sessions, provided care to the patients, collected data and prepared the manuscript. MM cooperated in data collection, ZF analyzed the data statistically and participated in writing manuscript and MSh prepared the Royal Jelly and placebo. All authors have read and approved the content of the manuscript.

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