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ORIGINAL ARTICLE

The Effect of ANGIPARS™ on Wound Healing in Patients with Diabetes: A Systematic Review

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KEYWORDS

Angioparesis;
Diabetic foot ulcer;
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ABSTRACT: About 15% of patients with diabetes develop a Diabetic foot ulcer (DFU). It is an open sore or wound commonly located on the bottom of the foot. ANGIPARS™ is an Iranian-produced herbal remedy based on the extract of *Melilotus officinalis*. The aim of this study was to make a systematic review focused on determination of the effect of ANGIPARS™ on wound healing in patients with diabetes. The study was conducted in accordance with the PRISMA guidelines. Articles included in the review cover the period from the discovery of ANGIPARS™ to August 18, 2018. The data were analyzed using a descriptive method of Excel 2007 Software. Five articles with total number of 171 patients were included in the systematic review (SR) phase. In three articles, the methods were based on mm^2 units and in the two others on cm^2 units. Patients' follow-up varied from 4 weeks to 6 months after the intervention. In all patients, ANGIPARS™ responds well to the DFU disease. Due to the positive effect of the herbal drug, it is recommended to administer it for wound healing in patients with diabetes.

INTRODUCTION

Low adherence to a healthy lifestyle in the present century has led to the incidence of chronic diseases, such as diabetes [1-3]. Diabetes is one of the most common metabolic disorder caused by impaired insulin secretion or/and function [4]. Prevalence of diabetes is variable and it could be expected in 88.5% of pregnant women (4) while its prevalence is 5.9% in patients with thalassemia major. Diabetic patients are suffering from health complications leading to poor quality of life [5-7]. Moreover, it has been reported that diabetes increase the stress and anxiety with a prevalence of 61.8% in Iranian patients [8]. Diabetes also leads to diabetic foot ulcer

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(DFU) [9] which is a global concern. Ulcers form due to a combination of factors, such as lack of feeling in the foot, poor circulation, as well as duration of diabetes. DFU gained attention because it may lead to amputation of the lower limb [10]. Additionally, DFU is the common cause for hospitalization of diabetic patients, and its treatment is costly worldwide [11]. Wound healing occurs in several stages, and these stages overlap with each other. Wound healing might be delayed and defective and would be a risk factor for other health complications in diabetic patients [12].

Numerous findings on the prevalence of DFU in patients with diabetes have been reported [13] showed that DFU worldwide distribution is 6.3%, and announced that it is higher in men than in women. The meta-analysis showed that the prevalence of DFU was 5.5% in Asia (13). In another meta-analysis by Crawford et al., the prevalence of DFU was reported as 8-17% [13]. The most disquieting problem is the infection due to DFU, subsequent gangrene and foot amputation [14]. Appropriate control of blood glucose, reduction of mechanical stress, debridement of necrotic tissue, appropriate antibiotic therapy, proper dressing, and modification of blood flow are the most common treatments [15, 16].

Many clinical studies aimed at healing DFU patients have been performed. There are two main groups of clinical interventions: pharmacological and non-pharmacological. Non-pharmacological interventions include physical activities and exercises. Matos *et al*. confirmed the positive effects of physical activities on DFU [17]. Additionally, neurologic and circulatory assessments were considered as primary steps prior to conducting interventions [18]. For pharmacological intervention purposes, Semelil (ANGIPARS™) could be an effective indication [19-24]. ANGIPARS™ is an Iranian remedy produced from the extract of *Melilotus officinalis* [25-27]. This medicinal plant is a member of *Fabaceae* with high anti-inflammatory and anti-edematous activities. It is wide used for treatment of inflammatory and congestive edema [25]. ANGIPARS™ has been administered in laboratory animals and its effect has been proven [28].

Objectives

Due to a lack of systematic review and meta-analysis on the effects of ANGIPARS™ on wound healing in patients with diabetes, this study aimed to review the effect of ANGIPARS™ on wound healing in diabetic patients through a SR.

MATERIALS AND METHODS

Study Protocol

This study is a SR conducted in accordance with the PRISMA guidelines [29].

Search Strategy

Two researchers conducted the search of databases. Diabetic patients treated with ANGIPARS™ were included in the study (Figure 1).

Articles included in the review cover the period from the discovery of ANGIPARS™ to August 18, 2018. This study summarizes the findings of clinical trial studies by systematic searches in PubMed, Scopus, Web of Science, Science Direct, Cochrane Library, Embase and EBSCO electronic databases. The following keywords were used to search the databases: Diabetes mellitus, Semelil, Foot ulcer, ANGIPARS™, Topical, Oral, *Melilotus officinalis*, Wound healing, Pressure ulcer. The “AND” and “OR” search strategy was used with a combination of the above keywords as well as the reference study of the extracted articles. Two independent researchers (AT & MB) without knowledge of existing scores examined the selected studies based on the criteria described above to resolve any discrepancies. When there was a theoretical difference between the researches, the problem was evaluated by a third researcher (MF). The search was conducted for 4 months.

Inclusion and Extraction Criteria

Inclusion criteria

Examination of wounds in patients with diabetes. 2. Evaluation of ANGIPARS™ for wound healing.

Exclusion criteria

Studies on animal species. 2. Qualitative data report. 3. Data report in case reports and case series format. 4. SR and meta-analysis articles.

Data Extraction

For data extraction, a checklist was used that consisted of author's name, sample size, city, type of study, study population, intervention, FU area pre-, FU area post-, age, weight (kg), duration of DM (years), FBS (mg/dl).

Statistical analysis

The data were analyzed using a descriptive method of Excel 2007 Software.

RESULTS

According to the findings in Figure 1, the total number of five studies were entered the SR phase. Of these five articles, the sample size was 171 patients, studied between 2008 and 2015. In all of the studies, angioparesis has improved the wound healing in diabetic patients (Table 1).

The findings in Tables 1 and 2 show the demographic characteristics of patients who are included in the SR phase. The age of the patients in five studies, their weight in two studies, duration of diabetes mellitus (DM) in years in two studies, and FBS level of patients were reported in the one study

According to the findings in Table 3, Number of three studies reported the condition of the wound before and after the intervention in mm^2. Two studies were performed without having control group. Two studies followed-up the wound healing for 4 weeks and the other two studies – for 6 weeks after the intervention with ANGIPARS™. All the studies proved that the remedy had improved wound healing.

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Table 1. Characteristics of interventions performed for study entered into the SR studies.

	N	City	Type of study	Study population	Intervention	Time	Foot ulcer area pre	Foot ulcer areapost	Year	Reference number
1	25	Tehran Tabriz Dubai	RCT	Permuted Balanced Block	E: 4 cc of ANGIPARS™™ in 50 ml NaCl, daily for 28 days and infused for 39-60 minutes, 16 patients, plus routine treatment C: routine treatment	End of the 2nd and 4th week	E: 479.93±379.75 mm^2 C: 766.22±960.50 mm^2	E: 198.93±143.75 mm^2 (P=0.000) C: 689.11±846.74 mm^2 (P=0.076)	2008	[20]
2	75	-	RCT	Non- probability consecutive sampling.	E: Angioparesis group received 100 mg oral capsule twice daily and 3% topical gel	6 weeks	E: 6.05±11.1 cm^2	E: 2.4±6.8 cm^2 (P=0.000)	2015	[21]
3	10	Shiraz	Single arm before-after clinical trial		The time and amount of angioparesis administered as an infusion was as follows: 1st and 2nd day: 1 ml ANGIPARS™™ in 20 ml 0.9% NaCl 3rd and 4th day: 2 ml ANGIPARS™™ in 50 ml 0.9% NaCl 5th and more days: 4 ml ANGIPARS™™ in 100 ml 0.9% NaCl	2 months	Start: 12.32±11 cm^2 P: (0.0001, 0.002, 0.009).	P: (0.0001, 0.002, 0.009)	2008	[30]
4	21	Tabriz	Randomized, single-blind, parallel groups clinical trial	Permuted Balanced Block	E1: 100 mg oral administration of ANGIPARS™™, 6 patients, twice daily, plus conventional therapy E2: 100 mg oral administration of ANGIPARS™™ in addition to topical application of 3% gel containing ANGIPARS™™, 6 patients, twice daily, plus conventional therapy C: Conventional therapy, 9 patients	6 weeks	E1: 375.000±118.145 mm^2 E2: 916.666±228.643 mm^2 C: 766.222±320.169 mm^2	41.666±32.702 mm^2 (p= 0.040) 137.500±41.708 mm^2 (p= 0.010) 689.111±329.067 mm^2 (p= 0.076)	2008	[31]
5	40		Double–blind placebo-controlled trial	computer-generated randomization schedule	E: 100 mg ANGIPARS™, oral, twice daily, 20 patients C: Conventional therapy, 20 patients,	12 weeks	E:(cc^2)	1st week: 63.9±2.5 cm^2 2nd week: 46.0±21.6 cm^2 4th week: 15.8±18.7 cm^2 6th week: 10.3±14.6 cm^2 8th week: 5.5±20.5 cm^2 12th week: 4.2±15.2 cm^2	2010	[15]
							C:	1st week: 85.5±46.9 cm^2, p= 0,07 2nd week: 67.1±46.7 cm^2, p=0.01 4th week: 44.1±36.2 cm^2, p= 0.01 6th week: 32.5±42.5 cm^2, p= 0.16 8th week: 24.3±49.5 cm^2, p=0.35 12th week: 20.4±45.9 cm^2, p=0.27		

Table 2. Demographic data entered into the SR studies.

	Age	Weight (kg)	Duration of DM (years)	FBS (mg/dl)	Year	Reference
1	C: 59 (10.95) E: 50.6 (12.65)	C: 65.42 (9.44) E: 73.07 (18.2)	C: 14.83 (9.64) E: 10.64 (4.76)	C: 155 (35.35) E: 182.85 (74.42)	2008	[20]
2	C: NE E: 56.77± 9.7	C: NE E: NE	C: NE E: NE	C: NE E: NE	2015	[21]
3	C: NE E: 57± 2.3	C: NE E: NE	C: NE E:NE	C: NE E: NE	2008	[30]
4	C: 59.00±3.651 E1: 60.67±2.951 E2: 51.00±3.742	C: 65.429±3.5714 E1: 78.750±3.9407 E2:79.417±12.0751	C: NE E1: NE E2: NE	C: NE E1: NE E2: NE	2008	[31]
5	C: 59.8±8.7 E: 57.5±10.2	C: NE E: NE	C: 160.00±72.6 E: 145.00±59.2	C: NE E: NE	2010	[15]

Table 3. Wound area status before and after intervention into the SR studies

	Control group	Pre	Post	Post	Year	Reference
1	Yes	E: 479.93±379.75 mm^2	E: 198.93±143.75 mm^2 (4 weeks)	-	2008	[20]
2	No	E: 6.05±11.1 cm^2	E: 1.1±3.5 cm2 (6 months)	E: 1.1±3.5 cm2 (6 months)	2015	[21]
3	No	123.2±110 mm^2	69.6±60 mm2 (8 weeks)	69.6±60 mm2 (8 weeks)	2008	[30]
4	Yes	916.666±228.643 mm^2	137.500±41.708 mm^2 (6 weeks)	-	2008	[31]
5	Yes	E: 63.9±2.5 cm^2	4.2±15.2 cm^2 (12 weeks)		2010	[15]

DISCUSSION

One of the most troublesome complications of diabetes is formation of DFU . DFU has negative effects on the patient . This study is the first SR worldwide, aimed to determine the effect of ANGIPARS™ on wound healing in patients with diabetes. No studies have been evaluated the healing properties of this Iranian remedy since its discovery to date. There is only one study focused on the effects of *Melilotus officinalis* for treatment of knee pain and stiffness in elders [32]. The results obtained concord to the observations in our study and confirm the healing properties of the herb and its extracts.

A meta-analysis of randomized clinical trials with aimed at investigation of the efficacy of Chinese herbal medicine (CHM) on DFU showed no complications with the application of CHM. However no consensus on positive effects of the medication was found [33] inconsistently with the current findings.

The mechanism by which ANGIPARS™ is effective in wound healing is due to the chemical content of *Melilotus officinalis* (yellow sweet clover). The most abundant biologically active substances are kaempferol, quercetin glycosides and triterpene saponins. One of the supposed mechanisms of action of the herb is associated with increase of venous return and lymphatic flow[22, 30 and 31].

One of the weaknesses of this study is that the published articles on ANGIPARS™ medicine have been done on national level in Iran and have not been included in international studies in other countries. One of the strengths of this review is that it is the first SR study on the healing properties of such a successful remedy. However, the information obtained from this study will have an important role in improving the health of diabetic patients.

CONCLUSIONS

Due to the positive effect of ANGIPARS™ on wound healing in patients with diabetes, it is recommended to administer this remedy in cases of DFU.

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Conflicts of Interests

The authors report no conflicts of interest.

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Abbreviation

RCT: Randomized controlled trial

CC: one milliliter

E: experimental

C: control

NE: not evaluated

FU: Diabetic ulcers

DM: Diabetes Mellitus

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