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Effects of intravenous Semelil (ANGIPARS™) on diabetic foot ulcers healing: A multicenter clinical trial

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ABSTRACT

Some diabetic foot ulcers, which are notoriously difficult to cure, are one of the most common health problems in diabetic patients .There are several surgical and medical options which already have been introduced for treatment of diabetic foot ulcers, so some patient will require amputation. The purpose of this study was to evaluate the efficacy of intravenous Semelil (ANGIPARS™), a naive herbal extract to accelerate healing of diabetic foot ulcers. A multi-centric randomized controlled trial was conducted to evaluate intravenous Semelil for healing of diabetic foot ulcers. Sixteen diabetic patients were treated with intravenous Semelil, and nine other patients were treated with placebo as control group. Both groups were otherwise treated by wound debridement and irrigation with normal saline solution, systemic antibiotic therapy and daily wound dressing. Before and after intervention, the foot ulcer surface area was measured, by digital photography, mapping and planimetry. After 4 weeks, the mean foot ulcer surface area decreased from 479.93±379.75 mm^2 to 198.93±143.75 mm^2 in the intervention group ($p = 0.000$) and from 766.22±960.50 mm^2 to 689.11±846.74 mm^2 in the control group ($p = 0.076$). Average wound closure in the treatment group was significantly greater than placebo group (64% vs. 25%, $p= 0.015$). This herbal extract by intravenous rout in combination with conventional therapy is more effective than conventional therapy by itself probably without side effect. However, further studies are required in the future to confirm these results in larger population.

Keywords: Diabetes mellitus, Foot ulcer, Treatment, Semelil, ANGIPARS™

INTRODUCTION

It is estimated that 300 million persons worldwide will have diabetes by the year of 2025 (1). Today about 2566000 people (6%) are suffering from diabetes and its complications in Iran (2).

Foot ulcers develop in approximately 15% of patients with diabetes, and foot disorders are a leading cause of hospitalization among such patients (3-5) and 15-20% of them require amputation. Neuropathy, poor circulation, and decreased resistance to infection are the three major contributors to the development of diabetic foot; which when present, foot deformities or minor trauma can readily lead to ulceration and infection(6).

The overall rate of lower extremity amputation is 4.1 per 1,000 person/years with diabetes as compared with about three per 10,000 person/years in the entire population (7). High-quality patient care and education has reduced the risk of amputation by 40–50% (8-9). The rate of lower limb amputation secondary to diabetic foot ulcer is higher in Iran than the global average (10).

Several clinical studies have recently shown the efficacy of new therapies to heal foot ulcers in diabetics whose ulcers are associated with neuropathy (11-14).

Novel therapeutic strategies and drugs are required for the treatment of diabetic foot ulcers (15).

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Early studies suggest that Semelil (ANGIPARS^{TM}) (a naive herbal extract) may have a role in healing of diabetic foot ulcers (16-18). Other studies have showen, Semelil without sever acute or chronic toxicity (17, 19-21**).**

Considering the results of previous clinical trials (17, 18) we conducted a study to assess the therapeutic effects of intravenous Semelil in treatment of diabetic foot, to find a novel approach in treatment of diabetic foot ulcers.

MATERIALS AND METHODS

Experimental procedure was a randomized clinical trial, with a control group treated according to a conventional protocol, carried out on human with following details:

Patients

The study was designed as a Multi center Randomized Controlled Trial in Tehran (Endocrinology and Metabolism Research Center-EMRC, Medical Sciences/ University of Tehran, Tehran, Iran), Tabriz (Endocrinology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran), and Dubai (Internal Diseases Ward, Iranians' Hospital, Dubai, UAE). A total number of 25 patients (M: 18; F: 7) were completed the study. Sixteen patients (M: 13; F: 3) received Semelil in addition to conventional therapy (treatment group) and nine patients (M: 5; F: 4) received only conventional therapy (control group).

The method of randomization in each study center was "Permuted Balanced Block" method. After initial assessments and obtaining inclusion criteria and signing the written informed consent, patients were allocated as treatment and control groups.

All patients enrolled for the study suffered from chronic non-healing diabetic foot ulcer for several weeks to months according to the following inclusion criteria:

- Patients with proven diabetes mellitus (type 1 or 2) on medication either oral hypoglycemic or insulin.
- Both genders, male or female patients between 18 and 75 years of age.
- Ulcers, which remained open without healing and had not shown improvement for more than 2 weeks (irrespective of the ambulatory treatment administered).

Patients with severe heart failure under treatment, with class III or higher functional classes of antiarrythmics and showing signs and symptoms of chronic and severe ischemia with pulse less lower limbs, and other disease or situation that impairs ulcer improvement (such as malignancies, vasculitis, *etc*.), alcohol and drug abuse, chronic renal failure and dialysis, progressive liver failure, corticosteroid consumption, immuno-suppressive therapy, radiotherapy, chemotherapy and any known drug hypersensitivity were excluded.

For the Phase III study of ANGIPARS^{TM}, patients were screened voluntarily after clear explanation of the nature of study for them. Informed written consent was obtained from each patient prior to recruitment. The study protocol was approved by the Medical Ethics Committee of Medical Sciences/ University of Tehran, Tehran, Iran.

Methods

Patients were treated and followed in 2 groups (intervention group): combination of ANGIPARS^{TM} and conventional therapy, (control group): which received only conventional therapy) as follows:

In intervention group, patients were treated by intravenous administration of ANGIPARS^{TM} 4cc daily for 28 days. The drug diluted in 50-100 cc normal saline and infused during 30-60 minutes. Drug was kept away from light exposure and heat and was protected from the direct light during infusing.

In both groups, other conventional and routine necessities such as betadine bath, antibiotic therapy, wound debridement, pressure decompression, and foot deformities corrections if required were employed.

The Case Record Form had sections containing previous medical history of the patient, concomitant use of medications observations during active treatment with ANGIPARS^{TM}, a section for recording adverse events and finally the investigator's statement.

Each patient was assessed for the following parameters:

Exact inspection of ulcers, measurement of its diameters (including the longest length of the ulcer and the width perpendicular to it), by digital photography, mapping and planimetry to evaluate its improvement, steadiness or regression at the beginning, at the end of the second week and at the end of the forth week of the investigation (during digital photography laying a ruler beside the ulcer is necessary and ulcers must be saved with patient's name and date).

Daily inspection of the ulcer before drug admission and change of the dressing, debride the wound between treatment periods according to physicians' diagnosis, physical examination and history at the beginning of the research, and recording any probable side effect and necessary managements at the end of the second week and at the end of the forth week

Necessary laboratory assessments (e.g. Na, K, CBC, PT, PTT, ALT, AST, Bilirubin, ALK

Phosphatase and Amylase) and EKG at the beginning, at the end of the second week and at the end of the forth week of investigation were assessed. Biochemical variables were estimated by standard laboratory methods.

Statistical methods

Data were collected from different sources and analyzed statistically using SPSS 11 (SPSS Inc, Chicago, Illinois). Tests for Normality were performed for all quantitative outcome variables. Levene's and heterogeneity tests were used for equality of variances and efficacy of results among study centers, respectively. Independent and paired t-tests were used for comparison between pretreatment and posttreatment test results between groups and within groups, respectively. Chi square test was performed for qualitative variables. Two-tailed significance level of P-value<0.05 was accepted. All data are presented as mean±SD.

RESULT

A total of 25 subjects (M: 18; F: 7) were enrolled into the study. The baseline characteristics data are presented in Table 1. The baseline characteristics of subjects had no statistically significant difference in comparison with sixteen patients received ANGIPARS™ in addition to conventional therapy and nine patients whom only received conventional therapy alone.

There were no statistically significant differences between two groups about laboratory assessments over the 4-weeks of study.

Before treatment, the mean foot ulcer area in the treatment and control groups were 479.93±379.75 mm^2 and 766.22±960.50 mm^2 respectively (P=0.413). After 4 week treatment the mean ulcer surface area was compared between the two groups (ANGIPARS™ and conventional and conventional alone therapy by itself) to determine the effects of both treatment protocols **(**Table 2**).**

The percentage of decrease in ulcer surface area differs significantly in the treatment group (64%) compared with the control group (25%) (P=0.015).

The effect of intravenous administration of ANGIPARS™ on healing of some patients' foot ulcers are illustrated in Figure 1.

All patients tolerated treatment by intravenous ANGIPARS™ very well. There were no adverse effects to report.

DISCUSSION

From the results, the potential efficacy of intravenous ANGIPARS™ as an adjunct to conventional wound care have been convincingly shown in patients with diabetic foot ulcers, that probably would decrease the amputation rate.

Early researches have suggested that ANGIPARS™ therapy may have a role in acceleration of wound healing (17, 18). Attempts have made to use ANGIPARS™ in encouraging wound healing in diabetics.

Our finding showed that foot ulcer surface area decreased after 28 days with the drug and conventional therapy compared with conventional therapy alone.

Four recent studies have suggested that healing progression at 2^{nd} to 4^{th} weeks are good predictors of eventual wound closure (22-25). In our study healing percent of wound was 64% for ANGIPARS™.

The majority of recent investigations have shown that one of the most common problems in diabetic patients is delayed wound repair due to vascular insufficiency and decreased blood flow (24-26). Establishing appropriate blood flow over the affiliated limb is the robust goal of the treatment that eminently improves healing process (29, 30).

Some investigations for patophysiological effect of ANGIPARS™ have revealed that this drug probably improves total tissue blood flow and oxygenation (Unpublished data).

Decreased blood flow may result in insufficient oxygen delivery, which makes healing impossible unless angioplasty or a vascular bypass is performed. Another contributing factor is micro vascular disease. It is generally considered that improved blood supply, through angiogenesis, for example, may improve ulcer healing.

Our results indicate that the herbal extract by intravenous rout in combination with conventional therapy is more effective than conventional therapy alone and is without any side effect (17-21). This drug can be used probably in all types of diabetic foot ulcers.

This new treatment decreased mean duration of hospitalization and direct and indirect costs and probably decreased amputation rate in patients with diabetic foot ulcer.

From results it may be concluded that ANGIPARS™ is useful in healing process of diabetic foot ulcers, it would be wise to use this preparation in patients.

The absence of any significant side effect indicates that ANGIPARS™ could well become a part of routine therapy for diabetic foot ulcers. However, further studies with greater sample size are necessary for evaluation of the effects on other variables, such as hemoglobin A1C. In conclusion, our results support the contention that ANGIPARS™, in addition to good foot care, is more effective than conventional alone in healing diabetic ulcers, and may assist in reducing healing times.

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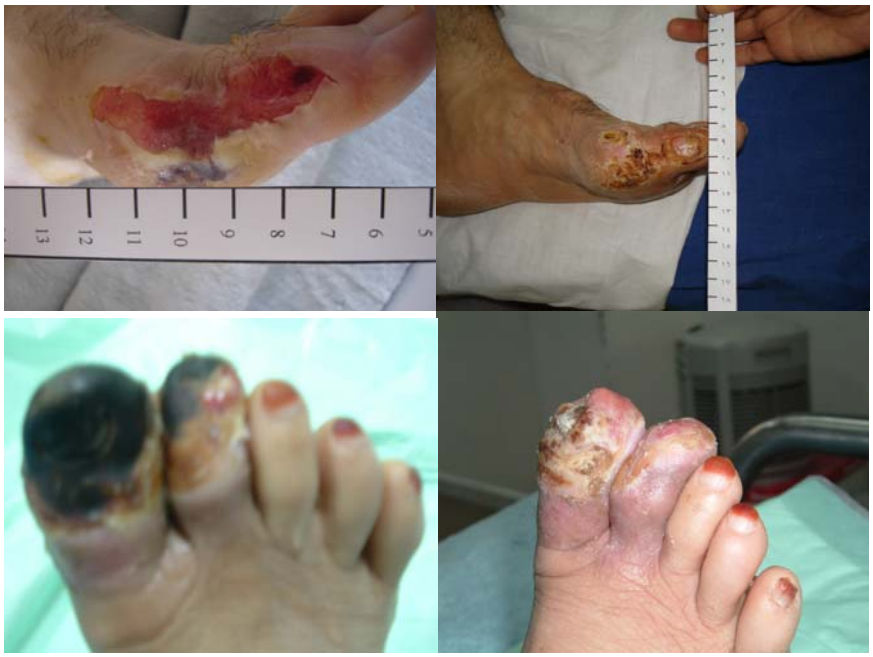
Table 1. Baseline characteristics of subjects among treatment and control groups

Variable		Treatment group (n=16)	Control group (n=9)	P value
Sex	Male (%)	13 (81.2)[a]	5 (55.6%)[a]	NS
	Female (%)	3 (18.8)[a]	4 (44%)[a]	
Age (years)		50.6(12.65)[b]	59(10.95)[b]	NS
Weight (kg)		73.07(18.2)[b]	65.42(9.44)[b]	NS
Duration of DM (years)		10.64(4.76)[b]	14.83(9.64)[b]	NS
Type of DM	I	2 (12.5)[a]	0	NS
	II	14 (87.5)[a]	9 (100)[a]	
Size of wound (mm^2)		479.93(379.75)[b]	766.22(960.5)[b]	NS
FBS (mg/dl)		182.85(74.42)[b]	155(35.35)[b]	NS

[a] Number (%), [b] Mean(SD)
FBS, fasting blood sugar; NS, not significant

Table 2. wound size before and after treatment among two groups

Group	Before (mm^2)	After (mm^2)	P value
Treatment (ANGIPARS™)	479.93±379.75	198.93±143.75	0.000
Control	766.22±960.50	689.11±846.74	0.076



Before 4 weeks After

Figure 1. Photographs of patients before & after treatment with ANGIPARS™.

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