Effect of ANGIPARS™, a new herbal drug on diabetic foot ulcer: A phase 2 clinical study

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ABSTRACT

Diabetes foot ulcers are a major predictor of future lower-extremity amputation in patients with diabetes. The animal studies have indicated that treatment with a new herbal extract named ANGIPARS™ improves healing of chronic ulcers. The main objective of the study was to evaluate the safety and healing rates of diabetic foot ulcers in patients treated with ANGIPARS™.

Ten diabetic patients (7 males and 3 females) were eligible for enrollment in this single arm before-after clinical trial. The target wound's greatest length and width was measured at baseline. The target wound was photographed at baseline and then every two weeks. The wound area was determined by means of planimetry.

The mean age of patients was 57± 2.3 years. The mean surface area of ulcers was 12.32±11 cm^2, 9.55±9 cm^2, and 6.96±6 cm^2 at baseline, one month and two months of study, respectivly. Our results showed that the drug could reduce the wound size at least 50% during 8 weeks period. We found no adverse side effects in our patients.

The main conclusion of the present study was to show the efficacy and safety of ANGIPARS™ as a novel therapy in diabetic foot ulcers.

Keywords: Diabetic foot ulcer, ANGIPARS™, treatment, Phase II, Intervention

INTRODUCTION

Among people with diabetes, 15% will experience a foot ulcer in their lifetime. Foot ulcers are a major predictor of future lower-extremity amputation in patients with diabetes. Indeed, about 14–24% of people with a foot ulcer will require an amputation (1). So it is not surprising that diabetes is the leading cause of non-traumatic lower-extremity amputations. Despite much effort directed toward amputation prevention in the last decade, the incidence of lower-extremity amputation in people with diabetes continues to rise. Thus, appropriate techniques for wound care that can reduce amputation rates are an essential prevention strategy.

The most common location for foot ulcers is the plantar surface of the forefoot. These ulcers are often caused by repetitive mechanical stress that is not recognized by the patient because of peripheral neuropathy and loss of protective sensation. In addition, the presence of peripheral vascular disease and infection can lead to poor healing of foot wounds and to the development of gangrene. Despite substantial morbidity resulting from foot wounds in people with diabetes, there are no widely accepted evidence based guidelines for assessment and treatment of foot ulcers and preventing their recurrences.

The composite material provides a combination of the wound-healing properties of the individual components. The animal studies and subsequent phase I trial on human subjects have indicated that treatment with a newly introduced herbal drug named ANGIPARS™ provides a safe management and may improve healing of chronic ulcers (2-6). As the diabetic foot ulcer is stuck in the inflammatory phase and therefore is the chronic ulcer, treatment with this medication could help to promote wound healing in such patients.

The main objective of the present study was to evaluate the safety and healing rates of diabetic foot ulcers in patients treated with ANGIPARS™.

MATERIALS AND METHODS

This single arm before-after phase II clinical trial was conducted in endocrine and metabolism research center, Shiraz University of medical

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sciences over a period of 8 months (from January to August 2004). Patients were eligible for enrollment in the study if they met the following inclusion criteria: 18 years or older with a diabetic foot ulcer of at least 30 days' duration not responding to routine management and an area of at least 1 cm^2 (greatest length x greatest width). The main exclusion criteria included followings: clinical signs of infection; a target wound that had exposed bone; a concurrent illness or a condition that may have interfered with wound healing (eg, carcinoma, vasculitis, connective tissue disease, or an immune system disorder); known current abuse of alcohol or other substances or treatment with dialysis, corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy, known hypersensitivity to any drugs; unwillingness or inability of an ambulatory patient to be fitted with appropriate shoe gear or an off-loading device.

After informed consent, at the baseline/initial visit, a full medical history and assessment of the patient's present conditions were obtained and recorded. Concomitant medications and their indications were also recorded. The diabetic status of the patient, including duration, type, and management, was noted with current activity level, ambulatory status, and history of ulceration or amputations. Blood test results included levels of glycosylated hemoglobin, glucose, albumin, creatinine, serum urea nitrogen, and alkaline phosphatase; liver function; and human chorionic gonadotropin levels in women of reproductive age.

The target wound's greatest length and width was measured at baseline. The target wound was photographed at baseline and then every two weeks. The target wound was assessed before and after cleansing and/or debridement for local infection and for wound condition (improving, stable, or deteriorating).

Surgical debridement of healthy tissue was performed in the studied ulcer during the initial and all follow-up visits when necessary. The wound area was determined by means of planimetry (the greatest length x the greatest width, measured in centimeters).

The wounds were cleansed with isotonic sodium chloride solution at the time of the dressing change. The patient and/or health care provider were instructed on dressing change procedures. All patients were instructed to limit weight bearing, ambulating only for necessary activities.

Protocol of drug

In this study a newly herbal drug, ANGIPARS™, was used as a daily Intravenous infusion with dosage mentioned in table 1.

Follow-up evaluations

Follow-up evaluations were completed on every two week basis. At each clinic visit, the investigator assessed and recorded the following: examination of the wound, compliance with drug use, the use of foot gear and/or off-loading, and the presence or absence of any adverse events.

Statistical analyses

Data are presented as means ±standard deviations (SD). Measured variables were compared by Wilcoxon signed rank test. Statistical analyses were performed using SPSS for windows, release 11.5 (SPSS .Inc). P-values<0.05 (2-sided test) were considered statistically significant.

RESULTS

Ten individuals (7 males and 3 females) who met our criteria enrolled in the study. The mean age of patients was 57± 2.3 years. Fig 1 shows the difference between mean surface area of ulcers at start (12.32±11 cm^2), after one month (9.55±9 cm^2), and after two months (6.96±6 cm^2). Surgical intervention was necessary for three patients; ulcer debridement for two and amputation of gangrened small toe finger in the other one. Fig 2 shows the almost complete healing ulcer in two of our patients during study (8 weeks). Seven patients (70%) showed complete healing within 12 weeks from start of study.

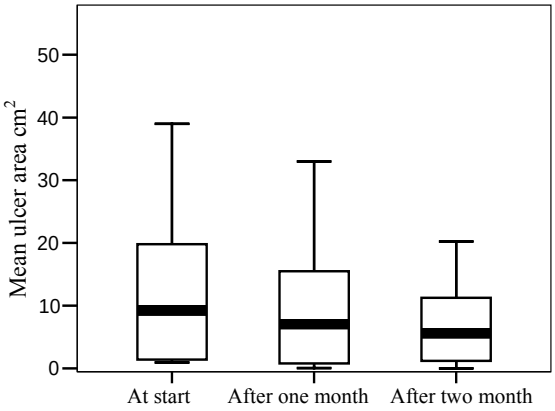

Figure 1. The mean ulcer area (cm^2) of patient at start, after one and two months of therapy with ANGIPARS™. Difference between each pairs are statistically significant.(P value 0.0001, 0.002, 0.009).

There was no statistically significant differences between peaks gradient (mmHg) of femoral, poplitial, and posterior tibialis arteries, before and after treatment with ANGIPARS™ (Table 2). The nerve conduction study also showed no significant changes after treatment with the drug (Table 3).

We found no adverse effect in our patient. The laboratory data including; glucose, albumin, creatinine, serum urea nitrogen, alkaline phosphatase, and liver function did not show significant changes after treatment with selenium-based drugs (Data not shown).

Table 1. The time and dosage of ANGIPARS™ for I.V. infusion

Day of Injection	ANGIPARS™ (ml)	0.9% NaCl (ml)*
1st and 2nd	1	20
3rd and 4th	2	50
5th and more	4	100

Table 2. The Mean of peak gradient (mmHg) of lower extremities of participants before and after therapy.

Mean of peak gradient in arteries (mmHg)	At start	After 2 month	P Value
Rt Femoral art.	1.02±0.8	0.73±0.9	0.39
Lt Femoral art.	1.02±0.9	0.9±1	0.71
Rt Poplitial art.	0.67±0.4	0.62±0.6	0.87
Lt Poplitial art.	1.4±0.5	1.07±0.8	0.43
Rt P. Tibial art.	1.13±1	1.34±1.4	0.28
Lt P. Tibial art.	1.12±0.8	2.12±1.7	0.20

Table 3. The mean of distal latency of nerves (ms) in nerve conduction study of participants before and after therapy

Mean of distal latency of nerves(ms)	At start	After 2 month	P Value
Rt Median N.	5.2±0.4	5±0.6	0.5
Lt Median N.	4.9±0.3	4.98±0.5	0.78
Rt Ulnar N.	4±1.2	4.01±0.7	0.9
Lt Ulnar N.	3.71±0.5	3.48±0.4	0.2
Rt Tibial N.	2.6±2.8	2.93±3.2	0.17
Lt Tibial N.	2.92±2.7	2.34±3.1	0.58

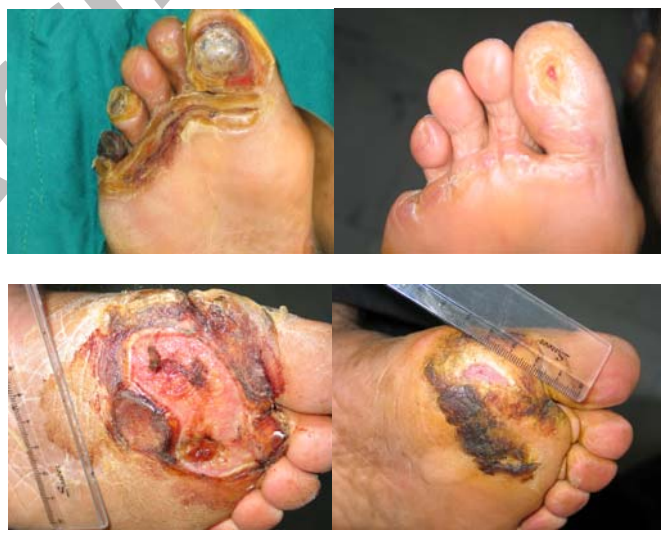

Figure 2. The picture of patient's foot ulcer before therapy (left upper and lower panel) and after therapy (right upper and lower panel) with ANGIPARS™

DISCUSSION

The main objective of the present study was to evaluate the efficacy and safety of a newly introduced herbal drug named ANGIPARS™, as a naive adjuvant therapy in diabetic foot ulcers. Our results showed that ANGIPARS™ could reduce the wound size at least 50% during 8 weeks period without any significant adverse effect in the studied patient population. However in the present study, we have not found an overall benefit of the drug on the nerve conduction and color Doppler studies due to short course of the study.

Wound healing is a complex process that involves the timely expression of numerous growth factors that promote cellular migration and proliferation, production of new connective tissue matrix, and collagen deposition (7, 8). In addition, diabetic foot ulcers are chronic wounds that are stuck in the inflammation phase and show a cessation of epidermal growth or migration over the wound surface (9-11). Thus, theoretically, ANGIPARS™ may have an advantageous in addition to the current standard of care, via immunomodulation (12-14), and perfusion improvement; Lu X and colleagues (15) have shown that in rats, selenium deficiency impairs endothelium dependent vasodilatation; the impact of selenium status in this regard is lost if endothelial NO synthase is inhibited, suggesting that adequate selenium nutrition is crucial to effective nitric oxide function.

As it has been shown in previous studies selenium has insulin-mimetic properties, an effect that is probably brought about by stimulating the tyrosine kinases involved in the insulin signaling cascade. Furthermore, in the diabetic rat, selenium not only restores glycaemic control but it also prevents or alleviates the adverse effects that diabetes has on cardiac, renal and platelet function (16).

Our study had several limitations. First, small sample size of subjects, so our results are suggestive rather than conclusive. Second, due to relatively short duration of study we may have missed late beneficial effect and probable side effects of ANGIPARS™ drug. Third, our study was not a randomized clinical trial. Nevertheless, our results show that this drug could reduce the wound size without any significant adverse effects.

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