Clinical application of oral form of ANGIPARS™ and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial

[1]Bahrami A, [2]Kamali K, [1]Ali-Asgharzadeh A, [3]Hosseini P, [2,3]Heshmat R, [4]Khorram Khorshid HR, [5]Gharibdoust F, [6]Madani SH, [*3]Larijani B

[1]Endocrinology Research Center, Tabriz University of Medical Sciences, Tabriz, [2]Department of Epidemiology and Biostatistics, Public Health School, [3]Endocrinology and Metabolism Research Center (EMRC), Tehran University of Medical Sciences, Tehran, [4]Genetic Research Centre, Social Welfare and Rehabilitation Sciences University, Tehran, [5]Rheumatology Research Center, Tehran University of Medical Science, Tehran, [6]Department of Biotechnology, Rabe Rashidi Institute, Tabriz, Iran.

ABSTRACT

ANGIPARS™ is a new herbal extract which has been produced in oral, topical, and intravenous forms. The present article contains preliminary results of the study which was planned to evaluate the efficacy and safety of orally applied ANGIPARS™ and to compare it with the combination of oral and topical forms and also with conventional therapy in patients with diabetic ulcers of the lower extremities.

Twenty one patients with diabetic foot ulcers were divided into 3 groups. The first group received 100 mg of oral ANGIPARS™ twice a day for 6 weeks in addition to conventional therapies. In the second group, ANGIPARS™ gel 3% was added to the oral form of the same product besides the conventional therapies for the same period of time. Finally, in the third group which was considered as control, only conventional therapies were performed. The patients were followed for 6 weeks. Parameters such as granulation tissue formation, skin epithelization, and wound surface areas changes were analyzed to determine the effectiveness of the compound in wounds healing. Furthermore, drug safety was assessed by monitoring adverse events and by clinical and laboratory evaluations.

The study data showed significant differences between the intervention and control groups with respect to efficacy and tolerability. In each intervention group, primary wound healings occurred following 2 weeks. Complete wound healing which was greater than 70% improvement in wounds surface areas was achieved in 83% and 100% of group 1 and group 2 participants, respectively after 6 weeks. On the other hand, at the same period of time, only 22.2% of patients in control group revealed complete healing. Therefore, ANGIPARS™ had significant positive effect in increasing the incidence of complete wound closure compared with control group ($p = 0.042$). However, our evaluations indicated that adding topical treatment with 3% gel once a day to the oral therapy with the same product did not make significant difference in healing outcomes statistically ($p = 0.769$). Clinical and paraclinical evaluations did not show any adverse events during the study.

This study showed that in diabetic foot ulcers, either treatment with oral ANGIPARS™ capsules (100mg) twice a day or combination therapy with oral and topical forms, in conjunction with good wound care significantly increased the incidence of complete wound closure. In addition, the application of this product was safe and did not make any unexpected adverse event.

Keywords: ANGIPARS™, Diabetic foot, Ulcer, Topical, Oral

INTRODUCTION

Diabetic foot ulcer (DFU) which is generally the consequence of neuropathy, peripheral vascular disease (PVD), anatomical deformities, and environmental influences remains the major complication (1). It is the leading cause of lower extremity amputations with the incidence of 12% (2–5). The overall rate of lower extremity amputation among patients with diabetes is 17-40 times higher than non-diabetic population (6)

Correspondence: emrc@tums.ac.ir

which will, in turn, have a profound effect on individuals' quality of life and will be associated with increase in mortality risk and health-care costs.

The treatment of diabetic foot ulcers is complex. The primary goal in the treatment is to achieve closure as quickly as possible since the prompt resolution of a foot ulcer and initiation of interventions may reduce the rate of recurrence, the risk of a secondary infection, and the risk of lower-extremity amputation in patients with diabetes (7-11). Over the past decade, newer treatment approaches have been introduced to be able to increase the probability of wound closure in difficult-to-heal foot ulcerations in patients with diabetes. In this regard, the main trials have been performed to evaluate the efficacy of growth factors (12), bone marrow-derived stem cells (13), and low-level laser therapy (14) in the healing of chronic wounds caused by pressure, diabetic neuropathy, and venous insufficiency. Furthermore, some studies have shown the positive effect of herbal components in the treatment of diabetic foot ulcers (15).

All of the above mentioned new therapies and the current approaches for the treatment of diabetic foot ulcers (i.e. topical agents, dressings, mechanical offloading, surgical interventions, and finally biological therapy (16)), have had relative effectiveness in wound healing or in preventing amputations (16). Therefore, it is necessary to find new non-invasive remedies which have maximum healing effect at minimum period of time.

ANGIPARS™ is a new herbal extract produced by Iranian scientists for the treatment of diabetic foot ulcers (17). The product safety was established by conducting a complete set of preclinical studies and in *in vivo* and *in vitro* tests for acute, sub-acute toxicity and genotoxicity (18-20). Previous clinical studies have shown that this drug is significantly effective and very safe in diabetic patients by intravenous administration (21-23). Yet, it has not been defined whether this herbal component has positive effects on wound healing if it is taken orally or in combination with other forms of drug.

This study was conducted to evaluate and to compare the healing efficacy and safety of ANGIPARS™ capsules (100 mg dry material) orally twice a day, and in combination with ANGIPARS™ 3% gel applied topically in patients with diabetic foot ulcers.

MATERIALS AND METHODS

Study Design
The Phase III randomized, single-blind, parallel groups clinical trial was carried out in 21 subjects with diabetic foot ulcers at Sina University Hospital in Tabriz, Iran to determine the safety and healing efficacy of the oral form and the combination of oral and topical forms of the herbal extract. The Institutional Ethics Committees of Medical Sciences/ University of Tehran approved the study protocol and it was conducted in accordance with the provisions of the Declaration of Helsinki. Subjects who met the following inclusion/exclusion criteria were enrolled for the study:

Inclusion criteria
Adult patients of either sex with type 1 or 2 diabetes mellitus between the ages of 18 and 75 years with diabetic foot ulcers were included. The ulcers might have been caused by various disorders such as peripheral neuropathy, uncontrolled hyperglycemia, trauma, foot deformity, and diminished joints range of motion. All patients enrolled for the study had ≥1 diabetic foot ulcers which remained open without healing and/or improvement for at least 2 weeks. Patients had to be able to understand and sign the informed consent form. In the case of compromised mental capacity, a legal guardian approved and signed the consent form. Patients were expected to be available for the 6-week study period and had to be able to adhere to the treatment regimen.

Exclusion criteria
Subjects were excluded if they were not compliant with the study. Additionally, patients with ≥Grade III Wagner classification diabetic foot ulcers, evidence of systemic or local infection such as purulent drainage and osteomyelitis, erythema in the edge of wound with 3 centimeter width, and exposed bone at the wound site were excluded from the study. Moreover, those with life-threatening or serious cardiac failure (Function Class ≥III), sever and chronic ischemia of lower limb without presence of pulsation, simultaneous diseases which had impact on healing process such as vasculitis or different types of cancers, hepatic or renal failure, endocrine, hematological, or immunologic disorder, past history of/current acute or chronic autoimmune disease, history of hypersensitivity to the incipient(s), chronic alcohol or drug abuse, immunosuppressive drugs, cytotoxic agents, radiation therapy, and chemotherapy were excluded.

Eligibility for randomization was determined at a screening visit and 21 patients were randomly assigned to either two experimental or a control groups.

Study Protocol
On inclusion into the trial, a detailed history was taken with emphasis on the duration of ulcer and

diabetes, its treatment, previous ulcerations, amputations and other associated illnesses. Then, a detailed clinical examination was performed. The ulcer included in the trial was classified by wound morphology, severity and location with a total wound severity score according to Wagner's ulcer classification. The target ulcers were surgically debrided if necessary to remove all nonviable tissue and callus. Afterwards, ulcer mappings and planimetry were performed and the wounds diameters were determined. Ulcer depth was measured by means of a blunt-tip probe from the level of wound surface. Finally, wounds photographs were taken at a standard focal length that was repeated after 2 weeks and at the end of the procedure to show healing via changes in ulcers surface areas which were determined by AutoCAD and Photoshop softwares.

Patients were randomized into one of 2 experimental or a control group. The first experimental group (Group 1) included 6 patients who received 100mg of ANGIPARS™ capsules orally twice a day for 6 weeks. In the second experimental group (Group 2), in addition to oral therapy with 100mg of ANGIPARS™ capsules twice a day, 3% gel was administered topically in another 6 patients for the same period. It should be noticed that in the intervention groups, beside of administration of ANGIPARS™, all standard wound treatments were done. Study visits were scheduled every two week for 6 weeks. Baseline laboratory investigations including a complete hemogram, differential count, ESR, fasting and postprandial blood sugar, liver and renal function tests were also performed which were repeated after 2, 4, and 6 weeks. Finally, the patients were visited again after 2 months according to potential clinical problems.

On the other hand, the control group were subjected (Group 3), only to standard wound care and therapies such as irrigation, dressing, pressure off-loading, debridement, and antibiotic therapy.

Randomization Procedure
In this study, the sample size, interventional approach, and patients follow-up, sample randomization was based on Permuted Balanced Block method by an epidemiologist. However, the study was not performed double blindly since no proper placebo substance was available. Moreover, the healing outcome was measurable by doing digital photography from the wounds and subsequent determination of the surface areas.

Wound Measurements
Wound healing was typically expressed as a change in the surface area over time. Wound measurements were divided into 2 major groups:

ruler-based assessment schemes, and optical methods. The wound area was measured using tracings of photographs to avoid direct contact with the wound. The photographs were arranged sequentially according to patient visits, and healing progress was monitored throughout the study process. Finally, the wounds surface area values were estimated by applying AutoCAD and Photoshop softwares.

Statistical Analyses
Data were analyzed statistically using SPSS 11 (SPSS Inc, Chicago, Illinois). Kolmogorov-Smirnov test for normality was performed for all quantitative outcome variables. Levene's test was used for equality of variances. Independent and paired t-tests were used for comparison between pretreatment and posttreatment test results between groups and within groups, respectively. One way Analysis of Variance (ANOVA) with Bonferroni Post Hoc test was performed for multiple comparisons between three studied groups. Chi square test was used for comparison of qualitative variables. Two-tailed significance level of P-value<0.05 was accepted. All data are presented as mean±SD.

RESULTS
Basic characteristics of the study subjects
A total of 21 subjects (M: 13; F: 8) with type 2 diabetes were enrolled into the study. Baseline descriptive characteristics for the subgroups are listed in Table 1. Among three parallel groups, no significant differences were observed in any of the evaluated characteristics, such as sex, age, weight, type of diabetes, or primary size of wounds. In all participants, according to Wagner's classification, the primary ulcers grade was equal to 2. All of the 21 patients randomized to treatment completed the study.

Assessment of wound healing
All patients enrolled in intervention groups and completed the study showed good clinical outcome in terms of significant improvement in percentage of wound closure and quality of ulcer healing after 6 weeks. According to the progress of granulation or epithelization, the quality of wound healing was primarily assessed by visual examination by physician at periodic intervals and recording them in the Case Record Form. In this regard, primary wound healings occurred after two weeks of treatments in all individuals of intervention sub-groups.

The mean ulcer surface area was compared among and within the three groups to determine the effects of both treatment protocols and conventional therapy (Table 2). The interventions

Table 1. Patient demographics and target ulcer characteristics

Characteristic	Group 1	Group 2	Group 3	Total	P-value
n	6	6	9	21	
Sex					0.874
Male	4 (66.7)	4 (66.7)	5 (55.6)	13 (61.9)	
Female	2 (33.3)	2 (33.3)	4 (44.4)	8 (38.1)	
Age	60.67±2.951	51.00±3.742	59.00±3.651	57.19±2.168	0.191
Weight	78.750±3.9407	79.417±12.0751	65.429±3.5714	74.053±4.2583	0.319
Wound Size(mm^2)	375.000±118.145	916.666±228.643	766.222±320.169	697.428±156.771	0.417
DM Type					
I	0	0	0	0	
II	6 (100)	6 (100)	9 (100)	21 (100)	

Data are *n*, *n* (%), or means ± SE.   Group 1 = oral administration of Angi compound;   Group 2 = oral and topical administration of Angi compound; Group 3 = conventional therapy

Table 2. Mean ulcers surface areas changes in both experimental and control groups before and after treatment.

Group	Mean Ulcers Surface Areas (mm^2)		P-value	Mean improvement ratio (%)
	Before treatment	After treatment		
1	375.000 ± 118.145	41.666 ± 32.702	0.040	87.847 ± 10.950
2	916.666 ± 228.643	137.500 ± 41.708	0.010	84.380 ± 3.521
3	766.222 ± 320.169	689.111 ± 329.067	0.076	25.092 ± 14.540

Data are means ± SE. ;   Group 1 = oral administration of Angi compound; Group 2 = oral and topical administration of Angi compound; Group 3 = conventional therapy

Table 3. Clinical improvement outcomes in diabetic ulcers within experimental and control groups according to the percentage of wounds surface changes.

Outcome	Group 1 (oral)	Group 2 (oral + topical)	Group 3 (conventional)
Worsening	0 (0)	0 (0)	1 (11.1)
Ineffective	0 (0)	0 (0)	5 (55.6)
Relative improvement	1 (16.7)	0 (0)	1 (11.1)
Complete improvement	5 (83.3)	6 (100)	2 (22.2)

Data are *n*, *n* (%); Worsening outcome: < -10% changes in wounds surface areas; Ineffective outcome: -10% to +10% changes in wounds surface areas; Relative improvement: +10% to +70% changes in wounds surface areas; Complete improvement: > +70% changes in wounds surface areas.

decreased foot ulcer surface areas from 375.00 ± 118.14 mm^2 to 41.67 ± 32.70 mm^2 (p = 0.040) in group 1, and from 916.67 ± 228.64 mm^2 to 137.50 ± 41.71 mm^2 (p = 0.010) in group 2. On the other hand, in group 3, the ulcer surface areas reduced from 766.22 ± 320.17 to 689.11 ± 329.07 which was not statistically significant (p = 0.076). The deviations from pretreatment to posttreatment measurements were calculated as improvement ratio in each group and expressed in percentage. The improvement ratio among three groups was then compared. These ratios in the experimental (groups 1 and 2) and control groups were 87.85 ± 10.95, 84.38 ± 3.52, and 25.09 ± 14.54 percents, respectively. Therefore, the mean foot ulcer surface area significantly decreased in the experimental groups compared to the control group (p = 0.002). The improvement ratio of wound size in group 1 was identified as no

significant compared to the second group (p = 0.769). Therefore, the wound surface areas considerably decreased in the experimental groups, but either oral therapy with ANGIPARS™ capsules alone or its combination with topical form did not make significant difference in reducing wounds surface areas.

Finally, the clinical improvement outcomes within the groups were determined (Table 3). Accordingly, post-treatment wounds surface changes from -10% up to +10% were considered ineffective treatment; while, 10 – 70% and greater than 70% wound surface changes were considered as relative and complete improvements, respectively. On the other hand, wound surface changes of lesser than -10% were considered as worsening. Our evaluations revealed that in contrast to control group, in both experimental groups, the wounds were clinically improved in

Table 4. Clinical laboratory parameters of intervention groups before and after treatments

Variable	Group 1 (oral)		P-value	Group 2 (oral + topical)		P-value
	Pretreatment	Posttreatment		Pretreatment	Posttreatment	
WBC	8115 ± 874.94	8295 ± 1352.77	0.832	6998.33 ± 621.576	6628.33 ± 341.579	0.685
Hgb	13.05 ± 0.89	13.20 ± 0.85	0.399	13.417 ± 0.8101	13.183 ± 0.9741	0.538
Plt	283500 ± 26498.74	237000 ± 14924.25	0.124	315666.67 ± 54337.014	255833.33 ± 44203.632	0126
Na	140 ± 0.856	140.33 ± 1.542	0.793	140.83 ± 0.601	140.00 ± 0.816	0486
K	4.817 ± 0.242	4.783 ± 0.083	0.887	4.833 ± 0.1498	4.550 ± 0.1839	0.312
Creatinin	1.240 ± 0.2062	1.192 ± 0.1675	0.465	0.950 ± 0.0719	0.917 ± 0.0477	0.611
ALT	27.00 ± 5.209	20.83 ± 4.078	0.270	30.83 ± 10.278	25.00 ± 4.980	0.603
AST	25.33 ± 2.186	22.83 ± 2.982	0.305	24.33 ± 5.408	25.50 ± 3.775	0.842
ALP	102.00 ± 12.954	106.17 ± 10.045	0.755	148.00 ± 51.264	106.67 ± 19.024	0.356
Bilirubin (T)	0.7533 ± 0.11081	0.9600 ± 0.11733	0.091	0.9717 ± 0.31081	0.8617 ± 0.12518	0.598
Bilirubin (D)	0.1283 ± 0.01833	0.1583 ± 0.02104	0.370	0.1400 ± 0.02582	0.1267 ± 0.01764	0.566
Amylase	57.33 ± 9.468	57.00 ± 8.311	0.927	55.33 ± 11.555	56.17 ± 11.074	0.780
ESR1st	42.00 ± 9.883	22.00 ± 4.480	0.089	52.5 ± 11.144	46.67 ± 12.420	0.515
FBS	138.33 ± 21.087	171.17 ± 21.669	0.261	153.00 ± 26.532	130.00 ± 18.787	0.538

all subjects. As an illustration, therapy with oral and combination of oral and topical ANGIPARS™ led to complete clinical improvement of diabetic foot ulcers in 83% and 100% of patients respectively. While, in the control group, only 22.2% of patients, achieved complete wound healing and most of patients (55.6%) revealed no improvement. Hence, investigations demonstrated a significant difference in clinical improvement outcomes between the experimental groups and the control group (p = 0.042).

Safety results
Safety was evaluated by monitoring adverse events, discontinuations, clinical laboratory measurements, and vital signs. During and 2 months after the study, patients monitoring made by investigators reveled no clinical side effects and all of the participants completed the study. There were no clinically meaningful changes from baseline in clinical laboratory parameters (including serum chemistry, hematology, and urinalysis) or vital signs in any of the treatment groups (Table 4).

DISCUSSION
In this study, we provide evidence that diabetic foot ulcers surface area considerably decrease following 6 weeks treatment either with oral or the combination of the oral and topical forms of ANGIPARS™ compound. This finding is supported by the comparison of the improvement ratios and the mean ulcers surface area after treatment. It was shown that adding ANGIPARS™ oral capsules (100 mg) twice a day to conventional therapy for 42 days led to greater than 85% decrease in surface area among 83% of patients. As well, this outcome was shown in 100% of participants by daily administration of topical 3% gel of ANGIPARS™ in addition to the oral form.

Beside of the significant improvement of wounds surface areas, the interventions provided excellent quality of granulation and reepithelization after two weeks, all of which led to faster wound closure. Comparison of improvement ratios between oral and combination of oral and topical administration of ANGIPARS™ compound revealed no significant difference. This is explained by the complete improvement of wounds in all patients in both intervention groups. Yet, there was only one individual in oral ANGIPARS™ group who showed relative improvement within 6 weeks of treatment. It means that even single therapy with oral ANGIPARS™ has similar effectiveness as combination therapy with oral and topical forms.

Phase II studies have also demonstrated the clinical efficacy of ANGIPARS™ in the treatment of diabetic foot ulcers [22]. Furthermore, another study indicated that 1 month intravenous injection of ANGIPARS™ compound results in 64% reduction in diabetic wound size [23].

The majority of research has shown that peripheral vascular disease (PVD) and diabetic neuropathy are the main risk factors for diabetic foot ulceration (16). Moreover, some factors such as poor glycemic control, chronic inflammation, infection, motor disorders of the foot, and edema in the ulcer area in addition to PVD or neuropathy may delay or prevent diabetic wound healing (24-27). Although all of these problems have roles in the development of a diabetic wound, it has been proved that appropriate establishment of circulation in limbs and regional tissues is critical for the treatment of diabetic ulcer (28). In another word, any factor that improves blood flow in the limb helps the ulcer to be healed (29-31). In this regard, we believe that ANGIPARS™ compound does improve total tissue blood flow and oxygenation via angiogenesis phenomenon (Unpublished data). During this process, periwound perfusion is increased and consequently wound healing is accelerated. In addition, qualitative and parametric improvement of chronic wounds indirectly indicates increased phagocytic activity as well as enhancement of granulation tissue formation (32). Hence, it may be concluded that ANGIPARS™ compound induces proliferation of granulation tissue and phagocytic activity.

The efficiency of our new product is comparable with other conventional and new diabetic ulcers treatment options. Recent advances in the treatment of diabetic wounds have shown to be promising (33). In this regard, cell therapy, also called biological therapy is the main field of research (16). The first of such therapies is recombinant human platelet derived growth factor (rhPDGF) which is applied for neuropathic ulcers and has been approved by the Food and Drug Administration (FDA) (34,35). The placebo-controlled trials performed on this product indicate that after 20 weeks, in the growth factor-treated group, 50% of neuropathic diabetic ulcers healed; while, in the placebo group, only 37% of participants achieved healing (36,37). However, it should be considered that rhPDGF such as Regranex or Becaplermin is solely restricted to neuropathic foot ulcers (38). Therefore, there is a need to improve therapeutic outcomes and effects of growth factor therapy. In this regard, the efficiency of recombinant human epidermal growth factor (rhEGF) has been evaluated (39).

Citoprot-p is a rhEGF which can be an alternative for end-stage diabetic foot ulcers patients, either ischemic and/or neuropathic, where the amputation is the only available choice (40). A double blind trial without control group showed that 75 µg and 25 µg intralesional injections of Citoprot-p compound in diabetic ulcers led to 56.5% and 50% complete healings respectively after about 20 weeks (40). However, this treatment method caused some adverse events such as sepsis (33%), burning sensation (29%), tremors, chills and local pain (25% each). Clinical application of fresh fibroblast allografts for the treatment of diabetic foot ulcers has also been considered safe and effective (41), but it may be difficultly accepted by the patients due to its costs and invasiveness.

In recent years, there is a great interest in autologous stem cell therapy as a promising new therapeutical option for the diabetic patient with chronic foot ulcers induced by critical ischaemia (42, 43). Accordingly, the initial response to treatment appears to be vascular in nature with the formation of new blood vessels which stimulate recalcitrant wounds to heal (44). Early data about the application of this method appear encouraging, but much work remains to be done (45). One study showed that stem cell application for diabetic wounds rescued 73% of patients' limbs from amputation (46). However, the delivery of autologous stem cells either from peripheral blood or bone marrow may require some additional interventions which may be surgical or medical (46,47). Moreover, this type of treatment is very expensive for the patients. In addition to the new mentioned biological therapies, there are some other treatment modalities which have been employed and investigated in some diabetic wound cases, but they have not shown dramatic results. For instance, low-level laser therapy has been suggested as one of those treatment options for diabetic foot ulcers (14). One trial showed that all diabetic ulcers were cured in about 1.5-2 months following low-level laser irradiation (14). Nevertheless, the results of studies have been contradictory about the efficacy of this method in achieving wound healing (14).

From the results of the present study, in spite of small sample size, we believe that ANGIPARS™ compound has superiority over all recent therapeutic approaches to diabetic foot ulcers which mentioned above. This preference is considered from different aspects such as healing efficacy, safety, simplicity of application, and cost effectiveness.

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