Randomized Double-Blind Placebo-Controlled Trial of Angipars[TM] in Diabetic Foot Ulcer, Study Protocol

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Abstract

Diabetes Mellitus (DM) is the most common metabolic disease in the world. About 15% of diabetic patients experience diabetic foot ulcer (DFU). Despite all the efforts in treating DFUs, the incidence of lower extremity amputations remains rather high. There are different modalities for treating this complication of DM. Angipars[TM] is a novel safe herbal formulation, recently presented for treating the condition. This study presents a trial which has been designed to evaluate the efficacy and safety of Angipars[TM] in treatment of DFUs in larger scale. In this randomized double-blind placebo controlled trial, a total of 300 participants (150 in each of the two arms) will be recruited from a tertiary clinic in Tehran. The patients aged between 18 and 75 years and are diagnosed with grade II or III of foot ulcer based on the Wagner's wound classification. The closure of the wound surface area is determined as the primary outcome, whereas the secondary outcome consists of ankle brachial index, toe pressure, wound bed temperature, overall clinical and patient impression of change, and the adverse effects of Angipars[TM]. These factors will be measured at baseline as well as 2, 4, 6, 10 and 18 weeks after the six weeks treatment period by an individual unaware of the participants' baseline characteristics and their treatment allocation. We will also collect data and analyze intention-to-treat of our intervention. The results of this study will provide valuable new information regarding Angipars[TM], a novel herbal drug hypothesized to be effective in treating DFUs.

Keywords: Angipars[TM]**,** Diabetes Mellitus**,** Diabetic Foot Ulcer**,** Clinical Trial

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Background

DM is the most common metabolic disease worldwide. About 15% of diabetics suffer from DFU, making it an important complication of the disease as it may lead to amputation in near 15-20% of the sufferers [1]. Serious complications of lower extremities are also one of the most common leading causes of hospital admissions among these individuals [2].

Despite all the efforts in treating DFUs, the incidence of lower extremity amputations remains rather high [3]. Peripheral neuropathy, structural deformities of the foot with abnormal foot biomechanical forces, trauma, uncontrolled hyperglycemia and peripheral vascular diseases (angiopathies) are among the main risk factors contributing to ulcer [4, 5]. Different treatment methods such as effective infection control, debridement, offloading, and revascularization are used for treating DFUs [6-10]. Platelet derivative factor (Becaplermin) [11], epidermal growth factor [12, 13], Tretinoin [13], Skin equivalents [14, 15], local and systemic hyperbaric oxygen [16, 17], local Phenytoin [18], Negative-pressure wound therapy [19-21], heat and LASER therapy [22-24], modern dressings [25-27], Maggot therapy [28], Chinese herbal medicines [29], and dermagraft (cryopreserved human fibroblast–derived dermal substitute) are among the local factors used in treating such patients [30].

The rate of amputation considerably declines with providing standard care and education to the patient [31, 32]. The main objective of treating DFUs, however, is wound closure. Despite the introduction of different therapeutic measures, none of them are influentially believed to be effective, indicating that more efficient treatments are needed.

AngiparsTM is a novel safe herbal formulation, recently introduced for treating DFUs. The product has shown few toxic effects and has been effective in improving these ulcers through not only reducing the wound size but also enhancing its microvascularization [33-40].

The objective of the designed study is to assess the efficacy and safety of Angipars^{TM} in a double-blind placebo-controlled phase III trial.

A six-week treatment with oral-topical form of AngiparsTM has shown promising results in the treatment of DFUs. Accelerated angiogenesis at the wound site may explain the effectiveness of the drug [10].

AngiparsTM, the extract of a herb known as Melilotus Offcinalis, can effectively treat chronic wounds especially DFUs. Previous studies have shown that the main ingredient of this product (Melilorus) has anti-inflammatory properties and can prevent skin aging and subsequently induce microvascularization at the site [41, 42].

Possible acute, sub-acute, fatal and genotoxicity of AngiparsTM along with its apoptotic, mutagenic and allergic effects have been evaluated through several pre-clinical and experimental studies. The studies, however, did not show any acute or chronic toxicity for the drug and warrants further clinical studies on a large scale [36, 37].

Maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of AngiparsTM were studied in a phase I clinical trial study. In this study, the intravenous injections of 10 cc AngiparsTM per day resulted in no clinical or laboratory adverse effects. Phlebitis at the site of injection, however, was the only adverse effect reported following prescription of 13.5 cc per day. As a result, the dose equal to 10 cc per day was considered as the maximum tolerated dose which did not caused phlebitis [35].

In a phase II clinical trial study, the safety and efficacy of parenteral AngiparsTM was studied in DFUs. The study revealed efficacy of the drug in decreasing at least 50% of the wound size. No adverse effects were seen in these patients [34].

In a multicenter study, the wound improved in at least 83% of patients receiving the oral-topical form of AngiparsTM whereas in the control group, complete closure was reported only in 22% of the patients. It should be noted that wound improvement in this study was defined as at least 70% decrease in the wound size. No serious adverse effects were seen in this study [33].

Recently, one study aimed to local post-marketing surveillance on safety and effectiveness of AngiparsTM among 75 diabetic foot patients, revealed significant decrease in mean surface area of DFUs and a significant rise in ankle brachial index without obvious side effects or toxicity [39].

Methods

Study design

This randomized, double-blind, placebo-controlled clinical trial aims to assess the effectiveness of Angipars[TM] in treating DFUs. This protocol has been initiated by the principal investigator and accepted by the Ethics Committee of EMRC and will be conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

Aims and Objectives

Primary end-point was to determine the effects of Angipars[TM] on the wound surface area in patients with DFUs.
Secondary end-points were:
• To determine the effects of Angipars[TM] on the ankle brachial index in patients with DFUs.
• To determine the effects of Angipars[TM] on the toe pressure in patients with DFUs.

• To determine the effects of Angipars[TM] on the wound bed temperature in patients with DFUs.
• To determine the effects of Angipars[TM] in improving the global impression of patients regarding their overall status in DFUs.
• To determine the effects of Angipars[TM] in improving the global impression of physicians regarding the overall status of the patients with DFUs.
• To determine the possible adverse effects of Angipars[TM] in patients with DFUs.

Study population

Total number of 300 diabetic patients with DFUs lasting for more than 2 weeks who are seeking medical care in a referral Diabetic and Metabolic Center of Tehran affiliated to EMRC will be recruited in this study. The inclusion and exclusion criteria are listed in Table 1.

Table 1- The inclusion and exclusion criteria for study recruitment

Inclusion criteria
• Diagnosis of diabetes mellitus (type 1 or 2) defined as the American Diabetes Association criteria
• Age equal or more than 18 years and less than 75 years
• Presence of one or more grade II or III foot ulcers based on the Wagner's wound classification, for at least 2 weeks. Infection should successfully be treated prior to the recruitment.
• Haemoglobin A_{1C} less than 10%
• Signing a written informed consent

Exclusion criteria
• Receiving any investigational drug within the last 30 days
• Severe Peripheral Arterial Diseases (PAD), (Ankle Brachial index less than 0.5)
• Any local or systemic signs of active infection including purulent discharge or marginal skin erythema (up to three centimetres from the margin of the wound)
• Presence of acute osteomyelitis or exposed bone
• Presence of any other systemic or chronic illnesses such as:
o Chronic hepatic diseases
o Chronic renal diseases (GFR <60 ml/min per 1.73 m^2)
o Clinically complicated pulmonary, cardiac, hematologic, gastrointestinal diseases
o Any endocrine diseases other than DM
o Serious psychological problems such as severe anxiety or depression
• Malignancy
• Pregnancy or intention to become pregnant during the study period (4.5 months)
• Inability to give an informed consent
• Corticosteroid therapy
• Any drug hypersensitivity
• Radiotherapy, Chemotherapy or the use of any immunosuppressive drugs
• Electrolyte imbalance
• Alcohol or substance misuse

Baseline assessments

Demographic data will be gathered at the baseline. A comprehensive physical examination and medical and drug history in addition to necessary laboratory investigations will be done at the baseline and at the pre-determined intervals during the study period (See Table 2).

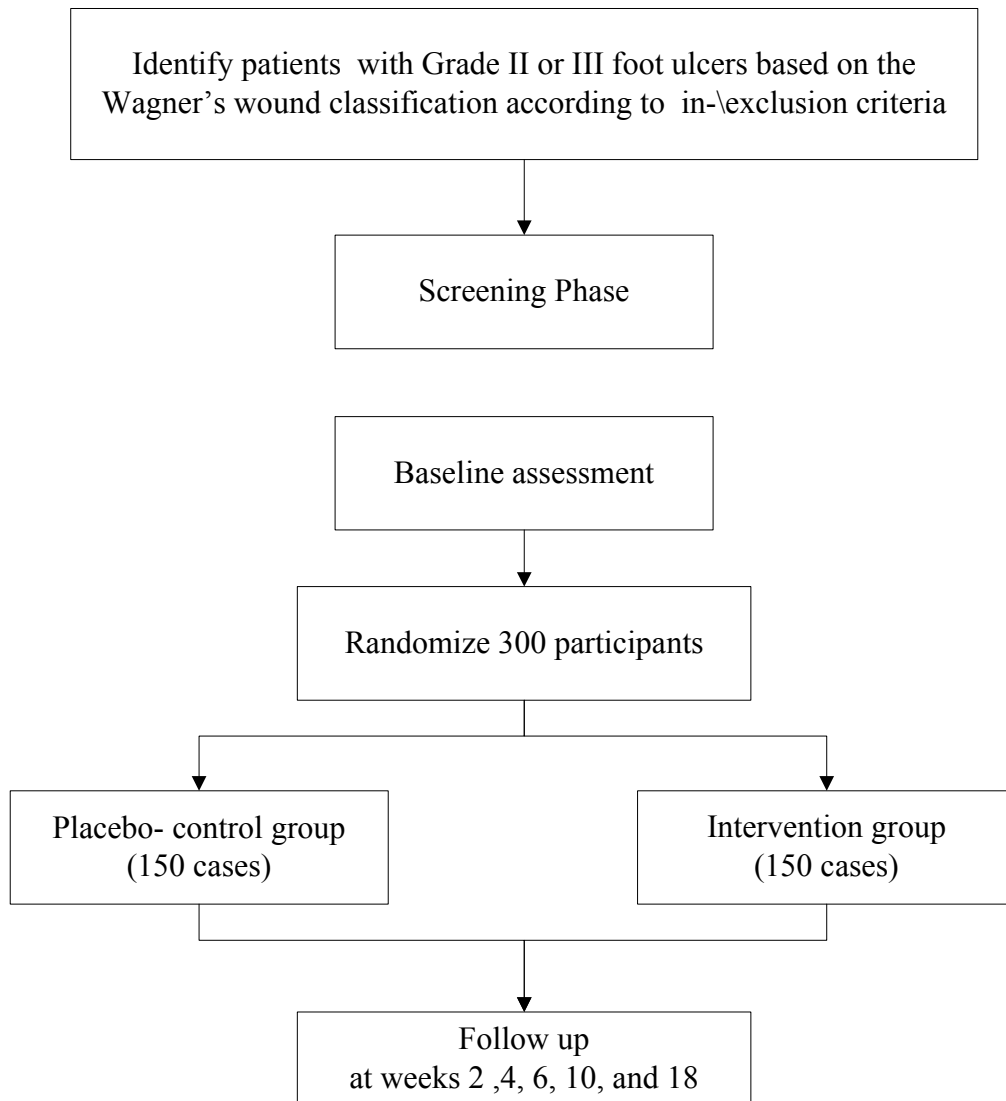**Table 2- Baseline assessment parameters of the study**

➢ **General and life-style characteristics:**
- Age
- Sex
- Contact details
- Smoking history
- Alcohol consumption history
- Gravidity if female

➢ **Lab tests:**
- Complete Blood Count (CBC)
- Erythrocyte Sedimentation Rate (ESR)
- C-Reactive Protein (CRP)
- Liver Function Tests (LFT)
- Thyroid Function Tests (TFT)
- Renal Function Tests (BUN, Creatinine)
- Urinalysis
- FBS
- HbA_{1C}
- Lipid profile (TG, Total Cholesterol, HDL, LDL)
- Electrolytes (Na, K)
- Serum amylase
- β-HCG

Recruitment

After providing a comprehensive explanation to the eligible patients about the aims of the trial, patients with DFUs referred to the Diabetic and Metabolic Center affiliated to EMRC will be invited to participate in this study. They will be asked to sign an informed consent form. In case of suffering from multiple ulcers, the wound with the largest surface area will be considered as the target wound.

In this step, patients will be evaluated in terms of inclusion/exclusion criteria and drug compliance; those who meet the criteria, therefore, will be enrolled and randomized after a two-week period (screening phase). After completing the baseline questionnaire, patients who are volunteers to participate in the trial, will randomly be allocated to one of the two treatment arms (see Figure 1).

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┌─────────────────────────────────────────────────────────┐
│   Identify patients  with Grade II or III foot ulcers     │
│   based on the Wagner's wound classification according    │
│   to  in-\exclusion criteria                              │
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                            │
                            ▼
                ┌───────────────────────┐
                │    Screening Phase     │
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                ┌───────────────────────┐
                │  Baseline assessment   │
                └───────────────────────┘
                            │
                            ▼
                ┌───────────────────────┐
                │ Randomize 300          │
                │ participants           │
                └───────────────────────┘
              ┌─────────────┴─────────────┐
              ▼                           ▼
    ┌──────────────────┐      ┌──────────────────┐
    │ Placebo- control │      │  Intervention    │
    │ group            │      │  group           │
    │ (150 cases)      │      │  (150 cases)     │
    └──────────────────┘      └──────────────────┘
              └─────────────┬─────────────┘
                            ▼
                ┌───────────────────────┐
                │      Follow up         │
                │ at weeks 2 ,4, 6, 10,  │
                │      and 18            │
                └───────────────────────┘
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Figure 1- Study flowchart; the process of recruitment, randomization, treatment provision, and outcome assessments

Follow-up visit description and schedule

Patients will be visited every two weeks during the first 6 weeks (treatment period) and thereafter at the first and the third month after the treatment (follow-up period) by a trained general practitioner and, if necessary, by endocrinologist.

Table 3- Visits schedule

Period	Visit 1 Screening	Visit 2 baseline	Visit3 week2	Visit 4 Week4	Visit 5 Week6	Visit 6 Week10	Visit 7 Week18
Informed consent	×						
In-/exclusion criteria	×	×					
Education	×	×	×	×	×	×	×
Medical history	×	×					
Physical examination	×	×	×	×	×		
Foot X-Ray	×						
EKG		×			×		
Laboratory test		×			×		
Angipars/Placebo administration		×	×	×	×		
Dressing & Debridement	×	×	×	×	×	×	×
Digital Photography		×	×	×	×	×	×
ABI		×	×	×	×	×	×
Toe pressure		×	×	×	×	×	×
Wound bed temperature		×	×	×	×	×	×
Quality of Life		×	×	×	×	×	×
Clinical assessment of adverse events		×	×	×	×	×	×
Clinical Global Impression of Change		×	×	×	×	×	×
Patient Global Impression of Change		×	×	×	×	×	×

Intervention allocation (Randomization)

This study has two arms:
1. Angipars[TM] 1 capsule, 100 mg, bid in addition to 3% topical cream bid for a period of 6 weeks is prescribed in addition to standard wound care including glycemic control, debridement, dressing, offloading and infection control [43].
2. Placebo, the same drug preparations contained inert ingredients, with the same dosage and administration route as intervention group in addition to standard wound care.

Patients in our center will be allocated to the intervention or control groups using a separate complete block randomization method. Blocks of four will be used for this purpose. Randomization will not be disclosed to those conducting the study and will be provided in closed letters with successive numbers. The envelope will be opened when the patient joins the study.

Blinding process

The study will be a double blind study, both the patients and those who conducting the study. For this purpose, patients will receive placebo which is identical to the active drug in appearance but contains a biologically inert substance. To blind those conducting the study, the administrative individual who are responsible for delivering or controlling the drugs will be different from those who treating the patients. The drug packages will also be identified only through unique numbers. Finally the randomization table will be concealed from research staff by using closed envelops.

Efficacy assessments

Wound surface area
To determine this outcome, a ruler will be placed at the wound margin, a digital photograph will be taken and thereafter the wound surface area will be calculated using special software (Hakim Software) through planimetry methods.

Toe pressure

This outcome is determined by fastening a small calf around the toe and measuring the capillary pressure by PPGI probe using arterial Doppler ultrasonography.

Ankle-Brachial Index (ABI)

This outcome will be measured using arterial doppler ultrasonography device-basic 110674 made by ATYS S.A.R.L, France- The pressure of the brachial artery and one of the arteries in the lower extremity will be measured using an 8 MHz probe. ABI will be measured as the proportion of the ankle to brachial pressure.

Wound bed temperature

DermaTemp^{TM} -Model DI-1001, USA by Water Town MA Company- will be used to measure the temperature of the wound. The device has three modalities (Scan/Max/Min) and measures the temperature of the wound 10 times per second, while recording the maximum, minimum and the last temperature.

Quality of life

This will be measured through applying Iranian version of SF-12 Health Survey questionnaire validated for Iranian subjects. Both physical and mental scores will also be calculated.

Clinical Global Impression of Change (CGIC)

This will be measured through a 10-point scale on which the clinician rates the changes observed in the patients' overall status since the beginning of the study.

Patient Global Impression of Change (PGIC)

This will be measured at the end of the treatment and the follow-up period through a 10-point self-report scale on which the patients present any changes which observe in their own overall status since the beginning of the study. The scores of this scale vary from "much improved" to "much worse".

Data managements

All the original data will be recorded in the patient's file records. Adequate attention will be given in order to collect accurate and valid data. The data will also be recorded in a special electronic database, identical to the original forms, and will be sent to the chief investigator in successive time points. Principal investigators are responsible for this purpose in the centre.

Statistical methods

Sample size calculation

Mean ulcer surface area in our previous studies was between 700 and 900 mm² with a standard deviation ranging between 100 and 300 at the baseline. Based on our practice, we estimated an effect equal to 50% for standard wound care in grade II & III Wagner's ulcers, and expecting a 60% effect for intervention under study. The estimated sample size for each study group would be 98 patients (α = 0.05, power = 0.80, mean surface area=800, and standard deviation=200). We assumed the equal standard deviation in both study groups. To handle probable loss to follow-up and subgroup analysis, we decided to add 50% to the calculated sample size and enroll 300 patients in the two groups (150 in the Angipars^{TM} group and 150 in the control group).

Statistical analysis

Data will be analysed on intention to treat basis, defined as all randomized patients should receive at least a single dose of the study medication. Patients with no recorded data for a single parameter will be excluded from the analysis of that particular factor. After enrolment about 50% of the ideal sample size, an interim analysis will be conducted and a report will be submitted to the scientific steering committee for consideration. The main statistical analysis will be conducted after the trial is finished or a decision has been made to stop the trial by scientific steering committee after the interim analysis if the members are satisfied of the strength of the evidence. To compare mean differences between study groups, we will use independent t-test or Mann-Whitney test based on the distribution of variables. We will also use Chi-square test to compare categorical variables between the groups. We will also analyze the data using an ANCOVA model to control baseline values and confounding variables.

Conclusion

This trial will investigate the clinical effectiveness of a novel introduced approach for treatment of patients with diabetic foot ulcer. To date, this innovative approach has not been tested in a large scale double-blind, placebo-controlled trial with effectiveness analysis. We estimate that we can recruit 300 patients in this trial within a 12-months time period. According to the limitations of the previous studies, we believe that Angipars^{TM} is effective in reducing the size of the wound while increasing the ankle brachial index, toe pressure, and wound temperature in diabetic foot ulcers.

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