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TREATMENT OF CHRONIC DIABETIC FOOT ULCER WITH CLEXANE: A RANDOMIZED, SINGLE-BLIND, CONTROLLED CLINICAL TRIAL

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ABSTRACT

Introduction: Diabetes is one of the most common diseases worldwide and Iran. Diabetic foot ulcer is one of the most common and debilitating complications of diabetic patients which is associated with delayed wound healing and can lead to limb amputation. In the current study, we aim to investigate the effect of Clexane treatment on the healing of chronic diabetic foot ulcer.
Method: This randomized, single-blind, controlled clinical trial was performed on 136 patients with chronic diabetic foot ulcers referred to Razi Medical Educational Center in 2016. In this study, eligible individuals were randomly divided into treatment and placebo groups and Clexane ampoule with a low molecular weight of 40 mg followed by 0.2 ml of normal saline were prescribed for 30 days. Patients were visited once a month and three months later and evaluated in terms of ulcer improvement rate. Finally, the results were analyzed using SPSS VER 22 software.
Results: In this study, 74.2% of patients were male and patient's mean age was 74 years and 76.6% of patients had type 2 diabetes. The results of this study indicate that there is a statistically significant difference between the changes in area of diabetic foot ulcer in the pre-treatment and 30 days after treatment and 3 months after treatment in both groups receiving Clexane and placebo (P = 0.0001).

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Introduction

Diabetes is a rapidly growing problem worldwide and is undoubtedly one of the most challenging health problems of the 21st century. In 2013, an estimated 382 million people lived with DM worldwide and current projections suggest this number will rise to 592 million by 2035 [1]. According to the latest WHO official statistics, 9% of population over the age of 18 is suffering from diabetes [2]. ~80% of people with diabetes live in low- and middle-income countries and communities. The number of people with diabetes worldwide has more than doubled during the past 20 years. One of the most worrying features of this rapid increase is the emergence of type 2 diabetes in children, adolescents, and young adults [3]. The incidence of diabetes has already escalated across our country. It is estimated that more than 1.5 million people with diabetes live in the Islamic Republic of Iran [1]. Chronic complications of diabetes include ocular diseases

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(macular edema, retinopathy neuropathy), neuropathy: (motor, sensory and autonomic), nephropathy, heart diseases and coronary artery disease, lower limb complications, infections, skin problems and delayed healing of the wound [4]. Foot infections are the most common problems in persons with diabetes (foot thumb or metatarsophalangeal joint (MTP) are the most common location of wound) and a significant percentage of them will ultimately undergo amputation (14% to 24% risk with that ulcer or subsequent ulceration [4]. The risk factors for foot ulcers or amputation are: male sex, history of diabetes over 10 years, peripheral neuropathy, abnormal foot (bone anomalies, callus, thickening of the nails), peripheral arterial disease, smoking, previous history of wound or amputation, visual impairments and inappropriate blood glucose control, large pineal often precede ulcer, or they tend to cause ulcer [5, 6]. In spite of the implementation of prevention methods, wounds and foot infections are common and cause serious problems. Due to the multifactorial pathogenesis of lower limb ulcers, treatment of these lesions should be performed in various ways that often require experience and expertise in orthopedics, vascular surgery, endocrinology, foot medicine and infectious diseases. Wound infection is diagnosed by clinical, because several bacteria are most likely to be found on the surface of each wound. There are many studies that have been done to investigate the efficiency of different materials on diabetic foot ulcers including honey, iodine, hydrogels, and foams, skin transplantation, growth factors, proteases and protease inhibitors and vasoactive substances such as Clexane [7]. Clexane has beneficial effects on local tissue microcirculation and oxygenation through the inhibition of thrombin generation and improving the degradation of fibrin gel, resulting in fibrin degradation, and may therefore be useful and effective in the treatment of diabetic foot ulcers. Beyond its well-known antithrombotic effect, Clexane also has positive effects, including promotion of the synthesis of heparin sulphate in endothelial cell cultures, and the proliferation of fibroblasts (cells involved in wound healing) obtained from diabetic ulcers, preventing damage to the basement membrane of endothelial cell, as well as improving the structure and number of capillaries. Previous studies have suggested that low molecular weight Clexane might improve the clinical outcomes of chronic foot ulcers in diabetic patients with peripheral arterial disease [8, 9]. In addition, studies have shown that in diabetic patients with peripheral vascular disease, who underwent skin grafting, those treated with dalteparin which is a product of Clexane with low molecular weight reported more than 50% improvement than the control group [7]. Therefore, the aim of this study was to evaluate the effect of low molecular weight Clexane on the improvement rate of chronic diabetic foot ulcer with longer treatment and more doses compared to other studies. It should be noted that if the clinical outcomes of this study confirm the efficacy of treatment with Clexane in the improvement of chronic diabetic foot ulcer, then these findings can be used in the treatment protocol for diabetic foot ulcer.

Materials and methods

This randomized, single-blind, controlled clinical trial was performed on 136 patients with chronic diabetic foot ulcers referred to Razi Medical Educational Center in 2016. In this study, eligible individuals with informed consent were randomly divided into treatment and placebo groups and Clexane ampoule with a low molecular weight of 40 mg followed by 0.2 ml of normal saline were prescribed for 30 days. Patients were visited once a month and three months later and evaluated in terms of changes in foot ulcer area using digital images.

Inclusion Criteria:

1. Current neuropathic chronic diabetic foot ulcer (less than 10 days)
2. Wagner grading of foot ulcer 1 or patients underwent debridement or restricted amputation with Wagner grading of 2, 3 or 4 foot ulcer
3. (ABI > 0.9) Non-ischemic and neuroischemic
4. Open ulcer or debridement or restricted amputated ulcer

Exclusion criteria:

1. Presence of chronic diabetic foot ulcer caused by ischemia
2. Treated with anticoagulants entering the study
3. Contraindications for administration of low-molecular weight Clexane, including severe renal failure (creatinine less than 30 ml / min), Child-Pugh class B or C, bleeding impairments and proliferative diabetic retinopathy at risk of bleeding
4. Active osteomyelitis
5. Systemic sepsis

Statistical analysis of data

Data was analyzed by SPSS VER 22 software. Mean and standard deviation were used to describe quantitative variables with normal distribution; mean and range were also employed for quantitative variables with abnormal distribution. In addition, qualitative variables were described by number and percentage. Normal distribution of quantitative variables was assessed using Kolmogorov-Smirnov test. To compare the two groups (placebo and placebo), T-test and chi-square tests were used for different variables. Moreover, the difference between the variables before and after intervention in the groups was evaluated using paired t-test. The significance level of the tests was considered ($P < 0.05$).

Findings

In this study 74.2% of patients were male and patient's mean age was 74 years and 76.6% of patients had type 2 diabetes.

According to the results, no statistically significant relationship was found between variables of sex, age groups, type of diabetes and smoking in patients with chronic diabetic foot ulcer in the two groups receiving Clexane and placebo. The results of this study showed that there was no significant relationship between the duration of diabetes in two groups of patients with chronic diabetic foot ulcer in both groups (P = 0.298). Also, no significant association was found in any of the underlying diseases of hypertension - hyperlipidemia - IHD-CHF in the two groups of patients (P> 0.05). Additionally, no statistically significant association was found between Vegner Score in both groups of patients in (Table 1).

Table 1: Assessment of response status to treatment during initial treatment in patients with chronic diabetic foot ulcer in both groups receiving Clexane and placebo

Group Response status to treatment	Clexane (n=62)		Placebo (n=62)		Total		Statistical Estimate
	Number	Percent	Number	Percent	Number	Percent	
Complete treatment (loss of wound surface area)	18	29	12	19.4	30	24.2	
Treatment (decreased ulcer surface on less than 50% of the area of the primary wound)	24	38.7	15	24.2	39	31.5	
No change in the area of the wound	11	17.7	17	27.4	28	22.6	P= 0.101
Increased wound surface	7	11.3	12	19.4	19	15.3	
Amputation	2	3.2	6	9.7	8	6.5	
Total	62	100	62	100	124	100	

The results of using Fisher's exact test showed that there was no significant statistical relationship between the response status of the treatment in both groups of chronic diabetic foot ulcer patients receiving Clexane and placebo (P = 0.101) in (Table 2).

Table 2: Assessment of the response status to treatment during initial treatment and three months after initiation of treatment in patients with chronic diabetic foot ulcers by two groups receiving Clexane and placebo

Group	Three months after starting treatment, the initial treatment	Improvement		No Improvement		Total		Statistical Estimate
		Number	Percent	Number	Percent	Number	Percent	
Clexane	Improvement	19	86.4	23	57.5	42	67.7	P=0.0001
	No Improvement	3	13.6	17	42.5	20	32.3	
Total		22	100	40	100	62	100	
Placebo	Improvement	18	85.7	9	22	27	43.5	P=0.146
	No Improvement	3	14.3	32	78	35	56.5	
Total		51	100	41	100	62	100	

The results of MC Nemar test revealed that there is a significant relationship between the response status of the treatment at the initial treatment (30 days before the treatment) and the time interval of 3 months after initiation of treatment in the diabetic foot ulcer patients group (P = 0.0001), but this difference was not significant between the patients with chronic diabetic foot ulcer and placebo (P = 0.146) in (Table 3).

Table 3: Comparison of response time to treatment (reduction of the ulcer surface to less than 50% of the initial level) (day) in patients with chronic diabetic foot ulcer in two groups receiving Clexane and placebo

Group	Number	Mean ± SD	Median	Test value	Statistical Estimate
Clexane	42	14.28 ± 3.69	15	t= 4.76	P = 0.0001
Placebo	27	19.92 ± 5.38	18		

In this study, no significant difference was observed in the area of the diabetic foot ulcer surface in the two groups of patients receiving Clexane and placebo before treatment - one month after the start of treatment - three months after initiation of treatment. However, there was a significant difference between the area of the diabetic foot ulcer surface before treatment and 30 days after treatment in the patients receiving Clexane and the placebo group (P = 0.0001). These results generally show that there is a significant difference between the area of diabetic foot ulcer in the pre-treatment and 30 days after treatment and 3 months after treatment in the Clexane group (P = 0.0001). It was also determined that there was a significant difference between the area of diabetic foot ulcer in the pre-treatment and 30 days after treatment and 3 months after treatment in the placebo group (P = 0.0001) in (Table4 , 5).

Table 4: Comparison of values of area of diabetic foot ulcer before treatment and 30 days after treatment in two groups receiving Clexane and placebo

Group	Time	Number	Mean ± SD	Median	Test value	Statistical Estimate
Clexane	Before the treatment	62	462.8± 191.03	540	t = 5.43	P = 0.0001
	30 days after the treatment	62	284.51± 269.12	200		
Placebo	Before the treatment	62	459 ± 177.7	495	t = 3.17	P = 0.001
	30 days after the treatment	62	400.24 ± 287.5	475		

Table 5: Comparison of values of area of diabetic foot ulcer before treatment and 30 months after treatment in two groups receiving Clexane and placebo

Group	Time	Number	Mean ± SD	Median	Test value	Statistical Estimate
Clexane	Before the treatment	60	456.06± 19.52	540	t = 6.73	P = 0.0001
	30 days after the treatment	60	174.66 ±136.6	240		
Placebo	Before the treatment	56	435.55 ±173.6	495	t = 6.51	P = 0.001
	30 days after the treatment	56	203.39 ±142.83	265		

The results obtained using Willcoxon test showed that there was a significant difference between the surface area of the diabetic foot ulcer before treatment and 3 months after treatment in the patients receiving Clexane (P = 0.0001) in (Table 6).

Table 6: Evaluation of changes in the area of diabetic foot ulcer at pre-treatment and 30 days after treatment and 3 months after treatment in both groups receiving Clexane and placebo

Group	**Before treatment**	**30 days after treatment**	**3 months after treatment**	**Intra-group statistical estimation**	**Inter-group statistical estimation**
Clexane	456.06 ±190.5 Median= 540	268.66 ±258.7 Median = 200	174.66 ±136.6 = 240	F= 890 P = 0.001	F= 7.24 P = 0.001
Placebo	437.55 ±173.6 Median= 495	358.1 ± 270.1 Median = 475	203.4 ± 142.83 Median = 265	F= 84.1 P = 0.0001	

Using repeated analysis of variance (Repeated measurement), it was shown that there is a statistically significant difference between the area of the diabetic foot ulcer during the pre-treatment and 30 days after treatment and 3 months after treatment in the group receiving Clexane (P = 0.0001). According to the results, there is a statistically significant difference between the area of diabetic foot ulcer in the pre-treatment and 30 days after treatment and 3 months after treatment in the placebo group (P = 0.0001) as well as a statistically significant relationship between changes in area of diabetic foot ulcers at pre-treatment and 30 days after treatment and 3 months after treatment in both groups receiving Clexane and placebo (P = 0.001).

Discussion and conclusion

In this study, 74.2% of patients were male and patient's mean age was 74 years and 76.6% of patients had type 2 diabetes. In a study by Markuson, 65% of patients were male and 85% of patients had type 2 diabetes, which is consistent with the current study. In addition, in a study by R.Serra et al. (2012) on 120 patients with chronic venous leg ulcers (CEAP C6), secondary to primary chronic venous insufficiency, 81 of these patients were female and 39 male which was not in line with the results of our study [11]. In this study, the area of diabetic foot ulcer was not significantly different between two groups of patients receiving Clexane and placebo before treatment - one month after the start of treatment - three months after the treatment. However, there was a significant difference between the surface area of the diabetic foot ulcer before treatment and 30 days after treatment in the patients receiving Clexane, which was observed in the placebo group as well (P = 0.0001). These results generally show that there is a significant difference between the area of diabetic foot ulcer in the pre-treatment and 30 days after treatment and 3 months after treatment in the Clexane group (P = 0.0001). Moreover, it has been found that there is a statistically significant difference between the area of diabetic foot ulcer in the pre-treatment and 30 days after treatment and 3 months after treatment in the placebo group (P = 0.0001) as well as a statistically significant relationship between changes in area of diabetic foot ulcers at pre-treatment and 30 days after treatment and 3 months after treatment in both groups receiving Clexane and placebo (P = 0.001). The results of intra- and inter-group comparison indicated that a statistical improvement was observed during the follow-up period. Furthermore, in a study by Kalani M et al in 2007, the effects of dalteparin on skin microcirculation and hemostasis function on 87 patients were investigated; the results of this study showed beneficial effects on haemostatic function are likely to contribute to the improved skin oxygenation observed during treatment with dalteparin. In each wound healing disorder group, 5 patients experienced an area greater than or equal to 50%. The results of this study showed that dalteparin contributes the improvement of chronic foot ulcers in diabetic patients with peripheral arterial obliterative disease [12] which was consistent with the results of the current study. Furthermore, no significant correlation was found in the mean improvement time between the two groups and the percentage of the improved area did not show significant difference, but ulcers outcomes were significantly better [13]. Several studies have been conducted to investigate the role of Clexane in both in vitro and in vivo conditions to determine its effects on wound healing. In cell culture studies, Clexane is associated with growth factors for the rapid and effective repair of endothelial cells. Clinical studies have shown an increase in capillary flow and a decrease in healing time in patients with chronic skin ulcers [11, 14]. The exact mechanism of the wound healing is still unknown, and the actual effects of Clexane on angiogenesis are controversial. Some studies on neovascularization in tumor showed that Clexane can affect the various phases of angiogenesis, including fibrin formation, endothelial cell migration, and ECM degradation [11, 15] as well as the dual effect of Clexane , which also appears to be related to both inhibitory and stimulatory effects on angiogenesis [11, 16]. Recent research has shown that Clexane has anti-inflammatory properties, improved wound healing capabilities by increasing angiogenesis and inducing neovascularization and its anti-inflammatory properties appear to be due to its modulation of pre-inflammatory cytokines during the wound healing process [17]. Some studies reported on the role of VEGF165 in promoting myogenic activity. VEGF165 is the major VEGF isoform.

Conclusion

According to the results, the wound healing process has been reported in both groups receiving Clexane and placebo for 3 months, which seems to have improved early in the group receiving Clexane.

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