

## Diltiazem Gel Versus Nitroglycerin Ointment in Healing Process of Scleroderma Digital Ulcers: A Blind Randomized Controlled Trial

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Assessing the effect of Diltiazem gel on scleroderma digital ulcers compared to Nitroglycerin ointment and placebo.

A single blind randomized controlled trial was done on 90 scleroderma patients, randomly divided to three groups: one receiving Diltiazem gel 2%, the other receiving Nitroglycerin ointment 2% and control one receiving Vaseline as placebo for 2 times per day for 8 weeks. The patients' demographic information and disease characteristics were summarized. The longest diameter of the ulcers was measured in 3 groups at the beginning and at the end of the study. The site of the ulcers and the number of new ones were, also, determined for each patient

The effect size of the ulcers, in each three groups, was significantly lower at the end of the survey (Diltiazem  $P$  value $<0.001$ , Nitroglycerin  $P$  value= 0.002 and Control  $P$  value= 0.027). However, comparing the induced difference in size of the ulcers between three groups revealed that both Diltiazem gel and Nitroglycerin ointment can significantly more lower the size of ulcers, especially ones at distal part of digits, in comparison to placebo ( $P$  value $<0.001$ ,  $P$  value=0.003). The number of new ulcers did not have significant difference between three groups. More complications were seen by Nitroglycerin ointment (42%) compared to Diltiazem gel (28%) and placebo (28%).

Both Diltiazem gel and Nitroglycerin ointment can be effective in healing of scleroderma digital ulcers; yet, through its lower complications, Diltiazem gel was superior to Nitroglycerin ointment.

**Keywords:** Scleroderma, Diltiazem, Nitroglycerin, Ulcer

### Introduction

Systemic sclerosis (SSc), also known as scleroderma is an autoimmune disease characterized by small vessels vasculopathy, collagen deposition in the skin as well as multiple internal organs [1]. Vasoconstriction following Raynaud phenomenon and structural change in blood vessels including intimal proliferation and obstruction leads to distal extremities specifically digital infarction and ulcer [2]. About 30 to 60% of scleroderma patients developed digital ulcers (DUs) in the course of their disease; these ulcers can affect the quality of life of the patients through the pain experienced and the delay in the healing process [3, 4]. Notwithstanding, few studies have investigated the effective treatment processes, specifically for SSc DUs.

Some studies carried out on SSc digital ulcers, investigated the effect of therapies previously applied in Raynaud's phenomenon as the most common vascular complication

of the disease [2]. Nitroglycerin ointment was considered to be an effective topical agent on Raynaud's phenomenon. Nonetheless, according to a study, it has been observed to have no effect on SSc digital ulcers [5, 6].

Systemic calcium channel blockers (CCB), such as Diltiazem, have also been utilized for decreasing the number of attacks and severity of Raynaud's phenomenon in scleroderma patients. Yet, some of their potential side effects like peripheral edema, hypotension, and headache, hinder their up titration [7]. However, no specific study has been carried out to determine the effectiveness of this group of drugs on the healing process of SSc DUs.

In addition to the systemic form of CCBs, a topical form such as Diltiazem gel has also been made available. Previous studies introduced this form of Diltiazem as a topical therapy for chronic anal fissure as a result of its vasodilator effects [8]. Comparing the effects of Diltiazem gel with

topical nitrates in anal fissure showed some controversies. While some studies showed no significant difference between these two topical therapies, others concluded that Diltiazem gel had a superior effect over nitroglycerin ointment because it is more effective and has lower side effects [9, 10].

The vasodilator effect of Diltiazem gel as well as its lower side effects compared to the systemic form, triggered the idea that it may also be effective for scleroderma DUs. In addition, comparing the effect of Diltiazem gel with topical nitrate in anal fissure, was mostly in favor of Diltiazem gel superiority. However, no study was found to have compared the effects of these two topical vasodilators in the treatment of DU. Thus, the present study aimed to assess the effect of Diltiazem gel and Nitroglycerin ointment on SSc digital ulcers and compare them with placebo.

### Materials and Methods

A single blind, randomized clinical trial was done on 90 scleroderma patients referred to Tertiary Centers of Rheumatology Diseases of Shiraz University of Medical Sciences, Shiraz, Iran from June 2016 to March 2017. This study was registered in ClinicalTrials.gov with number NCT02801305 and the ethical committee approval was obtained from Shiraz University of Medical Sciences as per provision of Helsinki guideline [11]. The informed consent was obtained from the patients and the ones who agreed with the content were entered into the study.

#### Inclusion Criteria

The patients' scleroderma was diagnosed based on the LeRoy criteria [12]. Patients with age ranging from 20 to 70 years were entered into the study. The type of the disease was determined for each patient based on his/her extent and degree of skin thickening as well as visceral involvement. The recruited patients had to have at least one active digital ulcer. The ulcers were defined as loss of epithelialization and tissue involvement in different degrees from epidermis to bone [13].

#### Exclusion Criteria

The patients with co-morbidities such as diabetes, thyroid disease, cardiovascular complications like ischemic heart disease, and those who were smokers, opium addict or alcohol abusers were excluded from the survey. In addition, the individuals who received or inhaled oral prostanoid in the last 3 months, phosphodiesterase inhibitors (with the exception of intermittent treatments of erectile dysfunction) in the last one month, and antibiotics 2 weeks prior to the study were also excluded from the study. The baseline hepatic function test was measured and the cases with moderate to severe hepatic impairment or increase in aminotransferase levels more than 3 times were also excluded from the survey.

### The study design

The patients were divided into 3 groups using computer-randomized division in block size 4. The patients were divided up to 4 block of equal size and an intervention was assigned to each group randomly. One control group and two experimental groups, each consisting of 30 patients. The control group (C) received Vaseline ointment (Samin Vaseline, Golafshan company, Tehran, Iran) as placebo twice a day for 8 weeks, the experimental group 1 (E1) received Diltiazem gel (2%) (DILTIGEL 2%, Sobhan Darou, Rasht Industrial City, Rasht, Iran) twice a day for 8 weeks and experimental group 2 (E2) received Nitroglycerin ointment (2%) (NITROCARD, CHEMA-ELECTROMET company, Poland) also twice a day for 8 weeks. All topical agents were put in the same pharmaceutical plates and given to the patients.

The longest diameter of the ulcers was measured using a standard ruler by the same examiner and same scale at the beginning and at the end of the study. The examiner was a physician who was familiar to the types of scleroderma's ulcers. Moreover, the site of the ulcers (fingertip, proximal interphalangeal joint (PIP), distal interphalangeal joint (DIP), metacarpophalangeal joint (MCP)) was also taken into account and submitted for each ulcer. In addition, the number of new DUs developed during the study, was counted and compared between the 3 groups.

### Statistical Analysis

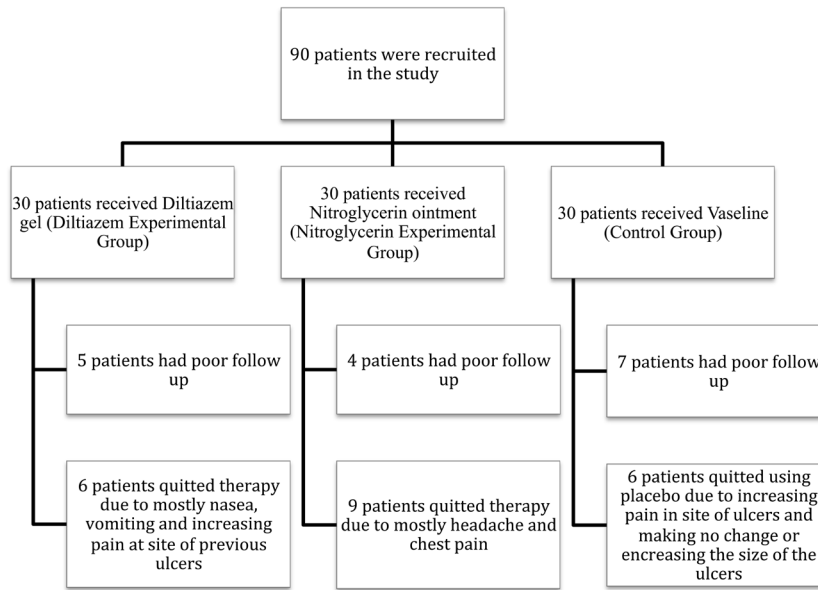
Data was entered into SPSS 19. Kruskal-Wallis test was applied for comparing continuous variables between three groups and Mann-Whitney test was used for the pairwise comparison of these variables. Moreover, for comparing continuous variables in each group before and after intervention, the Wilcoxon test was applied. Statistical significance was considered as  $P$  value < 0.05.

### Results

Ninety patients with mean age of  $42 \pm 9$ , 9 males and 81 females, were recruited in this case control study and divided randomly into three groups; each consisting of 30 patients.

About 17.8% (16/90) of the patients were excluded from the study as a result of poor follow up or a low compliance in continuing the treatment. Also, 23.3% (21/90) of the patients were excluded due to having problem with the medications in the course of the study; 42% (9/21) of them were in the Nitroglycerin group, 28% (6/21) were in the Diltiazem group and 28% (6/21) were in the control group. The number of patients recruited and the ones that remained till the end of the study are shown in detail in Fig-1.

The characteristics of the patients who remained till the end of the study are summarized in Table-1. Also, the details on complication of interventions are summarized in Table-2.



**Figure 1.** The number of patients entered in to the study and remained up to end of the study

**Table 1.** Details and characteristics of the patients remained up to end of the study

Patients Characteristics	Control Group (N=17)	Diltiazem Group (N=18)	Nitroglycerin Group (N=16)	P value
Age (mean± SD)	43 ± 19	40 ± 7	44 ± 6	0.72
Sex (Female/Male)	13/4	18/0	15/1	0.16
<b>Type of Disease</b>				
1. Diffuse	12	10	6	0.06
2. Limited	5	8	10	0.06
<b>Site of the ulcers (No. /total No.)</b>				
1. Tip of the fingers	33 / 43	46 / 60	46 / 62	0.56
2. PIP*	7 / 43	9 / 60	8 / 62	0.36
3. DIP*	0 / 43	5 / 60	8 / 62	0.63
4. MCP*	3/ 43	0 / 60	0 / 62	0.16

\*PIP: proximal interphalangeal joints, DIP: distal interphalangeal joints, MCP: Metacarpophalangeal Joint

**Table 2.** Most common complications of the drugs used in this study, which led the patients to quit the study

Complications	Placebo(%)	Diltiazem Gel (%)	Nitroglycerin Ointment (%)	P value
Headache	0	6.60	20	0.02
Chest pain	0	0	3.30	0.36
Nausea and Vomiting	3.30	6.60	0	0.35
Dizziness	0	3.30	0	0.36
Pain	3.30	13.30	23.30	0.07
Hypersensitivity	3.30	3.30	0	0.60

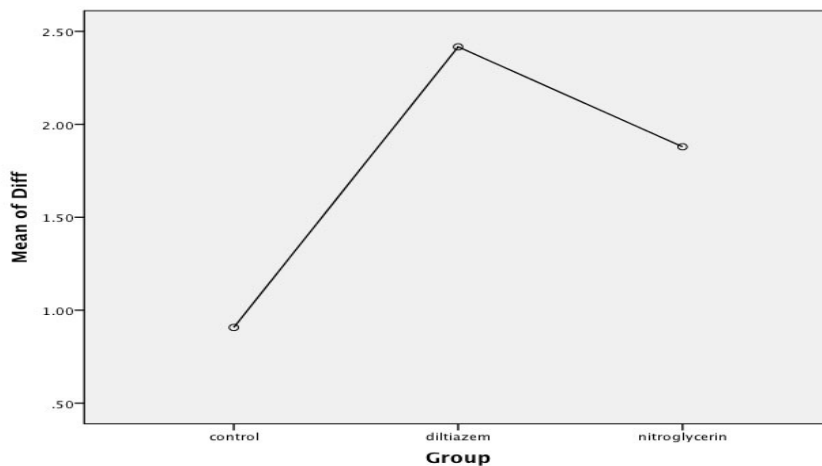
A comparison of the difference in size of ulcers induced by topical medications and placebo between the three groups showed a  $P$  value  $<0.001$ . A pairwise comparison of the three groups revealed significant differences between the Diltiazem group and the control ( $P$  value  $<0.001$ ), as well as the Nitroglycerin group and the control ( $P$  value = 0.003). However, no significant difference was found between Diltiazem gel and the Nitroglycerin ointment ( $P$  value = 0.179). The mean difference in the size of ulcers in relation with each other in the three groups is presented in Fig- 2. In each three groups, the size of the ulcers after applying intervention significantly decreased comparing to their size before the study. In addition, comparing the induced difference in the size of the ulcers between diffuse and limited types of the disease in each group showed no significant difference.

Also, the size of the ulcers at the beginning and at the end of the study was compared separately with each other in

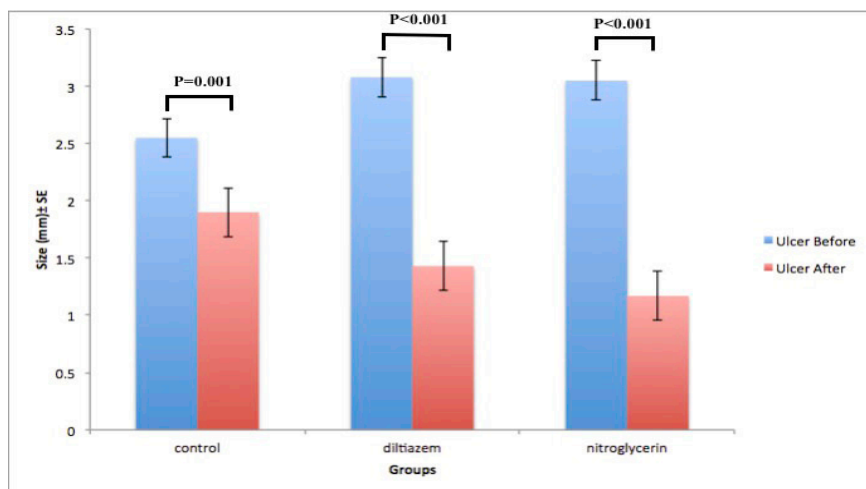
each group. The results are summarized in Fig-3.

The number of new ulcers that emerged during the study was also determined and compared between the three groups (5 in the control group, 4 in the Diltiazem group, 2 in the Nitroglycerin group); however, no significant difference was detected for this variable ( $P$  value = 0.41).

With regards to the site of the ulcers, only induced differences in the size of the ulcers on the tip of the fingers was shown to differ significantly between the three groups ( $P$  value= 0.002) (with mean values of  $2.28 \pm 1.8$  mm in the Diltiazem group,  $1.92 \pm 1.6$  mm in the Nitroglycerin group and  $0.93 \pm 0.96$  mm in the control group). Pairwise comparison showed a significant difference between the Diltiazem and control groups ( $P$  value = 0.01), as well as the Nitroglycerin and the control groups ( $P$  value= 0.007). No significant difference was found between the Diltiazem and Nitroglycerin groups ( $P$  value= 0.018).



**Figure 2.** Mean reduction in digital ulcers' size in three studied groups. The mean of difference in size of ulcers before and after giving topical medication and placebo in each of three groups is shown in this figure. (mm= millimeters)



**Figure 3.** Comparing the size of the ulcers at the beginning and at the end of the study in three studied groups

## Discussion

Scleroderma (SSc) is a systemic disease associated with microvasculature and connective tissue dysfunction [13]. Vascular injury through loss of capillary and structural change in the walls of vessels can lead to progressive luminal narrowing and ultimately, vascular occlusion [14]. This pathologic process leads to clinical features, which are the hallmarks of scleroderma like the Raynaud's phenomenon and digital ulcer [13].

Considering the aforementioned pathophysiology of SSc DU formation, most recent therapies including CCBs, have been shown to be effective through their vasodilator effects [15, 16]. However, due to the side effects of systemic forms of these medications, topical therapies may be more preferable.

Regarding our results, comparing the mean of digital ulcers at the beginning and at the end of the study in the three groups, it was concluded that Diltiazem gel, Nitroglycerin ointment and placebo are all capable of significantly reducing the size of ulcers. However, comparing the induced difference in size of the ulcers between the three groups revealed that both Diltiazem gel and Nitroglycerin ointment decreased the size of the ulcers when compared with placebo ( $P$  value $<0.001$ ,  $P$  value= 0.003, respectively). However, no significant difference was found between Diltiazem gel and Nitroglycerin ointment.

Some earlier studies have insisted on the efficacy of nitroglycerin ointment in reducing the severity of Raynaud's phenomenon, as one leading cause of DU in SSc [17, 18]. However, no studies were found which specifically assessed the effect of this topical treatment on digital ulcers of scleroderma patients. Furthermore, no studies were found which assessed the impact of topical CCBs on digital ulcers. Nevertheless, reviewing the results of studies on chronic anal fissure has led to the conclusion that Diltiazem gel, even if it does not have any statistically significant difference with the Nitroglycerin ointment, was superior to it because of its fewer complications [9, 19].

The present study also revealed that diltiazem gel caused lesser complications for the patients compared to the nitroglycerin ointment. As a result, we can also give superiority to Diltiazem gel in healing of scleroderma digital ulcers compared to the Nitroglycerin ointment, although no statistical significance was found between them.

Systemic sclerosis based on the extent and degree of skin thickening as well as visceral involvement is mainly divided into two types of diffuse and limited [20]. According to our results, the difference in size of the ulcers between diffuse and limited types of the disease in the three groups showed no significant difference. It can be concluded that the effect of these topical therapies do not differ between two types of the disease. No specific study was found which

determined the effect of topical therapies on scleroderma digital ulcer based on the type of disease; nonetheless, the studies which assessed the effect of systemic vasodilators on scleroderma digital ulcers showed more effectiveness of the therapy on diffused forms of the disease [21].

Our results on new ulcer formation during the study showed that none of the topical therapies and placebo was significantly different from each other in this respect. Accordingly, it can be suggested that neither Diltiazem gel nor Nitroglycerin ointment can be effective in preventing new DU formation. However, other clinical trials are needed to investigate the role of these treatments on specific etiologies of DU formation and consequently, its prevention in scleroderma patients.

Our results on the effects of topical Diltiazem and Nitroglycerin on DUs, depending on their locations, revealed that both therapies were significantly more effective in reducing the size of the ulcers on the tip of fingers compared to the control group. This may be as a result of the different pathogenesis of scleroderma DUs, depending on their location. According to one study, ulcers at the distal aspects of digits are mainly due to ischemia; yet, the ones over bony prominences such as phalangeal joints are mainly caused by micro-trauma and resulting slow healing process [18]. Thus, it would be reasonable that these two vasodilator agents have more effect on the ulcers at the tip of fingers.

One limitation of this study was the poor follow up, which is inevitable in clinical trials, especially in those dealing with patients with chronic diseases and resulting to social and medical outbreaks. Moreover, as a result of the effect of seasonal weather changes on the digital ulcer formation of the patients, all the patients were recruited in the same season (from the end of Spring to the end of Summer) and thus, it was not possible to substitute patients with poor follow-up with new ones. Another limitation of our study is the fact that it was conducted as a single blind trial. This was also unavoidable because Diltiazem gel should be kept around 2-8°C and the staff who gave the medication to the patients should be aware of this. Also, there was not enough staff at the time of the study to apply topical agents and measure the ulcers, separately. However, an attempt was made to minimize the possibly induced bias by using a computer randomized division system.

Despite the mentioned limitations, the present study can be introduced as the first clinical trial which investigated the effects of Diltiazem gel and Nitroglycerin ointment as topical therapies, directly on scleroderma digital ulcers by considering their possible side effects.

## Conclusion

Both Diltiazem gel and Nitroglycerin ointment can be effective in the healing of scleroderma digital ulcers; how-

ever, as a result of its lower complications, Diltiazem gel was considered superior to the Nitroglycerin ointment. To confirm this finding, more studies in the form of double blind randomized clinical trials should be conducted with a larger sample size.

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**Conflict of Interest** —————

The authors declare no conflicts of interest.



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