

## Original Article

# The Effect of Grapex on Wounds Healing in Patients with Scleroderma: A Randomized Controlled Clinical Trial

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Received: January 28, 2021; Accepted: March 7, 2021

## Abstract

**Background and Aim:** Scleroderma (SC) is a connective tissue disease, characterized by diffuse microangiopathy and excessive production of collagen. The current study aimed to investigate the effectiveness of Grapex extract in improving the wound of patients with scleroderma.

**Methods:** This randomized controlled double-blind clinical trial was performed from 2018 to 2019 on patients with scleroderma referred to Golestan Hospital in Ahvaz, Iran. Forty patients with active SC were selected and randomly divided into two groups. Patients applied the ointment twice a day for 4 weeks on the surface of their wounds. After four weeks of using the cream, the rate of wound healing was determined by clinical examination of the wounds.

**Results:** 6 people were excluded from the study due to the lack of referral and final analyzes were performed on 34 patients (16 patients in the control group and 18 patients in the case group). The results of this study showed that there was a significant difference between the two groups in terms of response to treatment ( $p < 0.0001$ ). At the end of the fourth week, 88.89% of the patients in the case group (16 of the 18 patients) achieved complete healing of the wounds in comparison with 18.75% of the control group (3 of the 16 patients). Neither the control group nor the case group had a significant association between response to treatment with age and gender of patients, type of scleroderma, duration of illness, and symptoms.

**Conclusion:** This study showed the effectiveness of Grapex cream ointment in healing scleroderma wounds. Therefore, Grapex cream is an effective, inexpensive, safe, and available medicine that can be used to accelerate wound healing in patients with scleroderma.

**Keywords:** Sclerosis Scleroderma; Grapex; Sclerosis Scleroderma Wounds; Wound Healing; Randomized Controlled Clinical Trial.

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**Please cite this article as:** Hemmati AA, Deris Zayeri Z, Rajaei E, Ghanavati M. The Effect of Grapex on Wounds Healing in Patients with Scleroderma: A Randomized Controlled Clinical Trial. Arch Med Lab Sci. 2021;7:1-10 (e1). <https://doi.org/10.22037/aml.v7.31059>

## Introduction

Scleroderma is a connective tissue disease, characterized by diffuse microangiopathy, excessive production of collagen by altered fibroblasts, skin and internal fibrosis, and multiple changes in the immune system (1). The natural course of the disease makes the pathogenic role of microscopic conflicts in this disease very important; In fact, various vasculopathy manifestations such as Raynaud's phenomenon is often seen in the clinical stage of scleroderma (2). However, renal crisis and

pulmonary artery hypertension (PAH) are the most harmful complications of scleroderma. Finally, skin lesions are the symptoms of the severity of microangiopathy in patients with scleroderma. Wounds are the most common complications of scleroderma and are reported in approximately 50% of patients. These wounds further affect hand function and quality of life (3). The wounds of SC are very painful and painful and complicated which are more common in the acrylic areas of the hands and feet. They might be multiple, recurrent, and

relapsing (4, 5); scleroderma wounds are divided into 5 groups based on their pathological mechanism and location: finger wounds on the hands and feet, wounds on bony prominences, calcinosis wounds, lower limb wounds, and finger wounds with gangrene (1). These wounds cause disability and decreased hand function, which results in fibrosis and tissue loss, and cause major limitations in patients' daily activities and work, and they have adverse effects on the patient's quality of life (4, 5).

Scleroderma wounds in some people may be associated with osteomyelitis (OM), infection, and severe gangrene and finally, lead to amputation (6). Because these wounds have important clinical effects, treatment, and prevention of these wounds is very important and is one of the most important therapeutic goals of patients with scleroderma (7). Additionally, reducing the healing time of the wound is important because it reduces the risk of infection, complications, and costs. Recently, studies have reported that the use of herbal sources alone or in combination with chemical drugs is helpful in wound healing (8).

Proanthocyanidins are a group of biologically active polyphenolic bioflavonoids that are synthesized by many plants. Proanthocyanidins facilitate wound healing. Grape seed extract (Grapex) is a rich source of powerful antioxidant compounds such as Proanthocyanidins and polyphenols. The effect of Proanthocyanidins in the body is 20 times and 50 times greater in comparison with vitamin C and vitamin E, respectively.

These antioxidant compounds prevent cell damage caused by free radicals and neutralize the effects of free radicals (9).

So, Grapex is used to treat disorders associated with increased free radicals. Grape seed has also been reported to have good protective effects against oxidative damage of DNA (10). Other beneficial effects of grape seed reported in various studies include anti-carcinogenic (anti-cancer) effects, protecting the body against sun damage, improving vision, improving joint flexibility, arteries and tissues such as the heart, improving blood circulation by strengthening capillaries. , Arteries

and veins and lower blood pressure (11). Also, various extracts of grape seed such as gallic acid, hydroxyl cinnamic acid, flavonols have antimicrobial and antiviral effects (12). Angiogenesis plays an essential role in wound healing. vasoconstrictive endothelial growth factor (VEGF) is the most common, most effective, and long-term signal in stimulating wound angiogenesis. VEGF is a homodynamic glycoprotein that maintains structural homology with placental growth factor and platelet-derived growth factor. VEGF stimulates the migration and proliferation of endothelial cells and improves vascular permeability and the ability to stimulate angiogenesis (9).

Proanthocyanidins in grape seed extract stimulate the release of VEGF, and its topical use contract, close and heal the skin of the wound. Treatment of skin lesions with grape seed extract causes proliferation of areas with protected borders in the epithelium, increases cell density and increases connective tissue deposition at the wound site, which generally improves cellular structures in the wound. Additionally, the anti-inflammatory and antimicrobial nature of grape seed is effective in wound healing (8).

Although several studies have shown the effectiveness of grape seed extract in wound healing in animals however studies on human have been very limited and no studies have been performed on the effectiveness of grape seed extract on the healing of scleroderma wounds. Therefore, the present study aimed to investigate the effectiveness of topical use of the creams containing grape seed oil (Grapex) on the healing of scleroderma wounds. Grapex cream is an inexpensive, affordable, herbal remedy with minimal side effects. Therefore, if the effectiveness of this drug is confirmed, it can be used to manage patients with scleroderma and heal wounds and reduce the need for high-dose chemical drugs.

## Methods

### The community under study, sampling and research plan

The present study is a double-blind randomized controlled trial study performed on patients with scleroderma referred to the rheumatology clinic of Golestan Hospital in Ahvaz from 2018 to 2019. All eligible individuals were included. There were no similar articles in the present study, this study is a Phase II clinical trial, so there was no need to determine the sample size, and initially, 20 individuals were selected in each group. However, in the study process, 6 people were excluded from the study, and final analyzes were Inclusion criteria were the presence of at least one active scleroderma active wound (diffuse/limited), age between 20 to 80 years, and patient satisfaction.

Exclusion criteria were the presence of allergies and sensitivity to grapes and its compounds, the presence of comorbidities such as diabetes, thyroid disorders, and cardiovascular disease, addiction to alcohol, cigarettes, and any drugs, receiving progestins (whether inhaled or taken orally) for at least the last 3 months, receiving antibiotics 2 weeks before the starting of the study, moderate to a severe hepatic impairment or increased aminotransferase levels by more than 3 months, the existence of any kind of malignancy, pregnancy and lactation, and lack of adherence to treatment and timely referral for follow-up.

Initially, this study was approved by the Ethics Committee in the research of Ahvaz University of Medical Sciences (Ahvaz, Iran). Also in this study, the provisions of the ethics statement in Helsinki research and the principles of confidentiality of patient information were observed. At the beginning of the study, the patients underwent a complete examination and the wounds were carefully examined and the wounds were photographed. The presence of an active wound on the skin was diagnosed by a doctor. Demographic characteristics, disease symptoms, medical records of patients, and the results of Cr, BUN, ESR, and CRP tests, and the presence of underlying diseases and disorders were recorded.

Eligible patients were divided into two groups based on random blockade. Randomization was performed by a person who did not interfere with the study process. Both groups were given routine

scleroderma treatment. Also, the first group was given 2% Grapex cream and the second group was given a placebo. Grapex cream as well as placebo were prepared by the Faculty of Pharmacy of Ahvaz Jundishapur University of Medical Sciences and provided to patients. Grape seed extract cream was 2% based on Eucerin and the liquid phase is more than the lipid phase (about 60%). In the formulation of this drug, red grape seed extract and preservatives have been used. Special compounds have also been used to stabilize color and flavor. Certain agents have also been used to homogenize the mixture of liquid and lipid phases. The content of placebo cream, except for the active ingredient (grape seed), is similar to the original composition. All thermal steps, durability, high-speed centrifuges, biological testing, and ensuring the non-separation of the liquid-lipid phase of the drug were fully performed at the Pharmaceutical Technology Development Center at the School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences. Patients were instructed to apply the creams (Grapex/Placebo) twice a day for 4 weeks on the surface of their wounds. Patients were given full explanations on how to use the cream. Patients were advised to use the cream enough to cover the wound after washing the wound (about half a fingertip). Patients were also instructed to visit the clinic in case of any complications or problems. They were also instructed to take pictures of their wounds every three days and to visit the clinic at the end of the fourth week of treatment to check the response to treatment. It should be noted that the patients, as well as the researcher, were unaware of the type of treatment and grouping, and thus the study remained double-blind until the end of the study.

#### **Evaluating the response to treatment**

At the end of the study, after the end of the 4<sup>th</sup> week, wound healing in patients in both groups was evaluated and compared. For this purpose, the number and size of the wound and the presence of new wounds were examined by the treating physician. Patients were then divided into three groups based on response to treatment: no response, partial response, and appropriate response. The

appropriate response was defined as complete wound healing (complete re-epithelialization) and lack of response as non-healing and change in the wound (13).

#### Methods of data analysis

Version 22 of SPSS software was used to perform statistical analysis. Descriptive information in quantitative variables, the mean deviation was used to describe the data center and the standard deviation was used to describe the data scatter. In qualitative variables, frequency and percentage were used to describe the data.

#### Statistical Analysis

Data normalization was assessed by Kolmogorov-Smirnov and Q-Q diagram and variance homogeneity were tested by the Loon test. Due to the non-compliance of the data with the normal distribution, in this study, more non-parametric tests were used to analyze the results. Non-parametric tests of Mann-Whitney and Kruskal-Wallis tests and Chi-square tests were used to analyze the data.

The significance level in the tests was considered to be 0.05.

## Results

#### Results of basic characteristics of the patients

The study involved 34 patients with scleroderma aged 33 to 78 years. 27 (79.4%) of the participants were female and 7 (20.6%) were male. The basic characteristics of the participants in this study are presented separately in two treatment groups with Grapex and placebo (Table 1). Both groups did not significantly differ in terms of age, gender, disease duration and the number of pregnancies, type of scleroderma, and results of laboratory parameters (ESR, Cr, BUN, and CRP) ( $p > 0.05$ ). The symptoms of scleroderma are presented in two groups in Table 2. The frequency of different symptoms of the disease, except for telangiectasia, did not differ significantly between the two groups ( $p > 0.05$ ).

**Table 1.** Comparison of basic characteristics of the patient in case and control groups

Variables	Unit	Control group (16 patients)	Case group (18 patients)	p-Value
Gender	Female	15 (75.93)	12 (0.7766)	0.061
	Male	1 (25.6)	6 (33.33)	
Age	years	13.11 ± 0.3144	65.8 ± 83.46	0.464
Numbers of pregnancies	-----	0.672 ± 0.202	54.1 ± 08.2	0.889
Duration of the illness	Hears	29.9 ± 0.638	29.6 ± 0.838	0.940
Type of Scleroderma	Limited	10 (5.62)	7 (89.38)	0.303
	Diffused	6 (0.537)	11 (11.61)	
CRP	Positive	7 (75.43)	5 (78.27)	0.467
	Negative	8 (25.56)	12 (22.72)	
ESR	mm/h	0.9020 ± 28.31	94.25 ± 32.41	0.252
BUN	mg/dL	0.894 ± 85.11	63.18 ± 92.15	0.472
Cr	mg/dL	12.0 ± .680	.551 ± 20.1	0.257

\*Numbers are in the form of frequency (percentage) or average deviation of the standard. \* $p < 0.05$  is significant  
Abbreviations: CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate, BUN: Blood Urea Nitrogen, Cr: Creatinine, mm/h: millimeter per hour, mg/dL: milligram per deciliter

#### Results related to the effectiveness of the intervention

A comparison of the response to treatment with Grapex and placebo creams in the healing of patients with scleroderma' wounds are presented in Table 3. In this study, there was a significant difference between the response to treatment

between placebo and Grapex ( $p < 0.0001$ ). Based on the observed results, 88.89% of the patients in the group treated with Grapex at the end of the fourth week of treatment achieved complete wound healing (appropriate response), which was 18.75% in the placebo group. Also, 56.25% of the control group did not show any response to treatment,

while no response to treatment was observed in any of the patients in the case group.

**Table 2.** The frequency of symptoms of scleroderma in both groups

Symptoms	Control group	Case group	p-value
Raynaud's phenomenon	16(100)	16(0.8988)	0.487
Redness around the nails	11(0.7568)	15(33.83)	0.429
Fingers wounds	16(100)	18(100)	1.000
Finger amputation	8(50)	11(11.61)	0.730
Telangiectasia	8(50)	16(89.88)	0.023
Sclerodactyly	11(0.7568)	11(11.61)	0.729
Pitting digital scars	8(50)	9(50)	1.000
Calcinosis	2(0.5012)	2(0.1111)	0.662

- Numbers are presented as frequency (percentage)

**Table 3.** The Comparison of response to treatment and wound healing of patients with scleroderma in two groups

Group	Case	Control	p-Value
No response	0(0)	9(25.56)	
Partial response	2(11.11)	4(.025)	0.0001
Appropriate response	16(89.88)	3(75.18)	

-Numbers are presented as frequency (percentage)

Comparison of the effectiveness of treatment in wound healing of diffused patients with scleroderma and patients with scleroderma is presented in Table 4. None of the group revealed a significant relationship between response to treatment and type of scleroderma (limited or diffuse) ( $p > 0.05$ ). There was no significant

relationship between gender and the response to treatment in both groups ( $p > 0.05$ ). There was no significant relationship between response to treatment and the age of patients in both groups ( $p > 0.05$ ). There was no significant relationship between response to treatment and scleroderma duration ( $p > 0.05$ ).

**Table 4.** The Comparison of the effectiveness of treatment in wound healing of patients with scleroderma based on the type of scleroderma

Group	Case		Control	
	Diffused	Limited	Diffused	limited
No response	0(0)	0(0)	2(33.3)	7(70)
Partial response	2(18.18)	0(0)	33(50)	1(10)
Appropriate response	9(81.82)	7(100)	1(16.67)	2(20)
p-Value	0.245		0.423	

-Numbers are presented as frequency (percentage)

**Table 5.** Comparison of the effectiveness of treatment in wound healing of patients with scleroderma based on disease symptoms in the control group.

Symptoms	Response to Treatment	No Response	Partial Response	Appropriate Response	p-Value
Raynaud's phenomenon	Yes	9(56.25)	40(25)	3(18.75)	-
	No	-	-	-	
Redness around the nails	Yes	6(63.63)	30(27.27)	1(9.0)	0.21
	No	2(40)	10(20)	2(40)	
Fingers wounds	Yes	90(56.25)	40(25)	3(18.75)	-
	No	-	-	-	
Finger amputation	Yes	50(62.5)	20(25)	1(6.25)	0.535
	No	40(50)	20(25)	2(25)	
Telangiectasia	Yes	40(40)	30(37.5)	1(12.5)	0.473
	No	50(62.5)	10(12.5)	20(25)	
Sclerodactyly	Yes	70(63.63)	20(18.18)	2(18.18)	0.558
	No	20(40)	20(40)	10(20)	
Pitting digital scars	Yes	50(62.5)	20(25)	1(12.5)	0.535
	No	40(50)	20(25)	20(25)	
Calcinosis	Yes	10(50)	10(50)	0	0.815
	No	80(57.2)	30(21.4)	30(21.4)	

-Numbers are presented as frequency (percentage)

The results of the relationship between the effectiveness of the treatment healing of patients with scleroderma based on the symptoms of the disease in the control group are presented in Table 5 and the case group in Table 6. The result showed

that there was no significant relationship between the response to treatment and symptoms in the placebo group. In the case group, there was no significant relationship between response to treatment and various symptoms of the disease.

**Table 6.** The Comparison of the effectiveness of treatment in wound healing of patients with scleroderma based on the symptoms of the disease in the case group

Symptoms	Response to treatment	No response	Partial response	Appropriate response frequency
Raynaud's phenomenon	Yes	2(12.05)	14(87.5)	0.606
	No	0	2(100)	
Redness around the nails	Yes	2(13.3)	13(86.7)	0.514
	No	0	3(100)	
Fingers wounds	Yes	2(11.1)	16(88.9)	-
	No	-	-	
Finger amputation	Yes	0	11(100)	0.068
	No	2(28.6)	5(71.4)	
Telangiectasia	Yes	2(12.5)	14(87.5)	0.606
	No	0	2(100)	
Sclerodactyly	Yes	2(18.2)	9(81.8)	0.245
	No	0	7(100.)	
Pitting digital scars	Yes	2(22.2)	7(77.8)	0.145
	No	0	9(100)	
Calcinosis	Yes	1(50)	1(50)	0.071
	No	1(6.25)	15(93.75)	

-Numbers are presented as frequency (percentage)



## Discussion

Using herbs and plant products to heal wounds has a long history. Especially in countries such as India, China, and Iran, there is a strong desire to use traditional medicine and there is valuable information about the use of plants in this subject (11). But little scientific research has been done to verify their effectiveness. Today, the use of various herbal extracts with a long history in traditional medicine has been considered in accelerating wound healing (14, 15). Numerous studies indicated that Grapex has many benefits due to its antioxidant effects (8). Grapex is a rich source of flavonoids, and the most important flavonoid found in grape seed is procyanidin oligomers (Proanthocyanidins), that its antioxidant properties have been shown to improve wounds healing. Proanthocyanidins can protect cells from radical oxygen damage (14).

A clinical trial by Soorgi et al examined the effectiveness of grapeseed oil (2.5% and 5% ointment) in cesarean section wound healing. The results showed that on days 6 and 14 after treatment, the size of the wound in the 5% ointment treatment group was significantly smaller than the other two groups, and the wound size in the 2.5% ointment treatment group was significantly smaller than the placebo. These results indicated the effectiveness of grape seed ointment in accelerating the healing of cesarean section wounds. Therefore, this ointment can be used to heal wounds after the cesarean section (16). In a double-blind clinical trial by Hemmati et al the effectiveness of 2% grape seed ointment in healing surgical wounds of skin lesions such as tag and moles on various parts of the body (neck and limbs) were examined. The results indicated that the recovery time in the group receiving the grape seed extract cream was significantly shorter in comparison to the placebo. The wounds healed completely in the grape seed extract group during the eighth day after surgery and the duration was fourteenth days in the placebo group. In this study, it was reported that grape seed extract is a rich source of Proanthocyanidins, which, can play an important role in wound healing besides other flavonoids (8). In another study by Hemmati et al in 2011, they found that 2% grape

seed extract accelerated the wound healing process and reduced wound healing time (20 days in placebo versus 13 days in grape seed extract group). It was also reported that the wound healing process and the restorative effects of grape seed extract begin on the first day of the treatment. However, high concentrations of grape seed extract did not show better results compared to 2% grape seed extract (17). The findings of the mentioned studies all confirm the results obtained in the present study. The results of a study on mice with similar induced wounds showed that grape seed oil cream had a better effect on wound healing compared to placebo so that on days 1, 3, 5, 7, and 10 after wound healing the wound of the grape seed treatment group was smaller. This effect was due to the antibacterial and antioxidant synergy of grape seed extract. They also found that treatment with this extract was well defined by the epithelial-proliferative epithelial area, higher cell density, increased connective tissue deposition, and improved histological structure. Additionally, grape seed extract stimulates the production of VEGF at the edge of the wound. Therefore, grape seed cream facilitates wound healing (18). The results of another study on experimental mice with induced skin lesions showed that topical application of Proanthocyanidins in grape seed could be used as an appropriate treatment for skin lesions (9). However, researchers believe that clinical trials on humans are essential to confirm the effectiveness of grape seed on wound healing in humans.

Grape seed extract contains antioxidant, antihistamine, anti-allergy, and anti-inflammatory effects that can strengthen the immune system. Additionally, grape seed extract is a rich source of phenolic compounds such as gallic acid, catechin, resveratrol, and a wide range of Proanthocyanidins (19). Grape seed extract can increase the volume of collagen fibers and facilitate the healing of skin wounds. Also, phenolic compounds (such as epigallocatechin gallate) are determinants of proliferation and differentiation of keratinocytes (20). Additionally phenolic compounds, the grape seed also contains tannins and vitamin D, which can accelerate wound healing (21). It also helps enter

vitamin C into cells, so it can strengthen cell membranes and protect cells from oxidative damage (22). The efficacy mechanisms of grape seed extract in wound healing have not been fully elucidated. However, Proanthocyanidins in grape seed extract have been shown to stimulate the release of VEGF and its topical application causes the wound to contract and close. Therefore, the treatment of skin lesions with grape seed extract causes proliferation of the areas with protected borders in the epithelium, increases cell density, and increases connective tissue deposition at the wound site, which generally improves the cellular structures in the wound. The anti-inflammatory and antimicrobial nature of grape seed is effective in wound healing (8). Finally, the results show the high effectiveness of Grapex topical cream in healing scleroderma wounds and it can release endothelial growth factors and its topical application repairs wounds. Therefore, it is recommended that herbal medicines can be used as alternatives to the chemical in scleroderma to treat scleroderma wounds to reduce the high cost of treatment and possible side effects of chemical drugs and increase the effectiveness. However, due to the lack of the studies on Grapex in compare to other available treatments for skin wounds we were very limited and no study has been done on the use of this herbal medicine for the treatment of scleroderma wounds. Therefore, further studies are needed.

The present study was the first study to evaluate the effectiveness of Grapex cream in wound healing in patients with scleroderma and obtained valuable information. However, there were some limitations, including the fact that only short-term effects (4 weeks) were investigated in this study and the effects of using this herbal cream were not studied in the long term. Also, the effect of disease severity and wound size at the beginning of the study on drug efficacy was not investigated. The recovery time was not checked (it was not clear how much recovery would occur on day one).

We also had no control over patients' personal health in this study. Some factors, such as hygiene, nutrition, adherence to treatment, and the proper use

of medication and disease specifications, can affect the wound healing process; In this study, we were unable to control the possible effects of these factors. Also, the socio-economic status of the participants, religion, education, and family history of patients can affect their treatment adherence. However, by randomizing the grouping and also providing sufficient explanations to the patients at the beginning of the study, we tried to minimize the effect of these factors. Other limitations of the study were the small sample size of the studied group. Further studies with larger sample sizes and multicenter studies can help to confirm the results.

The effective results of using topical cream containing grape seed extract (Grapex cream) and/or placebo in improving the wound of patients with scleroderma showed a significant difference between the case and control groups so that after 4 weeks of treatment the wound healed completely 89.89% of the case group who used Grapex and 18.75% of the control group were healed. Other members of the Grapex group (11.11%) also showed a relative response to treatment, while scleroderma ulcers did not improve in most control group (56.25%) individuals within 4 weeks. Also, no side effects were reported in the subjects. These results indicate the high efficacy of Grapex herbal cream in the treatment of scleroderma wounds. Also, based on the results of this study there was no significant relationship between response to treatment and age and gender of the patients and the type of scleroderma (limited or diffuse), duration of disease, and symptoms of the disease which reflect the ineffectiveness of these factors is in the treatment of the wounds. The results of the present study showed that the use of Grapex topical cream is effective in healing the wounds of patients with scleroderma and does not have any dangerous side effects.

Therefore, Grapex cream can be used as a cheap, available, and safe herbal medicine in the management and treatment of scleroderma wounds and reducing the need for high-dose chemical drugs.

## Conclusion



This study showed the effectiveness of Grapex cream ointment in healing scleroderma wounds. Therefore, Grapex cream is an effective, inexpensive, safe, and available medicine that can be used to accelerate wound healing in patients with scleroderma.

## Conflict of Interest

The authors have declared that no competing interests exist

## Acknowledgment

Notably, the Qamar Bani Hashem Hospital of the School of Medical Sciences would be greatly acknowledged for their support.

## Funding/Support

The authors declared that there is no financial support for this work.

## Ethics

All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was approved by the Ethics Committee in the research of Ahvaz University of Medical Sciences (IR.AJUMS.REC.1397.948).

This study is registered in Iranian Registry of Clinical Trials (IRCTID: IRCT20201010048984N1); URL: <https://www.irct.ir/trial/51719>

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