Assessment of an anti-cellulite cream: A randomized, double-blind, placebo controlled, right-left comparison, clinical trial

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Background: Cellulite is a common disease whose exact mechanism is unknown. This study was aimed to assess the safety and efficacy of an anti-cellulite preparation compared with placebo in a randomized double-blind, right-left comparison clinical trial.

Methods: Twelve healthy women aged 22 to 58 years with mild to moderate cellulite on their thighs and buttocks participated in this trial. The anti-cellulite preparation (Three O cream, Pouya Varzan Tejarat Sepahan Co., Iran) and an identical placebo were randomly applied on the right or left thigh and buttock twice a day for 2 months. The mentioned areas were photographed and the circumference, subcutaneous fat thickness, and dermis density and thickness were measured before and after treatment. A satisfaction questionnaire was completed by all volunteers to assess their satisfaction with the efficacy of treatment on each side.

Results: There was no significant difference between active and placebo treatment sides in any of measurements**.** About 90% of participants had an overall satisfaction of 5 and more than 5 based on a 0 to 10 visual analogue scale on the side of anti-cellulite cream. This score was similar on the sides treated with placebo and the active product.

Conclusion: Although Three O cream provided more satisfaction in volunteers than placebo, the objective measurements did not show any difference between them.

Keywords: anti-cellulite, efficacy, clinical trial

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INTRODUCTION

Cellulite is characterized by irregular relief alterations in the appearance of the skin surface which acquires an orange peel, cottage cheese or mattress aspect [1]. It is unsightly dimpling frequently found on the hips, buttocks, thighs, and even on the abdomen of women, especially after puberty, which progresses with age [2]. Cellulite is not a disease, but it is a serious cosmetic concern as a

non-inflammatory phenomenon with topographic skin changes that affects 80 to 90% of the women over the age of 20 year. It is rarely seen in men [3].

Although excessive weight gains increases the risk of cellulite, it can appear in young women with a normal Body Mass Index (BMI). Other risk factors involved in the pathogenesis of cellulite include genetic factors and gender; changes in the natural secretion of hormones, especially female sex hormones (estrogen at different ages such as puberty, pregnancy, lactation and menopause); lack of a proper diet and nutrition program; aging; prolonged stress and fatigue; immobility and lack of physical activity, dehydration; and Caucasian race [4,5].

The histopathologic changes of cellulite includes excessive hydrophilia of interstitial matrix leading to edema, alterations in connective structures, collapse of collagen fibers in the dermis, disorders in the lipogenesis-lipolysis system which leads to fat accumulation (hypertrophy of adipocytes), microcirculatory alteration, and stasis in the venous-lymphatic system [4,6,7].

Several therapies have been proposed and employed to treat cellulite including weight loss, a variety of topical agents, skin massage, mechanical equipments, surgical procedures, as well as oral supplements [3]. Among the mentioned therapies, topical agents are preferable as a non-invasive modality.

The aim of this study was to assess the safety and efficacy of a topical anti-cellulite cream in comparison with placebo in the treatment of mild to moderate cellulite of buttock and thigh areas.

PARTICIPANTS AND METHODS

Participants

In this study, 12 healthy female participants aged 22 to 58 years were enrolled in a double-blind, right-left placebo-controlled, clinical trial. The inclusion criteria were age 18 to 60 years, cellulite grade 2 to 4, no changes in diet, lifestyle, and exercise program during the study, and signing the informed consent form. The exclusion criteria were acute medical problems, allergy to the components of cream, using any treatment for cellulite in the past 2 months, any history of surgery or scar in the cellulite area, and venous thrombosis in the last 2 years.

Products

The test product Three O containing 0.015% Coenzyme A (CoA), 5% L-Carnitine, 1% caffeine, 1.5% ginger root extract and 2.5% Bodyfit (as the mixture of glycerin, water, coco-glucoside, caprylyl glycol, alcohol, glaucine) and the placebo that was a cream with similar appearance and foundation lacking the active ingredients were provided by Pouya Varzan Tejarat Sepahan Co., Iran.

Study design

This study was a randomized, double-blind, right-left comparison clinical trial. The weight and height of the participants were measured by a dermatologist. The anterior surface of both thighs was marked 20 and 30 cm above the upper edge of the patella and the thigh circumference was measured and recorded with a measuring tape. The subcutaneous fat thickness was measured subsequently by a clipper on the anterior surface of the thigh in the supine position in all four mentioned areas. The epidermis and dermis thickness and the density of the dermis were measured with a 20 MHz skin ultrasound (DUB Skin Scanner, tpm, Luneburg, Germany) [8]. Furthermore, photographs were taken from the anterior, posterior, and right and left lateral aspects of the thigh with a digital camera (Nikon S300, Japan) at a distance of 60 cm with constant light conditions in the upright position.

Then, based on a computer generated randomization list, the volunteers were asked to apply the anti-cellulite Three O and the identical placebo creams twice a day through rotational motions to the right and left thighs for 2 months. They were also required not to use any other topical products on the treatment areas. Furthermore, they were advised to perform physical activity regularly for half an hour every day.

After 2 months, all measurements were repeated in both areas and the results were recorded. The changes in variables in each treatment side were calculated according to the following formula:

Change = (value after 2 months - value at baseline) / value at baseline

Also, photography was repeated and the changes were scored by a blinded dermatologist on a 4-point Likert scale: much better, slightly better, without change, worse.

The patient's satisfaction with the efficacy of treatment on each side was evaluated on a 0-10 scale according to a Visual Analogue Scale (VAS) by the patients [9].

The incidence of side effects (itching, irritation, swelling, redness and scaling) was also evaluated and recorded on a 0-3 scale (0-none, 1- slight, 2- moderate and continued use, 3- severe leading to discontinuation of use). Any moderate or severe adverse effect was photographed. If a severe adverse effect occurred, the use of cream was stopped and the measurements were done on the same or next day.

Statistical analysis

The obtained data were entered in Case Report Forms (CRF) and then analyzed with the IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) software version 20. Due to lack of normal distribution of data, Wilcoxon Rank-Sum statistical test was used for analysis and *P*-values less than 0.05 were considered significant.

Ethical issues

The study was conducted in accordance with the ethical principles provided by Good Clinical Practice (GCP) and the Declaration of Helsinki and all volunteers provided written informed consent.

RESULTS

The mean reduction in weight and BMI was -0.80±2.18 and -0.32±0.84 kg/m^2 respectively, which indicated that the participants' weight and BMI did not change considerably during the study.

The reduction in the thigh circumference 20 and 30 cm above the patella was higher on the side treated with Three O cream compared with placebo, but the change was not significant (*P*=0.25 and 0.08 respectively, Table 1).

The thickness of the subcutaneous fat 20 and 30 cm above the patella decreased with both treatments and the difference was not significant (*P*= 0.21 and 0.66 respectively, Table 1). Also, the changes in the echo-density of the dermis was not different between the two sides (Table 1).

The thickness of the dermis 20 and 30 cm above the patella increased with both treatments and the difference was not significant (*P*= 0.94 and 0.64 respectively, Table 1).

The alteration indicator of the skin density 20 and 30 cm above the patella in both areas increased but the change was not significant (*P*= 0.76 and 0.6 respectively, Table 1).

By increasing the use of the anti-cellulite cream and sample size, the changes of the parameters can become significant.

Visual assessment of cellulite

Assessment of the changes of the cellulite appearance by the dermatologist showed that the side treated with the anti-cellulite cream was

Table 1. The change in thigh and buttock circumference, subcutaneous fat thickness, and echo- density and thickness of dermis 20 and 30 cm above the patella 2 months after treatment.

variable		Median ± interquartile range (%)	*P*
Thigh circumference 20 cm above the patella (cm)	Active	0.00±6.74	0.248
	Placebo	2.14±6.95	
Thigh circumference 30 cm above the patella (cm)	Active	-0.75±5.93	0.075
	Placebo	0.67±3.17	
Subcutaneous fat thickness 20 cm above the patella (μm)	Active	-4.91±26.21	0.213
	Placebo	-7.62±32.28	
Subcutaneous fat thickness 30 cm above the patella (μm)	Active	2.08±53.20	0.657
	Placebo	-3.49±38.32	
Dermis thickness 20 cm above the patella (μm)	Active	3.29±16.84	0.937
	Placebo	5.13±38.15	
Dermis thickness 30 cm above the patella (μm)	Active	-03.08±53.71	0.638
	Placebo	13.46±52.16	
Skin density 20 cm above the patella	Active	9.63±85.15	0.754
	Placebo	5.05±23.34	
Skin density 30 cm above the patella	Active	5.37±97.25	0.583
	Placebo	-4.41±99.49	

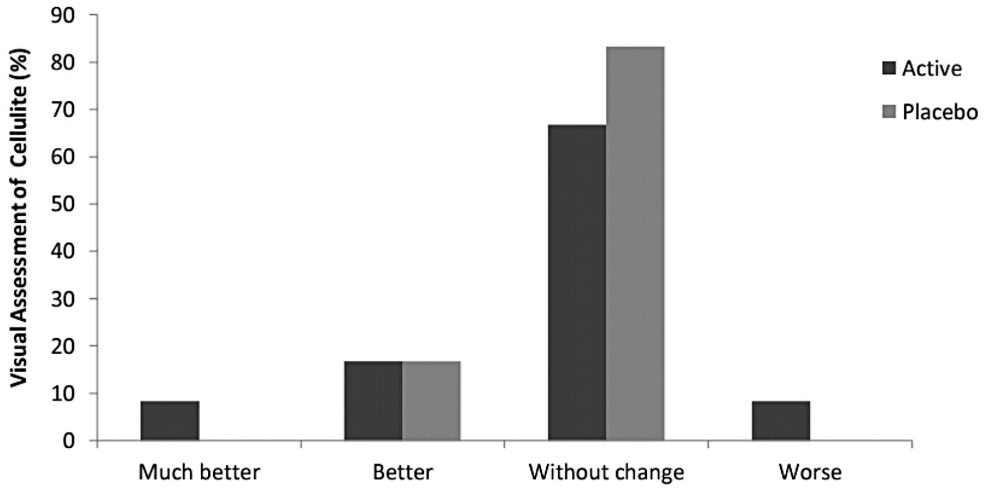

Figure 1. Changes of cellulite appearance assessed by the dermatologist.

much better in 8.3%, better in 16.7%, worse in 8.3%, and without any change in the rest of the participants. The side treated with placebo did not change in 83.3% and was better in 16.7% of the participants (Figure 1). Moreover, based on the dermatologist's evaluation of the skin quality improvement after using the cream, it was positive in 25% of volunteers.

Patient self-assessment

All participants (100%) expressed smoothing on the skin on both sides of anti-cellulite and placebo creams. About 30% and 40% of the participants experienced skin firming on the side of anti-cellulite cream and placebo, respectively. About 44.4% and 56.6% of the participants expressed that the orange peel appearance decreased on the side of anti-cellulite and placebo, respectively. 30% on usage side of anti-cellulite and 30% on usage side of placebo noted that the thigh format has been slimmer appropriately. More than 30% of the study participants were satisfied with smoothing and firming effects of the product. Moreover, based on a visual scale assessment (VAS), 90% of the volunteers had a satisfaction score of 5 and on the sides treated with anti-cellulite and placebo creams. One participant experienced slight irritation for 10 days and another patient had slight itching and irritation for 1 month on the placebo side. As a whole, two months regular use of Three O anti-cellulite cream did not show any adverse effects, so this cream is safe.

DISCUSSION

Cellulite seems to be one of the problems affecting many women these days. Despite its high prevalence and various physiological aspects have been described, the precise etiology of cellulite has not been established yet [10,11].

This clinical trial was a randomized, double-blind, placebo-controlled study which evaluated the efficacy of the test product in improving the appearance of cellulite and reducing the circumference of the affected areas. The test product was an anti-cellulite and topical slimming cream containing some active ingredients such as L-Carnitine, Coenzyme A (CoA) and caffeine (a known stimulator) that stimulate lipolysis within adipocytes via lipid unloading of the fat tissue, glaucine which is effective on lipolysis through glycerol release in adipocytes, and ginger root extract which facilitates and accelerates microcirculation and helps with physical activity for reducing fat layers [3,12-15].

As it is demonstrated in table 1,using anti-cellulite cream, indicates some active ingredients of product are able to affect adipocytes (fat cells) and make them smaller or eliminate. One of the ingredients of the cream is caffeine that acts directly on adipocytes, promoting lipolysis, inhibiting phosphodiesterase, and thus augmenting cyclic AMP; it activates the triglyceride lipase enzyme and breaks down triglycerides into free acids and glycerol [16]. The second ingredient is L-Carnitine which allows fatty acids to be transported across

the cell membrane to their oxidation sites within the mitochondria. The next one is Coenzyme A (CoA) that forms a thioester bond with free fatty acids in earlier stages; this molecule is then able to react with carnitine-acyltransferase and L-carnitine [12,13,17]. Finally, glaucine is a multifunctional molecule that stimulates lipolysis and inhibits the appearance of new adipocytes through calcium flow regulation [14].

The water release which is later drained by blood vessels and the lymphatics leads to an increase in the dermis thickness (Table 1). In addition, with the elimination of the fat mass, pressure on the dermis is reduced which causes an increase in the dermis thickness; moreover, the orange peel appearance either resolves or reduces. Therefore, this process can be due to Bodyfit (as a mixture of glycerin, water, coco-glucoside, caprylyl glycol, alcohol, and glaucine) that visibly reduces the appearance of cellulite, while contributing to an improvement in drainage and water distribution throughout the tissue. Therefore, as the cellulite diminishes, the skin firmness is restored [18]. Moreover, ginger extract increases the circulation due to its spicy ingredients and regulates the moisture due to its content of polysaccharides and amino acids [15].

According to the results, another parameter was the skin density and firmness which increased via elimination of adipocytes, replacement or activation of fibroblasts, and collagen production in the dermis. In the presence of the active ingredients of Three O anti-cellulite cream, the adipose tissue is replaced by a tissue possessing fibroblastic characteristics with contractile properties [19].

As mentioned earlier, all subjects expressed smoothing of their skin on both sides. This effect of the placebo was probably due to the use of an occlusive emollient and moisturizing compounds in the cream base that is identical to the active product. In addition, decreased fat mass on the placebo side was probably due to the effect of massage during the use of the product as mentioned in scientific papers as a way to treat cellulite; therefore, the reduction in the orange peel appearance and slimming were the result of massage [20]. If the anti-cellulite cream was applied for more than 60 days, the effectiveness of active product on affected areas would be better. Besides cream, complementary activities were helpful in for improving the condition.

Cellulite is a complex phenomenon and its treatment includes rather prolonged use of topical agents, physical activity, and applying massage to the target area. This study showed that the use of Three O anti-cellulite and topical slimming cream was safe as a non-invasive treatment. Furthermore, even though the changes were not significant, increased dermis thickness and skin density indicated the efficacy of this combination of ingredients in eliminating adipocytes, diminishing the orange peel appearance, and improving the skin firmness. This improvement in the skin firmness and also the slight increase in the density index were confirmed by the physician through patient assessment.

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