Efficacy assessment of topical brimonidine 0.33% in the treatment of rosacea in Middle Eastern patients with darker skin types

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Background: Brimonidine tartrate is an alpha-2 adrenergic receptor agonist approved for treating rosacea. This study aimed to assess the efficacy and safety of a brimonidine gel in rosacea patients with skin types III and IV.

Methods: This study was a phase II before-after clinical study in 20 patients with moderate to severe rosacea treated with brimonidine 0.33% gel. Clinician's Erythema Assessment (CEA), Patients' Self-Assessment (PSA), skin erythema (ΔE), lightness (ΔL), and biophysical parameters were measured before treatment and 4 and 8 weeks later. Ultrasound parameters were also measured at the same time points.

Results: Eighteen patients completed the study. CEA and PSA decreased significantly from 3.05 to 2.10 and 2.15 after 4 weeks and 2.20 and 2.15 after 8 weeks, respectively ($P < 0.01$ for both). Furthermore, ΔE and ΔL, as well as the skin erythema index, improved after 4 weeks of treatment. The skin echo density of both the epidermis and dermis also increased after 8 weeks ($P < 0.05$). During the study, no serious adverse events occurred other than some reports of temporary moderate redness.

Conclusion: Daily application of brimonidine 0.33% gel is safe and effective for the treatment of rosacea in darker skin types.

Keywords: brimonidine, rosacea, Middle Eastern People, biophysical parameters

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INTRODUCTION

Rosacea is an inflammatory skin disease. The most important clinical manifestations include persistent facial erythema, telangiectasia, papular and pustular skin lesions, and flushing [1]. It affects up to 10% of the population in the world, especially in the United States and northern Europe [2].

The exact cause of rosacea is unknown, but it could be due to a combination of genetic and environmental factors that lead to immune system response and activation of inflammatory and vasoregulatory pathways. Patients are reported to have a hyperresponsive immune system, which can be activated by foods (hot drinks, spicy nutrients, and alcohol), extreme temperature, sunlight, wind, emotions, exercise, and certain pharmaceutical and cosmetics preparations [3,4]. Also, previous studies have suggested that the symptoms of rosacea may be caused by skin reactions to mites (*Demodex folliculorum* and *Demodex brevis*) [5].

As rosacea affects facial appearance, it causes psychosocial issues like embarrassment, anxiety, depression, and low self-confidence. Facial erythema

is the main factor that impairs the quality of life, so adequately treating it is an important issue [6]. Several topical (metronidazole, azelaic acid, steroids, and retinoids) and oral (antibiotics and isotretinoin) treatments have been used to reduce the inflammatory lesions of rosacea but are not much effective in the treatment of the erythema of rosacea [7].

Brimonidine tartrate is a strong vasoconstrictive alpha-2 adrenergic receptor agonist, approved as a topical gel 0.33% by the FDA and EMA for facial erythema of rosacea [8]. Previous studies assessed the efficacy and safety of brimonidine in short and long-term applications in the United States, Canada, and Europe [9-11].

As most of these studies were performed on patients with light skin phototypes. This study aimed to evaluate the safety and effectiveness of topical brimonidine tartrate (Janu-brim® gel, Janus Pharmaceutical Co., Tehran, Iran) in treating rosacea in Middle Eastern patients with darker skin types.

PARTICIPANTS AND METHODS

Study design

This phase II before-after study was conducted on patients referred to the Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), Tehran University of Medical Sciences Tehran, Iran, between September 2017 and July 2018.

This study adhered to the tenets of the Declaration of Helsinki and the guidelines of Good Clinical Practice (GCP). All protocols and forms were studied and accepted by the research council of CRTSDL and the Ethics Committee of Tehran University of Medical Sciences (acceptance code: IR.TUMS.VCR.REC.1396.2072) before the study. The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT) with registration number IRCT20161207031288N4. All patients provided written informed consent.

Product

The test product was brimonidine 0.33% gel, produced by Janus Pharmaceutical Co., Tehran, Iran, in which one gram of gel contains 3.3 mg of brimonidine (equivalent to 5 mg of brimonidine tartrate) in polyvinyl carboxy polymer cross-linked with pentaerythritol ethers.

Study subjects

Male or female patients aged 18 and 50 years who had moderate to severe erythema according to the 5-point Clinician's Erythema Assessment (CEA) and Patients Self-Assessment (PSA) grading scale were recruited (Table 1) [12]. There were no restrictions on the number of inflammatory rosacea lesions.

Exclusion criteria included pregnancy or lactation, specific forms of rosacea including isolate rhinophyma or pustulosis in the chin, as well as rosacea conglobata and rosacea fulminans. Other exclusion criteria included concomitant facial dermatoses, demodicidosis, facial keratosis pilaris, seborrhoeic dermatitis, acute lupus erythematosus, actinic telangiectasia, any other active skin disease in the test area (atrophy, acne, eczema, and scar), allergy to any contents of brimonidine 0.33%. Patients were also excluded in case of a history of liver or renal diseases, recent UV-exposure or receiving systemic adrenergic receptor agonists, antagonists, or other treatments that may interact with the noradrenergic transmission like monoamine oxidase inhibitors, and tricyclic or tetracyclic antidepressants.

Prohibited treatments included topical or systemic corticosteroids, oxymetazoline, ivermectin, azelaic acid, peeling agents, retinoic components, and any antibiotic preparations within the last month; laser treatment or dermabrasion or deep facial peels within the past 3 months; and any light sensitive drugs within three months prior to the study.

Table 1. Five-point Clinician's Erythema Assessment (CEA) and Patients Self-Assessment (PSA) scale

Scores	Description	Clinician's Erythema Assessment (CEA)	Patients Self-Assessment (PSA)
0	Clear	Clear skin with no signs of erythema	Clear of unwanted redness
1	Almost clear	Almost clear; slight redness	Nearly clear of unwanted redness
2	Mild	Mild erythema; definite redness	Somewhat more redness than I prefer
3	Moderate	Moderate erythema; marked redness	More redness than I prefer
4	Severe	Severe erythema; fiery redness	Completely unacceptable redness

Intervention

The subjects applied a thin film (approximately half of fingertip or pea-sized amount) of brimonidine 0.33% gel on dry and clean areas of their face affected with rosacea once daily for 8 weeks, in accordance with the European Medicines Agency product information. They were instructed to avoid the application of this medicine on other parts of the body, especially moist body surfaces (e.g., eyes, mouth, nose, or vagina).

Evaluations

Safety and efficacy evaluations were done on baseline (0) and after 4 and 8 weeks of treatment. The efficacy was evaluated by a blinded investigator using the CEA and by the patient using the PSA.

Standard digital photography was performed at a fixed position and distance from the participant. The biophysical parameters of the skin lesions including transepidermal water loss (TEWL), hydration, erythema, melanin, pH, and sebum were measured, respectively, using the Tewameter, Corneometer, Mexameter, pH meter, and Sebumeter probes of Cutometer®MPA 580 (Courage & Khazaka electronic GmbH, Cologne, Germany) at standard temperature (20 ± 1° C) and humidity (40 ± 5%). Before the measurements, patients remained in the test room for almost 30 minutes to adapt to the room humidity and temperature. Skin erythema (ΔE) and lightness (ΔL) were determined by VisioFace camera and CSI software (Courage & Khazaka electronic GmbH, Cologne, Germany). The thickness and the echo density of the epidermis and dermis were measured using the 22 MHz probe of the ultrasound device (DUB skin scanner tpm Co. Luneburg, Germany).

Finally, all the patients completed a questionnaire regarding the change of redness and improvement of skin appearance after the product application [13].

For safety evaluation, the patients were asked and examined for possible side effects including burning, itching, desquamation, dryness, and redness in each follow-up visit. These side effects of skin irritation were graded as follows: none, mild, moderate, and severe. In case of interruption of the trial, the suspected cause and reason were described. Immediately after an interruption, an evaluation of safety was performed.

Statistical analysis

SPSS Software version 20.0 (IBM, USA) was used for statistical analysis. Descriptive statistics (mean, standard deviation, and percentages) were obtained, and statistical differences were tested among the three visits using repeated measured ANOVA-test and Bonferroni's post hoc test. The significance level was set as $P < 0.05$.

RESULTS

Among 30 screened patients, 20 who met all the eligibility criteria (52.6% female and 47.4% male aged 32.2 ± 8.9 years, range 20–50) were enrolled in this study, and 18 completed the study and were included in the analysis. Six of them had skin type III, and 12 of them had type IV. Two patients were unreachable and lost to follow-up.

Based on CEA and PSA classification, most subjects (90%) had moderate erythema, and 10% suffered from severe erythema. Both CEA and PSA significantly improved after 4 and 8 weeks of treatment with brimonidine 0.33% compared with baseline scores (Figure 1 and Table 2). In other words, subjects achieved at least 1-grade combined improvement from baseline on CEA and PSA at the following two visits.

Figure 2 shows the effect of topical brimonidine 0.33% gel on biophysical parameters of skin lesions following 4 and 8 weeks of treatment. Figure 2a shows that skin lightness (ΔL) promoted an increase in luminosity at week 4 and week 8. Also, skin erythema (ΔE) decreased after 4 weeks but returned to baseline after 8 weeks (Figure 2b). This reduction and reverted pattern was also shown by the non-invasive measurements of erythema with the Mexameter (Figure 2c). As depicted in Figure 2d, the melanin index increased significantly at week 8 ($P = 0.03$).

There were no significant differences detected in the levels of hydration, TEWL, and pH at weeks 4 and 8 (Figures 2e, f, and g, respectively). However, the sebum content significantly decreased from visit 0 (54.78 ± 44.90) to week 4 (31.72 ± 21.28) ($P = 0.02$), although this change was not significant at week 8 (Figure 2h).

Table 3 shows the thickness and echo density of the epidermis and dermis before and after treatment.

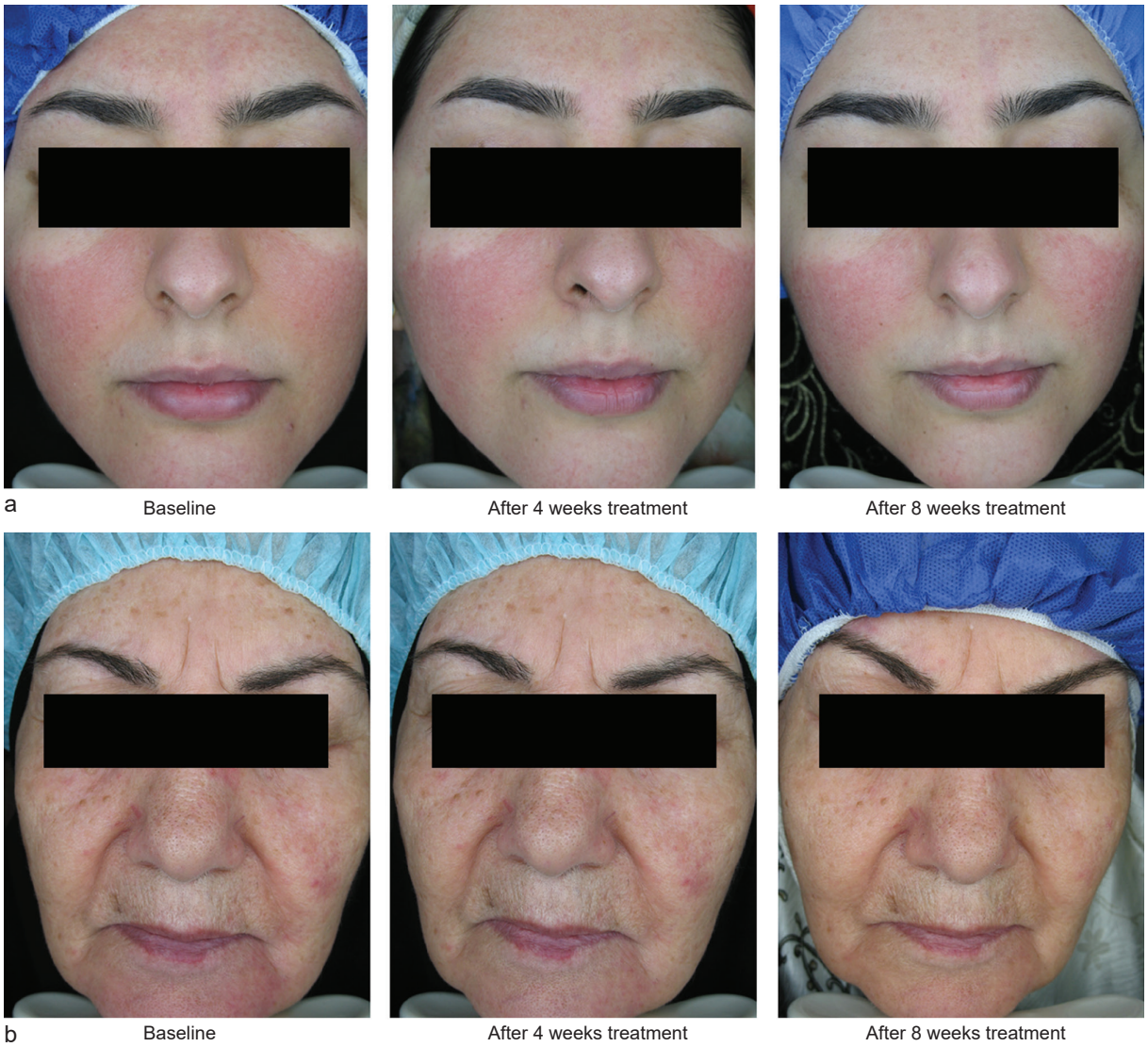

Figure 1. Significant improvement of facial erythema in a patient after application of brimonidine 0.33% for 8 weeks.

Table 2. The mean ± standard deviation of Clinician's Erythema Assessment (CEA) and Patients Self-Assessment (PSA) scale at baseline and 4 and 8 weeks after treatment with brimonidine 0.33%

Variable	Baseline	Week 4	Week 8	*P*-value	Specific comparison	*P*-value
CEA	3.05 ± 0.22	2.10 ± 0.31	2.2 ± 0.41	<0.01	Baseline vs. week 4	<0.01
					Baseline vs. week 8	<0.01
PSA	3.05 ± 0.22	2.15 ± 0.37	2.15 ± 0.37	<0.01	Baseline vs. week 4	<0.01
					Baseline vs. week 8	<0.01

There were no significant changes in epidermis and dermis thickness, while the echo density of both epidermis and dermis increased in the follow-up visits and reached statistical significance 8 weeks after treatment ($P < 0.05$).

After 8 weeks of treatment, 90% of subjects were satisfied with the whole treatment results and reduction of the facial erythema. All participants confirmed that they had improved self-confidence to stand in public. None of the patients reported

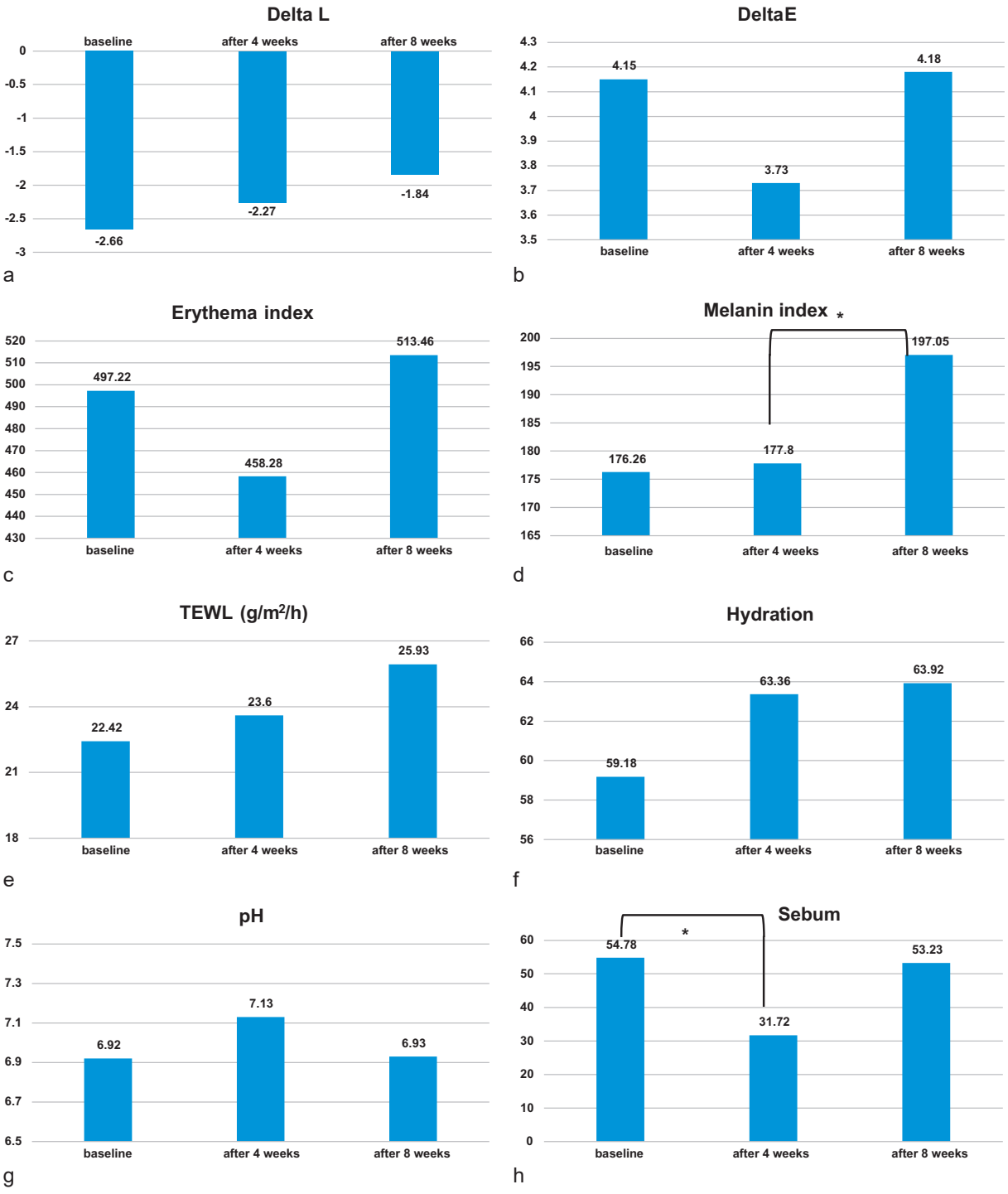

Figure 2. Effect of topical brimonidine 0.33% gel on skin biophysical parameters: (a) skin lightness (ΔL), (b) skin erythema (ΔE) by VisioFace, (c) erythema with Mexameter probe, (d) melanin index, (e) hydration, (f) TEWL, (g) pH, and (h) sebum content after 4 and 8 weeks.

the feeling of warmth in the skin, stinging, desquamation, itching, and dryness. The majority of subjects had moderate erythema, but this adverse effect was transient.

Table 3. The mean ± standard deviation of thickness and echo-density of epidermis and dermis at baseline, 4 and 8 weeks after treatment with brimonidine 0.33%.

Tissue	Variable	Baseline	Week 4	Week 8	*P*-value	Specific comparison	*P*-value
Epidermis	Thickness (μm)	112.31 ± 87.24	104.57 ± 27.14	117.76 ± 16.05	0.19	-	-
	Density	141.01 ± 17.32	146.56 ± 17.26	152.66 ± 14.41	0.03	Baseline vs. week 4	0.64
						Baseline vs. week 8	0.04
Dermis	Thickness (μm)	1282.42 ± 575.66	1235.57 ± 464.39	1209.38 ± 195.46	0.83	-	-
	Density	19.83 ± 6.02	22.00 ± 6.83	24.93 ± 6.72	0.05	Baseline vs. week 4	0.32
						Baseline vs. week 8	0.03

DISCUSSION

Rosacea is a chronic inflammatory condition that results in various signs and symptoms, such as flush-like temporary dilation of capillaries, persistent facial erythema, and telangiectasia in the central face. In severe cases, pustules and other inflammatory lesions on the nose and other facial regions (like ocular manifestations) occur [14,15].

Rosacea can appear at any age, in any gender, and even in people of Asian and African ethnicities. However, it is the most prevalent among European females aged 30–50 with fair skin [16]. In exceptional cases, rosacea can already occur in children [17].

Today, the treatment of rosacea has expanded, and many topical (brimonidine, oxymetazoline, azelaic acid, and ivermectin) and off-label (isotretinoin and many antibiotics) preparations as well as laser therapy (Nd:YAG, PDL and IPL) are used to manage rosacea [7].

In 2013, topical brimonidine tartrate 0.33% was approved for the symptomatic treatment of erythema in patients with rosacea [18].

Until now, there are not enough clinical trials on brimonidine to assess the skin biophysical parameters. In addition, no data were collected on the efficacy of brimonidine in darker skin types. Accordingly, this open-label, single-center, before-after, eight-week long clinical trial assessed treatment with brimonidine 0.33% in Middle Easterners patients with rosacea.

All the patients were evaluated by clinicians (CEA) as well as self-perceived erythema severity scales (PSA). The baseline data in Table 1 indicate that the CEA and PSA grade was equal to each other; therefore, it demonstrates that the subjects in this study estimated the severity of their erythema similar to the clinicians.

During the treatment period, all the patients had at least a 1-grade improvement from the baseline ($P < 0.05$), noticeable by both investigators and patients. The outcomes are comparable to the previous research. Brimonidine is an alpha-2-adrenergic receptor agonist with high selectivity and strong vasoconstrictive effects. Clinical studies on patients with rosacea showed that topical brimonidine significantly reduced facial redness within half an hour after treatment, which persisted for up to 12 hours [8,19-20].

Likewise, we examined three biophysical parameters (ΔL, ΔE, and erythema index) that directly demonstrated the skin erythema. The increase of skin lightness at weeks 4 and 8, similar to the reduction in skin erythema at week 4, shows that the objective assessment confirms the subjective ones (Figures 2 a-c); however, due to the small sample size, these results were not significant.

Using non-invasive assessments like what we conducted in this study can help researchers accurately investigate the other indications of topical brimonidine. There are many studies evaluating the effect of brimonidine after a dermatological procedure like lasers [21-23] and in non-rosacea erythema [24-27], for which subjective evaluations such as CEA, PSA, and Investigator's Global Assessment of Disease Severity are not appropriate assessment tools.

Using the Mexameter and CSI software, a reverting effect in two biophysical parameters at week 8 was seen (Figures 2 b and c), which were not in line with the ΔL, CEA, and PSA. We considered that this increase was related to the temperature (near 40 °C) and UV index of June and July in Tehran, which could affect the erythema index.

In addition, rosacea in severe conditions may contain papules, pustules, and hyperplastic sebaceous glands on the nose and other facial regions. Fig. 2d indicates the increase of the melanin index at subsequent visits (significant at week 8, $P = 0.03$). Indeed, this pigmentation could signify post-inflammatory hyperpigmentation (PIH) after the healing of the rosacea lesions [28]. Equally, as Figure 2h depicts, there was a reduction in sebum content at week 4 ($P < 0.05$) and 8 ($P > 0.05$) compared with the baseline. Consequently, our results support the hypothesis that the combination of brimonidine gel with other topical preparations (metronidazole, azelaic acid and oral antibiotics) can facilitate better control over rosacea [8,29].

In rosacea, the presence of the activated immune system (T cells, macrophages, mast cells, and neutrophils) accompanied by reactive oxygen species (ROS) and other cytokines causes dilation of vessels leading to cutaneous inflammation as well as micro-edema and erythema [30].

Eight weeks after treatment with brimonidine 0.33%, an improvement in the echo density of the dermis and epidermis was seen ($P < 0.05$). This effect might be due to brimonidine's vasoconstrictive and anti-inflammatory activity, decreasing the dermis and epidermis thickness and increasing the related density (Table 3) [29,31]. Thus, for the first time, our quantitative ultrasonic results confirmed the anti-inflammatory and skin edema-diminishing effects of topical brimonidine.

During the study, no serious adverse events occurred except for some reports of temporary moderate redness. Overall, the gel formulation was well tolerated by the patients and did not disrupt the skin barrier, as confirmed by no significant changes in hydration, TEWL, and pH (Figures 2e-g).

Rosacea management includes patient education. Dermatologists advise patients who frequently flush to firmly avoid trigger factors such as skincare preparations, food, and environmental features [32]. In addition, frequent use of moisturizers is more important [33].

Moisturizing ingredients improve the skin's defective barrier function and reduce its sensitivity. In brimonidine 0.33%, the manufacturer added glycerin and propylene glycol as humectant ingredients and omitted ethanol from the formulation. Thus, the formula can relieve dry skin and improve dermatological properties.

The study participants described the product as "easy to apply". The product was cosmetically acceptable without any greasy sense or appearance. In this regard, they were very satisfied with brimonidine's overall efficacy, including no rebound erythema. The patients thought their facial appearance had improved since starting the treatment, and they could control their impressions (embarrassment, depression, stress, or anxiety (more than before.

A possible limitation of this study is the timing of follow-up visits during the hot months, affecting some biophysical parameters. Another limitation is the small sample size, although most of the study assessments demonstrated significant improvements.

CONCLUSION

Our trial on treating rosacea in Middle Easterners with darker skin types suggests that brimonidine 0.33% gel's once-daily application is effective according to subjective and objective assessments. The topical formulation improved the patients' facial redness and self-confidence with no adverse effects.

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All tested brimonidine 0.33% gel was donated by Janus pharmaceutical company. The company did not provide further funding or compensation, nor had any role in the design or the conduct of the trial, and had no access to study data.

ETHICS APPROVAL

All protocols and forms were reviewed and approved by the research council of CRTSDL and the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1396.2072)

Consent to participate: All patients provided written informed consent.

Conflict of interest: None declared.

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