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Original Article

Brimonidine tartrate 0.1% eyedrops new and effective treatment of rosacea

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Abstract

Objective To determine the efficacy of brimonidine tartrate eye drops for treatment of erythema associated with rosacea.

Methods Fifty patients with rosacea (41 females and 9 males, mean age 35 years) were randomized to receive once daily single application of BT or vehicle for 4 weeks. Evaluation at 8 weeks included clinician's erythema assessment (CEA), patient's self-assessments (PSA) and photographic documentation.

Results Based on CEA and PSA, clinical response of 96.5% was seen with BT eyedrops as compared to 20.8% with placebo ($p<0.05$). Increased burning sensation and dermatitis was seen with BT in 2 (8.7%) patients, while rebound erythema occurred in 1 (4.3%) after BT use.

Conclusion Single daily application of BT eye drops provides significantly greater efficacy than vehicle for treatment of moderate to severe erythema of rosacea.

Key words
Rosacea, brimonidine tartarate.

Introduction

Rosacea is a chronic cutaneous disorder that typically presents in middle age.[1] It predominantly affects the central face and is characterized by congestion, flushing and marked nodular swelling of tissue. It is a skin condition of abnormal inflammation and vascular dysfunction. Emotional stress, spicy food, hot beverages, sun exposure, alcohol and certain drugs exacerbate the disease.[2,3]

Even though fair skinned Caucasians are the main sufferers of the disease. Asians also frequently have rosacea due to topical application of potent steroids.[3]

The disease undergoes the course of recurrent exacerbations and remission. Several therapeutic modalities are available for papules and pustules of rosacea. Erythema is the most challenging clinical sign.[4] The exact cause of erythema is not known but it is hypothesized that erythema results from dysregulation in cutaneous vasomotor response.[4] Therefore, agents with vasoconstrictive activity may have a symptomatic effect on erythema.[5,6,7]

Brimonidine tartrate (BT) is a highly selective α2-adrenergic receptor agonist. It has potent vasoconstrictive activity. It is an approved drug for the treatment of open-angle glaucoma.[8] Topical application of BT is also approved for treatment of rosacea.[7] BT gel (Mirvaso®) is

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costly and not available in Pakistan. BT eye drops are a cheap alternative.

We planned this study to compare the efficacy of BT eyedrops with a placebo in the treatment of erythematous rosacea

Methods

Fifty patients, 41 females and 9 males, age range 18 to 52 years, (mean 35 years) were enrolled in a single center. Informed consent was taken from all patients. Patients of erythematous rosacea only were enrolled. Patients with any of the following were excluded: papulopustular lesions on face, acne, photosensitive disorders, dermatitis on face, oral corticosteroid treatment, a previous history of facial laser treatment or other surgical procedures within 4 weeks prior to study enrolment. Patients with a history of glaucoma, pregnant and lactating women were also excluded.

All patients were randomly segregated into two groups. Patients in both groups were given oral doxycycline 100 mg and sunscreen to apply. Group A received Alphagan P® (containing 0.1% BT) eyedrops to be applied once a day in the morning, only on areas having erythema. Group B received PhysioGel® lotion (moisturizer as placebo) to apply every morning only on the affected area. Similar packing was used to hide the identity of BT and placebo.

All subjects received 4 weeks of either BT eye drops or placebo and then followed up after another 4 weeks without treatment.

At baseline, 4 and 8 weeks, photographs were taken with mobile camera (Samsung Galaxy S4, 13 mega pixel), using same light intensity and postures and Clinician Erythema Assessment (CEA) and Patients Self-Assessments (PSA) were noted. The primary efficacy endpoint (successful treatment) was defined as the proportion of subjects with a 2-grade improvement in both CEA and PSA measured at week 4 and week 8 (**Table 1**). Any side effects were also noted.

Table1 Grades of improvement used in the study.

Grades of improvement	*CEA*	*PSA*
1	Clear	Clear
2	Almost clear	Nearly clear
3	Persistent mild redness	More redness than I prefer
4	Persistent moderate redness	Definite redness
5	Severe	Unacceptable

CEA, Clinician erythema assessment
PSA, Patients self-assessments

Table 2 Treatment response week 8 assessed by 2-grade improvement.

	Group A	*Group B*
Lost to follow-up	2	1
Evaluable patients	23	24
Improvement by CEA	23 (100%)	8 (33.3%)
Improvement by PSA	22 (95.6%%)	5 (20.8%)

CEA, clinician erythema assessment
PSA, patients self-assessment

Results

Study was completed in 47 subjects, 2 patients of group A and 1 patient of group B were lost to follow-up (**Table 2**). BT eyedrops were effective in reducing erythema for up to 12 hours after a single application. Efficacy of BT eye drops was noted in all patients. At 8 weeks, the greatest effect was noted in group A (**Figures 1** and **2**).

At 8 weeks, the response rate to BT was significantly greater than that of placebo (95.6% vs. 20.8%). In the placebo group also showed slight reduction in both parameters which in authors' opinion was due to oral doxycycline and sunblock.

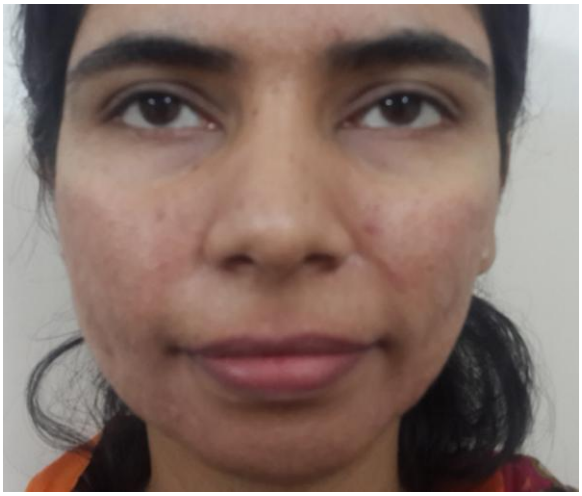

Figure 1 Visible erythema on face of a 23-year-old girl.

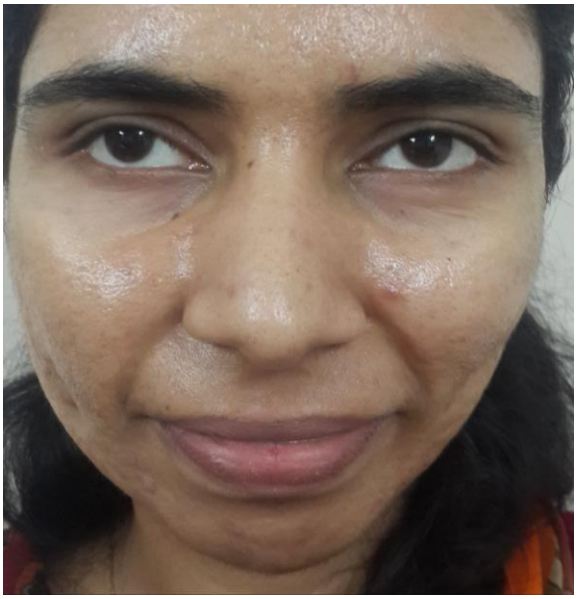

Figure 2 Marked improvement after 4-week therapy with topical brimonidine tartarate.

Two (8.7%) patients in group A reported increased burning sensation and dermatitis. Rebound erythema i.e. worsening of erythema was noted in one (4.3%) patient of group A. None of the patient in group B noted any side effects.

Discussion

Rosacea is relatively uncommon in our country but steroid-induced rosacea is becoming the most common dermatitis and is usually caused by the prolonged application of topical corticosteroid to the face.[1,4] Steroids are mostly applied to achieve lightening of skin. Prolonged corticosteroid use in this manner leads to persistent erythema, papules and pustules, telangiectasia with an itching and burning sensation. The pathogenesis of steroid-induced rosacea differs from that of rosacea and is thought to be multifactorial.[1,2]

Rosacea patients with erythema and flushing may also have papules and pustules on the central portion of the face.[14] Several medications including topical metronidazole, azelaic acid and oral antibiotics have been used successfully to reduce inflammatory lesion counts, but their effect on the erythema of rosacea has not been successfully demonstrated.[5,6,7] This study focused on facial erythema of rosacea and its management with topical brimonidine tartarate. Topical brimonidine 0.33% gel was approved by FDA for treatment of erythema of rosacea and it is available in Western countries as Mirvaso®.[9] Due to non-availability and high cost of topical gel, we studied a cheap alternative of brimonidine eyedrops (Alphagan P®). It is quite affordable and freely available locally.

In the present study, treatment with topical BT was successful. We measured the improvement in the degree of erythema by using two statistically validated scales CEA and PSA. It was well-tolerated by all patients. Only a marginal number of subjects showed side effects. Only one patient showed rebound erythema.

Our results are in agreement with the previous studies.[10,11,12] Fowler *et al*.[10,11] demonstrated the effectiveness of topical BT in phase II trials. They noticed that a single application of topical

BT gel reduced facial erythema in a dose-dependent manner. They observed a significant difference between BT 0·5% gel and vehicle in Chroma Meter redness value from 30 min to 12 h after application. In the second part of study, they also demonstrated that BT 0·5% gel once daily had a statistically superior success profile (defined as a two-grade improvement on both CEA and PSA over 12 h) compared with vehicle once daily on days 1, 15 and 29 (all P <0·001). No tachyphylaxis, rebound of erythema or aggravation of other disease signs (telangiectasia, inflammatory lesions) was observed. All regimens were safe and well-tolerated with similarly low incidence of adverse events.

Similarly, Jackson *et al.*[13] treated 260 patients and reported that 1-grade improvement in both CEA and PSA was significantly increased at 30 minutes post-dosing with BT 0.5% gel compared to vehicle gel day 1 (27.9 vs. 6.9%, P <0.001), day 15 (55.9 vs. 21.1%, P <0.001) and day 29 (58.3 vs. 32.0%, P <0.001) for BT 0.5% gel vs. vehicle). They concluded that once-daily topical BT gel 0.5% is not only efficacious at reducing facial erythema but also exhibits response within 30 minutes of application in a significant number of patients.

The effectiveness of BT is supported by the pathogenetic mechanism involved in the disease. Diffuse central facial erythema is a very common feature in rosacea and steroid-induced rosacea. Erythema intensifies during flares and persists to varying degrees between flares.[4] This background facial redness develops secondary to vasodilation and fixed vascular changes that develop over time. These fixed changes in superficial cutaneous vasculature do not remit with tetracyclines, metronidazole, azelaic acid etc.[5,6,7] which are more effective in inflammatory stages of rosacea. However, these enlarged superficial cutaneous vessels remain vasoactive to sympathetic nervous system innervation, topical α-adrenergic receptor agonists, namely brimonidine and oxymetazoline, have shown promising results in facial erythema of rosacea.[5,6,7] Oxymetazoline (α1-receptor agonist)[13] and nadolol[14] and propranolol (β-adrenergic receptor antagonist)[15] have been used in isolated cases for the treatment of flushing⁄erythema among patients with rosacea. In subcutaneous tissue, vasoconstriction of the small vessels depends mainly on postsynaptic α2-adrenergic receptor stimulation of vascular smooth muscle.[16] Therefore, topical application of a highly selective α2-adrenergic receptor agonist like BT should be more efficacious than α1-agonist and β-adrenergic antagonists, with fewer systemic safety issues.[16]

BT gel is considered to a safe and tolerable drug. The reported side effects are rebound eythema[17] and contact dermatitis.[18] The side effects were more during the initial phase of treatment and gradually decreased subsequently.[19]

Conclusion

Topical brimonidine tatarate brimonidine is an effective and safe remedy for erythematous rosacea.

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