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Meeta Aggarwal

Philadelphia College of Osteopathic Medicine, meetaag@pcom.edu

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Is Brimonidine Tartrate gel 0.5% effective in reducing facial erythema of Rosacea?

Meeta Aggarwal, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective Evidence Based Medicine (EBM) review is to determine whether or not “Is Brimonidine Tartrate gel 0.5% effective in reducing facial erythema of Rosacea?”

Study Design: Review of two randomized controlled trials (RCT), and one 1-year longitudinal open-label study.

Data Sources: All studies were published in peer-reviewed journals found via the use of PubMed or Medline.

Outcomes Measured: Patients were divided into two groups: those who received the Brimonidine Tartrate gel and those who received the vehicle (placebo) gel. Efficacy of Brimonidine tartrate gel was compared to the efficacy of the vehicle gel. Outcomes were measured at baseline and at various intervals post treatment using Clinician’s Erythema Assessment (CEA) and Patient’s Self-Assessment (PSA) scales. Both scales were designed as tools for evaluation of erythema. In the 1-year open label study, inflammatory lesion counts and telangiectasia were also evaluated to determine the long-term efficacy of the drug. Additionally, in this study, the subjects were asked to complete a questionnaire regarding the impact of rosacea on their social life at various points during the study.

Results: In both RCT, (Fowler – 2011 and Fowler – 2013) results of Brimonidine tartrate gel versus Vehicle gel reached statistical significance and proved to be an effective form of treatment in patients with facial erythema of Rosacea ($p < 0.001$ and $p < .05$ respectively). In the open-label study, the effects measured showed that Brimonidine tartrate gel was more effective than the vehicle gel for long-term treatment of moderate to severe facial erythema of Rosacea even in the presence of other therapies being used for inflammatory lesions caused by rosacea. Also, the study showed a decrease in the number of inflammatory lesions and telangiectasias throughout the study. In addition, this study also showed significant improvement in quality of social life as reported by patients by completing a questionnaire.

Conclusions: Both RCT and one-year open label studies included in this review indicate that Brimonidine Tartrate gel 0.5% is an effective treatment for facial erythema of Rosacea in regards to quality of life and self-confidence due to the appearance.

Keywords: Brimonidine Tartate gel, Rosacea, Facial Erythema

INTRODUCTION

Rosacea is a very common and chronic dermatologic condition. It is characterized by flare-ups and remissions of persistent flushing, redness, irritation as well as visible blood vessels. The areas commonly affected by this condition include forehead, chin, cheeks and nose. It may also involve the ears, scalp or the neck. If left untreated, it may cause small-red bumps filled with pus. In severe cases, nose may become bumpy and swell up due to excess tissue – a condition known as rhinophyma. Since the outbreak of Rosacea can occur at any time unexpectedly, it can cause psychological and social problems in some patients.¹ This paper evaluates two randomized controlled trials (RCTs) and one 1-year open label study, looking at the effectiveness of Brimonidine Tartrate gel 0.5% in reducing facial erythema of rosacea, which allows patients to live a quality of life.

Rosacea affects as many as 16 million people in the United States alone and approximately 45 million people worldwide.² In 2014, there were 1,750,000 visits per year for rosacea and this was due to reasons such as discoloration of the skin, and abnormal pigmentation.³ The disease typically occurs between the ages of 20 and 50. Even though it can occur in both men and women, it is more common among women.⁴ Most people are known to have fair skin and are known to be Caucasian.² There is not an exact estimate of the money spent on treatment of rosacea, however, over \$2.16 billion was spent in 2004 worldwide for acne and rosacea therapeutics.⁵

Rosacea not only impacts the external appearance of the patient, it has an impact on their inner aspect as well. It has a psychosocial impact and may cause embarrassment, anxiety and low self-esteem in some patients.⁴ According to Millikan and co-authors, many patients have to go through troublesome of having to deal with rude comments, stares, and misconceptions due to

effects of rosacea on their appearance.¹ Many patients are afraid to eat the food they used to enjoy the most because of their fear of triggering their flare-up of rosacea.¹

The exact cause of rosacea is still unknown; however, it is thought to be due to reduced ability of the body to diminish inflammation that is caused by environmental factors such as sunburn.² Patients are typically advised to avoid specific triggers such as: emotional factors (stress, fear, anxiety), environmental changes (strong winds, change in humidity), and sun exposure, all of which can exacerbate their symptoms.^{2,4} In addition, it is noted that people with rosacea have excess of *Demodex Folliculorum* – a mite that lives on everyone’s skin which might contribute to the development of rosacea.^{1,2} The skin condition may also occur due to dysfunction in the vasomotor response causing abnormal dilation of blood vessels of the face.⁴

Unfortunately, there is no cure or one standard treatment for rosacea. However, there are many methods available that can control exacerbations of rosacea. There are several types of topical ointments or oral medications that are currently approved for the treatment of papules and pustules caused by rosacea and these treatments may include any of the following: azelaic acid, metronidazole and anti-inflammatory dose of doxycycline. However, currently there is no medication that has been approved to treat erythema that is caused by rosacea.^{4,6} Other treatment therapies that are available for patients with rosacea include: lasers, photodynamic therapy, pulsed-light therapies, and antibacterial washes.² Sodium Sulfacetamide is another topical agent that is known to be effective.² All the treatment methods described above are effective and are dependent on the severity of the symptoms caused by rosacea. The results tend to vary from patient-to-patient and are dependent upon compliance of the patient.¹ Brimonidine Tartrate gel 0.5% may be used as a topical medication for the relief of symptoms of Rosacea.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is Brimonidine Tartrate 0.5% gel is effective in reducing facial erythema of Rosacea?”

METHODS

The investigation looks at two randomized controlled trials (RCTs) and one 1-year open label study. In order to participate in these studies, a specific selection criteria was used. This criteria included the following: men or women 18 or older with a clinical diagnosis of rosacea with moderate to severe erythema. All studies included Brimonidine Tartrate gel 0.5% as the intervention therapy. All studies used vehicle gel (placebo) as a method of comparison. The studies also looked at different doses of Brimonidine Tartrate gel and whether they are effective in treatment for moderate-severe erythema of Rosacea. However, this EBM review focuses on Brimonidine Tartrate gel 0.5% concentration. The main outcome measured was the reduction in facial erythema caused by rosacea. In addition, 1-year open label study and Fowler 2011 study also looked at the effect of Brimonidine Tartrate gel 0.5% to reduce the number of inflammatory lesions and telangiectasias that were caused by rosacea.

All studies were published in English in peer-reviewed journals that were obtained using either PubMed or Medline. The key words used to search the articles included “Brimonidine Tartrate gel”, “Rosacea”, and “Facial Erythema.” All studies were published after the year of 1999 and were selected based on their relevance to the topic and whether or not they included patient oriented evidence that matters (POEMs). Inclusion criteria for the purpose of this paper included two randomized controlled studies and one 1-year open-label longitudinal study. Exclusion criteria included previous cochrane reviews, and systemic reviews submitted by

previous students. Additional inclusion and exclusion criteria for the individual studies are included in table 1. The statistics of this study used to evaluate patient outcomes included p values, RBI, NBI, and NNT. All studies used similar statistics to evaluate the outcomes where p-value is considered statistically significant if it is less than or equal to 0.05. The demographics of the studies are included and outlined in Table 1.

Table 1 – Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Fowler ¹ (2011)	RCT	53 (Study B)	18-63	Men and Women \geq 18 years of age, Moderate to Severe erythema according to both Clinician's Erythema Assessment (CEA) and Patient's Self-Assessment (PSA)	Subjects with 3 or more facial inflammatory lesions of Rosacea.	2 (Study B)	During the first 4 weeks, subjects applied gel once daily in the morning. No medication was applied during the follow-up phase (last 4 weeks).
Fowler ² (2013)	RCT	293 (Study B)	19-78	Men and Women \geq 18 years of age with a clinical diagnosis of Rosacea and moderate to severe erythema according to both CEA and PSA	Patients with 3 or more inflammatory lesions of Rosacea.	10 (Study B)	First 4 weeks (treatment phase), apply a thin film of gel on the entire face. No medication was applied during the last 4 week follow-up phase.

Moore ³ (2014)	Open Label Study	449	19-81	Men and Women ≥ 18 years of age with a clinical diagnosis of Moderate-Severe Rosacea at both the screening visit and baseline visit.	Dx of Raynaud’s syndrome, severe cardiovascular disease, cerebral/coronary insufficiency, scleroderma. Treatment with monoamine oxidase inhibitors, barbiturates or opiates.	170	Thin film of topical Brimonidine Tartrate gel 0.5% once daily in the morning over the entire face for 12 months.
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OUTCOMES MEASURED

The main outcome measured in all the selected studies is the effectiveness of Brimonidine Tartrate gel 0.5% to reduce facial erythema caused by rosacea. In all the articles, participants’ subjective impression of reduction in facial erythema was measured using the Patient’s Self-Assessment Scale (PSA). In addition, Clinician’s erythema Assessment scale (CEA) was also used to determine the impression of the Clinicians’.^{4,6,7} Both scales were designed as tools for evaluation of erythema. A one-grade improvement on both scales represents an effect that is noticeable by both the patient and the investigator and is therefore clinically relevant, see Table 2. The primary endpoint of the study was the profile of success, defined as a two-grade improvement on PSA scale.⁴

Table 2 Clinician’s Erythema Assessment and Patient’s Self-Assessment (Fowler 2011)

Scores	CEA	PSA
0, Clear	Clear skin, 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

In addition to using PSA and CEA scales, both Fowler (2013) and Moore et al., also measured the decrease in the number of inflammatory lesions and telangiectasia throughout the course of use of the medication. They measured Telangiectasia using a 5-point scale ranging from 0 (clear) to 4 (severe). Inflammatory lesion count (sum of papules, pustules, and nodules) were also done throughout the study. Additionally, in Moore et al., a questionnaire was used to see the social impact of rosacea on patients' daily lives. Correspondingly, in Fowler (2013), Investigator's Global Assessment (IGA) scale was also utilized to determine the lesion severity using a 5 point scale ranging from 0 (clear) to 4 (severe).

RESULTS

Fowler (2011) and co-authors, conducted two studies: Study A and Study B. However, this paper will be focusing on Study B. The duration of this study was 8 weeks (4-week treatment phase and a 4-week follow-up phase -no medication was applied during this phase). On days 1, 15 and 29 CEA, PSA and telangiectasis were assessed at 0, 3, 6, 9, and 12 hours. Inflammatory lesion counts and investigator's global assessment (IGA) of the lesions were evaluated at baseline (0 hour on day 1) and at 12 hour on day 29. On day 30, and at weeks 5, 6, and 8 CEA, PSA, telangiectasia, inflammatory lesion counts and IGA were evaluated. Safety was evaluated using adverse events, vital signs and intraocular pressure throughout the study. This EBM review looked at the results of Brimonidine Tartrate gel 0.5% and vehicle gel 3 hours after the application on Day 29 of the experiment. Study B consisted of 53 patients (11 male 42 female) that were 18 years of age or older who were assigned to the group that was given the Brimonidine Tartrate gel 0.5% QD and 55 patients (10 male 45 female) were assigned to the group that was given the vehicle gel QD. Two patients lost to follow-up for the study. At the end of the treatment phase (day 29), significantly greater success was achieved with Brimonidine

Tartrate gel 0.5% once daily vs. vehicle once daily ($p < .001$) (Table 3). The study found that 30% of patients using the Brimonidine Tartrate gel 0.5% had a two-grade improvement in their facial erythema as compared to 4% of patients on day 29 with the use of vehicle gel. The NNT was calculated to be 4 (see Table 3), this positive number indicates that 4 people are needed to treat in order for one person to have a therapeutic response from Brimonidine Tartrate gel 0.5%. The obtained p-value is less than .001 which is significant and precise. No tachyphylaxis, telangiectasias, or inflammatory lesions were observed in this study along with no aggravation of facial erythema during the follow-up phase. The incidence of AEs was similar among all groups and majority of them were dermatological. During the study, there was no shift or changes in vitals or intraocular pressure.

Table 3 Efficacy of Brimonidine Tartrate gel 0.5% in treatment of facial erythema of Rosacea as measured by Fowler 2011

Study	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)	P-value
Fowler (2011)	6.5	.26	4 patients	<.001

Fowler (2013) and co-authors, conducted two studies: Study A and Study B, both were similar in terms of demographics, disposition and baseline characteristics and both involved 4-week treatment phase and a 4-week follow-up phase. The intervention criteria is listed in Table 1. There were 6 visits in each study: screening visit, day 1, 15, and 29 during the treatment phase which assessed CEA and PSA prior to study drug application and 30 minutes, 3, 6, 9 12 hours after application and weeks 6 and 8 during the follow-up phase. Telangiectasias, IGA of the lesion severity and inflammatory lesion counts were also assessed on day 1 before application and at hour 12 on day 29. During the follow-up phase of the study, CEA, PSA telangiectasia, and inflammatory lesion count were assessed at each visit. Safety was measured by monitoring

adverse events, and vital signs throughout the study. This EBM review looked at effect of the treatment on Day 29, 3 hours after application in study B which consisted of 293 participants. 148 participants (43 male and 105 female) were assigned to the Brimonidine Tartrate gel 0.5% group and 145 participants (37 male and 108 female) were assigned to the vehicle gel group. 10 participants were lost to follow-up. In this study, significantly greater result was seen with BT gel 0.5% compared with vehicle gel. 25.4% of patients had an improvement in their facial erythema after using Brimonidine Tartrate gel as compared to 9.2% of patients using the vehicle gel. These patients had a 2-grade improvement in both CEA and PSA. The NNT was calculated to be 7 (see Table 4), this positive number indicates that 7 people are needed to treat in order for one person to have a therapeutic response from Brimonidine Tartrate gel 0.5%. The obtained p-value of less than .05 is precise and relatively significant. In both studies, the adverse effects were mild in intensity and consisted of: worsening of erythema or flushing, and pruritus. No abnormal vitals, tachyphylaxis were noted and there was no aggravation seen in severity of telangiectasia or inflammatory lesion counts.

Table 4 Efficacy of Brimonidine Tartrate gel 0.5% in treatment of facial erythema of rosacea as measured by Fowler 2013

Study	Control Event Rate (CER)	Experiment Event Rate (EER)	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)	P-value
Fowler (2013)	9.2% = .092	25.4% = .254	1.76	16.2	7 patients	<.05

Moore and co-authors conducted a study that was carried out in 27 centers across United States. The inclusion criteria, exclusion criteria and intervention directions are listed in table 1. Additionally, there was no restriction seen in terms of number of inflammatory lesions on a participant’s face. The study contained 8 total visits: screening, day 1, week 1, and month 1, 3, 6,

9 and 12. Safety was measured at screening, month 1, 6 and 12 by checking vitals, adverse events, physical exams, laboratory tests and intra-ocular pressure. Telangiectasia, inflammatory lesion count and CEA and PSA were measured prior to study drug application and 3 hours after application of the drug. Subjects were also required to complete a questionnaire at baseline, month 3, 6, 9, and 12. 449 patients took part in this study (113 male and 336 female), however, 279 patients resulted in normal completion time whereas 170 people discontinued from the study due to adverse events, subject request, protocol violation, pregnancy, etc. This means that only 74.6% of patients had completed the study for at least 6 months so there was a dropout rate of 25.4% and only 62.1% had completed the study for up to 12 months and there was a dropout rate of 37.9%. The treatment effect that was measured in this study was mean change from baseline. According to the results, the mean change from baseline after 1 month period and 0 hours was .5 (large value), mean change from baseline after 1 month period and 3 hours was .2 (small value) and mean change from baseline in inflammatory lesion count and telangiectasia was .8 (large value). Over the course of the study, the mean PSA score at hour 0 (prior to daily application of BT gel 0.5%) reduced gradually from 3.1 on day 1 to 2.6 by the end of the 1st month and decreased further until the 3rd month and remained stable until month 12. One day 1, after the first application of topical BT gel 0.5%, the mean PSA decreased from 3.1 at hour 0 to 2.1 at hour 3. By end of first month, the result of application of Brimonidine tartrate gel after 3 hours went down to 1.9 from the mean baseline score of 2.1 at day 1. This improvement in erythema of rosacea as evaluated by patients themselves was also observed at each study visit, and maintained until the end of study at month 12. Also, the percentage of subjects who considered that their rosacea inhibited their social life decreased from 29.5% at baseline to 14.2% at month 3, and varied little until the end of the study as measured by the questionnaire that the patients

were required to fill-out. Overall, this study shows that Brimonidine Tartrate gel 0.5% is an effective method to reduce facial erythema of rosacea.

DISCUSSION

Rosacea is a very common skin disorder that affects both men and women worldwide. It comes with persistent flushing and anxiety with low self-esteem in many patients.⁷ Although, there are many treatments out there for the treatment of papules, pustules or telangiectasias, there is no FDA approved medication for the treatment of erythema of rosacea which is a major complain by many patients.⁷

Brimonidine Tartrate gel 0.5% is a selective alpha-2 adrenergic receptor agonists which has a potent vasoconstrictive activity.⁷ Rosacea deals with vasodilation of the blood vessels, brimonidine tartrate gel 0.5% works to counteract that effect and causes cutaneous vasoconstriction.⁸ Currently, FDA approved Brimonidine (Mirvaso) 0.33% is available for the treatment of persistent facial erythema of rosacea. The cost of this drug is \$431.94 for 0.30g tube, and it is not available in a generic form.⁹ However, with the availability of cost reduction cards, many patients may be eligible to pay \$50 or \$80 depending on their insurance.¹⁰ This medication is not indicated for inflammatory lesions such as pustules or papules of rosacea. It is to be used with caution in patients who may have chronic illnesses such as: severe heart disease, Raynaud phenomenon, orthostatic hypotension, scleroderma and sjogren's syndrome. It is unknown whether this drug is safe in pregnancy, in animal studies, it had been shown to be excreted in breast milk.¹¹

In conclusion, Brimonidine is FDA approved for the treatment of open angle glaucoma.⁹ The first line medical therapy for open angle glaucoma involves many agents such as beta-

blockers, sympathomimetics, carbonic anhydrase inhibitors and prostaglandins. Currently, the alpha 2-agonists, clonidine and now brimonidine have been proven to be powerful inhibitors of aqueous humor production in order to lower the intraocular pressure (IOP).¹² According to Wilensky, Brimonidine is becoming a first-line therapy for primary open-angle glaucoma and has the capacity of lowering IOP as comparable to timolol but without the adverse cardiopulmonary side effects that is caused by timolol.¹²

CONCLUSION

Brimonidine Tartrate gel 0.5% does appear to reduce facial erythema caused by rosacea. It has a faster onset when compared to vehicle gel without evidence of rebound, tachyphylaxis or aggravation of other common clinical signs of rosacea with very limited adverse effects and is considered safe and well-tolerated.^{4,6,7} When combined with one of the other therapies: azelaic acid, metronidazole and oral antibiotic that are used for other clinical signs of rosacea, it can provide most effective treatment for rosacea.⁴

Further research studies may be necessary to evaluate long-term efficacy of this drug. Even though the current studies demonstrated that the long-term side effects of this drug are limited,^{4,6,7} supplementary studies are needed to determine the long-term data profile. In further studies, the inclusion criteria should include patients that have more than 3 inflammatory lesions. Further studies are needed to aim for insurance approval of this drug. Even though there are sliding scales available that help lower the cost of the medication, it can still be unaffordable by some patients. The use of Brimonidine tartrate gel 0.5% to reduce facial erythema of rosacea will likely to be further explored in the future.

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