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Role of Topical Brimonidine in The Treatment of Dermatological Diseases: Review Article

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ABSTRACT

Background: Topical Brimonidine is approved by FDA for the treatment of rosacea-associated erythema. It has anti-inflammatory action, in additional to its vasoconstrictive activity, it preventes leucocyte recruitment via inhibition of transendothelial cells migration. Briominidine has been studied for many indications rather than rosacea with positive results. **Objective:** Review of the literature on the effectiveness of topical brimonidine in the treatment of various dermatological diseases.

Methods: A comprehensive search was conducted in PubMed, Google Scholar, and Science Direct for information on Topical Brimonidine dermatological diseases. However, only the most current or comprehensive study from May 2011 to November 2022 was considered. The authors also assessed references from pertinent literature. Documents in languages other than English have been disregarded since there are not enough resources for translation. Unpublished manuscripts, oral presentations, conference abstracts, and dissertations were examples of papers that were not considered to be serious scientific research.

Results: Mild, temporary skin-related adverse effects have been reported with 0.33 percent brimonidine topical gel. Maximum erythema reduction may occur 3–6 hours after application, while some patients report seeing results as early as 30 minutes. **Conclusion**: Combination therapy with brimonidine gel and other treatments for face papules and pustules is safe and does not enhance the risk of adverse outcomes.

Keywords: Topical Brimonidine, Seborrehic Dermatitis, Combined Therapy.

INTRODUCTION

Rosacea is a chronic skin disorder that causes redness, dilated blood vessels, papules, pustules, phymatous changes, and sometimes even eye involvement. Common signs and symptoms are divided into four categories by the National Rosacea Society (NRS) Expert Committee in 2002: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous (PHY), and ocular **(1).**

Rosacea causes face redness in more than 40 million people throughout the world. The NRS estimates that 16 million American adults have rosacea symptoms at some point in their lives. It is believed that the incidence of rosacea is on the rise in the United States, but this may be due to the country's ageing population **(1).**

Facial erythema, papules, and pustules are just some of the symptoms that can appear at the same time, making rosacea treatment more complicated. The best results for a patient with several rosacea symptoms can be achieved with a multimodal approach **(2).**

In order to decrease vasodilation and edema, brimonidine, a highly selective alpha 2 agonist, binds to alpha 2 receptors on the vasculature and induces direct vasoconstriction of both small arteries and veins. With this review, we hope to sum up the research on brimonidine topical gel for the treatment of rosacea-related facial erythema in terms of its safety, effectiveness, and patient acceptability **(3)**.

Clinical investigations with brimonidine tartrate (BT) found it to be effective and safe for the treatment of facial erythema associated with rosacea for up to 1 year, with a rapid onset. Three percent to seven percent of participants in the two pivotal studies lasting one month and up to nine point one percent of participants in the long-term safety study lasting one year reported an increase in the severity of their erythema and/or flushing **(3).**

Rosacea patients with moderate to severe erythema had an optimal dosing regimen of brimonidine that was identified after two randomized, double-blind, vehicle-controlled investigations were conducted. The effectiveness of three different topical brimonidine gel doses was studied. For 12 hours, brimonidine was able to significantly reduce the redness. At 0.5% concentration, researchers saw the most benefit; it was also well tolerated **(4).**

The FDA has approved BT for topical use in the treatment of erythema associated with rosacea **(5).**

The objective of the current study was to review the effectiveness of topical brimonidine in the treatment of various dermatological diseases.

A comprehensive search was conducted in PubMed, Google Scholar, and Science Direct for information on Topical Brimonidine dermatological diseases. However, only the most current or comprehensive study from May 2011 to November 2022 was considered. The authors also assessed references from pertinent literature. Documents in languages other than English have been disregarded since there are not enough resources for translation. Unpublished manuscripts, oral presentations, conference abstracts, and dissertations were examples of papers that were not considered to be serious scientific research.

Mechanism of action of Brimonidine:

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Brimonidine has been prescribed for the treatment of glaucoma and ocular hypertension since it was given the green light by the FDA in 1996. Direct vasoconstriction of tiny arteries and veins is induced by the highly selective alpha 2-agonist brimonidine, which decreases vasodilation and edema by binding to alpha 2 receptors of the blood vessels [(6)].

It has anti-inflammatory action, in additional to its vasoconstrictive activity, it prevents leucocyte recruitment via inhibition of transendothelial cells migration. Endothelial cells that mediate cell arrest, adhesion, and subsequent transendothelial migration are less likely to express VCAM-1 after being treated with brimonidine. It also reduces integrin Macrophage 1 Ag (Mac-1), which included in neutrophils rolling [(7)].

Moreover, regarding mechanism of action of brimonidine, **Choi *et al.*** [(8)] demonstrate that brimonidine has dual action mechanisms in inhibition of Propionibacterium acne-induced inflammatory reaction; besides being able to narrow blood vessels, it also has anti-inflammatory effects. Briminidine strongly reduces P. acnes-induced cytokine expression, including IL-1β, IL-6, and IL-8 in THP-1 cells and IL-1β, IL-6 in keratinocytes, via its influence on messenger RNA level of pro-inflammatory cytokines [(8)].

Further, it is well established that a2 receptor agonists reduce cyclic adenosine monophosphate by inhibiting adenylate cyclase activity (cAMP). cAMP stimulates protein kinase A, which in turn increases NF-kappaB (nuclear factor kappa-light-chain-enhancer of activated B cells) activity. Therefore, brimonidine may ameliorate the progression of inflammatory skin conditions like acne by decreasing cAMP and thereby suppressing NF-κB signalling in immune cells and keratinocytes [(8)].

Mast cells (MCs), which play a key role in the pathogenesis of rosacea, have been studied in animals to gain insight into the therapeutic action of brimonidine in rosacea and other inflammatory dermatoses. Results showed that the number of MCs and mRNA levels of MC proteases: tryptase and chymase were reduced by brimonidine gel in rosacea-like mouse skin [(9)].

Brimonidine in its most common indication (rosacea):

Though reducing rosacea-related redness is challenging, topical 0.33 percent brimonidine gel has been shown to be an effective therapeutic alternative to the standard treatment plan. Erythema can be managed both temporarily and permanently with brimonidine tartrate. Daily treatment leads in lowered baseline erythema for long-term management; however, as-needed use may be helpful for patients seeking short-term erythema control for specific situations [(6)]. Brimonidine gel 0.33 percent has been demonstrated to be an effective and safe treatment for chronic facial erythema associated with rosacea when applied once daily [(10)].

When using brimonidine gel, a pea-sized amount should be applied in a thin layer once daily to the centre of the forehead, the chin, the nose, and each cheek, while keeping the gel out of your eyes and lips. The brimonidine tartrate in this gel comes to 5 milligrammes per gramme, or around 3.3 milligrams of the free base [(11)].

Trials of Brimonidine use in variable indications throughout the literature:

Briominidine has been studied for many indications rather than rosacea with positive results. Through a therapeutic trial, **Del Barrio-Díaz *et al.*** [(12)] stated that the use of brimonidine gel for the treatment of facial erythema in three patients with dermatomyositis (DM), pityriasis rubra pilaris (PRP), and systemic lupus erythematosus (SLE) who had not responded to other treatments was described, and the patients' condition improved significantly and remained stable for 6 months.

In addition, folliculitis, contact dermatitis, rhinophyma, and seborrheic dermatitis are all inflammatory disorders, wherein 4 patients continued to have erythema from their skin problems despite receiving standard medical care. After one week of using a brimonidine gel applied to the face once a day as prescribed, all patients reported significantly less facial erythema [(13)].

In addition, the use of topical brimonidine tartrate for the treatment of post-acne erythema has been shown to be both effective and safe. It has minimal incidence and moderate negative effects. The most noted side effect was the pallor as well as contact dermatitis, and burning sensation [(14)].

BT gel is clearly beneficial in reducing post laser erythema. It is recommended to cautiously apply a thin layer of BT gel as well as other alpha-agonists immediately after lasers and IPL sessions, as there have been case reports of topical BT 0.33 percent gel application just after laser sessions for three patients who underwent an IPL session, 1,927-nm thulium fibre laser, and fractional CO2 laser, with results of a significant reduction in erythema within 30 minutes [(15)].

However, because of the possibility of systemic toxicity, topical brimonidine should be avoided after ablative laser procedures, which damage the skin barrier and significantly increase BT absorption and facilitate cutaneous drug absorption, as happened in one of the trial patients. This would have resulted in a significantly higher amount of absorbed BT, causing central nervous system depression with symptoms including lethargy, apnea, and hypotension [(15)].

Except for mild, transient contact dermatitis, there was no evidence of systemic toxicity or drug-related side effects. Additionally, brimonidine over-absorption is a possibility with ablative device

treatments. So, when brimonidine is used before an ablative laser therapy, the total amount used should be lowered and it should be wiped off right before the laser process to minimize systemic toxicity [16].

Moreover, another study found that topical brimonidine reduced IPL-induced erythema and post-intervention pain with significant improvement in patient satisfaction. In light of this, its potential utility following IPL therapy for facial telangiectasias should not be discounted. Extant research also demonstrates that brimonidine decreases vascular endothelial growth factor concentration, suggesting that prolonged use of brimonidine following IPL may help to keep telangiectasia at distance [17].

An anesthetic cream with brimonidine as an adjuvant ingredient could make harsh laser treatment more bearable [16].

In the scope of laser approaches, the topical application of brimonidine has been shown to be effective in reduction of treatment-related complications such as erythema and postinflammatory hyperpigmentation (PIH) [15].

When compared to the effects of sunscreens and light-blocking silver plaster, topical briominidine proved to be more effective in reducing the post-treatment erythema of daylight photodynamic therapy (DL-PDT). Therefore, BT may help make intolerable substances more bearable. As a result, BT has the potential to be a useful method for shortening the recovery period associated with other dermatological therapies, including as chemical peels and laser procedures, for which post-treatment erythema is a major drawback [18].

Due to its vascular nature, pyogenic granuloma may be an indication for topical brimonidine .In one study after paronychia surgery, brimonidine was applied twice daily for 15 days, which is a shorter course than that of other regimens, with significant improvement of pyogenic granuloma. So it`s a good noninvasive option especially recurrence may occur after invasive semi-invasive treatments [19]. Haemangioma is another vascular lesion which may be indicated for brimonidine [20].

Research has established the protective effect of topically applied brimonidine, showing that when applied prior to UVR exposure; it did not hasten photocarcinogenesis or induce dermal carcinogenicity in hairless mice. Therefore, it was not obvious if brimonidine may be functioning as a sunscreen. There has been no research on what causes photocarcinogenesis to be slowed. However, it might be because of repression of DNA damage, oxidative stress, inflammation, immunosuppression, and atypical signal transmission [21].

Adverse effects of topical brimonidine use:

Because of the potential for potentiation of vascular insufficiency, individuals with depression, orthostatic hypotension, Raynaud's phenomenon, thromboangitis obliterans, scleroderma, or Sjögren's syndrome should use topical brimonidine tartrate gel with caution [11].

Due to its adrenergic effect on tone of the blood vessels, which may alter blood pressure, brimonidine is theoretically associated with more serious adverse effects, such as cardiovascular events, especially in patients with co-morbid cardiovascular conditions such as hypertension, orthostatic hypotension, or heart disease, cerebral or coronary artery insufficiency. Patients with narrow-angle glaucoma may also be at an elevated risk for angle closure glaucoma [22].

Literature reports that side effects from using brimonidine gel are uncommon, and when they do occur, they tend to be minor, skin-related, and temporary. Paradoxical erythema and increased recurrence of erythema are two such symptoms, along with flushing, skin irritation, pruritus, a burning feeling of the skin, and a worsening of papules and pustules of rosacea [11]. Additionally, 0.33 percent brimonidine tartrate gel has the potential to cause allergic contact dermatitis in certain people [23].

Concerning paradoxical erythema, some physiologic mechanisms are assumed to contribute to worsening erythema most likely, they include [23]:

- Enhanced pharmacological impact to release mediators and generate persistent vasodilation is caused by local inflammation with perivascular inflammatory cells, which enhances or changes brimonidine- adrenegic receptors (ARs).
- Brimonidine was absorbed at a high concentration through the skin because of a breakdown in the skin's protective barrier. However, brimonidine at greater doses can cause vasodilation by penetrating to the apical receptors (AR) of endothelium and nerve terminals.
- Norepinephrine (NE) release from sympathetic nerve terminals may be blocked by brimonidine's interaction with a2-ARs, leading to a decrease in NE availability and, consequently, a widening of blood vessels.

Precautions of Brimonidine use:

Clinicians should stress the need of instructing patients to apply only a thin coating of medication at first, in addition to other techniques that help maximize brimonidine therapy, such as the use of moisturizers to promote skin barrier function [24].

Repetition of topical BT gel use does not result in a buildup of brimonidine in the system. Treatment of facial erythema was successful with little systemic side effects after applying BT gel directly to the affected area. This was likely due to the drug's high local bioavailability inside the facial skin and its low systemic absorption [25].

CONCLUSIO N

Mild, temporary skin-related adverse effects have been reported with 0.33 percent brimonidine topical

gel. Maximum erythema reduction may occur 3–6 hours after application, while some patients report seeing results as early as 30 minutes. Combination therapy with brimonidine gel and other treatments for face papules and pustules is safe and does not enhance the risk of adverse outcomes.

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