Original Article

Comparison of Tacrolimus versus Bimatoprost in Patients with Vitiligo: A Randomised Controlled Trial

Dr. Archana Kumari[1], Dr. Arun Kumar[2]*, Dr. Murli Manohar[3], Dr. S.M. Inamul Haque[3], Dr. (Prof.) Asha Singh[4]

1. Junior Resident, 1st Year PG Student, Department of Pharmacology, NMC, Patna, Bihar, India.
2. Senior Resident/Tutor, Department of Pharmacology, NMC, Patna, Bihar, India.
3. Associate Professor, Department of Pharmacology, NMC, Patna, Bihar, India.
4. Professor & HOD, Department of Pharmacology, NMC, Patna, Bihar, India.

***Corresponding author's E-mail:** ARUNAKASH71@gmail.com

Received: 06-07-2024; **Revised:** 23-09-2024; **Accepted:** 05-10-2024; **Published on:** 15-10-2024.

ABSTRACT

Background: While not constituting a life-threatening ailment, vitiligo can greatly affect one's quality of life, particularly if it manifests on the face or hands. Feelings of shame can lead to diminished self-esteem. The predominant adverse effects of "topical calcineurin inhibitors, like tacrolimus," are cutaneous burning, pruritus, and redness. Hence, it is imperative to develop novel, more effective, and safer therapies. This study aimed "to compare the efficacy and safety of bimatoprost 0.03% solution and tacrolimus 0.1% ointment in repigmentation of localized vitiligo."

Methods: 25 patients in Group I (Bimatoprost) received bimatoprost 0.03 % solution twice daily and 25 patients in Group II (Tacrolimus) received Tacrolimus 0.1% ointment twice daily for 3 months. Comparisons of continuous data such as VSA, age, and disease duration were performed using unpaired t-tests. Other outcome measures and baseline parameters such as repigmentation grade were expressed as percentages and ratios and compared using chi-square test.

Results: Most of patients in Group I (Bimatoprost) and Group II (Tacrolimus) achieved grade I-II pigmentation at 3 months of pharmacotherapy. There were 2 cases with 76-100% pigmentation in Bimatoprost group as compared to Tacrolimus group. There was significantly less area with vitiligo in bimatoprost group (3.91 ± 0.69) as compared to tacrolimus group (4.08 ± 0.57) at three months of pharmacotherapy (p=0.03). There was higher incidence of skin infection in Group II (Tacrolimus). Also, incidence of pruritus, dryness and burning sensation was higher in Group II (Tacrolimus).

Conclusion: Bimatoprost is a viable alternative for treating vitiligo in cases when traditional steroid-sparing medications are unavailable.

Keywords: Bimatoprost, Tacrolimus, Vertigo, Repigmentation, Vitiligo surface area.

INTRODUCTION

Vitiligo is a common acquired pigment condition characterised by small areas of skin depigmentation shown as white patches. The phenomenon is attributed to the degeneration of "melanocytes" in specific regions. Vitiligo affects near "0.5-1%" of the worldwide population.[1] Vitiligo affects individuals of every ethnic group, as there does not exist disparity in the occurrence of the condition between males and females. While vitiligo might appear at any stage of life, females tend to experience its onset at younger ages, with nearly fifty percent of females experiencing symptoms prior to "the age of 20." [2]

The cause of vitiligo is complicated, including "genetic and environmental factors" playing significant roles in its onset. A variety of ideas have already been suggested, encompassing "autoimmunity, melanocytorrhagy, oxidative stress, neurological processes, and somatic mosaicism." [3] While not constituting a life-threatening ailment, vitiligo can greatly affect one's quality of life, particularly if it manifests on the face or hands. Feelings of shame can lead to diminished self-esteem. As much as one-third of vitiligo patients experience reportable symptoms of depression or generalized health issues. [4] Effective management of vitiligo continues to be a highly complex dermatological issue. First and foremost, it is crucial to acknowledge that vitiligo has become not only a cosmetic condition and that there are reliable and efficient therapies available for the condition. The selection of therapy is contingent upon the specific form of vitiligo as well as the severity of the condition.

The predominant adverse effects of "topical calcineurin inhibitors, like tacrolimus," are cutaneous burning, pruritus, and redness. Adverse effects such as "warts, paresthesia, and contact dermatitis" are infrequently documented. [5]

Hence, it is imperative to develop novel, more effective, and safer therapies. At now, bimatoprost has shown efficacy in multiple "observational studies" and a few pilot trials. [6]

"A synthetic prostaglandin F2α analogue" has been released as "Bimatoprost ophthalmic solution." Topical application of bimatoprost in eye drops is employed to contain the advancement of "open-angle glaucoma", while in dermatology it is used to address eyebrow hypotrichosis. Nevertheless, there have been reports of

eyelid pigmentation as an adverse reaction. [7-10] Empirical evidence has demonstrated that Bimatoprost solution effectively addresses eyelash hypotrichosis by promoting growth, as well as enhancing length, thickness, and blackness. [11] Remarkably, patients receiving "prostaglandin analogues for glaucoma" exhibited adverse effects such as increased pigmentation of the eyelids and hirsutism. Furthermore, it has expanded the range of applications for several dermatological disorders, including alopecia, which mainly impacts "the eyelashes and eyebrows, and vitiligo." [12,13] Prior studies have established that topical bimatoprost is effective in treating facial vitiligo. [14]

Prior research exhibited intrinsic constraints and disadvantages, such as insufficient control measures, limited sample size, inadequate statistical power, and incapacity to make generalizations.

This study aimed "to compare the efficacy and safety of bimatoprost 0.03% solution and tacrolimus 0.1% ointment in repigmentation of localized vitiligo."

MATERIALS AND METHODS

This was “a randomised controlled trial with parallel 1:1 allocation” conducted on patients with vitiligo visiting out-patient Department of skin and venereal diseases (VD), NMCH, Patna from January 2024 to June 2024. The study was started after takin “written informed consent” from study participants under guidelines of “Good Clinical Practice” and “Declaration of Helsinki.”

Sample Size: Consecutive sampling was done to enrol 50 patients with vitiligo. The enrolled patients were randomised to Group I (Bimatoprost) and Group II (Tacrolimus) with 25 patients in each group.

Inclusion Criteria:

- Patients diagnosed with stable vitiligo noticing either no progression of existing lesions or the emergence of new lesions within the last 6 months.
- The size of the lesion limited to less than one percent of the total body surface area.
- Patient having not more than five patches.
- Participants undergoing other therapies for vitiligo become eligible for inclusion following a washout phase of 4 week.

Exclusion Criteria

- Patients with lesions that exceed one percent of the total body surface area
- Lesion count is 6 or greater.
- Current active infections
- Hypersensitivity to Bimatoprost / Tacrolimus
- Pregnant and Lactating Women

Intervention: Group I (Bimatoprost) received bimatoprost 0.03 % solution twice daily and Group II (Tacrolimus) received Tacrolimus 0.1% ointment twice daily for 3 months.

Primary End Point: The repigmentation grade classified based on following criteria: [15]

0	No Change (GO)
0-25%	Mild Improvement (G1)
26-50%	Moderate Improvement (G2)
51-75%	Good Improvement (G3)
76-100%	Excellent Improvement (G4)

Secondary End points:

Vitiligo Surface Area (VSA): VSA was calculated using transparent graph paper. The VSA of an irregular disease surface was calculated from the formula: “A= C+ ½ P” [16]

Where,

- “A = Area in sq.cm
- C= Number of squares with complete involvement
- P= Number of squares with partial involvement”

Incidence of adverse events

Patients were assessed at baseline, 1 month, 3 months (end of therapy) and 6 months to detect any recurrences.

Statistical Analysis

Statistical analysis was done using Microsoft Excel 2010 and Graph Pad 8.4.3 software. The data obtained were presented in tabular form and calculations of percentages, means, and standard deviations (SD) of the parameters were performed. Comparisons of continuous data such as VSA, age, and disease duration were performed using unpaired t-tests. Other outcome measures and baseline parameters such as repigmentation grade were expressed as percentages and ratios and compared using chi-square test. A P-value less than 0.05 was taken as a measure of significance.

RESULTS

Most of the patients were females of age group 25-45 years with facial vitiligo as most common location. There was no significant deference between between Group I (Bimatoprost) and Group II (Tacrolimus) with respect to age, gender, duration and site of vitiligo.

Table 1: Comparison of Baseline Demographic and Clinical Characteristics between Group I (Bimatoprost) and Group II (Tacrolimus)

Parameters	Group I (Bimatoprost) N = 25	Group II (Tacrolimus) N = 25	P-Value
Age in Years (Mean ± SD)	35.34 ± 12.62	37.28 ± 11.79	0.58*
Gender (n)			0.57**
Male	10	12	
Female	15	13	
Duration of Vitiligo in Years (Mean ± SD)	5.03 ± 1.98	5.11 ± 2.06	0.89*
Site of Vitiligo			0.98**
Facial	10	9	
Acro-Facial	3	4	
Acral	7	6	
Chest or Back	2	2	
Abdomen	3	4	

*Unpaired t test **Chi-Square Test

Table 2: Comparison of Re-pigmentation Grade at 3 Month of Therapy between Group I (Bimatoprost) and Group II (Tacrolimus)

Parameters	Number of Patients (%)		P-Value (Chi-Square Test)
	Group I (Bimatoprost) N = 25	Group II (Tacrolimus) N = 25	
0 (0%)	6	10	0.36
1 (1% - 25%)	9	5	
2 (26% - 30%)	5	6	
3 (51% - 75%)	3	4	
4 (76% - 100%)	2	0	

Most of patients in Group I (Bimatoprost) and Group II (Tacrolimus) achieved grade I-II pigmentation at 3 months of pharmacotherapy. There were 2 cases with 76-100% pigmentation in Bimatoprost group as compared to Tacrolimus group.

Table 3: Comparison of VSA between Group I (Bimatoprost) and Group II (Tacrolimus)

Parameters	VSA in cm^2 (Mean ± SD)		P-Value (Unpaired t test)
	Group I (Bimatoprost) N = 25	Group II (Tacrolimus) N = 25	
0 Month	5.22 ± 1.78	5.09 ± 1.59	0.79
1 Month	4.61 ± 0.73	4.49 ± 0.55	0.51
3 Months	3.91 ± 0.69	4.07 ± 0.62	0.03
6 Months	3.89 ± 0.94	4.08 ± 0.57	0.03

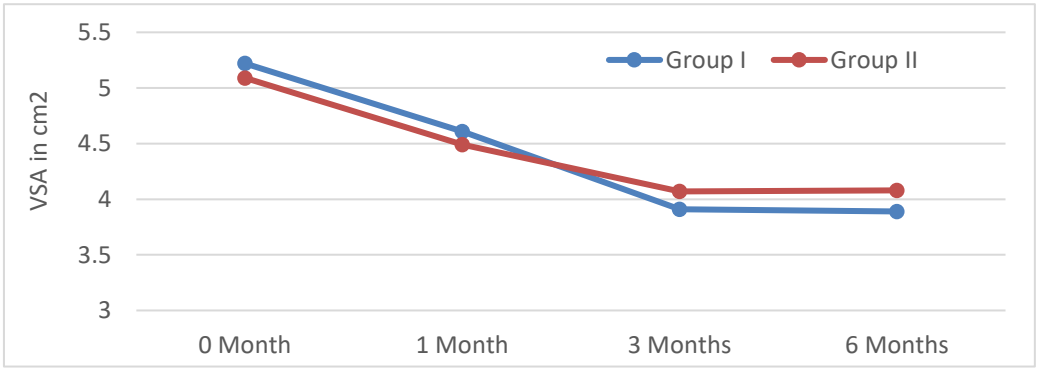

Figure 1: Comparison of VSA between Two Groups

There was significantly less area with vitiligo in bimatoprost group (3.91 ± 0.69) as compared to tacrolimus group (4.08 ± 0.57) at three months of pharmacotherapy (p=0.03).

Table 4: Comparison of Adverse Events between Group I (Bimatoprost) and Group II (Tacrolimus)

Parameters	Number of Patients (%)	
	Group I (Bimatoprost) N = 25	Group II (Tacrolimus) N = 25
Hypertrichosis	3 (12.00)	0
Pruritus	3 (12.00)	5 (20.00)
Dryness	3 (12.00)	4 (16.00)
Burning Sensation	2 (8.00)	3 (12.00)
Erythema	2 (8.00)	4 (16.00)
Bacterial Folliculitis	0	4 (16.00)
Dermatophytosis	0	3 (12.00)

3 cases of hypertrichosis were reported from patients in Group I (Bimatoprost). There was higher incidence of skin infection in Group II (Tacrolimus). Also, incidence of pruritus, dryness and burning sensation was higher in Group II (Tacrolimus).

DISCUSSION

In this RCT, Bimatoprost shown comparable effectiveness to Tacrolimus in terms of repigmentation grade following 3 months of treatment, while also achieving a superior decrease in VSA.

Bimatoprost had been previously utilized for the treatment of vitiligo, particularly in two research investigations where significant "repigmentation of periocular vitiligo" was observed. [18, 19]

Prostaglandins (PGs) are bifunctional lipid molecules produced by different cell types in response to certain physiological events including inflammatory processes, blood vessel development, as well as exposure to ultraviolet radiation. "Keratinocytes in human skin" are the primary producers of prostaglandins, particularly PGE2 and PGF2α.

Prior investigations have demonstrated that each of PGE2 as well as PGF2α induce the formation of "dendrites in human melanocytes." Additionally, PGF2α stimulates the activity as well as expression of tyrosinase, which is the enzyme responsible for restricting the production of melanin. [20, 21] Hence, the application of topical PG analogues might lead to skin hyperpigmentation.

The study of Anbar et al. investigated the impact of 3 topical PGF2α analogues, specifically latanoprost, bimatoprost, as well as travoprost, in skin pigmentation of guinea pigs. The findings demonstrated that the PGF2a analogue increased pigmentation in all regions, and this effect was amplified when utilized in conjunction with ultraviolet (UV)B rays. [22]

Commercially available prostaglandin analogue includes latanoprost as well as bimatoprost. Bimatoprost is a synthetic counterpart of PGF2α. It is utilized as "an ophthalmic solution to treat glaucoma," elevated IOP, as well as eyelashes hypotrichosis. Consistent with alternative synthetic PGF2α analogues, bimatoprost is associated with the unwanted side effect of "periocular skin hyperpigmentation." [27-30]

Kapoor et al. documented histological alterations observed in skin biopsy specimens from two patients diagnosed with periocular hyperpigmentation. Significant augmentation of melanin granules was observed in the epidermis along with a lesser degree in the dermis. The tumors primarily metastasize to "the basal keratinocytes and melanocytes" located in the superficial as well as deep dermis. Increased melanogenesis has been suggested as the underlying cause of "bimatoprost-induced periocular hyperpigmentation."[23]

A majority of patients in both groups attained grade 1-2 repigmentation. A retrospective clinical investigation conducted by Grim et al. Executed on non-facial vitiligo using a "0.03% bimatoprost solution," no one of the participants achieved repigmentation over 50%.18 A separate investigation conducted by Jha et al. examined the effectiveness of a "0.03% bimatoprost" regimen in the treatment of persistent vitiligo patches in the face. The findings from his study, as well as another study, provide evidence in favor of the idea that management of facial lesions has the most favorable outcome.[14, 24]

The results of a RCT demonstrated that bimatoprost 0.03% resulted in superior repigmentation compared to mometasone alone. [25] A separate study determined that the combination of latanoprost with NB-UVB can cause repigmentation in affected areas that have proven resistant to therapy. [26]

The research carried out by Seema S et al. found that the combo side offered superior responses compared to NB-UVB alone during the entire investigation period. A statistically significant mean declines in BSA were observed among the two groups after 1-6 months of pharmacotherapy. [27]

There was higher incidence of skin infection in Group II (Tacrolimus). Also, incidence of pruritus, dryness and burning sensation was higher in Group II (Tacrolimus).

Moreover, the intraocular pressure remained unchanged following the topical administration of bimatoprost in the periocular region, which aligns with the findings of prior investigations, thereby emphasizing the advantageous safety characteristics of bimatoprost solution within the ocular region. [28]

CONCLUSION

In terms of repigmentation grade after 3 months of treatment, bimatoprost was equally effective as tacrolimus. In both groups, the repigmentation achieved was consistent even after stopping the pharmaceutical treatment.

Following a 3-month course of bimatoprost and tacrolimus, there was a notable reduction in the size of the vitiligo area, with better outcomes in Bimatoprost group. The safety of bimatoprost was evaluated to be superior to that of tacrolimus. Bimatoprost is a viable alternative for treating vitiligo in cases when traditional steroid-sparing medications are unavailable. While it appears to be a potential treatment choice for isolated vitiligo lesions, rigorous large-scale researches are necessary to enhance the data supporting its reasonable use.

Acknowledgement: We are thankful to the healthcare workers of NMCH, Patna, India.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Taieb A, Picardo M, Members V. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment Cell Res. 2007;20(1):27-35.
2. Kyriakis KP, Palamaras I, Tsele E, Michailides C, Terzoudi S. Case detection rates of vitiligo by gender and age. Int J Dermatol. 2009;48(3):328-329.
3. Speeckaert R, van Geel N. Vitiligo: an update on pathophysiology and treatment options. Am J Clin Dermatol. 2017;18(6):733-744.
4. Lai YC, Yew YW, Kennedy C, Schwartz RA. Vitiligo and depression: a systematic review and meta-analysis of observational studies. Br J Dermatol. 2017;177(3):708-718.
5. Kanwar AJ, Dogra S, Parsad D. Topical tacrolimus for treatment of childhood vitiligo in Asians. Clin Exp Dermatol. 2004;29(6):589-592. doi: 10.1111/j.1365-2230.2004.01632.x
6. Kubelis-López DE, Zapata-Salazar NA, Said-Fernández SL, Sánchez-Domínguez CN, Salinas-Santander MA, Martínez-Rodríguez HG, Vázquez-Martínez OT, Wollina U, Lotti T, Ocampo-Candiani J. Updates and new medical treatments for vitiligo (Review). Exp Ther Med. 2021 Aug;22(2):797. doi: 10.3892/etm.2021.10229. Epub 2021 May 25. PMID: 34093753; PMCID: PMC8170669.
7. Wand M, Ritch R, Isbey EK Jr, Zimmerman TJ. Latanoprost and periocular skin color changes. Arch Ophthalmol. 2001;119(4):614-615.
8. Priluck JC, Fu S. Latisse-induced periocular skin hyperpigmentation. Arch Ophthalmol. 2010;128(6):792-793.
9. Doshi M, Edward DP, Osmanovic S. Clinical course of bimatoprost-induced periocular skin changes in Caucasians. Ophthalmology.2006;113(11):1961-1967.
10. Galloway GD, Eke T, Broadway DC. Periocular cutaneous pigmentary changes associated with bimatoprost use. Arch Ophthalmol.2005;123(11):1609-1610.
11. Law SK. Bimatoprost in the treatment of eyelash hypotrichosis. Clin Ophthalmol. 2010 Apr 26;4:349-58. doi: 10.2147/opth.s6480. PMID: 20463804; PMCID: PMC2861943.
12. Barrón-Hernández YL, Tosti A. Bimatoprost for the treatment of eyelash, eyebrow and scalp alopecia. Expert Opin Investig Drugs. 2017 Apr;26(4):515-522.
13. Barbulescu CC, Goldstein NB, Roop DR, Norris DA, Birlea SA. Harnessing the Power of Regenerative Therapy for Vitiligo and Alopecia Areata. J Invest Dermatol. 2020 Jan;140(1):29-37. doi: 10.1016/j.jid.2019.03.1142. Epub 2019 Jun 10. PMID: 31196751.
14. Jha AK, Prasad S, Sinha R. Bimatoprost ophthalmic solution in facial vitiligo. J Cosmet Dermatol. 2018;17(3):437-440.
15. Lei TC, Hearing VJ. Deciphering skin re-pigmentation patterns in vitiligo: an update on the cellular and molecular events involved. Chin Med J (Engl). 2020;133(10):1231-1238. doi: 10.1097/CM9.0000000000000794.
16. Narasimhan H. Vitiligo Area Assessment by Manual Planimetry for Statistical Precision. Clin Dermatol J 2021, 6(2): 000241.
17. Feily A. Vitiligo Extent Tensity Index (VETI) score: a new definition, assessment and treatment evaluation criteria in vitiligo. Dermatol Pract Concept. 2014 Oct 31;4(4):81-4. doi: 10.5826/dpc.0404a18.
18. Jha AK, Sinha R, Prasad S, Nandan N. Bimatoprost in periorbital vitiligo: A ray of hope or dilemma. J Eur Acad Dermatol Venereol. 2016;30:1247–8.
19. Jha AK, Sinha R. Bimatoprost in vitiligo. Clin Exp Dermatol. 2016;41:821–2.
20. Scott G, Leopardi S, Printup S et al. Proteinase activated receptor-2 stimulates prostaglandin production in keratinocytes: analysis of prostaglandin receptors on human melanocytes and effects of PGE and PGF on melanocyte dendricity. J Invest Dermatol 2004; 122: 1214–24.
21. Scott G, Jacobs S, Leopardi S, et al. Effects of PGF2alpha on human melanocytes and regulation of the FP receptor by ultraviolet radiation. Exp Cell Res. 2005;304(2):407-416.
22. Anbar T, El-Ammawi T, Barakat M, Fawzy A. Skin pigmentation after NB-UVB and three analogues of prostaglandin F2α in guinea pigs: Acomparative study. J Eur Acad Dermatol Venereol. 2010;24:28–31.
23. Kapur R, Osmanovic S, Toyran S, Edward DP. Bimatoprost-Induced Periocular Skin Hyperpigmentation: Histopathological Study. Arch Ophthalmol. 2005;123:1541–6.
24. Kapoor R, Phiske MM, Jerajani HR. Evaluation of safety and efficacy of topical prostaglandin E2 in treatment of vitiligo. Br J Dermatol. 2009 Apr;160(4):861–3.
25. Grimes PE. Bimatoprost 0.03% Solution for the Treatment of Nonfacial Vitiligo. J Drugs Dermatol. 2016 Jun 1;15(6):703-10. PMID: 27272076.
26. Stanimirovic A, Kovacevic M, Korobko I, Situm M, Lotti T. Combined therapy for resistant vitiligo lesions: NB-UVB, microneedling, and topical latanoprost, showed no enhanced efficacy compared to topical latanoprost and NB-UVB. DermatolTher. 2016;29(5):312-6.
27. Sharma S, Parsad D, Bhattacharjee R, Muthu SK. A prospective right-left comparative study to evaluate the efficacy and tolerability of combination of NB-UVB and topical bimatoprost 0.03% eye drops versus NB-UVB given alone in patients of vitiligo vulgaris. Journal of the European Academy of Dermatology and Venereology. 2018 Mar 9;32(8):e330–1.
28. Anbar TS, El-Ammawi TS, Abdel-Rahman AT, Hanna MR. The effect of latanoprost on vitiligo: a preliminary comparative study. Int J Dermatol. 2015;54(5):587-593.