Advanced Medical Journal, Vol.9, No.2, P.64-74, 2024 https://doi.org/10.56056/amj.2024.258

Clinical and Dermoscopic evaluation of post acne erythema after treatment with topical timolol maleate 0.5%

Sawen Jihanger Omer* Mohammed Yousif Saeed Jaf ** Shawkat Abubakr Hassan ***

Abstract

Background and objectives: A common consequence of acne inflammation is called post-acne erythema, which describes telangiectasia and erythematous lesions that persist even after acne treatment, although some post-acne erythema lesions may become better with time. For some patients, having prolonged post-acne erythema might not be acceptable. Many studies have assessed the effectiveness of various post-acne erythema therapeutic approaches; however, there is no standard treatment. The aim of this study was to evaluate efficacy and safety of topical timolol maleate 0.5% in the treatment of post-acne erythema clinically and by dermoscopy.

Methods: A randomized therapeutic clinical trial conducted in Sulaimanyah city-Kurdistan region over a period from March to September of 2022.Thirty patients (24 female and 6 male) with persistent post-acne erythema were enrolled in this study. Treatments with timolol 0.5% ophthalmic solution: apply 3-5 drops of timolol over the affected area every night at bedtime for 12 weeks. Our objectives were patient satisfaction, dermoscopy-assessed erythema assessment, and physician-reported clinical improvement.

Result: After 12 weeks of treatment, there were no patients with severe erythema, clinically and statistically; there was a marked decline in the mean clinician erythema score and its standard deviation from 2.7± 0.98 to 1.0 ± 1.0 Also by dermoscopy-assessed erythema assessment, there was a substantial decrease in the mean erythema score and its standard deviation from 2.0±0.72 to 0.70±0.70, no participants after therapy exhibited severe erythema by dermoscopy.so statistically there is significant reduction in erythema clinically and dermoscopically.

Conclusion: The results of this study show that there was very good response of post-acne erythema lesions with no obvious side effects, further therapeutic clinical studies with larger sample size is needed.

Keywords: Acne, Dermoscopy, Post-acne erythema, Timolol maleate

* M.B.Ch.B, KHCMS/ Dermatology trainee, Sulaymaniyah Dermatology Teaching Hospital, KRG, Iraq. Email: sawen.jihanger@gmail.com
** M.B.Ch.B, FIBMS (Dermatology), ISDS, ESLDC, Assistant Professor of Dermatology, University of Sulaimani, college of medicine, Head of Sulaymaniyah Dermatology Teaching centre.
*** M.B.Ch.B , ABMS/Dermatology lecturer, Sulaymaniyah Dermatology Teaching Hospital, KRG, Iraq

Introduction

Acne is a persistent inflammatory condition affecting the pilosebaceous unit.[1] About 85% of teenagers and young adults suffer from acne.[2] It is distinguished by inflammatory as well as non-inflammatory lesions such as papules, pustules, nodules, as well as comedones.[3] several etiological factors, including aberrant pilosebaceous unit keratinization, stimulation of sebum production by androgen, and cutibacterium acnes growth with concurrent cutaneous inflammation caused by increased inflammatory mediators, have been linked to the etiology of acne.[4] The idea of acne etiology has recently been concentrated on inflammatory actions that take place including both early and later phase of acne lesions.[5]

Among the main issues throughout or following the therapy of acne vulgaris with any treatment method is post-inflammatory erythema, which is described as telangiectatic and erythematous macule lesions that develop due to inflammation of skin.[6] Post-acne erythema(PAE) is hypothesized to be generated by wound healing-induced dilatory changes in microvascular structures in the superficial dermis. These microvascular structures are not readily apparent to the bare eye as obvious telangiectasia but rather as widespread erythema. Additionally, epidermis is thinner since it is in the process of recovering from tissue damage, which makes it easier for light to reflect off the dilated microvasculature. Exogenous stimuli, such as application of particular topical medications, were also thought to lead to post-acne erythema.[7]

The post-inflammatory erythema of acne is currently treated with lasers and radiofrequency and micro-needling devices. However, outcomes vary, and multiple therapy sessions are typically necessary to get good outcomes.[7-12] Recently topical timolol has been used, which showed clinical improvement in PAE.[13]

Timolol maleate is a nonselective β-blocker that results in constriction of blood vessels, apoptosis, suppresses provocative cytokines like matrix metalloproteinase 2 and 9, interleukin 6, as well as angiogenic factors like VEGF.[14] It has been used to treat infantile hemangioma since it can constrict blood vessel and impede neo-angiogenesis.[15] It can reduce redness and flushing in rosacea by blocking beta-adrenergic receptors on the smooth muscles encircling blood vessels, which cause blood vessels to constrict.[16] As a result, the anti-inflammatory effect of timolol maleate could be helpful in therapy of post-inflammatory erythema of acne. Accessibility, affordability, ease of use, and a minimal rate of side effects are another significant benefit of topical timolol.[17]

Dermoscopy is an interesting link combining both clinical and histological assessment and has emerged as an essential method to assess pigmented and non-pigmented skin cancers since it can reveal features that are invisible to the human eye.[18, 19] In addition to this classical use, it is becoming more popular in fields other than dermato-oncology, including inflammatory dermatology.[18, 19] The purpose of this study was to assess efficacy and safety of topical timolol maleate 0.5% in the treatment of PAE clinically and by dermoscopy.

Patients and methods

Thirty patients (24 females and six males) with post-acne erythema that persists for more than three months were enrolled in this study over a period of 3 months between March to September 2022.Exclusion criteria included a history of beta-blocker allergy, pregnancy or lactation, hypotension, bradycardia, asthma, or bronchospasm.

Before beginning the treatment trial, each patient provided written consent after being fully informed about the drug's efficacy, adverse effects, method and length of

therapy, and follow-up, along with the necessity for pre- and post-therapy images. The Kurdistan Higher Council of Medical Specialties granted ethical approval.

Each patient's history was documented, including age, gender, duration of disease, history of any medical illness, and drug allergy. A clinical examination was done to evaluate the grade of post-acne erythema using the Clinician's Erythema Assessment Scale[20] (Table 1) then photography and dermoscopic images were taken.

Each patient was monitored for a 12 weeks period of time. The images obtained prior to and after therapy were compared. All images were captured by the same operator using the exact digital camera, with the same lighting and the same patient poses. Each cheek was divided into four quadrants for dermoscopic examination, and the most seriously affected area was photographed before and after completing therapy. (Using FotoFinder handyscope).

Treatment with timolol 0.5% ophthalmic solution: apply 3-5 drops of timolol over the affected area every night at bedtime for 12 weeks. We let the participant to use topical clindamycin solution to their breakout acne.

The safe limit dosage of topical timolol should be less than 0.2 mg/kg/day, and one drop (0.05 mL) of 0.5% timolol solution provides 0.25 mg of timolol.[21]

Table (1): Clinician Erythema Assessment scale

Score	Clinician Erythema Assessment
0 = Clear	Clear skin with no signs of erythema
1 = Almost clear	Almost clear; slight redness
2 = Mild	Mild erythema, definite redness
3 = Moderate	Moderate erythema; marked redness
4 = Severe	Severe erythema; vivid redness

The main primary goal was to evaluate the patient's erythema clinically using Clinician's Erythema Assessment Scale.[20] (Table 1) which is done by two independent dermatologists and the secondary goal was evaluation of acne erythema by dermoscopy through dermoscopic photo using a four-point scale.[22] (Table 2) For assessment of erythema, clinical and dermoscopical pictures were taken at the beginning of clinical trial and compared with those which were taken at week 12 after finishing the treatment. The safety of the treatment was determined by monitoring side effects. Patient satisfaction was measured at the end of the trial using the following questionnaire: 0 dissatisfied: "patient feels worse than usual or remains the same as before," 1 slightly satisfied: "patient feels mildly better but it isn't worth it," 2 moderately satisfied: "patient feels fine with a need for small improvement," or 3 highly satisfied: "patient feels the perfect cosmetic result."

Table (2): The four-point grading of acne erythema

Grade	Level of disease	Characteristics
0	None	Clear
1	Mild	Faintly detectable erythema, light pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red

Descriptive data were expressed as numbers, percentages, or means ± standard deviations. The Wilcoxon Signed Ranks Test was used to compare the clinical responses with different clinical variables. p values of less than 0.01 were regarded statistically significant.

Results

Our study featured 6 males and 24 females; their average age was 19.9±4.6 years, with the minimum of 14 years and the maximum of 33 years. 90.1% of the patients have post-acne erythema for 1 year, and only 9.9% have it for >1 year. no difference in treatment outcomes was found between male and female patients or with duration of post-acne erythema less than and greater than 1 year.

The clinician's erythema assessment scale ranged from 0 to 4. The mean clinician erythema score and its standard deviation was dropped from 2.7± 0.98 to 1.0 ± 1.0 after twelve weeks of treatment, with 40% n(12) being clear (0), 33% n(10) being almost clear (1), 17% n(5) being mild (2), and only 10% n(3) being moderate (3). There were no patients with severe erythema clinically after therapy (Table 3).

Table (3): Clinician Erythema Assessment Scale before and after treatment

Scale		Clinician Erythema Assessment (n=30)	
		Before	After
Score	0	-	12 (40%)
	1	4 (14%)	10 (33%)
	2	7 (23%)	5 (17%)
	3	12(40%)	3 (10%)
	4	7 (23%)	-
	Mean ± SD	2.7±0.98	1.0±1.0
	Mean improvement	1.7	

In this study, dermoscopy was used to grade post-acne erythema in all patients. There was a marked decline in mean erythema score and its standard deviation from 2.0±0.72 to 0.70±0.70, 33% n (10) showed no sign of erythema, 50% n (15) showed mild erythema,

and only 17% n(5) showed moderate erythema after treatment; no participants after treatment had severe erythema (grade 3) by dermoscopy(Table 4).

Table (4): Assessment of erythema by dermoscopy before and after treatment

Scale		Clinician Erythema Assessment (n=30)	
		Before	After
Score	0	-	10 (33%)
	1	7 (23%)	15 (50%)
	2	15 (50%)	5 (17%)
	3	8 (27%)	-
	Mean ± SD	2.0±0.72	0.70±0.70
	Mean improvement	1.3	

At the end of therapy, participants were asked to score their therapeutic outcomes using baseline images and compared how they appeared in the mirror versus actual pre-treatment images using a scale (0 dissatisfied, 1 slightly satisfied, 2 moderately satisfied, and 3 highly satisfied). Approximately 83 percent of participants rated their general advancement as moderately to highly satisfied (Grades 2, 3). After treatment, all participants reported that their post-acne erythema had reduced, not only in regard to color diminishing but also the number of lesions has decreased. As shown in the pie chart, (Figure 1)

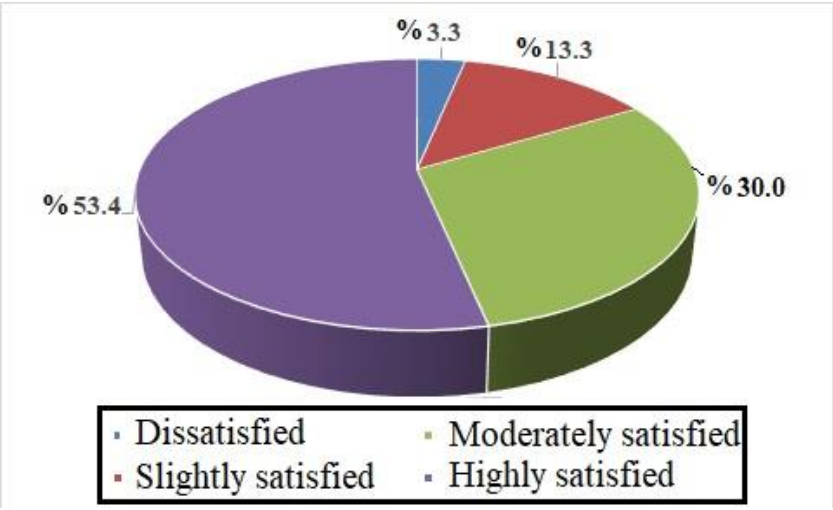

Fig. (1): Patient self-evaluation following 12 weeks of topical timolol 0.5% treatment

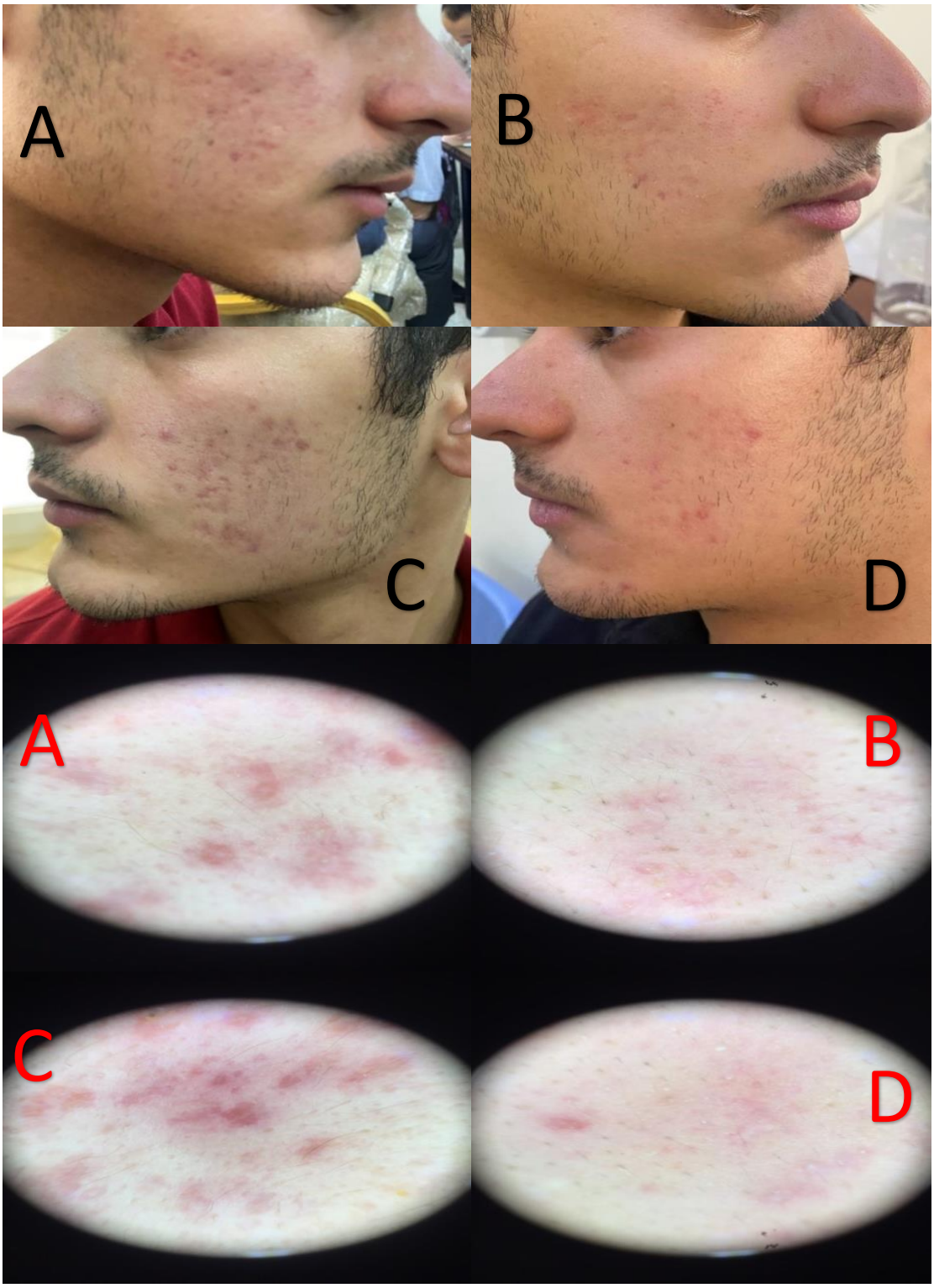

Fig. (2): Clinical and dermoscopic studies show progress in erythema and pigmentation. (A&C): Erythema and pigmentation on the left side at the initial assessment. (B&D): Improvement in erythema and pigmentation on the right side after 3 months of nightly topical timolol maleate 0.5% treatment.

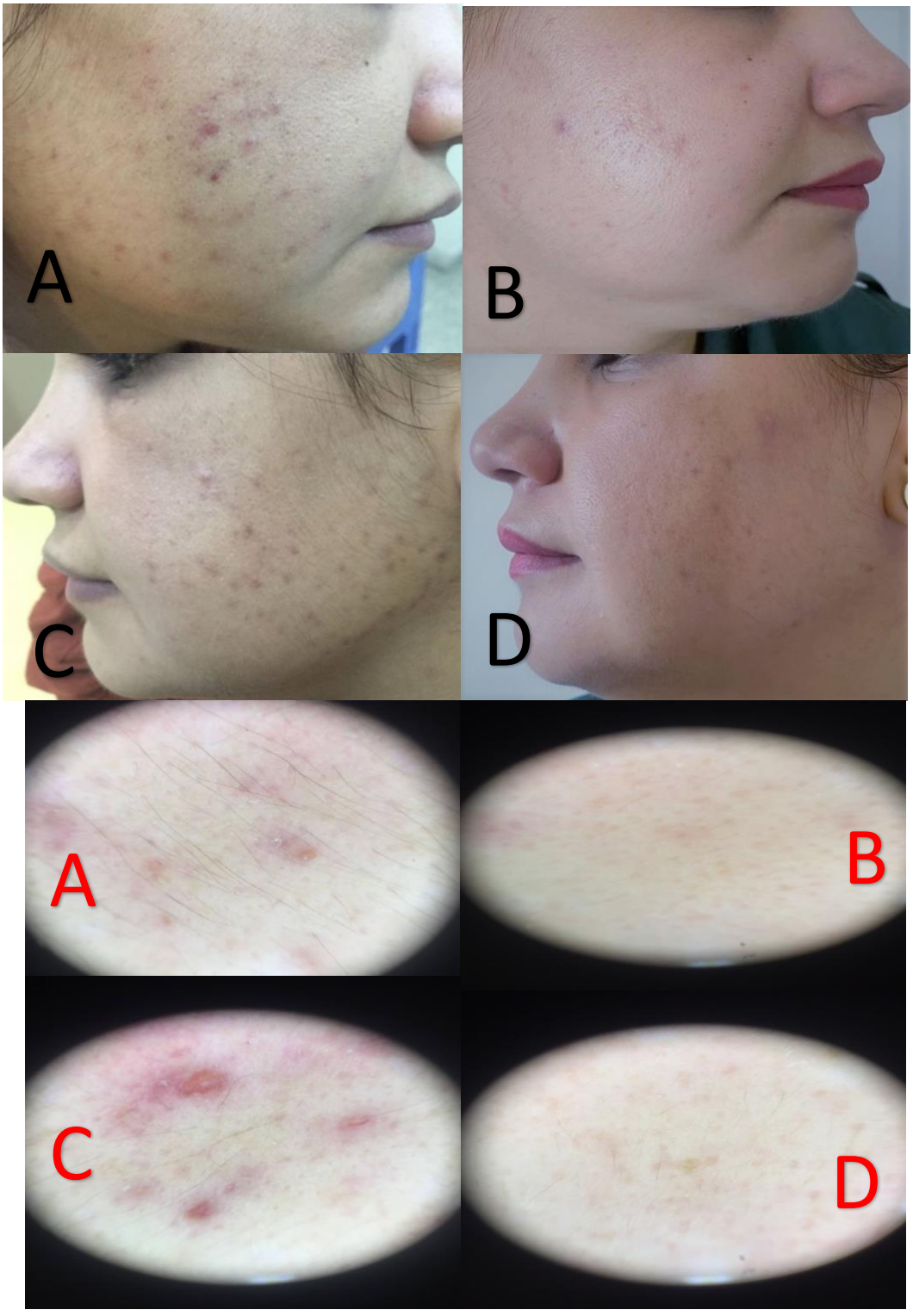

Fig. (3): Clinical and dermoscopic studies show progress in erythema and pigmentation. (A&C): Erythema and pigmentation on the left side at the initial assessment. (B&D): Improvement in erythema and pigmentation on the right side after 3 months of nightly topical timolol maleate 0.5% treatment.

Discussion

Nearly 85% of teenagers and young adults suffer from acne vulgaris,[2] which can have a number of negative cutaneous effects on the skin, includes post-acne erythema, post-inflammatory hyperpigmentation, and scarring, imposing a significant emotional as well as sociological burden on those who are affected even after the disease has stopped being active.[23] Therefore, treating acne should not only focus on clearing up existing lesions; it should also aim to prevent and treat any potential side effects.[7] One of the most troublesome cosmetic issues for acne sufferers is post-acne erythema.[6] Long-term post-acne erythema is fairly common, lasting several months to years on average; however, these lesions usually fade with time.[7]

Timolol maleate is a potent a nonselective β-blocker that results in constriction of blood vessels, apoptosis, suppresses provocative cytokines like matrix metalloproteinase 2 and 9, interleukin 6, as well as angiogenic factors like VEGF.[14] Timolol's anti-inflammatory activity may be beneficial in the management of post-acne erythema due to the inflammatory etiology of this skin condition. Recently, topical timolol was used in one acne patient with significant post-inflammatory erythema.[13] In our study, however, we used topical timolol on 30 patients who had PAE. A study with a large number of participants is better than a smaller one, which is the advantage of our study. In both studies, topical timolol maleate 0.5% solution achieved satisfactory clinical responses as stated by the inspectors and dermoscopic assessments. There were no reported local or systemic negative effects.

In previous studies, a selective α1-adrenoreceptor agonist such as oxymetazoline 1.5% was used in the cure of PAE in a controlled left to right face comparison study.[24] because of its vasoconstrictive action on subcutaneous blood vessels and substantial anti-inflammatory effects. According to this study, participants used oxymetazoline 1.5% in liposomal base twice daily for 12 weeks, throughout the four weeks of treatment, the erythema score steadily improved; this response was statistically relevant at the end of therapy, depending in both the Clinician's Erythema Assessment Scale and the patient's rating scale, but in our study, we also assessed the patient's erythema by dermoscopy, a noninvasive tool that reveals erythema that is invisible to the human eye which is not used in previous study. And the occurrence of therapies related adverse events was 4.2%, with the most common being erythema at the location of application, this occurred in 0.7% of participants; dryness and pruritus; pallor; rebound; and paradoxical erythema has also recorded but in our study no reported local or systemic negative effects were observed.

Jakhar previously treated PAE with tranexamic acid (TXA). He was able to cure post-acne erythema with a topical solution of the injectable TXA (500 mg/5 ml).[25] In a another study, Abdelrazik et al. used just microneedling on the right side of the face while using TA (50 mg/ml) and Vitamin C (10 mg/ml) on the left side. He discovered similar results on both sides in terms of the PAE improvement over the baseline, and he suggested that the synergistic skin repair benefits of micro-needling were proposed as a viable therapeutic strategy, TA, and vitamin C [8], but in our study, likely the outcome of therapeutic result were vasoconstriction, induction of apoptosis, and suppression of inflammatory mediators. Also, topical timolol is less expensive than micro-needling with tranexamic acid and vitamin C, which is one of the advantages of topical timolol.

The most common technique for treating blood vessels is pulsed dye laser (PDL) therapy, which has been also studied in treatment of inflamed acne, but outcomes were variable.[26–32] Yoon et al. Studied the

efficacy of a long-pulsed, 595-nm PDL for the management of 20 individuals with post-acne erythema.[10] Following two laser therapy sessions with little downtime, the study demonstrated a marked decrease in the terms of post-acne erythematous lesions and erythema index, along with increased skin elasticity; however, the study participants were limited, and there wasn't a controlled study. And all participants were permitted to keep taking their acne prescription drugs (oral and topical antibiotics) and the negative effects included laser-related discomfort, temporary erythema, and edema at treated areas. In the current study, we just prescribed topical clindamycin for breakout acne, and no negative effects were seen. Also, using pulsed dye lasers typically requires many sessions for optimal clearing. Also, topical timolol is cheaper than laser and light-based interventions, which is a huge asset, particularly in developing countries.

Conclusion

Topical timolol maleate 0.5% is both safe and reliable for post-acne erythema lesions. The advantages are that no side effects were found and that it is inexpensive, affordable, and easily accessible. And yet, further therapeutic clinical studies in this sector are required with a broader sample size and a prolonged treatment period is advised.

Conflict of interest

The authors recording no conflict of interest.

Reference

1.Tuchayi S, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR, Zouboulis CC. Acne vulgaris. Nat Rev Dis Primers 2015; 1: 15029.

2. Bhate K. Williams H.C. Epidemiology of acne vulgaris. Br J Dermatol. 2013; 168: 474-85

3. Bellew S, Thiboutot D, Del Rosso JQ. Pathogenesis of acne vulgaris: what's new, what's interesting and what may be clinically relevant. J Drugs Dermatol. 2011;10(6):582–5.

4. Suh DH, Kwon HH. What's new in the physiopathology of acne? Br J Dermatol. 2015;172:13–19. 1

5. Tanghetti EA. The role of inflammation in the pathology of acne. J Clin Aesthet Dermatol 2013;6(9):27–35.

6. Bae-HarboeYS, GraberEM. Easy as PIE (Postinflammatory Erythema). J Clin Aesthet Dermatol 2013;6(9):46–7.

7. Panchaprateep R, Munavalli G. Low-fluence 585 nm Q-switched Nd:YAG laser: a novel laser treatment for post-acne erythema. Lasers Surg Med 2015; 47:148-55.

8. Abdelrazik, Combination of skin micro-needling and topical application of tranexamic acid and vitamin C: New clinical application: A pilot study for treatment of persistent post acne erythema. J Am Acad Dermatol. 2016;74(5): AB4

9.Glaich AS, Goldberg LH, Friedman RH, Friedman PM. Fractional photothermolysis for the treatment of postinflammatory erythema resulting from acne vulgaris. Dermatol Surg. 2007;33(7):842–6

10. Yoon HJ, Lee DH, Kim SO, Park KC, Youn SW. Acne erythema improvement by long-pulsed 595-nm pulsed-dye laser treatment: a pilot study. J Dermatolog Treat 2008;19-(1):38–44.

11.Park KY, Ko EJ, Seo SJ, Hong CK. Comparison of fractional, nonablative, 1550-nm laser and 595-nm pulsed dye laser for the treatment of facial erythema resulting from acne: a split-face, evaluator-blinded, randomized pilot study. J Cosmet Laser Ther. 2014;16(3):120–3

12. Wang B, Wu Y, Luo YJ, et al. Combination of intense pulsed light and fractional CO(2) laser treatments for patients with acne with inflammatory and scarring lesions. Clin Exp Dermatol 2013;38: 344-51.

13. Afra TP, Razmi T M, De D. Topical timolol for postacne erythema. J Am Acad Dermatol. 2021;84(6):255–6
14. Krakowski AC, Nguyen TA. Inhibition of angiofibromas in a tuberous sclerosis patient using topical timolol 0.5% gel. Pediatrics. 2015; 136(3):709–13.
15. Khan M, Boyce A, Prieto-Merino D, et al. The Role of Topical Timolol in the Treatment of Infantile Hemangiomas: A Systematic Review and Meta-analysis. Acta Derm Venereol. 2017, 97 (10). 1167-71.
16. Raghallaigh SN, Powell FC. Rosacea. In: European Handbook of Dermatological Treatments. Berlin, Germany: Springer; 2015: 835-43
17.Arora P, Meena N, Sharma PK, Bhardwaj M. Angiolymphoid hyperplasia with eosinophilia and its response to the combination of radiofrequency ablation and topical timolol. Indian Dermatol Online J. 2017;8(4):267–70.
18. Errichetti E, Stinco G. Dermoscopy in general dermatology: a practical overview. Dermatol Ther (Heidelb) 2016;6(4):471–507
19.Errichetti E, Stinco G. The practical usefulness of dermoscopy in general dermatology. G Ital Dermatol Venereol. 2015;150(5):533–46.
20. Tan J, Liu H, Leyden J, Leoni M. Reliability of Clinician Erythema Assessment grading scale. J Am Acad Dermatol. 2014; 71:760–3
21. Frommelt P. Juern A.Siegel D.et al. Adverse events in young and preterm infants receiving topical timolol for infantile hemangioma. Pediatr Dermatol. 2016; 33: 405-14
22.Abdel Hay R, Hegazy R, Abdel Hady M, Saleh N. Clinical and dermoscopic evaluation of combined (salicylic acid 20% and azelaic acid 20%) versus trichloroacetic acid 25% chemical peel in acne: an RCT. J Dermatolog Treat . 2019;30(6):572–7
23. Harper JC. An update on the pathogenesis and management of acne vulgaris. J Am Acad Dermatol. 2004;51(1 Suppl):36–8.
24. Agamia N, Essawy M, Kassem A. Successful treatment of the face post acne erythema using a topically applied selective alpha 1-Adrenergic receptor agonist, oxymetazoline 1.5%, a controlled left to right face comparative trial. J Dermatolog Treat. 2022;33(2):904–9
25. Jakhar D, Kaur I. Topical 5% tranexamic acid for acne-related postinflammatory erythema. J Am Acad Dermatol. 2020;82(6):e187–8
26. Glaich AS, Friedman PM, Jih MH, Goldberg LH. Treatment of inflammatory facial acne vulgaris with combination 595-nm pulsed-dye laser with dynamic-cooling-device and 1,450-nm diode laser. Lasers Surg Med 2006;38(3):177–80.
27.Erceg A, de Jong EM, van de Kerkhof PC, Seyger MM. The efficacy of pulsed dye laser treatment for inflammatory skin diseases: A systematic review. J Am Acad Dermatol 2013; 69(4):609–15.
28. Karsai S, Schmitt L, Raulin C. The pulsed-dye laser as an adjuvant treatment modality in acne vulgaris: A randomized controlled single-blinded trial. Br J Dermatol 2010; 163(2):395–401.
29. Leheta TM. Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. J Cosmet Laser Ther 2009;11(2): 118–24.
30. Jung JY, Choi YS, Yoon MY, Min SU, Suh DH. Comparison of a pulsed dye laser and a combined 585/1,064-nm laser in the treatment of acne vulgaris. Dermatol Surg 2009;35(8):1181–7.
31. Haedersdal M, Togsverd-Bo K, Wiegell SR, Wulf HC. Long-pulsed dye laser versus long-pulsed dye laserassisted photodynamic therapy for acne vulgaris: A randomized controlled trial. J Am Acad Dermatol 2008;58- (3):387–94.

32. Seaton ED, Charakida A, Mouser PE, Grace I, Clement RM, Chu AC. Pulsed-dye laser treatment for inflammatory acne vulgaris: randomised controlled trial. Lancet 2003;362- (9393):1347–52.