



Effect of Topical 0.5% Timolol Maleate after Fractional Carbon Dioxide Laser Versus Carbon Dioxide Laser Alone in Treatment Acne Scars

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ABSTRACT

Background: Commonly affecting the face, chest, and back, acne is an inflammatory disorder that can be treated with a variety of modalities, with laser treatment remaining a key option for scar treatment. This study aimed to compare the efficacy and safety of topical timolol after fractional CO₂ versus fractional laser alone in the treatment of acne scars. **Patients & Methods:** This Interventional comparative study was carried out on 62 patients different skin types suffering from mild, moderate and severe facial acne scars, patients were divided into 2 groups; Group one: 31 patients were treated by topical timolol maleate 0.5% after fractional laser twice daily for seven days to be repeated every two weeks until complete response or for maximum of six sessions. Group two: 31 patients were treated by fractional CO₂ laser alone every two weeks until complete response or for maximum of six sessions. **Results:** There was highly statistically significant improvement post acne scar after application of Timolol with LASER ($P < 0.001$). Moreover, there was statistically significant improvement post acne scar after application of Timolol with LASER. The findings suggest that the combination of topical timolol maleate with fractional CO₂ laser therapy may offer enhanced benefits compared to CO₂ laser treatment alone. This is evident in the observed improvements in acne scar outcomes, such as texture, pigmentation, and overall skin appearance. **Conclusion:** Applying topical 0.5% TM twice a day could result in a noticeable improvement, enhances the function of the skin's barrier and may encourage re-epithelialization following laser treatments.

Keywords: Afractional carbon-dioxide laser, Timolol, Acne Scars

INTRODUCTION

During adolescence, males and females alike might suffer from the common skin condition known as acne vulgaris. In both sexes, acne is frequently caused by an increase in hormones like testosterone throughout adolescence. When oil from the skin and dead skin cells clog hair follicles, acne results. It affects skin in places like the face, upper chest, and back that have a comparatively high concentration of oil glands. It is distinguished by patches of whiteheads or blackheads, acne, oily skin, and even scars [1].

The appearance of acne varies with skin color. Lesions include comedones, inflammatory papules, and pustules. Severe acne presents with tender nodules and cysts. Nodulocystic acne is

less common in African people, but when nodules and cysts occur, they often heal with hypertrophic scarring and keloids. This leads to social and psychological issues [2].

Ninety-five percent of individuals with acne vulgaris have acne scars; this is because inflammation occurs in the skin's dermal layer. After this cutaneous inflammation, the scar is the result of aberrant healing. Although it can happen with any form of acne vulgaris, scarring happens with severe acne. The classification of acne scars is determined by whether the aberrant healing reaction that follows skin inflammation results in an excess of collagen deposition or loss at the location of the acne lesion. Scars can be categorized as keloidal, hypertrophic, or atrophic [3].

Dermatologists and patients alike continue to face significant challenges when it comes to treating facial acne scars. Over the years, a variety of therapeutic techniques have been employed, with varying degrees of success. These techniques include chemical peels, surgical excision, punch grafting, dermabrasion, and filler injection. These differing results have been attributed to a number of factors, including as tissue fibrosis, insufficient scar removal, inadequate intraoperative vision, transmission of infectious material, worsening of the scar, and irreversible pigmentary modification [4].

One of the best treatments for atrophic acne scars is relative fractional carbon dioxide laser therapy. Microthermal treatment zones (MTZs) are created by this therapy's fractional laser beam, which has a wavelength of 10600 nm. The beam is absorbed by water in the upper dermis and epidermis. The surrounding healthy skin facilitates wound healing while these MTZ columns cause collagen remodeling [5].

The beta-adrenergic blocking drug timolol maleate (TM) may hasten keratinocyte migration through beta-adrenergic receptors, which are expressed on healthy human keratinocytes. Migration of keratinocytes is crucial for re-epithelialization during the healing phase of wounds [6].

Aim of the Work

The aim of this study was to compare the efficacy and safety of topical timolol after fractional CO₂ versus fractional laser alone in the treatment of acne scars.

METHODS

This Interventional comparative study was carried out in the out-patient clinic of Dermatology, Venereology and Andrology Department at Zagazig University Hospitals and Al Ahrar Teaching Hospital as well as The Clinic of Dermatology & Leprosy in Zagazig city on 62 patients different skin types suffering from mild, moderate and severe facial acne scars, patients were split into two groups. Thirty-one patients in group one received topical timolol maleate 0.5% following fractional laser treatment twice daily for seven days to be repeated every two weeks until complete response or for maximum of six sessions. Group two (including 31 patients) were treated by fractional CO₂ laser alone every two weeks until complete response or for maximum of six sessions.

Each patient gave their informed consent after being educated about the study's purpose and receiving approval from the Institutional Review Board (IRB#10196/6-12-2022). This study was carried out in accordance with the Declaration of Helsinki, which is the worldwide medical association's code of ethics for human subjects' research.

Inclusion criteria: Adult patients with acne scars of different types and durations were included in this study.

Exclusion criteria: The patients unwilling to follow-up regularly, Pregnant, Lactating women and patients who received any wart treatment in the last month before the start of the trial were excluded from this study.

Patients were divided into 2 groups; Group one (including 31 patients) were treated by topical timolol maleate 0.5% after fractional laser twice daily for seven days to be repeated every two weeks until complete response or for maximum of six sessions.

Group two (including 31 patients) were treated by fractional CO₂ laser alone every two weeks until complete response or for maximum of six sessions.

All patients in this study were subjected to thorough history taking and proper dermatological examination.

Study procedures:

Every procedure was carried out in compliance with the applicable rules and regulations. To obtain a good anesthetic effect, a topical anesthetic cream containing a eutectic mixture of topical tetracaine and lignocaine in a cream base (TetralidR cream) was administered for one hour on the treatment area. Each atrophic scar that was present was treated with a fractional CO₂ laser (SmartXide DOT; DEKA, Calenzano, Italy) once a suitable level of anesthesia had been reached. With a dwell period of 0.5 ms and a power of 15-20 W, a range of 2.8 to 3.5 J/cm² was employed, yielding a density of 13.5% and approximately 25-30 mJ of energy.

Every scar and its edges were covered in two passes. Every morphological type of scar was treated in the same way, and to address post-treatment erythema, oedema, and burning sensation, the patient was instructed to chill their skin with ice packs for five to ten minutes after the surgery.

Subjects applied 10–15 drops of TM 0.5% solution (TimololR, Epico Pharma, Egypt) exclusively to the right side of their cheeks after laser therapy. The patients were directed to apply 10–15 drops of TM solution 0.5% on the right side of their faces and to avoid being in the sun for the next 4–5 days. They were also encouraged to repeat this application process twice a day for 7 days. They were also instructed to put sunscreen on both sides of their faces and apply the hydrophilic cream that was made in-house.

Throughout the trial period, no additional topical treatments or preparations were applied. Every five weeks, laser operations were repeated, and each patient underwent three to four sessions in total. Every visit involved maintaining the same laser parameters, and if the patient was happy with the outcome after the third session, there was no need for a fourth. At each appointment and at the last follow-up appointment, which was held eight weeks after the last laser session, digital photos were shot using the same settings for face position and angles.

Outcome evaluation The Scar Quartile Grading Scale (SQGS) and the Acne Scar Assessment Scale (ASAS), which ranges from 0 (Clear) to 4 (Severe), are tools used to evaluate the severity of scars. Level of development Digital photos taken before and after the procedure were evaluated by an independent, blinded dermatologist, who assigned a grade of 0 for no improvement, 1 for less than 25% improvement, 2 for 26–50% improvement, 3 for 51–75% improvement, and 4 for more than 75% improvement. The results were then graded based on the percentage improvement.

Follow-up was made every month for 4 months to detect any side effects.

Statistical Analysis: The collected data was analyzed by SPSS software. Categorical data was presented as number and percentage and analyzed by chisquance test or Fisher`s test accordingly. Continuous variables were tested for normality by Kolmogrov Smirnov tests and were analyzed by

suitable statistical tests of significance. $P \leq 0.05$ was considered significant.

RESULTS

Table 1; showed that there is no significant difference between the two groups as regards the demographic data .The mean age (years) of the group A was 30.4 (\pm SD 4.7), but in group B it was 29.7 (\pm SD 5.2). Among the study group A cases, 14(45.2%) were males and 16(51.6%) in group B. We found the percentage of positive family history cases was 25.8% in group A and 22.6% in group B.

Table 2; showed that there was highly statistically significant improvement post acne scar after application of Timolol with LASER ($P < 0.001$). Moreover, there was statistically significant improvement post acne scar after application of Timolol with LASER ($P = 0.001$).

Table (3) showed insignificant difference between the two groups as regarding patients satisfaction ($P = 0.07$). Eight patients expressed excellent pleasure and fifteen exhibited good satisfaction on the AFCO2 + TM 0.5% (right) treated side; three patients reported outstanding satisfaction and thirteen indicated good happiness on the AFCO2 only (left) treated side.

Table 4; On the right side (AFCO2 + TM0.5%), erythema was reported by 2 (7%) of the patients, edema by 1 subject (3%), infection by 1 subject (3%), pain by 3 (10%), and hyperpigmentation by only 1 subject (3%) was observed. Three participants (10.0%) had hyperpigmentation, two subjects (6.7%) reported edema, and four patients (13%) had erythema on the left side (AFCO2). On both sides of the face, the side effects were similar and barely different ($p = 0.13$).

Case Presentation:

Case (1): Male patients 28 years old suffereing post acne scar before and after (4 sessions) AFCO2 + TM. (Figure 1 and figure 2)

Case (2): Female patients 28 years old suffering post acne scar before and after (4 sessions) AFCO2 + TM. (Figure 3 and figure 4)

Table (1): Demographic data

Variables	Group A AFCO2 + TM (RT) N(31)	Group B AFCO2 (LT) N(31)	p
Age	30.4 \pm 4.7	29.7 \pm 5.2	0.61
Sex(males)	14(45.2%)	16(51.6%)	0.38
Positive family history of scar	8 (25.8%)	7(22.6%)	0.84

*Significant p <0.05. *** Highly significant p<0.01

Table (2) : Comparison of Acne Scar Assessment Scale before and after Timolol + LASER in group A and LASER alone application.

Group A AFCO2 + TM (RT side)	Before	After	P
Grade I	0(0%)	14(45.6%)	< 0.001**
Grade II	9(29%)	10(32%)	
Grade III	16(51.6%)	6(19.4%)	
Grade IV	6(19.4%)	1(3%)	
Group B AFCO2 (LT side)			
Grade I	0(0%)	12(39%)	0.001*
Grade II	10(32.3%)	11(35%)	
Grade III	15(48.3%)	7 (23%)	
Grade IV	6(19.4%)	1 (3%)	

Table (3): Patient satisfaction of the study population

Patient satisfaction	Group A AFCO2 + TM (RT side) N(31)	Group B AFCO2 (LT side) N(31)	P
Poor	1 (3%)	3 (10%)	0.07
Fair	7 (23%)	12 (39%)	
Good	15 (48%)	13 (42%)	
Excellent	8 (26%)	3 (10%)	

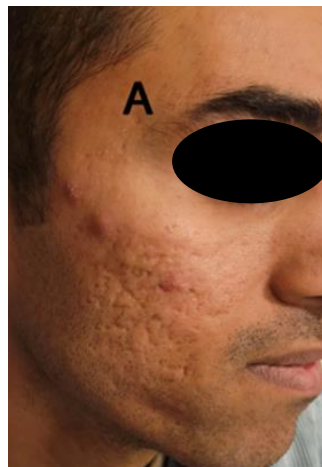
Table (4): Side effect after management of the studied cases

	Group A AFCO2 + TM (RT side) N(31)	Group B AFCO2 (LT side) N(31)	P
Erythema	2 (7%)	4 (13%)	0.13
Edema	1 (3%)	2 (7%)	
Infection	1 (3%)	0 (0.0%)	
Hyperpigmentation	1 (3%)	3 (10%)	
Pain	3 (10%)	2 (7%)	

Figure (1): Right side of face before and after treatments.

Case (1)

Before



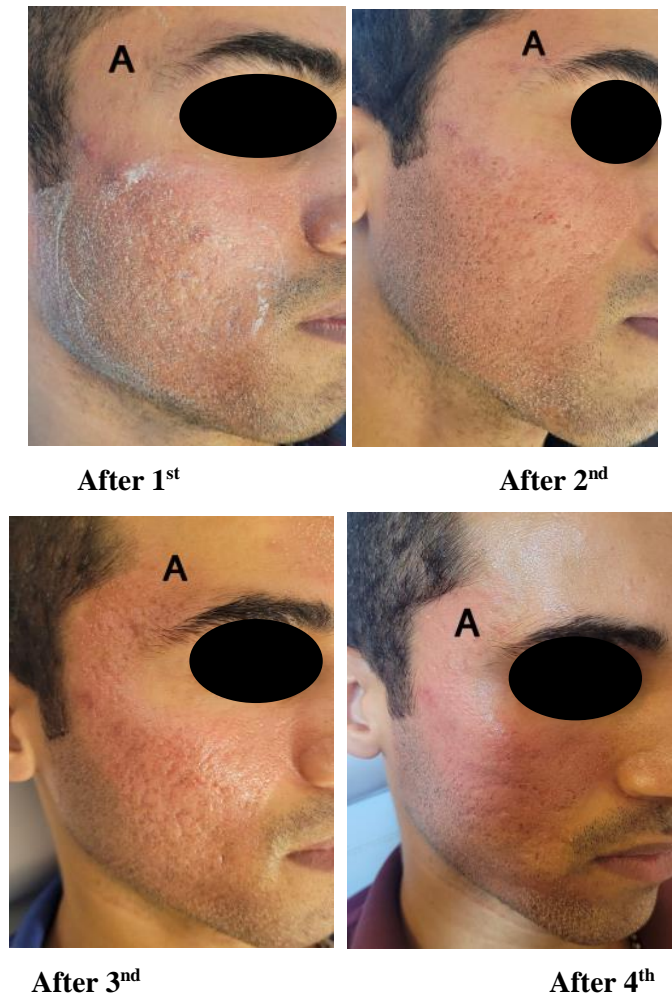
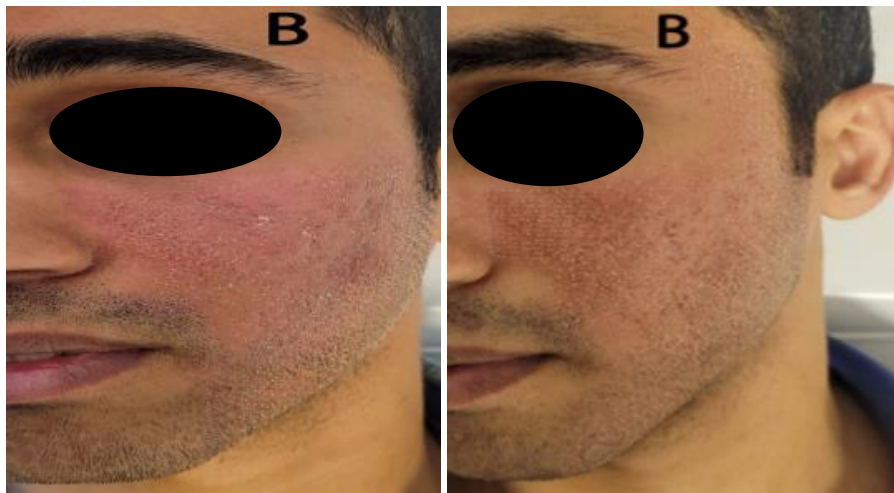


Figure (2): Left side of face before and after treatments.

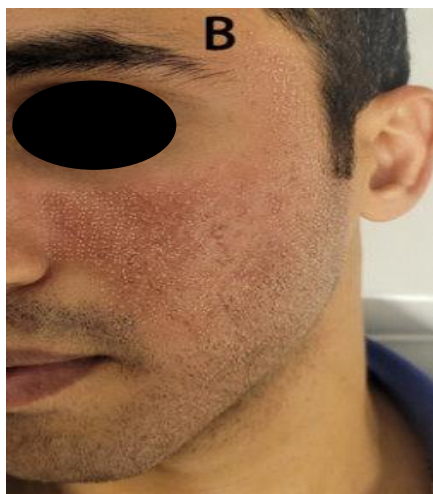


Before



After 1st

After 2nd



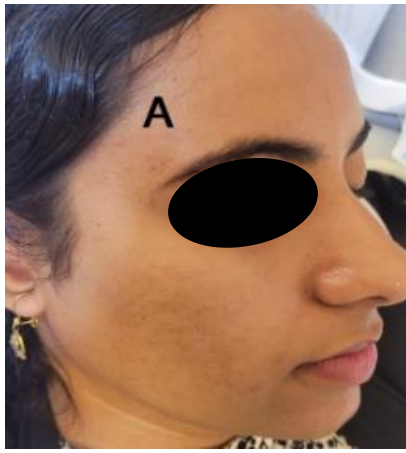
After 3rd

After 4th

Case (2): Figure (3): Right side of face before and after treatments.



Before



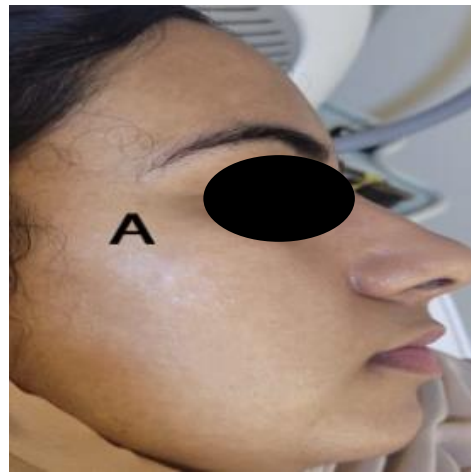
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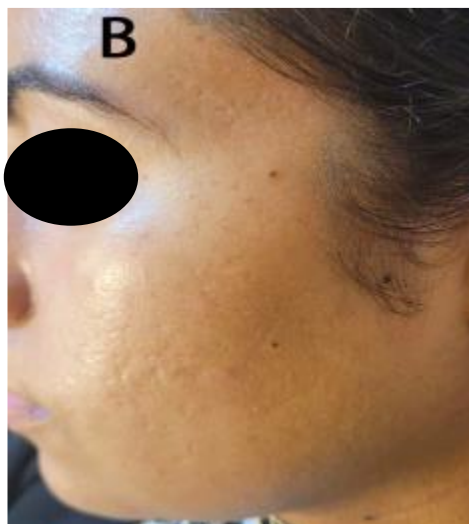


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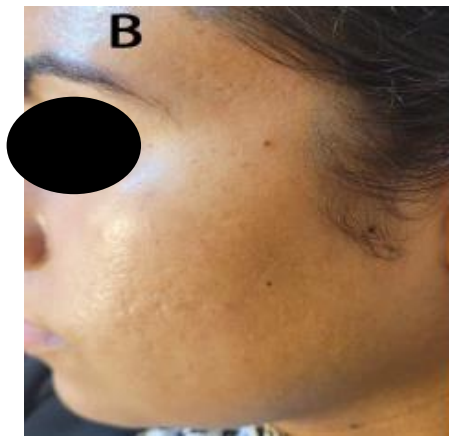


After 4th

Figure (4): Left side of face before and after treatments.



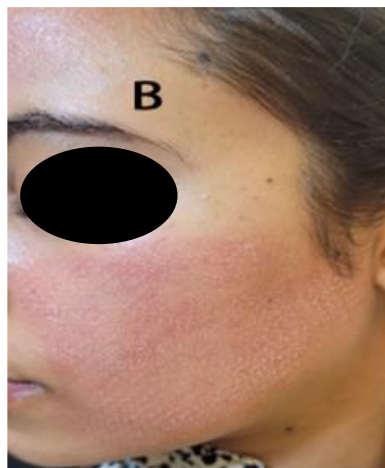
Before



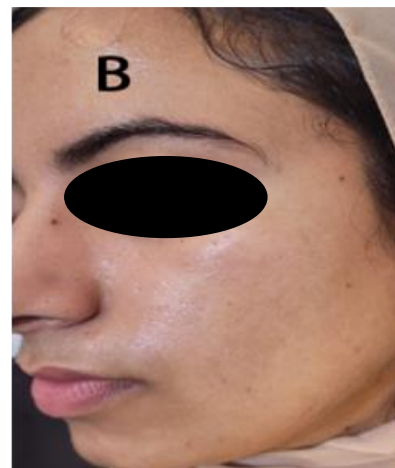
After 1st



After 2nd



After 3rd



After 4th

DISCUSSION

Our results reveal that there is there was no discernible change between the two groups as regards the demographic data. The mean age (years) of the group A (AFCO2 + TM) was 30.4 (\pm SD 4.7),but in group B(AFCO2) it was 29.7 (\pm SD 5.2).Among the study group A(AFCO2 + TM) cases, 14(45.2%) were males and 16(51.6%) in group B(AFCO2). We found the percentage of positive family history cases was 25.8% in group A (AFCO2 + TM) and 22.6% in group B (AFCO2).

The current study showed that there was highly statistically significant improvement post acne scar after application of Timolol with LASER ($P < 0.001$).Moreover, there was statistically significant improvement post acne scar after application of Timolol with LASER.

Our research also shown the effectiveness of fractional CO2 in treating active acne, which is consistent with a study conducted on 20 acne patients by Shin et al. [7].

The results of this study showed that mean improvement scores rose over time in a

significant way ($p < 0.001$). When the progress score was divided into classes of exceptional and moderate, it was demonstrated that there was a considerable variation in the improvement grades between sessions.

The evaluation of the investigator and the two blinded dermatologists revealed a clinical improvement in all of the patients studied by Majid and Imran [8] and Hedelund et al. [9] who employed fractional CO2 lasers to treat atrophic scars. The skin texture of the depression scar and acne scar groups improved after each treatment session. All dermatologists reported statistically significant improvements in skin texture in both scar groups throughout the course of the three therapy sessions.

According to a different study, using topical timolol before utilizing a damaging CO2 laser increased the rate of wound healing. Compared to ablated areas where no timolol was applied, treatment sites ablated by laser and for which topical timolol 0.5% was applied showed reduced inflammation and a considerably lower transepidermal water loss (TEWL) [10].

Moreover, it was shown that timolol causes apoptosis and inhibits inflammatory mediators like interleukin (IL)-6, matrix metalloproteinase (MMP)-2, and MMP-9 as well as angiogenic factors like vascular endothelial growth factor (VEGF). These characteristics had indicated that it would be beneficial for treating rosacea and acne [11].

Kimwattananukul et al [12] proved that topical TM was safe and effective in helping individuals with acne scars restore their skin barrier after receiving AFCO2 therapy. At 48, 96, and 168 hours after laser therapy, they used clinical and biophysical indicators to assess the overall results. Regarding the restored skin barrier, the TM-treated side demonstrated positive results, indicating an enhanced wound-healing efficacy.

Afra et al [13] used topical timolol to a patient with severe acne who also had atrophic scars and PIE. Before going to bed, the patient was instructed to apply topical timolol maleate 0.5% ophthalmic solution on the PIE sites (which is sold as a topical gel version in the US). We permitted her to use topical clindamycin gel for her breakout acne. Dermatoscopy was used to document PIE. Her PIE significantly improved after 12 weeks, leaving just 105 shallow rolling scars devoid of pigmentation. Improvements in pigmentation and erythema 106 were seen by dermoscopy. There were no systemic or local side effects noted.

The current study showed that showed insignificant difference between the two groups as regarding patients satisfaction ($P=0.07$). Eight patients expressed excellent pleasure and fifteen exhibited good satisfaction on the AFCO2 + TM 0.5% (right) treated side; three patients reported outstanding satisfaction and thirteen indicated good happiness on the AFCO2 only (left) treated side.

With fractional laser therapy for acne scars, patient satisfaction ratings have been usually excellent. After getting the surgery, several patients report enhanced self-esteem and life quality. With fractional laser therapy, patient-reported outcomes and surveys regularly reveal high levels of satisfaction and pleasant experiences [14].

In a study published in the Journal of Cosmetic and Laser Therapy, researchers assessed patient satisfaction after fractional laser therapy for acne scars. The research found a high satisfaction rate of 80%, with patients reporting

better scar appearance, greater self-esteem, and overall happiness with the treatment results [15].

According to the current investigation, 2 (7%) patients on the right side (AFCO2 + TM 0.5%) had erythema, 1 subject (3%) had edema, 1 subject (3%), had an infection, 3 subjects (10%) had pain, and only 1 subject (3%) had hyperpigmentation. Three participants (10.0%) had hyperpigmentation, two subjects (6.7%) reported edema, and four patients (13%) had erythema on the left side (AFCO2). On both sides of the face, the side effects were similar and barely different ($p=0.13$).

According to comparable research, the patients' initial adverse effects included discomfort, erythema (39.4%), erythema and edema (21.2%), and erythema [16].

Pain, erythema with edema, and erythema were more common in subjects treated with fractional CO2 laser alone. This suggests that topical application of autologous PRP following fractional CO2 laser treatment reduces immediate side effects (such as erythema, edema, and pain), likely because of PRP's regenerative properties [17].

There were three patients with hyperpigmentation, two patients with erythema, acne, and discomfort, and one patient with a secondary infection [18].

When conducted by trained experts, fractional CO2 laser therapy is usually regarded safe. However, it is essential to be aware of any adverse effects and difficulties. These may include transient redness and swelling that normally diminish within a few to seven days. Some patients may suffer moderate discomfort or pain, which may be addressed with topical anaesthetics or painkillers. Changes in skin pigmentation, such as the darkening or lightening of treated regions, may also arise during fractional laser therapy, particularly in persons with darker skin types. There is a tiny danger of infection or scarring, which may be minimised by adhering to pre- and post-treatment cleanliness standards and correct pre- and post-treatment care [19].

CONCLUSION

Applying topical 0.5% TM twice a day could result in a noticeable improvement, enhances the function of the skin's barrier and may encourage re-epithelialization following laser treatments. Timolol is an excellent option for treating acne scars because of its simple accessibility, low cost, and non-invasive nature. However, further

research using bigger, replicated samples and controlled trials is required to confirm these results.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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Citation

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