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Comparative Study for Treatment of Normolipidemic Xanthelasma Using Ablative CO_2 Laser with Intralesional Injection of Platelet Rich Fibrin versus its Topical Application

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ABSTRACT

Background: Xanthelasma palpebrarum is a benign lesion with significant cosmetic impact and therapeutic challenges. Fractional CO_2 (FCO_2) laser has been used successfully, though with limitations. Platelet-rich fibrin (PRF), a novel platelet concentrate with anti-inflammatory properties, may enhance healing.

Aim: To compare intralesional PRF injection versus topical PRF membrane application following ablative FCO_2 laser in bilateral normolipidemic xanthelasma.

Patients and Methods: Thirty patients with bilateral xanthelasma (60 lesions) underwent ultra-pulsed ablative CO_2 laser. Lesions were randomized into two groups: group A (30 lesions) treated with topical PRF membrane and group B (30 lesions) with injectable PRF fluid. Clinical evaluation and sequential photographs were recorded before and at 1, 3, and 6 months post-treatment.

Results: Baseline characteristics were comparable between groups. Both methods produced significant cosmetic improvement with no recurrence at one-year follow-up. Group B (injectable PRF) demonstrated better, though statistically non-significant, improvement compared to group A. Only one patient developed a keloid scar after intralesional PRF.

Conclusion: Ablative FCO_2 laser followed by either topical or injectable PRF is safe and effective for normolipidemic xanthelasma. Injectable PRF provided relatively superior outcomes, but both modalities achieved excellent healing and sustained clearance, offering a promising therapeutic approach.

Keyword: Xanthelasma palpebrarum, Ablative CO_2 Laser, Platelet Rich Fibrin.

INTRODUCTION

Xanthelasma palpebrarum (XP) is the commonest type of xanthomas that can present as soft, semisolid, or calcified papules, plaques, or nodules over both eyelids. Lesions typically occur symmetrically, more common in females and its prevalence increases with age. They usually cause significant cosmetic burden [1].

XPs are progressive and permanent, and they can only be resolved with treatment [2].Though several methods of treatment have been tried, but presented with long term sequalae. Each has its own respective indications and risks [3].

Carbon dioxide (CO_2) laser remains a keystone in xanthelasma management that can give good results, but several treatment sessions are often required, and this can be costly. Yet, post-laser adverse events which include post-inflammatory hyperpigmentation or scar formation have to be taken into consideration [4,5].

Autologous PRF is composed of the plasmatic fraction of centrifuged blood. In recent years, it has been considered a novel generation of platelet concentrate that has a lot of benefits over PRP without utilizing anticoagulants [6]. PRF also serves as a reservoir of bioactive molecules being rich in growth factors (GFs), platelets and leucocytes. GFs activate and attract stem cells to the injured area [7]. So that injectable PRF (i-PRF) and its membrane can reduce the proinflammatory response promoting faster and prolonged healing. Also, it can be effective in repairing radiation-induced skin injury (RSI) and its long term sequalae [8,9].

Aim of Work

To compare the therapeutic efficacy of PRF injection versus topical platelet rich fibrin membrane application after ablative FCO_2 laser in treatment of bilateral normolipidemic xanthelasma cases.

PATIENTS AND METHODS

This prospective randomised comparative study was conducted on 30 patients with bilateral normolipidemic xanthelasma, recruited from the outpatient clinic of Dermatology, Andrology, and STD department, Mansoura University Hospitals, at the period between April, 2024 and April, 2025.

This study included 30 patients (6 males and 24 females) with bilateral more or less symmetrical normolipidemic xanthelasma who did not receive any treatment for the previous 3 months, excluding pregnant or lactating mothers, patients with any systemic disease such as acute infection or malignancy, patients taking corticosteroids or anticoagulant drugs, patients suffering from other dermatological diseases as recurring herpes infections or history of keloids.

Entire patients were subjected to history taking, thorough general and dermatological examination comprising body mass index and dermatological examinations of the studied lesions as regards site, size, extent, shape, number of lesions and skin phototypes according to Fitzpatrick schedule. Assessment of disease severity included clinical evaluations of each group according to Xanthelasma Grading System depending on site and extent of the lesion [10].

Routine laboratory investigations were done. Digital photographs of all lesions were taken before

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treatment, immediately after treatment and (two weeks, one month, three months and six months) after treatment.

The 60 studied lesions were categorized randomly into 2 groups, both were treated with ablative fractional CO_2 laser session, group (A): 30 lesions were treated with PRF membrane spread over laser-treated areas with massage and group (B): 30 lesions were injected by PRF fluid in laser-treated areas. Ablative CO_2 laser was applied in one session, which might be repeated after 4 weeks according to the outcome in follow up [7].

Ablative Fractional Carbon Dioxide (CO_2) Laser Session

The session was performed using the surgical hand piece of DEKA laser machine, DEKA (SmartXide Dot, Florence, Italy) at LASER unit, Dermatology Department, Mansoura University. Using ultra-pulse mode of ablative fractional CO_2 laser with parameters: (wave length 10,600 nm; power output 2 to 5 watts, 2-3 w for thinner skin areas near medial canthus and up to 5 w for slightly thicker lesions; frequency 100- 200 Hz; pulse duration 200-400 μs often <1 millisecond), the number of passes had an average 4-7 passes depending on the thickness of each lesion with assessment in between to avoid over-ablation and to reduce the risk of scarring. Between passes, gentle removal of charred tissue was done by using a normal saline soaked gauze piece to expose the planes. Complete removal of yellowish fatty tissue and appearance of underlying whitish membrane was taken as the endpoint of therapy, 0.3% tobrin eye ointment was applied before and after the session. Patients were instructed to keep the area sterile, follow sun protective measures, and apply 0.25% burnasores ointment twice daily for two weeks after the session.

Preparation of PRF

PRF fractions were prepared from non-coagulated blood, where 5 ml of autologous venous blood were collected, taken into the plain sterile vacutainer without anticoagulant, immediately centrifuged for 1500 rpm for 15 min. Fluid PRF clots within 15-20 minutes after spinning, so timing is critical. Prepared PRF-membranes were spread over the laser-treated areas with massage and kept for thirty min in group (A). 20-25 units with insulin syringe containing the PRF fluid were injected at 30 degrees angle into laser-treated areas in group (B), after injection, cases were asked to press on the injection areas with a swab for ten min.

Patient Evaluation

Patients returned to the clinic for post-procedure assessments, result evaluation and photography once all crusting subsides (after 14 days). Clinical evaluation of the studied lesions was done before and after treatment by two independent observers using serial photography (every two weeks for one month, after three months and after six months) after the approach to assess the outcome of the procedure and percent of improvement then follow up was done one year after treatment for recurrence assessment.

Complications evaluation included erythema, infection, pigmentation disorders, recurrence and scars.

The results were scored from zero to three according to comparing pre-treatment and 6 months post-treatment clinical photographs using a quartile scale of lesion clearance. At the end of the study, patient's satisfaction was graded using a subjective 4 point scale, unsatisfied (>25%), slightly satisfied (25%-50%), satisfied (51%-75%) and very satisfied (>75%) [11].

Ethical considerations:

Mansoura Faculty of Medicine's Institutional Review Board (IRB) approved this report (MS.24.01.2682). Informed written consent was obtained from all subjects following explanation of the benefits and possible complications of the approach, and the privacy was respected. All data were kept confidential. The study was conducted in accordance with the Helsinki Declaration.

Statistical Analysis

The collected data were coded, processed and analysed using the SPSS version 26 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were assessed for normal distribution using the Shapiro-Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) was utilized to calculate difference between qualitative variables. Quantitative data were expressed as mean±SD and range. Independent samples t-test was utilized to compare between two independent groups of normally distributed variables (parametric data), whereas Mann-Whitney U test was used for non-normally distributed Data (non-parametric data). P-values < 0.05 were significant.

RESULTS

This study included 30 patients with bilateral normolipidemic xanthelasma. Their female to male ratio was 4:1, aging from 30-63 years with mean age 48.9±8.60, according to BMI their mean was 29.26±5.65 and they were confined to skin type III and skin type IV. Patients' disease duration was 1 year up to 3 years. The lesions were categorized randomly into 2 groups; both were treated with ablative fractional CO_2 laser ultra-pulsed mode.

Group (A): (30) lesions were treated with PRF membrane spread over laser-treated areas with massage.

Group (B): (30) lesions were injected by PRF fluid in laser-treated areas.

As in **table (1)** insignificant difference was detected between studied groups as regard size, thickness and number of lesions i.e., both groups were cross matched.

Table (1): Clinical Criteria of the Studied Lesions before Treatment.

	Group A		Group B		P value
	N	%	N	%	
Number of lesions					
1	23	(76.7)	22	(73.3)	P=0.37
2	5	(16.7)	4	(13.3)	
>2	2	(6.7)	4	(13.3)	
Sites					
Upper lid	20	(66.7)	15	(50)	P=0.403
Lower lid	4	(13.3)	7	(23.3)	
Both lids	6	(20)	8	(26.7)	
Size					
Mean	16.68±3.82		16.34±3.19		P=0.63
<10 mm2	12	(40)	10	(33.3)	P=0.849
10-20 mm2	14	(46.7)	15	(50)	
>20 mm2	4	(13.3)	5	(16.7)	
Thickness					
Plane	7	(23.3)	7	(23.3)	P=0.954
Papule	9	(30)	8	(26.7)	
Plaque	14	(46.7)	15	(50)	
Grading					
Grade I	25	(83.3)	24	(80)	P=0.896
Grade II	2	(6.7)	3	(10)	
Grade III	3	(10)	3	(10)	
Grade IV	0		0		

Used tests: Chi-Square test, student t-test.

As in **table (2)** and **Fig. (1)** there was a decrease in size of the studied lesions during follow up after treatment with a statistically significant decrease in size among group B using i-PRF after 2 weeks and after one month of treatment. On the other hand, there was a non-statistically significant difference detected between both groups regarding size assessed before treatment, after 3 and 6 months as both gave approximately same results at this period. Among group A; treated with PRF membrane, there was a statistically significant better improvement and a decrease of mean affected area with the highest percentage of improvement was detected while comparing between before treatment with that after 6 months follow up with final complete clearance. Among group B; treated with injectable PRF, there was a statistically significant better improvement and a decrease of mean affected area with the highest percentage of improvement was detected while comparing it before treatment with that after 6 months follow up with complete clearance finally. The percentage of improvement while comparing the readings with that before treatment values demonstrates that group B shows better and more rapid improvement without a statistically significant difference from group A.

Table (2): Comparison of Therapeutic Response among Both Groups Along Study Period

Study period of both groups Parameters	**Before**		**2 Weeks**		**1 Month**		**3 Months**		**6 Months**	
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Size Mean±SD	16.68± 3.82	16.34± 3.19	14.68± 1.91	12.98± 1.77	10.62± 1.71	9.23± 1.62	6.97± 2.45	6.61± 1.64	0	0
Percent of change	-		11.9%	21.1%	36.3%	43.5%	58.2%	59.5%	100%	100%
-P1 value	0.693		0.001*		0.002*		0.515		1.0	
-P2 value			<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

Used tests: Chi-Square test, student t-test, *Statistically significant, Zero=Complete resolution. P1= compare between both groups as regard size before, after 2 weeks, after 1 month, after 3 months and 6 months after treatment. P2= compare between percent of change in size in the same group, before treatment and (after 2 weeks, after 1 month, after 3 months and 6 months after treatment).

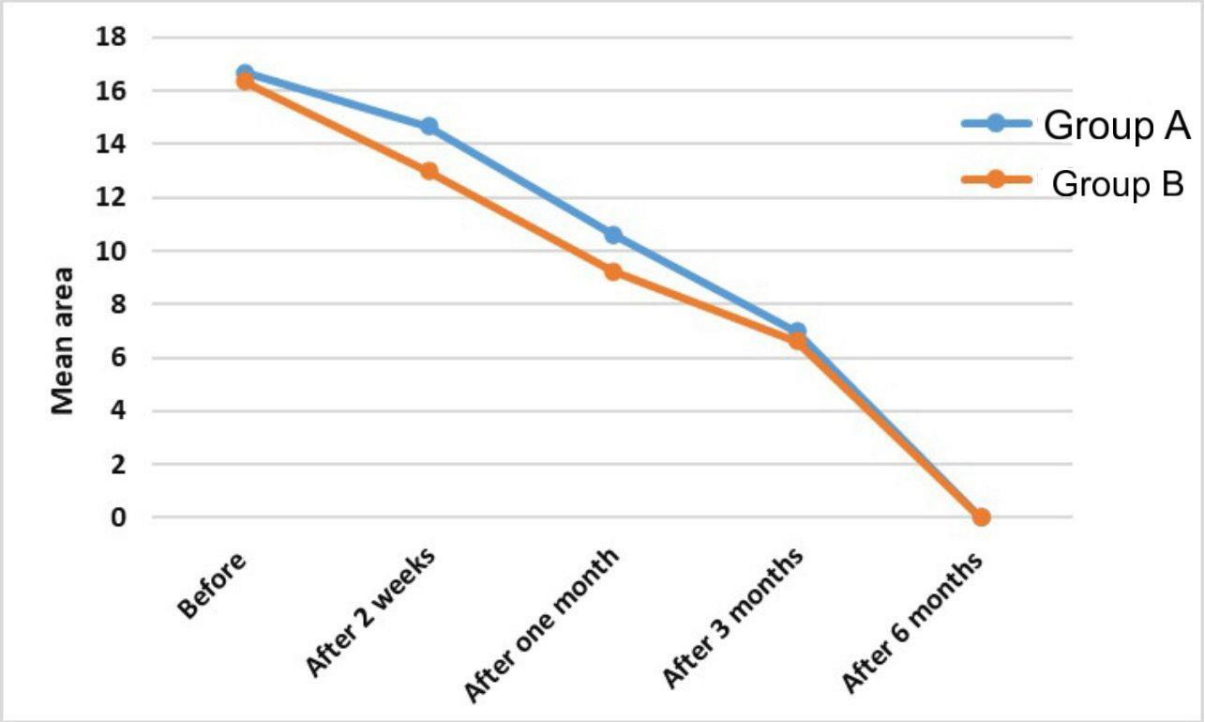

Figure (1): Difference of mean area change before treatment and during follow up between group A and group B.

As in **table (3)** the number of sessions among studied cases was as following: most of cases received only one session, some of them received two sessions and only one case had three sessions. Although both groups used the same number of sessions, there was statistically significant difference between studied groups as regards improvement which started and completed earlier among group B (injected with PRF).

Table (3): Number of Used Laser PRF Sessions in Both Groups with Comparison of Therapeutic efficacy Between Them According to Chronological Improvement.

	Group A (PRF gel)		Group B (Injectable PRF)		P value
	N=30	%	N=30	%	
Number of sessions					
One	21	(70.0)	21	(70.0)	
Two	8	(26.7)	8	(26.7)	P=1
Three	1	(3.3)	1	(3.3)	
Improvement started after					
2 weeks	21	(70.0)	24	(80.0)	
1 month	9	(30.0)	6	(20.0)	P=0.371
Improvement completed after					
1 months	21	(70.0)	24	(80.0)	
3 months	8	(26.7)	5	(16.7)	P=0.640
4 months	1	(3.3)	1	(3.3)	

Used test: Chi-Square test, *Statistically significant, P<0.05 is significant.

As in **table (4)** significant excellent response to treatment and improvement completed after one session mostly when the lesions were solitary, small<1 cm, grade I, in the form of plane or papule, located in the upper eyelid of skin type III and associated with short disease duration. However, it was non-statistically significant as skin type and disease duration.

Table (4): Clinical Correlation between Number of Used Laser PRF Sessions and Clinical Criteria.

	1 session N=21(%)	2 sessions N=8(%)	3 sessions N=1(%)	P value
Age (years) Mean±SD	47.36±7.66	48±8.78	63.0±0	P=0.001*
Skin type				
III	12 (57.1)	2 (25)	0	P=0.191
IV	9 (42.9)	6 (75)	1 (100)	
Disease duration				
<1 y	13 (61.9)	4 (50)	0	P=0.067
1-2 y	7 (33.3)	2 (25)	0	
>3 y	1 (4.8)	2 (25)	1 (100)	
Number of lesions				
1	19 (90.4)	4 (50)	0	P=0.031*
2	1 (4.8)	3 (37.5)	1 (100)	
>2	1 (4.8)	1 (12.5)	0	
Sites				
Upper lid	18 (85.7)	2 (25)	0	P=0.006*
Lower lid	2 (9.5)	2 (25)	0	
Both lids	1 (4.8)	4 (50)	1 (100)	
Size				
<10 mm2	12 (57.1)	0	0	P=0.001*
10-20 mm2	9 (42.9)	5 (62.5)	0	
>20 mm2	0	3 (37.5)	1 (100)	
Thickness				
Plane	7 (33.3)	0	0	
Papule	9 (42.9)	0	0	P=0.005*
Plaque	5 (23.8)	8 (100)	1 (100)	
Grading				
GI	20 (95.2)	5 (62.5)	0	P=0.007*
GII	1 (4.8)	1 (12.5)	0	
GIII	0	2 (25)	1 (100)	
GIV	0	0	0	

Used tests; One Way ANOVA test, Chi-Square test, *Statistically significant.

Cases Presentation

Photo (1) shows a 48-year-old female case with bilateral normolipidemic xanthelasma grade I on both sides after one laser PRF session. Group (A) right sided lesion for 1.5 years treated by PRF gel with massage after CO_2 laser while group (B) left sided lesion for 1 year treated by injectable PRF after CO_2 laser.

Photo (1): A) before treatment, B) complete improvement after One month

Photo (2) shows a 60-year-old female case with bilateral normolipidemic xanthelasma grade I on both sides after one laser PRF session. Group (A) right sided lesion for 1.5 years treated by PRF gel with massage after CO_2 laser while group (B) left sided lesion for 1.5 years treated by injectable PRF after CO_2 laser.

Photo (2): A) Pre-treatment, B) One-month post-treatment

Photo (3) shows a 38-year-old female patient with bilateral normolipidemic xanthelasma grade I on both sides after one laser PRF session. Group (A) right side lesion for 1.5 years treated by PRF gel with massage after CO_2 laser while group (B) left sided lesion for 1.5 years treated by injectable PRF after CO_2 laser

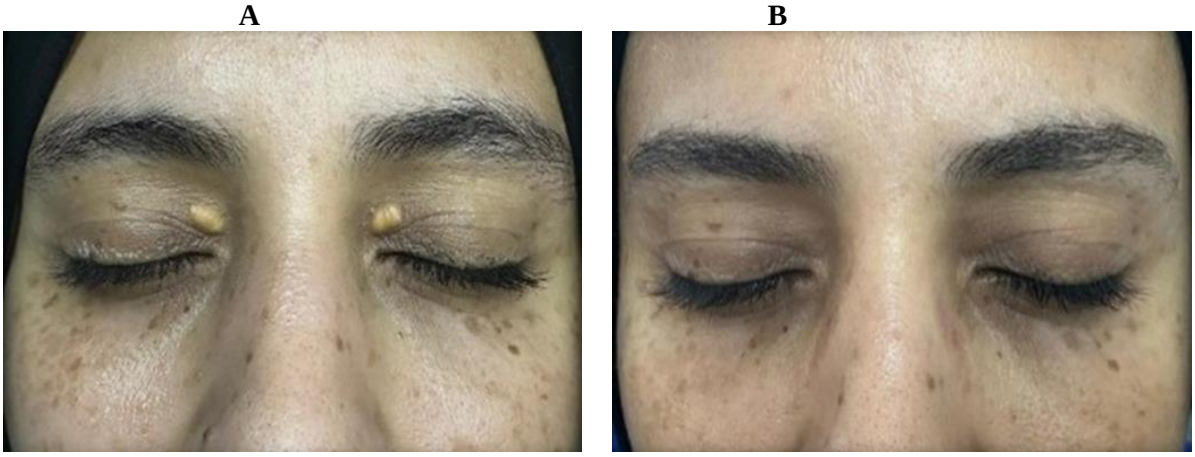

Photo (3): A) Before treatment, B) One month after treatment.

DISCUSSION

Fractional CO_2 (FCO_2) laser remains a keystone in the management of xanthelasma but there are few drawbacks of it e.g., scarring and post inflammatory hyperpigmentation clearance [4,5]. PRF acts as a reservoir of bioactive molecules being rich in growth factors, platelets and leucocytes that can reduce the proinflammatory response clearance [7].

To our knowledge, this is the first study to assess the efficacy of PRF after CO_2 laser in the treatment of xanthelasma. So, our study was conducted to compare the therapeutic efficacy of PRF injection versus topical PRF membrane application after ablative CO_2 laser in management of bilateral normolipidemic xanthelasma patients. Thirty cases with bilateral normolipidemic xanthelasma were included in this study where lesions were categorized randomly into 2 groups, group (A) included (30) lesions were treated with PRF membrane spread over laser treated areas with massage and group (B) included (30) lesions were injected by PRF fluid in laser-treated areas.

In this study, all cases were confined to skin type III in 14 patients and skin type IV in 16 patients and most of them had disease duration one year. Similar distribution of skin type was shown in a study by **Soliman *et al.*** [12] who showed that skin type III was reported in 12 patients and skin type IV in 16 patients. However, the disease duration was ranging from one to ten years. The difference in disease duration was mostly due to differences in the inclusion and exclusion criteria between the studies.

Our study displayed that most of lesions in both groups were solitary (76.6% in group A vs 73.3% in group B), grade I (83.3% in group A vs 80% in group B), located in the upper eyelid (66.7% in group A vs 50% in group B) and sized 10-20 mm^2 (46.7% in group A vs 50% in group B) in the form of plaque. Similar findings were shown by **Wang *et al.*** [13] who reported higher prevalence of grade 1.

There were insignificant differences between both groups regarding size, thickness and number of lesions, so any differences in results were related to study protocol.

The number of sessions among studied cases was as following: Most of cases received only one session, some of them received two sessions and only one case had three sessions. In another study by **Esmat *et al.*** [14] included XP lesions which were randomly managed by single session of ablative SP CO_2 laser or three to five sessions of ablative FCO_2 laser with monthly intervals.

In this study, there was a decrease in size of the studied lesions during follow up after treatment with a statistically significant decrease in size among group B using i-PRF after 2 weeks and after 30 days of treatment. In contrast, there was a non-statistically significant difference detected between both groups regarding size assessed before treatment, after 3 and 6 months as both gave approximately same results at this period. The percentage of improvement while comparing the readings with that before treatment values demonstrates that group B (injected with PRF) showed better improvement without a statistically significant difference from group A. In both groups, when comparing the readings before treatment with that after 6 months follow up, there was a statistically significant better improvement and decrease of mean affected area with the highest percentage of improvement associated with complete clearance finally.

According to quartile scale of lesion clearance [11], all lesions showed complete resolution as a final response after different periods of time without recurrence in any case i.e., clearance rate exceeded 99%. The response score was recorded and there was a non-significant difference between studied groups regarding overall response to treatment. However, an excellent better response was detected among group B as compared to group A. Matching with our study treatment response, a recent study by **Wang *et al.*** [13] that included 295 patients with xanthelasma, all underwent CO_2 laser excision. The clearance rate exceeded 99%.

Our study showed an excellent response to treatment after one session in 21 cases mostly when the lesions were solitary, small<10 mm^2, grade I, in the form of plane or papule, located in the upper eyelid, of skin type III and associated, with short disease duration, excellent response to treatment after two sessions recorded in 8 cases and excellent response to treatment after three sessions recorded only in one case. There was significant difference as regard number of lesions, disease duration, thickness and grading.

In this study, for group A (treated by PRF membrane), the commonest complications were transient post laser erythema, edema and hyperpigmentation. For group B (treated by injectable PRF), the commonest complications were pain during session, transient edema and erythema. **Nicoletti *et al.*** [15] published immediate post-operative erythema and edema that were routinely observed and peaked immediately after treatment. Another study by **Wang *et al.*** [13] who claimed that the main complications in his study after removing xanthelasma with CO_2 laser over 12-months follow up were scare formation (4.4%), hyperpigmentation (8.1%) and hypopigmentation (8.5%), with no severe complications recorded.

Only one case in our study developed keloid scar (p=1.0) after one month of treatment by PRF injection in group B. Although it was reported that the super pulse and ultra-pulse modes of non-fractional CO_2 laser cause scarring because of using the full ablative approach, but the creating microthermal treatment zones formed by the ablative FCO_2 laser permit limited ablation with proper healing, collagen remodeling, and rejuvenation with minimal risk of scar formation [16]. Also, **Pan *et al.*** [17] recorded that ultra-pulse mode of FCO_2 laser approach could efficiently improve the condition of facial atrophic scars.

In the present study, using ablative FCO_2 laser with ultra-pulse mode, there was no recurrence in any lesion after treatment as for both groups. On the other side, a study that was carried out by **Wang *et al.*** [13] in 2024 on 295 patients of xanthelasma treated by CO_2 laser, the recurrence rate was 6.8%, and lesions larger than two mm in height had greater recurrence rates than those smaller than two mm (p<0.001). Because it is theorized that CO_2 laser prevents recurrence by using thermal energy, which damages the perivascular foam cells and coagulates the dermal vessels, causing the block of lipid leaking within the tissue [18].

Based on a preceding study comparing the effects of the super pulsed mode and the fractional mode of the CO_2 laser, there was no recurrence in the xanthelasma managed with the FCO_2 laser, where the epidermal layer with lipid deposits and the underlying dermal layer were removed together. On the other hand, in xanthelasma managed with a super pulsed CO_2 laser, the lipid deposit mightn't be removed uniformly, causing recurrence [14]. It is possible to infer that full removal of lipid deposits and the depth of the removal of xanthelasma using an FCO_2 laser are essential to avoid recurrence. In conclusion, the residual lipid deposits following removal with a CO_2 laser could induce a recurrence of lesions [4].

Our study displayed that there was significant better difference in improvement between the studied groups as regards time which started and completed earlier among group (B) treated with PRF injection after laser. Other studies like **Pathania *et al.*** [19] applied his study on 10 patients (20 lesions) using ultra pulse CO_2 laser (10.600 nm) in one single session. The recurrences in two of the cases may be clarified by superficial and partial ablation of the lesions and an adverse lipid profile in at least one case. Post-inflammatory hyperpigmentation in two of the cases may be due to failure to notice sun-protective measures and/or

inherent liability for post inflammatory hyperpigmentation in skin type IV of his patients. **Basar *et al.* [20]** reported recurrence in six of 40 eyelids treated by argon laser within 8–12 months. The assessment depended mainly on scar formation and lesion color. The aesthetic outcome was considered good (absence of both visible scar and scar dyschromia) in 85% of the cases, fair (tiny visible scar and/or slight dyschromia) in 10% of the cases, and poor (visible scar and/or evident dyschromia) in 5% of the cases.

Farag *et al.* [21] included 36 lesions of 16 patients (28 upper lids and eight lower lids), argon laser therapy was used. All lesions gave response after treatment. After two weeks, the xanthelasmas had diminished in size or even disappeared. The esthetic outcome was good or very good in 28 lesions, but residual lesions were present in eight cases. Eight lesions were treated twice, while nine lesions of the 36 with a follow-up longer than six months developed a recurrence. One patient was lost to follow-up. No recorded intraoperative or postoperative complications, and no significant scar developed. They mentioned that the advantages of the approach described above included fast and easy performance and minimal tissue loss. In addition, surgery was avoided, and therapy was repeatable.

Limitations

Due to the limited treatment area in each session, larger xanthelasma lesions may require multiple treatment sessions, which could lengthen the duration and increase the cost of treatments. The multiple-session recommendation is reasonable, as larger wound sizes extend the healing process, increasing inflammation and fibrosis and therefore raising the risk of scar formation. In addition, it is of great significance to observe that wound healing happened by secondary intention, with epithelialization emerging in one–two weeks. Therefore, close follow-up and proper wound care are particularly essential for cases with larger xanthelasma lesions to minimize scar formation. The preparation process of PRF needs to be fast, or the fibrin polymerizes. The size is also limited, so it can only be applied to smaller defects. So, we recommend to perform further multicenter studies with larger sample size and perform further studies with more prolonged duration of follow up for better assessment of the results.

CONCLUSION

The cosmetic outcome after removal of the xanthelasma with ablative fractional CO_2 laser followed by PRF topical membrane application or followed by PRF injection was associated with significant reduction in the area of lesions. The area of lesions after 2 weeks and after one month was significantly lower in group B (injection of PRF). The two methods for application of PRF showed great healing results and were almost safe with no recurrence reported. So, we report that autologous PRF enhances the effect of the ablative CO_2 laser and decreases potential adverse events of the laser with fewer sessions when applied topically after the approach.

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