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Fractional Erbium YAG laser versus pulsed dye laser in the treatment of Xanthelasma palpebrarum: Randomized comparative intrapatient study

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ABSTRACT

Background: Xanthelasma palpebrarum (XP) is a disfiguring benign disorder. Both fractional Er:YAG laser and pulsed dye laser (PDL) have been used successfully in the treatment of XP.
Objective: To compare the efficacy of ablative fractional Er:YAG laser and nonablative PDL in the treatment of XP by using the Optical coherence tomography (OCT).
Patient and methods: Twenty-eight Patients with bilateral XP lesions were included in this randomized comparative study. The eyelids were randomly assigned to treatment by either fractional Er:YAG laser (2940 nm) or PDL (585 nm) at 2 weeks interval for a maximum of 6 sessions. Patients were evaluated objectively by the optical coherence tomography.
Results: XP lesions on both sides showed a significant improvement in area, color, and thickness. However, The PDL treated lesions showed better improvement and higher patient satisfaction. There were no complications with both modalities and no recurrence within 3 months.
Conclusion: Both laser modalities are effective and safe therapeutic options for XP however in small lesions PDL is more effective. Optical coherence tomography (OCT) can be used as an objective noninvasive method for evaluation.

1. Introduction

Xanthelasma palpebrarum is asymptomatic, soft, yellow and polygonal papules nearby the eyelids. It can occur in any race and in either sex. It is most common in middle age (Nair & Singhal, 2017). Even though XP is a benign lesion, it is permanent, it may increase in size, and it can cause cosmetic bothersome (Laftah & Al-Niaimi, 2018).

Knowing that XP can be an implication of accompanying internal diseases such as cardiovascular diseases (Khode et al., 2019), diabetes mellitus, insulin resistance, and metabolic syndrome (Agarwal et al., 2022), it is important to measure the lipid profile as well as direct the patients to further examination for early detection of such diseases to avoid and properly manage its complication. One of these investigations is measuring insulin level (Sanad et al., 2013). Insulin is an important metabolic hormone that affects body fat mass, its level was measured by the use of radioimmunoassay (RIA) (Mahmoud et al., 2015). RIA is extremely sensitive to the minutest biological molecule quantities by the use of radioactive isotopes therefore it is a very accurate measure (Grange et al., 2014). Moreover, several treatment options were previously introduced to treat XP, however a high risk of complications is possible when those are applied. In addition, XP is recurrent in nature. (Nair & Singhal, 2017). Therefore, the search for new treatment modalities that provide safety and efficacy is mandatory.

In search for safer and more efficient methods to treat XP, Fractional ablative Erbium YAG laser has been used efficiently. It creates microthermal zones, which allows for transepidermal elimination of dermal content (Hantash et al., 2006; Tuan et al., 2021). Moreover, the Pulsed Dye Laser also has been used successfully. The heat energy generated from the coagulation of the vessels causes damage to the perivascular foam cells of XP (Karsai et al., 2010; Thajudheen et al., 2019).

Matching the need for an objective non-invasive method to assess treatment progression, advancement in medical imaging technology and computer continues which is benefiting many medical fields (Wang et al., 2023). Therefore, comes the role of Optical coherence tomography (OCT); an imaging technology based on light reflection, which creates a cross-sectional image of the epidermis and dermis (Soglia et al., 2022). It allows one to see the real structures of the skin more clearly and up close to better evaluate the effectiveness of the treatment (Olsen et al., 2018).

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That being said, this study aims to compare the efficacy of ablative fractional Er:YAG laser and the nonablative PDL as therapeutic options for XP using OCT for objective evaluation.

2. Patient and method

This is a randomized intrapatient comparative study that is approved by the International Review Board of ethical committee (IRB 2-2017/27) of the National Institute of Laser Enhanced Sciences (NILES), and it is conducted according to the Helsinki Declaration rules. Patients were recruited from El Hude EL Marsoud Dermatology Hospital. Informed written consents were obtained from patients to be photographed.

Twenty-eight XP patients with bilateral lesions of both sexes were included in this study. Patients' ages ranged from 28 to 68 years old. History was taken from the patients regarding sex, age, onset, duration and course of the lesion, presence of any associated disorders, medications history, and family history.

Patients with a history of keloids, hypertrophic scars, pigmentation disorders, coagulation disorders, on systemic retinoid therapy within the last 6 months, and pregnant females were excluded.

3. Treatment protocol

The XP lesion on one eyelid was treated by ***Fractional Erbium: YAG laser*** (2940 nm, Fotona d.d., Slovenia); with the following parameters (spot size 5 mm, fluence 0.6–0.7 J, frequency rate 7.0 hz, short pulse (SP) mode, 2–4 passes), whereas the XP lesion on the other eyelid was treated by ***Pulsed Dye Laser*** (585 nm, Cynosure, Cynosure Inc, Germany); with these parameters (spot size 5–10 mm according to lesion size, fluence 7 J, pulse width 0.5 ms, pulse rate 1 hz, 2–3 overlapped pulses). A cold-air cooling device was used (Cryo 5 set at level 4, Zimmer Medizin Systeme GmbH, Neu-Ulm, Germany). Sessions were performed every 2 weeks for a maximum of 6 sessions. All patients applied topical anesthetic cream (Pridocaine cream; lidocaine/prilocaine, Global Napi Pharmaceuticals, Egypt) 30 min before the session. They used ice bags for cooling directly after the session and a topical antibiotic ointment (Terramycin eye ointment; oxytetracycline hydrochloride with polymyxin B sulfate, Pfizer, New York) for 1 week after the laser session. Patients were instructed as follows: use proper sunscreen, avoid friction of the treated areas, and avoid removing the crusts.

4. Evaluation methods

4.1. Clinical evaluation

Photos of patients were taken at baseline, at each session and 3 months after the last session by a digital camera (Nikon D90, Nikon Corp. Japan, Thailand). The comparative photographs were evaluated by a blinded physician. The XP lesions were assessed clinically by evaluation and their area, color, and thickness were recorded.

4.1.1. Baseline Patient assessment

Assessments were done at baseline according to the following grading systems: ***(1) The lesions area:*** Measured in square millimeters. ***(2) The lesions thickness:*** Graded 1, 2, 3 & 4 referring to flat, mildly elevated, moderately elevated, and markedly elevated lesions respectively. ***(3) The lesions color:*** Grade 1, 2 & 3 referring to yellowish, yellowish-orange, and orange lesions respectively.

4.1.2. Final Patient assessment

Three months following the last laser session, the patients were reassessed for the degree of improvement according to the degree of reduction in: ***(1) The lesions area:*** Scored from 0 to 3 (0 = <25%, 1 = 25%–50%, 2 = 51%–75% & 3 = >75%) ***(2) The lesions thickness:*** scored from 0 to 3 (0 = <25%, 1 = 25%–50%, 2 = 51%–75% & 3 = >75%), and ***(3) The lesions color:*** improvement scored from 0 to 2 (0 = no improvement, 1 = moderate improvement & 2 = marked improvement).

4.2. Objective evaluation

4.2.1. Optical coherence tomography (OCT)

Optical coherence tomography (OCT) (RTVue-100 system; SD Optovue, Inc., Fremont, CA) cross-line images, using CAM-L lens, was used in this study at baseline and 3 months after the last session to compare the difference between XP lesions before and after treatment to compare the efficacy of both treatments in the study.

4.2.2. Radioimmunoassay (RIA)

Blood samples were collected and estimated for ***lipid profile*** and ***fasting blood sugar*** at the Chemical Pathology Department of Al-Kasr Al-Aini Hospital, Cairo University. Also, plasma ***insulin*** was measured by ***radioimmunoassay (RIA)*** at Central Lab., Radioisotopes Department, Atomic Energy Authority using the Human Insulin Specific RIA Kit [250 tube (cat. # HI–14K), Millipore products, Missouri, USA].

5. Statistical analysisis

The statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA) was used. Quantitative data was analyzed using mean, median, standard deviation, minimum, and maximum. Furthermore, comparison between quantitative variables was done by the non-parametric Mann-Whitney test. On the other hand, categorical data was analyzed by frequency (count) and relative frequency (percentage). Comparing between them was done by a Chi square (χ^2) test or an Exact test when the expected frequency (count) is less than 5 (Chan, 2003a; 2003b). The non-parametric Wilcoxon signed-rank test was used to compare serial measurements within each patient (Chan, 2003a). Spearman correlation coefficient was used for correlations between quantitative variables (Chan, 2003c) and Cohen's weighted kappa was used to measure inter-rater reliability, to test agreement between categorical variables (Ashby, 1991). P-values were considered as statistically significant when they are less than 0.05.

6. Results

This study was conducted on 28 patients having bilateral XP (24 female [85.7%] and 4 male [14.3%]), age ranged from 28 to 68 years old (46.93 ± 13.67), skin type was III in 12 patients (42.9%) & IV in 16 patients (57.1%), disease duration ranging from 1 to 10 years (6.21 ± 5.58). Co-morbidity was hypertension in 10 patients (35.7%) & diabetes mellitus in 6 patients (21.4%). Family history of XP was found in 10 patients (35.7%). Six patients (21.4%) had previously been treated from XP using surgical excision or chemical cautery.

Their laboratory findings were as follows: 10 patients (35.7%) had hypercholesterolemia, 6 patients (21.4%) had hypertriglyceridemia, 6 patients (21.4%) had high HDL, 22 patients (78.5%) had above optimal LDL level, and 6 patients (21.4%) had high fasting blood sugar (105.50 ± 46.29).

6.1. Clinical assessment

At a maximum number of 6 sessions, complete clearance occurred in 12 of the patients (42.9%) treated with PDL; while in only 6 of the patients (21.4%) treated with fr. Er:YAG laser. It is to note that the size and depth of the lesion affected the number of sessions. For the small lesions, patients required less number of sessions (minimum of 2) for PDL.

The PDL treated lesions showed a significant reduction in their area ($p = 0.044$), thickness ($p = 0.002$), and color ($p = 0.028$) compared to fr. Er:YAG laser. The degree of improvement for PDL is more significant than fr. Er:YAG laser regarding the area ($p = 0.001$), and the thickness ($p = 0.001$) but is non-significant for the color ($p = 323$).

Table 1
Side effects of both types of laser.

Side effects	Fr. Er:YAG laser	PDL	P value
Pain			
• No pain	16 (57.1%)	8 (28.6%)	(p = 0.037)
•1–3 days	12 (42.9%)	18 (64.3%)	
•4–12 days	0 (0.0%)	2 (7.1%)	
Edema			
•No Edema	24 (85.7%)	12 (42.9%)	(p = 0.001)
•1–3 days	4 (14.3%)	16 (57.1%)	
Crust			
•No Crust	2 (7.1%)	0 (0%)	(p < 0.001)
•1–3 days	26 (92.9%)	18 (64.3%)	
•4–12 days	0 (0%)	10 (35.7%)	
Hypopigmentation	6 (21.4%)	16 (57.1%)	(p = 0.006)

P-values >0.05 = statistically significant, >0.001 = highly significant.

Side effects are as follows: treatment-induced purpra occurred in all patients treated with PDL and was resolved within 10–12 days while with fr. Er:YAG laser only erythema occurred in 6 pt. (21.4%) and no purpra. Other side effects include: pain, odema, crust, and hypopigmentation which were significantly higher with PDL than the fractional Er:YAG laser. There were no hyperpigmentation nor scarring with both treatments (Table 1). No recurrence of XP lesions 3 months after treatment for completely cleared lesions.

Patient satisfaction was more for PDL (80.00 ± 19.12) than fr. Er: YAG laser (67.50 ± 21.99), but with non-significant difference between both modalities (p = 0.094).

Cohen's Kappa, a statistic used to measure inter-rater reliability, was found to be moderate (0.462) for fr. Er:YAG laser (p < 0.001) and very good (0.823) for PDL (p < 0.001).

6.2. OCT assessment of XP lesions

To explain the OCT images we must know first how normal OCT skin image appears. The first to appear, is the first intensity peak (the entrance peak) as the stratum coreneum is nonvisible by OCT. Then follows the epidermis (hypo-reflective layer), which is the first distinguishable skin layer. After that, the second peak appears, which represents the dermo-epidermal junction. Lastly, the dermis appears (Park, 2014).

For the XP affected lesions, OCT images taken at baseline, and 3 months after laser treatment had shown differences in the extent of the lipid deposition. They were represented as difference in reflectivity. ***At baseline***, there was highly hyper-reflective shadows in the epidermis and upper dermis with irregularities in the surface, while **3 month *after treatment***, reflectivity and surface irregularities decreased, making the epidermis more distinguishable. Moreover, there were no marked differences between the two types of laser treated lesions (Figures, 1 & 2).

7. Discussion

In the present study, the authors tried to find an answer to the challenging question: which laser is better for treatment of XP. Both types of laser proved their efficacy. However, PDL caused higher significant improvement compared to Fr. Er: YAG laser regarding the decrease of area and thickness of the lesions. Complete clearance occurred in 42% of patients treated by PDL, while in 21% of patients treated by fr. Er:YAG laser. Moreover, PDL showed more patients' satisfaction as it gave better results with a less number of sessions. That is while side effects were less using fr. Er:YAG Laser.

PDL's better outcome may be owed to its deeper depth of penetration than Fr. Er: YAG laser as well as its different mechanism of action. The precise mechanism of PDL in XP is not completely understood. However, the assumption is that the coagulation of the vessels within the upper dermis generates heat energy that can cause damage to the perivascular foam cells (Schönermark & Raulin, 1996; Karsai et al., 2010; Thajudheen et al., 2019). That is while Fr. Er: YAG laser creates microthermal zones, which allows for transepidermal elimination of dermal content (i.e. esterified cholesterol and histiocyte aggregates) (Hantash et al., 2006; Tuan et al., 2021).

PDL was first used by Schönermark & Raulin, 1996 to treat a single case of XP with a single lesion. The lesion was completely cleared after 5

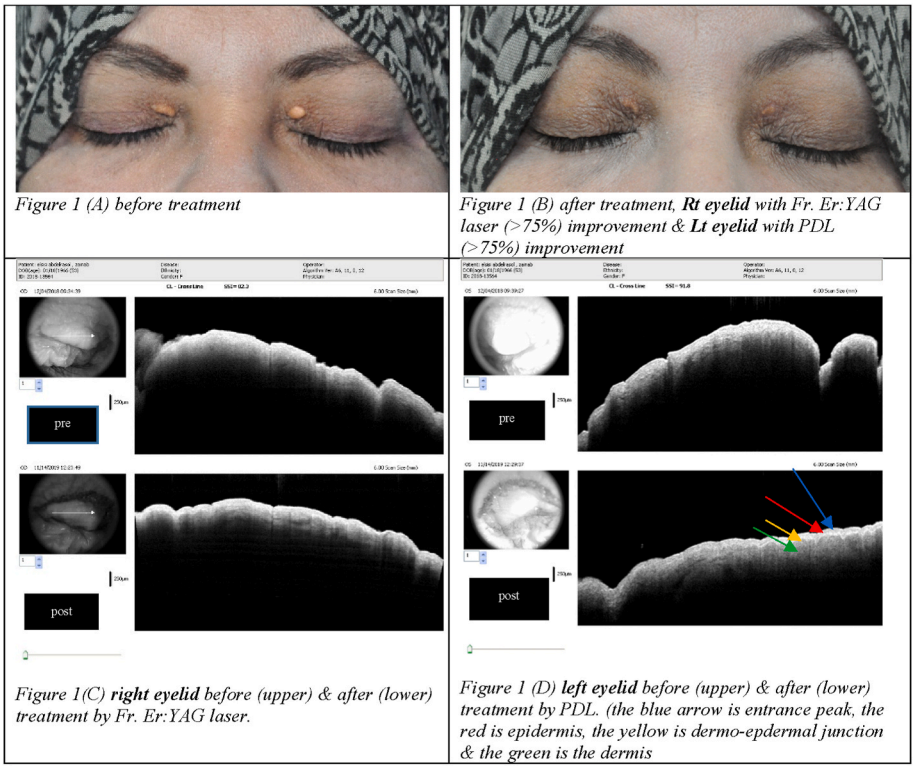

Figure 1 (A) before treatment

*Figure 1 (B) after treatment, **Rt eyelid** with Fr. Er:YAG laser (>75%) improvement & **Lt eyelid** with PDL (>75%) improvement*

*Figure 1(C) **right eyelid** before (upper) & after (lower) treatment by Fr. Er:YAG laser.*

*Figure 1 (D) **left eyelid** before (upper) & after (lower) treatment by PDL. (the blue arrow is entrance peak, the red is epidermis, the yellow is dermo-epdermal junction & the green is the dermis*

Fig. 1. A 54-year-old female with bilateral XP lesions on upper eyelid **(A)** ***before treatment***, **(B)** ***after treatment***; right side with fractional Er:YAG laser showing (>75%) improvement and left side with PDL showing (>75%) improvement, **(C)** ***A device compared OCT image; represents the right eyelid*** before treatment (upper part) and after treatment (lower part) with fractional Er:YAG laser (>75% improvement) & **(D)** ***A device compared OCT image; represents the left eyelid*** before treatment (upper part) and after treatment (lower part) with PDL (>75% improvement). ***In both OCT images; the upper part (before treatment)*** show hyper-reflective shadows in the epidermis and upper dermis with surface irregularities, ***the lower part (after treatment)*** show decrease reflectivity and more distinguishable epidermis with a smoother surface.

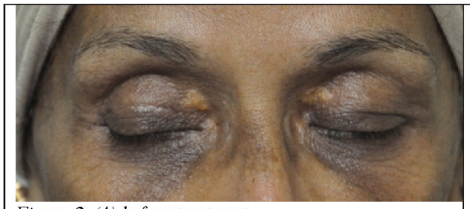

Figure 2: (A) before treatment

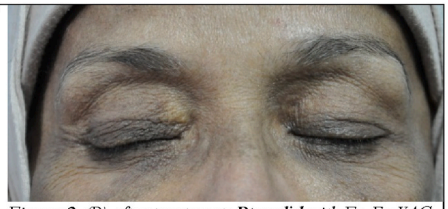

Figure 2: (B) after treatment; **Rt eyelid** with Fr. Er:YAG laser showing (51-75%) improvement & **Lt eyelid** with PDL showing (>75%) improvement

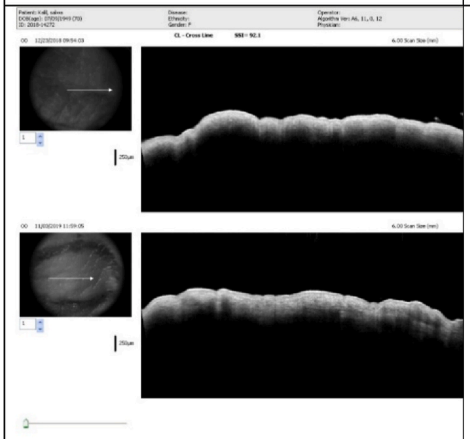

Figure 2: (C) **right eyelid** before (upper) & after (lower) treatment by Fr. Er:YAG laser

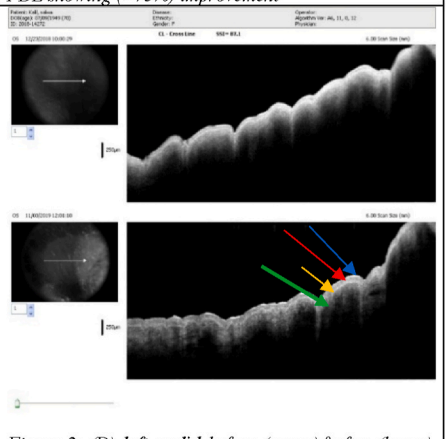

Figure 2: (D) **left eyelid** before (upper)&after (lower) treatment by PDL (the blue arrow is entrance peak, the red is epidermis, the yellow is dermo-epdermal junction & the green is the dermis

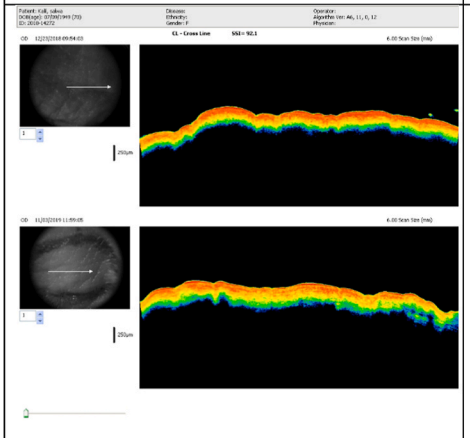

Figure 2: (E) **right eyelid** before treatment (upper) & after treatment (lower) by Fr. Er:YAG laser

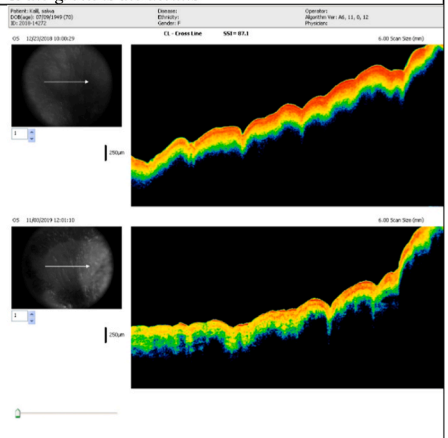

Figure 2: (F) **left eyelid** before treatment (upper) & after treatment (lower) by PDL

Fig. 2. A 69-year-old female with bilateral XP lesions on upper eyelid **(A)** ***before treatment***, **(B)** ***After treatment,*** the right eyelid with fractional Er:YAG laser showing (51–75%) improvement & left eyelid with PDL showing (>75%) improvement, **(C)** ***A device compared OCT image; represents the right eyelid*** before treatment (upper part) & after treatment (lower part) with fractional Er:YAG laser (51–75%) improvement, **(D)** ***A device compared OCT image; represents the left eyelid*** before treatment (upper part) & after treatment (lower part) with PDL (>75%) improvement. ***In both OCT images; the upper part (before treatment)*** show hyper-reflective shadows in the epidermis and upper dermis with surface irregularities***, the lower part (after treatment)*** show decrease reflectivity and more distinguishable epidermis with a smoother surface. **(E)** ***A colored image of C*** **(F)** ***A colored image of D. In both colored OCT images; The upper part (before treatment)*** show deep orange color in the epidermis and upper dermis with surface irregularities, ***the lower part (after treatment)*** show faint orange and yellow color with a smoother surface. This change in colors indicate change in reflectivity before and after treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

treatment sessions without any side effects (Schönermark & Raulin, 1996). This study was confirmed by Karsai and colleagues' study in 2010 where they used PDL to treat 20 patients with 38 XP lesions (Karsai et al., 2010). The current study has the same parameters of Karasi and differs from Schönermark & Raulin in the pulse duration. This study used a pulse duration of 0.5 ms, while in Schönermark & Raulin's study the pulse duration was 0.3–0.45 ms. Lesions showed clearance in 25% of patients in Karasi's study after 5 treatment sessions, while in 42% of patients in the current study, after 6 treatment sessions of PDL. This may suggest that better clinical clearance of lesions could be achieved by performing more treatment sessions. Moreover, in another study by Thajudheen and colleagues in India on a small group of patients (5 pt. with 14 lesions), PDL was used, but it was set on a different wavelength (595 nm), a different fluence (0.007–0.01 J), and a different pulse duration (1.5–3 ms.). They reported full clearance after the 4th session with no side effects and no recurrence for 2 years (Thajudheen et al., 2019). This suggests the following: the longer wavelength allows for more depth of penetration, the lower fluence allows for safer treatment, and the longer pulse duration allows for a greater effect.

Fractional Er:YAG laser was only used in one study done by Tuan et al. comparing 2 types of fractional laser, which are fr. Er:YAG laser & fr. CO_2 laser, to treat XP in 39 patients with 82 lesions. Like Tuan et al., the current study used the same type of laser, ***Fractional Erbium: YAG laser*** (2940 nm), and it used the same spot size 5 mm, but it differed to a large extent in the fluence. In the current study, the fluence was set at 0.6–0.7 J, at a short pulse (SP) mode, and 2–4 passes were used for 6 treatments sessions, at a 2 week interval. That is while in Tuan et al.'s study the fluence was set at 20 J, at a micro short pulse (MSP), and 2 passes were used, for up to 5 treatments sessions, with a 4 week interval. In the current study, complete clearance occurred in 21% of patients after 6 treatment sessions while in Tuan et al.'s study 85% of patients improved after 5 treatment sessions. This may be owed to the wide difference in the fluence used. Also, in the current study 6 patients (21%) developed transient hypopigmentation, while in Tuan et al.'s study 2 cases developed hyperpigmentation (5%), and 1 case developed hypopigmentation (2%). In the current study, there was no recurrence in the

3 month follow up period, while in Tuan et al.'s study 10 patients (24%) had recurrence in a 12–25 months follow up period (Tuan et al., 2021).

The OCT has been implemented in a large number of clinical studies in dermatology. It is helpful in the diagnosis of some inflammatory, bullous, and infectious skin diseases, and in the differential diagnosis of some tumors. Besides being used in monitoring the progress of therapy for skin diseases (Lentsch et al., 2022), and the evaluation of the effect of laser treatment on skin lesions (Esmat et al., 2014). That being said, it is still experimental, and it might lack some key features associated with other technologies (Olsen et al., 2018).

The OCT image captured of the skin of XP patients before and after laser treatment showed change in reflectivity. The epidermis and upper dermis appeared as hyper-reflective shadows then they changed to be less reflective after treatment, with decreasing amount of lipid, making the skin layers more distinguishable. This is owing to the fact that the higher the lipid content, the more hyper-reflective it appears. That was concluded by a study conducted by Davoudi et al. to determine the correlation between serum lipid levels and retinal hyperreflective foci. He found that higher total cholesterol and LDL were associated with retinal exudate containing lipids. They appear as hyper-reflective foci on the fundus OCT image (Davoudi et al., 2016). Moreover, according to Babalola et al., the change in reflectivity of OCT images results from change in the birefrigrance of the imaged skin tissue (Babalola et al., 2014). This indicates a change in the amount of lipid which was leaked into the dermis of XP patients after laser treatment.

A study done by Farid et al. had reported that triglycerides, cholesterol, and LDL are at elevated levels in several skin diseases as psoriasis and psoriatic arthritis (Farid et al., 2020). Similarly, in this current study, 10 patients (35%) had hypercholesterolemia, 6 patients (21.4%) had hypertriglyceridemia, 6 patients (21.4%) had high HDL, and 22 patients (78.5%) had above optimal LDL (124.84 ± 31.55), which suggests that LDL may be a causing factor for XP. In addition, a high fat diet leads to alteration in the lipid profile which might be one of the reasons causing XP (Abd Elmonem et al., 2022). Nevertheless, XP can occur with a normal lipid profile. As for association of XP with diabetes mellitus, insulin resistance, and metabolic syndrome, the fasting blood sugar was detected high (105.50 ± 46.29) in 6 patients (21.4%). In addition, insulin level was assessed by radioimmunoassay (RIA) and it was found to be (13.84 ± 2.46) which lay within normal range (from 2 to 25 mIU/ml), meaning it is insignificant, in all patients participating in the study.

That being said, when comparing the current study with previous aforementioned studies, the benefits are that this study was a randomized, intrapatient, and comparative study, which gave the chance to test two types of laser treatments on lesions of different sizes in the same patient. Moreover, it is the first study comparing the ablative Fr.Er: YAG laser to the nonablative PDL as methods for treatment of XP. It established that both types of laser can be repeated in case of recurrence without the need of local anesthesia and without the fear of scarring or major complications. It also used OCT as a non-invasive method for evaluation of laser treatment on XP, which was accepted by the patients as it is quick, comfortable, and pain free. In addition, it gives the chance to be repeated if needed, and it allows users to effortlessly save, keep, and share images.

Limitations of the study: Small sample size, short period of follow up, and difficulty to use OCT for lesions on the medial side of the eye. Moreover, there is a limited number of papers discussing the same topic with the same type of laser.

8. Conclusion

Pulsed dye Laser and fractional Er:YAG Laser are effective, safe and well tolerated therapeutic options for XP. They offer significantly shorter downtime than other methods of treatment with higher patient satisfaction, but they need multiple sessions. According to the results of this study, we recommend both types of lasers in small, shallow lesions. However, PDL is superior for its better cosmetic outcome.

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Declaration of competing interest

The authors declare that they have no competing interests.

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