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A Triple Laser Combination Treatment for Facial Angiofibromata Management in Tuberous Sclerosis and Literature Review

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:

Background: Angiofibromas are a common facial manifestation of Tuberous Sclerosis (TS). However, current treatments have proven ineffective due to high recurrence rates and non-compliance. To address this issue, we developed a new triple laser therapy protocol for more effective management of angiofibromas. We conducted tests to validate its efficacy. **Methods:** This is a prospective study of 10 patients with TS (4 women and 6 men, mean 26.3 years old {15-37 y/o}) with angiofibromata who received triple sequential laser therapy at our private dermatological clinic conducted from January 2000 to December 2022. We evaluated the outcome with the Facial Angiofibromata Severity Index (FASI) via clinical photography (0, 6 months, 1 year, 2 years) and Dermatology Life Quality Index (DLQI).

Results: All patients had a successful recovery without any complications. Among these 10 patients, 4 experienced localised recurrences at their 6th-month follow-up. These recurrences were treated with a second single CO2 laser session. After 2 years of follow-up, we observed no recurring facial cutaneous manifestations. Furthermore, all patients experienced a decrease in their FASI score after treatment. According to the Visual Analogue Scale (VAS), patients reported 95% satisfaction, and DLQI indicated only a minor impact on their everyday lives.

Conclusion: We believe that this protocol of 3-step Laser treatment is effective, safe, and compliable for patients with facial angiofibromata, providing a satisfactory outcome adaptable to the daily dermatological and plastic surgery practice.

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Table 1 3-step algorithm with Laser characteristics and settings

Step	Lasers	Wavelength (λ)	settings	Thermal Relaxation Time comparison	Advantages	Limitation
1	CO2	10.600nm	Pulse duration :350 μs Frequency: 75Hz	Thermal relaxation time < 1msec	Treating fibrous and protuberant lesions	Small percentage of recurrences if monotherapy, high thermal damage
2	Er:YAG	2.940nm	Spot size: 5 or 7mm		Resurfacing with minimal thermal necrosis zone (RTD)	Not satisfactory for protuberant lesions
2a	Long Pulse		Pulse duration:5 or 7 or 10 ms Frequency: 10 Hz Energy: 10-20J	Ablative with thermal relaxation time less than CO2, more collagen tightening	Less skin sublimation, collagen tightening, more superficial depth of resurfacing	
2b	Short Pulse		Pulse duration: 350 μs Frequency: 10Hz energy: 10-20J	Ablative with the least thermal damage, less collagen tightening	More skin sublimation, cleansing the debris, preparing skin for vascular laser	
3	PDL	585-595nm	Spot size: 7mm Energy Density: 6-10 j/cm2 (fluency)		1) Treating the vascular component of tuberous sclerosis 2) Preventing early recurrences, erythema, dyspigmentation	No ablation

Abbreviations: Er:YAG, Erbium -Yttrium Aluminum Garnet; PDL, Pulsed Dye Laser; RTD, residual thermal damage

Pt No	GEN DRE	A G E	F T	FASI before	FASI 2y	gDL QI before	gDL QI 2y	VAS 2y	FOLLOW-UP (y)	RECURRENCE 6m	RECURRENCE 2y	RECURRENCE 5y
1	M	25	3	8	1	10	2	10	2	NO	NO	N/A
2	M	27	3	8	1	15	3	10	2	NO	NO	N/A
3	F	15	3	8	1	19	2	10	7	NO	NO	NO
4	F	22	2	9	2	10	4	7	3	YES	NO	N/A
5	F	31	3	9	1	17	2	10	6	NO	NO	YES
6	M	24	2	9	2	11	3	10	2	NO	NO	N/A
7	F	24	2	8	2	13	4	10	4	YES	NO	N/A
8	M	37	4	8	2	20	2	9	10	YES	NO	YES
9	M	32	3	9	2	22	5	10	6	YES	NO	NO
10	M	26	3	7	1	11	3	10	2	NO	NO	N/A

Abbreviation FT, Fitzpatrick type; FASI, Facial Angiofibroma Severity Index; VAS, visual analogue scale; y, years; m, months; gDLQI, Greek Dermatology Life Quality Index

Table 2 The data includes information on population demographics, such as age and gender, as well as details on FT, FASI, and VAS scores, recurrences, and the length of follow-up periods.

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Abstract

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Conclusion: We believe that this protocol of 3-step Laser treatment is effective, safe, and compliant for patients with facial angiofibromata, providing a satisfactory outcome adaptable to the daily dermatological and plastic surgery practice.

Keywords

Angiofibroma, Erbium, Laser, Pulsed Dye Laser, Tuberous sclerosis

Introduction

Tuberous sclerosis (TS) is a rare genetic autosomal-dominant neurocutaneous disorder with a prevalence of 1 to 6,000 worldwide, affecting both sexes and all ethnic groups.¹ It is a multisystem syndrome involving the brain, skin, heart, kidneys, eyes, lungs, and liver, which manifests from childhood.² The classical triad of TS is seizures, mental retardation, and angiofibromata, but this occurs in only 29% of patients with TS.³ However, skin involvement is crucial for suspecting the diagnosis of TS.⁴ The most common cutaneous lesions in TS are hypomelanotic macule (90%), facial angiofibroma (75%), and Shagreen patch (20-30%) and less manifested periungual or subungual fibroma (Koenen tumour). Linkage studies have shown locus heterogeneity with a TSC gene mapped to chromosomes 9q34 and 16p13.3.⁵ Facial angiofibromata are often presented by excessive facial flushing in infancy and gradually become more prominent, causing cosmetic and hygienic troubles in adulthood.⁶

Carbon Dioxide laser (CO2 laser)

The CO2 laser is an ablative laser which uses the high absorption of infrared light in water ($\lambda=10,600$ nm), and it is indicated for cutting and vaporising tissue in a controlled manner. It has many applications in dermatology (condylomata acuminata, common warts, angiofibromata, syringomas, trichoepitheliomas, epidermal nevi, acne scars, rhytids etc.)⁷

and it has been used to treat satisfactory angiofibroma, especially when they are exophytic and large. Yet, several studies have demonstrated a high percentage of recurrences.⁸ This laser application is accompanied by thermal damage lateral to the area of treatment, which is increased if multiple passes are required.

Er-YAG (Erbium -Yttrium Aluminum Garnet) laser

Er-YAG laser is another ablative laser of $\lambda=2940$ nm strongly absorbed by water (absorption coefficient $12,000$ vs 800 cm^{-1} for CO_2) with less than 50 μm residual damage compared to the 80 to 150 μm typically of pulsed CO_2 laser exposure.⁹ Moreover, its application is wide in skin resurfacing, especially in photodamaged patients with wrinkles, acne scars, and superficial lesions. The Er-YAG laser system can deliver therapeutic intervention in both short and long pulse durations. This versatile technology offers a range of benefits for clinical applications, including precise tissue ablation, reduced thermal damage, and improved postoperative healing. The latter is the most essential advantage as wounds reepithelialise earlier than CO_2 laser wounds, yet its efficacy is lower.¹⁰

PDL (Pulsed Dye laser)

PDL technology is a vascular laser of λ ranging from 550 - 610 nm using the principle of selective photothermolysis via light absorption by oxyhaemoglobin.^{11,12} It is indicated for vascular lesions such as lower-extremity spider veins and facial vessels associated with rosacea, photodamage or simply heredity, diffuse erythema (e.g. rosacea), facial telangiectasia, Port Wine Stains (PWS), haemangiomas, scars and red striae with less risk of epidermal damage and hyperpigmentation.¹³

Materials & Methods

This is a prospective study of 10 patients (4 women and 6 men, mean $26,3$ y/o { 15 - 37 y/o}) with cutaneous tuberous sclerosis (TS) manifested as angiofibromata on malar, nasolabial regions, dorsum of the nose and the chin. All patients who were diagnosed with TS, and referred to our clinic from various dermatological outpatient clinics at public hospitals in Greece, received our suggested treatment after providing their informed consent. Only 4 patients suffered from mild mental retardation, while all experienced at least two episodes of epileptic seizures. They all received a triple laser therapy (CO_2 laser, Erbium laser- short and long pulse, Pulsed Dye Laser) in one session at our private dermatological clinic from January 2000 to December 2022. At our clinic, we have treated a total of 14 patients with TS. However, 4 of them were excluded from the study as they had undergone laser treatments in separate sessions. These 4 patients were used as a control group to establish our protocol

therapy pathway and minimise the number of sessions required. Before treatment, we obtained informed consent from all patients or their guardians, in case the patients could not obtain consent. We tested our protocol, which was delivered the same to the remaining ten patients. The efficacy of the treatment was assessed through a clinical photography-based evaluation of the Facial Angiofibromata Severity Index (FASI) at baseline and 2 years post-treatment. Thus, we employed the information panel of the published article by R. Salido-Vallejo et al.¹⁴. This comprises seven photographs depicting the complete range of FASI scores, from 0 (the best) to 3 (the worst), encompassing erythema (0-3), size (0-3), and extent (0, 2, or 3).

Additionally, we gauged the level of patient satisfaction using the widely accepted Visual Analogue Scale (VAS) scoring system during follow-ups and the Greek version of the Dermatology Life Quality Index (DLQI) before and at two years follow-up via telephone interviews (licence with ID CUQoL2236 has been granted for the purpose of our study). The DLQI is a tool used to assess the impact of a skin condition on an individual's quality of life. Scores on this scale range from 0 to 30, with a score of 10 or above indicating a significant impairment in daily functioning due to the skin disease.¹⁵

Operative Procedure-Algorithm

All patients received prescribed topical anaesthetic cream preparation CHEMCO® (benzocaine micronized 20%, lidocaine base 6%, tetracaine HCL 4%, propylene glycol, CHEMCO ® Lisolate ®) for 45 min followed by local anaesthesia with xylocaine 1% diluted with NaCl 0.9% 1:1, and 1 adrenaline 1:100.000. In some cases, we administered a bilateral infraorbital block using 1-2 ml of 1% xylocaine on each side. Protective goggles were given to the patient for eye safety.

All ten patients underwent the 3-step methodical laser treatments tailored to each patient according to the lesions' size and depth in one session.

In the first step, topical ablation of the skin lesions was performed with a CO₂ laser with a pulse duration of 350 µs and frequency of 75Hz to resurface the diseased skin and flatten the cobblestone area. The second step involved Er:YAG laser short and long pulse in a specific pattern. In more detail, the first pass was performed with the long pulse duration, while the second was with the short. The long pulse enhanced ablation, haemostasis and skin tightening. In contrast, the short pulse facilitates skin sublimation, and cleanses the surface from skin debris produced by CO₂ laser and Er: YAG long pulse with minimal thermal damage. Thus, it prepares the skin for vascular laser treatment.

The long pulse settings were pulse duration 5 or 7 or 10 ms, frequency 10 Hz and energy 10-20J. The short pulse was 350 μ s, 10 Hz frequency and 10-20J. The spot size used was 5-7mm, depending on the size of the lesions. The treatment was carried out as multiple passes until the pin-point bleeding was evident. (Table 1)

The last step of the treatment was with Pulsed Dye Laser (PDL) with energy density (fluency) 6-10 j/cm^2 , which was used to collapse the small vessels, and decrease the erythema and dyspigmentation, therefore diminishing the potential recurrence. (Table 1)

Post-treatment care included topical fusidic acid ointment, daily local compresses with cool NaCl 0.9% for 7-10 days and a silicone-based gel applied onto the skin for 1-2 months. Antiherpetic treatment was given only to patients prone to herpetic infection. There is no clear consensus on the requirement of routine prophylactic antibiotherapy before full-field ablative laser applications. However, we prescribed ciprofloxacin as prophylaxis, starting before and continuing five days after the treatment. All patients were followed up in 10 days, 1 month, 6 months, 1 year and 2 years post-treatment.

Results

All patients completed the study without complications and complied with the treatment and aftercare. None of our patients experienced complications, such as infection, scarring, dyspigmentation, or erythema. According to FASI, our clinical photography database shows a significant improvement in all elements (redness, size, extension) before and after two years of treatment. Of 10 patients, 4 presented with few localised recurrences on the 6th-month follow-up and a second single CO₂ laser session was performed. The clinical images of patients were evaluated before and during follow-up visits at 1 and 2 years in our clinic (Fig. 1-5).

After at least two years of follow-up, no patients showed signs of recurring facial angiofibromata. Only 4 patients had attended the five-year follow-up; of those, two experienced a mild recurrence of isolated small malar angiofibromata. One of them repeated CO₂ laser treatment for the few malar angiofibromata, while the other was satisfied with the outcome.

The Fitzpatrick skin type distribution among our patients is as follows: only three patients exhibited skin type 2, one had skin type 4, and the majority presented with skin type 3. Due to the limited population data, no correlation was found between skin type and treatment efficacy (Table 2).

According to the VAS survey conducted two years post-treatment, 95% of the participants reported high levels of satisfaction with the treatment (rating 7-10/10). The research study

involved administering the Greek version of DLQI to individuals before and after a two-year follow-up period. Prior to receiving treatment, all the patients had been experiencing a significant negative impact on their quality of life due to their skin condition. However, the results of the two-year follow-up revealed that the condition had a minimal impact on the daily lives of the participants. Detailed findings for each patient can be found in Table 2.

Discussion

In light of the literature, there are some case reports and a few case series with angiofibroma management in multiple sessions in TS patients. The first laser application of angiofibromata was reported in 1988 with argon laser, and the recurrence rates were high on long-term follow-up.¹⁶ Currently, lasers to treat angiofibromata can be mainly classified as ablative and vascular lasers. As ablative lasers, CO₂ and Er:YAG flatten the exophytic lesions and resurface the affected area, respectively. Both ablative lasers are needed to succeed in the best outcome as CO₂ manages well the exophytic lesions while the Er:YAG resurfaces the affected area, eliminating the small lesions with minimal residual damage, a trait the CO₂ laser cannot provide. Regarding vascular lasers, mainly PDL and, to a lesser extent Nd:YAG lasers, are efficient for alleviating excess vascularisation and minimising the potential erythema and hyperpigmentation. Only one case series involves 13 patients treated with a combination of Er:YAG laser, CO₂ laser and PDL. However, every laser application treatment was performed in different sessions 3 months apart.¹⁷ To date, no other study provides one-session management of angiofibromata.

There are many other treatment methods in the literature for the management of angiofibromata, such as chemical peels, curettage, electrosurgery, cryotherapy¹⁸, dermabrasion¹⁹, and shave excision²⁰ with a moderate aesthetic outcome, high recurrence rate and less compliant for the patient. Another modality is topical mTOR inhibitors, which serve as targeted treatment agents for TS regarding the role of the Pi3K-AKT-mTOR pathway in etiopathogenesis. A systematic review tested the efficacy and safety of topical sirolimus, which suggested 0.2% concentration as the most effective and safe in treating facial angiofibromata in patients with TS. However, many patients experienced irritative adverse effects, which led them to withdraw.²¹ Furthermore, the efficacy of topical sirolimus indicates that especially large lesions tend to be resistant. Limited data on the combination of topical sirolimus with laser treatments provide a rational alternative for larger lesions, less resistance, less concentration and shown to be more effective overall than solely tacrolimus treatment.²² In our study, 7/10 of our patients had utilised topical sirolimus. Yet, all had to halt this treatment due to persistent irritation, recurrence of issues, and non-compliance. The

remaining three patients opted for laser treatment without trying topical therapy despite it being offered. A multi-modal approach could potentially provide synergistic benefits for the treatment of angiofibroma. By incorporating adjunct interventions such as topical sirolimus or other targeted agents that modulate the mTOR pathway or integrating multi-modal treatments targeting different aspects of angiofibroma pathogenesis, treatment outcomes may be enhanced synergistically. However, it is essential to note that patient compliance poses a challenge as most patients may not be able to tolerate topical therapies and prefer laser therapies that can provide an immediate and long-lasting solution.

It is important to note that our study had certain limitations. Firstly, the rarity of the condition resulted in a relatively small sample size, which may have reduced the power of our analyses and the generalizability of our findings to a broader population. Furthermore, the patients we studied were from diverse regions of Greece, which posed a challenge in conducting a follow-up period of more than two years, as only four patients were able to participate. We believe that including cellular and molecular level assessments could have helped in a more comprehensive evaluation of patient outcomes. In order to include this level of testing in future studies, funding is necessary.

Conclusion

Our goal was to identify a standalone cost-effective treatment pathway for facial angiofibroma with reproducible efficiency. By using two ablative and one vascular lasers during one single session, it is possible to achieve desirable acceptable long-lasting results with no complications. Erbium (short and long pulse) and CO₂ lasers destructed and resurfaced the area without cicatrization, while PDL managed the vascular component and the likelihood of recurrence. This protocol of 3-step Laser treatment is effective, safe, and compliant for patients with facial angiofibromata, providing a satisfactory outcome adaptable to the daily dermatological or plastic surgery practice.

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Fig.1 male 37 y/o patient with TS preoperative side view

Fig.2 Postoperative side view at 2-year follow-up of the male patient

Fig.3 Preoperative enface view of 24 y/o female patient

Fig.4 Intraoperative view of the female patient

Fig.5 Postoperative enface view at 1-year follow-up of the female patient

Table 1

3-step algorithm with Laser characteristics and settings

Table 2

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