

## Comparative Study of Fractional CO<sub>2</sub> Laser versus Nd:YAG Laser with Tranexamic Acid in the Treatment of Perioral Hyperpigmentation

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**Abstract:** Perioral hyperpigmentation remains a challenging clinical condition, often necessitating advanced dermatological interventions to target underlying melanogenesis. (Bhatt, S. *et al.*, 2022) While ablative modalities such as fractional CO<sub>2</sub> laser effectively address pigment through epidermal resurfacing, the concurrent application of Nd:YAG laser with tranexamic acid offers a non-ablative pathway that specifically inhibits melanocyte activity and dermal vascular components. (Pour Mohammad, A. *et al.*, 2025) A total of 24 female participants enrolled in this study having hyperpigmentation around the mouth with multiple etiology, divided into 2 equal group, group A had 2 sessions of CO<sub>2</sub> fractional laser with topical tranexamic acid while group B had Q-switch Nd:YAG laser of multiple session with low fluence with topical tranexamic acid for 12 weeks. Visual analog scale (VAS) and physician global assessment (PGA) are used to assessing the effect of these laser on the disease. The findings in the current study reveal a significant reduction in the mean of VAS and PGA score following combination treatment (from 5.80 to 2.40 for VAS and from 6.10 to 2.7 for the PGA) at the end of 12 weeks in group A while the group B has less reduction of the mean of VAS and PGA score (from 5.90 to 3.42 for VAS and from 5.88 to 3.22 for the PGA). In conclusion the comparative study indicates that fractional CO<sub>2</sub> offers superior dermal remodeling, the Nd: YAG laser paired with tranexamic acid provides a more sustainable, low-risk approach for the complex management of perioral hyperpigmentation.

**Keywords:** Perioral, Hyperpigmentation, Tranexamic acid, CO<sub>2</sub> Laser, ND:YAG Laser.

### INTRODUCTION

Perioral hyperpigmentation is a common cutaneous disorder marked by the darkening of skin around the mouth, typically resulting from a complicated interaction of external and internal variables.<sup>1</sup> Clinical symptoms may vary from benign physiological observations to signs of systemic diseases, and the condition is commonly encountered in clinical practice, requiring thorough evaluation to rule out underlying syndromes. (Copcu, E. *et al.*, 2004) The cause is frequently complex, encompassing genetic susceptibility, UV exposure, and chronic inflammatory diseases such as allergic contact dermatitis or lichen planus pigmentosus. (Sarkar, R., & Das, A. 2018; Sarkar, R., & Verma, D. 2026) Furthermore, postinflammatory hyperpigmentation often arises as a principal response to skin damage or localized inflammation, leading to heightened melanin production and redistribution in the affected perioral epidermis. (Baby, T. 2019)

Effective management requires a layered therapeutic strategy that addresses both visible melanin deposition and the underlying pathophysiological drivers, such as chronic inflammation, hormonal fluctuations, and ultraviolet exposure. (Martínez-Gutiérrez, A. *et al.*,

2026) Therapeutic interventions typically integrate rigorous photoprotection with targeted topical agents, such as hydroquinone, as the clinical gold standard for modulating melanocyte activity. (Moolla, S., & Miller-Monthrope, Y. 2022; Caccavari. 2022) Beyond monotherapy, clinicians are increasingly adopting combination regimens that incorporate non-hydroquinone depigmenting agents and chemical peels to enhance efficacy while minimizing cutaneous irritation. (Gan, C., & Rodrigues, M. 2024) Furthermore, emerging protocols emphasize the integration of energy-based modalities, including laser therapies and microneedling, to target dermal pigment deposits that often prove refractory to topical interventions alone. (Covarrubias, S. B. *et al.*, 2025)

Recent clinical inquiries have focused on optimizing delivery systems, such as microneedling and fractional CO<sub>2</sub> lasers, to enhance the transdermal penetration of tranexamic acid. (Dawaud, S. M. K. *et al.*, 2023; Mekawy, K. M. *et al.*, 2021)

The clinical use of tranexamic acid in hyperpigmentation is due to its dual inhibitory effect on both the plasminogen-plasmin system and the release of inflammatory mediators like

endothelin-1, which otherwise propagate melanogenesis. (Lindgren, A. L. *et al.*, 2021; Behrangi, E. *et al.*, 2022). By modulating the interaction between keratinocytes and melanocytes, this pharmacological intervention effectively disrupts the cycle of pigmentation recurrence. (Nautiyal, A., & Wairkar, S. 2021) While fractional CO2 laser therapy facilitates drug delivery through thermal microchannels, the Q-switched Nd:YAG laser offers an alternative approach by targeting dermal melanocytes through photoacoustic disruption. (Beyzaee, A. M. *et al.*, 2021) Combined with microneedling, these modalities potentially offer synergistic effects by overcoming the stratum corneum barrier to maximize the efficacy of topical tranexamic acid. (Ghandehari, R. *et al.*, 2022; Searle, T. *et al.*, 2021) However, the distinct mechanisms of action—thermal ablation via fractional CO2 laser versus the pigment-selective destruction characteristic of Nd:YAG necessitate a comparative analysis to determine which platform provides superior safety profiles and clinical outcomes for perioral applications. (Tawfic, S. O. *et al.*, 2021; Khan, A. S. *et al.*, 2024) Furthermore, because microneedling is an established transdermal delivery mechanism, assessing its integration with these laser systems may offer a more standardized approach to managing recalcitrant pigmentary deposits while minimizing post-inflammatory hyperpigmentation. (Srijha, M. *et al.*, 2026; Kandi, D. K., & Osman, M. A. 2025)

Recent evidence further suggests that tranexamic acid, either administered systemically or via localized mesotherapy, offers a significant adjunct for patients with persistent, recalcitrant lesions.

## METHOD

The present study is a randomized design to evaluate the comparative efficacy of fractional CO2 laser-assisted drug delivery versus low-fluence 1064 nm Nd:YAG laser with topical tranexamic acid in the treatment of perioral hyperpigmentation. The participants are randomized into two groups, group A receiving fractional CO2 laser-assisted topical tranexamic acid, while group B undergoes serial sessions of low-fluence 1064 nm Q-switched Nd:YAG laser therapy plus topical tranexamic acid for both groups.

Patients' selection criteria for the study include participants diagnosed with perioral hyperpigmentation, requiring exclusion of individuals with active local inflammatory skin

disorders, pregnancy, or documented hypersensitivity to tranexamic acid. Additionally, participants with a history of major medical illnesses or those currently undergoing systemic hormonal or lightning therapies are excluded to minimize confounding variables that might influence melanogenesis.

Twenty-four females were enrolled in this study, with an average age of 18 years old, with hyperpigmentation around the mouth, with III-IV Fitzpatrick skin type. The hyperpigmentation was diagnosed by two dermatologists subjectively and using a wood's lamp in a dermatological and laser clinic in Baghdad city from May 2025 to December 2025, the study protocol consisted of 12 participants who were subjected to two sessions of CO2 fractional laser, which was performed by a skilled dermatologist using WON TECH CO2 fractional laser. The laser parameters were recorded as follows: (15 mJ, 0.6mm, 1 overlap) Prior to the session, all of the patients washed her faces with soap and applied Emla anesthetic cream for at least 35 minutes, followed by microneedling and topical tranexamic acid application ( group A), while group B consisted of 12 patients with perioral hyperpigmentation subjected to 4 sessions of low fluence Q- Switch Nd:YAG laser of Sanhe Laser Technology with microneedling and topical tranexamic acid application.

The study protocol was approved by the Baghdad University Medical Ethics Committee and Informed consent was obtained from patients after explaining the risks, benefits, and potential complications of each procedure.

Visual Analog Scale (VAS), starting from simple 0–10 grading of pigmentation severity and physician Global Assessment (PGA) standardized categorical scoring (mild / moderate / severe) are used to evaluate the patients prior to each session and assess the hyperpigmentation.

## RESULT

A total of 24 patients with a mean age of  $26.46 \pm 8.46$  years, with a minimum age of 19 years and a maximum age of 48 years.

After using the fractional CO2 laser and Q- Switch Nd: YAG laser with topical application of tranexamic acid for both groups, the VAS showed significant changes with improvement of the pigmentation in the CO2 fractional laser than Q-Switch ND: YAG as shown in Table 1.

**Table 1:** Mean and standard deviation of VAS.

	Fractional CO2 Laser		Q-Switched Nd:YAG Laser		p-Value
	Mean	Standard deviation	Mean	Standard deviation	
VAS - base line	5.80	0.80	5.90	0.90	0.844
VAS- 4 WK	4.4	0.84	4.90	0.86	0.000
VAS- 8 WK			3.83	0.69	0.000
VAS- 12 WK	2.4	0.72	3.42	0.79	0.007
P-Value	0.000		0.000		

While the PGA show the same improvement but with little more in CO2 fractional session as shown in table 2.

**Table 2:** Mean and standard deviation of PGA.

	Fractional CO2 Laser		Q-Switched Nd:YAG Laser		p-Value
	Mean	Standard deviation	Mean	Standard deviation	
PGA - base line	6.10	0.780	5.88	0.90	0.912
PGA - 4 WK	5.4	0.81	4.95	0.86	0.070
PGA - 8WK			4.10	0.69	0.030
PGA - 12WK	2.7	0.73	3.22	0.79	0.027
P-Value	0.000		0.000		

The predominant side effects seen were erythema and pain, which resolved within 24 hours. No notable difference was observed in the number and nature of adverse events across the groups ( $p > 0.05$ ).

## DISCUSSION

Perioral hyperpigmentation continues to be a difficult clinical condition, frequently requiring sophisticated dermatological interventions to address the underlying melanogenesis. (Bhatt, S. et al., 2022) The current study highlights that combining ablative fractional CO2 technology with topical tranexamic acid is compared to the milder, non-ablative Nd:YAG based protocols with topical tranexamic acid.

The findings in the current study reveal a significant reduction in the mean of VAS and PGA score following combination treatment (from 5.80 to 2.40 for VAS and from 6.10 to 2.7 for the PGA) at the end of 12 weeks in group A while the group B has less reduction of the mean of VAS and PGA score (from 5.90 to 3.42 for VAS and from 5.88 to 3.22 for the PGA).

Kim et al.'s study shows the effect of low fluence and multiple passes of Q-switch ND: YAG Laser

Toning in the treatment of perioral hyperpigmentation. (Kim, W. J. et al., 2021)

Eassa et al., Searle et al Fractional CO2 laser-assisted drug delivery systems have demonstrated utility in addressing dyschromia; the superiority of combining ablative resurfacing with topical agents remains a subject of ongoing investigation. (Eassa, B. I. et al., 2025; Searle, T. et al., 2021)

The superior tolerability and lower risk of post-inflammatory sequel associated with non-ablative Nd:YAG modalities suggest a more favorable risk-benefit ratio for long-term maintenance compared to the acute inflammatory responses triggered by fractional CO2. (Feng, J. 2022; AlJabr, A. et al., 2026)

Furthermore, the difficulty in assessing the therapeutic options for perioral hyperpigmentation lies in the diversity of disease etiologies, the multiple pathophysiologies of the condition, and the limited number of studies.

The comparative analysis indicates that while fractional CO2 offers superior dermal remodeling, the Nd:YAG laser paired with tranexamic acid provides a more sustainable, low-risk approach for the complex management of perioral

hyperpigmentation. Future investigations should prioritize larger, multicenter cohorts to validate these findings and standardize protocols for optimal therapeutic dosing. Additionally, exploring combination regimens—such as the integration of platelet-rich plasma—may further optimize disease severity reduction and tissue repair, particularly in cases where standardized tranexamic acid protocols yield suboptimal results, and implementation of split-face study designs will be instrumental in directly comparing the long-term safety profiles of fractional CO<sub>2</sub> lasers against Nd:YAG assisted delivery systems in diverse skin populations.

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