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Comparing Oral Tranexamic Acid and Q-Switched Nd-YAG Laser for Melasma: A Randomized Study

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ABSTRACT

Background: Addressing the challenges of limited therapeutic options for melasma, this study explores the novel approach of combining oral Tranexamic acid with Q switched Nd-YAG laser. The aim is to evaluate the efficacy of this combination against oral Tranexamic acid (TNA) alone in treating melasma.

Method: This study was conducted as a prospective, randomized, open-label study with a sample size of 50, Group A (25 patients) received oral Tranexamic acid along with Nd-YAG laser treatment every 15 days for 3 months. Group B received only oral Tranexamic acid for the same duration. Clinical photographs were taken at each session, and patients were followed up for 3 and 6 months.

Result: The study found a 49.96% mMASI change in Group A and a 38.74% change in Group B after 3 months. Both groups exhibited similar percentages of reversal, with the combination group showing a marginally higher percentage. However, the difference was statistically insignificant (p=0.55). A limitation of the study was its small sample size.

Conclusion: The combination therapy demonstrated better responses for both mixed and dermal melasma types. Notably, laser treatment alone did not yield significant outcomes and carried a higher risk of hyperpigmentation, making it unsuitable for treating epidermal melasma.

Key-words: Melasma, Tranexamic Acid, TNA, Q switched Nd-YAG Laser, Laser Therapy

INTRODUCTION

Melasma is a form of acquired symmetrical hypermelanosis of the face, mainly affecting the nose, chin, forehead, and malar area. It is characterized by irregular brownish-black macules.[1] Fitzpatrick skin types IV through VI are predominantly found in females in the reproductive age range and are common in the Indian, Chinese, and Hispanic ethnic groups.

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Three recognised types of behaviour exist: the most common is centrofacial, while mandibular is the least common. Although the precise origin of melasma is still unknown, Ortonne *et al.* [2] discovered that oral contraceptives, breastfeeding, and pregnancy all increased UVA exposure and had a hormonal effect on the condition's development. Based on the length of the condition, melasmas can be divided into two categories: temporary melasmas, which disappears a year after hormonal stimulation (such as pregnancy or OCP usage), and persistent melasmas, which is typically caused by UVR and continues longer than a year after the hormonal stimulus is stopped. It is possible to distinguish between four types of melasma thanks to Wood's light examination and visible light.

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Increased melanin and pigment accentuation on Wood's lamp epidermal type, primarily in the suprabasal and basal epidermis [3,4]. Although melanin-loaded macrophages are present in the perivascular distribution of the superficial and deep dermis, the dermal form does not exhibit Wood's lamp accentuation. The inapparent form appears murky in Wood's light; however, the mixed variety has a deep brown colour and features from both. The patient's quality of life has been adversely affected and their emotional and psychological stress levels have escalated due to their cosmetically unacceptable resistance to most forms of therapy. [5] Traditional therapeutic treatments include alpha and beta hydroxy acid peels, hydroquinone, tretinoin, mometasone, azeleic acid, and Kojic acid depigmentation lotions. All of these options, meanwhile, have disadvantages of their own.

According to recent studies, the hemostatic medication tranexamicacid (TNA) has a hypopigmentary effect on melasma lesions and lessens UVA-induced pigmentation. These results suggest that TNA may prove to be an effective melasma treatment. TNA reduces the activity of epidermal melanocyte tyrosinase by blocking the plasminogen/plasmin pathway, which keeps melanocytes and keratinocytes from interacting. [6] Tranexamic acid also decreases cutaneous vascularity and [7-9] the quantity of mast cells by inhibiting fibroblast growth factor, decreasing mast cell activity, and restricting plasmin activity triggered by UV light. [11–13]

This statement suggests that recent studies have demonstrated the efficacy and rapid action of Q Switched Nd-YAG lasers, highlighting them as more effective and faster-acting than traditional therapeutic approaches.

MATERIALS AND METHODS

This interventional study was conducted in Tertiary care Hospital from August 2020 to November 2021. All the patients with Melasma of age 18 to 50 years attending Dermatology OPD were included. Convenient randomized sampling method was used to divide 50 patients into two groups.

Inclusion criteria

- Patients without a history of coagulopathies, cardiac diseases, or severe systemic disorders
- No known allergy to Tranexamic acid
- Absence of oral anticoagulant drug usage or any other photosensitizing drugs (e.g., tetracycline, spironolactone, phenytoin, carbamazepine) in the last 1 month
- No use of other depigmenting oral or topical agents in the past 1 month
- Females without a history of pregnancy or lactation in the last 12 months
- Absence of oral contraceptive pill or hormonal replacement therapy usage in the past 12 months

Exclusion criteria

- Patients with a history of coagulopathies, cardiac diseases, or severe systemic disorders
- Use of oral anticoagulant drugs or any other photosensitizing drugs in the last 1 month
- Known allergy to Tranexamic acid
- Use of other depigmenting oral or topical agents in the past 1 month
- Use of oral contraceptive pills or hormonal replacement therapy in the past 12 months

Randomization- It was done by computerized random number allocation, 50 patients divided into two groups for oral plus laser therapy and oral therapy alone as Group A and Group B respectively. After obtaining written informed consent, thorough history, clinical examination and baseline investigations were done as per the data collection pro-forma. The lesions were examined under a Woods lamp. The intensity of melasma was evaluated using the modified mMASI method. Throughout treatment and for an extra three months after, all patients were instructed to use wide spectrum sunscreen with an SPF of at least thirty.

In Group A, patients Tab Tranexamic acid 250mg was given orally twice daily for 3 months, along with that Nd-YAG Laser was used simultaneously once in every 15days. In Group B patients only Tab Tranexamic acid 250mg was given orally in twice daily dose for a period of 3 months.

Laser Procedure- Participants in the study were excluded if they had taken any oral anticoagulants or other photosensitizing medications, such as tetracycline, spironolactone, phenytoin, or carbamazepine, in the month prior, or if they had a history of coagulopathies, heart problems, severe systemic disorders, or if they

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knew they were allergic to tranexamic acid. End point was noted when there was formation of erythema or white crusts. (Fig. 1). Possible side effects like erythema, edema, pain, hyperpigmentation or burning sensation in Group A and oligomenorrhoea or amenorrhoea in both groups patients were asked on every visit. Clinical photographs in front of green background were taken in before each session and at follow-up period up to 3 months.

Fig. 1: Procedures during Q-switched Nd-YAG laser ablation

The intensity of melasma was evaluated using the modified melasma area and severity index scoring (MASI) method as 0.3A(f)D(f)+0.3A(lm)D(lm)+0.3A(rm)D(rm)+0.1A(c)D(c)" in a range of 0-24 and was calculated by comparing the percentage of improvement for each patient's response to their original score (Fig. 2).

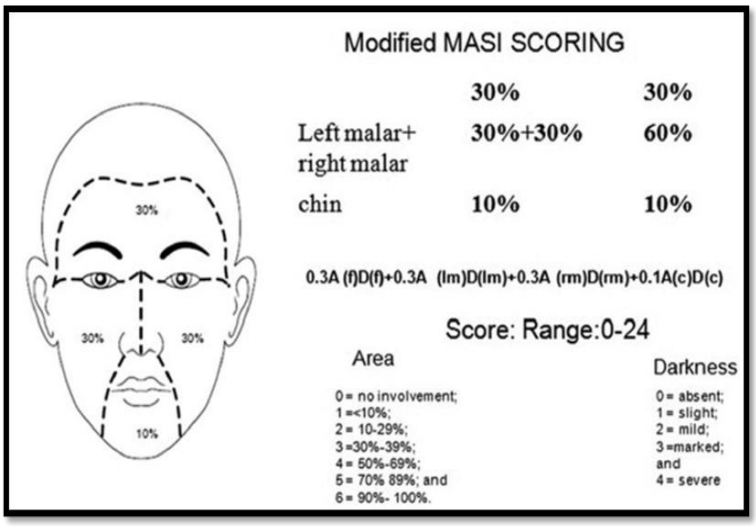

Fig. 2: Modified MASI Scoring

More than 60% change in mMASI after 3 months of treatment was considered as excellent response, 40-60% as good response and <40% was considered as poor response.

Statistical Analysis- The data was analyzed using SPSS 25.0. A component of the statistical analysis was calculating the means and proportions. An unpaired t-test was used to compare the mean mMASI scores of the two intervention groups at 0 and 3 months, as well as 3 and 6 months. The $p<0.05$ significance level was applied.

Ethical approval- Institutional ethical committee clearance and CTRI Registration was obtained (CTRI/2021/01/030539).

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RESULTS

Mean mMASI score among centrofacial pattern and malar pattern was tabulated among the treatment groups who received oral tranexamic acid with Q switched Nd YAG laser and only oral tranexamic acid (Table 1).

Table 1: Mean mMASI score according to pattern of skin involvement

Pattern	Group A mMASI 0 months (Mean ± SD)	Group B mMASI 0 months (Mean ± SD)
Centrofacial	6.95 (±2.84)	5.13 (±1.26)
Malar	4.33 (±1.75)	3.89 (±0.93)

Mean mMASI score among group with epidermal, dermal and mixed involvement in wood's lamp was tabulated among the treatment group A and B Table 2.

Table 2: Mean mMASI score according to woods lamp

Woods Lamp	Group A mMASI 0 months (Mean ± SD)	Group B mMASI 0 months (Mean ± SD)
Epidermal	5.75 (±1.96)	5.00 (±1.15)
Dermal	3.67 (±1.15)	4.00 (±1.00)
Mixed	7.80 (±3.33)	4.70 (±1.50)

Table 3 and Table 4 shows association between the mMASI score from 0 to 3 months within the two intervention groups clinically and in wood's lamp examination respectively. There was statistically significant association between the change in the mMASI score from 0 to 3 months.

Table 3: mMASI score change from 0 month to 3 months

mMASI score	Group A	Group B	t	p-value
Change from 0 month to 3 months	49.96% (±23.42)	38.74% (±13.71)	2.07	0.04

Table 4: 4mMASI score change from 0 month to 3 months according to woods lamp types

Change from 0 month to 3 months mMASI score	Group-A	Group-B	t	p-value
Epidermal	37.17 (±28.47)	39.19 (±18.33)	-0.19	0.85
Dermal	64.44 (±3.85)	35.33 (±10.95)	4.32	<0.01
Mixed	60.95 (±6.86)	39.99 (±10.18)	5.40	<0.01

Table 5 shows association between the mMASI score from 3 to 6 months within the two intervention groups. There was no significant association between the mMASI score within the two intervention groups.

Table 5: mMASI score change from 3 months to 6 months within the two intervention groups.

mMASI score	Group-A Mean change (%)	Group-B Mean change (%)	t	p-value
Change from 3 months to 6 months	-32.40% (±26.72)	-28.13% (±23.62)	-0.60	0.55

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Table 6 shows association of treatment response within the two intervention groups. Excellent treatment response was significantly higher among the patients who received oral Tranexamic acid with Q switched Nd YAG laser compared to those who received only oral tranexamic acid (p-value: 0.02) which was shown in following clinical image (Fig. 3 and 4).

Table 6: Treatment response at 3 months within the two intervention groups.

Intervention	>60% (Excellent)	40-60% (Good)	<40% (Poor)	p-value
Group A	6 (24.0%)	16 (64.0%)	3 (12.0%)	0.02#
Group B	1 (4.0%)	13 (52.0%)	11 (44.0%)	

#*Fisher's Exact Test*

Fig. 3: Patient treated TNA+Nd YAG at 0 month(A), showing excellent response at 3 months (B), visible recurrence at 6 months (C)

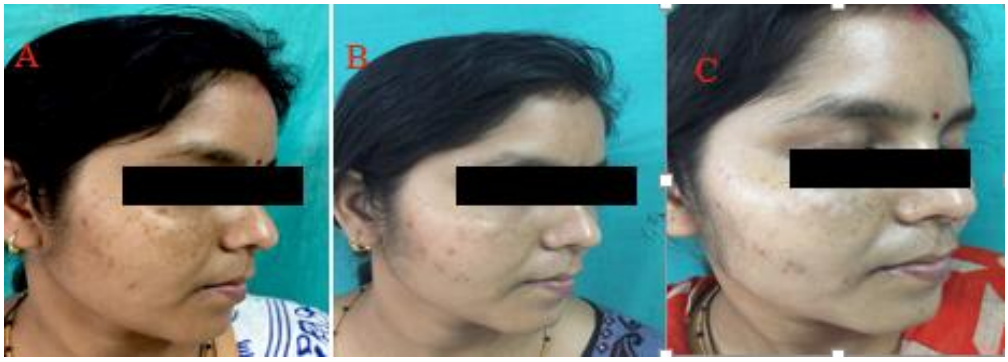

Fig. 4: Patients with TNA at 0 month (A), at 3 months (B) showing good response, at 6 months mild recurrence (C)

Table 7 shows association of treatment response with the type of disease involvement in Group-A according to wood's lamp examination. There was a significant association of treatment response with the type of disease based upon the region involved (p-value: 0.01).

Table 7: Treatment response in Oral Tranexamic acid with Q switched Nd YAG laser (Group-A) in wood's lamp examination

Woods Lamp	Excellent n (%)	Good n (%)	Poor n (%)	p-value
Epidermal	00 (0.0%)	09 (75.0%)	03 (25.0%)	
Dermal	02 (66.7%)	01 (33.3%)	00 (0.0%)	0.01#
Mixed	04 (40.0%)	06 (60.0%)	00 (0.0%)	

#*Fisher's exact test*

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Table 8 shows association of treatment response with the type of disease involvement in Group-B patients. There was no significant association of treatment response with the type of disease based upon the region involved.

Table 8: Treatment response with only oral tranexamic acid

Woods Lamp	Excellent n (%)	Good n (%)	Poor n (%)	p-value
Epidermal	01 (10.0%)	05 (50.0%)	04 (40.0%)	0.90[#]
Dermal	00 (0.0%)	02 (40.0%)	03 (60.0%)	
Mixed	00 (10.0%)	06 (60.0%)	04 (40.0%)	

[#]*Fisher's exact test*

Adverse Events- Treatment with Nd YAG laser resulted in hyperpigmentation in 3 patients (1 of them was lost to follow up). Single case of Hypomenorrhoea was seen in both the groups whereas 1 case of amenorrhoea was reported in Group treated with both Oral Tranexamic acid and Nd YAG laser (Fig. 5, 6).

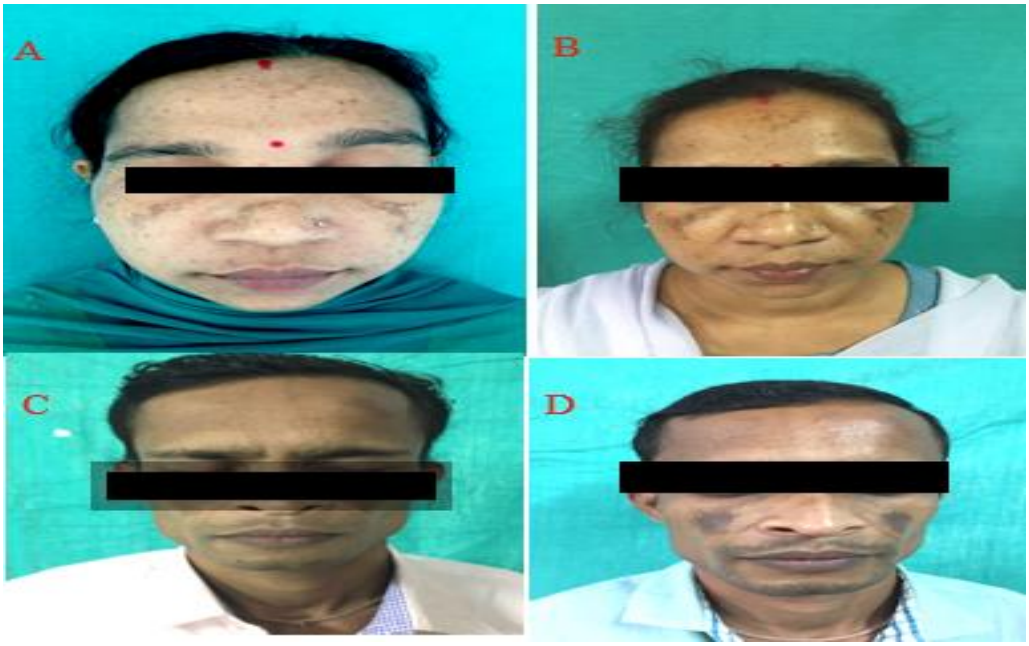

Fig. 5: Patients treated with TNA+Qs Nd YAG laser showing paradoxical hyperpigmentation at 3mnth, right side image

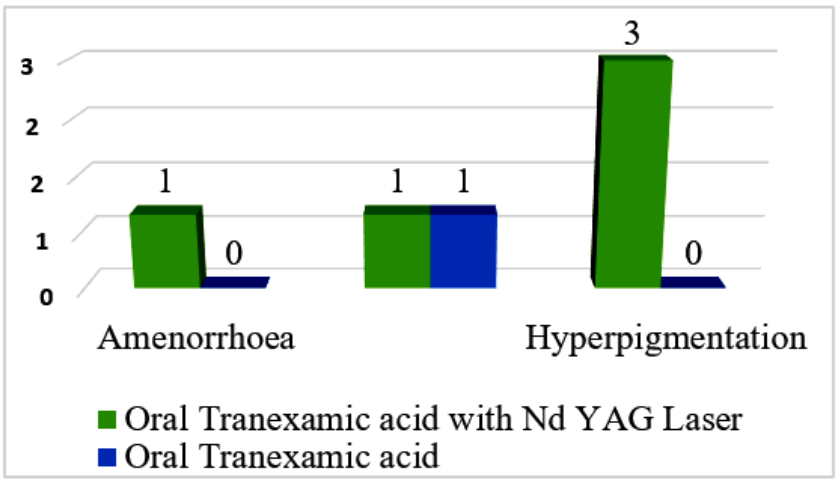

Fig. 6: Distribution of various adverse events within the two intervention groups

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DISCUSSION

Tranexamic acid (TNA) is an artificial lysine analogue having antifibrinolytic effects.[10] When exposed to UV radiation, keratinocytes create more plasminogen activator and increase the activity of plasmin. This ultimately results in the release of arachidonic acid, which employs prostaglandins to facilitate melanogenesis.[11–13] Nijor [14] conducted the first review and report on the effects of tranexamic acid on melasma in 1979. Hajime *et al.* [15] discovered in 1985 that the intensity of their melasma was lessened when they took 1 to 1.5 g of oral tranexamic acid every day. In 1998, eleven melasma patients were treated with oral tranexamic acid (0.75–1.5 g/day) [16]. But after the drug was withdrawn, the pigmentation came back. For a period of 6–8 weeks, vitamins C and E were given along with 250 mg of tranexamic acid three times a day by Zhu and Yang [17] and Liu *et al*. [18]. They saw a noticeable reduction in pigmentation. Mafune *et al.* [19] administered two 750 mg oral tranexamic acid pills three times a day.

In the first controlled trial, conducted in 2013, Cho et al. compared patients treated with neodymium-doped yttrium aluminium garnet laser or intense pulse light with those who received the same treatment but were not prescribed tranexamic acid. As an adjuvant, the patients were given 500 mg each day.[20-23] Kato *et al.* [21] found that oral TNA at 750 mg/day did not significantly reduce the risk of hyperpigmentation in individuals with senile lentigo following Q-switched ruby laser treatment. Darker skin types should avoid using Q-switched ruby lasers because of the increased risk of hyperpigmentation following treatment.[25,26] Wattanakrai *et al.* [24] report that there was a transient response to melasma treatment with Qs-Nd: YAG laser. Conversely, Shin et al. found that melasma patients could receive a minimally invasive treatment option when oral TNA was used in conjunction with a low-fluence QS-Nd: YAG laser.[28] They discovered a statistically significant drop in the mMASI score, just like we did.

In our study the mean mMASI at the baseline or at 0 months was overall found to be 6.49±3.29 in group A, whereas, the mean MASI by Kar et al was 13.54+7.19.[21] In group B the baseline mMASI was 4.75±0.78 in our study, and the same by Khurana et al was found to be 7.48±3.73.[22]

In our study the percentage of mMASI change from baseline to 3 months of treatment was 49.96% (±23.42) in group A patient treated with tranexamic acid and laser, in comparison to the group B patients treated with only tranexamic acid with mean change of 38.74% (±13.71), with statistically significant p-value of 0.04. Kar *et al.* [21] with usage of low fluence QS Nd-YAG laser found the change in MASI of 47.93% which is similar to our study. The study by Khurana et al. with only oral tranexamic acid treatment had the change in mMASI of 57.48% which is significantly higher to our study.[22]

In wood's lamp classification of melasma in group A patients treated with the combination therapy has shown change in mMASI percentage in mixed type and dermal type which is statistically significant when compared to the the group B patients of mixed type. The patients with epidermal type of melasma showed similar results in both groups. The study conducted by Agamia et al. the overall change in percentage of mMASI was maximum with epidermal type of melasma, followed by mixed type, and the least improvement was seen in dermal type which is not in accordance to our study.[23]

All the 49 patients that completed the treatment and follow up period have reported reversal in treatment response at the end of follow up period. Khurana *et al*. [22] reported that 6.25% of patients showed return of the pigmentation, but the percentage the reversal was not mentioned.

All the patients treated with combination therapy showed mild burning sensation and pain over the site of laser therapy, but it was transient and disappeared in 1-2 hours. Three (12%) patients treated with combination therapy showed development of paradoxical hyperpigmentation out of which one patient discontinued the treatment mid-way and was lost to follow up. Kar *et al*. [21] reported paradoxical hyperpigmentation or PIH in 28.5% cases treated with high fluenceNd-YAG laser. The other adverse events included temporary amenorrhoea during the treatment period in 1 patient, and 2 patients complained of hypomenorrhoea. Khurana et al reported gastritis as most common adverse effect is 6.5% of cases and oligomenorrhoea in 3.12% cases.[22] Agamia et al. reported slight menstrual changes in 33% of cases and GI upset in 16.7% age cases.[23] No other adverse effects were reported during the treatment and follow up period.

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CONCLUSIONS

To our knowledge the comparison of oral tranexamic acid with the combination of oral tranexamic acid and laser has not been studied much in Indian population. The combination therapy was found to act better on dermal and mixed type of melasma. The laser therapy was not found to be suitable for epidermal type of melasma for not been able to provide significant result and with increased rate of hyperpigmentation.

The objective of proving whether concurrent use of oral tranexamic acid with Nd-YAG laser will decrease the adverse effects of laser, could not be established significantly in our study. More such randomised trials in larger study sample are required to establish the above findings.

CONTRIBUTION OF AUTHORS

Research concept- Khan Sahid Abdul, Mohanty Prasenjeet

Research design- Mohanty Prasenjeet**,** Khan Sahid Abdul

Supervision-Mohanty Prasenjeet, Mohanty Jayashree, Bisoyi Diptiranjani

Materials- Khan Sahid Abdul**,** Mohanty Prasenjeet

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Data analysis and Interpretation- Khan Sahid Abdul**,** Bisoyi Diptiranjani, Sathyanath Anjana

Literature search- Khan Sahid Abdul, Mohanty Prasenjeet**,** Kurian Mary Ashitha

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Article editing- Dash Manjulata, Bisoyi Diptiranjani, Kurian Mary Ashitha, Sathyanath Anjana

Final approval-MohantyPrasenjeet, Bisoyi Diptiranjani, Khan Sahid Abdul

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