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ORIGINAL ARTICLE

Comparison of efficacy and safety of tranexamic acid mesotherapy versus oral tranexamic acid in patients with melasma undergoing Q-switched fractional 1064-nm Nd:YAG laser: A blinded RCT and follow-up

Elham Behrangi MD | Mahsa Shemshadi MD | Mohammadreza Ghassemi MD | Azadeh Goodarzi MD, Associate Professor | Sara Dilmaghani MD

Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran

Correspondence
Azadeh Goodarzi and Mahsa Shemshadi , Department of Dermatology, Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran.
Emails: goodarzi.a@iums.ac.ir; azadeh_goodarzi1984@yahoo.com(AG);mahsa.shemshadi@gmail.com(MS)

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Abstract

Background: Melasma is a common hyperpigmentation disorder. This study aimed to compare the efficacy of Nd-Yag fractional 1064 plus microinjection of tranexamic acid versus Nd-Yag fractional 1064 plus oral tranexamic acid in patients with melasma.

Materials and methods: This is a prospective, randomized study with a sample size of 40 patients, 20 in each treatment arm, which was done six times with 2-week intervals. Twenty patients were administered localized microinjections (4 mg/ml) of tranexamic acid and Q-switched 1064 laser every 2 weeks in one arm, while in the other arm, 20 were given oral tranexamic acid 250 mg three times a day and Q-switched 1064 laser every 2 weeks per visit.

Results: Twenty-one patients with mean SD 40.52+-4.95 y/o were treated with oral tranexamic acid, and 20 patients with 43.3+-5.87 y/o treated with microinjection of tranexamic acid were analyzed. There was no statistically significant difference between the two groups in terms of demographic and clinical characteristics at the baseline ($p > 0.05$). The patients MASI score and ΔE decrease over the study period in both treatments significantly ($p < 0.001$). However, patient's MASI score ($p = 0.99$) and ΔE ($p = 0.53$) did not differ significant between the two group over the time. Satisfaction ($p = 0.41$) and complication during the study period ($p = 0.09$) were not significantly different between the two group.

Conclusion: The combination treatment method can be a viable option for Middle Eastern patients having melasma disorder, and tranexamic acid appears to be an effective and safe treatment for melasma, irrespective of its route of administration. Tranexamic acid can increase the permeability locally by non-invasive methods such as microneedling which is less painful than microinjection and can also increase patient satisfaction.

Although the oral method is more tolerable for the patient, it may have systemic side effects, and its combination with Q-switch laser increases its effect regardless of the type of prescription. Therefore, it is recommended to use of this drug topically (cream

or lotion) by non-invasive methods like microneedling to reduce pain and laser treatment in future studies.

KEYWORDS
laser, melasma, microinjection, Q-switched, RCT

1 | INTRODUCTION

Melasma is one of the most prevalent acquired disorders of hyperpigmentation that commonly involves reproductive-aged females. Although melasma does not result in any serious medical comorbidities, it has a high psychological impact.[1]

There are several methods for the treatment of melasma; however, no single treatment has been discovered with the ability to maintain and control melisma effectively.[1] Moreover, the treatment of melasma becomes challenging for clinicians and frustrating for patients.[2]

Topical hydroquinone plus tretinoin have been the most effective treatment for melasma, but during long-term use for lightening the spots, it accompanies undesirable side effects such as skin irritation and hyperpigmentation after paradoxical inflammation; so, the use of this combination can lead to a difficult situation.[3] Although laser therapy in melasma disorder can stimulate melanocytes and inflammatory processes, the use of low-energy Q-switched with recurrent episodes is recognized as a safe and effective method in melasma treatment.[4] Tranexamic acid (TA) is a plasmin inhibitor and anti-fibrinolytic agent that prevents bleeding and has been recently used widely in all routes of administration to treat melasma with excellent results.[5]

The Q-Switched 1064 laser has been used to treat melasma with promising results.[6] According to the Fitzpatrick classification, Q-switch 1064 has been used to treat resistant melasma in patients with type III-V skin classification. Applying this technique, more than 80% of melasma lesions were reduced and there was no recurrence after 6 months. Furthermore, the melanin index at the site of the lesion decreased significantly.[7]

The Q-switch 1064 nm laser, a pigment-specific laser, is widely used in the treatment of melasma. Based on the hypothesis of selective subcellular photothermolysis, in the Q-switch 1064 nm laser mechanism, the targets are pigments not cells, so its damage is much less than that of thermal laser treatments. Therefore, there is no recovery period from treatment.[1]

This treatment regimen is known as "laser toning" with selective photothermolysis of target pigments, and has very good therapeutic effects against resistant melasma and hyperpigmentation after inflammation.[6]

Tranexamic acid inhibits plasmin production by inhibiting the plasminogen activator and also prevents the activation of melanocytes by keratinocytes. Moreover, tranexamic acid can enhance vascular-endothelial growth factor (V-EGF) and alpha-melanocyte-stimulating hormone; therefore, the use of (TA) has become a promising treatment for melasma patients.[8]

Tranexamic acid has been used as a topical, mesotherapy, and in oral form as a skin-lightening drug. Although TA has been used as a responsive treatment for melasma, it has not been approved by the Food and Drug Administration of the United States, and the treatment remains controversial.[9]

According to the explanations, it seems that combination therapies may have better results in the treatment of melasma. Due to recurrence and recalcitrance of melasma, a combination of methods such as topical medication, peeling agents, TA, and laser therapy can be an acceptable treatment.[6]

Due to high incidence and incomplete improvement as well as recurrence of melasma, it becomes a disappointing condition. Given the adverse psychosocial effects of melasma on patients, it can decrease quality of life, which demands safe and effective, and cost-benefit therapeutic interventions.

Although there are some articles regarding laser therapy, different routes of TA administration and their combination, this study compares the result of Q-switched laser combined with two different modes of TA administration.

2 | METHODS

This study was a single-center, parallel-group, assessor- and analyst-blinded RCT conducted in the dermatology clinic at the hospital with which the authors are affiliated, Tehran, Iran, between February 2018 and December 2019.

2.1 | Eligibility criteria

Patients who met the inclusion criteria were those with classic clinical features of melasma, and skin type I-IV and were aged between 18 and 50 years. Exclusion criteria were (1) any kind of treatment at least 1 month before the study; (2) history and type of coagulopathy such as deep-vein thrombosis, stroke, pulmonary thromboembolism, disseminated intravascular coagulation, and cancers; (3) current pregnancy or lactation; (4) having a planned pregnancy within a year following the initiation of treatment; (5) a history of any drug allergies; (6) use of drugs interacting with TA or other anticoagulants or hormonal drugs such as birth control pills; (7) having a history of post-inflammatory hyperpigmentation susceptibility and a skin type darker than class IV; (8) occurrence of treatment-related complications that were not resolved by dose reduction or not tolerated by the patient; and (9) unwillingness to continue the study for any reason.

2.2 | Patient recruitment

The selection of the patients was determined by assessor one, the main investigator of the study. The patients were then provided with an adequate explanation about the project, and informed consent was obtained from the patients before entering into the study. Most of the included patients had skin type of ranged III-IV.

All patients were photographed with the VisioFace® 1000 D - Courage - Khazaka Electronic, Köln device before treatment. The recruitment phase was finished in 12 months.

The patients were assigned to treatment groups through computerized randomization with a 1:1 allocation ratio. Of a box with 41 sealed envelopes, one envelope was selected for each patient, containing the code A or B (A: Oral TA; B: Microinjection of TA).

2.3 | Random sequencing and allocation

The patients were evaluated and followed for 1 month. To facilitate statistical comparisons, we used the comprehensive numeric Melasma Area and Severity Index (MASI) and delta E (ΔE) that comes from the Visio face and quality scale as a patient questionnaire.

2.4 | Outcome measures

Efficacy was assessed by changes of MASI score and ΔE during the time.

Melasma area and severity index scoring system allows for quantification of the severity of melasma and gives a clear idea of the disease activity and severity. This scale determined the area of conflict: Forehead (F) 30% and right malar (RMR) and left malar (LMR) 30% and mentum (M) 10%.

Based on area (A), melasma involvement is graded from 0 to 6. (Figure 1).

0 = 0%
1 = <10%
2 = 10%–29%
3 = 30%–49%
4 = 50%–69%
5 = 70%–89%
6 = 90%–100%

ΔE data detect the difference between pigmentation in lesional skin and normal skin, which determines with the VisioFace instrument at each visit.

Safety of treatment was evaluated by recording therapy-related side effects and the manner of proper management.

Patient questionnaire: As a qualitative questionnaire, it measures the satisfaction with treatment and subjective improvement as Low (<30%); Good (30%–70%); and Excellent (>70%).

2.5 | Evaluation and follow-up

Eligible enrolled patients after baseline visit and starting the trial were visited every 2 weeks, and the therapy ended after 12 weeks; all patients were followed for 1 month.

According to the studies related to our article, the average time in microinjections group was 2–4 weeks, so in this study, we decided 2 weeks intervals for the injections.

All patients were followed after 1 month of ending the treatment. Due to speed up the publication of the article and financial constriction, just one session was performed for patients.

Melasma area and severity index scores were determined by another physician, assessor two, who was blinded to the patients' treatment group. Assessor one screened the patients for any clinical

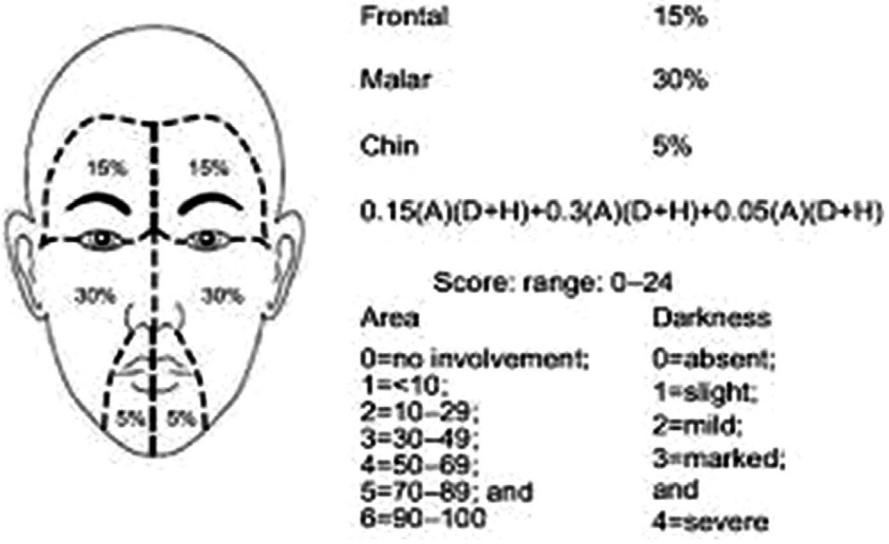

FIGURE 1 Melasma area and severity index scoring system

complication at each visit. Subjective outcomes of interest including satisfaction grade with treatment (low; good; and excellent) and tolerability were also checked with the patients' questionnaire. Also, it was possible to change the study group on the patient's request for any reason or at the discretion of assessor one, if it was in the patient's best interests.

2.6 | Blinding

Unlike assessor one, assessor two and the data analyst had access only to conventional A and B codes and were blinded to the actual treatment regimens.

2.7 | Treatment regimens

In group A, patients received Q-switched fractional 1064-nm Nd: YAG lasers (Helios Q-switched = energy: 1000, fluency: 2.60 frequency: 10, spot size: 10) and this procedure is performed on melasma lesions to developed mild to moderate erythema with oral TA (one capsule 250 mg of Amin pharma every 8 h for 3 months).

In group B, patients received Q-switched fractional 1064-nm Nd: YAG lasers (Helios Q-switched = energy: 1000, fluency: 2.60 frequency: 10, and spot size: 10) and this procedure is performed on melasma lesions to developed mild to moderate erythema with TA microinjection (one ampule TA 500 mg/5 ml of Caspian Tamin pharma). Although the concentration of TA in this study was 100 mg/ml, the maximum amount of injection for each patient was 2°cc.

All patients in the study were prescribed to use regular sunscreen, and none of the patients was allowed to take complementary or other lightening medications.

2.8 | Statistics and data analysis

Qualitative variables were reported by *n* (percentage), and quantitative variables were presented by mean ± standard deviation. Normality assumption was assessed for the outcome. Chi-square test and Fisher's exact test were used to compare categorical data between groups. *t*-test and repeated measures ANOVA were utilized to compare the MASI score and ΔE between two groups. Statistical analysis was conducted by SPSS version 16 (SPSS Inc). The level of significance was set to 0.05.

3 | RESULTS

In Figure 2, the flowchart diagram has been demonstrated.

Forty-one melasma patients completed the study follow-up with mean ± SD age of 41.88 ± 5.53 years. Twenty-one patients in the oral group had mean ± SD age of 40.52 ± 4.95 years and 20 patients in the microinjection group were 43.3 ± 5.87 years ($p = 0.1$). Mean ± SD MASI score was 26 ± 14.42 and 25.3 ± 8.8 in the oral and microinjection groups, respectively ($p = 0.85$). Notably, 62%–65% of all the patients had a positive history of sun exposure. Moreover, 9.5%–10% of all the patients had a positive history of past medical disease related to melasma; 67%–85% of all the patients had received medication for melasma; 52.5%–60% of all patients had

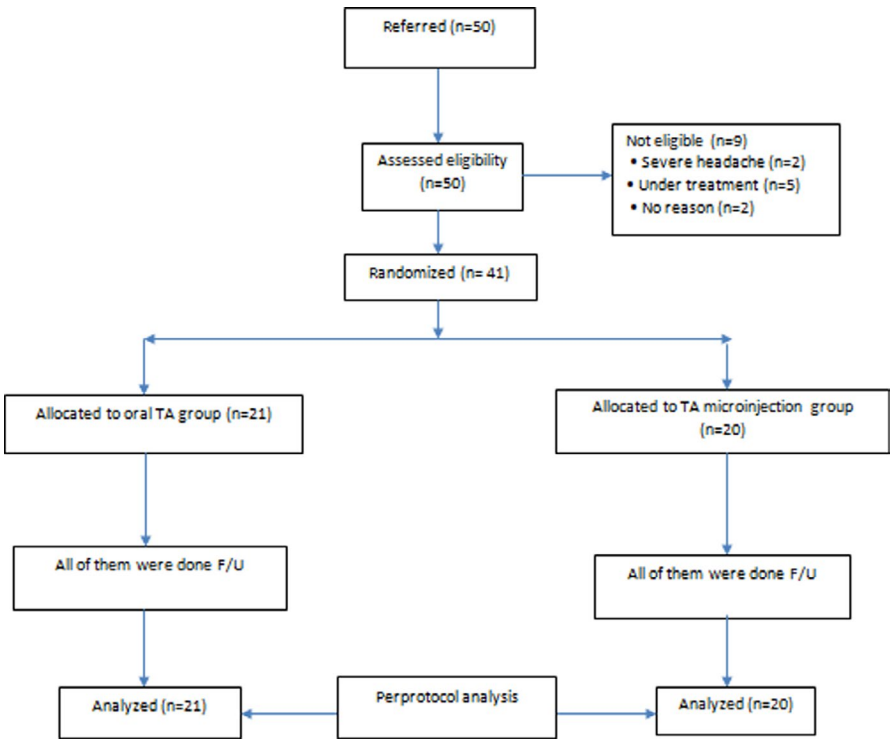

FIGURE 2 Study flowchart diagram

a positive familial history of melasma; and 20%–45% of them had received melasma-related medications (Table 1). Table 1 shows that the baseline characteristics of the patients in the two groups were homogenous ($p > 0.05$).

TABLE 1 Patient's characteristics, *N* (%) in the two groups

	N (%)		
Characteristics	**Microinjection**	**Oral**	***p***
Sun exposure			
Yes	13 (65%)	13 (62%)	0.83
No	7 (35%)	8 (38%)	
Disease history			
Thyroids	3 (10%)	2 (9.5%)	0.62
Others	4 (20%)	7 (33.5%)	
None	14 (70%)	12 (57%)	
Medication history			
Cream	13 (65%)	10 (47%)	0.55
Mesotherapy	1 (5%)	1 (5%)	
Laser	0	1 (5%)	
Cream and laser	2 (10%)	2 (10%)	
Others	1 (5%)	0	
	3 (15%)	7 (33%)	
Melasma family history			
Yes	12(60%)	11 (52.5%)	0.62
No	8 (40%)	10 (47.5%)	
Medications			
Melasma-related medications	9 (45%)	4 (20%)	0.06
Non–melasma-related medications	0	7 (33%)	
None	11 (55%)	10 (47.5%)	

Mean ± SD MASI score is presented in Table 2, showing no significant difference between the microinjection and oral treatment groups in none of the time points. The findings showed that the MASI score mean was higher in the microinjection group up to week 3, and the MASI score was higher in the oral group afterward. However, none of the differences was significant ($p > 0.05$, Table 2). Repeated measures ANOVA showed no significant effect of treatment ($p = 0.99$). Note that, as Figure 3 shows, despite the non-significant effect of treatment type, the MASI score decreased significantly over the study period ($p < 0.001$).

Table 2 shows that mean ΔE was higher in microinjection group compared with oral group for all the time point except for week 10, although the differences were not statistically significant ($p > 0.05$). This finding was also confirmed by repeated measures ANOVA ($p = 0.53$). As Figures 3 and 4 illustrate, MASI score and ΔE reduced over time significantly ($p < 0.001$), irrespective of the administered medication.

The findings in Table 3 showed that the mean % of MASI score change was not significantly different between two groups in the weeks 2, 4, 6, 8, 12, and follow-up ($p > 0.05$). However, as Figure 3 shows the patients in the microinjection group had a higher % change in MASI and this difference was apparent after week 10. Repeated measures ANOVA showed no significant effect of administered treatment on % of MASI score change over time ($p = 0.44$). As Figure 4 illustrates, ΔE reduced over time significantly ($p < 0.001$) in both groups. In addition, the % of ΔE change was significantly different between groups in none of the time points which are confirmed by the *p*-value of 0.6 from repeated measures ANOVA; however, percentage of ΔE change was higher in the microinjection group especially at the middle of the study period (Table 3, Figure 4). Figures 3 and 4 show that despite non-significant effect of administered treatment, the MASI score and ΔE changes decreased significantly over the study period ($p < 0.001$).

As a final investigation, there was a significant difference between the number of the patients with pain, which was higher in

TABLE 2 Values are presented as mean ± SD MASI score and ΔE or treatment in comparative study on efficacy of oral versus microinjection of TA

	MASI				ΔE			
	Mean±SD				Mean±SD			
Time	**Microinjection**	**Oral**	**Change**	***p***	**Microinjection**	**Oral**	**Change**	***p***
Baseline	25.3 ± 8.8	26 ± 14.4	0.7	0.85				
Week 2	22 ± 7.1	23.04 ± 13.28	1.04	0.28	4.07 ± 0.88	3.71 ± 0.88	−.35	0.2
Week 4	19.4 ± 8.25	19.76 ± 13.11	.36	0.84	3.61 ± 0.83	3.33 ± 0.88	−.28	0.28
Week 6	17 ± 8.3	17.85 ± 10.87	.85	0.68	3.1 ± 1.02	3.04 ± 0.95	−.06	0.84
Week 8	15.3 ± 7.18	15.38 ± 8.76	.08	0.79	2.66 ± 0.95	2.54 ± 0.92	−.11	0.68
Week 10	12.85 ± 8.19	12.57 ± 8.02	−.27	0.69	2.18 ± 0.71	2.25 ± 0.89	.06	0.79
Week 12	12.85 ± 8.82	11.71 ± 7.47	−1.13	0.59	1.88 ± 0.86	1.78 ± 0.74	−.09	0.69
Follow-up	**12.4 ± 9.5**	**10.57 ± 6.5**	**−1.82**	**0.48**	**1.82 ± 0.86**	**1.69 ± 0.7**	**−.13**	**0.59**

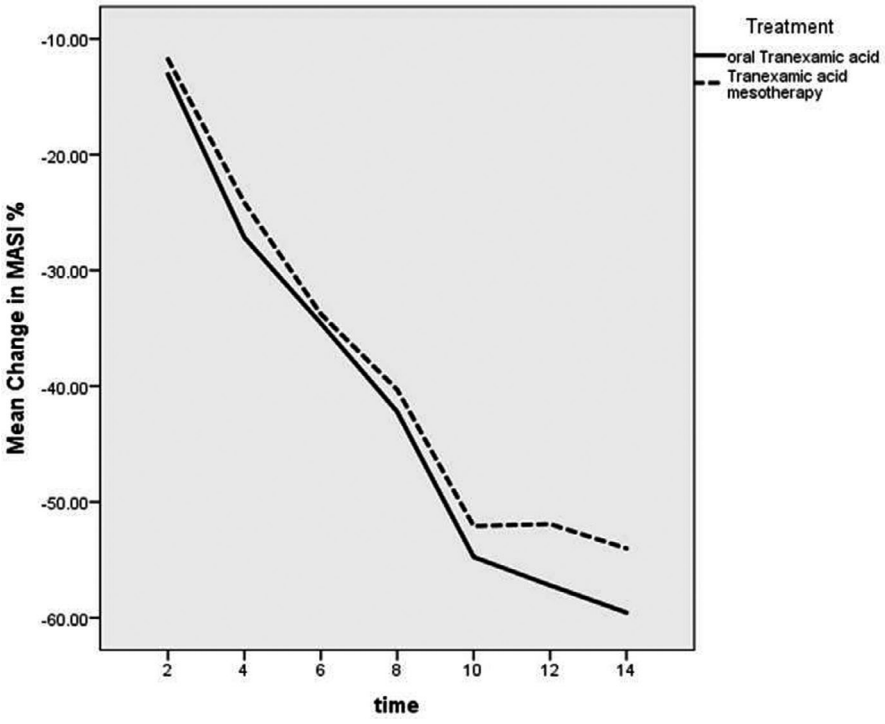

FIGURE 3 Trend of the percent of MASI score change for the microinjection and oral groups over the study period

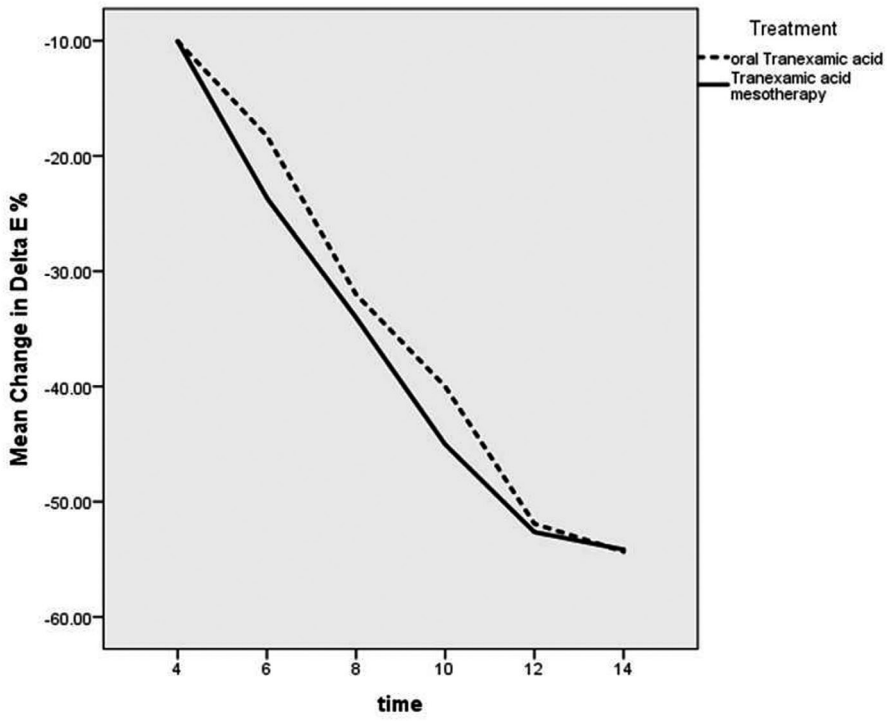

FIGURE 4 Trend of the percent of ΔE change for microinjection and oral groups over the study period

the microinjection group ($p = 0.04$). No significant difference was observed between groups in terms of GI, headache, and hypomenorrhea as the complications (Table 4).

Good to excellent satisfaction was observed in 57%–33.3% and 50%–25% of the patients in oral and microinjection, respectively.

Whereas 65% of patients in the microinjection group and 76% of the oral group had no side effect, 5% of the microinjection group and 19% of the oral group had GI problem and none of oral group and 5% of the microinjection group had headache and 5% of both had hypomenorrhea and 20% of the microinjection group and none of the oral group had pain.

One month after treatment, there was some reduction in the amount of melasma area in both groups, which is clear in ΔE and MASI scores. Given the effectiveness and safety of this combination therapy, it may be constant and have a low recurrence, but studies with longer follow-up are needed to determine this issue.

The observed difference in patient's satisfaction was not significant between the groups ($p = 0.41$; Figure 5).

TABLE 3 Mean ± SD percentage (%) of MASI score change and ΔE for two groups change for the microinjection and oral groups over at baseline and every 2 weeks and 1 month follow-up

	MASI				EΔ			
	Mean±SD				Mean±SD			
Time	Microinjection	Oral	Change	*p*	Microinjection	Oral	Change	*p*
Week 2	−11.77 ± 11.08	−13.06 ± 10.52	−1.29	0.7				
Week 4	−24.16 ± 11.87	−27.17 ± 14.05	−3.01	0.46	−10.05 ± 15.14	−10.05 ± 10.64	0.00	0.99
Week 6	−33.76 ± 14.62	−34.56 ± 15.24	−0.79	0.86	−23.64 ± 20.00	−18.26 ± 15.73	5.38	0.34
Week 8	−40.3 ± 16.95	−42.21 ± 12.44	−1.91	0.68	−34.02 ± 20.72	−32.01 ± 17.91	2.01	0.74
Week 10	−52.07 ± 15.74	−54.75 ± 13.58	−2.68	0.56	−45.04 ± 17.93	−40.01 ± 16.15	5.03	0.35
Week 12	−51.9 ± 18.57	−57.19 ± 14.73	−5.29	0.31	−52.63 ± 20.90	−51.91 ± 15.30	0.72	0.9
Follow-up	**−54.01 ± 22.16**	**−59.55 ± 15.83**	**−5.54**	**0.36**	**−54.15 ± 20.65**	**−54.33 ± 15.47**	**−0.18**	**0.97**

Note: ΔE and MASI score are decreased significantly as compared to the baseline on both groups (both significant vs. baseline, $p < 0.05$).

TABLE 4 The *n* (%) of the complication in oral and microinjection group during the treatment

Complication	Microinjection	Oral	*p*
None	13 (65%)	16 (76%)	–
GI	1 (5%)	4 (19%)	0.34
headache	1 (5%)	0	0.48
Hypo menorrhea	1 (5%)	1 (5%)	1
Pain	4 (20%)	0	0.04

In Figures 6-8, you can see the therapeutic results of microinjection and oral TA in melasma patients under the treatment with Q-switched laser, respectively.

4 | DISCUSSION

Melasma is one of the most common acquired disorders that presented with light-to-dark brown macules and patches in sun-exposed areas on the head and neck.[1] Melasma is more common in high skin phenotype.[10]

Studies have shown that the prevalence of melasma is about 5%–70% of the population. Most of the patients are women that most of them are Asian and Latin American and only 10% of patients are male.[10]

Although the exact cause of melasma is not yet known, the common factors associated with the disease include genetic susceptibility, UV radiation, pregnancy, sex hormones, oral contraceptive pill, thyroid diseases, cosmetic agents, and phototoxic drugs,[1] but sun exposure is the most important factor in the development and exacerbation of melasma, due to the direct melanogenic effect of UV light on melanocytes.[8]

Diagnosis of melasma is based on taking history and clinical findings including pigmented macule and patch with symmetrical distribution on the face and neck. Wood's lamp examination helps in detecting the pigmentation pattern.[11]

Treatment of melasma is very difficult and controversial because the lesions are so resistant and patients suffer from recurrence.[12]

Treatments for melasma include sunscreen, bleaching agents, peeling compounds such as glycolic acid and lactic acid and laser therapy. Recent studies identified that TA, as a homeostatic substance, has a reductive effect on melasma pigmentation and preventing UV-induced pigmentation.[13]

However, TA has not been approved by the FDA till now for treatment of melasma, since five last years, some studies had evaluated the impact and safety of TA in the treatment of melasma.[3] Sadako was the first one who introduces TA for treatment of melasma, in 1979. This was a coincidental finding that was identified during the study on the therapeutic effect of TA on urticaria, and then, a study was conducted to determine the effect of this drug on melasma.[3]

So many studies have demonstrated the efficacy of both oral and topical forms of TA in the treatment of melasma.[1]

Q-switched laser is another treatment for refractory melasma in patients with Fitzpatrick's skin type 1–5. This method reduced the pigmented lesions without recurrence. In addition, melanin index score in the melasma lesions was significantly reduced.[7]

Subcellular selective photothermolysis theory suggests that laser energy with photo-thermolytic fluency can fragment cytoplasmic melanin granules without cell damage.[14]

This study demonstrated that combination therapy is an effective method for melasma treatment and TA, and regardless of its prescription, it is one of the effective arms in the treatment of melasma that can be more effective along with Q-switched Nd-Yag laser.

A study by Sharma et al. was done on 100 patients with melasma, which compared the effect of oral TA and microinjection form. Thirty-nine patients in group A and 41 patients in group B completed the study. Any serious side effects had not been reported during treatment, and mean percentage reduction in MASI was comparable in both groups at each visit; none of the differences was statistically significant (79.00% ± 9.64% vs. 82.9%); it demonstrated that TA in different routes of administration can be effective in the treatment of melasma.[5]

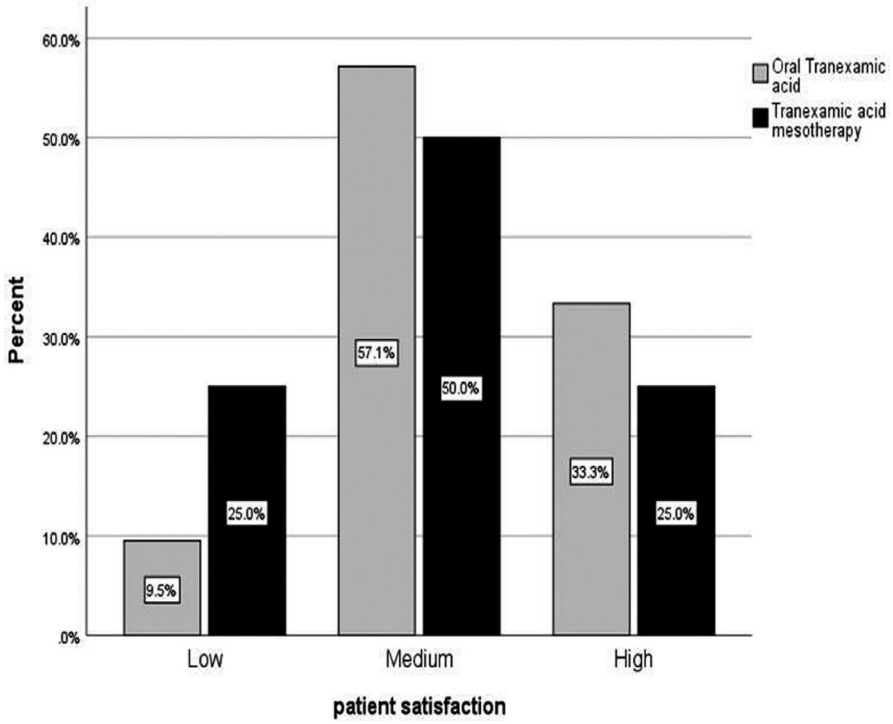

FIGURE 5 Percentage of the patient's satisfaction in microinjection and oral groups

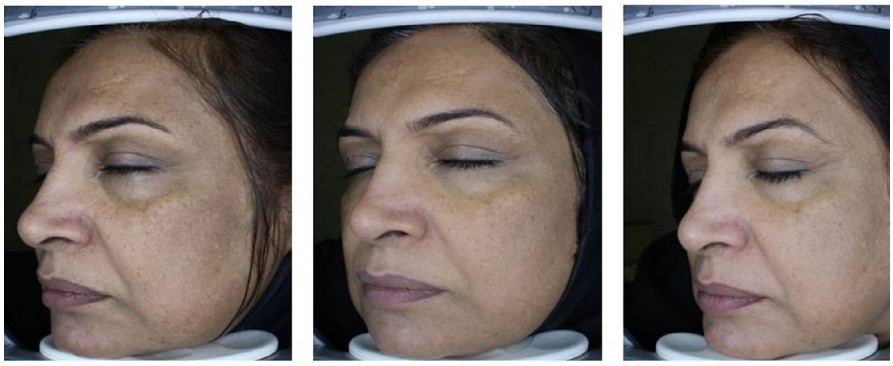

FIGURE 6 Patient in microinjection group of tranexamic acid group (start of trial, mid-trial, and end of trial)

We observed about 50% score reduction of melasma that was not statistically different between the groups. These results are similar to the above study regarding similar efficacy of different administration routes of TA, but the lower reduction of MASI score of ours could be explained by probable different demographic characteristics and baseline MASI score, and geographic and ethnic differences that affect severity and resistance of melasma.

A prospective pilot study by Kwon et al[6]. was done to evaluate the impact and safety of Q-switched laser combination therapy with hydroquinone and TA for resistant melanosis. Patients with recalcitrant Riehl's melanosis were enrolled in the study. The mean redness and melanin index decreased significantly during the treatment. The mean melanin index and erythema index values at the final visit showed a significant decrease compared with baseline (melanin index: 76.3 ± 25.3=>45.2 ± 17.6; erythema index: 23.5 ± 6.8 =>16.7 ± 5.2), and also, pathological evaluation showed a significant decrease in melanin content of melanophages (3.2=>1.3).[6]

A study by Laothaworn et al. was done which evaluates the efficacy and side effects of topical TA in combination with Q-switched laser, for melasma treatment. Nearly 50% of the subjects reported a more than 75% improvement on the side of the face with the combination therapy at the end of the study; so this study demonstrated that combination therapy with Q-switched laser is better than laser alone, and it was found that additional topical 3% TA could enhance the efficacy of the 1064-nm QSNYL. Furthermore, no significant adverse events were reported.[1]

Based on previous studies, we also found a better efficacy of combination therapy (laser and TA), but we did not have alone laser arm to calculate the exact additive efficacy of combination therapy. The above study also found higher efficacy than ours, which may be related to different demographic characteristics of patients or disease and ethnical properties.

A study by Budamakuntla et al. compared TA microinjections and TA with microneedling in patients with melasma. In this study, 60 patients with melasma participated, thirty patients in each of the treatment arms, after treatment course. There was no significant difference in the means of the MASI scores between the microinjection and microneedling group with the two tailed (35.72% improvement vs. 44.41%) that demonstrated that TA can be used as a safe, effective, and promising therapeutic agent

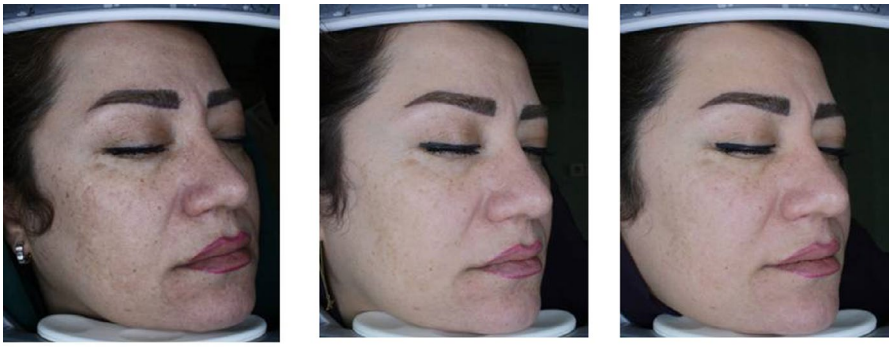

FIGURE 7 Patient in microinjection group of tranexamic acid group (start of trial, mid-trial, and end of trial)

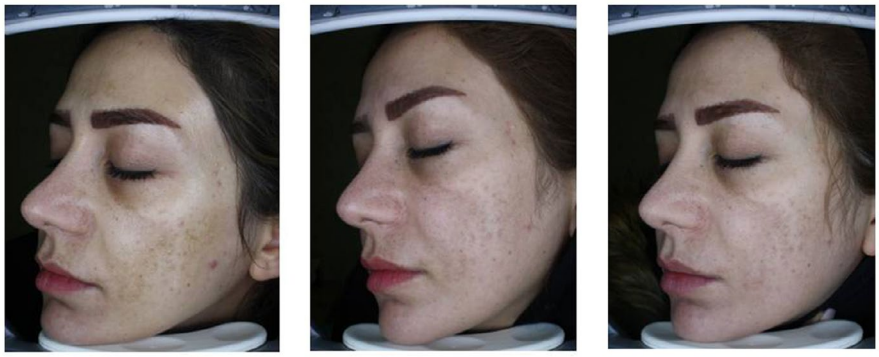

FIGURE 8 Patient in oral group of tranexamic acid group (start of trial, mid-trial, and end of trial)

for the treatment of melasma without considering the route of administration.[15]

We found a higher therapeutic response than the above study which shows better efficacy of combination therapy with laser. As ours, the above study did not show difference between administration routes.

A pilot study was conducted by Lee et al. to evaluate the efficacy and side effects of the new treatment of melasma, using mesoneedling TA. Eighty-five patients completed the study, and a significant decrease in the MASI was observed. MASI score after treatment decreased from 13.22 ± 3.02 at baseline to 7.57 ± 2.54 at 12 weeks; in the assessment by the patients themselves, 86% of them considered the results as "good or fair" improvement. According to this study, it seems that TA mesoneedling can be used as a new and effective and safe treatment for melasma.[16]

The result of this study is similar to ours, although did not have combined laser therapy. These results show that combination of laser therapy and TA (regardless of route of administration) have somehow higher efficacy than each one alone.

A systemic review of the systemic treatment of melasma was done by Zhou LL et al. In this article, eight RCTs met inclusion criteria. According to this review, oral medications include tranexamic appear to have a good response to melasma improvement and be effective and tolerable with a minimal number and severity of adverse effects.[17]

A review of light and laser therapy in patients with melasma was done by Trivedi MK et al, which showed that laser therapy is another method to treat patients with refractory melasma. These methods are limited by recurrence, PIH, and the need for several seasons. This article displays that picosecond lasers and fractional radiofrequency devices promise an effect on melasma treatments.[18]

In this study, we used Q-switched 1064 laser in both groups for the treatment of melasma. This treatment has known therapeutic effects on refractory melasma. In addition, this procedure is usually well tolerated and has no side effects even in high-risk individuals.

According to recent studies on TA and its lightening effect, the present study investigated the comparative effect of oral and mesotherapy forms (microinjection) of this drug. TA suppresses the formation of new vessels by inhibiting the conversion of VEGF to free form and other vascular components that stimulate melanocyte activity in melasma. TA also reduces mast cells activity, which plays an important role in the pathogenesis of melasma.

Peak concentration of TA is attained after 3 h of oral intake. Bioavailability of TA is 34% and is weakly bind to 3% of plasma protein, and exclusively around 95% of TA excreted unchanged in the urine. Only a small portion of the drug is metabolized in the liver.

In this study, we used MASI score as the main primary outcome measure and compared the result of Q-switched laser combined with two different modes of TA administration, and found them safe therapeutic options with a significant reduction of MASI score without any significant difference between the groups.[19] The authors of this study have been worked on various aspects of melasma and other pigmentary disorders for better management and therapy,[8,20-24] Nowadays, most trials in the field of dermatology are running on common skin diseases and cosmetic concerns, and even Coved 19. Since the ideas dealing with these concerns lead to novel recommendations that can be helpful for a large group of patients suffering from these diseases, therefore, we have designed new trials in the field of melasma. [25-28]

4.1 | Limitations and recommendation

Because of the high cost of laser therapy, we enrolled the least statistically acceptable sample size with regard to the probable loss to follow-up cases. The short duration of the follow-up period was another limitation of our study. It would be better to have other arms as laser or TA alone for better evaluation of additive therapeutic efficacy of combination therapy.

5 | CONCLUSION

Tranexamic acid appears to be effective and safe for melasma regardless of routes of administration, which may be oral, injectable, topical, and mesotherapy, and it can enhance the effect of laser therapies such as Q-switch. Oral administration of TA 250 mg three times daily is safe (few non-serious reversible adverse effects) and painless treatment; however, it requires daily drug consumption. Although TA microinjection can be painful, it has few side effects. Based on our results, oral forms of TA and TA microinjection are effective, safe, tolerable, and satisfactory for melasmatic patients over 3 months of treatment, without any significant difference. Recurrence is uncommon in both groups, but more studies with longer follow-up periods are needed.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

EB, MGh, and AG designed the research, conducted the experiments, wrote and edited the paper, and conducted the experiments. MSh, SD, and AG performed the data analyses and edited the manuscript. AG and MSh supervised the study, and wrote the manuscript. All authors have read and approved the content of the manuscript.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Iran University of Medical Sciences on June 2, 2018 (registration no. 1396.9511166001) and was registered on the Iranian Clinical Trial Registry (IRCT) on April 13, 2019 (registration no. 20140624018210N9).

INFORMED CONSENT

Informed consent was obtained from the patients for participating in the study, and the rights of the subjects were protected.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Azadeh Goodarzi https://orcid.org/0000-0002-1249-4429

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