Received: 1 June 2023 | Revised: 6 September 2023 | Accepted: 10 October 2023

DOI: 10.1002/hsr2.1636

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Evaluation of the effectiveness of microneedling with tranexamic acid in comparison with microneedling with vitamin C in the treatment of melasma: A prospective and single-blind clinical trial

Nader Pazyar[1] | Maryam Raeispour[2] | Reza Yaghoobi[1] | Maryam Seyedtabib[3]

[1]Department of Dermatology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[2]School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[3]Department of Biostatistics and Epidemiology, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Correspondence
Maryam Raeispour, Dermatology Resident, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Email: raeispour.maryam@gmail.com

Funding information
Ahvaz Jundishapur University of Medical Sciences, Grant/Award Number: U-00076

Abstract

Background and Aims: Melasma is a common skin condition. Microneedling acts as a dermal delivery system that facilitates the penetration of lightening agents such as vitamin C and tranexamic acid (TXA) into the deeper layers of the skin. Therefore, this study aimed to compare the effectiveness of microneedling with TXA with microneedling and vitamin C in treating melasma.

Methods: In patients with melasma, microneedling was performed at 2–3 mm depth. During that, TXA and vitamin C were poured on the skin of each side of the face, and then each ampoule was soaked for 15 min. This method was performed three times in 2-week intervals, and the results were compared by measuring the Melasma Area and Severity Index (MASI) score before, during, and 2 months after the completion of the treatment.

Results: The average MASI score in the baseline in the TXA group was 4.61, and in the vitamin C group was 4.58. The average MASI score in the patients treated with TXA in the last treatment session was 2.40, and the group treated with vitamin C was 2.44. The study results showed that the treatment was effective in both groups based on MASI score. Although there was a difference between the responses of the two groups, it was not significant.

Conclusion: Microneedling with vitamin C and TXA is a safe and effective treatment option without side effects for treating melasma.

KEYWORDS

ascorbic acid, dermatology, pigmentation disorders, tranexamic Acid

1 | INTRODUCTION

Melasma is an acquired pigmentation disorder that occurs mainly on the face. This disorder, more common in women and darker skin types, is primarily attributed to exposure to ultraviolet (UV) radiation and hormonal influences. Morphologically, it appears in symmetrical reticulated hyperpigmented spots with irregular borders on the face.[1–3]

Melasma is a complex condition that arises from various factors, including environmental influences, hormonal fluctuations, and genetic susceptibility.[4,5] Melasma is found in all ethnicities, while it can occur in all skin types, but it is more common in darker skin phototypes (Fitzpatrick III–V skin).[6] The management of this disorder is still challenging due to the incomplete understanding of its pathogenesis, chronicity, and recurrence rate.[1]

The estimated prevalence of melasma in the general population is approximately 1%, ranging from 9% to 50% in high-risk populations. The significant variation in people can be attributed to darker skin types, varying ethnic origins, and diverse levels of exposure to UV radiation in distinct geographical regions.[7,8] The precise age at which melasma first manifests remains uncertain; however, research suggests that the average onset typically occurs within 20–30 years.[2,4] Melasma is commonly observed in females but can also manifest in males.[8,9]

The precise etiology of the disease remains uncertain. Nevertheless, several factors can act as triggers for specific conditions. These factors encompass but are not limited to sun exposure, pregnancy, the utilization of oral contraceptives, the presence of ovarian tumors, hormone replacement therapy, photosensitizing drugs, cosmetics, inflammatory processes affecting the skin, and stressful events.[6]

Assessing the severity of melasma can pose challenges due to the diverse range of assessment methods available. The Melasma Area and Severity Index (MASI) is an established and reliable metric for quantifying facial hyperpigmentation.[10] Melasma significantly impacts an individual's physical appearance, leading to emotional and psychological distress, ultimately resulting in a diminished quality of life for the affected patient. The MelasQoL instrument assesses psychosocial dimensions related to the melasma condition. However, there is a tenuous association between MelasQoL and disease severity as evaluated by MASI; individuals with even mild cases of melasma may encounter a range of emotional challenges, including frustration, depression, dissatisfaction with their physical appearance, and diminished emotional well-being.[10,11]

The various treatment modalities for melasma encompass light protection, topical agents, oral medications, combined therapies, injection-based interventions, chemical peels, and laser-based approaches. The interventions above target multiple facets of melasma pathogenesis, encompassing the impact of sun exposure, inflammatory processes, vascular abnormalities, and dysregulation of pigmentation. Hydroquinone (HQ) is widely recognized as the preferred therapeutic option for treating epidermal melasma due to its superior efficacy. However, previous research has shown that the effects of HQ treatment are reversible.[3] Corticosteroids can inhibit melanogenesis and exhibit anti-inflammatory properties, thereby potentially preventing pigmentation. However, it is essential to note that prolonged usage of corticosteroids may result in adverse effects such as telangiectasia, acne, epidermal atrophy, striae, and hypopigmentation, as shown by previous studies.[12,13] The effects of retinoids encompass various aspects, such as the modulation of keratinocytes, melanosomes, and melanin synthesis, as well as the inhibition of tyrosinase activity. However, it is worth noting that in specific individuals, retinoids may lead to dermatitis and skin irritation.[14,15] The efficacy of chemical peels, specifically glycolic acid, lactic acid, and trichloroacetic acid (TCA), have been investigated as adjunctive therapies for managing recalcitrant melasma. They are frequently used with other topical products.[16,17] Laser therapy's efficacy in treating melasma has been examined to varying degrees of success. However, it is worth noting that using CO_2 lasers may carry the potential risk of postinflammatory hyperpigmentation (PIH), particularly in the surrounding areas of the affected lesions.[18,19]

Tranexamic acid (TXA) is a novel therapeutic intervention for melasma, whereby its primary mode of action is attributed to its antiplasmin activity, resulting in hypopigmentary effects. One aspect of the drug's composition resembles tyrosine, enabling it to impede the enzymatic activity of tyrosinase competitively. Additionally, plasmin is responsible for converting the vascular endothelial growth factor (VEGF) bound to the matrix into a form that can be easily accessed; as a result, plasmin contributes to reducing erythema and vascularity. According to the findings of meta-analytical studies, this pharmaceutical agent has demonstrated efficacy, safety, and accessibility as a treatment option. The topical application of this treatment offers a convenient solution that can be administered within a clinical setting, and it yields rapid recovery outcomes.[20–23]

Ascorbic acid, also known as vitamin C, is a crucial antioxidant not endogenously synthesized by humans and must be acquired through dietary sources. This particular vitamin exerts various effects on the skin, primarily by diminishing melanin production through competitive interaction with copper ions at the active enzyme tyrosinase site. Additionally, it hinders melanin synthesis by inducing intracellular acidification of melanocytes. Consequently, it has demonstrated efficacy in treating melasma.[24,25] The concentration of vitamin C in the epidermis is 2–5 times higher compared to the dermis. The concentration of the outermost layer of the epidermis is

Highlights

- Microneedling with vitamin C is an effective treatment option for melasma.
- Microneedling with vitamin C is a safe treatment without side effects.
- Combining tranexamic acid and vitamin C with microneedling is a vital treatment in the management of melasma.

comparatively lower when compared to the underlying layers of the epidermis. This issue occurs within the epidermis due to increased exposure to solar radiation and other forms of environmental pollution. Consequently, it is more substantially reduced in the outermost strata of the epidermis.[26,27]

Microneedling is an additional adjunctive therapy for melasma that involves the creation of minuscule channels in the skin. Through these channels, small quantities of localized medications are introduced into specific and predetermined layers of the skin.[18,28] Additionally, it has been shown that controlled skin lesions and injuries resulting from microneedling might elicit a favorable wound-healing response while exhibiting fewer adverse effects compared with traditional exfoliating techniques.[29] The mesoneedling approach facilitates a more profound and consistent deposition of the medication inside the epidermis and dermis. This approach is attributed to the precise and direct drug administration at the appropriate depth, substantially reducing the dosage needed for skin penetration.[19,30]

The research about vitamin C mainly focused on its use in topical formulations. However, it is worth noting that topical medications exhibit limited absorption and endurance as a result of their inherent instability, hence leading to potential adverse effects such as allergic reactions and skin irritation. Despite the increasing use of vitamin C in mesotherapy solutions, there is a need for more scientific research that substantiates the safety and efficacy of injectable vitamin C in dermal applications.[26] The administration of oral TXA is associated with notable adverse effects such as flatulence, headache, tinnitus, menstrual irregularity, and, in rare cases, deep vein thrombosis (DVT). Conversely, injectable TXA has indicated pain and uncontrolled depth of penetration, resulting in distinct reactions.[31]

The microneedling method has advantages such as low and tolerable pain, minimal drug consumption, and controlled penetration depth. So, in this study, we intend to investigate the effects of these two drugs using the microneedling method on improving melasma.

2 | METHODS

2.1 | Study design

The present investigation is a prospective and single-blind clinical experiment carried out at Imam Khomeini Hospital of Ahvaz, associated with the Faculty of Medicine of Ahvaz Jundishapur University of Medical Sciences. The research was done during a period spanning from May 2021 to September 2021. The Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences approved the present study under code number IR.AJUMS.HGOLESTAN.REC.1400.044. The study was also enrolled in and approved by the Iranian Registry of Clinical Trials (IRCT20210608051516N1). Written informed consent was obtained from all patients before initiating the trial. All patients were guaranteed that their information would be kept confidential.

The research sample included individuals sent to the Imam Khomeini Hospital skin clinic in Ahvaz seeking melasma treatment. These individuals voluntarily agreed to participate in the study and satisfied the inclusion criteria. The subject and the researcher affixed their signatures to a permission form, and the patient was provided copies of both versions.

Patients were informed about the purpose and method of conducting the study. Written and informed consent was obtained from all subjects to participate in the study. Subjects can withdraw from the study at any time and receive another treatment. There is no financial or physical harm to the patients. The information extracted from the files remains confidential and only at the project manager's disposal.

Inclusion criteria for the participants in this study were women aged 18–50 years with bilateral melasma of the face; however, the exclusion criteria included as follows: pregnant women and nursing mothers, use of oral contraceptive pills in the past 12 months and during this study, any history of coagulation disorders and thrombotic problems, use of anticoagulants and anticonvulsants, the existence of sensitivity to drugs investigated in this study, lidocaine, history of melasma treatment in the month before this study, active herpes simplex lesions on the face and facial warts.

2.2 | Sample size

According to the study plan (repeated measurements at 5-time points) and using the results of the MASI parameter values in previous studies, the minimum required sample volume was 34 samples, considering the first type error of 0.05 and a power of 80%.

2.3 | Implementation

All patients provided written consent after receiving comprehensive explanations. The patient's medical history was obtained during the initial consultation, followed by a thorough examination using Wood's lamp. This examination aimed to identify and classify the type of melasma present in each patient, distinguishing between epidermal, dermal, or mixed melasma. The classification of melasma as either epidermal or dermal was determined based on the degree of intensification observed under the illumination of Wood's lamp. When a portion of the lesion experienced exacerbation, and its role remained ambiguous, it was also classified as mixed.

The researchers recorded various demographic characteristics of the patient, such as age, sex, family history, aggravating factors, duration of melasma, previous treatments, skin phenotype, type of melasma, and affected areas.

The study employs a one-blind randomization method, wherein patients are unaware of the treatment allocation to the right and left side of the face. At the same time, the therapist possesses the necessary expertise and skills to administer the therapy effectively. The employed methodology involved the administration of vitamin C

and TXA, both of which were prepared in syringes that exhibited identical visual characteristics; nonetheless, the project manager was aware of their contents. TXA was administered on the right side, and vitamin C was issued on the left side of the face during the microneedling procedure; however, it is worth noting that the patient was unaware of the medications employed on each side of their face.

At first, the patient's lesions were photographed before the treatment. Anesthetic cream (containing 5% lidocaine and 5% prilocaine) was used with a closed dressing for more effect for the patients about an hour before the treatment. TXA ampoule was considered as 500 mg/5 mL ampoules and vitamin C ampoule was also considered as 500 mg/5 mL ampoules.

The microneedling procedure was performed using the DR. PEN A6 microneedling machine, utilizing a sterile disposable cartridge containing 36 needles. The needles were inserted into the skin of the targeted area at a depth of 2–3 mm, resulting in localized bleeding. The needling technique involved creating punctures in the skin in horizontal, vertical, and diagonal orientations. During the microneedling procedure, a total of 5 cc ampoules of TXA (Caspian Tamin) and 5 cc ampoules of vitamin C (Alborz Darou) were topically applied to one side of the face. Following the conclusion of the microneedling procedure, a sterile gas (SOAK) containing 5 mL of each ampoule was applied to the skin for 15 min. The experiment was conducted thrice at 2-week intervals (during Weeks 0, 2, and 4), and the outcomes were subsequently compared during Weeks 2, 4, 6, and 12.

2.4 | Outcome evaluation

Follow-up of patients was done by measuring MASI score, patient global assessment (PtGA), and physician global assessment (PGA) and taking pictures, which was repeated four times. MASI score was measured and recorded at the beginning of the study. After completing the treatment, the patients were followed up for 2 months to evaluate the recurrence of melasma. The calculation of the MASI score is as follows: hyperpigmentation was calculated based on the involved area A (area), D (darkness), and H (homogeneity). The right side of the forehead, the right side of the cheek, and the right side of the chin are calculated as 15%, 30%, and 5% of the whole face, respectively. Similar areas on the left side are calculated similarly to include 100% of the face. Each A evaluation score is 0–6. The D and H evaluation score is 0–4. MASI score is calculated from the product of A score and the sum of D and H for each of the six areas.

$$0.15(A)(D + H) + 0.3(A)(D + H) + 0.05(A)(D + H).$$

The highest MASI score for each side is 24, and the lowest is zero.

The subjects underwent assessments at various time points, including Day 0 (corresponding to the initial treatment), Week 2 (second treatment), Week 4 (third treatment), Week 6, and Week 12. Photographs were taken from frontal and lateral at the same distance and room light at each visit with a Canon digital camera (power shot S110 with 12.1 megapixels high-sensitivity CMOS sensor; Canon, Inc.). The pictures were taken from frontal and lateral perspectives, maintaining a consistent distance and utilizing room lighting conditions during each visit. The participants underwent interviews and evaluations to determine their MASI scores and identify potential side effects. These assessments were conducted at the beginning of the study and then repeated at Weeks 2, 4, 6, and 12. The evaluation of treatment response was conducted using Dynamic Physician's Global Assessment (Dynamic PGA), which involved capturing images of lesions at both the commencement and conclusion of the study. According to the scale utilized in this study, a range of improvement percentages was categorized into different levels. Specifically, an improvement of 0%–25% was classified as a poor improvement, while improvement percentages ranging from 26% to 50% and 51% to 75% were categorized as fair and reasonable improvement, respectively. Furthermore, a 76%–100% improvement in lightning was considered excellent.

At the 3-month follow-up, patients were polled about their experiences with TXA, microneedling, and vitamin C, using a 3-point scale ranging from dissatisfaction to satisfaction (Patient Global Assessment, or PtGA).

2.5 | Data analysis

Descriptive statistics were performed using Mean ± Standard deviation for quantitative variables, frequency, and percentage were used for categorical variables. The normality of data was checked using the Shapiro–Wilk test and was normally distributed. The proportions were compared using the Chi-square test. Independent samples *t*-tests were used to compare data between the two groups at different times. All reported *p*-values were based on two-tailed tests and compared to a significance level of 0.05. Data were analyzed using SPSS version 22.0 (SPSS Inc.).

3 | RESULTS

The demographic data and melasma characteristics of the study cohort are shown in Table 1. After receiving an informed written agreement, 40 female conjunctival and bilateral face melasma patients were included in the research. Four individuals were excluded from the trial after it began because of distance and transportation issues. Two patients were eliminated from the study because they chose another treatment approach outside the facility, whereas 34 patients completed the therapy. The patients in this research ranged in age from 25 to 49 years old, with an average age of 37.16 and 8.73 years. Examining the different age groups of patients shows that 7 (20.58%) of the patients were in the third decade, 17 (50%) were in the fourth decade, and 10 (29.42%) were in the fifth decade; in fact, the majority of patients were in the fourth decade.

TABLE 1 Demographic data and melasma features of the study population.

Variables	Category	Frequency, *N* (%) or Mean ± SD
Age	20–30	7 (20.5)
	30–40	17 (50.0)
	40–50	10 (29.5)
Duration of melasma (years)	Mean ± SD	3.58 ± 2.29
Family history of melasma, *N* (%)	Positive	24 (70.5)
	Negative	10 (29.5)
Fitzpatrick skin type	Type I	0 (0)
	Type II	2 (5.8)
	Type III	13 (38.2)
	Type IV	19 (56.0)
Distribution of melasma	Centrofacial	11 (32.3)
	Malar	23 (67.6)
Type of melasma	Epidermal	25 (73.5)
	Mixed	9 (26.5)
Previous treatment	Positive	22 (64.7)
	Negative	12 (35.3)
Predisposing factors	Pregnancy	7 (20.5)
	UV	8 (23.6)
	OCP	5 (14.7)
	OCP + UV	3 (8.8)
	Pregnancy + UV	7 (20.5)
	Pregnancy + UV + OCP	2 (5.8)
	Negative	2 (5.8)

Note: Frequencies are reported as number and mean ± SD.

Abbreviations: OCP, oral contraceptive pills; SD, standard deviation; UV, ultraviolet.

The average disease duration in the individuals evaluated was 3.58 ± 2.29 years, ranging from 1 to 12 years. Examining the patients' family history shows that 24 (70.58%) had a family history of the disease, and 10 (29.42%) had no family history. Examining the skin type of patients shows that 2 (5.88%) patients have skin type II, 13 (38.24%) have type III, and 19 (55.88%) have type IV. Examining the affected area in patients shows that 23 (67.64%) were involved in the malar region, and 11 (32.36%) were involved in the centrofacial area. Examining the melasma type of patients shows that 9 (26.47%) patients have a mixed variety, and 25 (73.53%) have an epidermal type. Examining the history of previous treatment in patients shows that 22 people (64.70%) have had a history of prior therapy, and 12 people (35.30%) have no history of previous medicine. Examining aggravating factors in patients shows that 2 (5.88%) patients without any aggravating factors, 7 (20.58%) with pregnancy factor, 8 (23.56%) with UV radiation factor, 5 (14.70%) have the aspect of taking OCP pills, 7 people (20.58%) have the elements of pregnancy and UV rays, 3 people (8.82%) have the characteristics of OCP pills and UV rays. Two people (5.88) also have the features of pregnancy, OCP pills, and UV rays.

The efficacy of a melasma MASI-based intervention in the TXA group is compared to vitamin C in Table 2. Patients in the vitamin C therapy group had a mean baseline MASI score of 4.58 ± 1.59. In contrast, those in the TXA treatment group had a mean score of 4.61 ± 1.54, with no statistically significant difference between the two groups ($p > 0.05$). The average MASI score for patients in the TXA therapy group at the end of the second week was 4.34 ± 1.51, whereas the average score for patients in the vitamin C treatment group was 4.32 ± 1.50; there was no statistically significant difference between the two groups ($p = 0.53$). The average MASI score for patients in the TXA therapy group at the end of the fourth week was 3.37 ± 1.28, and the average score for patients in the vitamin C treatment group was 3.43 ± 1.31; there was no statistically significant difference between the two groups ($p > 0.05$). The mean MASI score for patients in the TXA therapy group at the end of the sixth week was 2.40 ± 1.25, while the mean score for patients receiving vitamin C treatment was 2.44 ± 1.28, with no statistically significant difference between the two groups ($p > 0.05$). The average MASI score of the patients at the end of the intervention and during follow-up was 2.11 ± 1.14 in the TXA treatment group and 2.21 ± 1.17 in the vitamin C treatment group. There was no statistically significant difference between the two groups ($p > 0.05$) at the end of the 12th week.

Table 3 and Figure 1 present the results of PGA in individuals diagnosed with melasma who underwent an intervention involving the administration of TXA compared with vitamin C. The analysis of dynamic PGA reveals that within the treatment group receiving TXA, four patients (11.76%) achieved an excellent outcome, 20 patients (58.82%) experienced a good outcome, eight patients (23.52%) had a fair result, and two patients (5.88%) had a poor outcome. In the group receiving vitamin C treatment, it was observed that two patients (5.88%) exhibited excellent results, 17 patients (50%) showed promising results, 10 patients (29.41%) displayed fair results, and five patients (14.70%) demonstrated poor results. The patient PGA showed favorable outcomes in individuals who received TXA treatment, with a success rate of 58.82%. Similarly, the group treated with vitamin C exhibited a success rate of 50%. However, the difference in success rates between these two treatment groups was not statistically significant ($p > 0.05$).

Table 4 and Figure 2 present the satisfaction level of PtGA in individuals with melasma who received treatment with TXA compared to vitamin C. The data analysis indicated the patient satisfaction levels, as measured by the PGA, within the TXA treatment group, 12 individuals (35.29%) reported complete satisfaction, 13 individuals (38.24%) reported partial fulfillment, and nine individuals (26.47%) expressed dissatisfaction. Nine individuals (equivalent to 26.47% of the sample) reported complete satisfaction in the group receiving vitamin C treatment. In comparison, 16 individuals (47.06%) reported partial fulfillment, and another 9

TABLE 2 Comparison of the effectiveness of an intervention based on Melasma Area Score and Severity Index (MASI) in the tranexamic acid group versus ascorbic acid.

Timeline	Group ($N = 34$)	MASI score				p-Value
		Minimum	Maximum	Mean	SD	
Baseline	TXA	2.20	7.50	4.61	1.54	0.30
	VIT C	1.99	7.40	4.58	1.59	
2th week	TXA	2.00	7.00	4.34	1.51	0.53
	VIT C	1.92	7.20	4.32	1.50	
4th week	TXA	1.40	6.00	3.37	1.28	0.08
	VIT C	1.32	6.24	3.43	1.31	
6th week	TXA	0.8	5.60	2.40	1.25	0.07
	VIT C	0.9	6.00	2.44	1.28	
12th week	TXA	0.67	4.84	2.11	1.14	0.08
	VIT C	0.59	5.14	2.21	1.17	

Abbreviations: SD, standard deviation; TXA, tranexamic acid; VIT C, vitamin C.

TABLE 3 Physicians Global Assessment (PGA) in melasma patients who underwent intervention with tranexamic acid (TXA) versus ascorbic acid.

PGA	Excellent		Good		Fair		Poor	
Group	Number	Percent	Number	Percent	Number	Percent	Number	Percent
TXA treatment group	4	11.76	20	58.82	8	23.52	2	5.88
Vitamin C treatment group	2	5.88	17	50.00	10	29.41	5	14.70
p-Value	0.66							

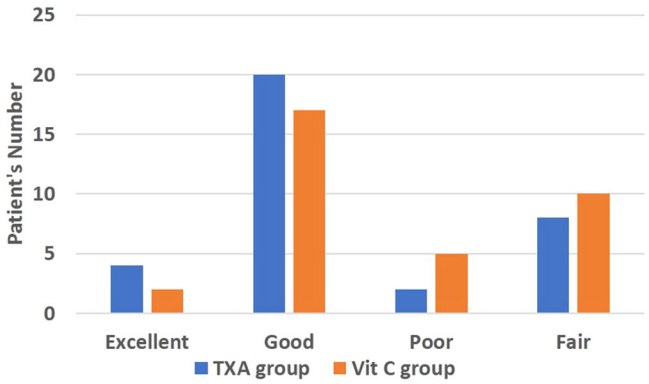

FIGURE 1 Physicians Global Assessment (PGA) in melasma patients who underwent intervention with tranexamic acid (TA) versus ascorbic acid.

(26.47%) expressed dissatisfaction. No statistically significant difference was observed between the two groups ($p > 0.05$).

Table 5 and Figure 3 compare the pain levels of patients treated with TXA and those treated with vitamin C. Examining the adverse effects of the treatment in the examined patients revealed that all patients in both the TXA treatment and vitamin C treatment groups experienced burning sensation. The patient's pain rating was recorded on a 10-point Likert scale, and the TXA treatment group had a mean survival time of 0.72 ± 0.11 years. The mean age of the vitamin C treatment group was 0.66 ± 0.10 years, and there was no statistically significant difference between the two groups ($p > 0.05$). Figures 4–8 compare microneedling treatment with TXA versus vitamin C.

The comparison of treatment effectiveness by comparing MASI score based on the type of melasma in the TXA treatment group is shown in Table 6. Patients with mixed melasma had a mean baseline MASI score of 5.20 ± 1.40. In contrast, those with epidermal melasma had a mean score of 4.22 ± 1.41, with no statistically significant difference between the two groups ($p > 0.05$). The average MASI score for patients with mixed melasma at the end of the second week was 5.05 ± 1.39, whereas the average score for patients with epidermal melasma was 3.97 ± 1.40; there was no statistically significant difference between the two groups ($p > 0.05$). The average MASI score for patients with mixed melasma at the end of the fourth week was 4.09 ± 1.04, and the average score for patients with epidermal melasma was 3.13 ± 1.28; there was no statistically significant difference between the two groups ($p > 0.05$). The mean MASI score for patients with mixed melasma at the end of the sixth week was 2.98 ± 0.97, while the mean score for patients with epidermal melasma was 2.20 ± 1.18, with no statistically significant

TABLE 4 Satisfaction level (Patient Global Assessment [PtGA]) in melasma patients who underwent intervention with tranexamic acid (TXA) versus ascorbic acid.

Satisfactory level	Satisfaction		relative satisfaction		Dissatisfaction	
Group	Number	Percent	Number	Percent	Number	Percent
TXA treatment group	12	35.29	13	38.24	9	26.47
Vitamin C treatment group	9	26.47	16	47.06	9	26.47
p-Value	0.33					

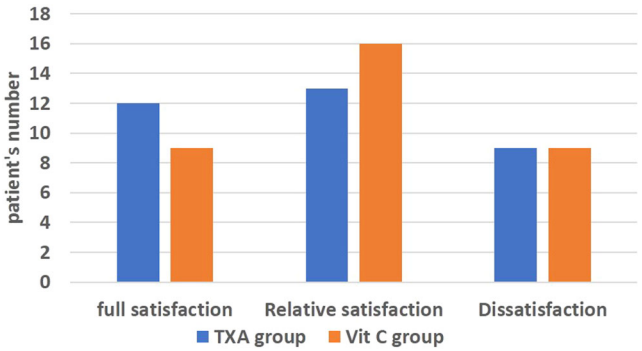

FIGURE 2 Satisfaction level (Patient Global Assessment [PtGA]) in melasma patients who underwent intervention with tranexamic acid (TA) versus ascorbic acid.

TABLE 5 Comparison of patient pain in the group treated with tranexamic acid (TXA) and treated with vitamin C.

	Indexes					
Patient pain	Number	Minimum	Maximum	Mean	SD	*p*-Value
TXA treatment group	34	0.40	1.00	0.72	0.11	0.11
Vitamin C treatment group	34	0.38	0.89	0.66	0.10	

Abbreviation: SD, standard deviation.

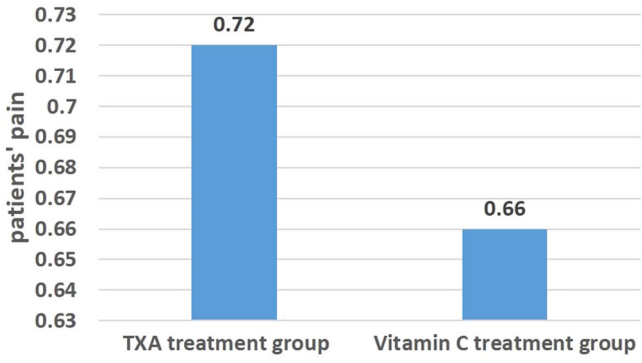

FIGURE 3 Comparison of patient's pain in the group treated with tranexamic acid (TXA) and treated with vitamin C.

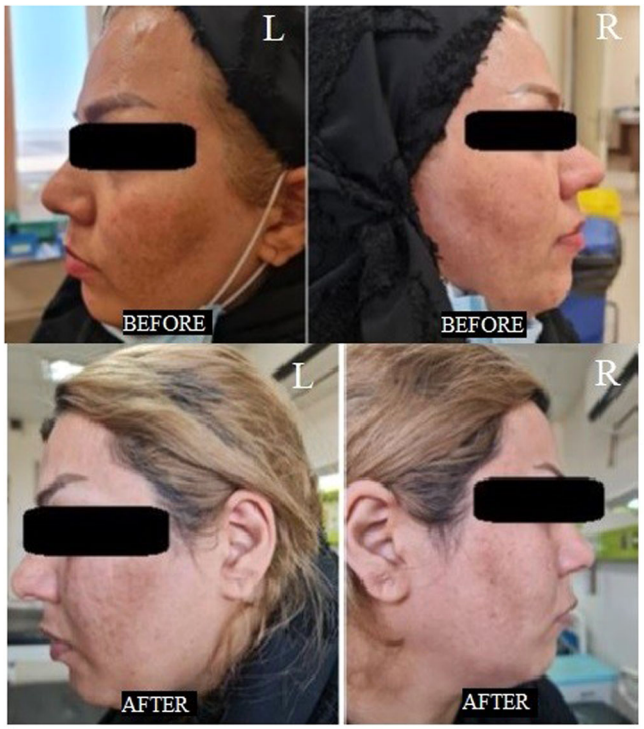

FIGURE 4 The right side of the face before treatment and after three treatment sessions with microneedling and tranexamic acid. The left side of the face before treatment and after three sessions of therapy with microneedling and vitamin C.

difference between the two groups ($p > 0.05$). The average MASI score of the patients at the end of the intervention and during follow-up was 2.67 ± 0.76 with mixed melasma and 2.09 ± 0.99 in the with epidermal melasma. There was no statistically significant difference between the two groups ($p > 0.05$) at the end of the twelfth week.

The comparison of treatment effectiveness by comparing MASI score based on the type of melasma in the vitamin C treatment group is shown in Table 7. Patients with mixed melasma had a mean baseline MASI score of 5.34 ± 1.27. In contrast, those with epidermal melasma had a mean score of 4.21 ± 1.49, with no statistically significant difference between the two groups ($p > 0.05$). The average MASI score for patients with mixed melasma at the end of the second week was 5.10 ± 1.22, whereas the average score for patients with epidermal melasma was 4.01 ± 1.43; there was no statistically significant difference between the two groups ($p > 0.05$). The average MASI score for patients with mixed

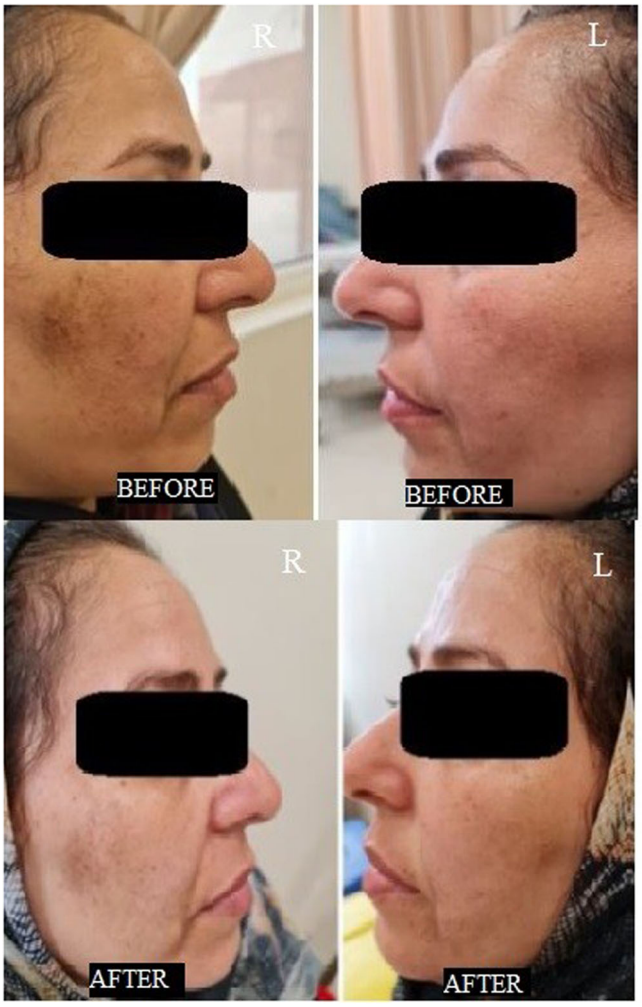

FIGURE 5 The right side of the face before treatment and after three treatment sessions with microneedling and tranexamic acid. The left side of the face before treatment and after three sessions of therapy with microneedling and vitamin C.

FIGURE 6 The right side of the face before treatment and after three treatment sessions with microneedling and tranexamic acid. The left side of the face before treatment and after three sessions of therapy with microneedling and vitamin C.

melasma at the end of the fourth week was 4.37 ± 1.08, and the average score for patients with epidermal melasma was 3.42 ± 1.38; there was no statistically significant difference between the two groups ($p > 0.05$). The mean MASI score for patients with mixed melasma at the end of the sixth week was 3.30 ± 1.06, while the mean score for patients with epidermal melasma was 2.67 ± 1.35, with no statistically significant difference between the two groups ($p > 0.05$). The average MASI score of the patients at the end of the intervention and during follow-up was 3.01 ± 0.98 with mixed melasma and 2.17 ± 1.01 in with epidermal melasma. There was no statistically significant difference between the two groups ($p > 0.05$) at the end of the 12th week.

4 | DISCUSSION

Melasma is an acquired facial skin disorder that predominantly affects reproductive women. It manifests clinically as a central pattern of plaques and macules with irregular facial borders. The disease has a refractory course and a high recurrence rate; consequently, the treatment of melasma requires more evidence and a combination of effective drug and nondrug interventions.[1–3]

TXA has been found to disrupt the interaction between melanocytes and keratinocytes through its inhibitory effects on the plasminogen/plasmin system and intracellular melanin synthesis.[20–23] Conversely, vitamin C possesses potent antioxidant properties and is among the suggested dietary supplements for individuals afflicted with melasma. The mechanism of action involves the chelation of copper ions involved in cellular pigmentation, thereby exerting an inhibitory effect on the process of melanogenesis. It is a scavenger of reactive oxygen species (ROS) and exhibits wide-ranging efficacy in treating melasma and other hyperpigmentation disorders.[24,25] Microneedling is known to stimulate the production of matrix metalloproteinases, which are believed to reduce hyperpigmentation by effectively suppressing melanin synthesis. As mentioned, the enhancement was noted after applying microneedling.[18,19,29]

A selection of studies about the same subject matter will be examined to enhance comprehension of the current study's findings and facilitate comparison with the outcomes of other studies. In a clinical trial conducted in Greece in 2019, Ismail et al.[32] investigated the impact of topical vitamin C microneedling as a treatment for melasma. The study involved a sample of 30 female patients diagnosed with melasma. According to a study conducted by

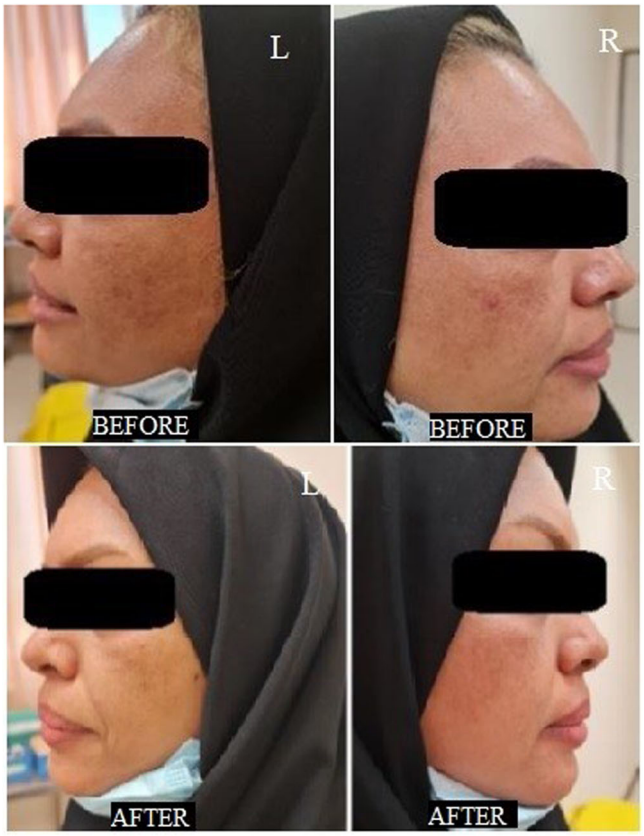

FIGURE 7 The right side of the face before treatment and after three treatment sessions with microneedling and tranexamic acid. The left side of the face before treatment and after three sessions of therapy with microneedling and vitamin C.

FIGURE 8 The right side of the face before treatment and after three treatment sessions with microneedling and tranexamic acid. The left side of the face before treatment and after three sessions of therapy with microneedling and vitamin C.

researchers,[32] using microneedling in conjunction with a 20% concentration of vitamin C is a successful therapeutic approach, exhibiting efficacy while minimizing adverse reactions. The current study aimed to assess the effects of vitamin C, TXA, and microneedling on a larger sample of individuals of Asian ethnicity. The findings were consistent with the existing body of research in this field. Similar investigations have been conducted in various world regions, yielding outcomes that align with the current study. Notably, Musarrat et al. conducted a study titled "SPLIT-Face Microneedling Comparative Analysis with TXA versus Vitamin C Serum in Melasma" in 2022. Their findings revealed that after 6 weeks, the modified melasma severity index and PGA and PTGA scores exhibited noteworthy enhancement when subjected to both acid transmits and vitamin C. However, it is essential to note that the disparity between these two treatments did not reach statistical significance.[33] TXA, vitamin C, and microneedling have been identified as essential therapeutic interventions for melasma, and the current study's findings are consistent with this assertion.

The study by Ashok Menon in 2020, entitled "A Comparative Analysis of the Safety and Efficacy of Microneedling with TXA and Microneedling with Vitamin C for Melasma," revealed significant improvement in both treatment groups. The findings of the current study align with the results reported by Menon. Several limitations were identified in Menon's investigation, including a limited number of microneedling sessions, a short-term follow-up period, a low drug concentration, a lack of examination of disease recurrence, and some patients who had previously received medication that the researchers tried to correct these limitations in the current study.[34]

Also, parallel studies were conducted in Iran by Pazyar et al.,[35] which showed that TXA was safe and effective in treating melasma, similar to the present study's findings. The final recommendation of the study is to increase the dose of TXA. Also, its combined use with other brightening drugs increases the rate of blindness.[35]

In the present investigation, the considerable reduction of MASI from the right side and the disappearance of melasma after TXA treatment demonstrate that TXA is an efficient pigmentation treatment. This result is attributable to the drug's high penetration level and consistent availability.

The observation of the disappearance of capillary vasculature following treatment represents a significant discovery. The study showcases the efficacy of TXA in enhancing the vascular aspect of melasma. A common speculation is that UV radiation stimulates the production of angiogenic factors such as VEGF, basic fibroblast growth factor (b-FGF), and interleukin-8. VEGF interacts with VEGF receptors present in epidermal keratinocytes, which release metabolites of AA and plasminogen from the proliferated vessels. This enhances

TABLE 6 Comparison of treatment effectiveness by comparing MASI score based on the type of melasma in the tranexamic acid (TXA) treatment group.

Timeline	Type of melasma	MASI score					*p*-Value
		Number	Minimum	Maximum	Mean	SD	
Baseline	Mixed	9	3.64	7.50	5.20	1.40	0.12
	Epidermal	25	2.20	6.84	4.22	1.41	
2th week	Mixed	9	3.24	7.00	5.05	1.39	0.13
	Epidermal	25	2.00	6.74	3.97	1.40	
4th week	Mixed	9	2.50	5.70	4.09	1.04	0.77
	Epidermal	25	1.40	6.00	3.13	1.28	
6th week	Mixed	9	1.84	4.50	2.98	0.97	0.66
	Epidermal	25	1.09	5.60	2.20	1.18	
12th week	Mixed	9	1.16	4.34	2.67	0.76	0.18
	Epidermal	25	0.89	4.58	2.09	0.99	

Abbreviations: MASI, Melasma Area and Severity Index; SD, standard deviation.

TABLE 7 Comparison of treatment effectiveness by comparing MASI score based on the type of melasma in vitamin C treatment group.

Timeline	Type of melasma	MASI score					*p*-Value
		Number	Minimum	Maximum	Mean	SD	
Baseline	Mixed	9	3.68	7.40	5.34	1.27	0.11
	Epidermal	25	1.84	6.90	4.21	1.49	
2th week	Mixed	9	3.46	7.20	5.10	1.22	0.11
	Epidermal	25	1.72	6.72	4.01	1.43	
4th week	Mixed	9	3.20	6.20	4.37	1.08	0.14
	Epidermal	25	1.32	6.24	3.42	1.38	
6th week	Mixed	9	2.00	5.00	3.30	1.06	0.31
	Epidermal	25	0.90	6.00	2.67	1.35	
12th week	Mixed	9	1.62	4.54	3.01	0.98	0.2
	Epidermal	25	0.77	5.20	2.17	1.01	

Abbreviations: MASI, Melasma Area and Severity Index; SD, standard deviation.

melanogenesis. TXA targets the vascular components of the skin and hence adds support to the vascular theory of melasma.[20] Our finding aligns with the observations made by Geddes et al.[36] Furthermore, George et al.[20] have documented that the TXA component acts explicitly on the vasculature in melasma, effectively inhibiting VEGF-induced angiogenesis. Moreover, it is also mentioned that plasmin plays an important role in the release of b-FGF, which is a potent melanocyte growth factor and promotes melanocyte proliferation. TXA indirectly reduces b-FGF production. It also suppresses angiogenesis and neovascularization induced by b-FGF. Experimental studies have shown a reduction in lesional mast cells, which might suppress various pathogenetic factors that initiate the development of melasma. These mechanisms point to the fact that TXA may be tried for other conditions like periorbital melanosis and even early keloids, where the vascularity component can be targeted.[20]

Significant reduction of MASI from the left supports vitamin C's role in treating melasma. However, the rate of decline of melasma with vitamin C was lower compared to TXA, indicating the superiority of TXA over vitamin C in the treatment of melasma, even though the effect of the two drugs was not significantly different.

Clinical severity alone is insufficient when making treatment decisions for skin diseases, especially in exposed areas; the psychological aspect must also be considered. In conclusion, topical TXA and topical vitamin C with microneedling are effective, well-tolerated treatments for melasma with negligible adverse effects.

Numerous studies have examined the risk factors for melasma. Melasma is a condition that has been linked to hormonal influences. There is a stimulus for melanogenesis during pregnancy, particularly in the third trimester, and elevated levels of placental, ovarian, and pituitary hormones may account for pregnancy-related melasma.

About skin type, approximately 75% of patients were IV, as in our study.[4–6]

The family history of melasma is a risk factor. In various investigations, more than onethird of patients reported a positive family history; in our study, this proportion exceeded 70%.[7,8] Previous research has shown that UV exposure substantially increases the risk of developing melasma by stimulating late melanogenesis through direct and indirect mechanisms. Visible light has been suggested to play a role in melasma because it can induce the production of new melanin and the discoloration of existing melanin. In addition, the results of this study corroborate the effect of hormones, particularly pregnancy and OCP, the influence of race and heredity, and the significance of solar exposure.[6]

Despite the availability of a wide variety of treatment options for melasma, including many active topical medications, laser-based technologies, and peels, the clinical management of this disease is fraught with numerous obstacles. The efficacy of microneedling in melasma has only been mentioned in a few studies, whereas the effectiveness of various medications with lightening effects has been extensively researched.

Vitamin C is an unstable compound that must be combined with other ingredients to have a more effective enhancing effect. Methods are being explored to transport vitamin C more effectively through the skin's outermost layer. If vitamin C can be transferred in a high concentration through the stratum corneum barrier, its storage and efficacy will increase in the epidermis.

The current investigation employed a split-face comparison methodology to assess the safety and effectiveness of microneedling with TXA and microneedling with vitamin C as therapeutic interventions for melasma. The improvement assessment was conducted using the MASI, the PGA, and the PtGA, and the twelfth week exhibited the highest degree of improvement. The efficacy of TXA was superior to that of vitamin C, although the difference was not statistically significant. This phenomenon can be attributed to the inhibitory effects of TXA on various biological processes, including the activation of melanocytes by UV light, the proliferation of melanocytes induced by hormones, the neovascularization generated by VEGF, and the damage to the basement membrane caused by mast cells.

This demonstrates that microneedling is an adjunct to vitamin C and TXA and is substantially effective in melasma. This finding was further confirmed by our study, even though in our study, there was no significant difference between treatment groups. With TXA treatment, vitamin C was undetectable. Our study has limitations due to the limited sample size. Nonetheless, the results are valuable contributions to the existing body of knowledge.

5 | CONCLUSION

The management of melasma continues to pose challenges, leading to considerable psychological and social implications. The efficacy of therapeutic interventions may exhibit variability due to multiple factors, encompassing divergent clinical presentations and differential treatment responses. The treatment of melasma necessitates a comprehensive approach that considers the various factors contributing to its development. These factors include photoprotection, inflammation, vasculature, pigmentation, and hormonal influences. Therefore, adopting a multifaceted treatment strategy addressing each aspect is crucial.

Enhanced comprehension of the pathogenesis of melasma holds promise for advancing therapeutic interventions targeting this prevalent and intricate dermatological condition. The research findings indicate that using microneedling with vitamin C demonstrates efficacy as a viable treatment modality for melasma. The treatment is considered safe and does not exhibit any discernible side effects.

In contrast, TXA administration exhibited more favorable outcomes than the administration of vitamin C. While a distinction was observed, it yielded no statistically significant results. Hence, using TXA, vitamin C, and microneedling is a potent therapeutic approach for managing melasma. These combined treatments offer a safe and productive option that can benefit many patients.

6 | RESEARCH LIMITATIONS

One notable constraint of the present study pertains to its relatively small sample size, which may impede the generalizability of the findings. Furthermore, the results obtained from the current investigation indicate a notable increase in the rate of improvement in both cohorts after 12 weeks. However, to validate these findings, it is imperative to undertake a study with an extended follow-up period, a larger sample size, and encompassing diverse gender and ethnic groups. It is essential to acknowledge that this phenomenon can yield varying outcomes.

7 | SUGGESTIONS

In future studies, it is suggested that, in addition to investigating the current variables, additional clinical and paraclinical variables of the patients should be examined, and a larger sample size of patients should be evaluated, for instance, in a multicenter treatment center. Focus on the possible side effects of each drug group and try to eliminate all confounding factors. Randomized clinical trials are recommended to compare the effectiveness of this combination with other treatment options and, in addition, to evaluate the effect of microneedling alone in the management of melasma.

AUTHOR CONTRIBUTIONS

Nader Pazyar: Conceptualization; formal analysis; investigation; writing—review & editing. **Maryam Raeispour**: Conceptualization; formal analysis; investigation; writing—review & editing. **Reza Yaghoobi**: Conceptualization; formal analysis; investigation; writing—review & editing. **Maryam Seyedtabib**: Conceptualization; formal analysis; investigation; writing—review & editing.

ACKNOWLEDGMENTS

This study was extracted from the thesis of dermatology resident Dr. Maryam Raeispour. Also, we would like to thank Ahvaz Jundishapur University of Medical Sciences. The present study was financially supported by Ahvaz Jundishapur University of Medical Sciences with the code U-00076.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

TRANSPARENCY STATEMENT

The lead author Maryam Raeispour affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Maryam Raeispour http://orcid.org/0009-0004-0532-9005

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How to cite this article: Pazyar N, Raeispour M, Yaghoobi R, Seyedtabib M. Evaluation of the effectiveness of microneedling with tranexamic acid in comparison with microneedling with vitamin C in the treatment of melasma: a prospective and single-blind clinical trial. *Health Sci Rep*. 2023;6:e1636. doi:10.1002/hsr2.1636