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Comparison of Efficacy of Mesotherapy with Tranexamic Acid versus Ascorbic Acid in the Treatment of Melasma: A Split-Face Comparative Study

Nida Khalid, Sameena Kausar, Ghazala Yasmin, Tooba Hadia, Hannah Hassan, Ammara Suleman

Abstract

Objectives: To compare the efficacy and safety of intradermal mesotherapy with tranexamic acid (TA) and ascorbic acid (AA) in patients with facial melasma.

Study Design and Setting: A quasi-experimental split-face comparative study was conducted at the Department of Dermatology, Tertiary Care Hospital, Malir Cantt, Karachi, over a period of six months after approval of the research protocol by the institutional review authority.

Methodology: Sixty patients aged 20–50 years with bilateral facial melasma were enrolled through non-probability consecutive sampling. Intradermal tranexamic acid (100 mg/mL) was administered on the right side of the face, while ascorbic acid (20%) was injected on the left side at two-week intervals for 12 weeks. Treatment response was assessed using the modified Melasma Area and Severity Index (mMASI) score at baseline and follow-up visits. Adverse effects were also recorded.

Results: Both treatment modalities showed significant reduction in mMASI scores after 12 weeks. However, the TA-treated side demonstrated a significantly greater mean reduction in mMASI score compared to the AA-treated side (73.9% ± 11.6 vs. 57.5% ± 13.2; $p<0.001$). Excellent response (=75% improvement) was observed in 56.7% of TA-treated sides compared to 30% of AA-treated sides. Adverse effects including erythema, burning sensation, and pain at injection site were mild and transient in both groups.

Conclusions: Intradermal mesotherapy with tranexamic acid was more effective than ascorbic acid in reducing the severity of melasma while maintaining a comparable safety profile. Both treatments were well tolerated; however, tranexamic acid produced faster and greater pigment reduction, particularly in patients with darker skin phototypes.

Keywords: Ascorbic Acid; Melasma; Mesotherapy; Skin Pigmentation; Tranexamic Acid

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INTRODUCTION

Melasma is a common acquired hyperpigmentary disorder characterized by symmetrical brown to gray-brown macules and patches involving sun-exposed areas of the face, particularly the cheeks, forehead, upper lip, nose, and chin.[1] The condition predominantly affects women of reproductive age and individuals with darker skin phototypes, especially Fitzpatrick skin types III–V.[2] Melasma is highly prevalent in Asian, Middle Eastern, African, and Latin American populations because of increased ultraviolet (UV) radiation exposure and genetic susceptibility.[3] Although melasma is not associated with physical morbidity, it has a considerable psychosocial impact on affected individuals. Facial pigmentation frequently causes emotional distress, low self-esteem, social embarrassment, anxiety, and impaired quality of life because the lesions are cosmetically disfiguring and often difficult to treat effectively.[4]

The prevalence of melasma varies widely across different ethnic and geographic populations, ranging from approximately 1% in the general population to nearly 40% in high-risk populations living in tropical regions.[5] Multiple

endogenous and exogenous factors contribute to disease development. Ultraviolet radiation is considered the most important precipitating factor because it stimulates melanocyte proliferation and melanogenesis through activation of inflammatory mediators and oxidative stress pathways.[6] Hormonal influences also play an important role, as melasma commonly occurs during pregnancy and in women using oral contraceptives or hormone replacement therapy.[7] Genetic predisposition is another recognized factor, with many affected individuals reporting a positive family history of the disease.8 Additional aggravating factors include thyroid dysfunction, cosmetic products, phototoxic medications, emotional stress, and chronic sun exposure.[3]

The pathogenesis of melasma is multifactorial and remains incompletely understood. Earlier theories primarily focused on melanocyte hyperactivity; however, recent evidence suggests that several cellular and molecular mechanisms are involved in disease progression.[9] Ultraviolet radiation induces the production of reactive oxygen species and inflammatory cytokines, resulting in increased tyrosinase activity and enhanced melanin synthesis.[10] Furthermore, dermal inflammation, solar elastosis, vascular proliferation, basement membrane disruption, and increased mast cell activity have been identified as important histopathological features in melasma lesions.[11] Interactions among melanocytes, keratinocytes, fibroblasts, inflammatory mediators, and vascular endothelial growth factors also contribute to persistent pigmentation and frequent recurrence. These mechanisms explain the chronic and treatment-resistant nature of melasma.

Several treatment modalities are currently available for melasma management, including topical depigmenting agents, oral medications, chemical peels, laser therapy, and energy-based procedures. Conventional topical agents such as hydroquinone, tretinoin, azelaic acid, kojic acid, and corticosteroids remain first-line treatment options.[12] However, these therapies often require prolonged use and may provide incomplete clearance with frequent relapse. In addition, adverse effects such as erythema, irritation, post-inflammatory hyperpigmentation, contact dermatitis, and exogenous ochronosis may limit patient compliance and long-term use.[13] Laser and light-based therapies have also shown variable efficacy and may worsen pigmentation in darker skin phototypes because of increased melanocyte sensitivity and inflammatory responses.[14] Consequently, there is increasing interest in minimally invasive therapeutic approaches that provide improved efficacy with fewer adverse effects.

Mesotherapy has recently emerged as a promising treatment modality for melasma and other pigmentary disorders. It involves intradermal microinjections of active therapeutic agents directly into affected skin, thereby enhancing local drug concentration and minimizing systemic adverse effects.[9] Among the agents used in mesotherapy, tranexamic acid (TXA) has gained considerable attention because of its anti-plasmin, anti-inflammatory, and anti-angiogenic properties. Tranexamic acid inhibits plasminogen activation and suppresses ultraviolet-induced melanocyte stimulation by reducing inflammatory mediators, arachidonic acid pathways, and vascular endothelial growth factor activity involved in melanogenesis.[10] Multiple clinical studies and systematic reviews have demonstrated significant reductions in Melasma Area and Severity Index (MASI) scores following oral, topical, and intradermal administration of tranexamic acid.[11]

Ascorbic acid (vitamin C) is another therapeutic agent increasingly used in melasma management because of its antioxidant and depigmenting properties. It inhibits tyrosinase activity, neutralizes reactive oxygen species, promotes collagen synthesis, and reduces oxidative stress associated with excessive melanin production.[6] Intradermal administration of ascorbic acid through mesotherapy has shown encouraging results in improving facial pigmentation and skin texture.[14] However, comparative evidence regarding the efficacy and safety of intradermal tranexamic acid and ascorbic acid remains limited, particularly in populations with darker skin phototypes and high ultraviolet exposure. Therefore, the present study was conducted to compare the efficacy and safety of intradermal mesotherapy with tranexamic acid and ascorbic acid in patients with facial melasma using a split-face comparative design.

METHODOLOGY

This quasi-experimental split-face comparative study was conducted at the Department of Dermatology, Tertiary Care Hospital from 1-Jan-2025 to 30-Jun-2025 after approval from the Ethical Review Committee of Tertiary Care Hospital. Ethical approval was granted through the Ethical Review Committee Certificate (File No. 158/2025/Trg/ERC). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

A total of 60 patients diagnosed with melasma were recruited through non-probability consecutive sampling. The sample size was calculated using the WHO sample size calculator by considering 95% confidence level, 80% power of study, and expected difference in treatment efficacy between the two groups based on previous published studies. Adult male and female patients aged 20–50 years having bilateral facial melasma with modified Melasma Area and Severity Index (mMASI) score =5 were included in the study. Patients with known hypersensitivity to tranexamic acid or ascorbic acid, pregnancy, bleeding disorders, systemic illness, use of hormonal contraceptives, or unwillingness to participate were excluded from the study. The inclusion and exclusion criteria were adopted from previously published studies on mesotherapy for melasma. [15-18]

Demographic variables including age, gender, marital status, and occupation were recorded on a predesigned proforma.

Clinical assessment included duration and distribution of melasma, Fitzpatrick skin type, and type of melasma (epidermal, dermal, or mixed) assessed through Wood's lamp examination. Baseline and follow-up digital photographs were taken under standardized lighting conditions and fixed distance for comparison. Baseline mMASI scores were calculated separately for both sides of the face.

In the split-face design, the right side of the face received intradermal tranexamic acid (100 mg/mL), while the left side received intradermal ascorbic acid (20% solution), serving as an internal control. Prior to each procedure, topical anesthetic cream containing 10.56% lidocaine was applied for 30 minutes followed by cleansing of the treatment area. Using a 30-gauge insulin syringe, approximately 1–2 mL of the designated solution was injected intradermally into the affected malar region through multiple evenly distributed microinjections. Ice packs were applied after the procedure, and all patients were advised strict photoprotection measures including regular use of sunscreen during the study period.

Treatment sessions were performed at baseline and repeated every two weeks for a total duration of 12 weeks. Clinical improvement and adverse effects including erythema, burning sensation, pain at injection site, localized swelling, and papule formation were assessed at each follow-up visit. The mMASI score was recalculated during every assessment visit to evaluate treatment response.

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Quantitative variables such as age, duration of melasma, and mMASI scores were presented as mean ± standard deviation or median with interquartile range according to data distribution. Normality of data was assessed using the Shapiro-Wilk test. Paired sample t-test was applied to compare pre- and post-treatment mMASI scores on each side of the face, while independent sample t-test was used to compare mean differences between tranexamic acid and ascorbic acid treated sides. Qualitative variables were presented as frequencies and percentages. Chi-square test or Fisher's exact test was applied where appropriate. A p-value =0.05 was considered statistically significant.

RESULTS

Sixty patients who had bilateral melasma of the face took part in the study. The average age of the participants was 32.80055 years (21-49 years). Most of them were females (83.3%), married (70%), and Fitzpatrick IV and V skin type. The average period of melasma was 28.5 months with standard deviations of 11.2.

The baseline mMASI scores showed no statistically significant difference between the right and left face ($p > 0.05$), thus, establishing comparability of the two sides of the face of treatment before intervention. Table 1 defines the background of the 60 patients who are involved in the study. The average age was 32.8 years which indicated that melasma primarily impacted young and middle-aged adults. They consisted of a definite female preponderance (83.3) as per the established hormonal effect on melasma. The Fitzpatrick skin types IV and V were the most common type of participants, which means that the darker phototypes were prevalent in this population.

In terms of the disease features, the mean of melasma was more than two years because the disease was a chronic and persistent disorder. The most common one was epidermal melasma, then mixed and dermal. These results indicate that the population that was studied was normal to the patient who turned up at dermatology clinics in high sun exposure areas. The two treatments led to an incremental decrease in the severity of pigmentation in 12 weeks. The decrease was however more on the tranexamic acid (TA) than the ascorbic acid (AA) side

A significant percentage (=75% improvement) of respondents was reported to have a good response on the TA-treated side. This table demonstrates progressive improvement in pigmentation severity on both sides of the face during the 12-week treatment. There was no statistically significant difference between the tranexamic acid (TA) side and the ascorbic acid (AA) side at baseline, which ensures that both sides have had a similar disease severity at baseline. Both treatments showed a progressive decrease in the scores of mMASI over time, which showed clinical improvement.

Nevertheless, the decrease was always bigger on the TA-treated side with the difference becoming statistically significant starting at week 4 and only escalating at week 12. The TA side significantly reduced the mean mMASI score than the AA side by the end of the research indicating that pigment reduction with tranexamic acid mesotherapy was superior. The trend in Table 2 is graphically illustrated in this line graph. The two lines are downsloping, being an affirmation that pigmentation was enhanced in both treatments. But tranexamic acid decreases at a steeper rate and demonstrated higher and quicker rate of melasma reduction. The fact that the gap between the two lines is increasing after week 4 reflects the better efficacy of TA. Table 3 provides an excellent, moderate, and mild improvement of patient response. Over (56.7%) percent of the patients respond excellently (75 percent improvement and above) on the side treated with TA versus 30 percent on the side treated with AA. On the other hand, the responses on the AA side were more of mild character. The effect was significant enough to make the difference between the groups significant and show that tranexamic acid was the more effective one in achieving the desired clinical improvement.

Tolerance of both treatments was good. The side effects were mild and short-term., there were no side effects necessary that forced a patient to stop the therapy. There were no incidences of post-inflammatory hyperpigmentation, ulceration or any systemic side effects. Table 4 is compared

with local side effects on both treatments. The most frequent adverse events include erythema, pain and burning sensation which were mild and short lived in nature. The number of adverse effects was found to be statistically significantly higher with ascorbic acid, although no significant difference was found between the two sides. Significantly, no severe complications, scarring, or post-inflammatory hyperpigmentation was present. This shows that, both treatments were well tolerated and safe.

Table 1: Demographic and Clinical Characteristics of Patients (n = 60)

Variable	Frequency (%) / Mean ± SD
Age (years)	32.8 ± 6.4
Gender	
Male	10 (16.7%)
Female	50 (83.3%)
Marital Status	
Single	18 (30%)
Married	42 (70%)
Fitzpatrick Skin Type	
Type III	9 (15%)
Type IV	31 (51.7%)
Type V	20 (33.3%)
Type of Melasma	
Epidermal	26 (43.3%)
Dermal	11 (18.3%)
Mixed	23 (38.3%)
Duration of Melasma (months)	28.5 ± 11.2

Table 2: Comparison of Mean mMASI Scores over time

Visit	TA Side (Right) Mean ± SD	AA Side (Left) Mean ± SD	p-value*
Baseline	8.12 ± 1.44	8.05 ± 1.39	0.62
Week 4	6.21 ± 1.30	6.78 ± 1.36	0.04
Week 8	4.32 ± 1.18	5.21 ± 1.27	0.002
Week 12	2.11 ± 0.98	3.42 ± 1.12	<0.001

*Independent sample t-test comparing both sides

The **mean percentage reduction in mMASI score** at week 12 was:

- **Tranexamic acid side: 73.9% ± 11.6**
- **Ascorbic acid side: 57.5% ± 13.2**

($p < 0.001$)

Figure : Comparison of Mean mMASI Reduction Over 12 Weeks

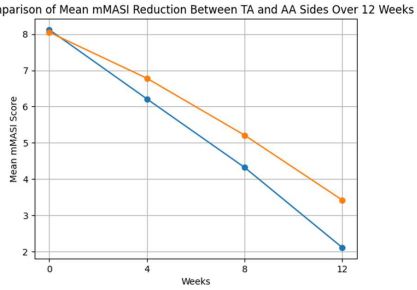

Table 3: Treatment Response at Week 12

Response Category	TA Side n (%)	AA Side n (%)	p-value
Excellent (=75%)	34 (56.7%)	18 (30.0%)	0.004
Moderate (50–74%)	19 (31.7%)	26 (43.3%)	
Mild (<50%)	7 (11.6%)	16 (26.7%)	

Table 4: Frequency of Adverse Effects

Adverse Effect	TA Side n (%)	AA Side n (%)	p-value
Erythema	9 (15%)	14 (23.3%)	0.21
Burning Sensation	7 (11.7%)	12 (20%)	0.18
Pain at Injection Site	11 (18.3%)	13 (21.7%)	0.64
Localized Swelling	6 (10%)	8 (13.3%)	0.57
Papules/Bumps	5 (8.3%)	7 (11.7%)	0.53

DISCUSSION

This split-face quasi-experimental study demonstrated that intradermal mesotherapy with tranexamic acid (TA) produced a greater reduction in mMASI scores and a higher percentage of excellent clinical response compared to ascorbic acid (AA) after 12 weeks of treatment. Both treatment modalities were well tolerated and associated with only mild and transient adverse effects.

The findings of the present study are consistent with previous studies reporting the efficacy of tranexamic acid in the management of melasma. Liao et al. reported that mesotherapy with tranexamic acid significantly reduced MASI scores and showed favorable safety outcomes in patients with melasma.[19] Similarly, Hasan et al. demonstrated superior clinical improvement with tranexamic acid compared to vitamin C-based therapy, particularly when delivered through minimally invasive techniques such as microneedling and mesotherapy.[20] The greater efficacy of TA may be attributed to its inhibitory effect on plasminogen activation, resulting in decreased melanocyte stimulation and reduced ultraviolet-induced melanogenesis. Ascorbic acid also demonstrated clinical improvement in the present study, although the response was less pronounced compared to TA. Vitamin C acts as an antioxidant and tyrosinase inhibitor, thereby interfering with melanin synthesis and reducing oxidative stress within pigmented lesions. Previous studies have shown that ascorbic acid can improve melasma severity, particularly when combined with adjunctive delivery methods or combination therapies.[21] However, its therapeutic response may be slower and less sustained than tranexamic acid in certain patient populations. The current findings are also supported by the meta-analysis conducted by Liao et al., which concluded that both tranexamic acid and vitamin C mesotherapy are effective treatment options for melasma, although tranexamic acid may provide greater clinical benefit in some cases.[22] Variations in treatment response among different studies may be related to differences in study

design, treatment duration, drug concentration, delivery technique, and patient characteristics. Regarding safety, both treatments showed good tolerability with mild and self-limiting adverse effects including erythema, burning sensation, and pain at injection sites. No cases of post-inflammatory hyperpigmentation, scarring, ulceration, or systemic adverse effects were observed. These findings are comparable with previous literature reporting favorable safety profiles of mesotherapy using tranexamic acid and ascorbic acid.[22] The present study has important clinical implications, particularly for patients with darker skin phototypes where melasma is more prevalent and difficult to manage with topical therapies alone. Intradermal tranexamic acid may serve as an effective minimally invasive therapeutic option for achieving faster and greater pigment reduction while maintaining an acceptable safety profile. Limitations: The present study had certain limitations. The sample size was relatively small, which may limit the generalizability of the findings. In addition, the duration of follow-up was limited to 12 weeks and long-term recurrence rates could not be assessed. The majority of participants were females with Fitzpatrick skin types IV and V, which may limit applicability of the results to other populations and skin phototypes. Furthermore, the split-face design may carry a possibility of local treatment interaction despite serving as an effective method for direct comparison between therapies. Future randomized controlled trials with larger sample sizes and longer follow-up periods are recommended to validate these findings and assess long-term outcomes.

Limitations: The present study had certain limitations. The sample size was relatively small, which may limit the generalizability of the findings. In addition, the follow-up duration was limited to 12 weeks; therefore, long-term efficacy and recurrence rates could not be evaluated. Most participants belonged to Fitzpatrick skin types IV and V, which may limit applicability of the findings to other skin phototypes. Further randomized controlled trials with larger sample sizes and longer follow-up periods are recommended.

CONCLUSION

Both tranexamic acid and ascorbic acid intradermal mesotherapy significantly improved melasma severity over 12 weeks of treatment. However, tranexamic acid demonstrated greater reduction in mMASI scores and a higher proportion of excellent clinical response compared to ascorbic acid. Both treatment modalities showed favorable safety profiles with only mild and transient adverse effects and no serious complications. The findings of this study suggest that intradermal tranexamic acid mesotherapy is a more effective treatment option for facial melasma, particularly in patients with darker skin phototypes, while ascorbic acid may serve as a safe alternative therapy. Further randomized controlled studies with larger sample sizes and longer follow-up durations are recommended to evaluate long-term efficacy and recurrence rates.

Authors Contribution:
Nida Khalid: Main conception of the study, manuscript writing, data collection, results and conclusion, data analysis, final approval.
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Tooba Hadia: Data collection, results and conclusion, data analysis, final approval.
Hannah Hassan: Data collection, results and conclusion, data analysis, final approval.
Ammara Suleman: Manuscript writing, results and conclusion, data analysis, final approval

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