Efficacy of Tranexamic Acid Mesotherapy Versus Oral Tranexamic Acid in Melasma

Aaisha Memon MBBS, PG Dip**,1, Bilal Fazal Shaikh** MBBS, MS,MBBS, MS **2,Saba Khan** MBBS, PG Dip**3**
Raheela Bilal Shaikh 4, MBBS, DGO **4, Syed Zafar Abbas** BDS, MCPS **5**

ABSTRACT

BACKGROUND: Mesotherapy involves micro-injections of pharmaceutical compounds into the dermis to treat various skin disorders, including melasma. This study aims to compare the efficacy of tranexamic acid (TXA) administered via mesotherapy versus oral TXA in treating melasma.

OBJECTIVE: To assess and compare the effectiveness of tranexamic acid mesotherapy versus oral tranexamic acid in the management of melasma.

METHODOLOGY: This 12-week interventional randomized controlled trial was conducted in a multi-center, Royal Facial Aesthetic Academy's affiliated private aesthetic setups in different cities, involving 20 female patients with symmetrical facial melasma aged up to 40. Enrolled patients, with an average MASI score of 30 (range 0-48), were randomly divided into two groups: Group A (N = 10) received oral TXA 250?mg twice daily, and Group B (N = 10) underwent trans epidermal administration of TXA (10?mg/mL) via micro needling every two weeks for 12 weeks.

RESULTS: Twenty participants with a mean age of 30 years (range 20–40) were included. Sixty percent exhibited a centrofacial pattern, while 40% had a malar pattern. Group B demonstrated favorable outcomes, suggesting that tranexamic acid administered intradermally with microneedling is a superior option for melasma treatment.

CONCLUSION: Intradermal tranexamic acid delivery through microneedling emerges as a cost-effective and novel treatment approach for melasma. This method not only enhances patient compliance but also alleviates stress, improves quality of life, and addresses psychological and social concerns related to melasma.

KEYWORDS: -Tranexamic acid, mesotherapy, aesthetics, melasma

(Citation: Memon Aaisha, Fazal Shaikh Bilal,KhanSaba, Bilal Shaikh Raheela, Abbas Zafar Syed)
MC 2023; 23 (2)----------

Author Affiliation:
Najaf Aesthetic Skin Clinic, Hyderabad Sindh1
Muhammad Medical College, Mirpurkhas 2
Al Raya Medical Centre, Abu Dhabi, UAE 3
Manchester Skin Clinic, UK 4
Dow International Dental College, Karachi 5

Corresponding Author:
Dr. Aisha Memon
Bungalow B 39, Bypass Town, Moro, Sindh, Pakistan
Phone: 03312951931
email:

Introduction

Melasma is an acquired disorder of melanogenesis that leads to hyperpigmentation mostly on facial area (cheeks, lips, nose, chine, forehead) and other sun exposed body parts like upper extremities, lower extremities and so on.1 It symmetrically affects the face or other parts with irregular border lines. It is most commonly found in women with the brown skin colour compared to the fair or dark skin colour women. Globally, prevalence of melasma ranges between 1% to 50%, but no any comprehensive study has been conducted to analyze the burden of melasma in Pakistani women.2 However, a study has been conducted only on Pakistani pregnant women for melasma shows 45% of burden of melasma in Pakistani pregnant women.

Melasma is one of the chronic and relapsing skin disorders. The aesthetic complication of melasma affects the quality of life of the patient and raises the concerns psychologically, socially and morally.3 The pathological factors causing the melasma are prostaglandins (PGs) D2-E-F2 and leukotriene (LTs) B4 and Plasmin that increase the level of melanogenic factors such as, melanocyte stimulating hormone (MSH) from the Pituitary Gland, Basic Fibroblastic Growth Factors (BFGF), Stem Cell Factors (SCF), increasing level of inflammatory mediators (Interleukin IL)- 1 Alpha- IL beta, IL-6,8 and Tumor Necrosis Factor(TNF) as well as Metalloproteinase (MMP)-2 and MMP-9.The Vascular Endothelial Growth Factors also leading to proliferation and activation of melanocytes that increase melanogensis, number of mast cells have role in melanin synthesis. In addition MMP, also enhances and activates Tyrosinase Enzyme that also leads to melanogensis. Therefore, TXA inhibits angiogenesis by suppression of Vascular Endothelial Growth Factor, Endothelin ILs and Leukoterine and reduce the number of mast cells, and also causes competitive inhibition of Tyrosinase an important enzyme for melanogenesis. 4

Melasma synthesis begins with the hydroxylation of amino acid Tyrosine to L3,4-Dihydroxyphenylalanamine (DOPA) in a reaction catalyzed by Tyrosinase. The conversion of DOPA to DOPA Quinone is also catalyzed by Tyrosinase. By this reaction of Tyrosinase, Eu-melanin and Pheo-melanin are synthesized. Melanin is produced by melanocytes in the basal layer of epidermis of the skin and consistently supplied to the surrounding Keratinocytes. However, aging, UV radiations, hormonal imbalance in pregnancy disrupt skin's regulatory mechanism that results in to increased melanin synthesis. Hence, excessive melanin accumulation and keratinocytes cause manifestation of hyperpigmentation. TXA (Trans-4-Aminomethyle Cyclo-Hexane Carbolic Acid) is the drug that has approximately tenfold of anti-plasmin action and has been used for more than thirty years to treat bleeding tendency and abnormal bleeding.5 Tranexamic Acid exhibits homostatic anti-inflammatory, anti-allergic effects. Transamic Acid acts through its anti-plasmin activity resulting from strong binding with lysine binding site and fibrin affinity site of plasmin and plasmogen. In the field of dermatology. Transamic Acid recently been shown to readily compete with the Tyrosinase inhibition activity that brings much stronger response in inhibition of hyperpigmentation.

The anti-fibrotic effect of Tranexamic Acid and its inhibitory effect on the release of reactive oxygen specie by neutrophils and inhibitory effect on the release of histamine by the mast cells have been observed. In addition, effectiveness of Tranexamic Acid by micro-injections into the dermis of the skin for melasma treatment of sun exposed parts contribute to its anti-plasmin action in the

skin specially in the epidermal layer of skin. Urokinase type Plasmogen (UPA) implement the conversion of plasmogen into plasmin and it is double standard enzyme.6 Cultured human epidermal melanocytes produce Pro-UPA, a single standard pre-curser with no enzymatic activity because cultured human melanocytes produce little or no Pro-UPA. Melanocytes are thought to be activated by epidermal keratinocytes, derived UPA and Plasmogen derived from Dermal Vascular (UPA/plasmogen system) in the basal layer of epidermis. Tyrosinase mRNA and Pro-mRNA are co-expressed in pigmented area suggesting the involvement of UPA/ Plasmogen system in the basal layer of epidermis in hyperpigmentation process of melasma. The melasma is thought to arise from an increase in the melanogensis in the epidermal layer of the skin resulting in hyper activity of melanocytes. Tranexamic Acid injected by micro-injections into the dermal layer of skin suppressed the prostaglandin E2 level and tyrosinase activity that increase as the days pass more rapidly. Tranexamic Acid antagonistically inhibits Tyrosinase with its substrate Tyrosine (a competitive inhibitory effect) and suppresses the hyperpigmentation to treat the melasma with less systematic side effects of the chemical induced.7

Material and Method

This was a multicenter private clinic-based, interventional RCT study carried over the time period of 12 weeks on 20 patients with symmetrical facial melasma aged up to 40. Those patients had MASI score of average about 30 (range 0-48). The enrolled patients were divided randomly into two groups of 10 patients each. The patients were enrolled only after history and clinical representation of melasma. Examination was done by Dermascopy. Group A patients were treated with oral tablet TXA in a dose of 250 mg twice a day for 12 weeks and Group B patients were treated with TXA solution transepidermally into the lesion of melasma using a derma pen 10mg/ml at 2 weekly interval for 12 weeks to observe the efficacy of intradermal lesion injections with TXA. The depth of the micro needling was 1.5mm for administering the solution into dermis. Micro-needling makes micro-wounds in the skin at a typical depth of 1.5?mm that ensures topical designs to pierce deeper into the skin while also stimulating collagen production and the release of growth factors. Micro needling can be done with several different devices. Dermapens allow needles to puncture the epidermis just at the location of the device, to enter the solution into the lesion. Clinicians generally roll over the entire face several times in different directions. Microneedling with TXA often is done with 10mg/ml TXA. Micro-needling allows for deeper penetration of topical TXA into the dermis in an even manner. Benefits to this method include a relatively quick and noninvasive method for introducing TXA into the skin. Thereafter, all patients were followed up for six sessions improvement in Melasma Area and Severity Index (MASI) score, adverse effects and relapse at 4 weekly intervals till 12 weeks. All the patients were evaluated for therapeutic outcome both objectively (by MASI) and photographical, Grading of improvement was done by assessing percentage reduction in MASI score. The study was conducted in a single racial population with the restricted number of patients with skin phenotypes. The results requisite to be applied to different racial groups and greater population with depiction from multi skin phenotypes. The consent forms were obtained from the patiens appropriately. In the form the patient(s) has/have given his/her/their

Table 1

Grades of improvement	Reduction in MASI score
0: No response	No improvement
1: Mild response	<25% improvement
2: Moderate response	25%–50% improvement
3: Good response	51%–75% improvement
4: Very good response	>75% improvement

Table I Patient's response to treatment

TABLE 2: -

PRETREATMENT CHARACTERISTICS OF ALL PATIENTS

Characteristics		Number of patients
		(*N* = 20)
Gender	Female	20
Age	Range (years)	20–40
	Mean (years)	30 ± 3.45
Duration of melasma	Range (years)	0.5–9
	Mean (years)	2.98 ± 2.24
MASI score	Range	8.50–32.20
	Mean	20.36 ± 2.32

The mean MASI scores in Group A at the end of 4, 6, 8, 10, and 12 weeks were 10.75 (±4.83), 7.09 (±3.64), 5.21 (±2.48), 3.56 (±1.95), and 3.10 (±3.38), whereas the values were 10.75 (±3.32), 7.06 (±2.75), 5.55 (±1.89), 3.94 (±1.36), and 2.59 (±1.32) for Group B, respectively.

consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Injection Transamine [Tranexamic acid=TA] of 500mg/5ml ampoule was used. With the help of derma pen first the ampule (500mg/5ml) was filled into the insulin syringe 100IU, 10IU (10mg) of TA which made the concentration of TA to 10 mg/100IU or 10 mg/ml. Initially face was cleaned by alcohol swab and then topical anesthesia (use of

Table-3

Side Effects Of Tranexamic Acid Mesotherapy.

Side effects	Numbers	Percentages%
Localized swelling	5	25.0
Erythema	1	5.0
Burning	2	10.0
Irritation	4	20.0

Table 4

Percentage reduction in MASI score as compared to baseline in both the groups with treatment

Percentage reduction in MASI score

Time (weeks)	Group A (oral), *N* = 10Group	B (microneedling), *N* = 10
4	18.61%	19.78%
6	49.16%	50.04%
8	64.85%	62.48%
10	74.63%	75.76%
12	74.12%	78.52%

local anesthetics, neocaine 10.56%) was applied for 30-45 minute . After clearing the extra anesthetic cream with sterile gauze piece. Solution of tranexamic acid were applied on the patches of melasma on the face and multiple microinjections with the help of derma pen by mesotheapry technique were injected into all patches of melasma to improve the absorption of solution. No other oral or topical cream was advised to use for home except sunblock..

Inclusion criteria:

- Age not greater than 40 years
- Symmetrical melasma on facial area

Exclusion criteria

- Patients have gone into any major surgery
- Patient is exposed to oral use before.
- Lactating or pregnant women.

Results

All the patients were evaluated for therapeutic outcome both by Melasma Area and Severity Index (MASI), which was the primary outcome measure. [Table 1] and pho-



tographically at 4, 6, 8,10, and 12. Side effects known to be associated with tranexamic acid as well as other side effects that seems to be relevant to the treatment were evaluated on every visit are mentioned into t

A total of twenty participants (20 females) with a mean age of 30 years (range, 20–40 years) were enrolled. The majority of the patients,1 2 (60%), had a centrofacial pattern followed by a malar pattern in 8 (40%) patients. These 20 patients were randomly assigned to Group A (N = 10) for oral TXA 250?mg, twice daily, and Group B (N = 10) for transepidermal administration of TXA (10?mg/mL) through microneedling given at an interval of two weeks for 12 weeks. Thereafter, they were followed up for improvement in MASI score, adverse effects, and relapse at a four-week interval for 12 weeks. Both the groups were statistically similar with regard to the age of patients, duration of melasma, and baseline MASI score [Table 2]. The baseline MASI score was 13.95 (±3.17) in Group A and 12.15(±5.37) in Group B.



The mean MASI scores in Group A at the end of 4, 6, 8, 10, and 12 weeks were 10.75 (±4.83), 7.09 (±3.64), 5.21 (±2.48), 3.56 (±1.95), and 3.10 (±3.38), whereas the values were 10.75 (±3.32), 7.06 (±2.75), 5.55 (±1.89), 3.94 (±1.36), and 2.59 (±1.32) for Group B, respectively.

Discussion:

Melasma is complex and poorly understood disorder various underlying risk factors for developing melasma have been described including oral contraceptive pills, sun exposure, hormonal changes during pregnancy, genetical predisposition.8 More-

over, to transfer melanosomes to keratinocytes through tyrosinase enzyme activation which controls the production of melanin. The melasma could be caused by melanogenesis dysfunction through increased sensitivity to risk factors. Management of cutaneous disorders of hyperpigmentation generally requires a long duration of treatment, and so does melasma. Historically, the treatment of melasma has been challenging because of the refractory and recurrent nature of the condition.9 The treatment for melasma is aimed to slow down the proliferation of melanocytes, inhibit the formation of melanosomes, and promote their degradation.10

In France, Pistor invented mesotherapy technique which is now widely used in medicine. It is a minimally invasive procedure of drug delivery that consists of intradermal injections with mixture of compounds 'Melange' in minute doses. Plant extracts, homeopathic agents, pharmaceutical vitamins and others bio active substances can be used but alcohol or oil based substances should not be used for mesotherapy due to risk factors of cutaneous necrosis. On exposure of UV lights, keratinocytes induce melanogenesis and promote angiogenesis by activation of plasminogen activator (PA) thus increase skin pigmentation.11 TA causes inhibition of plasmin activation which leads to decreased activation of the melanocyte, reverses dermal vascularity and increases mast cell number hence reduce area, darkness, and homogeneity of patches of melisma.12

In 2006, Lee at al. published the first study demonstrating the viability of localized micro injections of TXA for the melasma treatment. While in 2014, Carole and colleagues published the first time, study showed the trial was conducte with 100 Asian patients with melasma treated with the intradermal injecting of transamic acid and significant results were obtained with minimal risk factors.13 Melasma is one of prevailing pigmentery disorders of Asian skin. Its major clinical pattern is Centro facial which involves forehead, cheek, nose, chin, and lips. Different treatment modalities for melasma have been used in past including topical, oral medicine and interventional therapies. In 1979, Nijo reported a case of a patient of chronic urticaria treated with TA, showed improvement in melasma on face. After that many researches were done which showed the efficacy of TA for treatment of melasma in its oral, topical and intralesional forms. However, there are few studies of intradermal microinjection of TA for treatment of melasma in our population.14

Our study showed a statistically significant reduction in MASI score as compared to that of baseline after treatment with both oral and transepidermal administration of TXA with Significant improvement was noted from eight weeks onward at each follow-up visit Patients were further followed up to 12 weeks post-treatment to see long term effect of TA and recurrence of melasma. We observed that regimentation slowly appeared only in those patients who did not have strict sun protection. This finding was consistent with the study of Lee. Common side effects of intradermal injection TA are visual abnormalities, hypotension, nausea, and vomiting reported in past, In our study no serious side effects were observed except temporary localized swelling, erythema, burning and irritation bilaterally, that was subsided after 24 hours with and without ici

Insertion of transamic acid intraermally with microneedling hence proved to be a better option for treatment of melasma. It is one of the cost-effective newly treatment which do not only increase compliance of patient towards treatment but also decrease the stress of patient by improving

their quality of life, decreases the psychological concerns and social, moral confidential presentation.16

Intradermal Transamic acid appear significant effective than oral TXA, suggesting that the efficacy of TXA is perhaps Oral therapy is less convenient for patients.17 The duration of therapy is perhaps more important than the doses, higher than 500?mg/day for better therapeutic effect is the long term, but because of potential adverse effects such as coagulation abnormalities as compare o intra dermal.18 intra dermal therapy of TXA has the advantage of local action; hence, systemic side effects are avoided, but it is slight adverse effects such as inflammation, burning, irritation which easily resolved with in 24 hour.19 intradermal transamic acid requires a special instrument (dermpen), and the time period between consecutive microneedling sessions treated by doctor. Moreover, scheduling of maintenance sessions is necessary as melasma is prone to recurrence in case of oral but least chance of recurrence with intradermal transamic acid insertion.20

Conclusion:

In conclusion, the study suggests that tranexamic acid (TA) mesotherapy shows promise in treating melasma due to its anti-inflammatory and anti-redness effects. TA, being safe and affordable with low side effects, can be considered alone or in combination with microneedling for facial melasma. Its application demonstrates early reduction of hyperpigmented lesions with minimal side effects. However, the limited evidence necessitates further studies. Future investigations may explore topical TA formulations in combination with microneedling to enhance tolerability and reduce pain.

ARTICLE INFORMATION

Received on: 17-4-2022
Correction: 15-5-2022
Accepted : 20-5-2022

Authors Contribution:
Dr. Saad Abdul Razzaq contributed to the conception and design of the study acquisition of data, Dr Mariam Imran help in drafting the manuscript and interpretation of data.., Dr. Zahid Mehmood, Dr. Zawwar Reza, Dr. Ghansham, Dr Hazrat Bilal Burki contributed to the acquisition, analysis and interpretation of data along. All authors approved the final version of the manuscript.

Conflict of Interest : Non

Funding: non

REFERENCES:

1. Wang T, Gao H, Wang D, Zhang C, Hu K, Zhang H, Lin J, Chen X. Stem cell-derived exosomes in the treatment of melasma and its percutaneous penetration. Lasers Surg Med. 2023 Feb;55(2):178-189. doi: 10.1002/lsm.23628. Epub 2022 Dec 27. PMID: 36573453

2. Sofen B, Prado G, Emer J. Melasma and Post Inflammatory Hyperpigmentation: Management Update and Expert Opinion. Skin Therapy Lett. 2016 Jan;21(1):1-7. PMID: 27224897 Free article. Review.

3. Sheu SL. Treatment of melasma using tranexamic acid: what's known and what's next. Cutis. 2018 Feb;101(2):E7-E8. PMID: 29554171 Review.

4. Shenoy A, Madan R. Post-Inflammatory Hyperpigmentation: A Review of Treatment Strategies. J Drugs Dermatol. 2020 Aug 1;19(8):763-768. doi: 10.36849/JDD.2020.4887. PMID: 32845587 Review.

5. Sehgal VN, Verma P, Srivastava G, Aggarwal AK, Verma S. Melasma: treatment strategy. J Cosmet Laser Ther. 2011 Dec;13(6):265-79. doi: 10.3109/14764172.2011.630088. PMID: 21981383 Review.

6. Sarkar R, Katoch S. Chemical Peels in Treatment of Melasma. Dermatol Clin. 2024 Jan;42(1):21-32. doi: 10.1016/j.det.2023.06.003. Epub 2023 Jul 18. PMID: 37977681 Review.

7. Sarkar R, Bansal A, Ailawadi P. Future therapies in melasma: What lies ahead? Indian J Dermatol Venereol Leprol. 2020 Jan-Feb;86(1):8-17. doi: 10.4103/ijdvl.IJDVL_633_18. PMID: 31793496 Free article. Review.

8. Salem A, Gamil H, Ramadan A, Harras M, Amer A. Melasma: treatment evaluation. J Cosmet Laser Ther. 2009 Sep;11(3):146-50. doi: 10.1080/14764170902842549. PMID: 19340686 Clinical Trial.

9. Rivas S, Pandya AG. Treatment of melasma with topical agents, peels and lasers: an evidence-based review. Am J Clin Dermatol. 2013 Oct;14(5):359-76. doi: 10.1007/s40257-013-0038-4. PMID: 23881551 Review.

10. Rendon M, Berneburg M, Arellano I, Picardo M. Treatment of melasma. J Am Acad Dermatol. 2006 May;54(5 Suppl 2):S272-81. doi: 10.1016/j.jaad.2005.12.039. PMID: 16631968 Review.

11. Rajanala S, Maymone MBC, Vashi NA. Melasma pathogenesis: a review of the latest research, pathological findings, and investigational therapies. Dermatol Online J. 2019 Oct 15;25(10):13030/qt47b7r28c. PMID: 31735001 Free article. Review.

12. Pimentel B, Palmeiro A, Castro C, Silva L, Catorze MG, João AL. Use of Picosecond Laser for Melasma Treatment: A Narrative Review. Photobiomodul Photomed Laser Surg. 2023 Dec;41(12):674-682. doi: 10.1089/photob.2023.0096. PMID: 38085187 Review.

13. Passeron T, Picardo M. Melasma, a photoaging disorder. Pigment Cell Melanoma Res. 2018 Jul;31(4):461-465. doi: 10.1111/pcmr.12684. Epub 2018 Jan 12. PMID: 29285880 Review.

14. Neagu N, Conforti C, Agozzino M, Marangi GF, Morariu SH, Pellacani G, Persichetti P, Piccolo D, Segreto F, Zalaudek I, Dianzani C. Melasma treatment: a systematic review. J Dermatolog Treat. 2022 Jun;33(4):1816-1837. doi: 10.1080/09546634.2021.1914313. Epub 2022 Mar 23. PMID: 33849384 Review.

15. Morgado-Carrasco D, Piquero-Casals J, Granger C, Trullàs C, Passeron T. Melasma: The need for tailored photoprotection to improve clinical outcomes. Photodermatol Photoimmunol Photomed. 2022 Nov;38(6):515-521. doi: 10.1111/phpp.12783. Epub 2022 Mar 8. PMID: 35229368 Free PMC article. Review.

16. McKesey J, Tovar-Garza A, Pandya AG. Melasma Treatment: An Evidence-Based Review. Am J Clin Dermatol. 2020 Apr;21(2):173-225. doi: 10.1007/s40257-019-00488-w. PMID: 31802394

17. Mahajan VK, Patil A, Blicharz L, Kassir M, Konnikov N, Gold MH, Goldman MP, Galadari H, Goldust M. Medical therapies for melasma. J Cosmet Dermatol. 2022 Sep;21(9):3707-3728. doi: 10.1111/jocd.15242. Epub 2022 Jul 31. PMID: 35854432 Review.

18. Lee YS, Lee YJ, Lee JM, Han TY, Lee JH, Choi JE. The Low-Fluence Q-Switched Nd:YAG Laser Treatment for Melasma: A Systematic Review. Medicina (Kaunas). 2022 Jul 14;58(7):936. doi: 10.3390/medicina58070936. PMID: 35888655 Free PMC article. Review.

19. Lai D, Zhou S, Cheng S, Liu H, Cui Y. Laser therapy in the treatment of melasma: a systematic review and meta-analysis. Lasers Med Sci. 2022 Jun;37(4):2099-2110. doi: 10.1007/s10103-022-03514-2. Epub 2022 Feb 5. PMID: 35122202 Review.

20. Kwon SH, Na JI, Choi JY, Park KC. Melasma: Updates and perspectives. Exp Dermatol. 2019 Jun;28(6):704-708. PMID: 30422338