Journal of Pakistan Association of Dermatologists. 2023;**33(4)**:1412-1420.

Original Article

Efficacy of Intradermal Tranexamic acid versus topical 5% Magnesium ascorbyl phosphate in the treatment of melasma: A head-to-head comparison

Muhammad Fahim[1], Hina Khoso[2], Jahangir Khan[3], Huma Gul[4], Rabeeka Bakhtiar[5]

[1] Tehsil Headquarters Hospital Takhtbhai, Mardan.
[2] Department of Dermatology, Shaheed Mohtarma Benazir Bhutto Medical University/ Chandka Medical Collage, Larkana.
[3] Department of Dermatology, AL ADAN Hospital, Kuwait.
[4] Department of Dermatology, Khyber Teaching Hospital Peshawar.
[5] Department of Dermatology, Medical Teaching Institution Hayatabad, Peshawar.

Abstract

Background Melasma is a chronic skin hyperpigmentation disorder involving 50–70% of people worldwide, mostly women of childbearing age. Various treatment modalities are available, but no previous study has undergone a head-to-head comparison of intradermal tranexamic acid (TXA) and topical magnesium ascorbyl phosphate (MAP) to treat melasma. This study aimed to fill this research gap.

Objective To compare effectiveness of intradermal (TXA) and topical (MAP) in the treatment of melasma.

Methods A total of 128 patients were enrolled, 64 in each group. Patients were divided into groups A and B using randomization technique, and their melasma severity index score (MASI) was calculated. Patients in group A were treated with four cycles of intradermal TXA at weeks 0, 4, 8, and 12. Group B was treated with topical MAP cream once a day for 12 weeks. At the end of 12 weeks, efficacy was assessed by calculating the MASI score.

Results The mean age in the injected TXA group (A) was 39.4±7.9 years and 37.5±8.3 years in the MAP group (B). In the group-wise distribution of gender, 20.3% of males and 79.7% of females were enrolled in group A, while 17.1% of males and 82.9% of females were included in group B. Baseline MASI scores for groups A and B were 16.7±5.4 and 16.06±6.15, respectively. At the end of 12 weeks, the efficacy of injected TXA was noted as being 54.7%, while 78.1% effectiveness was noted in the MAP group (P- value=0.005).

Conclusion It has been concluded that topical MAP is better than intradermal TXA for the treatment of melisma.

Key words
Tranexamic Acid (TXA); Magnesium Ascorbyl Phosphate (MAP); Melasma; MASI score.

Introduction

Melasma is an acquired pigmentary disorder to which all racial groups are susceptible, but Asians with higher skin types and people who spend a lot of time in the sun (UV exposure) are more likely to develop it. Only 10% of patients are men, with women making up the majority.[1,2] It is found as brown to dark-brown patches and macules with irregular margins on the face, usually but not invariably in a symmetrical distribution.[3] The prevalence of melasma is

Address for correspondence
Dr. Jahangir Khan
M.B.B.S, FCPS (Dermatology),
Registrar, Department of Dermatology,
AL ADAN Hospital, Kuwait.
Ph: 96565613173
Email: kohatian3658@yahoo.com

reported at 46% in Pakistan.[4] Pregnancy and hormonal changes in the ovaries, in addition to sun exposure, are the main risk factors for this disease.[5,6] Although the precise pathophysiology is uncertain, it has been postulated that biologically active melanocytes that produce an excessive amount of melanin are the main contributing factors.[5-7] Another important factor in pathogenesis is the increased expression of various angiogenesis factors that lead to increased vascularity.[8,9] Melasma usually runs a chronic and relapsing course.[10]

There are multiple treatment options available for melasma that target various pathogenetic pathways. These include sunscreens, bleaching agents, chemical peels, azelaic acid, retinoid formulations, micro-needling, laser devices, and other light sources.[11,12] Various studies have documented the efficacy of intradermal injections of tranexamic acid (58.5%) and magnesium ascorbyl phosphate (81.1%) in the treatment of melasma.[14,15]

The synthetic lysine derivative tranexamic acid (TXA) is widely used as a hemostatic agent. It decreases tyrosinase activity and angiogenesis by blocking the production of prostaglandins and inhibiting plasmin respectively.[16] Using an intradermal route for TXA administration may be more helpful to treat the dermal/ mixed type of melasma.[17] Vitamin C (ascorbic acid) is highly unstable when applied topically. Magnesium-L-ascorbyl-2-phosphate (MAP) is a comparatively more stable derivative of vitamin C and suppresses melanin production.[15] Melanin is synthesized by the tyrosinase enzyme, which needs a basic (high PH) intracellular environment for optimal functioning, so being acidic in nature, MAP inhibits melanin synthesis by blocking tyrosinase activity (the rate-limiting enzyme).[18]

This study sought to evaluate the effectiveness of intradermal tranexamic acid (TXA) versus topical magnesium ascorbyl phosphate (MAP) to treat melasma. As various studies reported the efficacy of the above-mentioned treatments using various techniques like micro-needling, etc., there has been no study comparing head-to-head intradermal injected tranexamic acid versus magnesium ascorbyl phosphate on a local as well as international level, so this study will help us to deepen our insight into the effectiveness of these treatment modalities in the management of melasma.

Materials and Methods

This randomized control trial was carried out in the Dermatology Department of Shaheed Mohtarma Benazir Bhutto Medical University (SMBBMU), Larkana. Using the W.H.O. sample size calculator, the sample size was determined, keeping in mind the efficacy of intradermally injected tranexamic acid (58.5%) vs. magnesium ascorbyl phosphate (81.1%),[16] the power of the test (1-β)=80%, level of significance (α)=5%, and the estimated sample size was n=64 in each group. All patients were divided into two groups using non-probability sequential sampling. Basic data like age, gender, and disease duration are collected and the baseline MASI score is calculated using a specific formula.

Inclusion criteria All patients between the ages of 18 and 40 years having melasma duration of less than 24 months, of either gender, and have given informed consent.

Exclusion criteria Patients who are currently receiving or have recently received melasma therapy, pregnant and lactating women, and history of oral or injectable contraceptive pill use. Similarly, patients with mixed or dermal melasma (determined with the help of Wood's lamp), darker skin types having history of

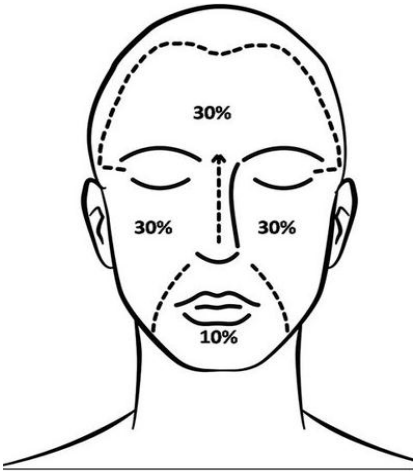
hypertrophic scars or keloids, or a history of recurrent herpes simplex infection were also excluded.

Data collection Following the College of Physicians and Surgeons of Pakistan's acceptance of the synopsis, data gathering was initiated. This study covered all patients who visited the SMBBMU Hospital in Larkana and met the inclusion criteria. Before enrolling patients in the study, informed written consent taken, and the purpose of the study, methods of drug administration, and follow-up were explained. Data regarding baseline study variables such as patient's age, gender, duration of melasma, clinical patterns of melasma, and pre-treatment MASI score were calculated before starting the treatment. Using the randomization procedure, patients were split into two groups (group A and group B) by creating folded papers with the name of the treatment and placing them in a jar. The patients were instructed to select one folded piece of paper.

Patients in group A; were treated by TXA injection at 10-mm intervals (0.5 ml (4 mg/mL) for each 1cm area) using a 1cc syringe (28G needle) under aseptic conditions, covering the area with maximum involvement by melasma. Four cycles of intradermal TXA treatment were given, and each cycle was repeated every 4 weeks (weeks 0, 4, 8, and 12). Group B was treated with 5% magnesium ascorbyl phosphate cream once daily for 12 weeks. All patients were followed at monthly intervals, and the final outcome was assessed at the end of the 12th week of treatment, using the criteria of efficacy as a 50% reduction of the MASI score from baseline.

Melasma Area And Severity Index Score [MASI] **[19]** The MASI score is an objective measure of melasma severity and is calculated based on three parameters: darkness (D), homogeneity (H), area (A). The parameters and specific formula is shown in **Figure 1**.

Data analysis The collected data was organized and analyzed using EXCEL and statistical packages for social science (SPSS Version 20). The mean & SD was calculated for age, disease duration and the MASI score at baseline and after 12 weeks of treatment. For gender and efficacy, frequencies and percentages were determined. To evaluate the effectiveness in the two groups, a chi-square test was used, using a two-sided $P< 0.05$.



1. MASI score is calculated by dividing the face into four areas; and each area is weighted such that the forehead (F), right malar area (MR), and left malar area (ML) are 30% each, and the chin (C) is 10%.
2. Amount of pigmentation involved by melasma in these four areas (F, MR, ML, and C) is graded as a numerical value:
   - 0 = no involvement
   - 1 = less than 10% involvement
   - 2 = 10–29% involvement
   - 3 = 30–49% involvement
   - 4 = 50–69% involvement
   - 5 = 70–89% involvement
   - 6 = 90–100% involvement
3. Severity of melasma is graded upon two factors; darkness (D) of melasma compared to the normal skin and homogeneity (H) of hyperpigmentation on a scale from 0 to 4: The rating scale for both darkness and homogeneity of melasma is:
   - 0 = absent
   - 1 = slight
   - 2 = mild
   - 3 = marked
   - 4 = maximum

1. MASI score is then obtained by adding the values of sum of severity ratings.
2. **The final formula for MASI Score** = 0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML + HML) AML + 0.1 (DC + HC) AC.
3. **The total MASI score is 0 to 48.**

Figure 1 MASI score calculation. [19]

Table 1 Demographic and basic patient data.

Parameter	*Group A(TXA)*		*Group B(MAP)*		*P-Value*
Number of Patients	64		64		
Age (Mean±SD)	39.4±7.9		37.5±8.3		0.18
Age VIZ distribution	≤40 years 33	>40 years 31	≤40 years 25	>40 years 39	
Duration (mean±SD)	19.3±9.8		16.9±9.1		0.16
Duration VIZ distribution	≤12 months 20	>12 months 44	≤12 months 28	>12 months 36	
Gender	Male 13(20.3%)	Female 51(79.9%)	Male 11(17.1%)	Female 53(82.9%)	
MASI Score (mean±SD)	Baseline 16.7±5.4	12 Weeks 9.4 ±4.5	Baseline 16.06±6.15	12 Weeks 6.9±3.4	0.0052
Mean MASI score VIZ distribution	≤14 *25*	>14 *39*	≤14 *33*	>14 *31*	

Both groups were compared by age, gender, MASI score at baseline and 12 weeks, and duration of disease. Stratification was carried out using a two-sided chi-square test to see the impact of these variables on patient outcome. Age, duration, and MASI score were divided into groups of ≤40 and >40, ≤12 months and >12 months, and ≤14 and >14, respectively. Results are summarized in the form of tables and figures.

Results

In this randomized control trial, a total of 128 patients, 64 in each group, were included to compare the efficacy of intradermally injected tranexamic acid versus magnesium ascorbyl phosphate in the treatment of melasma.

The basic demographic data of patients in both groups is shown in **Table 1**.

The mean age and disease duration was comparable in both groups. Overall female patients were greater in number. The mean MASI score at baseline was 12.4±4.0 and 11.6±3.8 in groups A and B, respectively. After 12 weeks it reduced to 9.4±4.5 in group A and 6.9±3.4 in group B (**Figure 2).** Efficacy of injected tranexamic acid was noted to be 54.7% while 50 (78.1%) effectiveness was noted in the magnesium ascorbyl phosphate group, (P=0.005), **Figure 3**. Stratification with respect to various variables is shown in **Table 2**. Among various factors, the Baseline MASI score and duration of the disease significantly affected the efficacy.

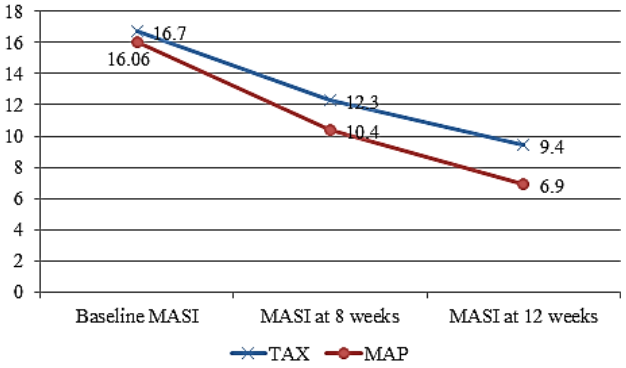


Figure 2 Changes in MASI score over time.

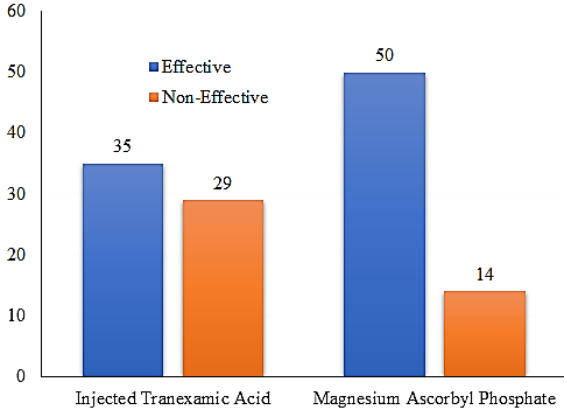


Figure 3 Efficacy of Tranexamic acid vs Magnesium Ascorbyl Phosphate(P-Value<0.005)

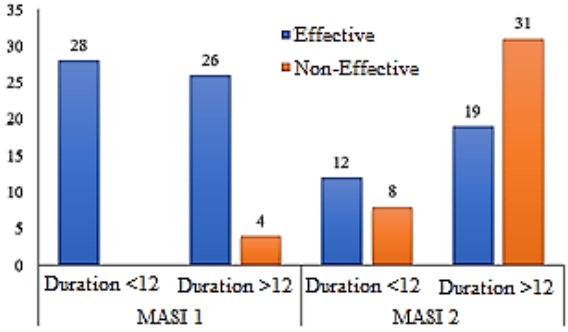


Figure 4 Impact of MASI score and disease duration on the efficacy. MASI 1=≤14, MASI 2=>14.

Table 2 Stratification with respect to various variables.

Group		*Efficacy*		*P -Value*
		Yes	*No*	
Age in years				
18-40	TXA	17	10	0.356
	MAP	23	8	
>40	TXA	18	19	0.0038
	MAP	27	6	
Gender				
Male	TXA	7	6	0.34
	MAP	8	3	
Female	TXA	28	23	0.0118
	MAP	42	11	
Duration months				
1-12	TXA	13	7	0.001
	MAP	27	1	
13-40	TXA	22	22	0.016
	MAP	23	13	
Baseline MASI				
1-14	TXA	23	2	0.77
	MAP	31	2	
15-48	TXA	12	27	0.0107
	MAP	19	12	

The lower the Baseline MASI score and duration of the disease, the better the efficacy, as shown in **Figure 4**. On the other hand, gender and age have no statistically significant impact on the results.

Discussion

Melasma is an acquired hyperpigmentary condition that only affects body parts that are exposed to ultraviolet radiation, primarily the face. All races are affected; however, darker skin tones with higher Fitzpatrick numbers have increased prevalence of this condition (Fitzpatrick skin types IV, V, VI). The majority of those affected are of Hispanic, East Asian, or South East Asian ancestry with extensive UV exposure.[20,21] Women of childbearing age are particularly affected. Various factors like genetics, UV radiation, and conditions of hyperestrogenemia like pregnancy and oral contraceptive pills are implicated in the pathogenesis, but the actual cause-and-effect relationship is yet to be unraveled.[22]

Tranexamic acid (TXA) is a drug used for homeostasis. Intradermal injection is associated with minimal systemic complications, while possible local adverse effects include irritation and an allergic reaction. Both systemic and topical TA has been used in melasma. Clinical trials using oral TXA, intradermal TXA microinjections, or trans-epidermal delivery of TA with micro needling techniques independently or in combination or comparison with topical vit. C have shown results in the treatment of melasma with variable efficacy.[22]

This study gives a clue about the demographic features like age, gender, and baseline MASI score in our local population of melasma patients and TXA/ MAP efficacy with respect to disease duration and changes in MASI score.

A study by Shakeeb N *et al*. compared the efficacy of topical tretinoin along with corticosteroid and hydroquinone, also called the "triple combination cream," (A) versus IPL (B) versus a combination of both (C) in the treatment of melasma. Each group consisted of 32 patients. The gender distribution and baseline MASI score were comparable in all groups. There was a predominance of females in all groups. After 2 months MASI score reduction was observed in 68.8%% of Group A, 62.5% of group B and 93.8% of Group C patients.[23]

A study by Soleman *et al*. evaluated the efficacy of 20% trichloroacetic acid alone versus combination with topical 5% vitamin C. Thirty female patients were enrolled in this study with the mean age of 34.27±5.8 years. At the end of 16 weeks, combination therapy was significantly better than trichloroacetic acid alone in terms of MASI score reduction (p-value 0.001). Similarly greater number of patients showed maintenance of their improvement in combination group compared to TCA alone group.[24]

A study by Batra *et al.* evaluated the efficacy of oral vs. Tran epidermal TXA. Twenty patients were given 250mg of oral TXA while another group of 20 patients received Trans epidermal TXA using derma roller at 2 weekly intervals. All patients were followed for 24 weeks. The baseline MASI score and melasma patterns were comparable in both groups. At the end of the study, patients in both groups achieved significant reduction in MASI score but there was no intergroup difference. Overall trans epidermal rout has got many advantages in terms of cost effectiveness and better side effects profile but it is slightly painful and needs hospital visits at specific intervals.[25]

An Indian study by Dogra *et al*. carried out at Dayanand Medical College and Hospital, Ludhiana, compared the efficacies of 50% glycolic acid and 20% trichloroacetic acid peels for the treatment of melasma. Amongst the overall 50 patients included in the study, females were 45 (90%) and males were 5 (10%), with a female-to-male ratio of 9:1. The mean baseline MASI, disease duration, and age in both groups were also comparable to our study All patients underwent 3 sessions of peels at 3 weekly intervals. The MASI score reduced in both groups but there was no significant intergroup difference (p value>0.05) although more local adverse effects were noted in patients using TCA peels.[26]

A study by Sharma R, *et al.* which compared oral TXA vs. intradermal TXA (4 mg/ml) every 4 weeks to treat melasma, noted that there were 3 (6%) males and 47 (94%) females included in group A, while 5 (10%) males and 45 (90%) females were in group B. The age range was similar in both groups. On the final assessment in the end of 12th week, patients in both groups showed significant reduction in MASI score compared to baseline but no statistically significant intergroup difference was observed in terms of effectiveness.[14] As The study did not find a significant advantage of one administration method over the other in terms of effectiveness, patients may prefer intradermal rout looking at the safety profile, cost effectiveness and lesser contraindications.

Study conducted by Murtaza F. *et al.*, compared trichloroacetic acid peels combined with topical vitamin C (group A) versus trichloroacetic acid peels alone (group B), stated that the mean age and gender distribution was comparable in both groups. The median baseline MASI score was 16 in both groups which reduced to 5 in group A and 5.5 in Group B in the end of the study (p value<0.05). Thus, overall efficacy was 81.1% (60 of 74 patients) in group A and 66.2% (49 of 74 patients) in group.[15] This finding suggested that the combination of TCA peels with topical vitamin C yielded better results in the treatment of melasma compared to TCA peels alone.

Study by Musarrat Raza *et al*. showed no statistically significant difference between tranexamic acid (spray form) and topical vitamin C when both were combined with micro-needling, although slightly greater improvement was observed in the tranexamic acid group. The mean baseline MASI in tranexamic acid and magnesium ascorbyl phosphate groups was 7.98±2.94 and 8.02±2.87, while after 6 weeks it decreased to 4.81±3.25 and 5.12±3.08, respectively. Similar to our study, this study also

showed a lower efficacy in both groups when baseline MASI was on the higher side.[27]

Another study of 30 female patients by Tahoun AI *et al*. evaluated the dermoscopic features of melasma treated with micro-needling (MN) and topical TXA on right side of the face, and with MN and topical vit. C on the left side. After 16 weeks, both sides had similar results in terms of MASI score, dark fine granules, homogeneous pigmentation, pseudo reticular brown network and DLQI (p value<0.05 for all parameters). However, on the TXA side, a more significant reduction was observed in telangiectasias than on the vit. C side ($p = 0.002$).[28]

Iraji F *et al*. conducted a study using cocktail A (TXA 4 mg/ml, vitamin C 3%, and glutathione 20%) and cocktail B (TXA 4 mg/ml, vitamin C 3%) consisting of 30 melasma patients. Fifteen patients applied cocktail A while another group of 15 patients applied cocktail B using Split face technique. All patients showed significant MASI score reduction on both sides, compared to baseline (p-value< 0.001 on both sides). However, on cocktail A side, after 12 weeks a greater reduction in the MASI score was observed, which was statistically significant. (1.28±0.64). Regarding erythema, bruising, and edema, there was no statistically significant difference between the two groups (P-value >0.05).[29]

Limitations of the study

First of all, the sample size was small in this study, and there was no long-term follow-up to see the impact on disease remission, progression, and relapse. Secondly, the MASI score was used for the assessment of disease severity, which is a highly subjective parameter with inter observer variations, and no objective methods of disease assessment like patient satisfaction, DLQI, etc. were used in this study.

Conclusion

It is concluded that topical vitamin C (magnesium ascorbyl phosphate) is superior than injected tranexamic acid for the treatment of melasma. Additional clinical trials are required to assess the efficacy of these treatment modalities with a larger number of patients in both groups and long-term follow-up with more objective parameters for disease progression and remission.

References

1. Ebrahimi B, Naeini FF. Topical tranexamic acid as a promising treatment for melasma. J Res Med Sci. 2014 Aug;19(8):753-7. PMID: 25422661; PMCID: PMC4235096.
2. Kim HJ, Moon SH, Cho SH, Lee JD, Kim HS. Efficacy and Safety of Tranexamic Acid in Melasma: A Meta-analysis and Systematic Review. Acta Derm Venereol. 2017 Jul 6;97(7):776-781. doi: 10.2340/00015555-2668. PMID: 28374042.
3. Kim MS, Bang SH, Kim JH, Shin HJ, Choi JH, Chang SE. Tranexamic Acid Diminishes Laser-Induced Melanogenesis. Ann Dermatol. 2015 Jun;27(3):250-6. doi: 10.5021/ad.2015.27.3.250. Epub 2015 May 29. PMID: 26082580; PMCID: PMC4466276.
4. Miot LD, Miot HA, Silva MG, Marques ME. Physiopathology of melasma. Ann Bras Dermatol.2009;84(6):623–35
5. 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.
6. Handel AC, Miot LD, Miot HA. Melasma: a clinical and epidemiological review. An Bras Dermatol. 2014 Sep-Oct;89(5):771-82. doi: 10.1590/abd1806-4841.20143063. PMID: 25184917; PMCID: PMC4155956.
7. Ho SG, Chan HH. The Asian dermatologic patient: review of common pigmentary disorders and cutaneous diseases. Am J Clin Dermatol. 2009;10(3):153-68. doi: 10.2165/00128071-200910030-00002. PMID: 19354330.

8. Kim SJ, Park JY, Shibata T, Fujiwara R, Kang HY. Efficacy and possible mechanisms of topical tranexamic acid in melasma. Clin Exp Dermatol. 2016 Jul;41(5):480-5. doi: 10.1111/ced.12835. Epub 2016 May 2. PMID: 27135282.
9. Sheth VM, Pandya AG. Melasma: a comprehensive update: part II. J Am Acad Dermatol. 2011 Oct;65(4):699-714. doi: 10.1016/j.jaad.2011.06.001. PMID: 21920242.
10. Kanechorn Na Ayuthaya P, Niumphradit N, Manosroi A, Nakakes A. Topical 5% tranexamic acid for the treatment of melasma in Asians: a double-blind randomized controlled clinical trial. J Cosmet Laser Ther. 2012 Jun;14(3):150-4. doi: 10.3109/14764172.2012.685478. PMID: 22506692.
11. Rajaratnam R, Halpern J, Salim A, Emmett C. Interventions for melasma. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD003583. doi: 10.1002/14651858.CD003583.pub2. PMID: 20614435.
12. Sarkar R, Puri P, Jain RK, Singh A, Desai A. Melasma in men: a clinical, aetiological and histological study. J Eur Acad Dermatol Venereol. 2010 Jul;24(7):768-72. doi: 10.1111/j.1468-3083.2009.03524.x. Epub 2009 Dec 15. PMID: 20015053.
13. Hong JW, Lee S, Kim DC, Kim KH, Song KH. Prognostic and clinicopathologic associations of BRAF mutation in primary acral lentiginous melanoma in Korean patients: a preliminary study. Ann of Dermatol. 2014 Apr 1;26(2):195-202.
14. Sharma R, Mahajan VK, Mehta KS, Chauhan PS, Rawat R, Shiny TN. Therapeutic efficacy and safety of oral tranexamic acid and that of tranexamic acid local infiltration with microinjections in patients with melasma: a comparative study. Clin Exp Dermatol. 2017 Oct;42(7):728-734. doi: 10.1111/ced.13164. Epub 2017 Jun 25. PMID: 28649780.
15. Murtaza F, Bangash AR, Khushdil A, Noor SM. Efficacy of Trichloro-Acetic Acid Peel Alone Versus Combined Topical Magnesium Ascorbyl Phosphate for Epidermal Melasma. J Coll Physicians Surg Pak. 2016 Jul;26(7):557-61. PMID: 27504543.
16. Perveen S, Rubin A, Berger L, Xiong W, Waqas N, Sharif S, Rao B. A Randomized Trial of Oral Tranexamic Acid With Fluocinolone-Based Triple Cream Versus Fluocinolone Based Triple Cream Alone for the Treatment of Melasma. J Drugs Dermatol. 2022 Mar 1;21(3):321-322. doi: 10.36849/JDD.6099. PMID: 35254752.
17. Lee JH, Park JG, Lim SH, Kim JY, Ahn KY, Kim MY, Park YM. Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. Dermatol Surg. 2006 May;32(5):626-31. doi: 10.1111/j.1524-4725.2006.32133.x. PMID: 16706756.
18. Miao F, Su MY, Jiang S, Luo LF, Shi Y, Lei TC. Intramelanocytic Acidification Plays a Role in the Antimelanogenic and Antioxidative Properties of Vitamin C and Its Derivatives. Oxid Med Cell Longev. 2019 May 12;2019:2084805. doi: 10.1155/2019/2084805. PMID: 31214276; PMCID: PMC6535878.
19. Pandya AG, Hynan LS, Bhore R, Riley FC, Guevara IL, Grimes P, Nordlund JJ, Rendon M, Taylor S, Gottschalk RW, Agim NG, Ortonne JP. Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. J Am Acad Dermatol. 2011 Jan;64(1):78-83, 83.e1-2. doi: 10.1016/j.jaad.2009.10.051. Epub 2010 Apr 15. PMID: 20398960.
20. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312 cases. Indian J Dermatol. 2011 Jul;56(4):380-2. doi: 10.4103/0019-5154.84722. PMID: 21965843; PMCID: PMC3178998.
21. Chung JY, Lee JH, Lee JH. Topical tranexamic acid as an adjuvant treatment in melasma: Side-by-side comparison clinical study. J Dermatolog Treat. 2016 Aug;27(4):373-7. doi: 10.3109/09546634.2015.1115812. Epub 2015 Dec 4. PMID: 26526300.
22. Bagherani N, Smoller BR. Efficacy of topical tranexmic acid in the treatment of melasma. Dermatol Ther. 2016 Nov;29(6):389-390. doi: 10.1111/dth.12332. Epub 2016 Jan 22. PMID: 26799239.
23. Shakeeb N, Noor SM, Ullah G, Paracha MM. Efficacy of Intense Pulse Light Therapy and Tripple Combination Cream Versus Intense Pulse Light Therapy and Tripple Combination Cream Alone in Epidermal Melasma Treatment. J Coll Physicians Surg Pak. 2018 Jan;28(1):13-16.

doi: 10.29271/jcpsp.2018.01.13. PMID: 29290184.

24. Soliman MM, Ramadan SA, Bassiouny DA, Abdelmalek M. Combined trichloroacetic acid peel and topical ascorbic acid versus trichloroacetic acid peel alone in the treatment of melasma: a comparative study. J Cosmet Dermatol. 2007 Jun;6(2):89-94. doi: 10.1111/j.1473-2165.2007.00302.x. PMID: 17524124.
25. Batra, J., Brar, B. K., Kumar, S., & Arora, H. (2022). Tranexamic acid in melasma: Comparative evaluation of therapeutic efficacy of oral tranexamic acid versus its transepidermal administration. J Cutan Aesthet Surg, 15(4), 394-399. DOI: 10.4103/JCAS.JCAS_237_20
26. Dogar A, Sunil G, Sarpriya G. Comparative effeciacy of 20% trichloro-acetic acid and 50% glycolic acid peels in treatment of recalcitrant melasma. J Pak Assoc Dermatol. 2006;16(2):81-7.
27. Raza MH, Iftikhar N, Anwar A, Mashhood AA, Tariq S, Bin Hamid MA. Split-Face Comparative Analysis Of Micro-Needling With Tranexamic Acid Vs Vitamin C Serum In Melasma. J Ayub Med Coll Abbottabad. 2022 Jan-Mar;34(1):169-172. doi: 10.55519/JAMC-01-9840. PMID: 35466647.
28. Tahoun AI, Mostafa WZ, Amer MA. Dermoscopic evaluation of tranexamic acid versus Vitamin C, with microneedling in the treatment of melasma: a comparative, split-face, single-blinded study. J Dermatolog Treat. 2022 May;33(3):1623-1629. doi: 10.1080/09546634.2021.1871582. Epub 2021 Jan 12. PMID: 33393842.
29. Iraji F, Nasimi M, Asilian A, Faghihi G, Mozafarpoor S, Hafezi H. Efficacy of mesotherapy with tranexamic acid and ascorbic acid with and without glutathione in treatment of melasma: A split face comparative trial. J Cosmet Dermatol. 2019 Oct;18(5):1416-1421. doi: 10.1111/jocd.12874. Epub 2019 Feb 8. PMID: 30735611.