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Original Article

Tranexamic Acid Mesotherapy Versus Triple Combination Cream in Melasma

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ABSTRACT

Objective: To compare the efficacy of Tranexamic acid mesotherapy versus combination of hydroquinone, tretinoin, and fluocinolone cream (Triple cream) for melasma.

Study Design: Randomized controlled trial (Iranian Registry of Clinical Trials = 20210823052264N1)

Place and Duration of Study: Department of Dermatology, PNS Shifa Hospital Karachi, Pakistan from Mar 2022 to Aug 2022.

Methodology: A total of 58 patients were divided randomly into two groups, A (29 patients) and B (29 patients). Group A patients received sessions of intalesional tranexamic acid 50mg/ml every 2 weeks. Group B patients were treated once nightly with Triple combination cream. Total Period of treatment was for twelve weeks for each patient. Measurement of Melasma Area Severity Index (MASI) Scores for both groups were calculated at 0, 4, 8, and 12 weeks. Final response was labelled at 12 weeks by comparing mean MASI reduction in both groups. SPSS, version 28 was used for data analysis and $p<0.05$ was considered significant.

Results: At the end of study comparison was made of Mean reduction of MASI Score for both groups, significant reduction was noted in mean score from 7.73±1.43 to 4.30±1.34 (44.37%) in group A Tranexamic acid as compared to decrease in scores in group B Triple combination cream from 7.90±1.11 to 5.20±1.39 (34.18%) *p*-value 0.081.

Conclusion: Tranexamic acid mesotherapy can be safe, effective and promising treatment option for melasma. It leads to better results, and lesser side effects than topical triple cream.

Keywords: Hydroquinone, Intralesional, Kligman's formula, Melasma, Mesotherapy, Tranexamic acid, Triple combination cream.

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INTRODUCTION

Melasma is a prevalent condition of hyperpigmentation primarily affecting women throughout their reproductive years and quality of life is significantly influenced.[1] It is more common in Asian, Latin American, and Hispanic people, as well as in Fitzpatrick skin types III–V.[2] It appears as bilateral irregular brown macules and patches on the face.[3] UV exposure, genetic predisposition, and hormonal influences are among the triggering factors4. The main cells involved are the neural crest-derived melanocytes, which produce pigment and are susceptible to influences from the nearby keratinocytes and fibroblasts.[5] Histologically there is increased melanin in all epidermal layers. Additionally, it is connected to substantial solar elastosis, an increase in vasculature, and enhanced vascular endothelial growth factor (VEGF) expression.[6] UV protection, topical whitening products, chemical peeling agents, and laser modalities are all options for treatment. Melasma is a frustrating condition due to partial clearance and repeated recurrences.[7] The triple combination cream (TC) is being used as standard treatment for melasma.[8] Hydroquinone (4%), the primary component of triple cream, exerts its depigmenting effects by inhibiting melanin formation through inhibition of tyrosinase enzyme in melanocytes resulting in in a reduced DOPA to melanin conversion.[9] Side-effects of hydroquinone include erythema, stinging, contact dermatitis, nail discoloration and ochronosis. Tretinoin (0.05%) is another component in TC, which exerts its effect by increasing keratinocyte turnover, therefore limiting the transfer of melanosomes to keratinocytes. The main adverse effects of tretinoin are skin irritation, photosensitivity and hyper-pigmentation. Fluocinolone acetonide (0.01%) is a mild steroid used in triple cream for its synergistic effects and for the reduction of irritation from other products. Adverse effects of flucinolone include atrophy, rosacea, telangiectasia, acne and hypertrichosis. Tranexamic acid (TA) has originated as an effective therapeutic option for melasma in recent years.[10] It

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exerts its effects by blocking the Ultra violet produced plasmin activity in the epidermal cells which leads to decreasing prostaglandins thus reducing melanogenesis in the melanocytes. It also decreases tyrosinase activity and reverses melasma related dermal changes such as vessel number. TA decreases both the formation of melasma and also reduce the chances of recurrence.

Since melasma mainly affects face and there is currently no such treatment that can completely treat melasma, It causes considerable psychosocial distress. Therefore our study aims to compare efficacy and side effects of intralesional TA with TC. There are only few studies and there is no registered randomized controlled trial (RCT) on this topic in our population. Intralesional TA if found successful, can be recommended as an effective treatment for melasma as it is safe, easily available and affordable for the patient.

METHODOLOGY

The conduction of this randomized controlled trial was from March 2022 to August 2022 in dermatology department PNS Shifa hospital Karachi, Pakistan after Ethical Committee approval (Ref No: ERC/2021/DERMA/ 48) and registration was done from Iranian Registry of Clinical Trials (20210823052264N1). Total Sample size came out to be 58, 29 in a single group by using the WHO sample size calculator with the hypothesis test for two population means (two-sided test), with mean reduction in MASI score 2.0±1.14 in intradermal TA group,[11] and 1.16±0.81 in TC group.[12] Population standard deviation of 0.975, level of significance 5 and power of study 90%. After explaining about the study informed consent form was signed by all the patients.

Inclusion Criteria: Patients aged 18-50 years with bilateral symmetrical melasma.

Exclusion Criteria: Patients with pregnancy, lactation, OCPs, bleeding disorder, anemia and patient on anticoagulation therapy were excluded from the study. Patients were randomly divided into two groups on simple method based on sealed envelopes, group A (29 patients) and group B (29 patients). During the first visit, after complete history and detailed cutaneous examination wood's lamp examination was done for each patient and coloured photographs were taken. Injection TA 50mg/ml was used in group A patients and TC once nightly in group B patients. All patients were instructed to stay out of the sun as much as possible and to abstain from topical preparations other than a sun screen with an SPF of 30 or higher. 5 mL vial of TA contains 500mg TA. 1ml (100IU) of insulin syringe was used. 0.50 mL (50IU) of TA and 0.5ml (50IU) normal saline were mixed preparing 50 mg TA in a single insulin syringe. After application of topical aesthetic for 45 minutes to 1 hour, TA mesotherapy was done into areas of melasma 1 cm apart bilaterally on the face. These sessions were done fortnightly for 12 weeks. Patient's follow-up was done for calculating MASI scores and assessment of side-effects of both the groups at week 0, 4, 8 and 12.

Following Calculations for MASI Score were used.

Frontal 30%, Malar 30%, Chin 10%

For frontal 0.3(A) (D), malar (left) 0.3(A) (D), malar (Right) 0.3(A) (D) and chin 0.1(A) (D)

Total score range from 0–24.

Area 0=no involvement; 1=<10; 2=10–29; 3=30–49; 4=50–69; 5=70–89; and 6=90–100

Whereas darkness was ranged as absent (0), slight (1), mild (2), marked (3) and severe (4)

Mean reduction in MASI scores at 12 weeks was compared to baseline and considered as response. Mean reduction in MASI scores of both groups was compared and p-value<0.05 was considered significant. Patient satisfaction score was calculated by asking the patients to rate the response out of 100 at the end of 12 weeks. Patients with a score of 75-100 was regarded as highly satisfied response, 50-74 score as moderately satisfied response, 25-49 score as partially satisfied response and score of 0-24 as not satisfied response.

Patient's evaluation was done at 0, 4, 8 and 12 weeks for the occurrence of any side effects.

Data was analysed by Statistical Package for the social sciences (SPSS) version 28:00. Frequencies and percentages were used for categorical data and numerical data was analysed by Mean±SD. Paired t-test was used for analysis of mean MASI score difference pre and post treatment for both groups. Paired t-test was used for calculation of the difference in mean of MASI score between the two groups post intervention.

RESULTS

We enrolled total of 58 patients, 29(50%) in each group. All patients completed study. Their age ranged from 18 to 50 years. The mean age of patient was

31.43±07.66 years. There was no significant difference between group A and group B (p=0.906). The majority of the patients (79.31%) were females. Most of the patients were with Fitzpatrick skin type IV (79.31%). Their demographics are illustrated in Table-I.

Table-I: Demographics and Clinical Data

Variables		Group A (TA)	Group B (TC)	Total
Age (Means±S.D)		31.31±07.22	31.55±08.19	31.43±07.66
Gender (n%)	Male	08(27.58%)	04(13.79%)	12(20.69 %)
	Female	21(72.42%)	25(86.21 %)	46(79.31%)
Marital Status (n%)	Married	18(62.07%)	16(55.17 %)	34(58.62 %)
	Unmarried	11(37.39%)	13(10.34 %)	24(41.38 %)
Fitzpatrick Skin Type (n%)	III	01(03.45 %)	03(10.34%)	04(06.90 %)
	IV	25(86.21 %)	21(72.42 %)	46(79.31 %)
	V	03(10.34%)	05(17.24%)	08(13.79 %)
Family History (n%)	Positive	17(58.62 %)	16(55.17 %)	33(56.90%)
	Negative	12(41.38 %)	13(44.83 %)	25(43.10%)

Comparison of the mean MASI at baseline in group A and group B shows that no statistically significant difference was observed between them (p=0.611). Significant MASI reduction was noted in both groups but intradermal TA group has higher MASI reduction (44.37%) than triple combination cream (34.18%). The comparison of the efficacy of treatment in terms of MASI scores of both groups is shown in Table-II.

Table-II: Mean MASI Scores Reduction

Variables		Group A (TA)	Group B (TC)	p-value
Mean MASI scores (Means±S.D)	Week 0	7.73±1.43	7.90±1.11	0.611
	Week 04	6.50±1.14	7.00±1.05	0.089
	Week 08	5.40±1.19	6.09±1.19	0.036
	Week 12	4.36±1.34	5.24±1.39	0.018

In terms of patient satisfaction, group A had more satisfaction response than group B and the difference was statistically significant (p=0.002). Patients experienced lesser side effects in group A as compared to group B but the difference was not statistically significant(p=0.607). Patient's satisfaction response and side effects are given in Table-III.

Table-III: Satisfaction and Side Effects

Variables		Group A (TA)	Group B (TC)	p-value
Satisfaction (n%)	Highly Satisfied	9(31.30%)	2(06.90%)	
	Moderately Satisfied	18(62.07%)	18(62.07%)	0.002
	Partially Satisfied	2(06.90%)	8(27.59%)	
	Not Satisfied	0(00.00%)	1(03.45%)	
Side Effects (n%)	Yes	13(44.80%)	15(48.30%)	0.607
	No	16(55.20%)	14(51.70%)	

DISCUSSION

Worldwide many clinical studies have been conducted for the determination of efficacy of TA for intervention of melasma. But currently there is no such study done in our population which compared TA mesotherapy with topical triple regimen. In our study we compared intradermal TA (50mg/ml) with most frequently used and FDA approved treatment of melasma i.e. topical triple cream (hydroquinone 2%, tretinoin 0.025%, fluocinolone acetonide 0.01%). In earlier studies TA dose, duration and interval of administration has been different.[13] We used 50mg/ml intradermal tranexamic acid every 2 weeks for 12 weeks. Which has not been previously compared in other studies. Our study showed better efficacy and lesser side effects as compared to topical triple cream. A pilot study performed in 2006 by Lee *et al.*[14] on the efficacy of intradermal TA microinjections (4 mg/ml), showed a statistically significant reduction in MASI at 12 weeks from the baseline. Our study showed similar results in TA group with 50mg/ml microinjections. A study performed by Shetty and Shetty,[15] on forty patents, with group A (20 Patients) receiving TA (4mg/ml) every 3rd week for 12 weeks from baseline and group B (20 patients) receiving TA 250mg twice orally for 12 weeks. Intradermal TA (35.6%) showed higher efficacy as compared to oral tranexamic acid (21.7%). This led us to take one group as intralesional TA which lead better efficacy than oral TA.

In a split face study Saki *et al.*[16] compared intradermal TA (20mg/ml) monthly on one side of face for three months whereas other side of face was treated with topical HQ (2%) once nightly for same duration. Significant improvement was noted on both sides of the face, however no significant difference was observed in both groups. Pazyar *et al.*[3] compared intradermal TA (4mg/ml) fortnightly with topical 4% HQ twice daily for 12 weeks in a split face study in 49 patients. No significant difference was noted in the

decrease in MASI scores in both groups. On the other hand in our study we evaluated topical TC with intralesional TA and found it to be more effective than topical TC (*p*-value 0.000).

Figure: Before and after Tranexamic Mesotherapy

In a RCT Basit *et al*.[17] enrolled patients in to two groups, TC and oral TA 250mg was used in group A whereas TC was used in Group B for 8 weeks duration. Both groups revealed significant MASI reduction. However both groups showed no significant difference from each other in mean reduction of MASI. In contrast we compared intalesional TA with triple cream for 12 weeks which showed significant mean MASI reduction. Another study performed by Patil and Deshmukh,[18] on 205 patients concluded that intradermal TA (4mg/ml) efficacy was more than both topical TC and topical TA (3%). In contrast to our study they used an additional group of topical TA and the dose of TA was lesser, still intradermal TA yielded better results than other groups which supports results of our study.

A split face comparative study was performed by Hawwam *et al*.[19] on 40 patients. Q-switched Nd:YAG laser and TA mesotherapy combination were used on one side of the face, whereas TA mesotherapy alone was performed on other side of the face. The combination treatment group showed significant reductuion in MASI scores than TA mesotherapy group both at 12 and 24 weeks. We did not combine TA with other modalities but combinations with intalesional TA could be explored which may lead to better treatment options for melasma in future.

According to Khalili *et al*.[20] side effects of intradermal TA mesotherapy were temporary and resolved in few hours to days which included pain, burning, itching, erythema, swelling, bruising, edema, irritation, ecchymosis and wheal formation. In our study we did not observe any serious side effects except transient pain, burning, swelling and irritation which resolved after 24 hours. Same side effects of TA were reported by Efar *et al*.[21] which is consistent with our study. Side effects associated with topical triple cream pruritis, scaling, itching, erythema,[12] were observed in TC group but none of the patient left the study due to these side effects. Some side effects like telangiectasia and skin atrophy are major concerns for long-term treatment in melasma patients.[22] In our study such side effects were not observed due to the reason that total study duration of study was small i.e 12 weeks.

The limitations of this study were single center study, small sample size and lack of follow up. A study performed by Lueangarun *et al*.[23] showed 60% recurrence of melasma in patients treated with intralesional TA at 48 weeks follow up. We did not follow up patients due to the reason of the patient load on tertiary care hospital, patients coming from different cities and far off areas leading to difficulty in follow up.

CONCLUSION

On the basis of our study we conclude that TA mesotherapy is more effective in treatment of of melasma and has lesser side effects than topical TC. It is easily available, cost effective, safe and satisfying treatment modality for melasma. In future multicenter studies with large sample size and long duration maybe recommended.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

NA & MR: Data acquisition, data analysis, critical review, approval of the final version to be published.

MT & TMM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SM & SA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Rahman A, Basit A, Mohsin S, Ahmed N, Tahir M, Ishfaq A. Quality of Life of Melasma Patients in Pakistan. PAFMJ 2022; 72(1): 307-310.
2. McKesey J, Tovar-Garza A, Pandya AG. Melasma Treatment: An Evidence-Based Review. Am J Clin Dermatol 2020; 21(2): 173-225. https://doi.org/10.1007/s40257-019-00488-w

3. Pazyar N, Yaghoobi R, Zeynalie M, Vala S. Comparison of the efficacy of intradermal injected tranexamic acid vs hydroquinone cream in the treatment of melasma. Clin Cosmet Investig Dermatol 2019; 12: 115-122. https://doi.org/10.2147/CCID.S191964
4. Rajanala S, Maymone MBC, Vashi NA. Melasma pathogenesis: a review of the latest research, pathological findings, and investigational therapies. Dermatol Online J 2019; 25(10): 13030/qt47b7r28c.
5. Khan KN, Ahmed N, Salik KM, Mahboob M, Niaz F, Panhwar M. Frequency of Hypothyroidism in Patients with Melasma in a Tertiary Care Hospital. InMed. Forum 2021 Dec (Vol. 32, No. 12, p. 133).
6. Colferai MMT, Miquelin GM, Steiner D. Evaluation of oral tranexamic acid in the treatment of melasma. J Cosmet Dermatol 2018 Dec 9. https://doi.org/10.1111/jocd.12830
7. Zhou LL, Baibergenova A. Melasma: systematic review of the systemic treatments. Int J Dermatol 2017; 56(9): 902-908. https://doi.org/10.1111/ijd.13578
8. Torok, Helen M. "A comprehensive review of the long-term and short-term treatment of melasma with a triple combination cream." American journal of clinical dermatology vol. 7,4 (2006): 223-230. https://doi.org/10.2165/00128071-200607040-00003
9. Riaz S, Ahmed N, Anwar A, Tahir M, Yousaf F, Kausar S. Comparison of 4% Topical Hydroquinone versus Combination of Oral Tranexamic Acid and 4% Topical Hydroquinone in the Treatment of Epidermal Melasma. Pakistan Journal of Medical and Health Sciences. 15. 3406-3409. https://doi.org/10.53350/pjmhs2115103406
10. Kim, Hyun Jung . "Efficacy and Safety of Tranexamic Acid in Melasma: A Meta-analysis and Systematic Review." Acta dermato-venereologica vol. 97,7 (2017): 776-781. https://doi.org/10.2340/00015555-2668
11. Pazyar N, Molavi SN, Hosseinpour P, Hadibarhaghtalab M, Parvar SY, Dezfuly MB. Efficacy of intradermal injection of tranexamic acid and ascorbic acid versus tranexamic acid and placebo in the treatment of melasma: A split-face comparative trial. Health Sci Rep 2022; 5(2): e537. https://doi.org/10.1002/hsr2.537
12. Ahmad Nasrollahi S, Sabet Nematzadeh M, Samadi A, Ayatollahi A, Yadangi S, Abels C et al. Evaluation of the safety and efficacy of a triple combination cream (hydroquinone, tretinoin, and fluocinolone) for treatment of melasma in Middle Eastern skin. Clin Cosmet Investig Dermatol 2019; 12: 437-444. https://doi.org/10.2147/CCID.S202285
13. Perper M, Eber AE, Fayne R, Verne SH, Magno RJ, Cervantes J et al. Tranexamic Acid in the Treatment of Melasma: A Review of the Literature. Am J Clin Dermatol 2017; 18(3): 373-381. https://doi.org/10.1007/s40257-017-0263-3
14. Lee JH, Park JG, Lim SH, Kim JY, Ahn KY, Kim MY et al. Localized intradermal microinjection of tranexamic acid for treatment of melasma in Asian patients: a preliminary clinical trial. Dermatol Surg 2006; 32(5): 626-631. https://doi.org/10.1111/j.1524-4725.2006.32133.x
15. Shetty, Vinma & Shetty, Monisha. (2018). Comparative study of localised intradermal microinjection of tranexamic acid and oral tranexamic acid for the treatment of melasma. International Journal of Research in Dermatology. 4. 363. 10.18203/issn.2455-4529. IntJResDermatol20183159.
16. Saki N, Darayesh M, Heiran A. Comparing the efficacy of topical hydroquinone 2% versus intradermal tranexamic acid microinjections in treating melasma: a split-face controlled trial. J Dermatolog Treat 2018; 29(4): 405-410. https://doi.org/10.1080/09546634.2017.1392476
17. Basit A, Rahman A, Uddin R. Oral Tranexemic Acid With Triple Combination Cream (Flucinolone+Hydroquinone+Tretinoin) Versus Triple Combination Cream Alone In Treatment Of Melasma. J Ayub Med Coll Abbottabad 2021; 33(2): 293-298.
18. Patil, ShrutiS & Deshmukh, AshishR. (2019). Comparative study of efficacy of intradermal tranexamic acid versus topical tranexamic acid versus triple combination in melasma. Pigment International. 6. 84. 10.4103/Pigmentinternational.Pigmentinternational_19_19.
19. Hawwam SA, Ismail M, El-Attar YA. Split-face comparative study between intradermal tranexamic acid injection alone versus intradermal tranexamic acid injection combined with Q-switched Nd:YAG laser in melasma treatment: dermoscopic and clinical evaluation. Lasers Med Sci 2022; 37(4): 2193-2201. https://doi.org/10.1007/s10103-021-03483-y
20. Khalili M, Amiri R, Iranmanesh B, Zartab H, Aflatoonian M. Safety and efficacy of mesotherapy in the treatment of melasma: A review article. J Cosmet Dermatol 2022; 21(1): 118-129. https://doi.org/10.1111/jocd.14644
21. Elfar, Nashwa & El Maghraby, Gamal. (2015). Efficacy of Intradermal Injection of Tranexamic Acid, Topical Silymarin and Glycolic Acid Peeling in Treatment of Melasma: A Comparative Study. jornal of Clinical and Experimental Dermatol research 6. 1-7. https://doi.org/10.4172/2155-9554.1000280
22. Ferreira Cestari T, Hassun K, Sittart A, de Lourdes Viegas M. A comparison of triple combination cream and hydroquinone 4% cream for the treatment of moderate to severe facial melasma. J Cosmet Dermatol 2007; 6(1): 36-39. https://doi.org/10.1111/j.1473-2165.2007.00288.x.
23. Lueangarun S, Sirithanabadeekul P, Wongwicharn P, Namboonlue C, Pacharapakornpong S, Juntongjin P et al. Intradermal Tranexamic Acid Injection for the Treatment of Melasma: A Pilot Study with 48-week Follow-up. J Clin Aesthet Dermatol 2020; 13(8): 36-39. Epub 2020 Aug 1. PMID: 33178380; PMCID: PMC7595366.