

ORIGINAL ARTICLE

ORAL TRANEXEMIC ACID WITH TRIPLE COMBINATION CREAM (FLUCINOLONE+HYDROQUINONE+TRETINOIN) VERSUS TRIPLE COMBINATION CREAM ALONE IN TREATMENT OF MELASMA

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Background: Melasma is an acquired cutaneous disorder characterized by hyperpigmentation of the face predominantly affecting the areas exposed to direct sun light. The triple combination cream, i.e., a mid-potency corticosteroid (Fluocinolone acetonide 0.01%), a retinoid (Tretinoin 0.05%), and Hydroquinone 4% is one of the widely used topical medicament for melasma treatment world over. Tranexamic acid is another agent found to be effective in melasma treatment when used topically, intra-lesionally or orally. This study has been conducted to compare mean decrease in Melasma Area Severity Index (MASI) score when tranexamic acid is combined with triple combination cream versus triple combination cream alone for melasma treatment. **Methods:** A randomized controlled trial was conducted in a tertiary care hospital of Pakistan. Sixty-three patients of melasma who met the inclusion criteria and gave written informed consent for the study were enrolled. These patients were randomly divided into 2 treatment groups. Group A was given triple combination cream and oral tranxemic acid while Group B was given triple combination cream for duration of 8 weeks. Severity of melasma was assessed by MASI, which was calculated at baseline and at the end of week 8. Mean decrease in MASI score was calculated in both groups and statistically analysed employing SPSS 20. **Results:** Sixty patients, 30 in both groups, completed the study. Study participants were predominantly female (81.67%), with mean age of 30.46±6.24 years in group A while 31.90±4.53 in group B. No statistically significant difference was noted in both treatment groups for mean decrease in the MASI score (6.4933±4.38358 in group A compared to 5.7833±5.04251 in the group B; *p*-value 0.56). **Conclusion:** The addition of oral tranexamic acid did not contribute significantly in decrease in MASI score when used in combination with topical triple regimen. It may have a role as an adjuvant to topical triple combination cream.

Keywords: Melasma; Fluocinolone acetonide; Tretinoin; Hydroquinone; Tranexamic acid

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INTRODUCTION

Melasma is a very common pigmentation disorder of skin which affects the sun-exposed sites, mainly the face. It is worldwide in its distribution affecting all races and both genders. Different patterns of melasma have been described; including centrofacial, malar and mandibular. Centrofacial distribution is the most common pattern followed by malar and mandibular.¹ It has a multifactorial etiology and factors like pregnancy, UV ray's exposure, genetics, hormonal influences, drugs (including oral and phototoxic drugs) etc. are implicated in the pathogenesis.^{1,2} Affecting the overall appearance of individual, it is not unexpected that melasma has psychosocial implications affecting the quality of life of the patient. Significantly, its treatment tends to be prolonged and difficult, at times refractory to treatment. Furthermore, the risk of relapse of the condition is considerably high.³ There is a

multitude of treatments modalities available for melasma. However, they all have inconsistent outcomes and potentially significant side effects. Topical skin lightening agents (e.g., triple and dual combination, hydroquinone, kojic acid, arbutin, mequinol, vitamin C) are the mainstay of treatment. However, they are frequently inadequate to treat the condition entirely. These shortfalls led to the augmentation with intense pulsed light (IPL), laser-based treatments, oral medications and chemical peeling etc.⁴

Evidence based studies have suggested that the triple combination cream (0.05% tretinoin, 4% hydroquinone and 0.01% fluocinolone acetonide) applied topically produces finest response.^{2,3} Recently tranexamic acid (TA) has been used in melasma as oral, topical and intra lesional agent.⁵ TA (trans-4-aminomethyl cyclohexanecarboxylic acid) is a synthetic derivative of the amino acid lysine. It is a plasmin

inhibitor and has useful effects in arresting bleeding. Hence, it has been successfully used to stop blood loss in epistaxis, menorrhagia and after other surgical procedures. Another effect of plasmin is on the epidermal basal cells where it stimulates synthesis of arachidonic acid, leading to increased levels of alpha melanocyte stimulating hormone (α MSH). Both arachidonic acid and α MSH potentially trigger melanogenesis. TA being plasmin inhibitor is postulated to inhibit UV-induced melanogenesis. Additionally, it also has a structural similarity with tyrosine, thereby competitively inhibiting tyrosinase enzyme. It has been found that use of TA in melasma patients leads to decrease melanin in the epidermis and mast cells in the dermis. Biopsy samples of melasma skin have shown an increase in size and number of dermal blood vessels. TA further helps in melasma by reducing these dermal blood vessels. Although the safety profile of oral TA is well established, there are certain significant adverse events associated with the drug.^{3,5} This would apparently make the use of TA inappropriate in melasma, which is a non-life-threatening condition. However, for melasma, it is commonly used in much smaller doses, i.e., 500-1000mg/day, significantly reducing the incidence of serious side effects.⁵

The triple combination cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) has established itself as an important agent in the treatment of melasma. It takes time about 4 weeks to first show any changes and 8 weeks are required to observe optimum results. Nowadays, this combination is considered gold standard and first line treatment in melasma but it shouldn't be used for more than 8 weeks at a time to minimize side effects.⁶ A Cochrane systematic review on interventions for melasma documented 23 different treatments. It showed triple combination creams (fluocinolone 0.01%, hydroquinone 4%, tretinoin 0.05%) to be the most effective. Other topical modalities like hydroquinone 2% or 4%, hydroquinone and tretinoin, hydroquinone and flucinolone acetonide, tretinoin and flucinolone acetonide were found less effective than the triple combination regimen.⁷

Management of melasma with topical agent alone, as discussed above, may not yield optimal results. Hence, other potentially useful agents are tried along with topical agents. There are few studies comparing the efficacy of TA in combination with established topical agents. However, Rajaratnam et al,⁷ after conducting Cochrane systematic review, have argued that the quality of some of the studies evaluating melasma

treatments was poor. They have suggested that high-quality randomised controlled trials should be carried out and more data should be gathered on long-term outcomes of management plan to conclude the duration of response.⁷ Taking into consideration the available evidence on melasma management, we conducted this study to determine the efficacy of these therapeutic modalities in our study population. The aim of the study was to compare mean decrease in MASI score with TA and triple combination cream (fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05%) versus triple combination cream alone in treatment of melasma.

MATERIAL AND METHODS

This randomized controlled trial was conducted at the Dermatology Department of a tertiary care hospital for a total duration of six months, i.e., from 25.12.17 to 24.6.18, after necessary approval from the hospital's ethical review committee. Sixty three patients of melasma presenting in the outpatient department of dermatology who met the inclusion criteria and were willing to participate in the study were recruited. Inclusion criteria included patients aged 18–60 years, of both gender having the clinical diagnosis of melasma and not taking any treatment for the past six months, as per their histories. Potential confounding factors were controlled by excluding certain patients. Pregnant and lactating females, patients with past or present history of thrombo-embolic phenomenon like deep vein thrombosis, pulmonary embolism, stroke and/or ischemic heart disease were excluded from the study. Similarly, patients with psychological disorders, thyroid dysfunction or those on recognized photo-sensitizing drugs were excluded.

Patients were selected by non-probability; consecutive sampling. The required sample size came out to be 60 patients (30 in each group) by using 95% confidence interval, 80% power of test with an expected mean decrease in MASI score as 2.19 ± 2.37 in cases treated with triple combination cream only while 6.99 ± 6.05 in cases treated with triple combination cream plus tranexamic acid group.

Melasma was diagnosed clinically in patients having macules or patches of dyspigmentation on face, varying in colour from brown to brownish grey, localized on cheeks, bridge of nose, forehead, chin, and/or above upper lip. Written informed consent was taken from every participant for enrolment in the study and for photography of their lesions. Detailed history was taken and relevant examination was done. Quantification of melasma severity was done by

Melasma Area Severity Index (MASI), which is the most established tool used to assess melasma objectively in clinical studies.⁸

MASI score was calculated as per the following formula: The face was divided into four areas; forehead [forehead (F) 30% of total facial area], right cheek and adjoining area of nose [right malar (RM) 30% of total facial area], left cheek and adjoining area of nose [left malar (LM) 30% of total facial area] and chin [chin (C) 10% of total facial area]. Involvement of melasma in each area was documented and denoted by “A”. Range of involvement was from 0–6, where the numbers indicated the extent of involvement. 0=no involvement; 1=<10% involvement; 2=10–29% involvement; 3=30–49% involvement; 4=50–69% involvement; 5=70–89% involvement; and 6=90–100% involvement. The colour change induced in facial skin by melasma was documented as darkness “D” and was measured by comparing melasma colour with normal skin colour. Range of darkness was from 0–4. 0=normal skin colour; 1=hardly perceptible hyperpigmentation; 2=mild hyperpigmentation; 3=moderate hyperpigmentation; 4=severe hyperpigmentation. The skin was assessed for the pattern of pigmentation and described as homogeneity “H”. Here too the range of severity was from 0–4. 0=normal skin colour; 1=only tiny flecks/specks of involvement; 2= patches of involvement <1.5 cm²; 3=patches of involvement >2 cm²; 4=unvarying skin involvement involving whole area.

MASI score was calculated by the formula:

$$F\ 0.3\ (D+H)A + RM\ 0.3\ (D+H)A + LM\ 0.3\ (D+H)A + C\ 0.1\ (D+H)A.^9$$

To remove personal bias while calculating the MASI score it was measured by a single physician only throughout the study, who was blinded to which group of treatment the patients belonged.

The study participants were divided by using random number table into the following two groups:

Group A – oral TA 250 mg twice daily + triple combination cream once daily at night time

Group B – triple combination cream only once daily at night time

The patients were advised to use a small pea sized cream, absorbed gently and completely into the affected facial skin and to wash the face next morning. The treatment was continued for 8 weeks. All patients were advised to apply the same broad spectrum sun screens 20–30 min prior to sun-exposure and to reapply after two hours if constantly out in the sun. The patients were called for follow-up visits at the end of weeks 4 and 8, after initiation of therapy. MASI was calculated, by a single dermatology resident to eliminate bias, at baseline and after the end of week 8. Mean Decrease in

MASI score was measured by subtracting post treatment MASI score from pre-treatment MASI score.

Data was recorded in the predesigned proforma and was statistically analysed using SPSS 20 software. Numerical variables; age, duration of disease, pre and post treatment MASI score and decrease in MASI score were presented by mean $\pm$ SD. Categorical variable, i.e., gender was presented by frequency and percentage. Independent sample T-test was applied to compare the mean decrease between the two groups taking $p \leq 0.05$ as significant. Data was stratified for age, gender and duration of disease to address effect modifiers. Post stratification T-test was applied taking $p \leq 0.05$ as significant.

RESULTS

Sixty patients completed the study. Three patients from group A no longer wished to participate in the study, after experiencing some side effects like headache, nausea and abdominal fullness and were withdrawn from the study and were excluded from the final data analysis process. All patients in group B completed the study. The patients' characteristics are given in table 1. The mean age of the patients in group A were 30.46 ± 6.24 years while 31.90 ± 4.53 in group B. Most of the cases were female; with 86.7% in group A and 76.7% in group B. No statistically significant difference was found amongst the two groups regarding age, duration of disease and baseline pre-treatment MASI scores. It indicates that these parameters were fairly similar in both groups; not confounding the study results. The mean pre-treatment MASI score of the patients in group A was 12.06 ± 5.51 while it was 11.35 ± 5.69 in group B. Mean post-treatment MASI score of the patients in the group A was 5.58 ± 3.28 while 5.71 ± 3.53 in the group B. Significant fall in MASI score was seen in both treatment groups ($p < 0.0001$), indicating successful treatment outcome with both. However, the groups did not yield any significant difference between them for the mean decrease in the MASI score. It was noted that the mean decrease in MASI score of the patients in the group A was 6.4933 ± 4.38358 while it was 5.7833 ± 5.04251 in the group B. This difference in decrease in MASI score was found to be statistically insignificant (p -value 0.56). While comparing the pre and post treatment MASI scores in both groups individually the fall in MASI was found to be statistically significant in both groups, as shown in table 2. Figures 1 and 2 show the improvement in melasma clinically in a female patient after 8 weeks of treatment with combination of oral tranxemic acid and topical combination cream. Our study results indicated that the addition of oral TA with topical triple regimen did not confer statistically significant improvement in melasma treatment.



Figure-1: Melasma in a young female at baseline



Figure-2: Same patient after completion of 8-week treatment of topical triple regimen and oral tranexamic acid

Table-1: Tabulated form of study participants' characteristics

Patient Characteristics		Group A (n=30)	(Group B n=30)	p-value
Age		30.4667(SD±6.24076)	31.9000(SD±4.53606)	0.3131
Gender	Male	4 (13.3%)	7 (23.3%)	
	Female	26 (86.7%)	23 (76.7%)	
Duration of disease		6.2333(SD±2.69972)	5.5333(SD±2.97962)	0.3443
Pre-treatment MASI score		12.0633(SD±5.51678)	11.3533(SD±5.69693)	0.6257
Post- treatment MASI score		5.5833(SD±3.28624)	5.7100(SD±3.53264)	0.8861
Mean decrease in MASI score		6.4933(SD±4.38358)	5.7833(SD±5.04251)	0.5628

Table-2: Treatment response in group A and group B

Study parameter	Group A	Group B
Pre-treatment MASI score	12.0633(SD±5.51678)	11.3533(SD±5.69693)
Post- treatment MASI score	5.5833(SD±3.28624)	5.7100(SD±3.53264)
p-value	$p < 0.0001$	$p < 0.0001$

DISCUSSION

Satisfactory treatment of melasma is a challenging task. There is an array of treatment options available and effective management plans include more than one treatment modality to tackle this chronic, cumbersome and relapsing condition. These include broad spectrum sun screens, skin lightening agents, antioxidants, chemical peeling and lasers. Well-designed studies are required to assess the response of different modalities. Calculating MASI score may be a time-consuming process but it is an important tool to objectively assess treatment response. It also has prognostic value. Greater MASI score indicates severe disease and worse prognosis.⁸ Such patients are more likely to receive multi-pronged and prolonged treatments. At the same time, such patients are more vulnerable to use substandard beauty products claiming to whiten and freshen up the skin, ultimately further worsening their melasma.

Our study results yielded no significant difference in both the treatment groups with respect to mean decrease in MASI score. However, a small statistically insignificant, increase in response was seen when oral TA was combined with triple regime (p -value 0.56). The addition of oral TA caused a further reduction of 0.71 in MASI score as compared to topical triple combination regimen alone. Meta-analysis of the three RCTs done, comparing routine topical treatment alone and in combination with TA as adjuvant, has shown an additional 0.94 MASI score (p -value 0.03 reduction in patients in whom TA was used as an additional agent. In the above mentioned RCTs two employed oral and one topical TA.⁵ In another retrospective cohort study employing oral TA as an adjuvant to IPL + Q switched Nd YAG laser there was an additional reduction of MASI score by 0.46 (p -value 0.10) as compared to the other group not using TA.¹⁰ Kim *et al*'s⁵ meta-analysis revealed that the oral form of TA results in greatest

standardized decrease in MASI as compared to TA given by topically or by intra-lesionally. Topical TA is effective in epidermal melasma but it has been found ineffective when melasma is dermal or mixed type.^{11,12} This led us to conduct our study with low dose oral TA in conjunction with triple combination cream aiming to find a safe and effective treatment modality for melasma.

Song *et al*¹³ and Tan *et al*¹⁴ have studied oral TA as a sole agent in the treatment of melasma and found MASI reduction of 3.27 and 1.89 respectively in their studies. We have found significant greater reduction in MASI when oral TA has been combined with triple regime. We have used low dose of TA 250 mg twice a day for 2 months which is the same dose and duration done by Padhi *et al*.¹⁵ Their study indicated a mean decrease in MASI score of 2.19 ± 2.37 in cases treated with triple combination cream only while a decrease of 6.99 ± 6.05 in patients treated with triple combination cream plus tranexamic acid group (p -value < 0.05). Our study found decrease in MASI score comparable to their study in the group of patients using oral TA and topical agent. However, we also found significant improvement when triple combination cream was used alone. Our study findings confer with the published medical literature on this subject. Triple combination cream has well established its place as first line of treatment in melasma.⁷ Karn *et al*¹² used TA 250 mg twice a day for a total duration of three months in combination with topical hydroquinone. Their study found MASI score decreasing from 11.08 ± 2.91 to 8.95 ± 2.08 at week 8 and further fall of 7.84 ± 2.44 at week 12 (p value < 0.05 for both) in the topical agent and TA group. While the topical agent alone group demonstrated decrease in mean MASI score 11.60 ± 3.40 at baseline to 9.9 ± 2.61 at eight weeks and 9.26 ± 3 at 12 weeks ($p < 0.05$ for former but $p > 0.05$ for later). They concluded that TA provides sustained improvement in the treatment of melasma.

The systematic review and meta-analysis by Kim *et al*⁵ has established the safety profile of TA as an innocuous treatment option for melasma. They found minor side-effects when oral TA was used in doses between 500mg and 1500 mg/day. This oral dose is lower than the usual dose of 1500–3000 mg/day employed as a haemostatic agent. Doses up to 4.5 gm/day have been mentioned in medical literature.¹⁶ Hypomenorrhoea, mild abdominal discomfort, urticarial and transient skin irritation were reported in few melasma studies. Serious thrombo-embolic side-effects well known to be associated with TA, such as deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction, have not been reported in melasma patients. This reflects use of low dosages of TA and

proper patient selection while offering this treatment modality to melasma patients. Future studies may venture to increase the dose of oral TA in combination with triple regime and assess if response becomes statistically significant. However, the researchers would need to be more vigilant and exercise caution in recruiting patients, performing detailed relevant examination and regular monitoring to avoid serious adverse events.

Melasma is difficult to treat satisfactorily with frequent relapses after cessation of treatment. The urge to enhance response has seen, over the last few years, replacement of milder steroids by potent steroids in triple combinations. The potent topical steroids should not be used for more than 4 weeks, should preferably be tapered to low potent steroids and they, too, to be stopped in another 2 months.⁶ Keeping this in mind, our study duration was limited to 2 months. The Cochrane systematic review⁷ found melasma studies varying greatly in study period durations, ranging from 8 weeks to 10 months. Variation in time reflected the outcome measures of the study. Some studies focused on initiation of lightening of skin pigmentation while others on factors implicated in the maintenance of lightening effect. In addition to topical steroids, non- steroid topical preparations are important adjuvants in melasma treatment. Topical retinoids have been found to be especially useful in photo-damaged and darker skin. Tretinoin 0.025–0.1% and adapalene 0.1% are the preferred preparations. The most common skin bleaching agent worldwide is hydroquinone and historically it has been the gold standard for management of hyperpigmentation.¹⁷

Lack of follow-up is the limitation of our study. Both groups demonstrated statistically significant reduction in MASI scores with treatment. However, melasma has very high relapse rates. Similar to topical agents, the transient effect of TA has been documented in the medical literature. Tan *et al*¹⁴ reported more than 70% of their study patients' melasma relapsed within 2 months of cessation of therapy. We did not include follow-up as there are other factors contributing in relapse of the condition, apart from cessation of skin lightening agents. We postulate that the follow-up period is difficult to assess accurately as different professions, outdoor activities and sun screen applications are potential confounding factors. Daily photo-protection is vital in the management of this therapeutically challenging condition which is characterized by high rate of relapse. The use of broad-spectrum sunscreens is essential. However, due to economic constraints many of the patients may not be able to purchase good quality sunscreens for their routine use, making

it difficult to conduct studies incorporating follow-up periods.

CONCLUSION

Although melasma is considered to be a benign facial pigmentary disorder its management is difficult and often unsatisfactory. Newer therapeutic agents will continue to be explored. We found statistically significant drop in MASI score when melasma is treated with triple regime alone or in conjunction with low dose oral TA. The combination therapy of triple regime and TA further decreased MASI score but it was statistically insignificant. Low dose TA was well tolerated by patients except for few minor side effects. In light of our study results we do not recommend oral TA as a drug for routine management of melasma. However, it may be used in resistant cases as an adjuvant to triple regime, conferring a slight improvement in overall decline of MASI score.

AUTHORS' CONTRIBUTION

AB: Study conception, design, and acquisition, write up, interpretation of data. AR: Study conception, design, manuscript writing, and proof-reading. RUD: supervision of study, proof reading

REFERENCES

1. Taylor SC, Torok H, Jones T, Lowe N, Rich P, Tschen E, *et al.* Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis* 2003;72(1):67–72.
2. Sarkar R, Ailawadi P, Garg S. Melasma in men: A review of clinical, etiological, and management issues. *J Clin Aesthet Dermatol* 2018;11(2):53–9.
3. Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. *J Dermatol Sci* 2007;46(2):111–6.
4. 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.
5. 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;97(7):776–81.
6. Chatterjee M, Vasudevan B. Recent advances in melasma. *Pigment Int* 2014;1(2):70.
7. Rajaratnam R, Halpern J, Salim A, Emmett C. Interventions for melasma. *Cochrane Database Syst Rev* 2010;7:CD003583.
8. Majid I, Haq I, Imran S, Keen A, Aziz K, Arif T. Proposing melasma severity index: A new, more practical, office-based scoring system for assessing the severity of melasma. *Indian J Dermatol* 2016;61(1):39–44.
9. Budamakuntla L, Loganathan E, Suresh D, Shanmugam S, Dongare A, Prabhu N, *et al.* A randomised, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with melasma. *J Cutan Aesthet Surg* 2013;6(3):139–43.
10. Cho HH, Choi M, Cho S, Lee JH. Role of tranexamic acid in melasma patients treated with IPL and low fluence QS Nd: YAG laser. *J Dermatolog Treat* 2013;24(4):292–6.
11. Lee JH, Park JG, Lim SH, Kim JY. Localized Intradermal Microinjection of Tranexamic Acid for Treatment of Melasma in Asian Patients: A Preliminary Clinical Trial. *Dermatol Surg* 2006;32(5):626–31.
12. Kam D, KC S, Amatya A, Razouria E, Timalisina M. Oral Tranexamic Acid for the Treatment of Melasma. *Kathmandu Univ Med J* 2014;10(40):40–3.
13. Song M, Park JM, Kim HS, Ko HC, Kim BS, Kim MB. Tranexamic acid for treatment of melasma in Korean patients: a preliminary clinical trial. *Pigment Cell Melanoma Res* 2014;27(5):e968.
14. Tan AW, Sen P, Chua SH, Goh BK. Oral tranexamic acid lightens refractory melasma. *Australas J Dermatol* 2017;58(3):e105–8.
15. Padhi T, Pradhan S. Oral tranexamic acid with fluocinolone-based triple combination cream versus fluocinolone-based triple combination cream alone in melasma: An open labeled randomized comparative trial. *Indian J Dermatol* 2015;60(5):520.
16. Pabinger I, Fries D, Schöchl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. *Wien Klin Wochenschr* 2017;129(9–10):303–16.
17. Grimes PE, Ijaz S, Nashawati R, Kwak D. New oral and topical approaches for the treatment of melasma. *Int J Womens Dermatol* 2018;5(1):30–6.

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