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Original Research Article

Comparative study of oral tranexamic acid and triple combination versus tranexamic acid through microneedling in patients of melisma

Vishal Wali, Hemangi Parwani*

Department of Dermatology, Venereology and Leprology, Basaveshwara Teaching and General Hospital, Kalaburagi, Karnataka, India

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***Correspondence:**
Dr. Hemangi Parwani,
E-mail: hemangi.parwani903@gmail.com

ABSTRACT

Background: Melasma can be difficult to treat due to the refractory and recurrent nature of condition. The aim of this study is to compare and evaluate the efficacy of oral tranexamic acid and triple combination versus tranexamic acid through microneedling in patients of melisma.
Methods: This is a prospective study with a sample size of 20, 10 in each treatment arm.10 patients (group-A) were given topical triple combination to apply daily at night and along with oral tranexamic acid 250 mg twice a day, while in the other arm (group-B), 10 patients were given procedural treatment of microneedling with tranexamic acid (4 mg/ml). Patients were followed up for 3 consecutive months. Clinical photograph was taken after each visit, and a modified melasma area and severity index was performed at the beginning and end of the treatment.
Results: According to melasma area and severity index, improvement in group-A was 65% as compared to 33% in group-B.
Conclusions: Triple combination is known as gold standard treatment in melasma, but because of its long term steroidal and tretinoin side effects we can consider microneedling with TXA as an adjuvant treatment.

Keywords: Camparative study, Melasma, Microneedling, Tranexamic acid

INTRODUCTION

Melasma is the most common cause of facial melanosis and is manifested by hyperpigmented macules on the face which become more pronounced after sun exposure. It accounts for 2.5%-4% of patients seen in dermatology clinic in South East Asia.[1,2] Increased pigmentation is almost invariable in pregnancy and is most marked in brunettes. Melasma is frequently seen in women on oral contraceptives. Mostly starts between the ages of 20 and 40 years. Up to 10% of cases of melasma occur in men. More common in light brown skin types, particularly latin Americans and those from the Middle East or Asia. Several factors have been linked to melasma, among them UV exposure and hormonal factors appear to be the most significant. Local or diffuse hyperpigmentation can be seen in a subset of women, probably due to these hormonal factors. Pregnancy and oral contraceptives have been linked to increased skin pigmentation. It has been speculated that this is due to increased levels of oestrogen and progesterone stimulating the activity of melanocytes. In the context of pregnancy, melasma is regarded as a normal physiological change, along with darkening of the nipples and linea nigra. Treatment of melasma can be difficult due to the refractory and recurrent nature of the condition. Different skin depigmentation formulations can be used and contain one or several active compounds. However, there are many ongoing studies aiming to find more effective and safe treatment.

METHODS

A prospective, randomized study was conducted on 20 clinically diagnosed melasma patients, with 10 patients in each group of the study. Patients were selected among those coming for treatment of various dermatoses in outpatient department of DVL, Basaveshwara Teaching and General Hospital during period of September 2017 to September 2018, after obtaining approval from institutional ethical committee. In this study patients with facial melasma belonging to both sexes between age group 20-45 years were selected. Pregnant, lactating females and patients with a history of hypertrophic scars, keloids, bleeding disorder, use of anticoagulant, oral contraceptives pills and patient who refuse to come for follow up were excluded from the study.

After taking complete history, bed site examination and baseline investigations, patients were randomly included in each group of the study. Bed site examination includes Woods lamp examination to classify the type of melasma. Modified melasma area and severity index (MASI) was recorded to assess the severity of melisma (Table 1) in the patient and to compare the improvement on every visit. Three parameters are considered in calculating the MASI score and i.e., darkness (D), homogenecity (H) and area (A) of the pigmentation. Multiplication factor for forehead, chin and cheeks are 0.3, 0.3 and 0.1 respectively. Therefore total MASI score is calculated by using the following formula i.e., 0.3(D+H)A+0.3(D+H)A+0.3(D+H)A+0.1(D+H)A. The baseline investigations like liver function test, renal function test, coagulation profile were done before initiation of the study.

Patient on group A were given oral tranexamic acid 250 mg twice a day with daily application of topical triple combination at night.

Patient on group B requires pre-procedure preparation and that includes, gentle cleansing of the skin and then application of topical EMLA cream over the area to be treated for 45 to 60 minutes. Meanwhile 4 mg/ml of tranexamic acid was prepared as it is available as 5 ml ampoule containing 500mg of the drug. About 1 ml of the tranexamic acid was withdrawn from the ampoule and was diluted with 25ml of distilled water to make it a concentrate of 4mg/ml. Prepared tranexamic acid (4mg/ml) was applied over the pigmented area with the peeling brush, then skin was stretched and microneedling was carried out in vertical, horizontal and both diagonal directions for about 4-5 times in above said directions. Ice packs were applied over the treated areas. The patient was instructed to follow the strict photo-protective measures.

Mironeedling was done with dermaroller with needle length of 2.5 mm and diameter of 0.25 mm. It was studded with 192 fine needles of medical graded stainless steel. This procedure was done three times at monthly interval (0, 4 and 8 weeks) and followed up for further 3 months at monthly interval. To assess the clinical response, clinical photographs were taken at the beginning of the therapy and then serially. MASI score was performed at monthly intervals. Any complications and side effects were also noted during these follow ups.

Statistical analysis was done with t-test using SPSS version 20.0 and p value <0.05 was taken as significant.

Table 1: Grading of the melasma area and severity index with its three parameters.

Area (A)	0=No involvement; 1=<10% involvement; 2=11-29% involvement; 3=30-49% involvement; 4=50-69% involvement; 5=70-89% involvement; and 6=90-100% involvement.
Darkness (D)	0=normal skin color; 1=barely visible hyperpigmentation; 2=mild hyperpigmentation; 3=moderate hyperpigmentation; 4=severe hyperpigmentation.
Homogenity (H)	0=normal without evidence of hyperpigmentation; 1=specks of involvement; 2=small patchy areas of involvement <1.5 cm diameter; 3=patches of involvement >2 cm diameter; 4=uniform skin involvement without any clear areas.

RESULTS

The study with 10 patients in each group, 62% of male patient belonged to the age group of 25-30 years, while 58% of female patients were between 25-35 years age group (Figure 1A). The number of women was more compared to men in group A i.e., 70% female patients while in group B there were equal distribution of female and male patients (Figure 1B). All patients had Fitzpatrick skin type 4 or 5. Patients had mixed pattern of melasma, the distribution of melasma was either centrofacial or malar. None of the patients were on drugs. Mean melasma area and severity index score of the patients at the beginning and end of the trial with percentage improvement is shown in (Figure 2). Mean decrease in melasma area and severity index score in group A was significantly higher than in group B. Figure 3 and 4 shows example of clinical improvement in some of the patients.

No major side effects were observed except for mild pain and erythema in microneedling with tranexamic acid group patients, which lasted for 2-3 days. In group A, no side effects were noted. There was no change in coagulation profile at the end of 3 months. At 3 months

of follow up, 4 patients in group A and 3 patients in group B complaint of repigmentation. There was also the history of not using any kind of photo protection which was adviced.

- Average MASI before treatment: Group A– 12.38%; Group B– 15.32%.
- Average decrease in MASI at the end of treatment: Group A– 4.07%; Group B– 10.35%.
- Percentage decrease in MASI at the end of treatment: Group A– 67.12%; Group B– 32.44%.

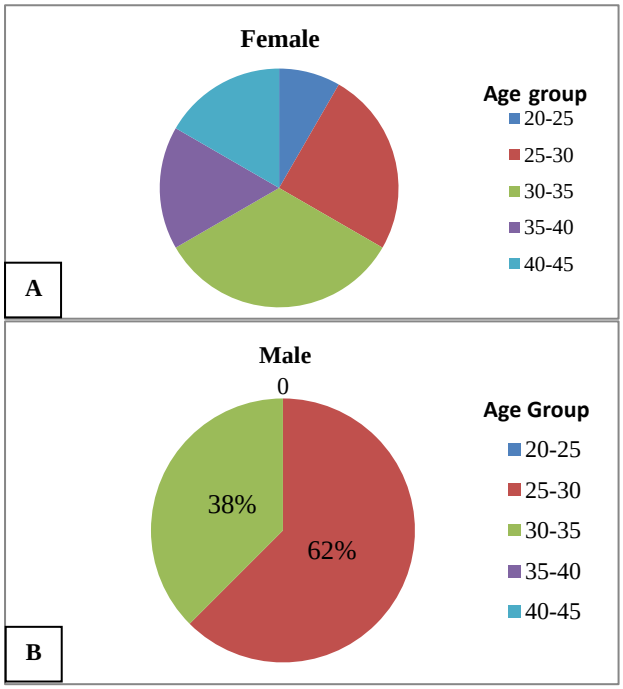

Figure 1: Percentage of female (A) and male (B) patients in different age groups.

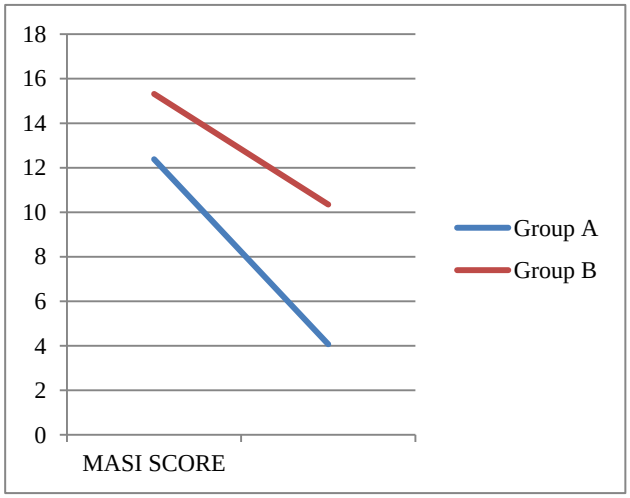

Figure 2: Mean MASI score of the patient before and after treatment in both the groups.

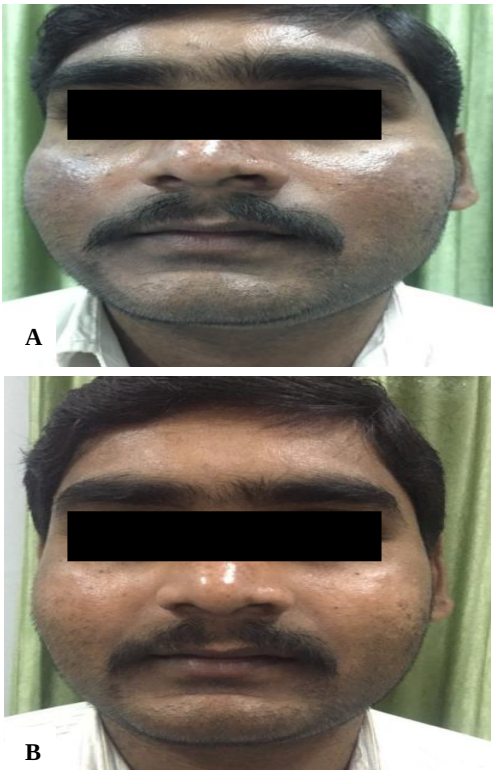

Figure 3 (A and B): Group A patient (clinical improvement in pigmentation after 12 weeks).

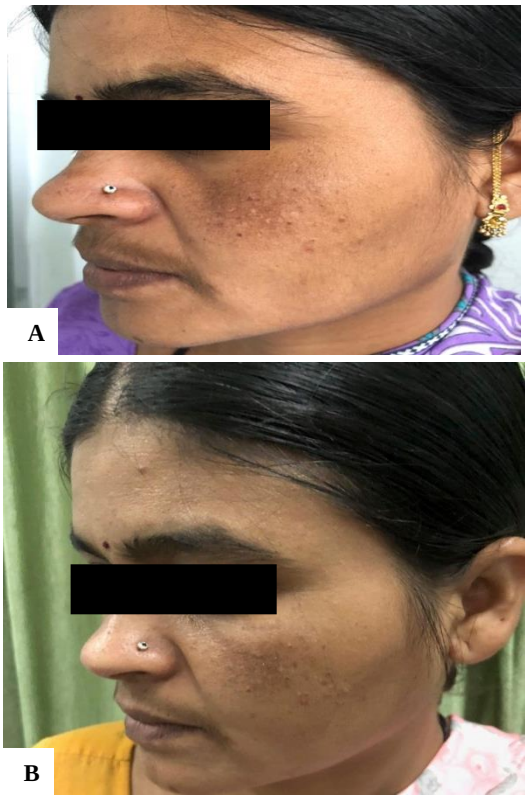

Figure 4 (A and B): Group B patient (clinical improvement in pigmentation after 12 weeks).

DISCUSSION

One of the most popular topical therapy for melasma worldwide is the triple combination regimen known as Kligmans formula. And considering its side effects tranexamic acid can be used as potentially a safe, effective, and promising therapeutic agent for the treatment of melasma. Tranexamic acid is possibly the only treatment of melasma that can prevent the activation of melanocyte by sunlight, hormonal influence, and injured keratinocyte (after UV radiation, chemical peeling, IPL, laser) through the inhibition of the plasmin activator system by preventing the binding of plasminogen to the keratinocytes, which ultimately results in decreased free arachidonic acid and a diminished ability to produce prostaglandins, which in turn decrease melanocyte tyrosinase activity.[3-8] Thus tranexamic acid has been demonstrated with depigmenting properties and combining this novel agent (oral, microneedling) with other modalities of treatment has shown promising results. In addition to this action, tranexamic acid exhibits antiallergic and anti-inflammatory effects on various skin diseases such as angioedema.[11]

Microneedling technology offers a minimal invasive and painless route of drug delivery.[9] This technology involves the creation of channels in the skin with micron-sized dimensions, thereby enabling the delivery of broad range of therapeutic molecules including proteins which would not otherwise cross intact skin.

Triple combination therapy, comprise of hydroquinone, retinoid and a corticosteroid, is a highly effective and safe treatment for melasma. A corticosteroid was introduced to this treatment to reduce the inflammation as it is a side effect of both hydroquinone and tretinion, in addition to this advantage, it also inhibits the melanocyte metabolism.[10,11] This combination of hydroquinone 5%, tretinion 0.1% and dexamethasone 0.1% was first introduced in 1975 and termed the Kliegman formula after its invention. Recently, the US food and drug approach has approved a modified combination of Kligman formulation, containing 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide. This association has proved its efficacy without significant side effects. But still considering the atrophogenic and other side effects of individual component of triple combination regimen, concomitant use of oral tranexamic acid would help in decreasing the duration of topical steroid based treatment. Since both group A and group B study showed 67.12% and 32.44% reduction in MASI score respectively, and simultaneously we also know the long-time side effects of use of any one treatment as disease has recalcitrant characteristics, therefore we can consider microneedling with tranexamic acid as an adjuvant treatment or as a sequential therapy and triple combination and oral tranexamic acid 250 mg twice a day being the mainstay of therapy.[11] With this approach long term side effects of individual drug can be prevented, duration of treatment taken can be decreased and patient satisfaction can also be achieved.

In the study conducted by Karn et al from Nepal, clinical effect of oral tranexamic acid combined with triple combination was compared with triple combination alone. Statistical analysis was done between the groups. Fall in MASI was significant at 8 weeks in patient receiving both oral tranexamic acid and treatment. Seong et al used neonatal foreskin cultured melanocytes to demonstrate effects of tranexamic acid after UVB irradiation and showed a significant inhibition of multiplication of melanocyte, decrease in tyrosinase activity, tyrosinase related peptide trp1/2, and melanin content. Zhu et al. reported that increasing the treatment duration was more effective than increasing the dose of txa.[12,13] The duration of therapy has varied in different studies ranging from 6 weeks to a maximum 6 months. In 2008 Mafune et al used 750 mg oral tranexamic acid two tablets three times a daily.[14]

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