

Original Research Article

A comparative study between micro needling with modified Kligman regimen versus micro needling with tranexamic acid in melasma patients

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ABSTRACT

Background: Melasma is common, acquired disorder of hyperpigmentation, with female predominance and occurrence of facial involvement mostly. Various modalities of treatment are available including topical, oral and procedural therapies.

Methods: Total 46 patients of melasma were studied. They were divided in two groups A and B. Micro needling with derma roller 1.5mm was done once in a month for 3 months. Group A patients received topical Modified Kligman regimen daily at night, while group B patients were advised topical tranexamic acid daily. Topical sunscreen was advised in both group patients. Patients were evaluated clinically and by Modified MASI score, and followed up for 3 more months after completion of treatment.

Results: Female predominance was noted with most common age group being 25-40 years. Epidermal type of melasma was common. Centro-facial type of distribution was found mostly in patients. Significant decrease was noted in modified MASI score ($p < 0.05$) which was more and rapid in group A patients.

Conclusions: Modified Kligman regimen has better efficacy but tranexamic acid is safer with lesser side effects. In spite of various treatment arms, melasma is still challenging.

Keywords: Melasma, Micro needling, Modified Kligman regimen, Tranexamic acid

INTRODUCTION

Melasma is also known as chloasma or mask of pregnancy. It is a common, acquired condition of symmetric hyperpigmentation with higher prevalence in females and darker skin types. It is characterized by irregular, light or dark brown macules or patches in sun-exposed areas symmetrically involving the face, neck and less commonly, the hands and the forearms.¹ Exact pathogenesis of melasma is not known but many etiological factors like light exposure, hormonal influences, family history have been implicated in its

causation and aggravation.^{2,3,4} Histopathologically three presentations are there epidermal, dermal and mixed. Different treatment modalities such as topical therapy, systemic therapy and various procedural therapeutic options have been utilized in different studies with varying but less satisfactory outcomes.^{5,6}

Derma roller is one of the instruments used for micro needling, studded with 192 fine microneedles in eight rows, 0.5-2 mm in length and 0.1mm in diameter. Micro needling helps in transdermal drug delivery and induces neovascularization and neocollagenesis. After topical anaesthesia and area preparation, rolling is done 10-20

times in horizontal, vertical, and both oblique directions till pinpoint bleeding occurs.

Tranexamic acid is a synthetic derivative of amino acid lysine. Probable mechanism of action is by preventing the activation of melanocytes from ultraviolet (UV) light, hormones and injured keratinocyte through the inhibition of plasminogen activator system present in epidermal basal cells and keratinocytes. It also reduces melanocyte tyrosinase activity by suppressing the production of prostaglandins and has an additional effect on the dermal blood vessels as it decreases the angiogenesis via inhibition of vascular endothelium growth factor (VEGF). By all these actions it not only improves melasma, but may also reduce the chances of recurrence.^{7,8,9}

Triple combination cream, modified Kligman regimen, contains hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01%. Still it remains the gold standard treatment for melasma. In our study we have done evaluation of efficacy as well as safety between micro needling with modified Kligman regimen versus micro needling with tranexamic acid in melasma patients.

Aim and objectives

Aim of our study is, to compare therapeutic efficacy and safety between micro needling with modified Kligman regimen and micro needling with tranexamic acid in patients of melasma.

METHODS

After approval of ethics committee, study of 46 patients with melasma was carried out at tertiary care center in department of dermatology, venereology and leprosy of Surat Municipal Institute of Medical Education and Research, Surat from April to October 2019. After obtaining informed written consent, adult patients between 18 to 50 years of age were included in the study. By wood's lamp examination and dermoscopy of lesions, diagnosis was confirmed and melasma was classified under different categories. Pregnant/lactating females, patients on hormone replacement therapy/OC pills/anticoagulants, H/O bleeding disorders, concomitant use of and H/O any other depigmenting treatment in previous 1 month were excluded from the study. All patients were divided in two groups-group A (23 patients) and group B (23 patients). In both groups micro needling was done with derma roller of needle length 1.5mm under topical anesthesia, in all directions until discrete punctuated bleeding occurred. After procedure, patients were advised to apply topical antibiotic ointment for 3 days. Micro needling was done at interval of 4 weeks for 3 sessions. In group A, patients were instructed to use daily topical sunscreen and modified Kligman regimen (0.05% tretinoin, 4% hydroquinone and 0.01% fluocinolone acetonide) at night.¹⁰ While in group B, patients were asked to apply daily topical sunscreen and

topical tranexamic acid cream 5% at night. Patients were followed up monthly for total of 6 months and assessed by modified MASI score also.¹¹ Data analysis was done by using STATA version 14.2 and the Wilcoxon signed rank test was used to compare the means of MASI scores.

RESULTS

Total 46 patients of melasma were studied which were divided into two groups equally. According to the age distribution, gender, Fitzpatrick skin types, type of melasma and MASI score, patients were matched in both groups. In patients of both groups, micro needling was performed at monthly interval for 3 sessions. Additionally, in group A, patients were asked to apply modified Kligman regimen daily at night, while in group B patients, topical tranexamic acid 5% cream was applied daily for 3 months. Assessment of patients was done on monthly basis for 3 more months after completion of treatment. Daily topical sunscreen was prescribed simultaneously in both groups till study completed. Apart from the clinical assessment, modified MASI score calculation, dermoscopic examination were performed which were compared by images taken.

Majority of patients 61% were between 25-40 years of age. Age distribution has been mentioned in (Table 1). Female preponderance was noted in both the groups (as shown in Table 2). All patients were having Fitzpatrick skin type IV or V.

Table 1: Age distribution of melasma patients.

Age (in years)	Group A	Group B
<25	2	2
25-30	6	4
30-35	5	4
35-40	4	5
40-45	4	5
>45	2	3

Table 2: Gender wise distribution of melasma patients.

Gender	Group A	Group B	Total
Female	18	17	35
Male	5	6	11

Table 3: Distribution of patients based on wood's lamp and dermoscopic examination.

Type of melasma	Group A	Group B
Epidermal	17	18
Dermal	1	2
Mixed	5	3

Based on wood's lamp examination and dermoscopy, epidermal type of melasma was the most common to be found, which is shown in (Table 3).

According to the region involved, centro-facial type of melasma was the most common type to be found followed by malar and mandibular types (Table 4).

Table 4: Distribution of patients according to the site involved.

Type of Melasma	Group A	Group B
Centro-facial	14	16
Malar	8	7
Mandibular	1	0

Table 5: Mean modified MASI score and p value.

Duration	Group A (mean ±SD)	Group B (mean ±SD)	P value
Day 0	7.56±1.30	7.68±1.17	-
Day 30	4.05±1.25	5.01±0.91	0.0005
Day 60	2.37±0.88	3.55±0.72	0.0003
Day 90	1.31±0.59	2.29±0.69	0.0031
Day 120	1.25±0.21	2.21±0.34	0.0004
Day 150	1.22±0.55	2.13±0.11	0.0003
Day 180	1.15±0.26	2.08±0.48	0.0002

Modified MASI score was recorded in all patients before and after treatment. Significant decrease was noted in modified MASI score ($p < 0.05$) in comparison to pre-treatment evaluation (Table 5). But more significant and rapid reduction was observed in group A patients (Figure 1). Subjective improvement was also noted by patients which was described in form of fair/good/excellent response.

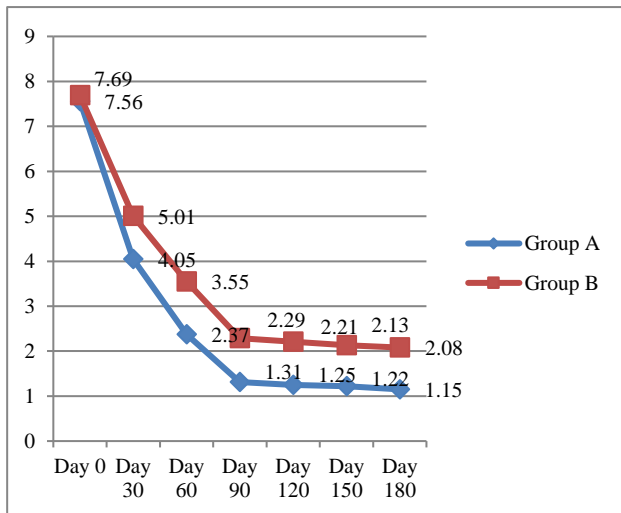


Figure 1: Reduction in modified MASI score.

No significant adverse effect was observed except transient erythema with burning sensation and irritation in both the groups. These adverse effects were seen more in group A patients (Figure 2). While in group B patients they were mild. Erythema and mild oedema were

developed in patients immediately after micro needling which was relieved within 2-3 days.

Overall, significant reduction was noted more in group A patients, but adverse effects were milder in group B patients.

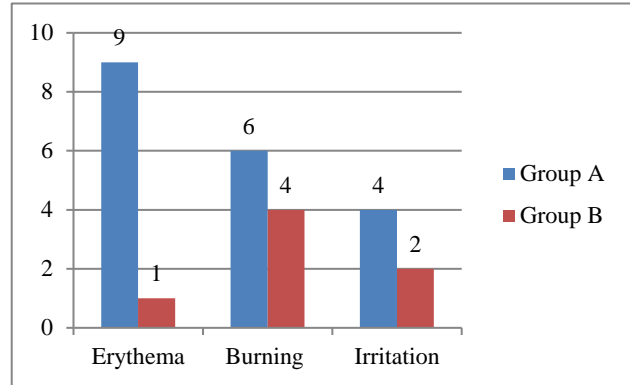


Figure 2: Showing detail of adverse effects in both groups.

DISCUSSION

Micro needling is relatively new, simple, safe, effective, and minimally invasive therapeutic technique now a days. By this technique micro punctures are created which produce controlled skin injury without actually damaging the epidermis. These microinjuries lead to minimal superficial bleeding and set up a wound healing cascade with release of various growth factors such as platelet derived growth factor (PGF), transforming growth factor alpha and beta (TGF- α and TGF- β), connective tissue activating protein, connective tissue growth factor, and fibroblast growth factor (FGF).⁵ It also enhances the transdermal delivery of various drugs across the skin barrier as it bypasses the stratum corneum and deposits the drug directly up to the vascularized dermis.¹²

TXA (trans-4-aminomethylcyclohexane carboxylic acid) is a synthetic lysine amino acid derivative which controls and diminishes the dissolution of haemostatic fibrin. TXA exerts its antifibrinolytic effects by reversibly blocking lysine binding sites on plasminogen. This prevents plasmin from interacting with lysine residues on the fibrin polymer, leading to subsequent fibrin degradation.^{13,14} UV exposure increases plasminogen activator production by epidermal keratinocytes in situ.¹⁵ TXA also prevents the binding of plasminogen to the keratinocytes and thus inhibits UV-induced plasmin activity in keratinocytes. Plasmin is a protease that enhances the intracellular release of arachidonic acid (AA) and alpha-melanocyte-stimulating hormone (a-MSH). AA and a-MSH have the property of stimulating melanogenesis by melanocytes. Tranexamic acid being a plasmin inhibitor depletes the keratinocyte pool of AA involved in UV-induced melanogenesis.¹⁶⁻¹⁸

Modified Kligman regimen still remains the gold standard treatment of melasma as it contains depigmenting agent like hydroquinone also

In present study, the efficacy and safety of micro needling with topical 5% TA was compared with micro needling and triple combination therapy in the treatment of melasma. Total 46 patients were studied. Majority of patients were in the age group of 25-40 years in our study. While 30-50 years of age group was common in study done by Budamakuntla et al and 21-30 years age group was common in study done by Khuraiya et al.^{7,19}

Female predominance was observed in our study 35 females and 11 males which was similar to the study done by Budamakuntla et al with a greater number of females 54 than males 6 in both the treatment arms, and in study done by Achar also.^{7,20}

Centro-facial type of melasma was most commonly found in our study in 65.2% patients. In study done by Budamakuntla et al also, 68.33% patients were having centro-facial type of melasma. In another study done by Oluwatobi et al also, major clinical pattern was centro-facial seen in 50-80% of cases.²¹ On the basis of wood's lamp and dermoscopic examinations, epidermal type of melasma was the most common type.

In our study we found superior result in micro needling with modified Kligman regimen group (group A) with 0.98 of more reduction as compared to micro needling with tranexamic acid group (group B). In group A, mean modified MASI score at day 0 was 7.56 ± 1.30 , 1.31 ± 0.59 at day 90 and 1.15 ± 0.26 at day 180 at the completion of study period. While in group B, mean modified MASI score was 7.68 ± 1.17 at day 0, 2.29 ± 0.69 at day 90 and 2.08 ± 0.48 at day 180.

A comparative study of topical 5% tranexamic acid and triple combination therapy of 25 patients was done by Khuraiya et al, in which equal result was achieved in both groups with lesser side effects but delayed response was achieved in topical 5% tranexamic acid group and showed a potential newer alternative of modified Kligman regimen group. This finding was somewhat comparable to our study.¹⁹

Another study by Menon et al showed 0.33 of more reduction of MASI score in micro needling with tranexamic acid group as compared to micro needling with vitamin C group at the interval of 8 week.²²

In another comparative study of 60 patients of tranexamic acid microinjections and tranexamic acid with micro needling done by Budamakuntla et al, 35.72% and 44.41% improvement in mean MASI score was seen respectively at the end of 8 week which showed that micro needling technique gives better result compare to microinjection group.⁷

Another randomized, split face study by Yang et al was done where one side of face was treated with topical TA 0.5% along with functional microarray of microneedles and other half was control, treated with a sham device plus topical TA at 4 weekly intervals (0, 4, 8 and 12 weeks). It showed that pre-treatment with a functional microarray of microneedles significantly increase the effectiveness of topical TA in treating melasma, and the combined therapy is safe and painless, without obvious side effects.²³

A study of 100 patients conducted by Sharma et al, comparing the therapeutic efficacy of 250 mg twice daily oral TA vs. local infiltration of TA of 4 mg/ml given at 4 weekly intervals (0, 4, 8 and 12 weeks) showed both treatment methods were equally effective, with an average reduction of MASI at 12 weeks of 77.96 ± 9.39 in group A and 79.00 ± 9.64 in group B. This study claims topical intradermal TA to be as effective as oral TA.²⁴

In a pilot study done by Lima et al, micro needling was done at interval of 30 days for 2 sessions followed by application of triple combination cream and broad-spectrum sunscreen. It showed reduction of MASI score from 37.1 to 11 (70%), 13% increase in luminance and 55% decrease in MELASQOL at day 45.²⁵

A prospective study of patients treated with topical lightening agents, rucinol and sophora-alpha, alone compared to use of those topicals with micro needling demonstrated a significant improvement in MASI scores when administered with microneedling.²⁶

TCT (triple combination therapy) with HQ 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% was superior to HQ 4% monotherapy in improving melisma.²⁷

There are many studies of topical uses of TA in various concentrations for melasma. Studies by Kondou et al, Ebrahimi et al and Kim et al with topical 2%, 3% and 2% TA emulsion respectively showed significant improvement at the end of the study and no significant side effect was recognized.^{28,29}

Melasma is a very distressing disease especially in females which causes psychological impact on patients. The exact mechanism is not known but various factors act as aggravating factors. Though there are many treatments available, none of the treatment is satisfactory.

CONCLUSION

In spite of availability of many treatment modalities, melasma still remains a challenging entity yet. It also causes psychological impact which may be frustrating and disturbing the routine life of patient. Response to treatment varies depending upon the clinical presentation, extent of involvement, gender, etiology, modality of treatment, compliance of patient etc. So, it is important to implicate multimodal therapeutic approach. There is an

emergence of new topical, oral, procedural, and combination therapies in last few years which are promising. To conclude, modified Kligman regimen has better efficacy but tranexamic acid is safer with lesser side effects such as erythema, irritation, burning.

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