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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/16429
DOI URL: http://dx.doi.org/10.21474/IJAR01/16429

RESEARCH ARTICLE

"A COMPARATIVE STUDY OF EFFICACY BETWEEN MODIFIED KLIGMAN'S FORMULA AND DERMAROLLER WITH TRANEXAMIC ACID IN TREATMENT OF MELASMA"

Dr. Vishal Wali[1] and Dr. Prajwalkumar S.[2]

1. Professor, Department of DVL, M.R. Medical College, Kalaburagi.
2. Postgraduate, Department of DVL M.R. Medical College, Kalaburagi.

Manuscript Info

Manuscript History
Received: 15 January 2023
Final Accepted: 18 February 2023
Published: March 2023

Abstract

Background: Melasma is a common hyperpigmentation disorder characterised by symmetrical, marginated, light to dark brown patches that occur mostly in sun exposed areas of skin, mostly on the face, occasionally affecting the neck and forearms. The exact cause of melasma is unknown, however many factors have been implicated in its etiopathogenesis, mainly sunlight, genetic predisposition, pregnancy and certain drugs. Among the factors mentioned above, excessive sun exposure is the most common cause.

Objectives: To compare the therapeutic efficacy of topical tranexemic acid (TXA) with Microneedling versus topical modified kligman's regimen in the treatment of melasma.

Methodology: Patients diagnosed with Melasma of the face attending the Outpatient department Department of Dermatology, explained about the study procedure and benefits of the study before enrolment. Patients fulfilling the inclusion criteria were recruited for the study. Written informed consent was obtained from all patients who are willing to participate in the study in a prescribed format and well explained in the regional language before starting the study. Detailed medical history, clinical examination and essential lab investigations were performed on the participants. This study was conducted on 60 patients with melasma, randomly divided into two groups. In group A, each patient was subjected to a series of 3 sessions of skin microneedling and TXA application, whereas in group B , modified kligman's regimen applied daily in the night .

Results: At the end of 12 weeks melasma area severity index(MASI) score was significantly decreased in both groups with statistically significant higher reduction of score in study group compared with control group . No significant adverse effect were observed in both treated sides.

Conclusion: The result of the study show that topical tranexemic acid along with Microneedling could be safe and effective in melasma treatment.

Corresponding Author:- Dr. Vishal Wali
Address:- Professor, Department of DVL, M.R. Medical College, Kalaburagi.

Introduction:-

Melasma is a common hyperpigmentation disorder characterised by symmetrical, marginated, light to dark brown patches that occur mostly in sun exposed areas of skin, mostly on the face, occasionally affecting the neck and forearms.The word melasma is derived from the Greek word "melas" meaning black and refers to its brownish clinical presentation. It accounts for 0.25 to 4% of the patients seen in dermatology clinics in South East Asia, and is the most common pigmentary disorder among Indians.

The exact cause of melasma is unknown, however many factors have been implicated in its etiopathogenesis, mainly sunlight, genetic predisposition, pregnancy and certain drugs (1, 2). Pregnancy is also a causative factor, because 20% of the pregnant women develops melasma during pregnancy and hardly regresses after pregnancy[3, 4], whereas women receiving oral contraceptives are found to develop melasma in about 38% of the cases. Genetic factors are also involved as more than 30% of patients with melasma have a family history and melasma has been reported in identical twins without affecting other siblings (5). The association of melasma with endocrinopathies and autoimmune thyroid diseases has also been suggested.On the basis of Wood's lamp examination melasma is classified into 4 types namely epidermal, dermal, mixed and indeterminate type. The epidermal type showing intensification under Wood's lamp, is the most common type. In the dermal type there is no pigment intensification. In the mixed type the pigmentation becomes more apparent in some areas, which in others there is no change. Indeterminate type is where the pigment is apparent in the Wood's light, in individuals with skin type VI. The clinical patterns of melasma include centrofacial, malar and mandibular.

Conventional treatment of melasma includes elimination of any possible causative factors coupled with use of a sunscreen and hypopigmenting agents like hydroquinone, kojic acid, azelaic acid, deoxyarbutin,ascorbicacid,singly, or in combination like the Kligman'sformula.Often these agents are used with other therapies like chemical peeling with glycolic acid or trichloacetic acid, dermabrasion, and laser therapy. Despite these measures, treatment of this recalcitrant disorder is often difficult and unsatisfactory.

The present study was undertaken to compare the therapeutic efficacy of some currently available modalities and to assess their safety in the treatment of melasma.

Methodology:-

A Randomized, Open label, prospective, interventional, comparative study on 60 patients Visiting Outpatient department of Dermatology, Basaveshwara teaching and general hospital during a period of 1st March 2021 to 31st August 2022.

A detailed history was taken with reference to the onset, duration, progression, family history, obstetric history, drug history, previous treatment, and sun exposure. Dermatological examination of the lesions was carried out with respect to morphology, configuration, distribution and the melasma was categorized into epidermal, dermal or mixed based on wood's lamp examination. The patients were further classified according to the distribution of the lesions into malar, centrofacial, or mandibular. All patients were informed regarding the nature of disease, course, prognosis, and the probable adverse effects of the treatment modalities.The patients were excluded if they had a history of recurrent infection, Pregnant women, Dermatitis on face, Keloid tendency, Bleeding disorders

The study was conducted after obtaining approval from Institutional Ethics Committee.

Patients fulfilling the inclusion criteria were recruited for the study. They were explained about the study procedure and benefits of the study before enrolment. Written informed consent was obtained from all patients who are willing to participate in the study in a prescribed format and well explained in the regional language before starting the study. Consent was also obtained for taking photographs of the lesions. The demographic details of the patients were elicited and recorded. Detailed medical history, clinical examination and essential lab investigations were performed on the participants.

Modified melasma area and severity index (MASI) was recorded to assess the severity of melasma in the patient and to compare the improvement on every visit.

The severity of melasma in each of the four quadrants (ie. Forehead (F), right malar region (rm), left malar region(lm) and chin(c)) is assessed based on three variables: percentage of the total area involved (A), darkness (D), and homogeneity (H).

A numerical value assigned for the corresponding percentage area involved is as follows:
0=no involvement;
1=<10% involvement;
2=10-29% involvement;
3=30-49% involvement;
4=50-69% involvement;
5=70-89% involvement;
6=90-100% involvement.

The darkness of the melasma (D) is compared to the normal skin and graded on a scale of 0 to 4 as follows:
0=normal skin colour without evidence of hyperpigmentation;
1=barely visible hyperpigmentation;
2=mild hyperpigmentation;
3=moderate hyperpigmentation;
4=severe hyperpigmentation.

Homogeneity of the hyperpigmentation (H) is also graded on a scale of 0 to 4 as follows: 0=normal skin colour 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).

To calculate the MASI score, the sum of the severity grade for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial quadrants (10-30%).

Total MASI score: Forehead 0.3 (D+H)A + right malar 0.3 (D+H)A + left malar 0.3 (D+H)A + chin 0.1 (D+H)A the maximum score is 48 and the least 0.

In Group A (Study group), 30 patients were subjected with Microneedling with tranexamic acid. Topical anesthesiawas applied for 45 min before the intervention. Meanwhile 4 mg/ml of tranexamic acid was prepared as it available as 5 ml ampoule containing 500mg of the of the drug. About 1ml of the tranexamic acid was applied over the pigmented area with the help of peeling brush . An instrument (dermaroller) with needle length of 1.5 mm was used. The treatment was proceeded with back and forth movements, approximately 10 times in four directions, drawing four bands that overlapped, resulting in a diffuse erythema and discrete punctuated bleeding. Patients were instructed to use daily the topical sunscreen and depigmentating cream (0.05% tretinoin + 2% hydroquinone + 0.01% floucinoloneacetonide) at night. The same procedure was carried out for 30 days after the first treatment.

In Group B(Control group), 30 patients were subjected to daily topical sunscreen and depigmenting cream (0.05% tretinoin + 2% hydroquinone + 0.01% floucinoloneacetonide) at night.

Results:-

The study done on 30 patients each Study group had more patients in 21 to 30 years age group. Where as control group had more patients in 31 to 40 years age group.

Basic demographic profile showed no significant difference in the mean age in both the control and study groups. The average age in both the groups was 28. The number of patches and the duration of disease were also comparable in both the groups. The pattern of distribution of melasma follows the “Malar pattern” which is the predominant finding in our study.

Among the women who were recruited, around 15%(9) patients gave history of OCP’s intake for a period of 6 months to 1 year following which they had developed melasmic lesions.

Among our patients, 28% (17) gave family history of first-degree relatives also being affected with Melasma. This finding is compatible with the study done by Sardesai et al which proves that 30% of patients with melasma have positive family history for the disease.(6)

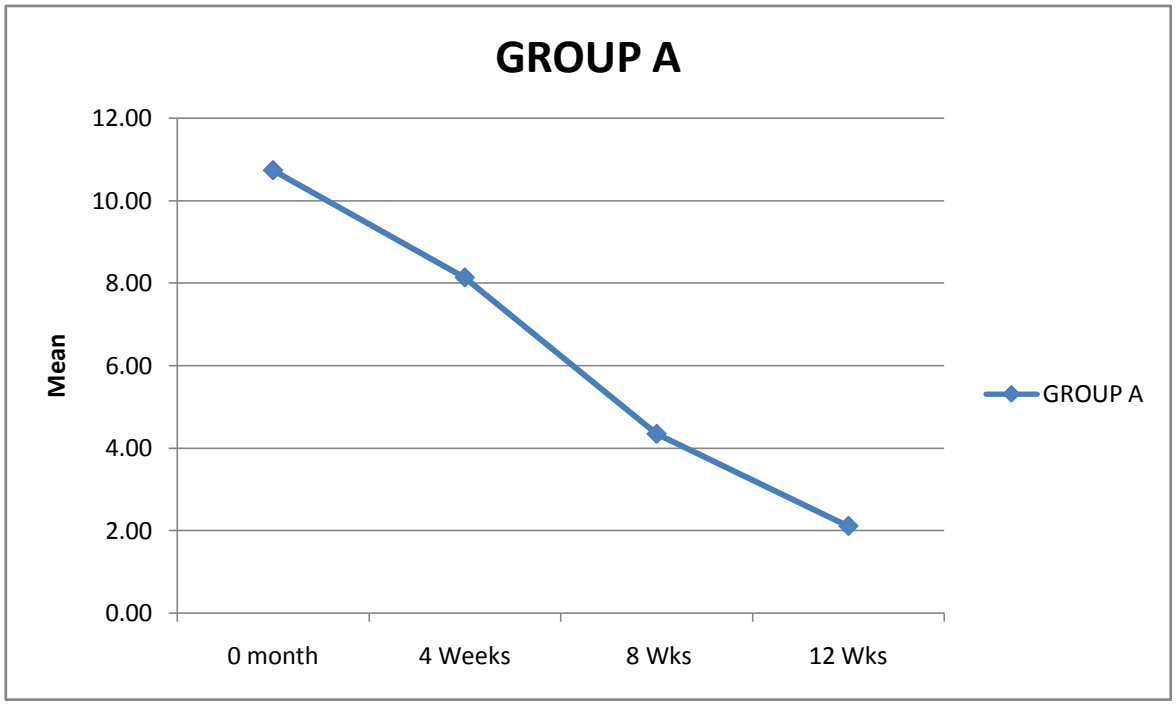
In our study, MASI score was assessed at the baseline, 4 weeks, 8 weeks and at the end of 12 weeks. MASI scores consistently decreased both in the control group and topical Tranexamic acid with microneedling group. There was notable improvement in both the groups and when intergroup comparison was made, the improvement was statistically significant at the end of 12 weeks. The mean MASI score of study group was 8.13 and mean MASI score of control group was 7.97. Comparison between the two groups showed no significant difference in the mean MASI scores at the end of 4 weeks and the 'p' value was 0.924. At the end of 8 weeks, the mean MSI score of study group was 4.34 and the mean MASI score of the control group was 5.29. The results of this intergroup analysis revealed a 'p' value of 0.392. which was not statistically insignificant. Whereas, the intragroup analysis revealed a significant fall in the MASI scores in both the groups. MASI scores, from the baseline to the end of 12 weeks, showed that the mean of study group was 2.21 and the mean MASI score of the control group was 3.80. Results of intergroup analysis showed that there was statistically significant difference between the two groups with the 'p' value of 0.014.. Thus, topical tranexamic acid with microneedling is better in improving the clinical condition than the modified kligman's formula and can also be concluded that the improvement is accelerated when used in combination with other standard treatment.

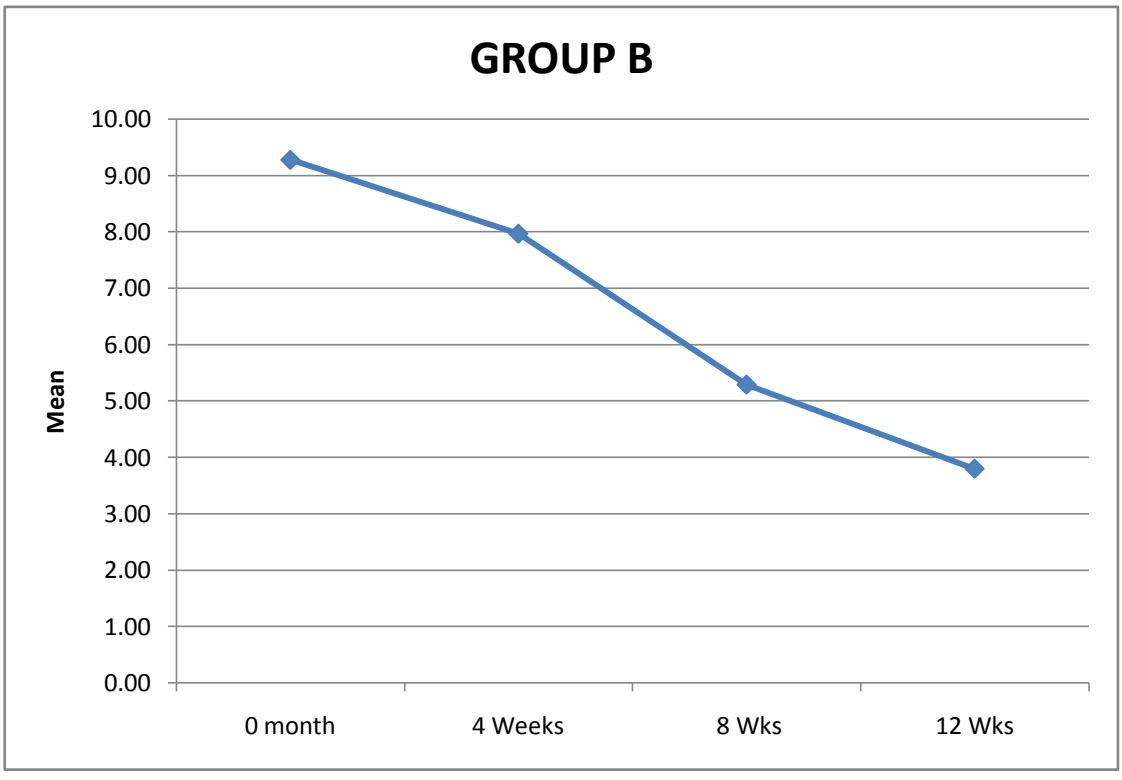
Out of 60 patients recruited in the study 16 patients reported adverse effects due to the medications. Most of the adverse effects were reported spontaneously. Some patients complained erythema after topical application of modified kligman's regimen (0.01% flucinolone,2% hydroquinone,0.05% tretinoin). The most common side effect noted in study group was erythema . A few patients reported with burning sensation. The other participants tolerated well. No life threatening or serious adverse reactions occurred.

In the Control group, Erythema is most common side effect others like dryness, burning sensations are noticed .

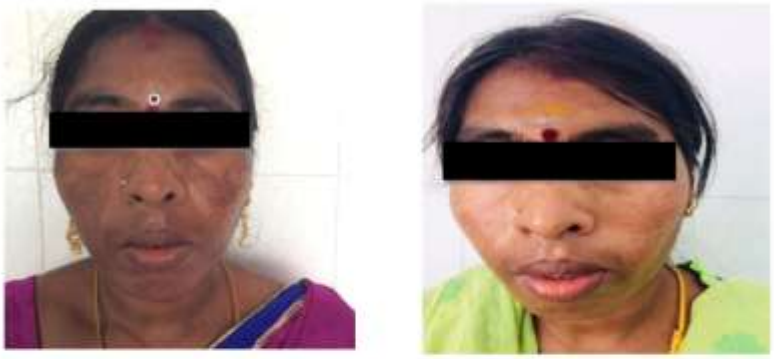
MASI SCORE					
DURATION	**STUDY**		**CONTROL**		**P VALUE**
	MEAN	**SD**	**MEAN**	**SD**	
0 weeks	10.73	10.35	9.28	5.46	0.499
4 weeks	8.13	8.22	7.97	4.53	0.924
8 weeks	4.34	5.23	5.29	3.04	0.392
12 weeks	2.11	2.61	3.80	2.57	0.014

Shows MASI score of study and control groups from baseline to 12 weeks. Intra group analysis showed a significant decrease in mean MASI. Score in both study and control group from baseline to 12 weeks . Between the two groups MASI score is similar in both control and study groups from baseline to 8 weeks . At 12weeks statistically significant improvement is seen in the study group when compared to control group.


GROUP A
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Mean
0 month
4 Weeks
8 Wks
12 Wks
GROUP A

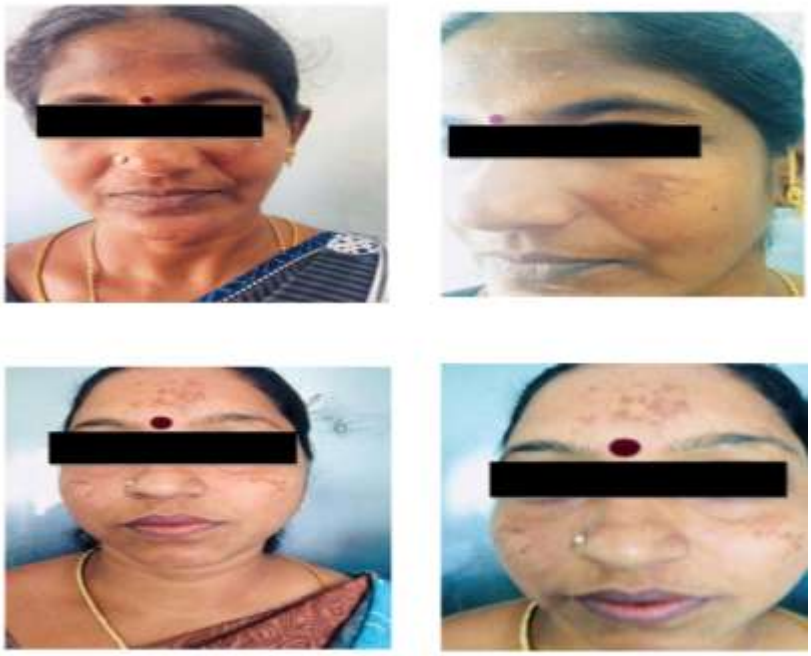

GROUP B
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Mean
0 month
4 Weeks
8 Wks
12 Wks

STUDY GROUP



BASE LINE **12 WEEKS**

CONTROL GROUP



BASE LINE **12 WEEKS**

Discussion:-

In India melasma is one of the common hyperpigmentary skin disorders. The diagnosis of melasma is mainly clinical. In this study, melasma was diagnosed in the similar manner and the severity of the lesions was classified based on the MASI score. In this study, sixty patients were enrolled and randomized into two groups of thirty each (control group and study group). The control group was treated with modified Kligman's regimen (standard treatment) and the study group was treated with Topical tranexamic acid with microneedling.

Tranexamic acid is 4 (aminomethyl) cyclohexane carboxylic acid. It was discovered in the year 1930. It is a synthetic lysine analogue and it is in use as an anti-fibrinolytic agent for more than 30 yrs.Tranexamic acid binds to the plasminogen on the lysine binding site reversibly. The plasmin cannot interact with the lysine residues on the fibrin polymer. Degradation of fibrin occurs thereby producing the anti-fibrinolytic effect [7, 8].

Plasminogen activity is said to be increased by the epidermal keratinocytes when they are exposed to excessive UV light. TXA blocks the conversion of plasminogen to plasmin. TXA prevents the binding of plasminogen to keratinocytes. Plasmin is involved in thintracellular release of Arachidonic acid and alpha- MSH. AA and MSH has the propensity to stimulate melanogenesis by melanocytes. TXA deplete the keratinocytes pool because it binds with the lysine binding sites of plasminogen there by preventing the primary mediators of melanogenesis and hence reduces the hyper-pigmentation (8, 9).

Microneedling is an unique, minimally invasive and simple novel procedure involving controlled and superficial puncturing of the skin using hand held rolling instrument with miniature fine needles. It involves repeatedly puncturing the skin with microneedles to create tiny wounds that trigger the body's natural healing process and this prompts skin cell turnover to lighten pigmentation and remodels the skin by boosting collagen and elastin production.

Modified Kligman's regimen: [10, 11] Its composition are as follows 0.01% fluocinolone, 2% Hydroquinone , 0.05% tretinoin . Hydroquinone is a dihydric phenol which inhibits the tyrosinase enzyme, an initial enzyme in the biosynthetic melanin pathway, there by inhibiting the conversion of dopa to melanin. It also inhibits the synthesis of RNA and DNA in melanocytes. It is also used in conditions like freckling, generalized and senile lentigo, dyschromia, hyperpigmentation due to photosensitisation and other hyperpigmentary disorders.

TretinoinPromotes lysis of keratinocytes and prevents horny cells from binding to each other. It is also shown to prevent and decrease pigmentation and photoaging. Epidermal cell turnover is stimulated and cause peeling. Tretinoin is used in the strength of 0.05%.

Topical Steroids are used topically for a variety of dermatological conditions. Its main action in melasma is due to its anti-inflammatory, immune- suppression, Vasoconstriction and anti- proliferative actions (12, 13)

Erythema which was the common adverse event reported by Torok et al for Modified Kligmans regimen was also commonly noted in our study. Patients were advised not to get exposed to direct sunlight and also to use protective clothing over the face. Burning was the common adverse event due to topical Tranexamic acid with microneedling. No serious adverse events were reported in our study.

Topical Tranexamic acid with microneedling for 12weeks is found to be efficacious in melasma patients. As no serious side effects were reported during this study period, it is considered to be safe in the above said dosages in the melasma patients.

Conclusion:-

Based on this study finding it may be concluded that topical Tranexamic acid used along with Microneedling is found efficacious in the management of Melasma. It showed sustained improvement in patients thus reducing the duration of treatment. Tranexamic acid may be an effective addictive for the management of melasma resistant to routine treatment.

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