VOLUME - 12, ISSUE - 05, MAY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Dermatology

A COMPARATIVE EVALUATION OF THE THERAPEUTIC EFFICACY OF MICRONEEDLING WITH TOPICAL 5% TRANEXAMIC ACID SOLUTION VS MICRONEEDLING WITH TOPICAL 2% KOJIC ACID CREAM IN THE TREATMENT OF MELASMA

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KEYWORDS :

1. INTRODUCTION

Melasma is an acquired hypermelanosis of the sun-exposed areas of skin and is the most common pigmentary disorder in India.[1] It affects millions of people all around the globe and its prevalence varies from 0.25-4% in Southeast Asia to 1.5- 33.3% in Latin American population. [2-4]

Melasma classically presents as symmetrical, hyperpigmented macules with irregular borders appearing as light brown to dark, muddy brown macules and patches on sun-exposed areas such as the face, particularly over the forehead and malar areas, and extra facial sites such as the neck and forearms. This disease is commonly observed in women[3]. It typically affects women of reproductive age with Fitzpatrick skin type IV-VI, though the condition can occur in men also.

Although the precise cause of melasma is still unknown, some commonly identified contributing factors are genetic susceptibility, ultraviolet light exposure, pregnancy, sex hormones, oral contraceptive pills, thyroid disease, cosmetics and phototoxic drugs.[5] Melasma rather than being a rigid linear epidermal problem, is in fact a complex interplay among the epidermal melanocytes, keratinocytes, dermal fibroblasts, and vascular endothelial cells.[6]

Multiple therapeutic modalities have previously been tried and touted as being successful, but the truly effective treatment options for this condition have been few and difficult to achieve. 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, ascorbic acid, singly, or in combination like the Kligman's formula. 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.[6]

Recently, studies have suggested that vascular endothelial growth factor (VEGF) could have a direct influence on melanogenesis which might be a possible cause of hyperpigmentation in melasma.[7] These findings led to the use of plasmin inhibitor, tranexamic acid in melasma, in both oral and topical forms.

Tranexamic acid (trans-4-aminomethyl cyclohexanecarboxylic acid) (TXA) is a synthetic lysine derivative that blocks the lysine site on plasminogen and inhibits fibrinolysis. Topical TXA inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes, which in turn decrease melanocyte tyrosinase activity. [8] TXA is one of the treatment strategies for melasma that has been a focus of attention in recent years.

Tyrosinase is a key enzyme that is responsible for melanogenesis and consequently pigmentation. The inhibition of tyrosinase greatly affects the melanogenesis process and melanin production, and is therefore the therapeutic target of many depigmenting agents. Kojic acid is a well-known antityrosinase agent widely used to treat melasma and is used, alone or in combination, in many depigmenting preparations. It is a natural antibiotic produced by various bacterial or fungal strains such as Aspergillus oryzae, Penicillium or Acetobacter species.[9] It is a slow binding inhibitor of the diphenolase activity of tyrosinase enzyme, resulting in antimelanogenic action.

The Dermaroller is a breakthrough device, simple in concept but yielding magnificent results. Over the past decade, microneedles have been developed to deliver drugs into the skin in a minimally invasive manner.[10] Microneedles work by creation of thousands of microclefts through the epidermis into the papillary dermis to facilitate transdermal drug delivery and stimulate skin's natural repair without causing permanent epidermal damage. It is a popular choice as there is little recovery time and the adverse effects are uncommon and transient. Microdermabrasion has been shown to improve the skin penetration of topical preparations, especially hydrophilic molecules.[10] This ability can theoretically be useful to enhance the therapeutic effects of kojic acid and tranexamic acid.

This study attempts to compare the efficacy of micro needling with tranexamic acid versus micro needling with kojic acid.

AIMS AND OBJECTIVES

This study will be designed and conducted with the following aims and objectives:

(1) To study the therapeutic efficacy of micro needling with 5% tranexamic acid solution in melasma
(2) To study the therapeutic efficacy of micro needling with 2% kojic acid in melasma
(3) To compare the therapeutic efficacy of micro needling with 5% tranexamic acid solution vs micro needling with 2% kojic acid in melasma.

2. MATERIALS AND METHODS

Study Design

- Type of study: Prospective, Randomized, Comparative Interventional study.

Study Centre

- Department of Dermatology Venereology and Leprology, Pacific Medical College & Hospital, Udaipur.

Study Duration

- January 2021 to September 2022

Source Of Data

- Dermatology, Venereology & Leprology department of Pacific Medical College & Hospital, Udaipur - 313001.

Study Population:

- Sample size taken: 60 cases.

Inclusion Criteria:

1. All patients of either sex with clinical features of melasma.
2. Patients willing to participate in the study.
3. Patients of age group of 18 years and above.

Exclusion Criteria

1. Patients below the age of 18 years.
2. Patients with hypersensitivity to study medication
3. Patients on OCP's, Pregnant or lactating women
4. Patients with clotting disorders or were on anticoagulant treatment
5. Patients not giving written consent.

Methodology

The present study entitled "COMPARATIVE EVALUATION OF THE THERAPEUTIC EFFICACY OF MICRONEEDLING WITH TOPICAL 5% TRANEXAMIC ACID SOLUTION VS MICRONEEDLING WITH TOPICAL 2% KOJIC ACID CREAM IN THE TREATMENT OF MELASMA" was conducted in the Department of Dermatology, Venereology and Leprology, Pacific Medical College & Hospital, Udaipur, Rajasthan for a period of about one and a half year from January 2021 to September 2022.

This was a prospective, single center, interventional, parallel group, randomized study to compare the efficacy of microneedling with 5% tranexamic acid solution vs microneedling with kojic acid in melasma This study was performed after obtaining clearance from Institutional Ethics Committee vide number- PMU/PMCH/IEC/PG/2020/10 dated 20th November at Pacific Medical College & Hospital, Udaipur, Rajasthan on 20th November'2020

- Written and informed consent was obtained from all patients.
- A total of 60 clinically diagnosed patients of melasma attending dermatology OPD were enrolled in the study
- All patients were subjected to full history taking and dermatological examination and randomly assigned into two groups

1) Group A - 30 cases of melasma undergoing microneedling with 5% tranexamic acid solution
2) Group B - 30 cases of melasma undergoing microneedling with kojic acid cream.

- Wood's light was used to determine the pattern of melasma (epidermal, dermal, or mixed). Photographing of the face was done at baseline and at the end of the last session.

Treatment Procedure :

Topical anesthetic cream of 2.5% lidocaine was applied to the treated areas under occlusion 1hour before microneedling. Three treatment sessions at 0, 4 and 8 weeks were done in both groups (A and B) at monthly intervals. In each session, microneedling was performed in both groups with application of tranexamic acid in group A and kojic acid in group B.

Skin microneedling was performed using Dermaroller that consists of a hand piece and needle tips with needle length of 1.5 mm.

4. RESULTS

This was a prospective, single center, interventional, parallel group, randomized study to compare the efficacy of microneedling with 5% Tranexamic acid solution vs microneedling with Kojic acid in melasma. The study was conducted for a period of one and a half year from Jan 2021 to September 2022 at the outpatient department of Dermatology Venereology and Leprosy at Pacific Medical College & Hospital, Udaipur.

A total of 60 clinically diagnosed patients of melasma attending dermatology OPD were enrolled in the study and randomly assigned into two groups1.

Group A - 30 cases of melasma undergoing micro needling with 5% tranexamic acid solution 2.

Group B - 30 cases of melasma undergoing micro needling with kojic acid cream.

Below is the detailed analysis of the collected data from the study subjects.

Age Distribution:

Mean age of the subjects who underwent treatment with tranexamic acid was 36.7 years and for the Kojic acid group it was 37.4 years. The difference was statistically insignificant. [P value > 0.05]

Table 1: Mean age of subjects

Age	Mean ± SD	P value
Tranexamic acid	36.7 ± 7.9	0.39
Kojic acid	37.4 ± 8.1	

Mean age of onset of Melasma:

Mean age of onset of melasma among subjects among subjects was slightly higher among the patients in the Kojic acid group. Though the difference was statistically insignificant. [P value > 0.05]

Table 2: Mean age of onset of the Melasma among subjects

Age of onset [years]	Mean ± SD	P value
Tranexamic acid	33.7 ± 7.4	0.98
Kojic acid	34.2 ± 7.1	

Mean duration of diasease

Mean duration of disease: Statistically insignificant difference was observed between the mean duration of disease. It was 3.7 years among patients in Tranexamic acid group and 3 years among kojic acid group. [P value > 0.05]

Table 3: Mean duration of disease

Disease duration [years]	Mean ± SD	P value
Tranexamic acid	3.7 ± 2.4	0.99
Kojic acid	3.0 ± 2.1	

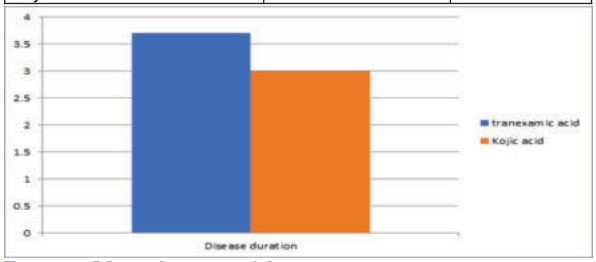

Figure 1: Mean duration of disease

Gender distribution:

Gender distribution among the subjects in two groups: More number of female subjects was observed among both the groups. [P value > 0.05]

Table 4: Gender distribution among the subjects in two groups

Gender	Tranexamic acid	Kojic acid
Female	23 (76.7)	26 (86.7)
Male	7 (23.3)	4 (13.3)
Total	30	30
P value	0.25	

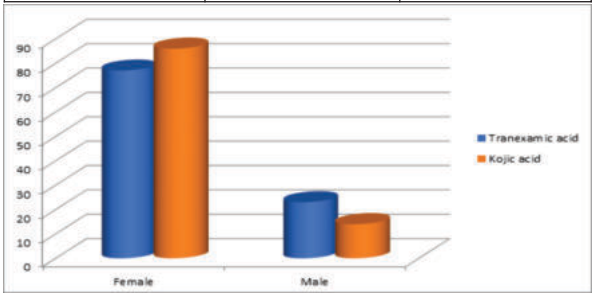

Figure 2: Gender distribution among the subjects in two groups

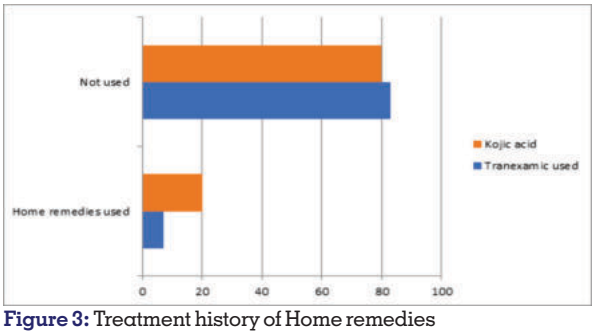

Figure 3: Treatment history of Home remedies

Treatment history of Betnovate : one patient in tranexamic acid group and 2 patients in kojic acid group gave history of use of betnovate for melama. The difference was statistically insignificant. [P value > 0.05]

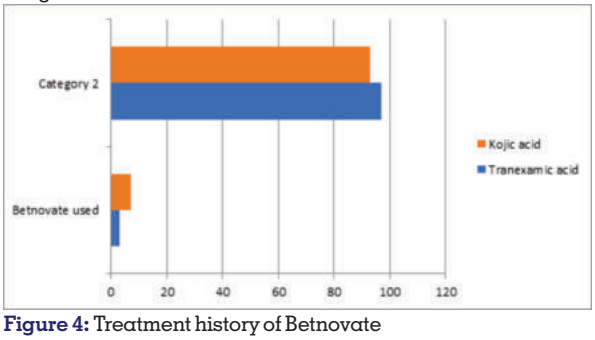

Figure 4: Treatment history of Betnovate

Skin type: Maximum number of patients in both the groups had 4th skin type as the most common. The difference was statistically insignificant. [P value > 0.05]

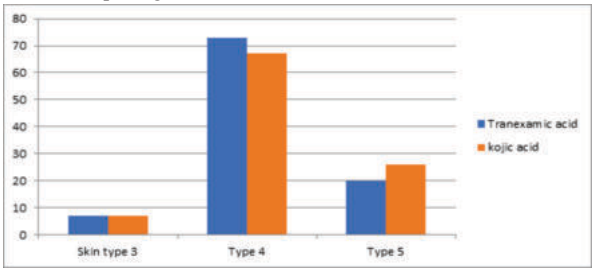

Figure 5: Distribution of patients according to skin type

Comparison of MASI score before and after treatment with Tranexamic acid: Before and after [12 weeks] comparison of MASI score in Tranexamic acid group showed statistically significant improvement in the MASI score. It reduced from mean 11.2 to mean value 8.9. [P value <0.05]

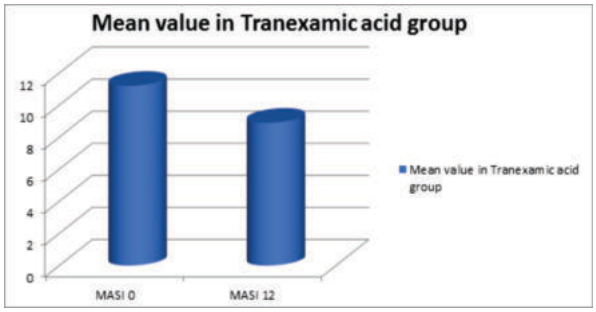

Figure 6: Comparison of MASI score before and after treatment with Tranexamic acid

Before and after [12 weeks] comparison of MASI score in Kojic acid group: Comparison of MASI score before and after treatment with Kojic acid revealed statistically significant reduction in MASI score after treatment. [P value < 0.05]

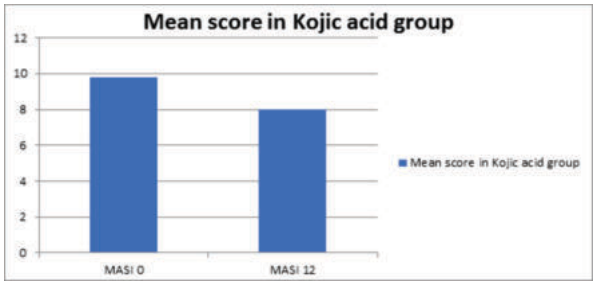

Figure 7 : Before and after [12 weeks] comparison of MASI score in Kojic acid group

Table 5: Comparison of percentage improvement between the groups

Time	Baseline	Week 4	Week 8	Week 12
Tranexamic acid	11.2±3.3	10±2.2	9.1±1.2	8.9±2.9
Percentage improvement		10.7	18.7	20.5
Kojic acid	9.8±3.3	9.2±1.9	9±1.4	8.0±3.2
Percentage improvement		6.1	8.1	18.3
P value		0.67	0.54	0.32

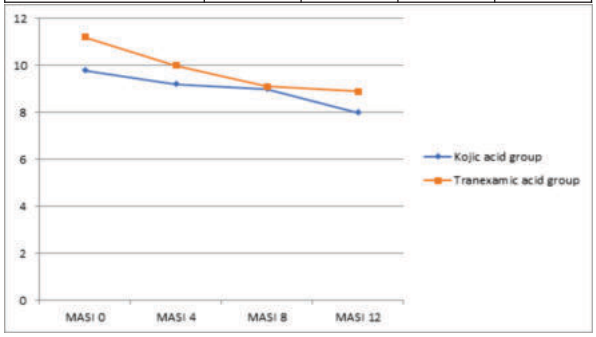

Figure 8: MASI scores within and between tranexamic acid and Kojic acid at 4 time intervals: Baseline, 4 weeks, 8 weeks and 12 weeks

Comparison of MASI score between both the groups before beginning treatment

Comparison of MASI score between both the groups before beginning treatment: There was insignificant difference in the pre treatment MASI score in both the groups. It was 11.2 in tranexamic acid group and 9.8 in Kojic acid group. [P value > 0.05]

Table 6: Comparison of MASI score between both the groups before beginning treatment

MASI score -0	Mean ± SD	P value
Tranexamic acid	11.2 ± 3.4	0.85
Kojic acid	9.8 ± 3.1	

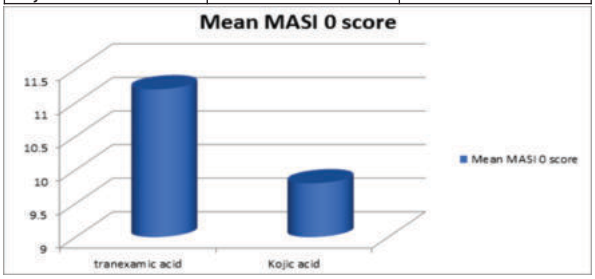

Figure 9: Comparison of MASI score between both the groups before beginning teatment

Distribution of melasma types among both the groups

Distribution of melasma types among both the groups: Mixed melasma type was most common presentation among both the groups. It was among 80% patients in tranexamic acid group and 66.7% among Kojic acid group. Next most common type was epidermal, followed by Dermal type in the Kojic acid group. In the tranexamic acid group, epidermal type and dermal type were present in equal no of patients. The difference was statistically insignificant. [P value > 0.05]

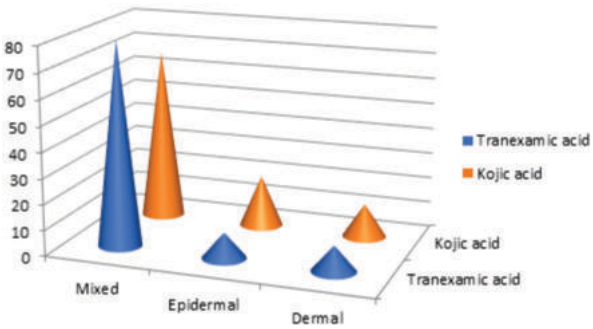

Figure 10: Distribution of melasma types among both the groups

Comparison of patient satisfaction score between both the groups

Comparison of patient satisfaction score between both the groups: There was statistically significant difference in the patient satisfaction score between both the groups. 13 % patients in tranexamoc acid group and 43 % patients in Kojic acid group were satisfied with the treatment. 65% f patients who received tranexamic acid as treatment responded good and only 33% patients on Kojic acid treatment responded good for satisfaction score. Equal number of patients in both the groups responded "very good" for the treatment satisfaction score. [p value <0.05]

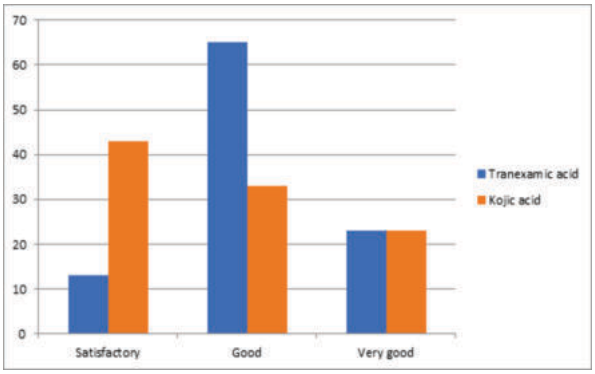

Figure 11: Comparison of patient satisfaction score between both the groups

5. DISCUSSION

Index research was a prospective, single center, interventional, parallel group, randomized study to compare the efficacy of microneedling with 5% Tranexamic acid solution vs microneedling with Kojic acid in melasma. The study was conducted for a period of one and a half year from Jan 2021 to September 2022 at the outpatient department of Dermatology Venereology and Leprosy at Pacific Medical College & Hospital, Udaipur. A total of 60 clinically diagnosed patients of melasma attending dermatology OPD were enrolled in the study and randomly assigned into two groups. Group A included 30 cases of melasma undergoing micro needling with 5% tranexamic acid solution. Group B included 30 cases of melasma undergoing micro needling with kojic acid cream.

Melasma is an acquired disorder of symmetrical hypermelanosis that involves sunexposed areas of the skin. It characteristically presents as symmetrical hyperpigmented macules and patches on face and frequently affects young women in reproductive age group. The exact cause of melasma is yet to be elucidated. Various factors implicated in its etiopathogenesis are genetic factors, sun-exposure, pregnancy, thyroid disease, vascular factors, cellular stress and certain drugs.[11] Although multiple therapeutic modalities have previously been tried, successful, truly effective treatment options for this condition have been few and quite elusive.

Since its description, various molecules have been used in the treatment of melasma. A vast majority of these molecules interfere at various steps of melanogenesis and inhibit the conversion of DOPA to melanin.

Tranexamic Acid

Tranexamic acid, though a popular antifibrinolytic, is a novel molecule in the armamentarium of dermatologists for the treatment of melasma. It has been tried through oral, topical and intralesional routes in melasma with varying success rates. Oral TA carries theoretical risk of thromboembolic phenomenon at higher doses. Paradoxical hyperpigmentation is reported with intralesional/intradermal TA injections.[12] It has been established that TA controls pigmentation by inhibiting the release of inflammatory mediators, specifically prostaglandins, which are involved in melanogenesis. With the current evidence in literature, topical TA appears relatively safe and effective. It has been well established that TA delivered orally or by injection is an effective approach in the treatment of melasma. However, only a limited number of studies have assessed the effectiveness of topical TA on facial dyschromia.

In the split face study where weekly microneedling was done on one side and sham device applied on the other followed by application of 0.5% TA over the entire face showed better results on the microneedling side which may have helped in the better absorption of the TA.[13]. A randomized, open label, comparative study of TA microinjections and TA with microneedling in patients of melasma where treatments were done three times at monthly intervals (0, 4 and 8 weeks) by 4mg/ml TA showed better results in the microneedling group (44.41% improvement in the MASI score vs 35.72%).[14]

Kojic Acid

Kojic acid(KA) is a molecule derived from *Aspergilline oryzae* and *Penicillium spp.* It inhibits tyrosinase by chelating copper at the enzyme's active site. KA is seldom used as a monotherapeutic agent. It is usually available in combination at a concentration of 2%. In addition to its skin lightening action, KA is known to have photoprotective, anti-inflammatory and pain relieving actions. It has been used as both single agent and combination agent with different

molecules like glycolic acid, hydroquinone, vitamin C and steroids in various studies. In a study by Cotellessa, *et al*. glycolic acid and KA combination was found to have a favourable outcome in melasma.[15] Another split-face trial studied the efficacy of a gel containing glycolic acid, hydroquinone and KA versus a gel that contained only glycolic acid and hydroquinone. More than half of the melasma cleared in 60% patients receiving KA compared to 47.5% patients receiving the gel without KA.[16] Deo et al. studied the efficacy of KA alone versus KA in combination with other agents like HQ, betamethasone valerate and concluded that KA in synergy with hydroquinone is a superior depigmenting agent as compared to its combination with betamethasone and hydroquinone.[69] Common adverse effects reported with KA are erythema, sensitization and irritant contact dermatitis.[17]

Kojicacid is a well-known skin-lightening agent that acts through inhibiting the rate limiting enzyme tyrosinase.[18,19]

Clinico-epidemiologic characteristics:

In the present study, mean age of the subjects who underwent treatment with tranexamic acid was 36.7 years and for the Kojic acid group it was 37.4 years. This is close to the results of multicentric clinic-epidemiologic study by Krupashankar et al. wherein the mean age of study population was 37.2 ± 9.3 year.[20] More number of female subjects was observed among both the groups.

Onset and duration of melasma

Mean duration of disease was 3.7 years among patients in Tranexamic acid group and 3 years among Kojic acid group. Almost equal percentage of patients had onset in pregnancy in both the groups. In the study by S J M etal, 12% of the patients developed melasma during pregnancy and majority (45%) had long standing melasma of 1-3 years duration. 40% and 50% of patients in TA and HQ groups respectively had melasma for 1-3 years duration indicating towards the chronic nature of the disease.[21]

Type Of Melasma

Maximum number of patients in both the groups had 4th skin type as the most common. Mixed melasma type was most common presentation among both the groups. It was among 80% patients in tranexamic acid group and 66.7% among Kojic acid group. Next most common type was epidermal, followed by Dermal type in the Kojic acid group. In the tranexamic acid group, epidermal type and dermal type were present in equal no of patients. However, in a study by Arun Achar et al. dermal melasma was the most common type (54.48%), followed by epidermal and mixed.[22]

Gender Distributuion

Gender distribution among the subjects in two groups: More number of female subjects was observed among both the groups. There were 23 females and 7 males in Group A whereas 26 females and 4 males in Group B.

Treatment History:

Treatment history of triple combination: Around 40% patients in both the groups had used triple combination therapy for melasma in the past. 12 patients out of 30 has used triple combination in Group A and also in group B.Treatment history of Hydroquinone: Only one patient in Group B had used hydroquinone in the past. None had used Hydroquinone in Group A. Treatment history of Peels : Only one patient in each group had history of use of Chemical peels.

Treatment history of Home remedies: around 16% patients in tranexamic acid group and 20% patients in Kojic acid group had history of use of home remedies. 5 patients out of 30 had used home remedies in Group A and 6 patients had used home remedies in group B.

Treatment history of Betnovate : one patient in tranexamic acid group (Group A) and 2 patients in (group B) kojic acid group gave history of use of betnovate for melasma.

MASI score

Before and after [12 weeks] comparison of MASI score in Tranexamic acid group and Kojic acid group showed statistically significant reduction in the MASI score. It reduced from mean 11.2 to mean value 8.9 in Tranexamic acid group. . [P value <0.05]. There was insignificant difference in the MASi score between both the groups before treatment initiation and after 12 weeks of treatment. It was 8.1 in tranexamic acid group and 8.9 in Kojic acid group at 12 weeks post treatment initiation. [P value > 0.05].

Lee et al studied 100 women receiving weekly intradermal TA microinjections for 12 weeks. After eight and 12 weeks, MASI scores were decreased. Similarly, Elfar and El-Maghraby assessed 60 women who received either weekly intradermal TA injections, topical silymarin cream, or glycolic acid peels. While all groups showed improvement in MASI, the intradermal TA group showed the least improvement compared to the other groups.[23,24]

A study of 40 women who had melasma showed that combining glycolic acid and hydroquinone with kojic acid improved the efficacy of these treatments alone, with 60% of the women reporting significant improvement [Reduction in MASI score] by the end of 12 weeks.[25]

More than half of the melasma cleared in 24/40 (60%) patients receiving Kojic acid compared to 19/40 (47.5%) patients receiving the gel without Kojic acid. In 2 patients, there was complete clearance of melasma, and this was on the side where Kojic acid was used.

Patient Satisfaction

There was statistically significant difference in the patient satisfaction score between both the groups. 13 % patients in tranexamoc acid group and 43 % patients in Kojic acid group were satisfied with the treatment. 65% of patients who received tranexamic acid as treatment responded good and only 33% patients on Kojic acid treatment responded good for satisfaction score. Equal number of patients in both the groups responded "very good" for the treatment satisfaction score. Due to scarcity of studies comparing Kojic acid and tranexamic acid in the treatment of melasma, we couldn't find studies comparing patient satisfaction scores between the two groups

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