e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(3); 83-92

Original Research Article

A Randomised Three Arm Comparative Study of Clinical Response between Topical Hydroquinone, Topical Hydroquinone with Oral Tranexamic Acid and Oral Tranexamic Acid Alone in the Management of Melasma

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Received: 25-12-2023 / Revised: 23-01-2024 / Accepted: 26-02-2024
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Conflict of interest: Nil

Abstract:

Introduction: Melasma is a widespread, acquired hypermelanosis that usually affects the face and other sun-exposed regions. Asian or Hispanic women with Fitzpatrick III to V skin types are frequently affected. Available therapies include lasers, peeling chemicals, and topical depigmenting agents like hydroquinone. The effectiveness and safety of all these treatments are still for debate, despite their widespread use. Because melasma recurs frequently, treating it can be quite difficult. Tranexamic acid (TA) has been added to the therapy of melasma, and several clinical trials conducted worldwide have demonstrated positive outcomes. In order to examine the effectiveness of topical hydroquinone and oral tranexamic acid, a prospective comparison research was carried out.

Material and Method: This one-year, outpatient, tertiary care hospital's Skin & VD department conducted a single-center, randomised, three-arm comparative prospective research. A tertiary care hospital in eastern India recruited 100 melasma patients between the ages of 20 and 60 who were attending dermatology outpatient clinics. The following patients were not allowed to participate in the study: those who were pregnant, nursing, had any history of coagulopathy, coronary heart disease, hypertension, diabetes mellitus, thrombosis, renal disease, mental illness, concurrent use of contraceptives, severe sunburn three months prior, use of anticoagulant or antiplatelet agents such as clopidogrel, topical steroids, oral and topical retinoid, hydroquinone, or topical bleaching agents, and lasers, among other conditions.

Result: Ten patients did not come back for follow-up out of a total of 100 patients because of a delayed response or prolonged therapy. In the end, the 90 patients who finished the therapy regimen were taken into account. The female to male ratio was 3.74:1, with over half of the patients being in their third decade of life. The comparison of mean MASI score between Groups at 8 and 12 weeks with initial MASI score showed statistically significant with p-value=0.000 among oral tranexamic acid users. The mean MASI score was maintained after 6month in group using systemic tranexamic acid (1.062±0.92) in comparison to only topical or combination therapy.

Conclusion: Melasma, which primarily affects women in their twenties causes symmetrical, chronic acquired hypermelanosis of the face or parts of the body exposed to the sun. Hydroquinone is one of the best treatments for treating melasma but remarkable facial side effects like ochronosis. Hence finding novel adjuvant therapies to boost the effectiveness of previous pharmaceuticals has become more difficult due to the lengthy treatment , side effects, and recurrence. Treatment for melasma has recently seen some optimism provided with the introduction of oral tranexamic acid (TA).

Keywords: Melasma, Hydroquinone, Tranexamic acid, oral route

Introduction

Melasma is a common, acquired hypermelanosis that occurs in sun-exposed areas, mostly on the face. [1]

It often can be found among Asian or Hispanic woman with skin types Fitzpatrick III to V. [2,3] The current treatments include topical depigmenting agents like hydroquinone, peeling agents and laser. Despite multiplicity of all these therapies, their efficacy and safety remains controversial. [4]

Treatment of melasma is a real challenge due to its frequent recurrence. Addition of tranexamic acid [TA] in treatment of melasma had showed good results in different clinical trials across the world. Hence this prospective comparative study was conducted to compare the efficacy of oral tranexamic acid with topical hydroquinone.

Material and Methods

It is a single-centred randomised three arm comparative prospective study done in outpatient Department of Skin & VD in a tertiary care hospital over a period of 1 year. The study enrolled 100 melasma cases aged 20-60 years attending dermatology outpatient in a tertiary care hospital in eastern India. Patients with pregnancy, lactation, any history of coronary or cerebral artery disease or coagulopathy, thrombosis, hypertension, diabetes mellitus, renal and mental disorder, concurrent use of contraceptives, severe sunburn 3 months prior, usage of anticoagulant or anti platelet agents like aspirin or clopidogrel, on dermatological treatments like topical bleaching agents, oral and topical retinoid , topical steroids and undergone procedures like peeling, dermabrasion and lasers within 3 months prior were excluded from the study. Other exclusion criteria were patients with family history of sensitivity to hydroquinone or tranexamic acid, over expectation of treatment , refusal to take photographs, failure to finish whole therapeutic period of 6 months due to various reasons and abnormal laboratory findings like bleeding time, clotting time, total platelet count, Prothrombin Time and activated plasma thromboplastin time (aPTT).

A detailed questionnaire was prepared to record detailed history including sunlight exposure, related medicine administration, former treatments, cosmetic usage and related habits. An explanation including the risks, benefits and potential complications was given to the patients and written informed consent was obtained from each.

Photographs were taken prior to treatment. Patients were instructed to return at every 4 weeks interval for analysis of changes in melasma along with photographs. They were also instructed to apply broad spectrum sunscreen more than SPF 30 and not to use any other therapies during treatment period. At the beginning and end of the study BT, CT, PT, TPC and aPTT were done to evaluate any changes.

The case selection was done as per pre-designed proforma. From 100 sealed envelopes in a box, one envelope containing A or B or C code (A: topical hydroquinone 4%, B: oral tranexamic acid+ topical hydroquinone 4%, C: oral tranexamic acid alone) was allotted randomly to each patient. 10 patients were lost to follow up and remaining 90 were divided into three groups for statistical analysis with each group having 30 patients. Tranexamic acid 250mg twice a day was prescribed for 3 months and the cases were followed at 4 week interval for 3 months and were asked for follow up after end of 6 month of treatment to detect any relapse. All groups were advised additionally for photo protection and regular use of a broad spectrum sun screen.

Response was evaluated on the basis of Melasma area severity index (MASI). MASI was done at baseline followed by 4 weeks interval till 12 weeks and after 6 month of follow up. Mean MASI score between three groups were compared. Patients were followed up every month to know the response to treatment and development of any side effects with the medication. Improvement was assessed by subjective criteria, serial photographs and mean MASI score.

Subjective criteria for evaluation was graded as excellent when melasma decreased by 90% Or hyperpigmentation almost vanished, good when melasma decreased by 60% or Significant diminishment of hyper pigmentation and poor when melasma size decreased less than 30% or no visible diminishment of hyperpigmentation. The MASI score was used as an objective index for a more precise comparison between treatment groups regarding the primary outcome. In this scoring system, three elements, Area (A), Darkness (D), and Homogeneity (H), are scored in the forehead, right malar, left malar, and chin. A is scored from 0 to 6 (0 = no involvement, 1 = <10%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%,6 = 90–100%) while D and H are scored from 0 to 4(0 = absent, 1 = slight, 2 = mild, 3 = marked, 4 = maximum). The MASI total score is calculated as:{forehead: 0.3A (D+H)} + {right malar: 0.3A (D+H)} +{left malar: 0.3A (D+H)} + {chin: 0.1A (D+H)} and can range from 0 to 48.

Statistical analysis

All collected data were described as mean standard deviation for quantitative variables, and number or frequency percentage for qualitative variables. Data analysis was performed using SPSS software,

version 21.Treatment efficacy during the 3-month study period was evaluated by comparing MASI score change between three groups by ANOVA and patient satisfaction and relapse rate was evaluated by chi-square test. P-value of 0.05 or less was considered for statistical significance.

This study was approved by the Ethics committee Regd.No.ECR/84/Inst/OR/2013 issued under Rule 122DD of the Drugs and Cosmetic Rules 1945 with IEC/IRB No: 366/2016

Results:

Out of total 100 patients, 10 patients did not return for follow up due to slow response or long term treatment. Remaining 90 patients who completed the treatment protocol were included in final analysis. Nearly half of the patients belonged to the 3rd decade and female: male ratio was 3.74:1. Other epidemiological data of this study are depicted in Table-1. The initial mean MASI score of Group- A, B and C were 7.433±3.09, 8.700±3.571 and 7.566±3.461 respectively. The mean MASI score of Group A, B and C was 6.493±2.930, 5.073±2.603 and 4.610±2.737 at 4 weeks respectively. The comparison of mean MASI score between three groups at 4 weeks was found to be statistically significant (p-value=0.026). similarly the mean MASI score of three groups at 8 wks were 5.563±2.669 , 2.786±1.760 , 2.683±1.841 and at 12 wks were 4.796±2.512, 1.200±1.125and 1.076±1.079 respectively.

The comparison of mean MASI score between Group A, B and C by ANOVA statistical analysis at 8 weeks with initial MASI score was found to be statistically significant with p value 0.001 and at 12 weeks, comparison of mean MASI score between three groups was also statistically significant with p value 0.000. (Figure 2) Similarly comparing mean MASI score among group B and C using unpaired t-test was also found to be statistically significant with p-value 0.023. The mean MASI score was maintained after 6month in group C (1.062±0.92) in comparison to increase in group B (1.86±1.023) and group A (5.78±2.326). (Figure-1) Satisfaction score comparison among three groups revealed 90% patients have excellent to good response in group C compared to only 3.3% among A group. The cause of poor satisfaction scores among group A was probably due to irritation and slow action. During 6 month follow up relapse rate was found to be significantly high in group A (40%) and group B (23.3%) and lowest in group C (10%) (P-value=0.025). (Table-2).

All side effects developed during study period is described in Table-3.These side effects were reduced on dose adjustment for 3 to 4 days and only 2 cases required withdrawal of drug due to diarrhoea. No serious side effects were noticed in this study during 3 months of treatment and 3 months follow up period. All clotting parameters and laboratory investigations done at the beginning and end of the study revealed no abnormality.

Table 1: Clinico- Epidemiological Data

Variables	Subdivision of variable	Group A	Group B	Group C	Total	p-value
Age		33.3±5.1	35±6.5	34±7.1	0.078	0.078
Gender	v Male	7	5	7	19 (21.11%)	0.766
	Female	23	25	23	71 (78.89%)	
Duration	< 1year	4	4	6		
	1-2 year	8	6	5		
	2-3 year	10	8	7		
	>3 year	11	12	9		
Sun exposure (> 1 hour)		15	14	15	44/90 (48.89%)	
OCP use		2	4	4	10/71	
Family history		3	4	5	12/90(13.34%)	
Pattern	Malar	12	10	10	32/90 (35%)	
	Centrofacial	5	4	4	13/90 (14%)	
	Mandibular	1	1	2	4/90 (4%)	
	Mixed	12	15	14	41/90 (45%)	

Table 2: Mean MASI Score, Satisfaction Score And Relapse Rate Comparison

MASI Score	Group A (HQ)	Group B (HQ+TNX)	Group C (TNX)	p-value
O WK	7.433±3.09	8.700±3.571	7.566±3.461	o.286
4 WK	6.493±2.930	5.073±2.603	4.610±2.737	0.026

8 WK	5.563±2.669	2.786±1.760	2.683±1.841	0.000
12 WK	4.796±2.512	1.200±1.125	1.076±1.079	0.000
Satisfaction Score (after 12 week of treatment)	**Group A (HQ)**	**Group B (HQ+TNX)**	**Group C (TNX)**	**P-value(** Chi-Square Test)
Excellent	1 (3.3%)	12 (40%)	16 (53.3%)	PVALUE=0.000
Good	11(36.7%)	16 (53.3%)	11(36.7%)	
Poor	18 (60%)	2(6.6%)	3(10%)	

Relapse Rate	**Group A (HQ)**	**Group B (HQ+TNX)**	**Group C (TNX)**	**P-value (** Chi-Square Test)
RELAPSE	12 (40%)	7 (23.3%)	3 (10%)	p-value= 0.025
NO RELAPSE	18 (60%)	23 (76.7%)	27 (90%)	

Table 3: Adverse Effects

Topical side effects	**Systemic side effects**
Itching 12/60 (20%),	Oligomenorrhea 8/60[13.3%],
Erythema 13/60 (21.67%),	Nausea 7/60 [11.6%],
Hyper pigmentation in 2/60 (3.33%)	Diarrhoea 3/60 [5%],
Allergic contact dermatitis 3/60 (5%)	Vomiting 3/60 [5%]
Ochronosis in 1 case	Palpitation -1 case

Table 4: Different Reference Study in Comparison To Present Study

Reference Study	**Study design**	**Reduction in MASI score**	**Patient satisfaction score**	**Relapse rate**	**Systemic Side effects during therapy**
Mafune et al, 2008	1.5 gram/daily TA for 2 month	76.8%	53.3%	Not measured	
Sufan et al, 2012	Oral TA 500mg/day for 6 m	Not measured	68%	9.5%	GI and menstrual irregularity
Lee HC et al	Oral TA for 4 month	89.7%	Not measured	27.2%	7.1% have adverse effect with 1 case of deep vein thrombosis
Lajevardi V et al	HQ vs HQ +TA	Significant reduction with p=0.015	82.2% in intervention vs 39.4% in controll	30% in HQ and 20% in HQ +TA	GI and menstrual abnormality more common
Padhi et al	Triple combination vs combination	88% at 12 weeks with p<0.05	95.9% is improvement rate	Not measured	Oligomennorhea-1 case
Saffora et al	Oral TA	Not measured	86%	12%	Oligomenorrhoea (7.1%) stomach upset (3%) palpitation (3%).
Present study	HQ vs HQ+TA vs TA	35.5% in group A, 86.2% in group B and 86.03% among group C at 12 week	40% in group A and 90% among group C	40% in group A, 23.3% in group B and only 10% in group C	Oligomenorrhea [13.3%] Nausea [11.6%], Diarrhea (5%), vomiting (5%) Palpitation-1 case

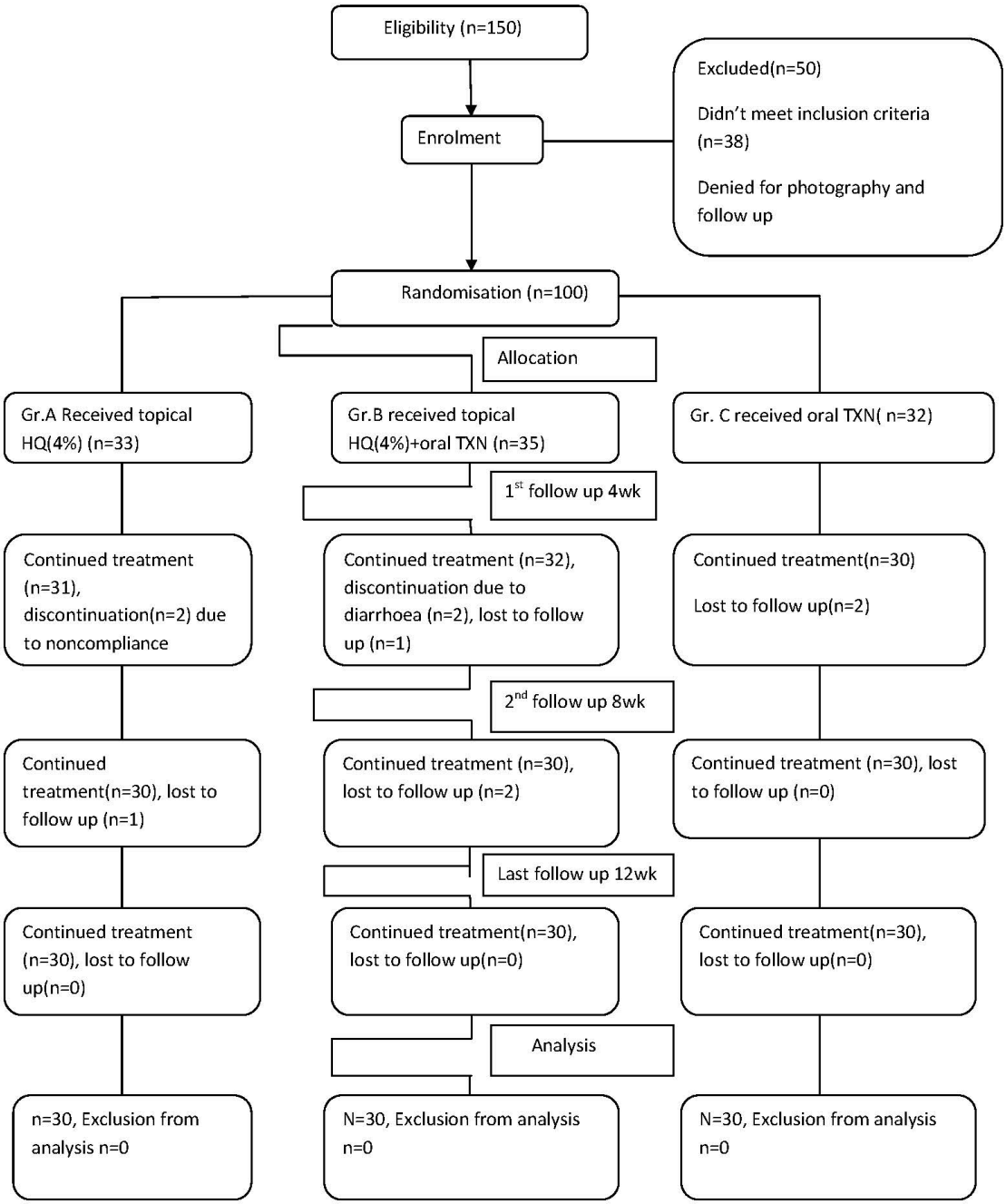

Figure 1: Flow chart of patient allocation and randomisation

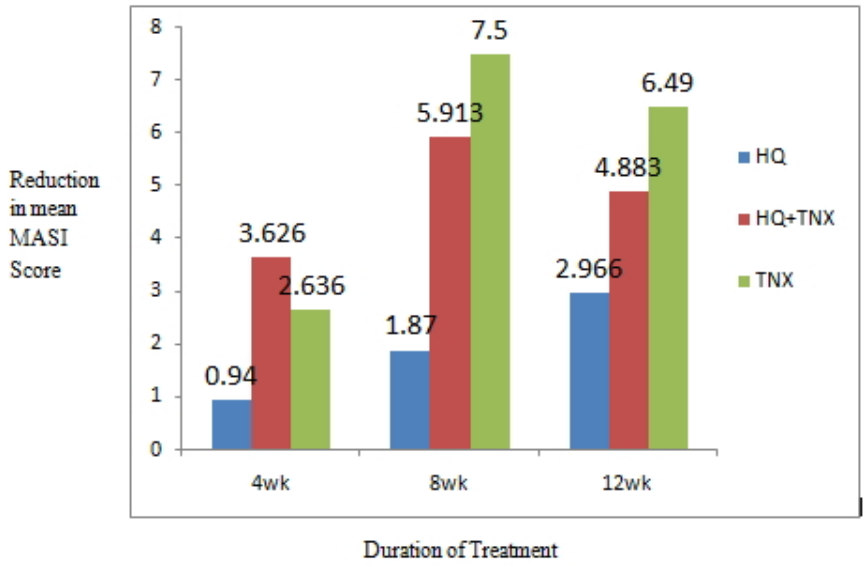

Figure 2: Comparision of mean MASI score among group A, B and C at 4week, 8week and 12 week

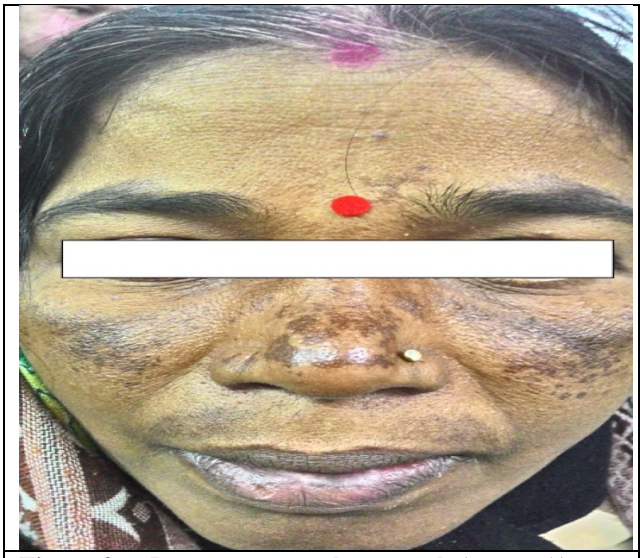

Figure 3 a: Pre-treatment photograph (group A)

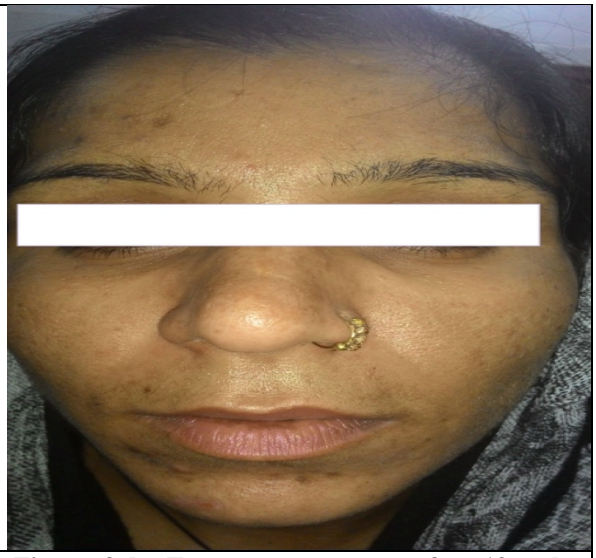

Figure 3 b: Treatment response after 12weeks (group A)

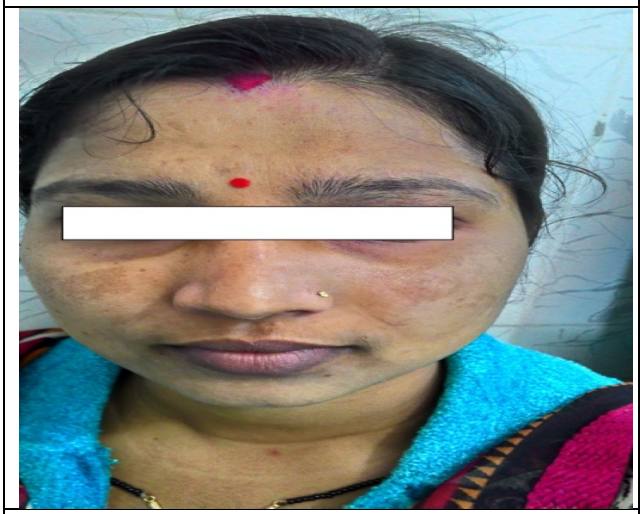

Figure 3 c: Pre-treatment photograph (group B)

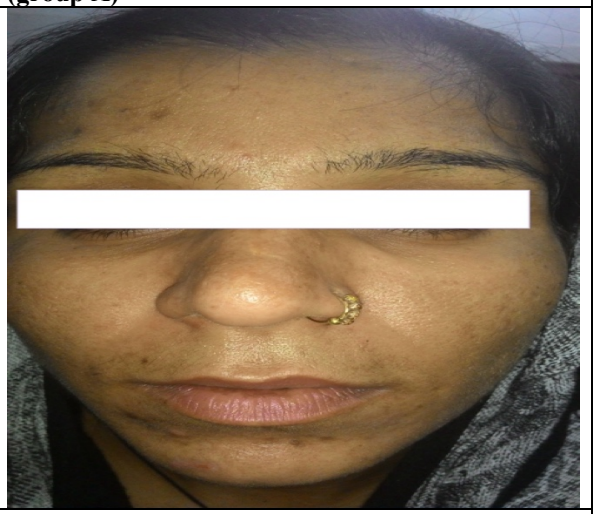

Figure 3 d: Treatment response after 12weeks (group B)

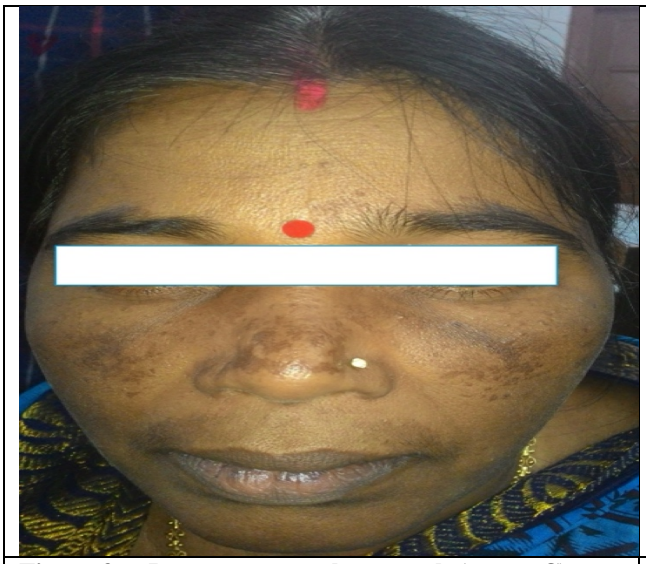

Figure 3 e: Pre-treatment photograph (group C)

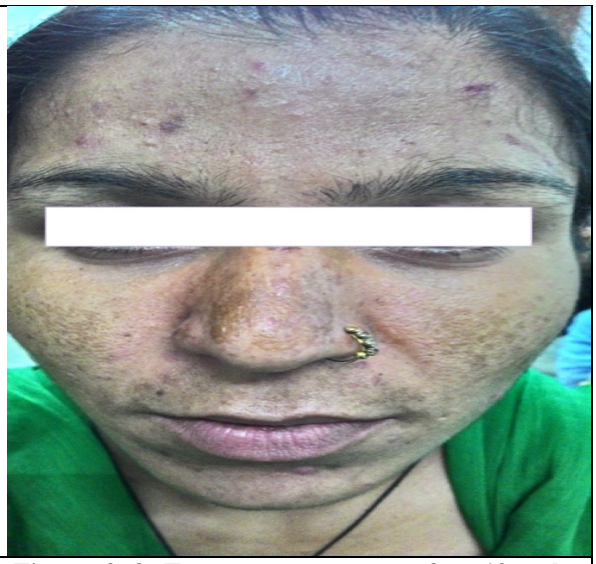

Figure 3 f: Treatment response after 12weeks (group C)

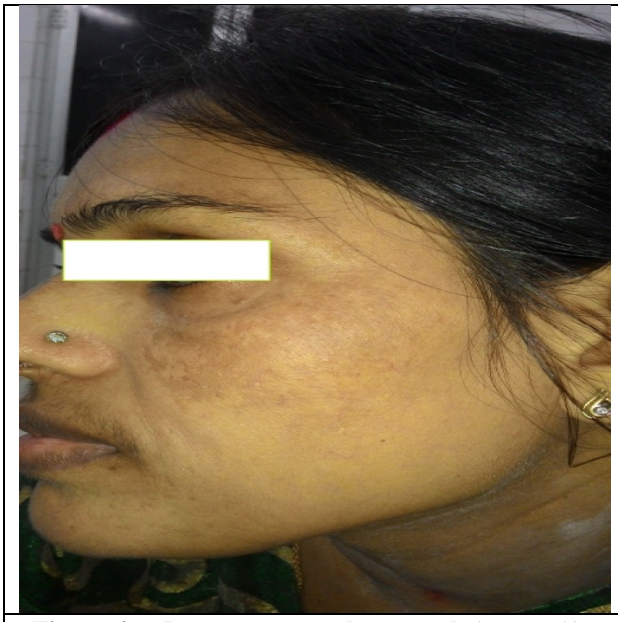

Figure 4 a: Pre-treatment photograph (group A)

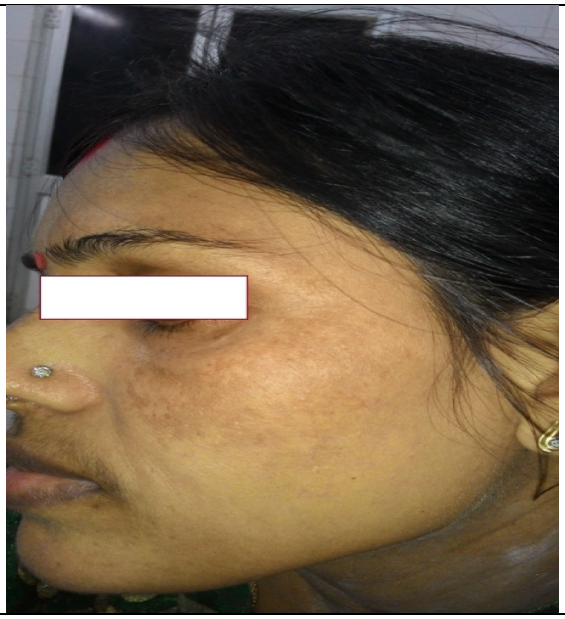

Figure 4 b: Treatment response after 8 weeks (group A)

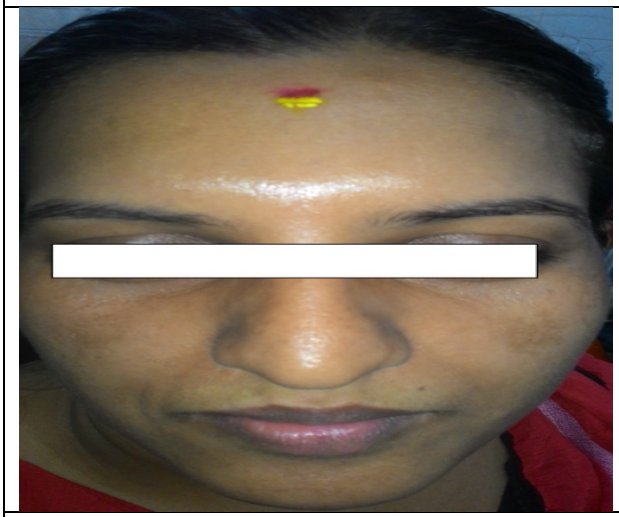

Figure 4 c: Pre treatment photograph (group B)

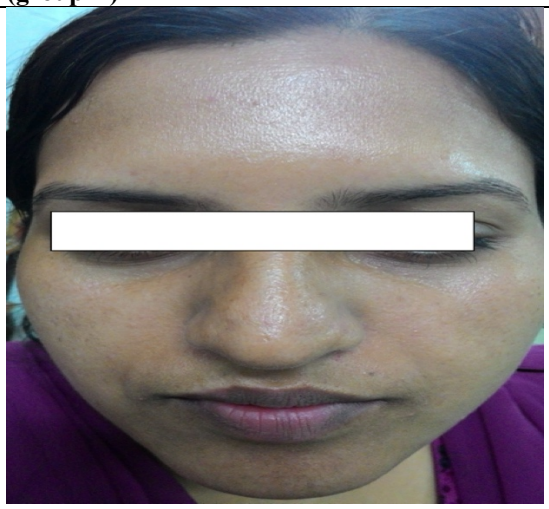

Figure 4 d: Treatment response after 8 weeks (group B)

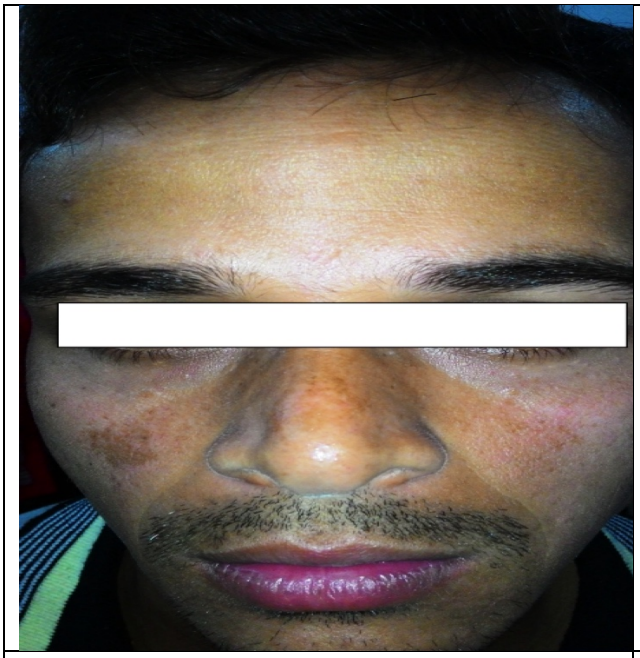

Figure 4 e: Pre treatment photograph (group C)

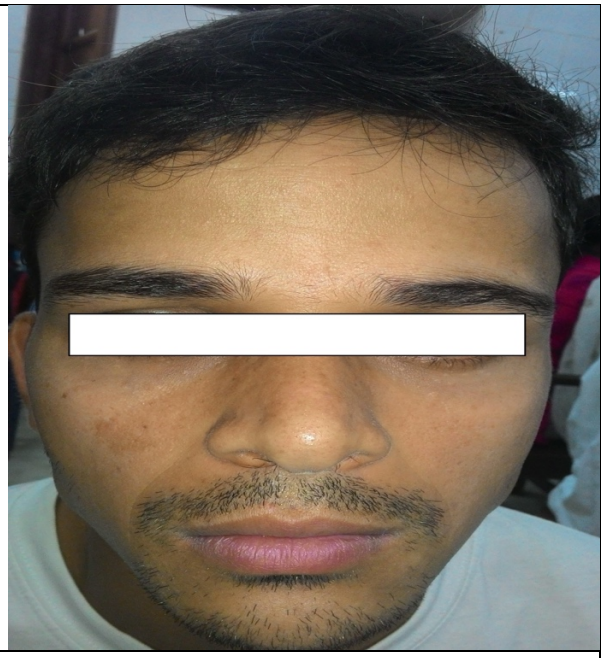

Figure 4 f: Treatment response after 8 weeks (group C)

Discussion

Melasma is a melanogenesis dysfunction that results in localized, chronic acquired hypermelanosis of the skin that occurs symmetrically on sun exposed areas of the body, and affects especially women in menacme. [1] Although hydroquinone is one of the most effective drugs for melasma treatment, the prolonged treatment duration required as well as side effects and recurrence have spurred efforts to find new adjunctive therapies to increase the efficacy of older medications. Recently, the use of oral tranexamic acid (TA) has added a ray of hope in the management of melasma. [18] Sun exposure induces production of plasminogen activator in keratinocytes while pregnancy and oral contraceptive pills increase its levels in the serum. Plasminogen activator converts plasminogen (present in human epidermal basal cells) into plasmin.

Plasmin in turn induces secretion of phospholipase A2, prostaglandin E2, and leukotrienes, which then stimulate melanogenesis.

Plasmin activity also releases fibroblast growth factor, a potent growth factor for melanocytes. By inhibiting plasminogen activator, tranexamic acid blocks plasmin production and prevents activation of melanocytes by keratinocytes. [5,8-10,13] Other proposed mechanisms of TA action include possible increases in vascular-endothelial growth factor (V-EGF) and alpha melanocyte- stimulating hormone. [7, 11]

However, supporting studies are limited. We therefore designed this RCT to evaluate the efficacy and safety of TA in comparison to conventional treatment HQ and also measured the effectiveness in combining them in the treatment of melasma. According to previous results, the effective dosage of TA for cosmetic goals (500–750 mg/daily) is lower than that for bleeding problems. Notably, a longer duration of therapy was found to be more effective than higher dosages. [5] In this study, reduction of mean MASI score after 4 weeks from initial value were 12.3%, 68.9%, 64.5%respectively in 3 groups. Comparison of mean MASI score between three groups at 4 weeks and 8 and 12 weeks with initial MASI score were also found to be statistically significant with p-value=0.000. Objective reduction of MASI score comparing above groups showed there was 86.20% reduction of MASI in TA+HQ group compared to only 35.53% among HQ group. The result was consistent with Karn D et al [19], Wu et al [20] and Padhi et al [21]. MASI score reduction among HQ+TA and only TA group was found to be nearly equal(86.2% in combination group and 86.03% in TNX group) at 12 weeks of treatment showing addition of HQ has no significant difference in response.

Similarly, Mafune et al. [15] and Sufan et al. [16] used oral TA in variable doses showed acceptable improvement of MASI score 76.8% and 68% respectively after 6 month of therapy which was lower than our study which shows 86% improvement of MASI score even after 12 weeks of therapy with lower dose (250mg twice daily). Hence addition of higher dose of TA or longer

duration of treatment is not required for effective improvement of MASI score.

Other retrospective studies by Lee HC et al. [17] analyzed data from 561 melasma patients, treated with oral TA for a median duration of 4 months. Improvement was seen in 89.7% of patients within 2 months of treatment initiation which was consistent with our result, and a relapse rate of 27.2% was observed which differs from this study with relapse rate being 10% in TA group.

Lajevardi V et al [18] on comparison of HQ and HQ+TA groups showed significant reduction of MASI score in combination group compared to only topical 4% hydroquinone group with p value =0.015 which was consistent with our result.

Padhi et al [21] also showed fall in MASI response after 8 Wks was 88% reduction in triple combination with tranexamic acid group with p value<0.05 which was nearly similar to our study with 86.2 reduction in group B, but this response can also be achieved with only tranexamic acid as we found in our study that there was 86.03 reduction in MASI among group C. Safoora et al[26] in a six months follow-up result after completion of treatment (with only oral tranexamic acid) revealed recurrence among only 12% patients which was similar to our study result that is 10% in Group C which is much lower than group B and A in our study. Thus, oral TA appears to be a promising and safe therapeutic option for melasma. However, considering that the improvement rate in our study was 86%, it may be used as both initial treatment option and for severe, chronic, and resistant cases of melasma with proper monitoring.

Most common side effects with tranexamic acid observed were oligomenorrhea (13.3%) followed by nausea (11.6%) which was consistent with Karn D et al23 (14.7% oligomenorrhea) and Saffora et al [22] (7.1%) oligomenorrhea, 3% stomach upset and 3% palpitation). Similarly Wu et al 20 reported GI upset being the most common side effect in 4.3% of cases and only 3.5% cases had decreased menses.

In this study, no serious systemic side effects were observed during treatment as in other studies by Liu et al [14], Zhu et al [23], Higasi et al [24], Hajime et al [25], Hyun Hee Cho et al [26] with tranexamic acid used as treatment modality for melasma for 6 months .There was no clotting abnormality noted during and after treatment as with previous studies by Wu et al, Saffora et al and Tan et al. But in contrast to this study, Mafune et al [15] had reported a single case of transient chest discomfort with tranexamic acid.

Our study also better from previous studies as it compared three treatment modalities with randomization , measured treatment response in terms of both patient satisfaction and MASI score improvement, measured relapse rate after 6 month of follow up, side effect recording and laboratory parameter measurement, whereas majority of previous studies failed to sight all the above parameters. Results of other studies are compared with the present study in table-4.

Study Limitation

The limitations of our study include small sample size and single-centred study. A long-term multicentre study is suggested with large sample size to establish the effectiveness and safety profile of oral tranexamic acid.

Conclusion

Oral tranexamic acid alone or in combination is a safe and effective option and also has faster and sustained effect in treatment of melasma with excellent satisfaction score and safety profile.

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