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Original Research Article

Clinical Evaluation of Efficacy and Tolerability of Oral Tranexamic Acid in Comparison with Hydroquinone plus Sunscreen in Subjects with Melasma: A Single Blind, Randomized Clinical Trial Study

Dr. Mohammad Saiful Islam[1*], Dr. Shamsun Nahar[2]

[1]Assistant Professor (Dermatology), Centre for Medical Education (CME), Mohakhali, Dhaka, Bangladesh
[2]Senior Consultant (Obstetrics & Gynaecology), Family Planning Department, Dhaka Medical College Hospital, Dhaka, Bangladesh

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Abstract: ***Background:*** Melasma is a common chronic acquired hyper pigmentary disorder of skin, particularly among Asian and Hispanics. Females are more affected than men. It has a significant impact on appearance, causing psychosocial and emotional distress and reducing the quality of life of the affected individual. Tranexamic acid (TA) can be used to treat melasma. ***Objectives:*** To compare the efficacy of oral Tranexamic acid and Hydroquinone (HQ) plus sunscreen in the treatment of melasma. ***Methods:*** It was prospective, interventional clinical trial conducted among 150 Bangladeshi melasma patients visiting the Dermatology and Venereology OPD of DMCH between January 2016 and June 2017. Patients were divided randomly into two groups, 75 in each, by lottery method. First group (Group A) was treated with 4% Hydroquinone plus sunscreen (regular) daily for 12 weeks and second group (Group B) was treated with Tranexamic acid 250mg twice a day for 12 weeks. Response was evaluated on the basis of Melasma Area and Severity Index (MASI) and Melasma Quality of Life (MELASQoL) Questionnaire. The mean scores of both variables were compared between both groups. ***Results:*** Epidermal melasma was comparatively quicker and better responded to the treatment than dermal or mixed variants. The mean MASI and mean MELASQoL scores between both groups were not significantly different at 4 weeks ($p>0.05$) but was significantly effective in Group B at 8 and 12 weeks ($p<0.05$). The mean MASI scores of Group A (HQ & sunscreen) were 11.43±1.82, 9.98±1.99 and 8.94±2.16 at 4, 8 and 12 weeks respectively. The mean MASI scores of Group B (TA) were 11.34±1.92, 9.30+2.07 and 7.19±2.16 at 4, 8 and 12 weeks respectively. Similarly, the mean MELASQoL scores of Group A (HQ & sunscreen) were 34.95±6.61, 29.40±6.60 and 25.87±7.19 at 4, 8 and 12 weeks respectively. The mean MELASQoL scores of Group B (TA) were 33.12±6.40, 26.19±6.43 and 20.63±6.70 at 4, 8 and 12 weeks respectively. ***Conclusion:*** Oral Tranexamic acid is more effective and has less side effects than topical hydroquinone for the treatment of melasma.

Keywords: Melasma, Tranexamic acid, Hydroquinone, Bangladesh.

INTRODUCTION

Melasma is an acquired benign pigmentary disorder [1]. Melasma manifests as slowly enlarging, usually bilateral and frequently symmetrical irregular tan to brown macules or patches. It is seen on the faces and arms, usually on the cheeks, forehead, nose and upper lip [2]. Although no race is spared, it is often found among Asian or Hispanic females with a skin type III – type V, in child bearing age group [3, 4]. However, the pathogenesis of melasma is still unclear [1]. Melasma is the result of increased deposition of melanin in epidermis and/or dermis and its occurrence is highly related to sunlight exposure, pregnancy, oral contraceptives, hormone replacement therapies, cosmetics, phototoxic drugs, and genetic effects [2, 5]. Melasma's therapy is based on suppression of the proliferation of melanocytes, inhibiting the formation of melanosomes and promoting the degradation [5]. The current treatments include topical use of depigmenting

***Corresponding Author:** Dr. Mohammad Saiful Islam
Assistant Professor (Dermatology), Centre for Medical Education (CME), Mohakhali, Dhaka, Bangladesh

agents such as hydroquinone and tretinoin; bleaching therapies using lactic acid, glycolic acid, trichloro-acetic acid and kojic acid; and laser treatments.

Hydroquinone (HQ), also known as dihydroxybenzene, is a hydroxyphenolic compound that is structurally similar to precursors of melanin. Today topical hydroquinone is considered to be the gold standard among topical treatments of melisma [6]. In addition, it is usually adjunct with standard sunscreen lotion for its protective action against ultraviolet (UV) spectrum [6].

Despite, its overall efficacy rate 80%, is associated with a higher frequency of adverse effects including burning, itching, dryness, erythema, contact dermatitis, and more importantly, toxic reactions such as permanent ‘‘confetti-like’’ depigmentation and does not guarantees satisfactory results [7-9]. Treatment remains a challenge, and the search for safe, effective therapy continues.

Oral tranexamic acid has been introduced as treatment option for melasma. The efficacy of Tranexamic acid (TA) lack study till 2000 but since after few studies were conducted reporting its overall efficacy ranges between about 20% to 100% without any severe complications in any study carried [2, 10, 11]. Also, it reverses melasma related dermal changes such as vessel number and increased numbers of mast cells [12]. Therefore, it has been used largely in case of relapse or failure of treatment for melasma. Very few studies had been carried out as a primary treatment option. The studies carried out in different parts of world on TA in melasma have shown significantly effective and safer.

We hypothesise that oral tranexamic acid is more effective treatment for melasma than hydroquinone plus sunscreen.In Bangladesh, this type of study has not been carried out before. This study was aimed to compare the clinical effectiveness between TA and HQ plus sunscreen among Bangladeshi patients with melasma in a tertiary dermatologic center.

MATERIALS AND METHODS

This randomized, parallel-group clinical trial study was conducted to compare the efficacy of oral tranexamic acid in comparison with hydroquinone plus sunscreen in patients with melisma between 2016 to June 2017.

Participants

The study population consisted of all subjects presenting with melasma referred to the Department of Dermatology and Venereology, Dhaka Medical College and Hospital, Bangladesh from January 2016 to June 2017. Subjects who met the inclusion criteria, including patients aged 18–50 years, and those who had been suffered from the melasma for at least 1 year and had received no medication for at least 6 months were included. The exclusion criteria were as follows: i) patients with dermatitis; (ii) patient with chronic diseases or skin diseases: (iii) patients with hyper coagulative disorder and bleeding disorder; (iv) history of pregnancy, and lactation.

Clinical Assessment

Eligible subjects were randomly divided into two equal groups treated with oral Tranexamic acid and topical Hydroquinone 4% plus standard sunscreen lotion. Patients with melasma in the group A were treated with topical Hydroquinone 4% plus standard sunscreen lotion for 12 weeks. Patients with melasma in the group B were treated with oral Tranexamic acid 250 mg twice daily, per oral after meal, for 12 weeks.

Operational Definition

Melasma Area and Severity Index (MASI) score

The severity of the melasma in each of the four regions (Forehead, Right Malar Region, Left Malar Region and Chin) is assessed based on three variables: percentage of the total area involved (A), pigmentation (P), and homogeneity (H). To calculate the MASI score [13], the sum of the severity grade for pigmentation (P) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas (10-30%). The minimum score for MASI can be 0 while maximum score can be 48.

The Melasma Quality of Life Questionnaires (MELASQoL)

MELASQoL questionnaires are used to measure the Health Related Quality of Life (HRQoL) of patients with melisma [14]. The minimum score of 10 indicates “not bothered at all” while maximum score of 70 indicates “bothered all the time”.

Melasma Diagnosis

Detailed history, particularly regarding melasma and for any known chronic diseases, hyper coagulopathy and bleeding disorders of both male and female subjects. If female, obstetric including menstrual history was also taken. Clinical examinations (general, systemic and dermatological) were done for each subject and relative information (melasma) recorded in predesigned data entry form. Melasma was confirmed by the certified dermatologist (Assistant Professor or above). The type of melasma was graded with Wood’s lamp examination. MASI score [13] was used to assess the severity of melasma, separately for each side of the face. MELASQoL was used for the quality of life assessment [14].

Sample Size Determination

Sample size was calculated to be 150 individuals according to Kirkwood and Sterne [15], using the following formula considering the type 1 error level of 5%, power of 80%, and 5% dropout rate in the

two-sided model as well as accounting for an analysis following the intention-to-treat principle:

$$n = \frac{P1\,(1-P1)+P2\,(1-P2)}{(P1-P2)2}(Z\alpha + Z\beta)^2$$

Randomization

Enrollment of the study subjects was done by purposive sampling method based on selection criteria. Then allocation of study subjects in both groups was done by simple randomization with the help of online lottery method. In this single blind study, the outcome evaluator (independent investigator) was fully unaware of the study protocol and had no role in the randomization and allocation.

Ethical Consideration

At the beginning of the study before randomized assignment, all eligible subjects were provided written informed consent. This clinical trial was approved by the ethics Committee of Dhaka Medical College. All the study subjects were assured of adequate treatment of any complications developed in relation to the purpose of the study. Each patient was assigned a unique identifcation code, with all data remaining confidential and anonymous. The study was performed in accordance with the Declaration of Helsinki.

Follow Up and Outcome Assessment

Three follow up were scheduled: first (after 4 weeks), second (after 8 weeks), and third (after 12 weeks of treatment initiated) for individual patient. Detailed history regarding the improvement/worsening of the melasma and any side effect(s) regarding the treatment was considered into account. MASI score was used to assess the severity of melasma. The MELASQoL was used for the assessment of quality of life. It was documented based on the score given by the patient's response for level of satisfaction for the treatment of melasma.

Statistical Analysis

Continuous parameters were expressed as mean ± SD and categorical parameters as frequency and percentage. Continuous parameters were compared by unpaired student *t*-test at significance level $p<0.05$ and categorical parameters were compared by Chi-square test (χ^2) or Mann-Whitney U test at significance level $p<0.05$. Results were presented in the form of comparative tables, bar diagram and graphs, which when applicable. Analysis was conducted on SPSS 24.0 for windows software.

RESULTS

The mean age in Group A was 33.75±7.25 while in Group B was 34.25±7.77 with age ranges from 20–50 in both groups (Table 1).The maximum numbers of subjects were within age group 31–40 in both groups (54.7% and 50.7% in Group A and Group B, respectively). Number of female participants was 5 times higher than male in both groups. The most common type of skin in studied subjects had Type IV (34.6% and 53.3%) and Type V (62.7% and 33%) in both age groups. Very few numbers had Type III skin in both groups. In both groups, maximum numbers of subjects had history of ≤ 5 years of melasma (49.3% vs 46.7%, in Group A and Group B, respectively). The mean duration of onset was 7.25±5.34 in Group A and 7.77±5.78 in Group B. In terms of clinical types of melasma, epidermal was most observed type in both groups (74.7% vs 85.3%, in Group A and Group B, respectively). Centro facial pattern of melasma was the most common pattern (85.3% vs 82.7%) in both groups. Bilateral distribution of melasma was observed in most of the subjects in both groups (65.3% and 70.7%, in Group A and Group B respectively). Symmetrical distribution (67.3% and 71.7%) was much higher than asymmetrical distribution (32.7% and 28.3%) in both groups.

Table 1: Baseline patient characteristics according to treatment group

Characteristics	Group A (n_1=75)		Group B (n_1=75)		*p*-Value
	n_2	%	n_2	%	
Age					
20 – 30	22	29.3	21	28.0	
31 – 40	41	54.7	38	50.7	
41 – 50	12	16	16	21.3	
Mean ± SD, range	33.7 ±7.3 [20 - 50]		34.2 ±7.7 [20 - 50]		0.69
Gender					
Female	62	82.7	65	86.7	0.49
Male	13	17.3	10	13.3	
Fitzpatrick skin type					
Type III	2	2.7	2	2.7	0.06
Type IV	26	34.6	40	53.3	
Type V	47	62.7	33	44.0	
Duration (in years)					
≤ 5	37	49.3	35	46.7	0.70
6–10	24	32.1	24	32.0	
11–20	13	17.3	14	18.6	

Characteristics	Group A (n_1=75)		Group B (n_1=75)		*p*-Value
	n_2	%	n_2	%	
≥ 21	1	1.3	2	2.7	
Mean ± SD, range	7.25±5.34 [1–25]		7.77±5.78 [1.2–30]		
Clinical types of melasma					
Dermal	7	9.3	4	5.1	0.26
Epidermal	56	74.7	64	85.3	
Mixed	12	16.0	7	9.3	
Patterns of melasma					
Malar	4	5.4	9	12.0	
Centrofacial	64	85.3	62	82.7	0.25
Mandibular	7	9.3	4	5.3	
Distribution of melasma					
Unilateral	26	34.7	22	29.3	
Bilateral	49	65.3	53	70.7	0.48
Symmetry of melasma					
Symmetrical	33	67.3	38	71.7	
Asymmetrical	16	32.7	15	28.3	0.63

p value reached from unpaired student's t test and p<0.05 considered as significant.

Outcome Assessment Result

Table 2 shows the mean MASI scores at baseline were not significantly different among groups (12.0±1.73 vs 11.99±1.85, *p*>0.05, in Group A and Group B, respectively). Similar result was noticed at 4 weeks follow up (*p*>0.05). At 8 weeks and 12 weeks, the difference were significant (*p*<0.05).

Table 2 shows the mean MELASQoL scores between both groups. At baseline and follow up at 4 weeks there were no significant difference of mean MELASQoL scores between both groups while it was significant at 8 weeks and 12 weeks follow up.

Table 2: Distribution of subjects by their of mean MASI scores and MELASQoL scores

Follow up schedule	MASI scores			MELASQoL scores		
	Group A (n_1=75)	Group B (n_1=75)	*p*-value	Group A (n_1=75)	Group B (n_1=75)	*p*-value
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Baseline	12.0 ± 1.7	11.9 ± 1.8	0.96	42.5 ± 6.1	43.0 ± 6.3	0.65
4 weeks	11.4 ± 1.8	11.3 ± 1.9	0.78	34.9 ± 6.6	33.1 ± 6.4	0.11
8 weeks	9.9 ± 1.9	9.3 ± 2.1	0.04	29.4 ± 6.6	26.2 ± 6.4	0.003
12 weeks	8.9 ± 2.1	7.2 ± 2.2	0.001	25.8 ± 7.2	20.6 ±6.7	0.001

Table 3 Participants with or without side effects between Group A and Group B

Characteristics	Group A (n=75)		Group B (n=75)		p-value
	n	%	n	%	
Side effects					
No	51	68.0	63	84.0	
Yes	24	32.0	12	16.0	0.04
Type of side effects					
Group A (n=24)					
Erythema	14	18.6	0		
Post inflammatory hyperpigmentation	10	13.3	0		
Group B (n=12)					
Transient headache	0		5	6.6	
Nausea	0		3	4.0	
Abdominal cramp	0		2	2.6	
Oligomenorrhea	0		2	3.0	

MASI Scores and MELASQoL Scores by Skin Types

Figure 1 shows the mean MASI scores of dermal, epidermal and mixed melasma on subsequent follow up in both groups. However, the statistically significant decrease was only observed at 12 weeks follow up among Group B patients in comparison to Group A patients (9.0±1.59 and 6.76±1.15, respectively, p<0.05) for the dermal melasma. However, on subsequent follow up at 8 weeks

(9.73±2.90, 9.33±1.08, p<0.05) and 12 weeks (8.66±2.08, 7.19±2.26, p<0.05) there was significant decrease in MASI scores in epidermal melasma. For the mixed melasma, the statistically significant decrease was only observed at 12 weeks follow up among Group B patients in comparison to Group A patients (7.45±1.78and10.22±2.51, p<0.05).

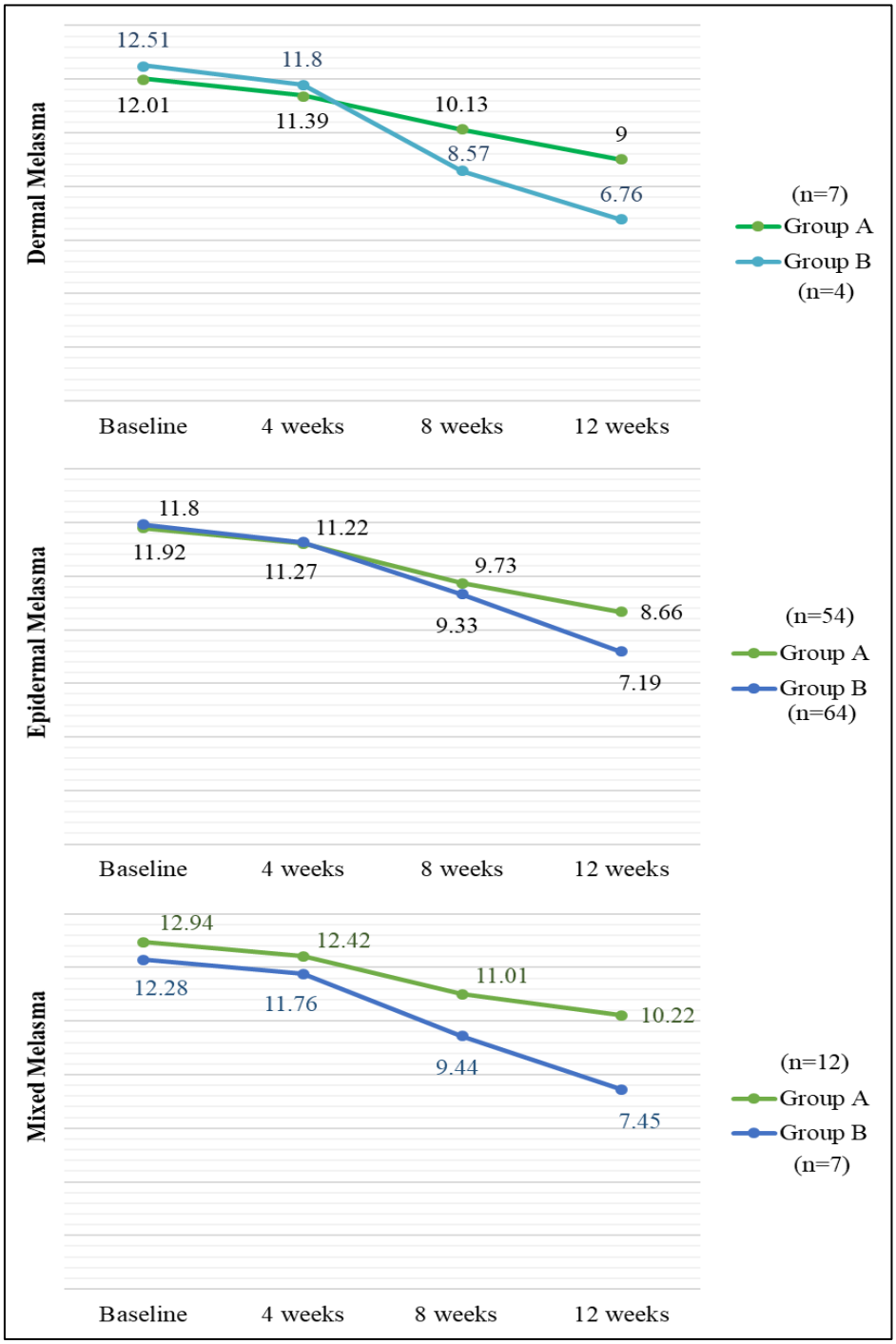

Figure 1: Comparative graph showing the decline in mean MASI scores of demal, epidermal and mixed melasma

Figure 2 shows the mean deMELASQoL scores of dermal, epidermal and mixed melasma on subsequent follow up in both groups. The subsequent follow up shows statistically significant difference between groups. At 4 weeks follow up, 30.0±2.16 and 39.29±6.84, p<0.05. At 8 weeks follow up, 23.0±2.44 and 32.0±5.32, p<0.05. And at 12 weeks follow up, 28.86±6.71 and 17.25±5.31, p<0.05 for the dermal melasma. There were significant decrease in mean MELASQoL scores on subsequent follow ups at 8 weeks (29.04±6.63, 26.84±6.70, p<0.05) and 12 weeks (25.23±7.22, 21.22±6.90, p<0.05) for epidermal melasma. There were significant decrease in mean MELASQoL scores on subsequent follow ups for the

mixed melasma at 4 weeks follow up, 35.0±6.09and 29.14±5.17, p<0.05; 8 weeks follow up, 29.58±7.29and 22.0±2.0, p<0.05; 12 weeks follow up, 27.08±7.28and 17.14±3.76, p<0.05, in Group A and Group B respectively.

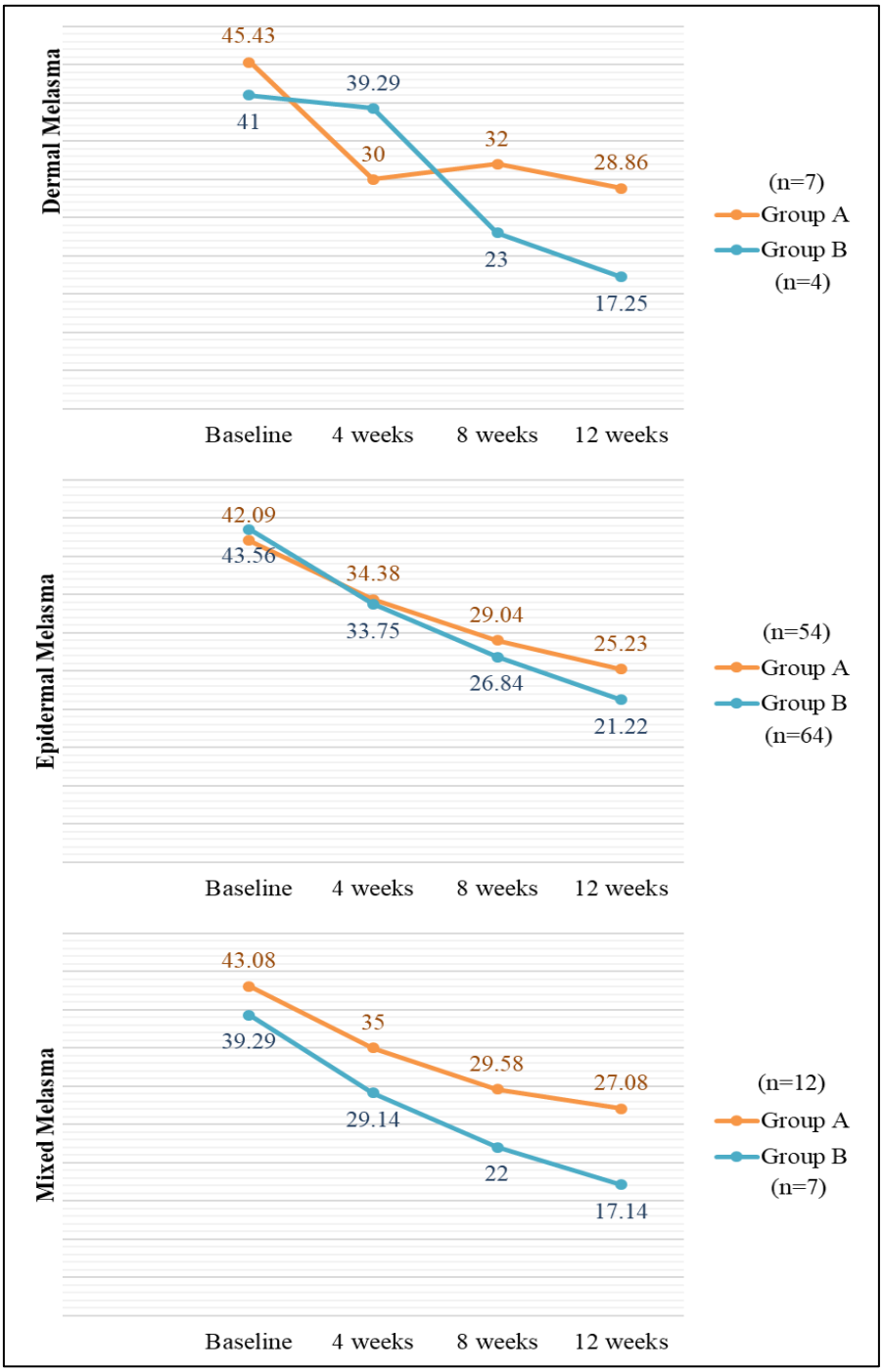

Figure 2: Comparative graph depicting the decline in mean MELASQoL scores of demal, epidermal and mixed melasma

Side Effects

In Group A, total 24 patients (32%) had side effects in comparison to Group B (16%). Chance to develop side effects is less among the Group B patients in comparison to Group A and it was found as statistically significant. Among 24 patients, 18.6% had erythema and 13.3% patients had post inflammatory hyperpigmentation in Group A. However, 6.6% patients had transient headache, 4% patients had nausea in Group B which was absent in Group A.

DISCUSSION

This study found that oral Tranexamic acid can be used for the effective treatment of melasma considering 250 mg orally twice daily doses. However,

robust study design with long-term follow up schedule, and intervention by different dosages of Tranexamic acid should be considered for further experiment. Oral tranexamic acid has been introduced as treatment option for melasma. It has been used largely in case of relapse or failure of treatment for melasma. Very few studies had been carried out as a primary treatment option. The studies carried out in different parts of world on TA in melasma have shown significantly effective and safer. We also found the effectiveness of the drug in Bangladeshi population remains better.

Age of the patient ranges between 20 to 50 years with the mean age of 34.3 years in Group A and Group B, respectively. The study of Karn *et al.,* [16]. In 260 Nepalese patients observed overall mean age of 30.3±9.01 and the age ranges from 17 to 55 years. Similar study done in China by Wu *et al.,* [2] also found the similar result. In the present study, the gender distribution was female predominant with overall 84.6% and male 15.4% (5.4:1, female: male). In most of the studies, the gender ratio was found to be similar [1, 16, 17]. This reflects one among others etio-pathology of melasma, a cyclic change in the hormones of female. Fitzpatrick skin type III – type VI among Asians are common as reflected by all most all studies carried out in the related field [5]. We got the similar result in the current study.

Examining under Wood's lamp revealed clinical types of melasma. Maximum number of patients had epidermal (74.7%, 85.3%) followed by mixed (16%, 9.3%) and lastly dermal (9.3%, 5.3%) variants in both groups. the pattern of melasma was found to be centro facial in majority of the cases (85.3% and 82.7%) in Group A and Group B, respectively. Our results reflected the similarities with the other studies [16, 18]. There was no significant association among the study subjects in two groups in relation to patterns of melasma and its distribution or symmetry.

In the present study, melasma assessment severity index (MASI) was considered as one of the outcome variables. The mean MASI scores at 8 weeks were 9.98±1.99 and 9.30±2.07 in Group A and Group B respectively and the difference was significant (p=0.043). Also, the mean MASI scores at 12 weeks were significantly different (p=0.000) of both groups (8.94±2.16 vs 7.19±2.16. Karn *et al.,* [16] also found significant decrease in the mean MASI scores from baseline to 8 and 12 weeks. Similarly, the mean MELASQoL scores at 8 weeks (29.40±6.6 vs 26.19±6.43) and 12 weeks (25.87±7.19 vs 20.63±6.70) follow ups the significant difference were seen (p=0.003 and p=0.000, at 8 weeks and 12 weeks, respectively).

While observing the individual skin types (dermal, epidermal and mixed) for treatment responses, the MASI scores and MELASQoL scores were compared individually at baseline and each follow up. This study showed epidermal melasma comparatively was quicker and better responded to the treatment than dermal or mixed variants. Patients with dermal and mixed melasma, in both groups, were compared statistically and noted that MASI scores were not statistically significant until 8 weeks follow up among groups (p=0.717 and p=0.161) but at 12 weeks follow up treatment with TA (Group B) was statistically significant (p=0.037). In contrast, MELASQoL scores were significant throughout the follow ups.

Topical Hydroquinone has some side effects. Oral Tranexamic acid at regular dose (2-3gm/day) has several side effects with some rare fatal side effects includes thromboembolism, pulmonary embolism and myocardial infarction. Side effect(s) of Tranexamic acid is dose depended and at low dose side effect(s) are of minor form as shown in different studies [16]. Similar result was observed during this study. Transient headache (6.6%), gastrointestinal side effects abdominal cramp (2.6%) and nausea (4%) and oligomenorrhea (3%); 1-2 cycles, in case of female patients were observed. In neither groups, any major complications were observed. Patients with side effects in both groups were managed by assurance and reassurance and in some cases with medication to relief symptoms. None of the patient required hospital admission. Chance to develop side effects is less among the Group B patients in comparison to Group A and it was found as statistically significant (p=0.043).

Limitations of the Study

This study enrolled participants by purposive sampling method which may arise selection bias. We only considered using a single dose of Tranexamic acid (250 mg) in this clinical trial. Long term follow up period not performed. Pathological samples such as skin histological findings were not considered. Sensitivity test and specificity test of the outcome were not considered.

CONCLUSION

We found that oral Tranexamic acid 250 mg twice daily is more effective therapeutic option than topical hydroquinone 4% plus sunscreen daily in the management of melasma. Side effects of the Tranexamic acid are less frequent in comparison to Hydroquinone 4%.

Authors' Contribution

MSI designed the study and collected data. MSI analysed the data. All authors wrote the paper.

Declaration of Competing Interest: None.

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