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ORIGINAL ARTICLE

Comparing Efficacy of Intradermal Tranexamic Acid (TA) Verses Fluocinolone-Based Triple Combination (Hydroquinone 4%, Tretinoin 0.05%, Fluocinolone Acetonide 0.01%) Therapy in the Treatment of Melasma

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ABSTRACT

Objective: To evaluate the efficacy of intradermal tranexamic acid (TA) verses fluocinolone-based triple combination (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%)therapy in the treatment of melasma.

Study Design: Randomized comparative trial

Place and Duration: Study was conducted at outpatient dermatology department of Sheikh Zayed hospital Rahim Yar Khan for period of six months i.e from September 2020 to February 2021.

Methods: Total 110 patients (age 18-40 year) of both genders having melasma on face were enrolled. Patients details demographics, age, sex and body mass index were recorded after taking written consent. Patients were divided into 2-groups. Group I had 55 patients and received intradermal tranexamic acid and group II had 55 patients andwere given topical fluocinolone-based triple combination (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%) cream. Follow up was taken for 2-months to determine efficacy and safety. Complete data was analyzed usingSPSS 22.0 version.

Results: Out of 110 patients 60 (54.54%) were females and 50 (45.46%) were males. Mean age of the patients in group I was 29.15±5.14 years with mean BMI 24.16±7.22 kg/m^2 and in group II mean age was 28.17±5.18 years with mean BMI 23.61±2.48 kg/m^2. Most of the patients (85 or 77.27%) had mixed melasma followed by dermal (16 patients /14.54%) and epidermal melasma(9 patients/8.18%). We found that malar-type pattern of melasma was most common, found in 66 (60%) of cases. A decrease in MASI score from baseline (15.4) was found 2.4 in group-Iand 5.6 in group-II. In group II erythema, hypertrichosis, hypopigmentation and acneiform lesions were the side effects found but there was no clinically significant side effect found in group I patients.

Conclusion: We found in this study that use of intradermal tranexamic acid (TA) in the treatment of melasma was effective and safe because there were no clinically significant side effects found after this treatment and reduction of MASI score was also significant.

Keywords: Triple combination, Melasma, MASI, Intradermal tranexamic acid

INTRODUCTION

Melasma is a common andacquired benign hypermelanotic skin disordercaused by defective melanogenesis.Clinically it presents as light to dark brown macules and patches, symmetrically arranged on face in a butterfly like distribution. [1]This condition is more common in young females most likely due to hormonal changes especially taking place during pregnancy. [2] Exact etiological agent for melasma is still unknown. Many proposed risk factors for melasma include genetic predisposition, pregnancy, oral contraceptives pills, sun exposure, ovarian tumors, hormone substitution therapy anticonvulsant medicines and steroids. [3]

There are many treatment options for melasma including topical therapies (triple combination cream, glycolic acid, trichloroacetic acid ,kojic acid, retinoids, Azelaic acid, arbutin, chemical peels etc.), invasive therapies (intradermal platelet rich plasma injection, intradermal steroid , lasers etc.) and systemic therapies (glutathione, vitamin C). [5, 6, 7] Gold standard treatment for melasma is still a fluocinolone-based triple combination (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%) cream. Hydroquinone (HQ) reduces hyperpigmentation by inhibiting the cytosine oxidation enzyme (tyrosinase), by reversibly limiting the synthesis of DNA and RNA and by affecting melanosomes formation. [4]Tretinoin increases the penetration of hydroquinone into skin and has many effects on the process of melanogenesis. [4] Fluocinolone acetonide (0.01%) has skin lightening effect due its inhibitory action on melanogenesis. [4] Possible side-effects of this triple combination cream are: erythema, irritation, UV sensitivity; dryness; skin irritation; exogenous ochronosis; desquamation and skin atrophy. [7, 8]

Recently many dermatologists started usingtranexamic acid (TA) for the treatment of melasma. In the course of the chronic urticaria treatment in 1979, Nijo Sadako unexpectedly found its beneficial effects. Tranexamic acid affects pigmentation due to its inhibitory action on UV rays–induced plasminogen activator and

plasmin activity [9]. UV radiation causes the synthesis of plasminogen activator by keratinocytes, which results in increased change of plasminogen to plasmin. Plasmin causes increase pigmentation in the basal layer of skin. [10,11, 12,13,14]. TA is used in various forms (i.e. topical, oral, intradermal injection). Dose of TA required to treat Melasma is significantly less than that required for antifibrinolytic action. [15]

MATERIAL AND METHODS

This randomized comparative study was conducted at outpatient dermatology department of Sheikh Zayed hospital Rahim YarKhan for period of six months i.e from September 2020 to February 2021.Total 110 patients (age 18-40 year) of both gender, having melasma on face of any type were enrolled in this study. All cases were randomly divided into groupI and II;each having 55 patients. Patient's demographics, age, sex and BMI were recorded after taking written consent.Patients with history of coagulation disorder, hypersensitivity to study drugs,pregnancy and lactation and thosewho did not provide written consent were excluded from this study.

Group I cases were given 0.05 mL of TA (having concentration 4 mg/mL) on every 15 day; intradermally into each 1 cm^2 area of melasma using an insulin syringe with a 30-gauge needle after application of topical anesthesia with lidocaine and prilocaine .

Group II cases received topical fluocinolone-based triple combination (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%)therapy, applied daily at night on melasma lesions for 3 hours. Each patient was told to use sunscreen daily 4 times/day (applied 30 minutes before sun exposure) and follow sun protective measures like use of scarfs and umbrellas. Patients of all groups were assessed for safety and efficacy every 2 weekly for 2 months. All the patients were examined throughout the course of the treatment for any adverse drug reactions. At each visit, patients were assessed for efficacy by melasma area severity index (MASI score) i.e.

Area	Darkness	Homogeneity
0 → No involvement	0 → Normal skin with out pigmentation	0 → Normal skin color without evidence of hyperpigmentation
1 → ≤ 10 %	1 → Barely visible hyperpigmentation	1 → Specks of involvement
2 → 10-29 %	2 → Mild hyperpigmentation	2 → Small patch areas of involvement <1.5cm diameter
3 → 30-49 %	3 → Moderate hyperpigmentation	3 → Patches of involvement >2cm
4 → 50-69 %	4 → Severe hyperpigmentation	4 → Uniform skin without any clear areas
5 → 70-89 %		
6 → 90-100 %		

The MASI score was calculated by subjective assessment of 3 factors: area (A) of involvement, darkness (D), and homogeneity (H), with the forehead (f), right malar region (rm), left malar region (lm), and chin (c), corresponding to 30%, 30%, 30%, and 10% of the total face, respectively. Formula to calculate total MASI score was as follows:

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.Complete data was analyzed SPSS 22.0 version. Categorical variables were assessed by frequencies and percentages.

RESULTS

Mean age of the patients in group I was 29.15±5.14 years with mean BMI 24.16±7.22 kg/m^2 and in group II mean age was 28.17±5.18 years with mean BMI 23.61±2.48 kg/m^2. Out of 110 patients 60 (30 in each) group were females and 50 (25 in each) group were males. Most of the patients 85 (77.27%) had mixed type of melasma followed by dermal 16 (14.54%) and epidermal melasma found in 9 (8.18%). (Table 1)

Table 1: Baseline detail demographics of enrolled cases

Variables	Group I (55)	Group II (55)
Mean age	29.15±5.14	28.17±5.18
Mean BMI (kg/m^2)	24.16±7.22	23.61±2.48
Gender		
Male	25 (22.73%)	25 (22.73%)
Female	30 (27.27)	30 (27.27)
Types of melasma		
Mixed	42 (38.18%)	43 (39.09%)
Dermal	8 (7.27%)	8 (7.27%)
Epidermal	5 (4.54%)	4 (3.64%)

Table 2: Differentiation between pattern of melasma and aggravating factors among patients

Variables	Group I	Group II
Pattern of melasma		
Malar-type	33 (30%)	33 (30%)
Centrofacial	18 (16.36%)	18 (16.36%)
Mandibular	4 (3.64%)	4 (3.64%)
Aggravating factors		
Sun exposure	42 (38.18)	42 (38.18)
OC pills	13 (11.82%)	13 (11.82%)

We observed that malar-type pattern of melasma was most common, found in 66 (60%) of cases followed by centrofacial 36 (32.73%) and mandibular pattern found in 8 (7.27%). Sun exposure was the most common aggravating factor found in 84 (76.36%) followed by pills 26 (23.64%). (Table 2)

Significantly decrease in MASI score 2.4 was found in group I from baseline (i.e. 15.4)and in groupII MASI score decreases to 5.6. Intradermal tranexamic acid (TA) in the treatment of melasma was effective and safe method as compared to triple base combination. (Table 3)

Table 3: Comparison of MASI score among both groups

Variables	Group I	Group II
MASI score		
At baseline	15.4	15.4
At last follow up	2.4	5.6

In group II erythema 3 (6%), hypertrichosis 1 (2%), hypopigmentation 1 (2%) and acneiform lesions 1(2%) were the side effects found but there was no clinically significant side effect ,found in group I patients. (Table 4)

Table 4: Comparison of side effects after treatment among both groups

Variables	Group I (n=55)	Group II (n=55)
Side effects		
erythema	0	3 (6%)
hypertrichosis	0	1 (2%)
hypopigmentation	0	1 (2%)
acneiform lesions	0	1 (2%)

DISCUSSION

Melasma is a common acquired and benign hyperpigmentary cutaneous disease, presents clinically symmetrically on the face in the form of hyperpigmented macules or patches. [1] Research has demonstrated that melasma causes cosmetic disfiguration and emotional suffering. In this randomized comparative study 110 patients of both genders were presented. Majority of the patients were females 54.54%. Mean age of the patients in group I (tranexamic acid) was 29.15±5.14 years with mean BMI 24.16±7.22 kg/m^2 and in group II (triple combination) mean age was 28.17±5.18 years with mean BMI 23.61±2.48 kg/m^2. Our findings were comparable to the previous some studies.[16,17]

In current study most of the patients 85 (77.27%) had mixed melasma followed by dermal 16 (14.54%) and epidermal melasma was found in 9 (8.18%). Like our study,in the Nicolaidou et al. investigation [18] the mixed type of melasma was more common. Achar and Rathi[19] were found that epidermal type of melasma was the most prevalent type under Wood's lamp exam (54.48%). This change of outcomes could be related to variances in the environment or regions. We found that malar-type pattern of melasma was most common found in 66 (60%) among cases followed by centrofacial 36 (32.73%) and mandibular pattern found in 8 (7.27%). Thappa[20] and Goh and Dlova[21] have noted that malar distribution is most common, according to our analysis, in their Singapore and South India investigations respectively. Sun exposure was the most common aggravating factor found in 84 (76.36%) followed by pills 26 (23.64%). This was comparable to the previous study.[22]

Significantly decrease in MASI score 2.4 was found in group I from baseline (15.4)and in group II MASI score decreases to 5.6. Intradermal tranexamic acid (TA) in the treatment of melasma was effective and safe method as compared to triple base combination.[16,23] For the split face study, Ebrahimi &Naeini[24] were suspended topically by 3% TA on one side of the face and by 3% hydroquinone, 2% vitamin C and 0.01% dexamethasone on the other side of the face. In both groups, there was a considerable decrease in MASI score, but no major difference between these two groups. This was the result of our study. The future open-label trial by Lee et al.[25] assesses the effectiveness of the weekly TA micro-injection in treating melasma has been undertaken. The MASI score decreased statistically from baseline to 8 at 12 weeks. Also in the various treatment groups, Kaushik et al.[26] reported statistical significance. The MASI score was highest improved in Group A in our study. The next MASI score with a P value increased in Group C. Ayuthayaetal.[27] reported no superior nor different therapeutic benefit from 5% of TA gel on melasma.

In our study we found that there was no significant side effect found in tranexamic acid patients but side effects like erythema 3 (6%), hypertrichosis 1 (2%), hypopigmentation 1 (2%) and acneiform lesions 1(2%) were found in group II .in the end we found result that intradermal tranexamic acid (TA) in the treatment of melasma was effective and safe method as compared to triple base combination. Our findings were comparable to the previous some studies. [20-27]

CONCLUSION

We found in this study that use of intradermal tranexamic acid (TA) in the treatment of melasma was effective and safe method because there were no clinically significant side effects found after this treatment and reduction of MASI score was also significantly observed.

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