

Original Article**The Role of Combination of 20% Azelaic Acid with 0.05% Tretinoin Cream in the Treatment of Melasma**SC Hazra¹, MR Siddique², L Khondker³, MSI Khan⁴, MM Mahmud⁵**Abstract**

Melasma is characterized by brown patches, typically on malar prominences and forehead. The pigmented patches are usually affect darker complexioned individual especially Asian. So it is a great problem in our country. A clinical trial was conducted to find out the effect of the combination of 20% azelaic acid cream with 0.05% tretinoin cream in the treatment of melasma. Thirty clinically diagnosed cases of melasma attending the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, were enrolled. Majority of the study subjects (43%) were between 26 to 30 years and most of them (73.3%) were female. Regarding occupation 56.7% were housewife. Out of the study subjects 70% were married and

86.7% were of middle class. Around 66.7% cases had positive family history of melasma and maximum 93.3% patient had no history of systemic drug and the maximum 73.3% patient had no history of use of cosmetics. It was observed that highest (93.3%) number of patients had malar area involvement and 6.7% had centro-facial area involvement. The study showed that after treatment, the average MASI (Melasma Area and Severity Index) score was decreased by 38.66% indicating moderate reduction of the severity of melasma. Out of the study subjects, 50%, 30%, 16% developed burning sensation, itching and erythema respectively. It could be concluded that combination of 20% azelaic acid and 0.05% tretinoin cream, has a moderate lightening effect in the treatment of melasma.

Key words: 20% azelaic acid, 0.05% tretinoin, melasma.

Introduction:

Melasma is a common acquired macular hyperpigmentation which involves mostly on sun exposed areas of face and neck. It is reasonably common particularly in women of child bearing age. However, up to 26 percent of cases have been reported in males.¹ There are three clinical patterns of melasma (i) centro-facial, most common pattern involving cheek, forehead, upper lip, nose and chin (ii) malar-involving cheek and nose (iii) mandibular-involving the ramus of mandible. The

type of hyperpigmentation may be epidermal (brown), dermal (blue-gray) or mixed (brown-gray).²

Melasma has been considered to arise from pregnancy, oral contraceptives, endocrine dysfunction, genetic factors, medications, nutritional deficiency, hepatic dysfunction, HIV (Human Immunodeficiency Virus) infection and other factors. Sun exposure would appear to be an exacerbating factor in otherwise predisposed individuals.³ Melasma like hyperpigmentation has been observed in patients taking phenytoin or mephenytoin. Melasma appears to be a chronic process that is exacerbated by sunlight and artificial UVA (Ultraviolet light A) and UVB (Ultraviolet light B). Up to a third of the cases in women and most in men are idiopathic.⁴

A recent study suggests that a high expression of MSH (Melanocyte Stimulating Hormone) in the lesional keratinocytes of melasma plays a key role in the pathogenesis of the hyperpigmentation of melasma skin.⁵ Histologic studies of melasma developed skin, reveal increased melanin in the epidermis (epidermal type), dermis (dermal type) or both (mixed type).⁶ Studies suggest an increase in the number and activity of melanocytes: there is an increase in the formation, melanization, and transfer of melanosomes to the epidermis as well as the dermis.⁷ The diagnosis is usually readily

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established by clinical features. Post inflammatory hyperpigmentation can usually be excluded by history, Wood's lamp examination and using infrared film.⁸

Azelaic acid is a dicarboxylic acid found in food (whole-grain cereals and animal products).⁹ The mechanism of action is thought to be normalization of the keratinization process (decreased thickness of the stratum corneum, decreased number and size of keratohyaline granules, and decreased amount of filaggrin).¹⁰ There is no risk of exogenous ochronosis which can be associated with higher concentration of hydroquinone.¹¹ Local irritation with azelaic acid is more common than with hydroquinone.⁹

Tretinoin is a yellow to light orange crystalline powder having characteristic floral odor.^{12,13} Tretinoin is a endogenous retinoid of vitamin A that binds with intra cellular receptor in the cytosol and nucleus. Cutaneous level of tretinoin in excess of physiologic concentration occurs following application of a tretinoin containing topical product.¹⁴ The local adverse effect observed include erythema, scaling, pruritus, stinging, dryness, irritation and patients also note a decreased tolerance to ultra violet radiation leading to photo toxicity reaction.¹⁵

Materials and Methods:

A clinical trial was conducted to find out the effect of the combination of 20% azelaic acid cream with 0.05% tretinoin cream in the treatment of melasma. Thirty clinically diagnosed cases of melasma attending the outpatient department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, fulfilling the inclusion criteria were enrolled. The study was carried out from February 2009 to July 2010. An informed consent was sought from the patients to take part in the study. Data were recorded on pre-designed case record form. At the baseline visit, history of melasma regarding length of time present, relationship to pregnancy, hormonal therapy, sun exposure and cosmetic use etc. were taken. Patients were asked about previous use of azelaic acid and tretinoin and any hypersensitivity to these agents. Family history of melasma was also taken. Wood's light examination was done during entry time of study and only patient with the epidermal variety of

melasma were recruited for the study. MASI (Melasma Area and Severity Index) was calculated and recorded. The patients were advised to apply this preparation over the melasma once at every night and the patients were asked to report on 4th, 8th and 12th week for evaluation. The effect was evaluated clinically using Melasma Area and Severity Index (MASI) Score as proposed by Kimbrough-Green et al.¹⁶ At each visit, side effects were recorded and assessed on four point scale as absent, mild, moderate or severe. Female patients who are on oral contraceptive pill, pregnant and lactating females, persons having hypersensitivity to azelaic acid or tretinoin and patient suffering from any concomitant systemic illness, were excluded from the study.

Results:

Table I: Distribution of the patients by age

Age (in year)	Frequency	Percentage
20-25	2	6.7
26-30	13	43.3
31-35	9	30.0
36-40	4	13.3
>40	2	6.7
Total	30	100.0

showed that age of the patients of melasma, where majority (43%) cases were between 26 to 30 years, 6.7% were between 20 to 25 years, 30% were between 31 to 35 years old, 13.3% were between 36 to 40 years old, 6.7% were more than 40 years old. Mean \pm SD of age (in years) was 32.43 ± 6.70 with range of 20-49 in the study.

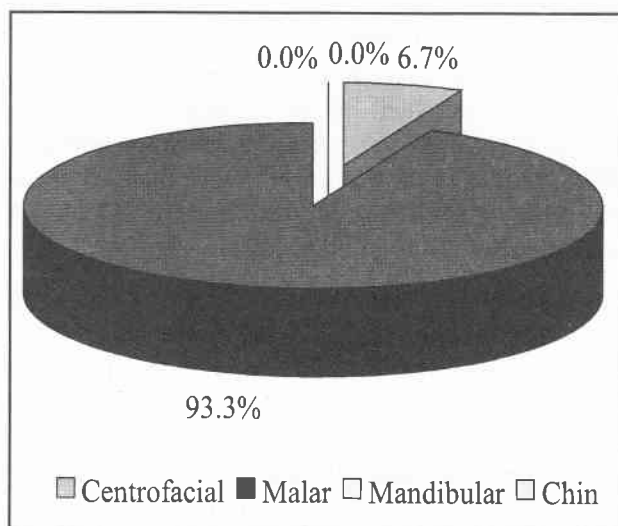
Table II showed that majority (73.3%) of patients was female and 26.7% were male and Male-Female ratio was 1: 2.75. Among the patients, 56.7% patients were housewives, 30% were students and 13.30% were involved in business. Regarding the marital status of the patient, maximum (70%) was married. On the basis of socio-economic condition, patients can be divided into 86.7% as middle class and 13.3% as lower class.

Table II: Distribution of the patient by epidemiological profile (n=30).

Epidemiological profile	Frequency
Sex	
Male	8(26.7%)
Female	22(73.3%)
Occupation	
Housewife	17(56.7%)
Students	9(30%)
Business	4(13.3%)
Marital status	
Married	21(70%)
Unmarried	9(30%)
Socio-economic condition	
Middle class	26(86.7%)
Lower class	4(13.3%)

Regarding family history of melasma, positive history was presents in 66.7% cases. Maximum (93.3%) patients had no systemic drug history and 73.3% patients had no history of use of cosmetics.

Figure 1: Distribution of the patients by site of involvement.

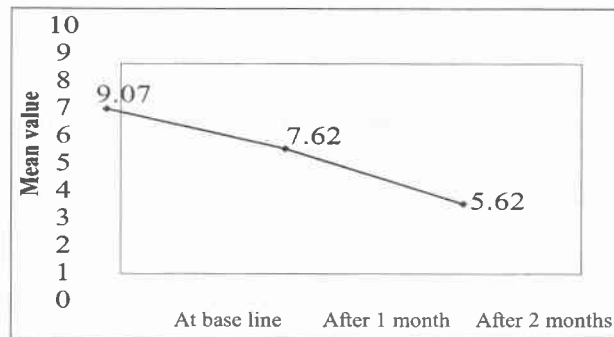


showed that highest (93.3%) number of patients had malar area involvement and 6.7% had Centروفacial area involvement

Table III: Distribution of the patient by personal profile (n=30).

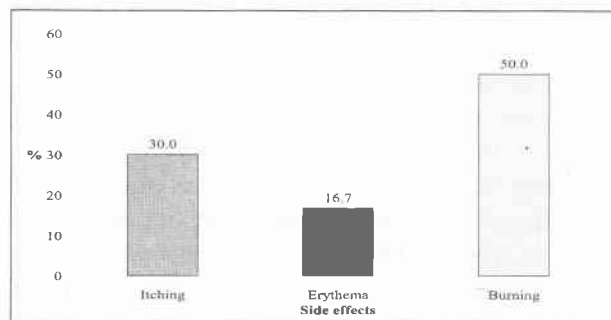
Personal profile	Frequency
Family History of melasma	
Positive	20(66.7%)
Negative	10(33.3%)
History of systemic drug	
Positive	
Negative	28(93.3%)
History of use of cosmetics	
Positive	8(26.7%)
Negative	22(73.3%)

Figure II: Changes of MASI score after treatment (Mean ± SD of MASI score)



showed the change in MASI Score after treatment with combination therapy. About 12 weeks of treatment the average MASI score was decreased by 38.66% indicating moderate reduction of the severity of melasma(0 = No reduction, up to 25% = mild, 26-50% = moderate, above 50% = remarkable reduction).

Figure III: Distribution of the patients by side effects.



showed that the 50%, 30%, 16% patient developed burning sensation, itching and erythema respectively.

Discussion:

A total of 30 clinically diagnosed cases of melasma fulfilling the inclusion criteria, were included in this study. MASI was calculated and recorded. The patients were advised to apply this preparation over the melasma once at every night and the patients were asked to report on 4th, 8th and 12th week for evaluation. The effect was evaluated clinically using Melasma Area and Severity Index (MASI) Score as proposed by Kimbrough-Green et al.¹⁶ The evaluations were recorded at baseline, at 4th week, 8th week. At each visit, side effects or tolerability were determined by itching, burning and erythema etc. The study showed that age of the patients of melasma, in majority (43%) cases were between 26 to 30 years, 6.7% were between 20 to 25 years, 30% were between 31 to 35 years old, 13.3% were between 36 to 40 years old, 6.7% were more than 40 years old. Majority (73.3%) of patients was female and male -female ratio 1: 2.75. These findings are similar to the research work, done by Garcia A.¹⁵

Among the patients, 56.7% patients were housewives, 30% were students and 13.30% were involved in business. Regarding the marital status of the patients, maximum 70% were married. On the basis of socio-economic condition, patients can be divided into 86.7% as middle class and 13.3% as lower class. Regarding family history of melasma, positive history was present in 66.7% cases. A strong family history of melasma suggests an important genetic factor in the pathogenesis of this condition. It showed that highest (93.3%) number of patients had malar area involvement and 6.7% had centro-facial area involvement, which is similar to the research work of Garcia A, where 91% of the patients had malar distribution and 9% of the patients had centro-facial distribution.¹⁵

The study showed the change in MASI Score after treatment with combination therapy. About 12 weeks of treatment the average MASI score was decreased by 38.66% indicating moderate reduction of the severity of melasma (0 = No reduction, up to 25% = mild, 26-50% = moderate, above 50% = remarkable reduction). It showed that the 50%, 30%, 16% patient developed burning sensation, itching and erythema respectively. The side-effects disappeared after 4 weeks of therapy. These findings are mostly in accordance with the

observations of Sarkar R, Bhulla M et al.¹⁷

Cutaneous side effects were limited to the burning sensation, itching and erythema. Limitation of time and financial support of this study subjects were this enormous restrictions. The study was done in a small scale with shorter duration, it can not reflect the proper effect and possible side effects of combination of 20% azelaic acid cream and 0.05% tretinoin cream in the treatment of melasma.

Conclusions:

An attempt was made to see the role of combination of 20% azelaic acid and 0.05% tretinoin cream in the treatment of melasma. It needs further elaborative study on a larger number of patients over a longer period of time. It could be concluded that combination of 20% azelaic acid and 0.05% tretinoin cream has a moderate lightening effect in the treatment of melasma.

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