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Original Article

The efficacy of combination of 20% azelaic acid with 0.05% tretinoin cream in the treatment of melasma

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Abstract

Background Melasma is a common acquired macular hyperpigmentation which involves mostly the sun exposed areas of face and neck.

Objective To assess the efficacy of the combination of 20% azelaic acid with 0.05% tretinoin cream in the treatment of melasma.

Patients and methods 30 patients of melasma were treated with daily night application of 20% azelaic acid and 0.05% tretinoin. Patients were assessed at 4, 8 and 12 weeks of treatment using melasma area severity index. Side effects during therapy were also noted.

Results Majority i.e. 43% cases were between 26 to 30 years, 73.3% of patients were females and 56.7% were housewives, 70% were married and 86.7% were in middle class. Family history of melasma was positive in 66.7% cases. 93.3% patients had no history of systemic drug and 73.3% had no history of use of cosmetics. 93.3% of patients had malar area involvement and 6.7% had centrofacial area involvement. After treatment, the average MASI score decreased by 38.66% indicating moderate reduction of the severity of melasma. Burning sensation, itching and erythema developed in 50%, 30% and 16%, respectively.

Conclusion The combination of 20% azelaic acid and 0.05% tretinoin cream in the treatment of melasma has a moderate lightening effect with some remarkable side effects.

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

Introduction

Melasma is a common acquired macular hyperpigmentation, and it is reasonably common, particularly, in women of child bearing age. However, up to 26% of cases have been reported in males.[1] There are three clinical patterns of melasma (i) centrofacial, most common pattern involving cheeks, forehead, upper lip, nose and chin (ii) malar - involving cheeks 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 infection and other factors. Sun exposure appears 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

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and UVB. 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 melanocyte stimulating hormone in the lesional keratinocytes of melasma plays a key role in the pathogenesis of the hyperpigmentation of melasma.[5] Histologic studies 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 established by clinical features. Postinflammatory hyperpigmentation can usually be excluded by history, Wood's lamp examination and using infrared film.[8]

Azelaic acid (AZ) is a dicarboxylic acid found in food (whole-grain cereals and animal products). The normal human plasma level is 20-80 ng/mL which does not significantly alter with topical application of azelaic acid.[9] The mechanism of action is thought to be normalization of the keratinization process i.e. decreased thickness of the stratum corneum, decreased number and size of keratohyaline granules, and decreased amount of filaggrin. In aerobic microorganisms, there is inhibition of oxidoreductive enzymes e.g. tyrosinase, mitochondrial enzymes of the respiratory chain, 5α-reductase, and DNA polymerases. In anaerobic bacteria, there is disruption of glycolysis, as well. AZ is used primarily in the treatment of acne vulgaris, although some researchers advocate its use in the treatment of hyperpigmentation e.g. melasma[10] and report that AZ is superior to 2% hydroquinone and equivalent to 4% hydroquinone for treatment of melasma. There is no risk of exogenous ochronosis which can be associated with higher concentration of hydroquinone.[11] Up to 10% of patients report itching, burning, scaling which may last 4 weeks. Local irritation with azelaic acid is more common than with hydroquinone.[9]

Tretinoin is a yellow to light orange crystalline powder having characteristics floral odour.[12] It is soluble in water, mineral oil and glycerine.[13] Tretinoin is an endogenous retinoid that binds with intracellular receptor in the cystosol and nucleus.[14] The local adverse effect observed include erythema, scaling, pruritus, stinging, dryness, irritation and patients also note a decreased tolerance to UV radiation leading to phototoxicity reaction. It is also teratogenic, when used in pregnancy.[15] Tretinoin has been used in the treatment of melasma.

The following clinical trial was conducted to find out the efficacy of the combination of 20% azelaic acid cream with 0.05% tretinoin cream in the treatment of melasma.

Patients and methods

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 for a period from February, 2009 to July, 2010. An informed consent was sought from the patients to take part in the study. Patients' data were recorded on pre-designed case record forms. At the baseline visit, history of melasma regarding duration, relationship to pregnancy, hormonal therapy, sun exposure and cosmetic use etc. was 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 and patients with the epidermal variety of melasma only were recruited for the study.

The combination product of 20% azelaic acid and 0.05% tretinoin was dispensed locally by qualified pharmacist. The patients were advised to apply this preparation over the affected areas once at night daily and the patients were asked to report on 4^{th}, 8^{th} ,12^{th} weeks for evaluation. The efficacy was evaluated clinically using MASI score as proposed by Kimbrough-Green *et al*.[16] At each visit, side effects and tolerability were determined in the treatment area. These factors were assessed on four-point scale as absent, mild, moderate or severe.

Inclusion criteria used in study were facial melasma diagnosed clinically and with Wood's lamp examination, informed consent to participate in the study, age ≥ 20 years and patients of both sexes. Patients with purely dermal melasma, female patients on oral contraceptive pills, pregnant and lactating females, outdoor workers, persons having hypersensitivity to azelaic acid or tretinoin, individuals on any form of topical or oral medication for at least 4 weeks prior to the study, or suffering from any concomitant systemic illness were excluded from the study.

Melasma Area and Severity Index (MASI)

The MASI score was used to quantify the pigmentation area, darkness and homogeneity in patients with melasma. For assessing the hyperpigmented area of the face, four areas of face were evaluated: forehead (F), right malar region (MR), left malar region (ML), and chin (C), corresponding to 30%, 30%, 30% and 10% of the total face, respectively. Melasma in each of the four areas was given a numerical value: 1, <10%; 2, 10–29%; 3, 30–49%; 4, 50–69%; 5, 70–89%; and 6, 90–100%. Darkness of pigment compared with normal skin (D) was assessed in each area on a scale of 0 (absent) to 4 (severe); homogeneity (H) was also assessed on a scale of 0 (minimal) to 4 (maximum). To calculate the MASI score, the sum of the severity score for D and H was multiplied by the numerical value of the corresponding area (A) involved. The total MASI score, the maximum score 48 and the minimum 0, was calculated as follows:

MASI = 0.3A(D+H) for forehead + 0.3A(D+H) for right malar area + 0.3A (D+H) for left malar area + 0.1A (D+H) for chin.

The reduction in MASI score was used to categorize efficacy: 0 = no reduction, up to 25% = mild, 26-50% = moderate, above 50% = remarkable reduction).

Results

Thirty clinically diagnosed cases of melasma fulfilling the inclusion criteria were enrolled. **Table 1** shows the demographic and clinical data of patients. The mean age of patients was 32.43±6.70 years with a range of 20-49 years. The majority (43%) of cases were between 26 to 30 years. Females outnumbered males 73.3% vs. 26.7% with ratio of 2.8:1. Positive family history of melasma was present in 66.7% cases and 93.3% patients had not used any systemic drug. Similarly, the majority had no history of use of cosmetics. The highest number of patients (93.3%) had malar area involvement and 6.7% had centrofacial distribution.

Figure 1 shows the change in the mean MASI score after treatment with combination therapy. About 12 weeks of treatment the average MASI score decreased by 38.7% indicating a moderate reduction of the severity of melasma.

Regarding side effects profile, burning sensation, itching and erythema were seen in 50%, 30% and 16% of patients, respectively. However, these side effects disappeared with continuation of therapy.

Table 1 Demographic and clinical data of patients (n=30).

	N (%)
Age (in year)	
20-25	2 (6.7)
26-30	13 (43.3)
31-35	9 (30)
36-40	4 (13.3)
>40	2 (6.7)
Sex	
Males	8 (26.7)
Females	22 (73.3)
Occupation	
Housewife	17 (56.7)
Students	9 (30)
Business	4 (13.3)
Marital status	
Married	21 (70)
Unmarried	9 (30)
Socioeconomic class	
Middle	26 (86.7)
Lower class	4 (13.3)
Positive family history	20 (66.7)
History of systemic drug use	2 (6.7)
History of use of cosmetics	8 (26.7)
Area of distribution	
Malar	28 (93.3)
Centrofacial	2 (6.7)

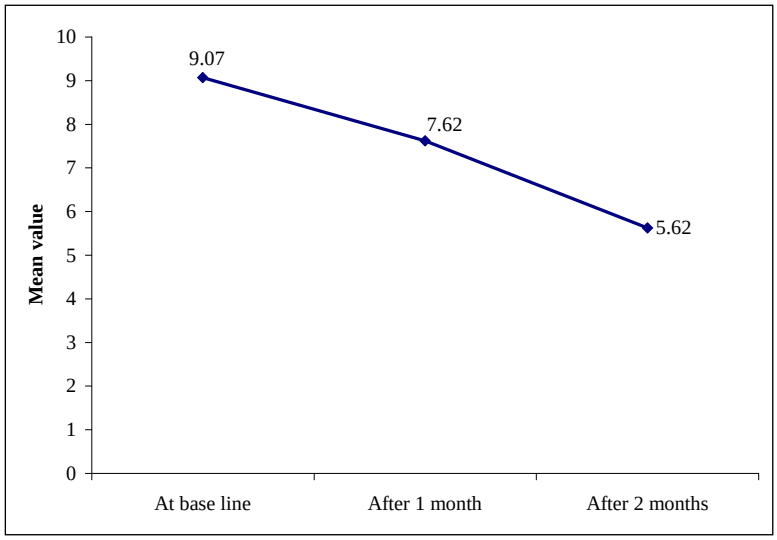

Figure 1 Changes of MASI score after treatment (Mean ± SD of MASI score)

Discussion

Our study showed that majority (73.3%) of patients were females with female:male ratio of 2.8:1, which is similar to the research work of Garcia and Fulton, where 97% of the patients were female and 3% of the patients were male.[15]

The majority of the patients were housewives (56.7%), married (70%) and belonged to middle class (86.7%). Due to lack of time and careless attitude about their health and more importantly, their tendency to give more attention and priority to their family, they failed to follow up and ensure their treatment properly.

Positive family history of melasma was present in 66.7% cases which suggests the significance of genetic factors in the pathogenesis of this condition. Malar area was the most frequent type (93.3%) and 6.7% had centrofacial area involvement, which is also similar to the research work of Garcia and Fulton, where 91% of the patients had malar distribution and 9% of the patients had centrofacial distribution.[15]

After 12 weeks of treatment, the average MASI score decreased by 38.7% indicating moderate reduction of the severity of melasma. 50%, 30% and 16% of patients 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 *et al*.[17]

This study demonstrates that daily night application of combination of 20% azelaic acid and 0.05% tretinoin cream has a moderate lightening effect on melasma and it is safe as well.

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