Faridpur Med. Coll. J. 2013;8(1): 22-25

Original Article

Study of Efficacy and Safety of Triple Combination Agent (4% Hydroquinone, 0.05% Tretinoin and 0.05% Clobetasone Butyrate) in the Treatment of Melasma

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Abstract :

Melasma is a very common disorder of hypermelanosis affecting face. The pigmented patches usually affect darker complexioned individual especially Asian. An interventional study was carried out to detect the efficacy and safety of triple combination agent (4% Hydroquinone, 0.05% Tretinoin and 0.05% Clobetasone butyrate) in the treatment of melasma. Total 50 clinically diagnosed cases of melasma attending in outpatient department of Dermatology and Venereology, Diabetic Association Medical College Hospital (DAMCH), Faridpur were evaluated. Maximum patients (40%) were between 31-35 years of age and 80% were female. Sun exposure (60%) and contraceptive pill (36%) were common precipitating factors. Of them 54% patients have skin type IV, 24% patients have skin type III. Centrofacial melasma (64%) was the commonest pattern of melasma. MASI score at base line was 9.45, and after 12th week were 4.62. After completion of therapy there was remarkable reduction (51.11%) of severity of melasma. The triple combination agent were well tolerated and commonly observed side effects were erythema (34%) and burning (22%). This study demonstrates that every night application of triple combination agents has significant lightening effect in the treatment of melasma.

Key words: Melasma, Tretinoin, hydroquinone.

Introduction :

Melasma is a very common disorder[1]. Melasma is an acquired, chronic, symmetrical hypermelanosis characterized by light to dark brown patches of hyperpigmentation on sun exposed areas, predominantly on the face but may also occur on neck and forearms as well[2,3]. It tends to affect dark-complexioned individuals, especially East, West, and Southeast Asian, Hispanics and black person who live in areas of intense sun exposure and have Fitzpatrick skin types IV and V. Melasma may be seen in up to 30% of middle-aged Asian females. Men are also affected especially those from Central America, who may have prevalence rates as high as 35%[1]. According to the clinical pattern of distribution, melasma is recognized as centrofacial, malar, and mandibular. Three histologic patterns of pigmentation have been described: Epidermal (brown), dermal (blue-gray) and mixed (brown-gray)[4,5].

Multiple factors have been postulated in the etiology and pathogenesis of melasma. However, many observations strongly suggest that sun exposure is the primary trigger. The prevalence of melasma increases with age in both men and women[1]. The second most important triggers for melasma are female hormones. It occurs frequently during pregnancy, with oral contraceptives use, or with hormone replacement therapy at menopause. Melasma may be seen in other endocrinologic disorders and with dilantin therapy[1,6].

The pathogenesis of melasma is not known. The areas of melasma have higher levels of inducible nitric oxide synthase and phosphorylated Akt, an element of the nuclear factor kappa B (NF-kB) pathway. Inducible nitric oxide stimulates tyrosinase activity of melanocytes, increasing local melanin production[1]. 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 hyperpigmentation of melasma skin. There is an increase

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in the formation, melanization and transfer of melanosomes to the epidermis as well as the dermis[7,8]. The diagnosis is usually readily established by clinical features. Post inflammatory hyperpigmentation can usually be excluded by history, woods lamp examination and using infrared film[9].

Treatment of melasma remains a challenge. Treatment consists of phenolic and non-phenolic depigmenting agents, chemical peels, lasers and dermabrassion[10]. USFDA approved hydroquinone as gold standard and are moderately efficacious. Hydroquinone applied topically inhibits the action of the enzyme tyrosinase, which acts on tyrosine to form the pigment melanin[1,10]. Tretinoin is an endogenous retinoid of vitamin A that binds with intracellular receptor in the cytosol and nucleus. Tretinoin cream may be added to hydroquinone to increase its efficacy. The combination of hydroquinone and tretinoin, administered in conjunction with a topical steroid has been called "Kligman's formula" and is excellent[1,11].

Materials and Method:

An interventional study was carried out in patients of melasma attending in outpatient department of Dermatology and Venereology of Faridpur Diabetic Association Medical College Hospital, Faridpur. During the period of January 2011 to December 2011 a total of 50 clinically diagnosed cases of melasma were studied. Patient's data were recorded on pre-designed case record form. Epidemiologic variables such as age, sex, marital status, occupation, family history was included. Clinical evaluation including skin colour type, distribution of melasma was also included. Patient were advised to apply the triple combination agents containing 4% hydroquinone, Tretinoin 0.05% and 0.05% Clobetasone butyrate over the melasma affected areas once daily at night and patients were evaluated on 4th , 8th and 12th week. The effect was evaluated clinically using Melasma Area and Severity Index (MASI) score as proposed by Kimbrough-Green et al[12]. At each visit side effects or tolerability were determined by itching, burning, erythema and scaling. These factors were assessed on four point scale as absent, mild, moderate or severe.

Results:

A total of 50 clinically diagnosed cases of melasma were included in study. Table I shows the age distribution of patients. Maximum patients (40%) were belongs to 31-35 years of age range followed by 24% between 36 to 40 and 20 % between 26-30 years range.

Table-I: Distribution of the patients by age

Age (in year)	Frequency (%)
20 -25	0 2 (4)
26 -30	10 (20)
31 -35	20 (40)
36 -40	12 (24)
>40	0 6 (12)
Total	50 (100)

Table II shows the demographic features of all patients. Majority of patient were female (80%) and male female ratio was 1:4. Among the patient 64% were married. 60% patients were involved in indoor service and 40% engaged in outdoor occupation. Most of the patient (62%) belongs to upper class family. 26% and 12% patient coming from middle and lower class family respectively.

Table- II: Distribution of the patients by epidemiological profile

Epidemiological Variables	Frequency (%)
Sex	
• Male	10 (20)
• Female	40 (80)
Marital status	
• Married	32 (64)
• Unmarried	18 (36)
Occupation	
• Indoor	20 (40)
• Outdoor	30 (60)
Socioeconomic condition	
• Upper	31 (62)
• Middle	13 (26)
• Lower	6 (12)

Table III shows different clinical characteristics of the patients. Positive family history of melasma was present in only 20% of cases. Regarding precipitating factors sun exposure was most common (60%) followed by contraceptive pill (36%). In 42% patient no precipitating factor could be identified. Total 54% patients have skin type IV, 24% patients have skin type III and 20% have skin type V. Among the study population 64% have centrofacial melasma. Malar and mandibular type melasma found 24% and 6% respectively.

Table- III: Clinical Characteristics of the patients

Clinical variables	Frequency (%)
Family history of melasma	
• Positive	10 (20)
• Negative	40 (80)
Precipitating factors	
• Sun exposure	30 (60)
• Pregnancy	5 (10)
• C ontraceptive pill	18 (36)
• None	21 (42)
Type of skin	
• Type III	12 (24)
• Type IV	28 (28)
• Type V	10 (20)
Distribution	
• Centrofacial	32 (64)
• Malar	12 (24)
• Mandibular	6 (12)

Analysis of MASI score showed that at baseline it was 9.45, at 4th week 8.52, at 8th week 6.81 at 12th week 4.62. After completion of therapy the average MASI was decreased by 51.11% indicating remarkable reduction of the severity of melasma (0= No reduction, upto 25% = mild, 26-50% = moderate and above 50% = remarkable reduction) (Figure-1).

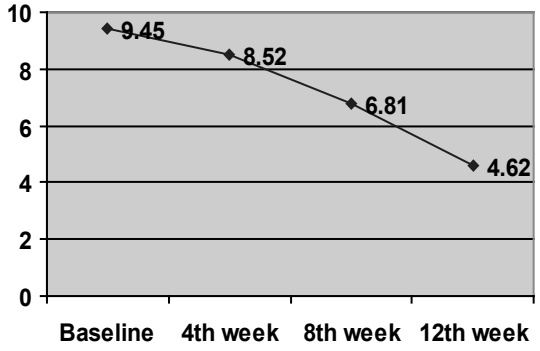

Figure-1: *Average MASI score (n=50)*

Most commonly observed side effect was erythema (34%). The other side effects were burning (22%), itching (7%) and scaling (6%) (Figure 2).

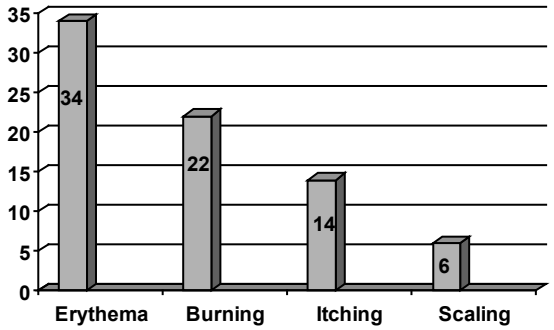

Figure-2: Side effect *(n=50)*

Discussion:

A total of 50 clinically diagnosed cases of melasma were studied. It predominantly affects young adults which is consistent with this study where we found 84% between the ages of 20 to 40 years[13]. In this study 80% patients were female may be due to female are more conscious about their beauty and seek treatment. This finding is also consistent with study conducted by Lapeere H et al[14], and Sarker R et al[15]. Total 64% patients were married. This finding is consistent with study conducted by Hazra et al[16]. Melasma most commonly seen in married women may be due to use of oral contraceptives and in few patients it started during pregnancy that may persist thereafter. On the basis of socioeconomic status 62% patients were in upper class may be due to consciousness and economic solvency.

Sunlight is an important pathogenic factor for melasma along with genetic and hormonal effect[14]. In this study 60% patients were found to engage in out door work. This finding also shows the relation of melasma and sun exposure. A positive family history was observed in only 20% cases. This low rate is surprising as genetic predisposition is considered to be an important factor in melasma. Familial occurrence of melasma has been reported to vary from 20% to 70% in different studies[17-19]. Total 60% patients give the history of regular sun light exposure indicating an important aggravating factor. Pathak also reported that sunlight exacerbated all melasma[18]. Among women 36% give the history of taking oral contraceptives for different duration. In a report from Thailand, 34% of women with melasma had taken oral contraceptives but about half of them had melasma even before they started the pill[18]. It was interesting that in 42% cases we did not found any aggravating factor. A large scale study may be undertaken to find out the role of aggravating factors and genetic susceptibility in the pathogenesis of melasma.

Most of our patient having skin type IV (56%) and III (24%). This observation is consistent with study conducted by Nahid et al[20]. Fitzpatrick also reported that melasma was a common problem in darker skin in particular to type IV and V[21].

In this study 64% patient have melasma that distributes centrofacially and 24% have malar distribution. This result is similar to study conducted by Sanchez NP et al[4]. In her study Nahid Parvin reported that malar presentation was the most common distribution followed by centrofacial pattern[20].

After 12 week use of triple combination therapy the average MASI was decreased by 51.11% indicating remarkable reduction of the severity of melasma. The result is consistent with others[22,23]. Observed side effects were erythema (34%), burning (22%), itching (7%) and scaling (6%). All these were mild and transient and did not necessitate interruption of treatment. The side effect profile in our study was a little bit higher than finding of Torok HM et al[24], Ferreira C et al[25] and R Begum et al [26].

Conclusion:

An attempt was made to evaluate the efficacy and side effect of triple combination agent (4% Hydroquinone, 0.05% Tretinoin and 0.05% Clobetasone butyrate) in the treatment of melasma. A total of 50 clinically diagnosed cases of melasma were studied for a period of 12 weeks. The study demonstrated that the application of the triple combination have significant lightening effect in treating melasma. The side effect of triple combination is mild and transient in nature. It needs further large scale study on large number of patient for longer period to assess safety and actual duration of the treatment. Still it could be concluded that combination therapy with 4% Hydroquinone, 0.05% Tretinoin and 0.5% Clobetasone butyrate has excellent efficacy in melasma.

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