

COMPARATIVE STUDY OF TRIPLE COMBINATION THERAPY AND THIRTY FIVE PERCENT GLYCOLIC ACID PEEL IN TREATMENT OF MELASMA

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Abstract

Background: Melasma is a chronic, recurring hyperpigmentary disorder most commonly affecting females, especially in their reproductive age groups. Risk factors include pregnancy, exposure to female sex hormones via consumption of OCP's. Various treatment modalities have come up to provide long lasting solution for this recurring problem. This study compares topical triple combination therapy vs 35% glycolic acid peel in treatment of melasma. **Materials and Methods:** 60 patients who were accordance with the inclusion criteria and newly diagnosed to have melasma, in the Department of Dermatology were randomly divided into two equal groups – glycolic acid group and triple combination group. **Result:** Age, gender, pattern of distribution, risk factors were similar in both groups. However, triple combination therapy group had fewer side effects than glycolic acid peel group. **Conclusion:** This study concludes that both the treatment options are feasible for treatment of melasma, with the triple combination group scoring better over glycolic acid peel group in terms of fewer side effects.

INTRODUCTION

Melanin is the primary determinant of skin colour produced by melanocytes that reside basal layers of epidermis.^[1] Hyperpigmentation is the result of excess melanocyte activity. Melasma (also known as chloasma faciei, or the mask of pregnancy) is a chronic hyperpigmentation disorders with the lesions mostly involving face and therefore is a source of major distress for the affected individuals.^[2] It usually involves the sun exposed areas, predominantly over the face, ie, cheeks, chin, bridge of nose, forehead, and above the upper lip in the majority of people. Melasma is more common in women (especially in their reproductive age) than in men since, female sex hormones estrogen and progesterone stimulate melanocytes, causing them to produce more melanin pigments when the skin is exposed to the sun. This explains the most frequent occurrence of melasma in pregnant women, and women on oral contraceptive pill.^[3-5]

Melasma has quite wide range of prevalence as 1% in general population to 50% in high-risk populations. It generally sets up in twenties.^[6]

Depending on the areas of face involved, melasma can be centrofacial, malar, and mandibular types., Melasma can be divided into 3 types based on visible

light examination, Wood's light examination and skin histology, ie, epidermal, dermal and mixed. The epidermal type is characterized by increased melanin in basal and suprabasal epidermis. Macules are highlighted when examined through Wood's lamp. The dermal type has melanin-laden macrophages (melanophages) in the perivascular distribution in the superficial and deep dermis. There is no Wood's lamp accentuation in dermal type. The mixed type has elements of both epidermal and dermal and there is accentuation of the epidermal component through Wood's lamp.

Due to unavailability of an effective agent and frequent recurrence of the condition, the treatment of melasma is a challenging one. Majority of existing treatments are used to fade the lesions. The fundamentals of therapy include avoiding sun exposure, inhibit melanin synthesis, removal of melanin, disruption & dispersion of melanin granules.^[7] Elimination of any risk factors along with use of a sunscreen and hypopigmenting agents like hydroquinone, azelaic acid, kojic acid often in combination with other therapies such as retinoids, topical corticosteroids and chemical peeling using alpha hydroxyl acids.

The most comprehensively studied and used pharmaceutical combination is the "triple

combination” introduced by Kligman and Willis. The original combination was composed of 5% HQ, 0.1% tretinoin, and 0.1% dexamethasone and was found effective in the treatment of various disorders with acquired hyperpigmentation, including melasma.^[8]

Hydroquinone (2–5%) is regarded as the major and most efficient topical medication. It acts by inhibiting the tyrosinase enzyme, responsible for melanin synthesis. However, melasma being a recurrent condition, Hydroquinone has a limited role as monotherapy. The total duration of hydroquinone is 6 months and it takes 4–6 weeks for visible results. Although larger quantities of hydroquinone may be more effective, but they also have a higher potential for discomfort (itching, burning, dermatitis). As a result, in the combination formula, 4% was employed as an ideal concentration with greater efficiency and fewer unpleasant responses.^[9,10]

Tretinoin, another component of the triple combination cream, works by motivating epidermal and dermal turnover, inhibition of tyrosinase enzyme, facilitates penetration of hydroquinone, and neutralizes the stratum corneum thinning effects of the corticosteroid.^[11]

Fluocinolone (a mid-potency class V steroid), the third component of triple combination, acts by reducing the possible irritation or inflammation caused by tretinoin and hydroquinone, especially in sensitive skins.^[12]

In time, due to the irritation potential of this combination, the original formula has been modified through addition or alteration of one or more of its components to adapt different skin types.

Chemical peeling follows the same skin healing pattern as chemical burns. A variety of chemicals have been used as peeling agents, with alpha hydroxyl acids (AHA's) being the most effective. These have been shown to improve photodamaged skin and fine facial wrinkles by regulating the stratum corneum barrier function. Glycolic acid is an alpha hydroxy acid and one of the most widely used and adaptable peeling agents.^[13,14]

The present study was conducted to measure efficacy of serial 35% glycolic acid peel in comparison with triple combination topical cream containing 2% hydroquinone, 0.025% tretinoin, 0.01% flucinolone acetamide.

MATERIALS AND METHODS

This hospital based prospective randomised study was conducted over a duration of 18 months (from November 2019 to May 2021), in the department of Dermatology Venereology and Leprosy, Kamineni Academy of medical sciences and research centre, LB NAGAR. 60 patients who have been newly diagnosed with melasma, aged 18yrs and above, and who have willing to participate in study were included in this study. Patients on OCP's or hormone replacement therapy, pregnant lactating mothers, patients with systemic diseases, and patients with

history of reactions to glycolic peel were excluded from the study.

60 diagnosed cases of melasma were randomly enrolled equally into two groups. One group was treated with 35% Glycolic acid peel and one group with triple combination cream (Hydroquinone 2%+ Tretinoin 0.025%+Flucinolone 0.01%) for 12 weeks. All patients were advised sunscreens/ sun protection during study period. A detailed clinical history including age, sex, occupation, duration of disease, precipitating factors, other associated illness, family history, previous treatment taken if any were recorded as per the proforma. Diagnosis was made mainly by clinical examination and categorized into centrofacial, malar and mandibular types. Wood's light was used to know depth of pigmentation (epidermal, dermal or mixed type). The area to be peeled was examined, paying attention to the tone, texture and quality of the skin and to the presence of any other skin disorder. A Informed written consent was obtained from all patients. A baseline Melasma Assessment and Severity Index (MASI) was performed. Photograph at the beginning of the study, during follow up and at the end of the study was taken.

Statistical Analysis

Data Entry was done using Microsoft excel 2013 and analysis done using SPSS V 16. Non parametric statistics i.e. Chi square test was used to find the significant association between the two qualitative variables. Independent t test and ANOVA were used to find the statistical significance between quantitative variables. Bar diagrams and pie chart were used to represent the data. p value of <0.05 was considered statistically significant.

RESULTS

The mean age in the glycolic acid group and in Triple combination group was similar. Females were the predominant in both groups. Centro facial (60%) pattern was the most common pattern observed in both glycolic acid group, and triple combination group. 40% of patients in Glycolic acid group had lesions of 1-3 years duration, while In Triple combination group, 33.3% had it for 1-3years. Both in glycolic acid group (40%) and in triple combination group (46.7%) positive family history of melasma was present. 36.7% in glycolic acid group had history of cosmetic usage whereas in triple combination group it was 23.3%. Sunlight was the aggravating factors in 26.7% of patients in glycolic acid group and 60% of patients in Triple combination group. Pregnancy as aggravating factor in 36.7% of glycolic acid group and 26.7% of Triple combination group. None of the patient was on systemic drugs in the present study.

Based on wood lamp examination, epidermal variant was observed in 33.3% in glycolic acid group and 20% in Triple combination group. Mixed variant was seen in 50% of glycolic acid group and 56.7% in

Triple combination group. Dermal variant was observed in 16.6% of glycolic acid group patients, 23.3% of Triple combination group patients.

Table 1: MASI

No of visits	Glycolic acid (N=30)	Triple combination(N=30)	P value
1st Visit	10.26 ±6.33	13.33 ±7.92	0.10
2nd Visit	8.99 ±5.67	9.96 ±6.57	0.54
3rd Visit	7.96 ±5.16	7.28 ±5.10	0.60
4th Visit	7.12 ±5.14	4.45 ±3.51	0.02*

Table 2: MASI of Glycolic acid treated patients

	Glycolic acid(N=30)	P value
1st Visit	10.26 ±6.33	T value = 9.62<0.0001*
4th Visit	7.12 ±5.14	
Difference between 1stand 4 th visit	3.14	

Table 3: MASI of patients treated with Triple combination

	Triple combination(N=30)	P value
1st Visit	13.33 ±7.92	T value = 6.86 P =<0.0001*
4th Visit	4.45 ±3.51	
Difference between 1stand 4 th visit	8.88	

Based on Melasma Area and Severity Index (MASI), reduction was observed in both groups at 4th visit, i.e. MASI = 3.14 in Glycolic acid group and MASI = 8.88 in Triple combination group which was statistically significant. Reduction of MASI is more in Triple combination group, compared to Glycolic acid group which was statistically significant.

Table 4: Side effects profile

Side effects	Glycolic acid (N=30)		Triple combination (N=30)		Total (N=60)	
	N	%	N	%	N	%
Mild Burning	18	60%	5	16.67%	23	38.33%
Mild Erythema	8	27%	2	6.67%	10	16.67%
Acneiform eruption	0	0%	7	23.33%	7	11.67%
Hypertrichosis	0	0%	4	13.33%	4	6.67%
No side effects	4	13%	12	40.00%	16	26.67%
Total	30	100.0%	30	100.0%	60	100.00%

Chisquare test =25.94, p =<0.0001*, Statistically significant

Comparing photos of triple combination cream on 1st visit and 4th visit:

Patient 1



Patient 2



Comparing photos of 35% glycolic acid on 1st visit and 4th visit

Patient 1



Patient 2



Most common side effect observed among Glycolic acid group is mild burning sensation (60%), followed by mild erythema (27%). 13% had no side effects. Among Triple combination group, 40% of patients had no side effects among the rest of patients; acneiform eruption was the most commonly observed side effect.

DISCUSSION

Melasma is an acquired hypermelanotic disorder involving the face. It predominantly is seen in woman, especially of reproductive age group.^[15]

It is commonly seen in individuals with a constitutionally darker complexion (skin types IV to VI).^[2] It usually presents as symmetric, hyper pigmented macules with irregular, serrated, and geographic borders affecting mostly the sun exposed areas of face like cheeks, upper lips, the chin, and the forehead.^[16]

Due to prolonged duration of therapy and recurrences despite of taking treatment, management of melasma is definitely a challenging condition. Of the numerous treatment modalities available, topical therapy includes application of sunscreens, hypopigmenting agents like hydroquinone, Kojic acid, Azelaic acid, Deoxyarbutin, Ascorbic acid. These hypopigmenting agents can be used singly, or in combination like The Kligman's formula. Often, topical therapy is used in adjunct with chemical peels with glycolic acid or trichloroacetic acid, dermabrasion, and laser therapy. The present study was done to compare the efficacy between Triple

combinations therapy versus thirty-five percentage Glycolic acid peel in the treatment of Melasma.

In the present study, the mean age in years in the glycolic acid group was 36.73 ± 5.94 and In Triple combination group was 38.73 ± 9.98 . Similar mean age was observed in study done by Handal AC et al.^[17]

Majority in both the groups were female i.e. 86.7% in Glycolic acid group and 76.7% in Triple combination group. Majority of the studies has also seen to have a strong female predisposition, which is explained by the role of female sex hormones in stimulating melanocytes.

Centrofacial was most common pattern observed in both groups. A statistically significant association was observed with relation to pattern and study groups as the p value calculated to be <0.05 . Similar distribution were seen in other studies like Sardesai VM et al,^[18]Badabagniet al.^[19]

Transient type of melasma usually vanishes by itself within one year of cessation of predisposing stimuli like pregnancy and OCPs. Whereas, the persistent type will be continued further even after cessation of stimuli. Here the aetiology of UV rays stays.

40% of glycolic acid peel group patients had lesions since 1-3 years. 20% had it for 3- 5 years and 16.7% with <1 year and >7 years. In Triple combination group, % had it for 1-3 years, 5-7 years in 20% and <1 year and >7 years in 16.7%. Similar observations were made in the study done by Sardesai VM et al and Badabagniet al.^[18,19]

In the present study distribution based on duration of sun exposure shows 43.3% in Glycolic acid group had <1 hr exposure, 36.7% with 1-2 hr exposure and 20% with >2 hr exposure to sun. In Triple combination group, 45% had <1 hr exposure, 31.7% had 1-2 hr exposure and 23.3% had >2 hr exposure. There was no statistically significant difference observed with relation to duration of sun exposure between the study groups as the p value calculated to be >0.05 .

But in majority of the studies a strong correlation between exposure to sun has been observed, but here in this study this contradictory finding is present, which might be due to even exposure of the study population to the sun, which could be due to a tropical geographical location of the study area and such similar observation is made in the study done by Sardesai VM et al,^[18] and a constitutionally darker skins might also be a reason to not seeing such a significant difference as opined in the study done by Handal AC et al.^[17]

positive family history was seen in 40% of glycolic acid group and in 46.7%. of triple combination group. Thus family history was seen to be a potential risk factor in the causation of melasma as observed in the studies done by Sardesai VM et al,^[18] and Handal AC et al.^[17]

Aggravating factors were Sunlight i.e. 26.7% in glycolic acid group and 60% in Triple combination group. Pregnancy as aggravating factor in 36.7% of glycolic acid group and 26.7% of Triple combination

group and such a similar type of risk pattern was seen in the study done by Handall AC et al.^[17]

Epidermal variant was seen in 33.3% in glycolic acid group and 20% in Triple combination group, Mixed variant in 50% of glycolic acid group and 56.7% in Triple combination group. 16.6% was Dermal in glycolic acid group, 23.3% in Triple combination group. Similar type of observations were made in the study done by Garg et al.^[20]

Kimbrough-Green et al developed the Melasma Area and Severity Index (MASI), an outcome measure designed to provide a more accurate quantification of the severity of melasma and changes during therapy. It was based on a similar scoring system developed for psoriasis. Significant reduction in mean MASI scores i.e. mean reduction of 3.14 was observed in Glycolic group from 1st visit to 4th visit. Significant reduction in mean MASI scores i.e. mean reduction of 8.88 was observed in Triple combination group from 1st visit to 4th visit. Although both the groups had good reduction of MASI Triple combination showed more reduction than Glycolic acid group. This finding observed was similar to the findings made by the observations made in Badabagni et al and Garg et al.^[19,20]

Different topical agents act on different stages of this process, providing a rationale for combining agents to improve therapeutic effect. Many different combinations of topical agents have been studied. The main ingredient in most formulations is hydroquinone. Glycolic acid, azelaic acid, kojic acid, retinoic acid, and corticosteroids are some of the drugs that are combined with it. Furthermore, arbitrary mixtures of various other demelanizing agents are marketed, despite the fact that most of them have not been proven effective or safe in controlled clinical trials.

The so-called 'triple combination,' a formulation containing HQ, retinoic acid, and corticosteroids, is the most extensively studied and widely used combination.

In the present study, among Glycolic acid group 60% had mild burning, 27% had mild erythema, 13% had no side effects. Among Triple combination group, 16.67% had mild burning, 6.67% had mild erythema, 23.33% had acneiform eruption, 13.33% had hypertrichosis and 40% had no side effects.

We found this triple combination cream (2% Hydroquinone + 0.025% Retinoid + 0.01% Flucinolone Acetonide) suitable for darker skin types with less and reversible side effects when used judiciously better than the international formulation that has higher percentage of Hydroquinone at 4% and Retinoid at 0.05% along with Flucinolone acetonide 0.01%. The study concludes that triple combination therapy has a better clearance of melasma compared to 35% glycolic acid peel with the advantage of fewer side effects.

CONCLUSION

This study concludes that both the treatment options are feasible for treatment of melasma, with the triple combination group scoring better over glycolic acid peel group in terms of fewer side effects.

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