Comparative Evaluation of Efficacy and Tolerability of Glycolic Acid, Salicylic Mandelic Acid, and Phytic Acid Combination Peels in Melasma

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BACKGROUND Melasma is acquired symmetric hypermelanosis characterized by light-to-deep brown pigmentation over cheeks, forehead, upper lip, and nose. Treatment of this condition is difficult and associated with high recurrence rates. Chemical peels have become a popular modality in the treatment of melasma.

OBJECTIVE To compare the therapeutic efficacy and tolerability of glycolic acid (35%) versus salicylic-mandelic (SM) acid (20% salicylic/10% mandelic acid) versus phytic combination peels in Indian patients with melasma.

MATERIALS AND METHODS Ninety patients diagnosed with melasma were randomly assigned into 3 groups of 30 patients each. Group A received glycolic acid (GA-35%) peel, Group B received SM acid, and Group C received phytic combination peels. Each group was primed with 4% hydroquinone and 0.05% tretinoin cream for 4 weeks before treatment. Chemical peeling was done after every 14 days in all groups until 12 weeks. Clinical evaluation using melasma area and severity index (MASI) score and photography was recorded at every visit and follow-up was done until 20 weeks.

RESULTS There was a decrease in MASI score in all 3 groups but it was statistically significantly lower in Group A than Group C (\(p = .00\)), and it was also statistically significantly lower in Group B than Group C (\(p = .00\)) but there was no statistically significant difference between Groups A and B (\(p = .876\)). Objective response to treatment evaluated by reduction in MASI scoring after 12 weeks was 62.36% reduction in GA group, 60.98% reduction in SM group, and 44.71% in phytic acid group.

CONCLUSION It is concluded that GA (35%) and SM acid peels are both equally efficacious and a safe treatment modality for melasma in Indian skin, and are more effective than phytic acid peels. Salicylic-mandelic peels are better tolerated and more suitable for Indian skin.

The authors have indicated no significant interest with commercial supporters.
considered the safest and the most versatile peeling agent because it has the smallest molecule and penetrates the epidermis the best. It is the only peel that is time-dependent, can be neutralized easily, has minimal complications and is found to be efficacious in dark-skinned patients such as Indians. Beta hydroxy acid peels such as superficial salicylic acid peels have also been found to be safe and efficacious for treatment of melasma in a small number of dark-skinned patients, but larger trials are required with these peels in Fitzpatrick skin types IV to VI. Phytic acid combination peel (50%) is a slow release commercial proprietary product that is composed of phytic acid, in addition to a mixture of glycolic acid, lactic acid, and phenyl glycolic (mandelic) acid and requires no external neutralization. There are barely any studies comparing the efficacy of GA with combination peels like salicylic-mandelic (SM) acid and phytic acid in treatment of melasma. This study was taken up to investigate this aspect in the treatment of melasma.

Materials and Methods

This prospective, randomized study was designed to compare the efficacy of 3 different chemical peels in the treatment of melasma. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Ethics Committee of Maulana Azad Medical College and associated hospitals. Blinding of the patients was not possible because of ethical reasons. Ninety patients of melasma of either sex attending the outpatient clinic of Lok Nayak Hospital, New Delhi, India, were taken up as subjects. Only motivated patients, who were willing to undergo the procedure of chemical peels and gave an informed consent, comprised the study subjects. Pregnant or nursing women, patients with hypersensitivity to the formulations, patients on any concurrent therapy, systemic illness, and history of herpes labialis, keloidal tendencies, unrealistic expectations, and women on oral contraceptives were excluded from study. All patients were told about the risks of the procedure and a written informed consent was obtained from all patients before the procedure.

A detailed history regarding age, sex, occupation, education, duration of complaints, age of onset, precipitating, and exacerbating factors as well as family history was taken. Melasma was clinically classified into malar, centrofacial, and mandibular types and Woods light examination was used to categorize it into epidermal, dermal, mixed, and apparent types. In all patients, skin typing was done according to Fitzpatrick classification.

All patients were given a priming regimen with 4% hydroquinone and 0.05% tretinoin cream for 4 weeks before the chemical peels. In this single-blinded study, patients were randomly divided into 3 groups (A, B, and C) with 30 patients each. Group A received GA peels (35%), Group B SM acid (20% salicylic and 10% mandelic acid), and Group C was treated with phytic acid combination peel (50%) for 6 sessions each, 2 weeks apart. A postauricular test peel was performed in all patients to determine any hypersensitivity to the ingredients of the peeling agent. Melasma area and severity index (MASI) score was evaluated by a blinded clinical investigator at baseline and before each peeling session (Figure 1). The patients were followed up for an additional 8 weeks to see if there was further improvement, maintenance, or worsening of results. During this entire period, the patients were advised to apply a broad-spectrum sunscreen at 2-hour intervals during daytime. No other topical treatment was advised. The primary outcome measures at the end of the study were based on improvement in MASI score as compared with baseline. The secondary outcome measures were based on the photographic assessment and patient’s subjective assessment of improvement at the end of the
study. The MASI score was calculated at the start of therapy, and at 4, 8, 12, and 20 weeks to assess the efficacy of priming and peeling agents.

Subjective assessment of improvement was done by the patients at 3 months as per the following scale: good (>50% improvement), fair (25%–50% improvement), poor (0%–25% improvement), no change, or worse. Statistical analysis of the results was done by calculating the average MASI scores for the 3 groups and comparing the percentage change in the average MASI scores from baseline at 4, 8, and 12 weeks of treatment using paired *t*-test and between groups using the Student *t*-test. A *p*-value of less than .05 was considered significant.

### Results

Ninety patients with melasma fulfilling the selection criteria were included in the study conducted between April, 2008 and July, 2009; however, only 72 patients completed the study. Eighteen patients were excluded from the study for the following reasons; 14 patients were lost to follow-up after the initial serial second or third peel, 2 became pregnant, and 2 developed hypersensitivity to GA (Figure 1) Demographic data are given in Table 1. The average age of the patients was 31.54 years and the average time melasma was present before the study was 3.32 years. There were no patients of dermal and indeterminate melasma.

The results were analyzed on the basis of MASI scoring (based on area of involvement, darkness, and homogeneity of pigmentation) done by an independent observer. The results obtained at 3 months were compared with the marital status, predisposing factors, lifestyles, pattern of melasma, and duration to record any difference in improvement based on these variables; however, no statistically significant results were obtained with respect to these variables.

The average MASI score at 0, 4, 8, 12, 16, and 20 weeks in patients in the 3 groups are given in Table 2. The average MASI score in the GA group A decreased from 12.59 ± 7.58 at baseline to 4.56 ± 2.98 at 12 weeks and 7.28 ± 3.890 at 20 weeks (Table 2). This represents a change of 62.36% at 12 weeks and 39.38% at 20 weeks. In the SM acid Group B, the average MASI score decreased from 11.85 ± 7.4 at baseline to 4.37 ± 3.01 at 12 weeks and 6.52 at 20 weeks, which represented a 60.98%, and 41.67% change, respectively. In the phytic acid combination peel group C, the average MASI score at baseline decreased from 11.04 ± 5.32 to 6.14 ± 3.18 at 12 weeks and 7.83 ± 3.972 at 20 weeks, which represents a change of 44.71% and 28.27% at 12 and 20 weeks, respectively (Figure 2). The change in MASI from baseline was significant in all 3 groups at 12 weeks whereas the change was significant at 20 weeks in Groups A and B only.

Statistical analysis revealed a significant difference in improvement between Groups A and C (*p* = .00) and between Groups B and C at 12 weeks (*p* = .00). But there was no statistically significant difference in improvement between Group A and Group B (*p* = .876) at 12 weeks.

The patients were asked to grade their improvement subjectively at the end of 3 months. Patients in Group A using GA peels had the most favorable response with 76.9% grading their improvement as good, 19.2%
fair, and only 1 (3.8%) as poor. The next favorable response was seen in group B receiving SM acid peels where 75% graded their response as good, 20.8% as fair, and only 1 (4.2%) as poor (Figure 3). In group C, good response was seen in 18.2%, fair in 77.2%, poor in 4.5%. None of the patients reported worsening of their condition.

Mild erythema and desquamation were seen in 19.2% patients using GA peel. During the peels, all patients developed mild cutaneous erythema and superficial desquamation. Postpeel hyperpigmentation was seen in 15.4% of the patients receiving GA peels only. Persistent erythema was seen in 15.4% patients who were on GA peels. 25% patients of SM acid and 31.8% patients of phytic acid group experienced burning sensation. Herpes simplex was seen in 18.2% patients in phytic acid group. None of these side effects merited the stoppage of treatment (Figure 4).

**Discussion**

Despite tremendous research into the etiology, pathogenesis, and possible treatment options for melasma, the disease remains a therapeutic challenge to dermatologists, and a definitive modality of treatment is still a distant reality. Therapeutic armamentarium of melasma consists of hypopigmenting agents, chemical peels, and lasers. Peels are a well-known second line modality to remove excess epidermal pigment in the epidermal and mixed types of melasma, both as a sole treatment as well as an adjunct to other topical therapies. They act by thinning the stratum corneum,

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**TABLE 2. Relevant Clinical Findings in Groups A, B, and C**

<table>
<thead>
<tr>
<th></th>
<th>Group A (26)</th>
<th>Group B (24)</th>
<th>Group C (22)</th>
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<tbody>
<tr>
<td><strong>Fitzpatrick skin type</strong></td>
<td>IV (17)</td>
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<tr>
<td></td>
<td>V (55)</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td><strong>Pattern of melasma</strong></td>
<td>Centrofacial (28)</td>
<td>13</td>
<td>9</td>
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<tr>
<td></td>
<td>Malar (38)</td>
<td>10</td>
<td>15</td>
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<tr>
<td></td>
<td>Centrofacial and malar (6)</td>
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<td>0</td>
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<tr>
<td><strong>Type of melasma</strong></td>
<td>Epidermal (41)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Mixed (31)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td><strong>MASI (Mean ± SD)</strong></td>
<td>Baseline 12.59 ± 7.58</td>
<td>11.85 ± 7.4</td>
<td>11.04 ± 5.32</td>
</tr>
<tr>
<td></td>
<td>4 weeks 8.94 ± 4.91</td>
<td>9.17 ± 5.09</td>
<td>8.84 ± 4.58</td>
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<tr>
<td></td>
<td>8 weeks 6.35 ± 3.47</td>
<td>6.43 ± 4.33</td>
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<tr>
<td></td>
<td>12 weeks 4.56 ± 2.98</td>
<td>4.37 ± 3.01</td>
<td>6.14 ± 3.18</td>
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<td></td>
<td>16 weeks 5.44 ± 3.098</td>
<td>5.37 ± 3.707</td>
<td>6.73 ± 3.657</td>
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<td>20 weeks 7.28 ± 3.890</td>
<td>6.52 ± 3.870</td>
<td>7.83 ± 3.972</td>
</tr>
</tbody>
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**Figure 2.** MASI score in each group at 4-weekly follow-up.

**Figure 3.** Subjective grading at end of 3 months.
promoting epidermolysis, dispersing basal layer melanin, and increasing collagen genes expression.

Although a number of new agents have come up, there is little published evidence supporting their use in day-to-day practice and the choice becomes relatively limited when you are treating a patient with a Fitzpatrick skin type IV or above. Superficial peels which include glycolic acid, salicylic acid (SA), Jessner solution, and trichloroacetic acid (TCA) peels, with appropriate titration of concentrations are generally safe and efficacious for Fitzpatrick skin type IV to VI.2,3 There are very few objective published studies comparing the efficacy and safety of different chemical peels for melasma in type IV and V skin. This article aims to fill this void by evaluating the therapeutic response of melasma in Indian patients to glycolic acid (GA-35%) versus SM acid (20% salicylic/10% mandelic acid) versus phytic acid combination peel (50%).

Glycolic acid peel is the most commonly used alpha-hydroxy peel which has the smallest molecular weight and therefore is easily able to traverse the skin. It is extremely hydrophilic and has anti-inflammatory, keratolytic, and antioxidant effects. Unlike some other chemical peeling agents that pose a risk of hyper or hypopigmentation to darker skin types, GA peels as a 30% to 70% GA solution, can be used on all Fitzpatrick skin types I through VI, male or female, teens to adults. Side effects are substantially minimized when lower concentrations of 20% to 35% are used.2 Higher concentrations often lead to irritation and may cause paradoxical hyperpigmentation in dark-skinned patients. It is time tested and has shown good response in epidermal and mixed type of melasma in Asian4–7 and Black patients, mostly as a second-line agent.8 A significant decrease in the MASI score from baseline to 12 weeks was observed in glycolic group with statistically significant results (p < .001) (Figure 5). The only side-effects observed with the GA peels were mild burning, erythema, desquamation, and a transient postinflammatory hyperpigmentation (PIH) which is a commonly observed side effect in darker phenotypes. It is known that epidermal-type melasma responds to GA peel, whereas dermal-type melasma does not, because of the deeper deposition of melanin in dermal

![Figure 4. Side effects observed in patients.](image)

![Figure 5. Participant’s photographs at baseline (A) and at 12 weeks (B) of treatment with glycolic acid peel.](image)
type melasma and the inability of GA in the given concentration to reach that level. Increased incidence of PIH in group A could be explained by the presence of more patients with skin phototype V, who are more prone to PIH.

Salicylic-mandelic acid peel is a combination of an alpha hydroxy acid with a beta hydroxy acid. Mandelic acid (MA), because of its large molecular weight (MW) tends to remain on the skin surface longer, penetrates stratum corneum slowly thus producing a uniform epidermal effect. It is associated with less stinging and burning as compared to the other lower-MW alpha hydroxy acid. It is an ideal peeling agent for sensitive skin and is well tolerated and more effective as compared to the traditional GA peels, in acne, postacne scarring, and pigment dyschromias.\(^1\) Salicylic acid peels are well tolerated in all skin types (Fitzpatrick I to VI) and in all racial/ethnic groups and are excellent peeling agents for numerous conditions including acne, melasma, and PIH in dark-skinned individuals.\(^2\) Grimes\(^10\) successfully demonstrated the efficacy and safety of 20% to 30% SA peel in patients of melasma with skin types V and VI, however, another randomized control split face trial found them to be ineffective in the treatment of melasma.\(^11\) In this study, SM peels were found to be as efficacious as GA in decreasing MASI score, were well tolerated and better received by the patient (Figure 6). Salicylic-mandelic peels had better sustained efficacy and fewer side effects than GA, presumably due to greater lipophilicity of SA and larger molecular size of MA. Mild transient burning sensation was noted in 25% of patients, which resolved in 1 to 2 days.

The phytic acid combination peel is a proprietary peel, made of a mixture of GA, lactic acid, MA, and phytic acid. Phytic acid combination peel has a slow release promoting continuous penetration of the skin, requires no external neutralization and therefore the danger of over peeling is avoided. It allows progressive and sequential actuation of its acid and is non-aggressive. Phytic acid (2%–4%) has proven to be efficient in the treatment of epidermal melasma, especially when associated with GA or retinoic acid. The typical burning sensation seen with the glycolic peel is not observed with the phytic acid peels.\(^12\) There was a statistically significant reduction in MASI in Group C at the end of 12 weeks although the results were less gratifying than GA and SM peels (Figure 7). Other authors have demonstrated momentous results of combination phytic peels in melasma.\(^13\) Chemical peels have been associated with lunch time procedure, and overnight application of phytic combination peels might have lead to decreased compliance and thus maximum dropout in this group. Randomization did not lead to an even distribution, and a higher ratio of mixed melasma was allotted in phytic group. Dermal component of melasma is known to be unresponsive to

Figure 6. Participant’s photographs at baseline (A) and at 12 weeks (B) of treatment with salicylic-mandelic peel.
superficial chemical peels which could have skewed the results in favor of the other 2 groups.

There are very few comparative studies of chemical peels in literature. In a split face comparative study for evaluation of efficacy of Jessner solution and 70% GA, both were found to work equally well in the treatment of melasma.14 Khunger and colleagues15 found no statistically significant difference in efficacy of 1% tretinoin as compared with 70% glycolic peels. In a study to compare the efficacy and tolerance of TCA and GA in melasma, GA was found to be a better peeling agent. The response with TCA was rapid but unpredictable and was associated with local reactions and significant relapse rate, whereas response with GA was slower at onset, not associated with local reactions, and was more prolonged.16

There were several drawbacks to the study. There was a high drop-out rate because of inclusion of patients from low socio-economic strata, for whom melasma was just a minor cosmetic impairment. We clinically classified the melasma into 4 types although there were no dermal and indeterminate melasma in the study. However a recent study had hinted that there might not be clear cut differentiating features between epidermal and dermal melasma histologically. True dermal melasma is probably non-existent.17 The study was not split face which could have helped in better comparative analysis, and contrast with triple combination may have better demonstrated the efficacy of peels. All the patients did not belong to the same Fitzpatrick type. Outcome measures selected for this study were subjective (MAr); objective measures like narrowband reflectance spectrophotometer (mexameter) are more reproducible, and complement the subjective measures but are not available in this setting. Unfortunately, most studies using peeling agents for melasma lack controls, blinding, and objective methods of evaluation, which causes difficulty in interpreting the results. Glycolic acid peels used in this study were of lower concentration. Other authors from India have used up to 50% glycolic acid with efficacy in melasma. However Indian skin is sensitive and more prone to PIH and thus we chose to be on the safer side and used lower concentration of the peels.

The presence of very few studies evaluating chemical peels is probably due to the fact that melasma is more prevalent in darker complexioned individuals in whom there is a higher tendency for pigmentary changes to develop and thus the reluctance to perform these procedures. There are no previous comparative studies between the above agents in melasma in Indian patients. Salicylic-mandelic peel is as effective as glycolic peels (35%) and more superior to combination phytic acid in the reduction of the pigmentation in melasma in dark-skinned patients. Compared to GA peel, SM peel was found to be less irritating, better tolerated, and provided equivalent efficacy with maintained improvement during the follow-up.
Treatment of melasma still remains challenging because of the prolonged duration of therapy. The substantial relapse rate, mainly attributed to inevitable persistence of the exacerbating factors (sun exposure) is still an obstacle. Salicylic-mandelic peel definitely appears to be a potentially new and promising therapeutic tool that appears to be almost as effective as a standard peeling agent GA and is better tolerated. Further, randomized, controlled trials using new depigmenting agents, peeling agents, lasers, and other technologies are warranted to improve the management of this recalcitrant disorder. Superficial peels with appropriate titration of concentrations are generally safe and efficacious for darker skinned racial-ethnic groups. However, in light of the labile responses of melanocytes of darker complexioned individuals, the clinician must always weigh the indication/necessity and benefit/risk ratio of the chemical peeling agent.

References


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