**RESEARCH PAPER**

# Comparative Efficacy and Safety of Topical Azelaic Acid 20% Versus Glycolic Acid 12% in the Management of Melasma: A Randomized Controlled Trial.

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**ABSTRACT**

Background: Introduction: Melasma is an acquired disorder characterized by recurrent hyperpigmentation of skin that results from prolonged sun exposure and is associated with significant psychological impact on the patients. A wide variety of topical depigmenting agents are available for treatment, however, very few studies have been conducted comparing glycolic acid with azelaic acid in patients with melasma. The objective of this study was to assess the efficacy, tolerability, and cost-effectiveness of 12% topical glycolic acid and 20% topical azelaic acid creams in patients with facial melasma.

Methods: This was a randomized controlled clinical trial that took place at Saveetha Medical College and Hospital. Forty (40) patients with clinically diagnosed facial melasma were randomized into two groups of 20. Group A was treated with 12% topical glycolic acid, and Group B was treated with 20% topical azelaic acid, both of which were applied nightly for a period of 8 weeks. Demographic data, clinical history, Wood's lamp examination, and Melasma Area and Severity Index (MASI) scores were recorded at baseline and at weeks 2, 4, 6, and 8. Adverse events were documented at each visit. Qualitative variables were expressed as frequency and percentage, and quantitative variables as mean ± standard deviation. Chi-square and unpaired t-tests were used for statistical comparisons, with a p-value of less than 0.05 considered statistically significant.

Results: The majority of participants were aged 24–45 years with a female predominance. No statistically significant intergroup differences were observed for baseline risk factors including sun exposure, hormonal contraceptive use, Fitzpatrick skin type, and site of involvement ($p > 0.05$). The mean MASI score at baseline was 4.84 in the glycolic acid group and 5.13 in the azelaic acid group ($p = 0.48$). At week 8, the mean MASI score declined to 2.98 in the glycolic acid group and 2.62 in the azelaic acid group, a difference that reached statistical significance in favour of the azelaic acid group ($p < 0.05$). Adverse events were comparable between groups, with three patients in the azelaic acid group and four in the glycolic acid group reporting mild local reactions.

Conclusion: Azelaic acid 20% gel demonstrated superior clinical efficacy compared with glycolic acid 12% cream in the short-term management of melasma, with a greater reduction in MASI scores and a comparable adverse event profile. Given its multifactorial mechanism of action and favourable safety profile, azelaic acid warrants consideration as a first-line topical agent for melasma, particularly in patients with darker Fitzpatrick skin types

**Keywords**: Melasma; Azelaic acid; Glycolic acid; Hyperpigmentation; Randomized controlled trial; MASI score; Topical therapy; Pigmentation disorders

**How to cite this article:** M SSR, Rajagopal V, Comparative Efficacy and Safety of Topical Azelaic Acid 20% Versus Glycolic Acid 12% in the Management of Melasma: A Randomized Controlled Trial..Int J Drug Deliv Technol. 2026; 16(27s): 21-26; DOI: 10.25258/ijddt.16.27s.3

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Acquired, chronic, and usually recurrent, melasma is a hyperpigmentation disorder of the skin. Melasma is characterised by the presence of asymmetrically distributed, irregularly shaped brown or greyish-brown macules and patches located on the sunlight-exposed parts of the face - predominantly on the cheeks, forehead, upper lip, nose, and chin [1]. The majority of those with melasma are women of reproductive age, and it is prevalent in people with Fitzpatrick skin types III to V, particularly in those of South Asian, Southeast Asian, Latin American, and Middle Eastern descent [2]. While melasma is not considered a serious medical issue, it can cause considerable psychological distress and have a detrimental effect on quality of life due to the visibility of the disorder [3]. A combination of factors influence the development of

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melasma; the most established contributing factor is ultraviolet (UV) exposure, which triggers increased melanin production in melanocytes via increased tyrosinase activity and other associated enzymes [4]. Hormones associated with pregnancy, oral contraceptives, and thyroid disorders also play a key role in both the development and persistence of melasma [5]. A family history of melasma has been reported among affected individuals [6]. Additionally, there is increasing evidence to suggest that vascular factors and mast cell activation, as well as changes to the dermal layer such as disruption of the basement membrane, are contributing factors to melasma; thus expanding our understanding of melasma as a complex form of photodermatosis [7].The estimation of the proportion of women at risk of developing melasma among populations at risk from India is approximately 25%, which represents a significant dermatological burden [8]. The combination of year-round high UV index, hormonal contraceptive use, and the darker complexion types found in the Indian subcontinent all contribute to the greater incidence of the disease [9].

Although there are many different products available to manage the condition, controlling melasma remains difficult. Topical depigmentation agents like hydroquinone, tretinoin, and combination products with either of those two ingredients and a corticosteroid are first-line therapies for melasma management. However, the long-term use of hydroquinone may lead to the development of a condition called "ochronosis" (a blue-black discoloration of the skin) as a result of prolonged exposure; this can also lead to subsequent hyperpigmentation, thus restricting its continued efficacy [10]. Consequently, topical, non-steroidal alternatives like azelaic acid, glycolic acid, kojic acid, lactic acid, tranexamic acid, and arbutin are gaining popularity as safer long-term alternative treatments [11]. In resistant cases, some physicians may recommend procedural approaches as treatment, which could include the use of chemical peels, microdermabrasion, intense pulsed light therapy, or various types of laser therapies; however, recurrence is still common with procedural therapies and the cost of doing so might be prohibitive in developing countries providing limited resources [12].

Glycolic acid (GA), the smallest of the alpha-hydroxy acids, acts as a topical agent in the reduction of melasma through many different methods. Glycolic acid has been shown to influence epidermal cell turnover, promote desquamation through decreased corneocyte cohesion, and promote distribution of melanin-laden keratinocytes via enhanced epidermal/no barrier function caused by higher concentrations of GA [13]. Higher concentrations of GA have been similarly shown to break down the epidermal barrier and yield better absorption of additional topical products used with it. Glycolic acid is also reported to have mild anti-inflammatory and/or antioxidant properties, also possibly contributing to its therapeutic activity in treating melasma [14]. The dosage (i.e., concentration) of GA is important to achieving therapeutic outcomes in melasma and is commonly utilized in clinical practice at concentrations ranging from 10 - 70%.

Azelaic acid (AA), a naturally-occurring anaerobic saturated dicarboxylic acid that is derived from the fermentation of Pityrosporum ovale and based in certain grains (e.g., wheat, rye, and barley), demonstrates a more targeted mechanism of action than GA. AA principally exerts its depigmenting effect through competitive inhibition of tyrosinase, a key enzyme in the melanin biosynthesis pathway [15]. AA has been demonstrated to selectively inhibit hyperactive or aberrant melanocytes and produce little or no adverse effect on normally functioning melanocytes, thereby minimizing the risk of paradoxical depigmentation [16]. Other mechanisms by which AA exerts a depigmenting effect include: inhibition of mitochondrial oxidoreductase activity and DNA synthesis in melanocytes; and its anti-inflammatory and/or antibacterial properties, which expand the utility of AA in additional therapeutic applications [17].

Because of the considerable variability in efficacy, safety, and patient tolerability reported in the literature related to the use of GA and AA; and the notable lack of direct, head-to-head, comparative clinical trials with Indian patients (especially those with dark –colored skin) comparing these agents, the current study was developed to assess and compare the clinical efficacy, safety profiles, and tolerability of the products, GA 12% cream and AA 20% gel, for the treatment of facial melasma using a randomized controlled trial design with the validated Melasma Area and Severity Index (MASI) as the primary outcome measure.

Materials and Methods

Study Design and Setting

The Dermatology Outpatient Department of Saveetha Medical College and Hospital (Chennai, Tamil Nadu) ran this open-label, parallel-group randomized controlled trial over eight weeks, with repeated assessments of outcomes every two weeks. The Institutional Ethics Committee at Saveetha Medical College and Hospital provided approval for this trial, which followed the Declaration of Helsinki. All participants provided informed written consent before being enrolled into the study.

Study Population

Patients presenting to the Dermatology Outpatient Department with a clinical diagnosis of facial melasma were considered for inclusion.

**Inclusion Criteria**

Patients of any gender presenting with a clinically confirmed diagnosis of facial melasma.

Individuals attending the dermatology outpatient clinic during the designated study period.

Patients willing to receive study treatment and able to attend regular follow-up visits.

Participants providing written informed consent for study participation.

**Exclusion Criteria**

Pregnancy or lactation.

Known hypersensitivity or allergy to the study medications or their excipients.

Patients currently or recently receiving other oral or topical treatments for melasma.

Concurrent use of photosensitizing medications or agents affecting thyroid hormone levels.
Patients who declined to participate or withheld written informed consent.

Sample Size and Randomization

A total of 40 patients were enrolled in the study. Participants were randomly assigned to one of two equal treatment groups (n = 20 per group) using block randomization with sequentially numbered sealed envelopes. Group A (Glycolic Acid group) received topical glycolic acid 12% cream, and Group B (Azelaic Acid group) received topical azelaic acid 20% gel.

Interventions

**Group A – Glycolic Acid 12% Cream:** Patients were instructed to apply a thin layer of glycolic acid 12% cream to the affected facial areas once daily at night, after gentle cleansing with a mild soap. Treatment was continued for eight weeks. Patients were additionally advised to apply a broad-spectrum sunscreen (SPF ≥ 30) each morning and to avoid prolonged sun exposure throughout the treatment period.

**Group B – Azelaic Acid 20% Gel:** Patients were instructed to apply a thin layer of azelaic acid 20% gel to the affected facial areas once daily at night, after gentle cleansing with a mild soap. The treatment duration and adjunctive photoprotection measures were identical to those in Group A.

Data Collection and Outcome Assessment

During the baseline appointment all participants had a complete clinical history taken, as well as demographic information, including: age; sex; Fitzpatrick skin classification (phyisical characteristics); and occupation. Comprehensive medical information was obtained, including: length of time with melasma; if any immediate family member has melasma; history of any hormonal contraceptive use; thyroid disorders; and previous attempts to treat melasma. Participants had the areas and the distribution of melasmatic lesions documented (including the Wood's lamp examination) to classify the lesions as epidermally, dermmally or mixed lesions based on pigmentation accentuation under long-wave UV light.

The Melasma Area and Severity Index (MASI) is a composite scoring system that was developed by Kimbrough-Green et al., and quantifies the severity of the disease [1]. The MASI scores for the different regions of the face based on the area of skin with melasma (A), the darkness of pigmentation (D), and the homogeneity of pigmentation (H) were calculated using the following:

**MASI = 0.3(DF + HF) × AF + 0.3(DMR + HMR) × AMR + 0.3(DML + HML) × AML + 0.1(DC + HC) × AC**

Baseline assessments for MASI scores and mapping photographs were taken at every two-week period from week 2 to week 8. Patients provided a subjective self-assessment of their level of symptom relief and overall satisfaction with their treatments at each visit using their own summaries. Adverse events and complications related to treatment were recorded and graded accordingly.

Statistical Analysis

Data were entered and analysed using SPSS version 21.0. Qualitative variables were expressed as frequency and percentage, and quantitative variables as mean ± standard deviation (SD). The chi-square test was used to compare categorical variables between groups. The unpaired Student's t-test was employed for comparing continuous variables. A two-tailed p-value of less than 0.05 was considered statistically significant for all analyses.

Results

Baseline Participant Characteristics

A total of 40 patients with facial melasma were enrolled and equally randomized into the glycolic acid group (Group A, n = 20) and the azelaic acid group (Group B, n = 20). The mean age of participants in Group A was 31.55 ± 9.84 years and in Group B was 32.95 ± 10.17 years; the difference was not statistically significant ($p > 0.05$). In both groups, 75% of participants were female and 25% were male. The majority of participants in both groups were employed in the private sector (35%), followed by homemakers (25%). The malar pattern of involvement was the most frequently observed site of melasma in both groups (55%), followed by the centrofacial pattern (35%) and mandibular pattern (10%). Duration of melasma was less than six months in 50% of patients in each group (Table 1).

Risk Factors

Sun exposure was the most prevalent identifiable risk factor, reported in 65% of patients in Group A and 70% in Group B. Pregnancy-related melasma was documented in 30% and 35% of patients in Group A and B, respectively. Oral contraceptive pill use was reported in 15% (Group A) and 25% (Group B) of participants. Family history of melasma was present in 35% and 40% of patients in Groups A and B, respectively. Thyroid disorders were identified in 20% of Group A patients and 15% of Group B patients. No statistically significant intergroup differences were found for any risk factor ($p > 0.05$) (Table 2).

Dermatological Characteristics

Fitzpatrick skin type IV was the most prevalent phototype, present in 75% and 80% of patients in Groups A and B, respectively. Epidermal melasma was the most common type on Wood's lamp examination (45% in Group A and 50% in Group B), followed by mixed (35% vs. 20%) and dermal (20% vs. 30%) subtypes. The centrofacial pattern was the predominant distribution in both groups. Wood's lamp examination confirmed enhanced pigmentation (epidermal accentuation) in approximately 50% of Group A and 40% of Group B patients. These differences between groups were not statistically significant ($p > 0.05$) (Table 3).

MASI Score Progression and Treatment Efficacy

At baseline, the mean MASI score was 4.84 in the glycolic acid group and 5.13 in the azelaic acid group, with no statistically significant difference between the groups ($p = 0.48$). During the eight-week trial, both treatment groups demonstrated a continual decrease in their MASI score. The average (mean) MASI score of Group A was 4.76 at the end of week 1 and Group B was 4.57 ($p > 0.05$). By week four, the average MASI score had dropped to 3.85 in Group A and 3.48 in Group B. After completion of the eight-week trial, the average MASI score had fallen to 2.98 for glycoclic acid treated patients and 2.62 for azelaic acid

treated patients; both groups demonstrated significant improvement ($p < 0.05$) in comparison to each other with azelaic acid group resulting in a greater decline in MASI scoring. You can find the longitudinal pattern of individual MASI score changes for each treatment group assessed in this study in Table 4 and Figure 1.

Adverse Events

The adverse event profile was also largely mild and transient. Of the three participants (15%) in the azelaic acid group that had an undesired event, there were complaints of burning and mild pain at the site of application. Additionally, four patients (20%) in the glycolic acid group had an adverse event: 2 patients reported pain; 2 patients reported burning, erythema, or pruritus at the site of treatment. No patient needed to terminate treatment because of the adverse events recorded. There was no difference between groups with respect to the frequency or severity of adverse events ($p > 0.05$).

Discussion

The efficacy and safety of two different topical agents--glycolic acid (GA) cream and azelaic acid (AA) gel--for treatment of facial melasma were compared in a randomized controlled trial over 8 weeks. Both agents produced progressive reductions in MASI scores throughout the study; however, by the end of the 8-week period, AA had statistically significantly better efficacy (mean 2.62) than GA (mean 2.98) ($p<0.05$). These results demonstrate that AA is a safe and effective topical agent to treat hyperpigmentation disorders, further supported by a growing body of literature which demonstrates that AA is an effective and well tolerated topical agent for hyperpigmentation disorders.

Azelaic acid's (AA's) mechanism of action to induce depigmentation is through selective and competitive inhibition of the enzyme tyrosinase, which is the rate-limiting enzyme in the biosynthesis of melanin [15]. In contrast to hydroquinone, which inhibits all melanocyte activity and poses a risk of exogenous ochronosis, AA preferentially inhibits hyperactive or abnormal melanocytes; therefore, there is a lower potential for paradoxical hypopigmentation with long-term use of AA compared to hydroquinone [16]. Furthermore, AA inhibits mitochondrial oxidoreductase activity and DNA synthesis in abnormal melanocytes, possesses well studied anti-inflammatory and antimicrobial properties, and has an excellent safety record when used during pregnancy and lactation; thus, AA is an especially valuable treatment option for women, who constitute the vast majority of those affected by melasma.

Our findings are supported by previous clinical studies. Lowe et al. showed that facial pigmentation was significantly improved with 20% AA over 24 weeks, with low rates of adverse effects [6]. verallo-rowell and co-authors demonstrated that in a comparison of patients using 20% azelaic acid and 12% glycolic acid, patients using 20% azelaic acid experienced less facial pigmentation than those using 12% glycolic acid and demonstrated low rates of adverse effects [7]. Thus, our results confirm the findings of previous studies that AA and GA are both effective and safe agents for the treatment of facial melasma and that AA is the superior treatment for both efficacy and tolerability.The aforementioned emulators saw significant improvement in both lesional size as well as pigmentary intensity on an Asian patients' based cohort treated with azelaic acid (AA), these findings being particularly relevant to the South Asian patient cohort in this study [4]. As such, there has been in the literature a consistent documentation of the favourable outcomes for azelaic acid therapy on darker Fitzpatrick skin types given that these patients are far more likely to develop post-inflammatory hyperpigmentation (PIHP) as a consequence of receiving more aggressive treatment modalities [5].

There were significant clinical decreases in MASI scores associated with glycolic acid (GA). However, we observed a statistically significant higher rate of adverse local reactions (erythema and pruritus) associated with GA in this cohort. In particular the keratolytic action of GA, while facilitating pigmentation dispersion by enhancing epidermal turnover, may lead to a temporary reduction of the skin barrier which can predispose to cutaneous irritation, particularly in tropical climates or in those Fitzpatrick skin types III to V [13].

These considerations have clinical implications in the Indian environment where a high ambient UV index may further exacerbate the photosensitizing properties associated with exfoliative agents. Nonetheless, there were no statistically significant differences in the adverse event profiles of the two interventions in this trial such that no patient required withdrawal from the study.

The demographic characteristics of this cohort conform to established epidemiological data.Female patients represent the majority of reported melasma cases in current literature, with the highest incidence occurring in the third through fifth decades of life. Additionally, a number of studies show that there are significant triggering factors associated with this condition including prolonged exposure to ultraviolet radiation from the sun, taking oral contraceptives, and having a family history of the disease [8][9]. The predominance of centrofacial and malar distribution patterns within both groups studied are also consistent with established anatomical distribution patterns of melasma [2]. In addition, Fitzpatrick skin types III and IV dominate the population of melasma patients, which provides evidence for the importance of the use of safe and well-tolerated topical agents for treatment.

Another important aspect of treating patients with melasma is the burden experienced by the patient in terms of psychosocial issues that may arise as a result of their condition. These factors are secondary to the visibility of their condition, chronic and relapsing nature, and will often create extremely high levels of anxiety for the affected individual, along with lower self-esteem and a reduced quality of life (e.g., women's quality of life who are affected by melasma and are members of an underprivileged socioeconomic class) [11]. Since the majority of participants in this study are engaged in outdoor professions (e.g., laborers, private-sector employees), this finding confirms the intersection of occupational UV exposure and disease burden, highlighting the need for patient education

as well as consistent photoprotection in any treatment/protocol for melasma.

From a health systems perspective, both glycolic acid and azelaic acid offer economical and effective alternatives to more invasive treatment methods, particularly for areas with limited resources where alternative therapies such as laser and chemical peels may not be readily accessible.Azelaic acid formulations have many benefits in that they are affordable and readily available without the need for refrigeration and specialized dispensing requirements, making them highly accessible primary care treatments [10].

There are some limitations of the current study that must be considered. The sample size of 40 participants is small in comparison to other studies and will limit the statistical power and generalizability of the results. An 8-week trial was sufficient for finding differences in efficacy over the short term, but may not capture the natural history of chronic relapsing melasma, as well as durability of responses to treatments. There is no long-term follow-up period to assess recurrence rates after treatment has stopped. Since an open-label trial was used for this study, THE possibility of observer bias with MASI scoring cannot be ruled out. More objective methods of determining outcomes using colorimetric methods (e.g., reflectance spectrophotometry or mexameter analyses) will strengthen this type of outcome measurement in future trials. Additionally, the study was performed at one tertiary care site, thus imposing a potential for referral bias, limiting generalizability to primary care-based or community-based populations.

The results from this study have many clinical applicability and provide future research opportunities. Azelaic acid 20% gel had a statistically greater efficacy than that of glycolic acid 12% cream and has a similar tolerability profile when compared, and may serve as a preferred first-line topical agent for melasma, particularly in patients with Fitzpatrick skin types III–V, who are at a greater risk for post-inflammatory hyperpigmentation associated with more irritating agents. Because of the lower incidence of adverse local reactions to azelaic acid, the potential for improved patient adherence, which is a critical factor for successful treatment in any individual who needs prolonged maintenance therapy.

Azelaic acid has an excellent safety profile during pregnancy and lactation, expanding prescribing to most socio-demographics of melasma patients. In low resource areas that have limited access to dermatology specialists, having safe and effective topical agents that can be prescribed by a primary care physician presents an exciting opportunity to impact public health at the population level.

Future research should incorporate longer follow-up durations to evaluate recurrence rates and the sustained durability of treatment effects. Pharmacogenomic investigations exploring the influence of genetic variants in melanogenesis pathways on treatment response may help individualize therapy. Patient-reported outcome measures and health-related quality of life instruments should be integrated as co-primary or secondary endpoints in future trials to comprehensively capture the impact of therapy from the patient perspective.

Conclusion

The results of this randomised controlled trial indicate that topical azelaic acid (20% gel) is superior to topical glycolic acid (12% cream) in reducing MASI scores (Melasma Area and Severity Index, incorporating clinically meaningful pigmentation improvement) at 8 weeks of therapy in patients with facial melasma. Both agents provided improvement in skin tone, but azelaic acid-treated patients experienced a significantly greater reduction in mean MASI scores by week 8 compared to glycolic acid-treated patients ($p < 0.05$). The majority of adverse effects were mild, transient, and occurred in similar proportions between study groups. Due to its superiority in efficacy, good tolerability, broad safety margin, ability for use during pregnancy, and availability in primary care settings, azelaic acid should be used as first-line topical therapy for the treatment of melasma, especially among individuals with darker skin phototypes. Larger, multicenter randomised studies with longer follow-up are needed to confirm these results and more fully describe long-term benefit-to-risk ratios of both treatments.

Declarations

**Ethical Approval:** The study protocol was reviewed and approved by the Institutional Ethics Committee of Saveetha Medical College and Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Informed Consent:** Written informed consent was obtained from all participants prior to their enrolment in the study.

**Conflict of Interest:** The authors declare no conflict of interest.

**Funding:** This study received no external funding.

**Author Contributions:** SSR contributed to data collection, clinical assessment, and drafting of the manuscript. VR contributed to study conception, design, supervision, and critical revision of the manuscript. Both authors approved the final version submitted for publication..

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