Original Article

Efficacy, safety, and cost-effectiveness of glycolic acid vs. azelaic acid in melasma

Purna Pandya[1], Nandini Raghva[2], Sreelakshmi TS[2], Rima Shah[3], Roshani Shetty[2], Snigdha Singh[2]

[1]Department of Dermatology, SAL Institute of Medical Sciences, Ahmedabad, Gujarat, India, [2]Department of Dermatology, GMERS Medical College and General Hospital, Gandhinagar, Gujarat, India, [3]Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Rajkot, Gujarat, India

Abstract

Objective: To compare efficacy, safety, and cost of the treatment among topical glycolic acid (GA) and azelaic acid (AA) in melasma patients. **Methodology:** A total of 80 patients with melasma were randomized into two groups of 40 each and received either topical GA (12%) or AA (20%). Their demographic data, detailed clinical history, and systemic and complete local skin examination were carried out. MASI scoring and adverse events were recorded at baseline, 2, 4, 6, and 8 weeks after treatment and compared. The total cost of therapy was calculated and compared. **Results:** Most patients belong to 24–35 years with a female preponderance. No statistically significant difference was found for risk factors like exposure to sunlight, hormonal contraceptives, Fitzpatrick skin type, and affected site among both groups ($P > 0.05$). The mean MASI score in the AA and GA groups, respectively, was 5.13 and 4.84 at the baseline ($P = 0.48$) which reduced to 4.57 and 4.86 in the AA and GA groups correspondingly ($P > 0.05$) in the first week. In the 8th week, the mean MASI score was 2.82 and 2.88 in the AA and GA groups ($P > 0.05$). There was no statistically considerable difference in the prevalence of side effects between the two groups ($P > 0.05$). The total cost of treatment was Rs. 1410 and Rs. 430 per patient for the AA and GA groups, respectively ($P < 0.05$). **Conclusion:** There is no noticeable difference between AA and GA in terms of their effectiveness and safety profiles while treating melasma but the cost of treatment was significantly higher with azelaic acid.

Keywords: Azelaic acid, cost of treatment, efficacy and safety, glycolic acid, MASI scoring, melasma

Introduction

Melasma is an acquired condition characterized by hyperpigmentation that appears on sun-exposed skin. The nose, face, upper lip, and forehead are the most often affected in females in the reproductive age range.[1] Fitzpatrick skin types III–V are typically affected in girls of Hispanic or Asian origin.[2] The primary contributing variables include high levels of UV exposure, hormonal contraception, pregnancy, medicines, and genetic abnormalities.[3,4] Around 5–6 million women are affected with melasma in the USA and prevalence in India is around 25% in high-risk patients creating a significant healthcare burden.[2-4] Primary care physicians can educate patients and help them understand the preventive measures to lessen the severity of hyperpigmentation or completely prevent the development of lesions because there is a clear correlation between modifiable risk factors and the development of lesions.[4]

Despite the plethora of treatment modalities for melasma, their results are poor. There is a high risk of recurrence and often incomplete treatment, justifying the primary care physician's role

Address for correspondence: Dr. Rima Shah, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Rajkot, Gujarat, India.
E-mail: rima_1223@yahoo.co.in

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in early diagnosis and prevention.[5] Various modalities include corticosteroid triple combinations, hydroquinone (HQ), and tretinoin, superficial chemical creams, nonsteroidal demelanizing creams, (trichloroacetic acid, GA, lactic acid, and kojic acid, AA, salicylic acid, etc.), lasers (Alexandrite laser, ruby laser, Q-switched Nd: YAG laser, Fraxel laser, and Er: YAG laser), and intense pulsed light (IPL).[5-7] Topical agents have a low rate of complications and are popular due to their low costs, ease of use, and confirmed efficacy in different studies.[7-10]

The anti-inflammatory, antioxidant, and keratolytic properties of glycolic acid (GA) help in melasma by promoting breakdown and reducing cohesion and corneosome desquamation.[11] The acid concentration affects how strongly a GA is utilized.[12] The investigations showed that topical GA had a photoprotective effect as well.[13]

Azelaic acid (AA) is a dicarboxylic acid used to treat mild to severe acne because it fights bacteria that invade skin pores. Because melasma is classified as a pigmentation condition, it acts as a tyrosinase inhibitor and interferes with the enzymatic processes of pigment formation inside melanocytes.[14]

Considering the variations in data by various researchers in terms of safety and the effectiveness of drug therapy for melasma, this study has been planned to compare the safety effectiveness, as well as the cost of treatment of topical GA vs AA in melasma treatment.

Methodology

This randomized open-label study was conducted on melasma patients who were undergoing outpatient dermatological treatment at a tertiary care teaching hospital. All participants provided written informed permission before enrolment, and the research protocol was reviewed and received approval from the institutional ethics committee via letter no. GMERS/MCG/IEC/40/2020.

Sample size: As per the earlier reports, GA causes a mean change in MASI to score by 4.81 ± 2.3[13] and AA also causes a change in MASI to score in melasma patients by 50%.[14] Considering the mean change in MASI score, standard deviation, and variance, the calculated sample size at 95% confidence interval and 80% power, was 39 in each group. This sample size was calculated by using Open Epi software.

Participant selection: Patients who visited the dermatology outpatient department throughout the research period and had a clinical diagnosis of facial melasma, irrespective of gender, age group, or willingness to receive treatment and return for follow-up, were involved in the trial. Patients who refused to participate in the study or who refused to provide written informed consent, women who were pregnant or breastfeeding, those with a thrombosis history or a tendency toward blood coagulation diseases, those with psychological disorders, and those taking medications that affect thyroid hormone levels or photosensitizing medications, those who refused to come for follow-up appointments or who had unrealistic expectations for the course of treatment, and those who had consumed other pills are all omitted from the study. Patients with known AA or GA allergies or sensitivities, as well as those with dense telangiectases, plaque-like facial edema, or moderate to severe rhinophyma, were also omitted from the trial.

Participant recruitment procedure: All the patients with hyperpigmentation disorders coming to dermatology OPD were screened, and those with a clinical diagnosis of melasma and meeting exclusion and inclusion criteria were enrolled for this trial. All the participants were explained clearly the nature and purpose of the study, and those willing to give written informed consent were included in the study. The patient who refused to participate in the study was also given appropriate treatment.

Study procedure: The patient's information, including demographic information, a thorough clinical history, comorbidities, and previous experience, was gathered using pre-defined criteria. A thorough personal and medical history was taken before a dermatologist conducted a Wood's lamp examination to find the kind of melasma. Melasma severity was determined using a MASI rating system. The technique introduced by Kimbrough-Green CK *et al.*[15] was utilized to determine MASI. The face will be categorized into four areas: the chin (A, 0-6), the MR (right malar), the ML (left malar), and the forehead (F), each with a percentage of 30%, 30%, 30%, and 10%, respectively. Melasma severity was calculated by multiplying the percentage and numerical value of each area by the sum of homogeneity (H, 0-4) and darkness (D, 0-4). Following the addition of these values, MASI was obtained.

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

After the general examination and local examination are finished, patients were taken to the procedure room for the intended intervention.

Randomization and blinding: Patients were divided into two groups (GA vs. AA) using a random number table. As it is an open-label study, patients and treating dermatologists were aware of the treatment given.

Intended intervention: A thorough history, MASI grading, clinical examination, and photographic documentation were all used in the pretreatment evaluation process. Affected regions of the face were given topical GA (12%) or AA (20%) as per the group. Both medicines are available as a cream and were prescribed by the treating dermatologist. Patients were directed to apply the cream once daily at night for eight weeks to the affected region.

Follow-up: A detailed background, MASI score, clinical examination, photographic analysis, and post-treatment

assessment were conducted on both groups. At each follow-up visit, the MASI score was recorded at the baseline and then 2,4,6, and 8 weeks following treatment.

Analysis for ADRs: All the patients were asked about any adverse reactions to the drug and their general and local skin examinations were done at each follow-up visit to observe adverse effects.

Cost analysis: Total cost of drug treatment was calculated for 8 weeks of treatment in both the groups and compared.

Outcome measures: The primary outcome measure was efficacy analysis by improvement in melasma based on the change in MASI score while the occurrence of adverse events in both the groups was the secondary endpoint for safety analysis.

Statistical analysis: Epi info software was used to examine the data once it was put into an Excel sheet. Data were expressed as actual frequencies, mean, percentages, and standard deviations as suitable. Chi-square test and Students' *t*-test were applied for association analysis as appropriate. The *P* value was determined to evaluate the levels of significance, and $P < 0.05$ was deemed to be significant.

Results

The study included a total of 80 individuals of melasma meeting inclusion-exclusion criteria and randomly divided into two groups of forty each in AA and GA groups. Demographic and baseline details of the study respondents have been demonstrated in Table 1. The mean age of the participants was 35.57 ± 7.62 years for a patient in the GA group while it was 36.76 ± 7.99 years for those who were in the AA group with no statistical difference at baseline ($P > 0.05$). Most of the participants in these groups belong to the 31–45 years of age group, female preponderance, and with poor education with laborer by occupation hence were more prone to sunlight exposure.

Table 2 demonstrates that both groups had a presence of melasma development risk factors. Risk variables were the same for both groups ($P > 0.05$), showing no statistically considerable difference. More than 70% of the patients had not taken any drug therapy or treatment or had any family history of melisma in both the groups. Table 3 also includes information on sun exposure history, hormonal contraceptives, and other factors without statistically considerable differences between the two groups ($P > 0.05$).

The clinical presentation of the melasma patients in the study groups has been shown in Table 3. The centrofacial pattern was the most often identified melasma pattern, accounting for 67.5 percent and 62.5 percent in each group, respectively, followed by malar and all area patterns. More than 70% of the 40 patients had skin phototype IV, which was the most often seen Fitzpatrick skin phototype among both the groups followed by Fitzpatrick skin

Table 1: Demographic profile and baseline characteristics of patients

Parameter	Glycolic Acid	Azelaic Acid	*P*
Age			
18-30	10 (25)	08 (20)	
31-45	24 (60)	25 (62.5)	0.852
46-60	6 (15)	7 (12.5)	
Gender			
Female	35 (87.5)	32 (80)	
Male	5 (12.5)	08 (20)	0.05
Education			
Illiterate	22 (55)	25 (62.5)	
1-12th STD	7 (17.5)	5 (12.5)	0.888
Graduate	5 (12.5)	4 (10)	
Postgraduate	6 (15)	6 (15)	
Occupation			
Labourer	25 (62.5)	26 (65)	
Business	7 (17.5)	6 (15)	0.762
Job	2 (5)	4 (10)	
Retired/Housewife	6 (15)	4 (10)	
Marital status			
Unmarried	5 (12.5)	04 (10)	
Married	35 (87.5)	36 (90)	0.343
Address			
Urban	33 (82.5)	34 (85)	
Rural	7 (17.5)	6 (15)	0.761

phototype III with less than 10% of the total study population. No considerable difference was seen with the treatment of AA and GA about Fitzpatrick skin type and affected site in melasma patients. [Table 4] Epidermal type of melasma was noticed in the most of patients on Wood's light examination in the various study groups, followed by the dermal type and mixed type with no statistical significance. Dermoscopy of melasma lesions showed that the majority of instances in all patients under study had a fine brown reticular pattern placed on a background of faint light brown patches.

Efficacy analysis: The efficacy of both drugs was evaluated using the MASI score. The AA group had a mean MASI score of 5.13 at the baseline, whereas the GA group had a mean MASI score of 4.84. There was no statistically considerable difference between the two treatments ($P = 0.48$). There was no noticeable difference in the mean MASI score decrease between the two treatments in the first week, with the mean MASI score in the AA group falling to 4.57 and the mean MASI score in the GA group falling to 4.86. The mean MASI score was measured every week for both therapies in treatment with AA and GA, and it was observed that it continuously reduced and by the end of the 8th week the mean MASI score was decreased to 2.82 in the AA group while in the GA group the mean MASI score was decreased to 2.88, and hence overall there was no significant difference between both the therapies, which suggested similarity in the efficacy of both therapeutic regimens. [Table 4] Comparison in terms of improvement in melasma lesions at the follow-up visits in both the groups has been shown in Figure 1.

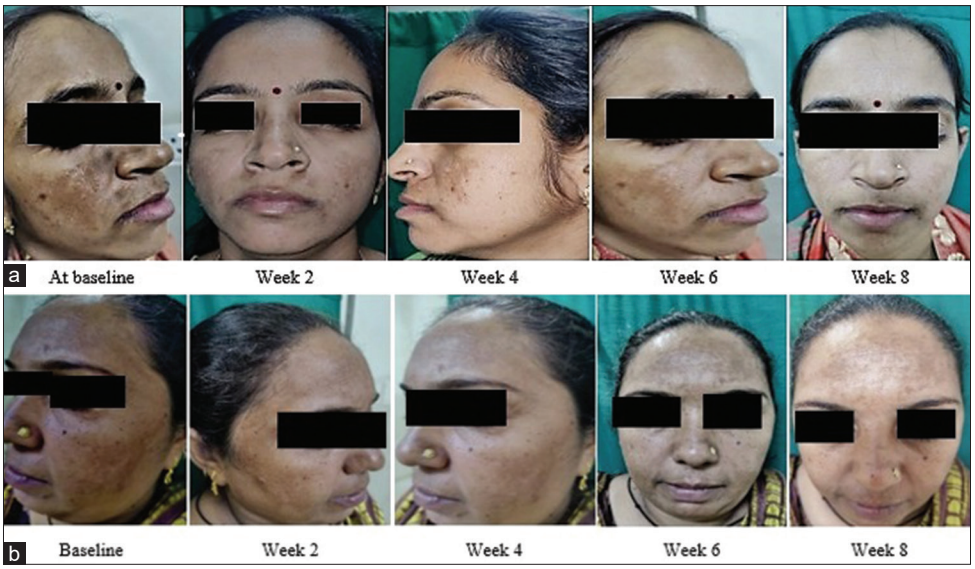

Figure 1: (a) Patient photograph after each visit in AA group (b) Patient photograph after each visit in GA group

Table 2: Presence of risk factors among melasma patients in both groups

Parameter	Glycolic Acid	Azelaic Acid	*P*
Drug History			
Absent	39 (97.5)	38 (95)	
Present	1 (2.5)	2 (5)	0.556
Family History			
Absent	32 (80)	30 (75)	
Present	8 (20)	10 (25)	0.592
Treatment History			
Absent	28 (70)	30 (75)	
Present	12 (30)	10 (25)	0.616
History of Sun Exposure			
Absent	32 (80)	35 (87.5)	
Present	8 (20)	5 (12.5)	0.363
Duration of Sun Exposure			
<1 Hour	4 (10)	5 (12.5)	
1-2 hour	3 (7.5)	3 (7.5)	0.971
3-4 hour	28 (70)	26 (65)	
5-6 hour	4 (10)	4 (10)	
>6 hour	1 (2.5)	2 (5)	
Treatment of Sun Exposure			
Intermittent	28 (70)	30 (75)	
Continuous	4 (10)	5 (12.5)	0.646
Occasionally	8 (10)	5 (12.5)	
Exposure to Other Heat Sources			
Absent	36 (90)	38 (95)	
Present	4 (10)	2 (5)	0.395
History of Cosmetic Use			
Absent	6 (15)	9 (22.5)	
Present	34 (85)	31 (67.5)	0.390
History of Hormonal Contraceptives			
Absent	3 (3.5)	5 (12.5)	
Present	37 (92.5)	35 (87.5)	0.456

Safety analysis: On analysis of the adverse events among both the groups, it was found that three participants experienced burning sensation and pain at the application area in the AA group while four patients developed pain, burning, erythema, and itching sensations in the application area in the GA group. In terms of adverse events, there was no noticeable difference between the two groups ($P > 0.05$).

Cost analysis: Total cost of the treatment for entire study duration for AA was approximately Rs. 1410 per patient while it was Rs. 430 per patient for the GA group. GA was a significantly cheaper alternative than AA ($P < 0.05$).

Discussion

More than 1% of the general population suffers from melasma, which is defined as a failure of melanogenesis resulting in persistent hypermelanosis of the skin.[12,13] Patients with melasma revealed to have increased oxidative stress marker levels because melasma activates inducible nitric oxide, which in turn induces reactive oxygen species.[16] Although several therapy options, including tyrosinase inhibitors, anti-inflammatory steroids, and topical retinoids, have been employed more often in studies, darker-complexioned individuals have not shown a noticeable improvement in melasma pigmentation.

The present study demonstrates the use of 20%AA in Melasma treatment and compares its efficacy and safety with topical 12%GA. It was observed that treatment with 20%AA cream was equivalently effective as 12% GA cream with reduced side effects and a considerable drop in mean MASI score in both the treatments without any statistically significant difference. GA has shown anti-inflammatory action, and AA causes reversible inhibition of tyrosinase and oxidoreductase enzymes reverting the symptoms of hypermelanosis. AA also possesses inhibitory action towards the synthesis of DNA in melanoma cells and also blocks thioredoxin reductase, which controls tyrosinase and

Table 3: Clinical presentation of melasma patients in both groups

Parameter	Glycolic Acid	Azelaic Acid	*P*
Fitzpatrick Skin Type			
III	10 (25)	07 (17.5)	0.412
IV	30 (75)	33 (82.5)	
Type			
Epidermal	18 (45)	20 (50)	0.280
Dermal	8 (20)	12 (30)	
Mixed	14 (35)	08 (20)	
Site			
Centrofacial	27 (67.5)	25 (62.5)	0.954
Malar	11 (27.5)	13 (32.5)	
Mandibular	0	1 (2.5)	
All Area	2 (5)	1 (2.5)	
Colour			
Brown	20 (50)	25 (62.5)	0.418
Greyish blue	9 (22.5)	5 (12.5)	
Mixed	11 (27.5)	10 (25)	
Woods Lamp examination			
Present	19 (47.5)	16 (40)	0.753
Absent	8 (20)	08 (20)	
Patchy	13 (32.5)	16 (40)	

Table 4: Comparison of MASI score between glycolic acid and azelaic acid groups

Week	MASI score (Glycolic Acid)	MASI score (Azelaic Acid)	*P*
Baseline	4.84	5.13	0.48
1	4.57	4.86	
2	4.25	4.29	
3	4.04	3.92	
4	3.76	3.47	
6	3.20	3.07	
8	2.82	2.88	

serves as the major electron source for the enzymes that control DNA synthesis in melanoma cells.[10,17]

The majority of patients included in the study belong to 31–45 years of age which was found to be in line with previous studies where patients had old age onset of melasma.[12,18] Also, it has been revealed in many previous studies that old age onset of melasma is associated with hormonal changes. Estrogen and progesterone are associated with stimulation of melanocytes resulting in higher production of melanin.[13,17] No considerable difference was noticed in the prevalence of melasma as compared to its prevalence in females which was found to be aligned with the results of previously reported studies in which males and females were equally affected.[12,19] It is well observed from the study that patients with poor education suffer from depression and higher emotional impact which is found to be consistent with the earlier study.[20]

The majority of patients with labor occupation and habitat in intertropical latitudes are more prone to exposure to sunlight as sun exposure and outdoor work are considered important risk factors that cause exacerbation of melasma.[21,22] Melasma is commonly observed in individuals with brown skin where the genetic component is the most significant risk factor results of which were aligned with the results of the present study as well. A study performed on South Korean patients who suffered from melasma revealed a reduction in expression of the H19 gene resulting in melanogenesis and melanin transfer to keratinocytes along with an effect on the expression of tyrosinase. The results were consistent with our study as well.[23,24]

In this study, we have determined the effect of consumption of hormonal contraceptives on safety as well as the efficacy of GA and AA in the melasma treatment, and it was determined that no adverse effects were reported with a non-significant difference in safety and efficacy among patient of both the groups. In the case of females with melasma higher levels of estradiol were observed while in male therapy constituting testosterone stimulators are more likely to develop melasma. The results were consistence with previously reported literature.[25-27]

In the present study, most of the participants belong to Fitzpatrick skin type III and IV in both the treatment groups which do not have a significant difference coinciding with earlier studies.[28,29] Centrofacial pattern was the most commonly observed type among melasma patients in both groups which involved hyperpigmented patches with irregular borders on upper lips, nose, forehead, and cheeks which was consistent with the results of previous studies. Other sites were less commonly observed which are associated with other facial patterns.[28,29] On Wood's lamp evaluation of patients belonging to both the groups, it was observed that the epidermal type of melasma wherein melanin is present throughout the epidermis was more prevalent dermal and mixed types of melasma were less prevalent in both the groups which is similar to previous research reports.[2,10]

Clinical quantification and severity evaluation of facial melasma are performed using the MASI assessment, and they did not statistically vary from one another. These findings were in line with those of Javaheri *et al.*,[30] who investigated the effectiveness of GA peels (50%) applied monthly for three months with pre-peel treatments using a lotion containing 10% GA and found that the MASI score significantly decreased from the beginning of the treatment to the end. An application of 52.5% GA for 3 minutes resulted in clinical improvement, according to dose-response research looking at the impact of different GA peel concentrations on melasma.[30] A parallel randomized trial was performed by Lowe *et al.*[31] to determine the effectiveness, safety, and tolerability of AA 20% cream reported a significant decrease in pigmentary intensity within 24-week treatment without any adverse effects which were found to be aligned with the outcomes of the present study. A randomized, double-blind study was performed by Verallo-Rowell *et al.*[32] on 155 participants suffering from benign pigmentary disorder to determine the efficacy of AA and found a considerable reduction in the size of the lesion and pigmentary intensity. A similar observation was also made in the present study with AA.

Patients frequently seek counsel for the ailment melasma. A person's mental health, quality of life, and face attractiveness can all be negatively impacted by melasma, a skin condition that can be prevented and treated early by a primary care physician. Patients can be educated about risk factors from their primary care physician, including exposure to UV and radiation and preventive role of sunscreen lotions.[2,17] Primary care doctors are frequently the first to diagnose the illness and explain available treatments, like AA, which is safe during pregnancy or lactation. During routine patient visits, the primary care physician can easily detect melasma as a cutaneous presentation of diabetes mellitus also. Patients may be referred to a dermatologist for further management if required. Overall, primary care physicians play a vital role in the early diagnosis, treatment and follow-up of the patients in developing countries like India.[12,33]

In the present study, a similar response rate was obtained for MASI score in both therapies with 20% AA and 12% GA cream. However, the short follow-up time of just one month was a drawback of this study, and evaluation of the long-term effect of hormonal contraceptive consumption could not be evaluated. Also, the effect of the genetic makeup of the patients on the persistence of melasma needs to be explored further in different populations. Studies with long-term follow-up and consistency in therapy are advised for better results since melasma recurrence is prevalent despite effective treatment.

Conclusion

Both AA and GA are effective in melasma treatment. Both the drugs showed no statistically significant difference in safety as well as efficacy profile for the melasma treatment. The cost of treatment was significantly higher with AA. Therefore, the judgment of the clinician plays a significant role in the prescription of both drugs for melasma for the betterment of the patient.

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Ethics approval

The study protocol was reviewed and approved by the Institutional Ethics Committee via letter no. GMERS/MCG/IEC/40/2020. The study was carried out following the standards of clinical study as laid down in Schedule Y and New Drugs and Clinical Trials Act 2020.

Consent to participate

The participants were explained clearly about the nature and purpose of the study in the language they understood and written informed consent was obtained from her. The participants were ensured that their identity would not be revealed at any stage of the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the all the images.

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Conflicts of interest

There are no conflicts of interest.

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