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Combination of 20% Azelaic Acid Cream and 20% Salicylic Acid Peel Versus Azelaic Acid Cream Alone in the Treatment of Melasma Patients

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Abstract

Background and Objectives: Melasma is a common hyperpigmentation disorder affecting mainly the facial skin. The study aimed to evaluate the efficacy and safety of a combination therapy involving 20% Salicylic acid chemical peel and 20% Azelaic acid cream compared to Azelaic acid cream alone for the treatment of melasma.

Methods: A comparative clinical trial done in Sulaymaniyah, Iraq, from October 2023 to March 2024, involved 40 melasma patients, they were split into Group A (Azelaic acid cream with Salicylic acid peel) and Group B (Azelaic acid cream only) for data collection and treatment interventions. Follow-up evaluations, including photographic assessments and modified Melasma Area and Severity Index scoring, were performed every two weeks to monitor melasma severity and treatment efficacy.

Results: The majority of patients were females 34 (85%), with a mean age of 36.58 ± 6.20 years, predominantly having Fitzpatrick skin type IV. The Centro facial pattern was the commonest (90%). After treatment, Group A showed a more significant reduction in modified Melasma Area and Severity Index score from 7.70 ± 2.64 to 4.47 ± 2.38 ($P<0.001$) compared to Group B, which reduced from 7.87 ± 2.06 to 6.03 ± 1.97 ($P<0.001$). The epidermal type of melasma showed more responsiveness compared to dermal and mixed types.

Conclusion: Treatment with 20% Azelaic acid alone or combined with 20% Salicylic acid peel effectively reduces modified Melasma Area and severity Index score in melasma patients; combination therapy shows better results and fewer side effects than Azelaic acid alone.

Keywords: Azelaic Acid, Combination Therapy, Melasma, Pigmentation Disorder, Salicylic Acid

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Introduction

Melasma is a pigmentation disorder on the face caused by sun exposure, hormones, and genetics, with different types (dermal, epidermal, and mixed) and patterns (centrofacial, malar, and mandibular).[1-3] It is more common in women and those with darker skin, affecting quality of life and self-esteem. The prevalence increases during reproductive years, ranging from 8.8% to 40%.[4] The pathophysiology is rooted in the overproduction of melanin by melanocytes, with subsequent deposition in the epidermis and dermis, stimulated by these various factors.[5] Clinically, melasma presents as hyperpigmented patches, often on the cheeks, forehead, upper lip, nose, and chin. These patches are typically asymptomatic but can cause significant cosmetic distress for patients.[6] Melasma is mostly diagnosed clinically, based on the distinctive look of the lesions.[7] Wood's lamp examination can help in determining the depth of pigment, and in some cases, a skin biopsy may be performed to exclude other causes of hyperpigmentation.[8] The most popular method for determining the extent of melasma is the Modified MASI Score, which considers the area affected and the darkness of the hyperpigmented areas.[9] The treatment of melasma includes a comprehensive approach involving sun protection, topical bleaching agents, chemical peels, and, in some cases, laser therapy.[10, 11] Among topical agents, azelaic acid (AA) cream has been favored for its effectiveness in inhibiting melanin synthesis.[12] Salicylic acid (SA) peels are also employed to promote skin exfoliation and pigment dispersion.[13] Since AA has been shown to suppress tyrosinase activity, diminish the growth of aberrant melanocytes, and have anti-inflammatory characteristics, it is a viable alternative for treating melasma.[14] On the other hand, SA, a beta hydroxy acid, is known for its keratolytic and comedolytic properties, and it is used in chemical peels to treat various pigmentation disorders, including melasma.[15] King et al. found that AA is particularly useful for the treatment of rosacea, acne, and melasma.[12] On the other hand, another study found that a 20% SA chemical peel is an efficient and safe exfoliator in treating melasma in Asian skin types.[1] The necessity of this study arises from the limited data on the combined use of 20% AA cream with 20% SA peel treatment for melasma. The current study aims to evaluate the efficacy and safety of the combination therapy versus AA cream alone, providing a more targeted and potentially more effective treatment modality for patients with melasma.

Patients and methods

This comparative clinical trial was conducted at the Dermatology Center in Sulaymaniyah, Kurdistan Region_ Iraq, from October 2023 to March 2024, involved 40 patients with melasma divided into two groups, each of 20 patients. Group A received a combination treatment of 20% Salicylic acid (SA) chemical peel and 20% Azelaic acid (AA) cream, while Group B was treated with only 20% Azelaic acid cream. Eligible participants included men and women over 18 years old with any type of melasma and skin types II, III, and IV. Exclusion criteria encompassed pregnant or breastfeeding women, patients with a history of recurrent herpes simplex, keloid tendency, or other skin diseases, or those who had undergone facial treatments like chemical peeling or surgical procedures within the last six months. Patients with melasma were identified and underwent a Woods light examination to determine the type of melasma. Informed consent was obtained before any procedures. A questionnaire gathered information on patient demographics, medical history, and melasma characteristics. For Group A, treatment involved applying a 20% SA solution (made by combining 20 gr of SA powder with 100 ml of pure ethyl alcohol) with a cotton

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applicator on affected areas within 30 seconds, followed by rinsing the face after the appearance of a white precipitate (1-3 minutes). This peel was applied every two weeks up to four sessions. Additionally, patients applied 20% AA cream nightly for eight weeks, pausing two days before and after each peel session. Post-treatment care included avoiding face washing with soap for 24 hours, limiting sun exposure, and using sunscreen. Patients were monitored for pain, erythema, and exfoliation throughout the treatment period. Additionally, group B patients applied 20% AA cream alone to the affected area every night for 8 weeks. Follow-up evaluation of participants was done regularly at 2-week intervals for four sessions with an additional two weeks SA - free after the last session to assess the response. At each appointment, Melasma severity was clinically assessed before and following each session using photographs and the modified MASI score that is calculated by assessment of 2 factors: area (A) of involvement and darkness (D), With the forehead (f), right malar region (rm), left malar region (lm), and chin (c) corresponding to 30%, 30%, 30%, and 10% of the total face, respectively. The total score range is 0 to 24, Area and darkness are scored as shown in Table (1).

Table (1): Melasma severity scores using modified Melasma Area Severity Index (MASI).

Area of involvement (A)	Darkness (D)
0=absent	0=absent
1=less than 10%	1=slight
2=10% - 29%	2=mild
3=30%-49%	3=marked
4=50% - 69%	4=sever
5=70%- 89%	
6=90%- 100%	

Modified MASI score=0.3A(f)D(f)+0.3A(lm)D(lm)+0.3A(rm)D(rm)+0.1A(c)D(c).[16]

The statistical package for the social sciences (SPSS) version 26 was used to analyze the data. The data's normal distribution status was ascertained using the Shapiro-Wilk test and a histogram picture. The association between the quantitative variables was examined using the Paired t-test, ANOVA, and independent sample t-test. A significant difference was defined as a P-value of < 0.05. The study protocol was approved by the Kurdistan Higher Council for Medical Specialties (KHCMS). Every patient provided written informed consent.

Results

In the current study a total of 40 melasma patients were studied, aged 21 to 48 years with a mean age of 36.58 ± 6.20 years, more than half of the patients (*n*=23, 57.5%) were between 30-40 years, 27.5% (*n*=11) were above 40 years, 15.0 % (*n*=6) was younger than 30 years. 85.0 % (*n*=34) were indoor workers and 15.0% (*n*=6) were outdoor workers. In this study, most of our patients were females (85.0 %, *n*=34), in comparison with males (15.0%, *n*=6). The majority (85.0%, n=34) were married, while only 15.0 % (*n*=6) were single. Seventy-point six percent (*n*=24) of the females had regular menstrual cycles, while 29.4% (*n*=10) of them had irregular periods. Based on Fitzpatrick skin type classification, the majority was type IV (47.5 %, *n*=19) followed by type III (45.0%, *n*=18) then type II (7.5%, *n*=3). The dermal and mixed melasma were equally distributed in our study (42.5%, *n*=17 for each), which was greater than epidermal melasma (15.0%, *n*=6), these classification of melasma was based on Wood's light examination. In respect of pattern of melasma, 90.0% (*n*=36) were Centro facial, 7.5% (*n*=3) were malar and 2.5%, (*n*=1) was mandibular. Forty-two-

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point five percent (*n*=17) had melasma for 1-10 years, 30.0% (*n*=12) for 11-20 years, and 27.5% (*n*=11) had melasma below one year as shown in Table (2).

Table (2): Demographic characteristics and clinical features of the patients.

Patient characteristics		Frequency *n* (%)
Age Mean±SD=36.58 ± 6.20) years	< 30 years	6 (15.0 %)
	30 - 40 years	23 (57.5 %)
	> 40 years	11 (27.5 %)
Occupation	Indoor	34 (85.0 %)
	Outdoor	6 (15.0 %)
Sex	Female	34 (85.0 %)
	Male	6 (15.0 %)
Marital state	Single	6 (15.0 %)
	Married	34 (85.0 %)
Menstrual cycle	Regular	24 (70.6 %)
	Irregular	10 (29.4 %)
Fitzpatrick skin type	II	3 (7.5 %)
	III	18 (45.0 %)
	IV	19 (47.5 %)
Type of melasma	Epidermal	6 (15.0 %)
	Dermal	17 (42.5 %)
	Mixed	17 (42.5 %)
Pattern of melasma	Centro facial	36 (90.0 %)
	Malar	3 (7.5 %)
	Mandibular	1 (2.5 %)
Duration of melasma	< 1 year	11 (27.5 %)
	1-10 years	17 (42.5 %)
	11- 20 years	12 (30.0 %)

The value of age was expressed as Mean ± SD, the categorical variables were expressed as numbers and percentages; n: number; %: percentage; SD= standard deviation.

As shown in Table (3), 87.5% (*n*=35) had a negative history of drug use for chronic diseases (like anti-hypertensive, anticonvulsants, etc.) while 12.5% (*n*=5) had a positive drug history. 80% (*n*=32) were not associated with a history of chronic disease and 20% (*n*=8) were associated with chronic disease, likely family history of melasma was negative in 80% (*n*=32), and 20% (*n*=8) had a family history of melasma. Forty five percent (*n*=18) had a history of melasma, while 55.0% (*n*=22) had no history of this disease. Twenty-two-point five percent (*n*=9) of them were sunscreen users and 77.5% (*n*=31) of them non-users. Pregnancy is considered the most common predisposing factor (35.0%, *n*=14) followed by sun exposure (27.5%, *n*=11), hormonal therapy was 12.5% (*n*=5), and one quarter (*n*=10) of the patients had more than one predisposing factors.

Table (3): History and risk factors in the studied groups.

Patient characteristics		Frequency *n* (%)
History of drug use for chronic diseases	Yes	5 (12.5 %)
	No	35 (87.5 %)
History of chronic disease	Yes	8 (20.0 %)
	No	32 (80.0 %)
Family history of melasma	Yes	8 (20.0 %)
	No	32 (80.0 %)
Previous history of melasma	Yes	18 (45.0 %)
	No	22 (55.0 %)
Sunscreen user	Yes	9 (22.5 %)
	No	31 (77.5 %)
Predisposing factors	Hormonal therapy	5 (12.5 %)
	Sun exposure	11 (27.5 %)
	More than one factors	10 (25.0 %)

The values were expressed as numbers and percentages; n: number; %: percentage.

The most predominant side effect (SE) of SA in our patients was exfoliation (35%, *n*=7), while erythema was recorded in 15% (*n*=3). Half of the treated patients with SA (*n*=10) had no side effects. At baseline, groups A and B had mean modified MASI scores of 7.70 ± 2.64 and 7.87 ± 2.06, respectively (P=0.826). After therapy, group A's mean modified MASI score (4.47 ± 2.38) was notably lower than group B's (6.03 ± 1.97) (P=0.029). A highly significant reduction was noted in group A in the modified MASI score

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(P<0.001) between before treatment (7.70 ± 2.64) and after treatment (4.47 ± 2.38), as seen in Figure (1). In group B, a highly statistically significant reduction was recorded in the modified MASI score between before (7.87 ± 2.06) and after treatment (6.03 ± 1.97) (P<0.001) Figure (1).

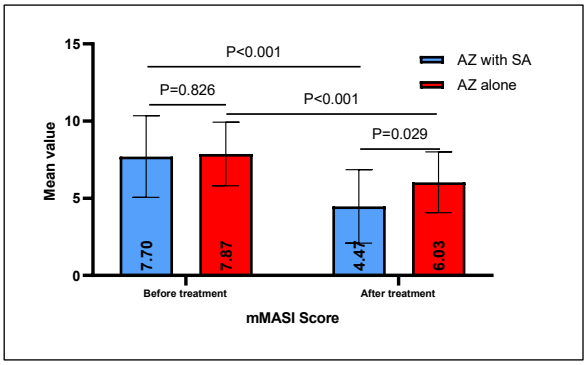

Figure (1): Comparison of the mean mMASI score of the two studied groups.

The values were expressed as Mean ± SD; SD standard deviation. AZ: Azelaic acid; SA: Salicylic acid; MASI: Melasma Area and Severity Index; ns: No significant difference; *: Significant difference; **: Highly significant difference. Independent sample t-tests and Paired t-tests were used for analysis of the data.

In group A, there was no notable difference in the modified MASI score between the types of melasma (P=0.951) at the baseline. On the other hand, after treatment the difference in the score was significant (P=0.005), the epidermal type of melasma recorded the highest level (7.33 ± 2.31 followed by mixed (4.99 ± 2.04) then the dermal type (2.79 ± 1.40). As shown in Table (4).

Table (4): Comparison of the score to the type of melasma in Group A

Modified MASI score	Epidermal	Dermal	Mixed	P- Value
Before treatment	8.17 ± 2.89	7.65 ± 3.18	7.59 ± 2.34	0.951 ns
After treatment	7.33 ± 2.31	2.79 ± 1.40	4.99 ± 2.04	0.005 *

The values were expressed as Mean ± SD; SD standard deviation; MASI: Melasma Area and Severity Index; ns: No significant difference; *: Significant difference. The data were analyzed using analysis of variance.

In group B treated with AZ alone, there was no notable difference in the modified MASI score between the types of melasma (P=0.107) at the baseline. After treatment the difference in the scores was significant (P=0.002), the epidermal type of melasma recorded the highest level (8.27 ± 0.64) followed by mixed (6.83 ± 2.05) then the dermal type (4.58 ± 0.74). Table (5).

Table (5): Comparison of the scores to the type of melasma in Group B.

Modified MASI score	Epidermal	Dermal	Mixed	P- Value
Before treatment	8.77 ± 1.50	6.80 ± 2.01	8.73 ± 1.88	0.107 ns
After treatment	8.27 ± 0.64	4.58 ± 0.74	6.83 ± 2.05	0.002 *

The values were expressed as Mean ± SD; SD standard deviation; MASI: Melasma Area and Severity Index; ns: No significant difference; *: Significant difference; ANOVA was employed in the data analysis.

Discussion

This study aimed to compare the efficacy of a combination therapy using 20% AA cream and 20% SA peel against the use of 20% AA cream alone in treating melasma. We observed a significant improvement in the Modified MASI scores in the combination therapy group (GA). Most participants were women with a mean age of 36 years. Mahajan et al found patients in both groups had a mean age of 35 years and were female.[17] Aslam et al. found that patients in their study had an average age of 28 years, lower than the overall mean age of the present study, possibly due to methodological differences and social/cultural characteristics. The sex distribution among patients was comparable

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to the current study, with a female predominance.[18] In the present study, the majority of participants were housewives, akin to findings in other studies regarding job statuses.[19, 20] Skin type assessment revealed a majority with Fitzpatrick types III and IV, consistent with findings in studies by Faghihi and Kim. [21,22] The distribution of melasma types showed a predominance of dermal and mixed melasma, contrasting with the prevalence of epidermal melasma in studies conducted by Gautam, et al and Wawrzyńczak suggesting possible influences of occupational and lifestyle factors. A systematic review by González-Molina et al. emphasized that combination therapies, particularly those including SA, remain the preferred treatment for melasma due to their efficacy and tolerability. [23,24,25] Chang et al. corroborated the effectiveness of 20% AA cream in melasma treatment, suggesting potential benefits when combined with SA peels. [26] Ejaz assessed SA for melasma in two patient groups. Their results showed that the SA had beneficial effect for melasma treatment. [27] The use of safe, risk-free drugs with the least therapeutic SE has always been a priority in interventions and studies.[28] Considering the adverse effects associated with hydroquinone, there has been a growing interest in alternative drugs with similar efficacy to hydroquinone but with fewer SE. In a study by Dahl et al. a solution containing SA was examined and compared to 4% hydroquinone for its effectiveness. The study randomly assigned 54 patients to receive treatment with either SA or 4% hydroquinone. The results demonstrated that the new solution containing SA had significant effects on reducing skin pigmentation.[29] The therapeutic effect of the combination of SA peel and AA cream is better than AA cream alone due to the synergistic effect of SA peel and AA cream or SA peel may increase the penetration of AA cream, corroborating the findings of Farshi et al. and Ahsan et al. which showed that AZ and SA peels are effective in the treatment of melasma, especially the epidermal type, in accordance to our study.[30,31] In this study, melasma patterns among the patients showed that the majority had the centrofacial pattern, followed by malar and mandibular patterns. This observation is consistent with the findings of Navya and Pai, Majid, Aleem, Navya and Pai who identified the Centro facial pattern as the common presentation among patients. This contrasts with a study by Charupalli, which found the malar pattern to be more prevalent, suggesting that the differences may be due to varying assessment methods across different studies. [8,32,33] Predisposing factors in melasma are hormone therapy and exposure to sunlight, in this study 25% of patients have more than one predisposing factor. Studies performed by Türkmen, and Handel et al. showed that pregnancy, a positive family history, and sun exposure are predisposing factors for the disease, which was not the case with family history in the current study.[34,35] The nature of the work and the study objectives could influence the differing outcomes. Since hereditary and genetic factors were not clarified in this study, it is recommended that future research should pay more attention to these factors. The most common side effect of SA use in GA was exfoliation then Erythema, The SE observed in this study are consistent with those reported in the review study by Arif, where exfoliation and erythema were common. [36]

Conclusions

The combination of AZ cream and SA peel has a better therapeutic effect with minimal SE in the treatment of melasma than AZ cream alone. Therefore, considering the superior effect, the combination treatment could potentially replace monotherapy.

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

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