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Original Article

Comparative Efficacy of Topical 20% Azelaic Acid alone versus 4% Hydroquinone 4% as an Adjuvant to Oral Tranexamic Acid in Melasma

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ABSTRACT

Objective: To compare the efficacy of 4% hydroquinone cream as an adjuvant to oral tranexamic acid versus topical 20% azelaic acid alone in the treatment of melasma.

Study Design: Randomized Controlled Trial (ClinicalTrials.gov: NCT05887219).

Place and Duration of Study: Department of Dermatology, Combined Military Hospital, Abbottabad Pakistan, from Nov 2022 to Apr 2023.

Methodology: Fifty females diagnosed with melasma were included. After randomization, they were allocated into two distinct groups. Group-A was administered with a 4% hydroquinone cream in conjunction with oral tranexamic acid at a dosage of 250mg twice daily, while Group-B received topical application of a 20% azelaic acid cream once daily, for a duration of six months. The clinical evaluation was conducted at the onset of therapy, as well as at the second, fourth-, and sixth-month intervals, utilizing the Melasma Area and Severity Index (MASI) score and assessing the patient's response. The assessment of efficacy was conducted in both groups following the completion of therapy, specifically after a duration of six months.

Results: Mean MASI score achieved with 4% hydroquinone cream adjuvant to oral tranexamic acid was significantly superior to topical 20% azelaic acid alone (4.99+0.69 vs 6.80+1.98, p=0.004) with "Excellent" patient response (66.7% vs 33.3%, p=0.03) at the end of therapy after six months of treatment.

Conclusion: The combination of 4% hydroquinone cream with oral tranexamic acid demonstrated superior efficacy compared to topical 20% azelaic acid after six months of therapy.

Keywords: Azelaic Acid, Melasma, Tranexamic Acid.

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INTRODUCTION

Melasma, a dermatological disorder, is frequently characterised by the presence of dark or grayish-brown patches on the facial region.[1] Pregnant women, those undergoing hormone replacement therapy and using oral contraception are at risk.[2,3] According to a study, the effectiveness of intradermal tranexamic acid in treating melasma was found to be 31.0% in terms of excellent response, but the topical azelaic acid group only achieved a 4.5% excellent response rate after six weeks of therapy.[4]

While individuals of all races are susceptible to its impact. Melasma exhibits a higher prevalence among those with darker skin tones, particularly those with light brown skin tones.[5,6] Though the prevalence of melasma in pregnant women ranges from 15 to 50 percent, estimates vary significantly, ranging from 1.5 to 33 percent, exhibiting substantial fluctuations across different populations.[7,8] The augmented production of melanin in the dermis of individuals with melasma can be attributed to the presence of dermal inflammation and the activation of fibroblasts, which are induced by prolonged exposure to ultraviolet (UV) radiation.[9]

Topical therapies are typically considered the initial course of treatment for melasma, with triple combinations (consisting of 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide) being the most efficacious.[10] The purpose of this study was to compare the efficacy of 4% hydroquinone cream as an adjuvant to oral tranexamic acid versus topical 20% azelaic acid alone in the treatment of melasma, as this can provide valuable insights into the most effective treatment strategies for this challenging skin condition. Moreover, this study will contribute to the existing body of knowledge on melasma treatment, helping dermatologists make evidence-based decisions and refine treatment guidelines.

METHODOLOGY

This Randomized Controlled Trial (Reg: ClinicalTrials.gov Identifier: NCT05887219) was

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conducted at the Department of Dermatology, Combined Military Hospital, Abbottabad Pakistan, from Nov 2022 to Apr 2023. Ethical approval (file no: CMHAtd-ETH-48-Derma22) was obtained from the Institutional Ethical Review Committee prior to commencement of study.

Inclusion Criteria: Female patients between the ages of 20 and 45 who were diagnosed cases of melasma were included.

Exclusion Criteria: Pregnant women, those who had been using contraceptive pills within the trial period or within the preceding 12 months, individuals with any chronic medical conditions, those with known allergies to any of the treatment agents employed, and those who had received any topical or systemic treatment for melasma within the last month were excluded.

Sample size was calculated by WHO Sample Size calculator using hypothesis test for two population proportions by taking 31.0% proportion of excellent response achieved with Intradermal Tranexamic acid as compared to 2.0% proportion of excellent response achieved with topical Azelaic acid.[11] Nonprobability consecutive sampling technique was used for data collection.

Written informed consent was obtained from all participants in the trial following a comprehensive description. The diagnosis of melasma was made based on the clinical appearance, as observed by a consultant dermatologist. This included the presence of symmetrically distributed hyperpigmented macules and patches on the face. In order to achieve randomization, the lottery method was employed to assign patients to their respective study groups. Group-A was administered with a 4% hydroquinone cream in conjunction with oral tranexamic acid at a dosage of 250mg twice daily. On the other hand, Group-B received topical application of a 20% azelaic acid cream once daily, specifically at night, for a duration of six months.

The initial Melasma Area and Severity Index (MASI) score was measured at the beginning of the investigation. Patients were instructed to use sunscreen with a Sun Protection Factor (SPF) of 60 or higher while exposed to daylight hours. The participants were monitored every two months at the Dermatology OPD, and the final evaluation took place at six months. During this evaluation, the effectiveness of the treatment was measured using the MASI scale and the patient satisfaction. Consequently, the patient's reaction was evaluated in relation to their MASI score at the conclusion of the 6-month therapy period. The patient's response was categorised as Excellent if their MASI score was below 5, Decent if their MASI score fell between 5 and 7, and Fair if their MASI score ranged from 8 to 10.

Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 23. Mean+SD were computed for quantitative variables, specifically the MASI score, at the baseline, as well as at the 2nd, 4th, and 6th month points. Frequencies and percentages were computed for qualitative factors, specifically the patient's response (categorised as Excellent, Good, and Fair) at the conclusion of the sixth month. Independent samples t-test and Chi-square test were used to compared parameters between groups, with a significance level of $p<0.05$.

RESULTS

Our study found that in patients of melasma, 4% hydroquinone cream as an adjuvant to oral tranexamic acid was more efficacious as compared to topical 20% azelaic acid alone in terms of decline in MASI score (4.99+0.69 versus 6.80+1.98, $p<0.004$), as seen in Table-I and achieving excellent patient's response (66.7% versus 33.3%, $p<0.03$) at the end of therapy after six months in the treatment of melasma (Table-II).

Table-I: Mean MASI Score at Baseline, 2nd Month, 4th Month and 6th Month of Treatment (n=50)

Outcome Variables	Study Groups		*p*-value
	Group-A (n=25)	Group-B (n=25)	
	Mean+SD	Mean+SD	
Baseline MASI Score	28.56+1.03	28.52+0.99	0.897
MASI Score at 2 Months	21.03+1.03	23.62+1.30	<0.001
MASI Score at 4 Months	14.73+0.54	16.45+1.35	<0.001
MASI Score at 6 Months	4.99+0.69	6.80+1.98	<0.004

**MASI: Melasma Area and Severity Index*

Table-II: Patient's Response at the end of Therapy after 6 months of Treatment (n=50)

Outcome Variables	Study Groups		*p*-value
	Group-A (n=25)	Group-B (n=25)	
Patient's Response, n(%)			
Excellent	12(66.7%)	06(33.3%)	0.03
Good	10(55.6%)	08(44.4%)	
Fair	03(21.4%)	11(78.6%)	

DISCUSSION

There exists a variety of therapeutic approaches for the treatment of melasma, which have demonstrated varying degrees of effectiveness and reliability. The most efficacious and well researched

treatments for melasma include hydroquinone (HQ) monotherapy and triple combination cream.[11,12] In previous research, the application of HQ 4% has consistently demonstrated a notable enhancement in melasma dyspigmentation, as indicated by various studies. However, our current study yielded contrasting results, as we observed statistically significant disparities in the mean MASI score after 2 months, 4 months, and at the conclusion of the 6-month therapy period.

In the present study, we compared the efficacy of 4% hydroquinone cream as an adjuvant to oral tranexamic acid versus topical 20% azelaic acid in the treatment of melasma, and we recorded statistically significant differences in terms of mean MASI score at 2 months, 4 months and at the end of therapy after 6 months as p-value of < 0.001 at each treatment session was recorded. Mean MASI score at the end of therapy after 6 months in Group-A and Group-B was 4.99+0.69 vs 6.80+1.98 (p=<0.004).

Different studies have demonstrated that a combination therapy involving intradermal tranexamic-mic acid (100mg/ml) and 4% topical hydroquinone, administered on a monthly basis, exhibited greater efficacy compared to the conventional approach of using 4% hydroquinone alone in the treatment of melasma.[12-14] The aforementioned findings corroborated our own results, as our study similarly yielded statistically significant outcomes through the implementation of combination therapy.

One randomised controlled trial demonstrated that intradermal administration of Tranexamic acid (4mg/ml) was more effective compared to the application of a topical triple combination (hydroquinone 2%, tretinoin 0.025%, fluocinolone acetonide 0.01%) followed by 3% topical tranexamic acid. This treatment was administered monthly for a duration of 6 months.[15] These findings contradict the results of our study, in which we observed a significant superiority of combination therapy. However, we acknowledge that this evidence is insufficient. Considering the growing body of evidence highlighting the interaction between keratinocytes and melanocytes in melanogenesis, specifically through the plasminogen activation system, we strongly advocate for the inclusion of tranexamic acid as an adjuvant in the treatment of melasma. Our study provides evidence that the implementation of this intervention can enhance the efficacy of a well-established treatment and reduce the likelihood of recurrence. Furthermore, this study aimed to assess the effectiveness of 4% hydroquinone cream as a supplementary treatment to oral tranexamic acid, in comparison to topical 20% azelaic acid, which has not been previously evaluated in any existing research. In addition, it should be noted that Azelaic acid has been established as a recognised therapeutic agent for melasma, since it effectively hinders the activity of tyrosinase and thereby reduces the occurrence of hyper-pigmentation. The medication is generally well tolerated and there are no documented instances of drug interactions.[16]

In their study, Karn *et al.,* conducted a comparison between the combined administration of oral tranexamic acid and topical hydroquinone, and the use of topical hydroquinone alone.[17] A notable decrease in MASI score was observed in the tranexamic acid group, which contradicted the findings of the current study. The study revealed statistically significant differences in the mean MASI score at 2 months, 4 months, and the end of the 6-month therapy period. A p-value of less than 0.001 was recorded for each treatment session.

In a randomised controlled trial conducted by Farshi *et al.,* in Iran, the efficacy of 20% Azelaic acid cream was compared to that of 4% hydroquinone in the treatment of melasma among two groups of women.[18] The study findings suggested that the 20% azelaic acid cream exhibited more effectiveness in reducing melasma symptoms following a two-month treatment period, when compared to the 4% hydroquinone cream. Nevertheless, the absence of subsequent data beyond a 2-month treatment period was noted. In contrast, our study encompassed a follow-up duration of 6 months, during which statistically significant disparities in mean MASI scores were observed at 2 months, 4 months, and the conclusion of therapy. Each treatment session yielded a recorded p-value of <0.001. The mean MASI score at the conclusion of therapy after a duration of 6 months was found to be 4.99±0.69 in Group-A, while in Group-B it was 6.80±1.98 (p=<0.004).

In a national study conducted by Sayyida *et al.,* the effectiveness of intradermal tranexamic acid was evaluated in terms of three response categories: poor response, good response, and excellent response.[19] The results indicated that the proportions of participants falling into these categories were 27.6%, 41.4%, and 31% respectively. The study observed that the efficacy of the topical azelaic acid group varied among

participants, with 62.1% experiencing a poor reaction, 20.7% experiencing a fair response, and 17.2% experiencing an exceptional response. The observed difference between the two groups was found to be statistically significant (p=0.001), hence providing support for the conclusions drawn in our study. Specifically, it was seen that 12 patients (66.7%) in Group-A and 6 patients (33.3%) in Group-B had a great response in terms of patient outcomes.

Hence, it is imperative for future research endeavours to closely monitor the dosage of oral tranexamic acid as well as the length of treatment. It is recommended that comprehensive and multicentered investigations be undertaken to compare the effectiveness of 4% hydroquinone cream as a supplementary treatment to oral tranexamic acid, as opposed to topical 20% azelaic acid, for managing melasma. This approach aims to yield reliable findings that may be extrapolated to the broader population within the specified region.

We found that combination therapy worked better than a single drug alone. However, it is important to note that individual patient characteristics, skin types, and tolerances may vary, and further research and clinical considerations are necessary to determine the most appropriate treatment approach for specific patients. Additionally, long-term safety and side effects should be considered in clinical decision-making.

LIMITATIONS OF STUDY

The main limitations of this study were its relatively small sample size of fifty patients, which may limit the generalizability of the findings to a broader population. Larger sample sizes are often needed for more robust statistical analysis and to capture variations in treatment responses among different subgroups of patients. Moreover, this study had a six-month treatment duration. Melasma is a chronic condition, and longer-term follow-up might be necessary to assess the sustainability of treatment effects and the occurrence of any delayed side effects. Furthermore, this study has not captured the full spectrum of side effects associated with the treatments, as it only reported on the decline in MASI score and patient satisfaction.

CONCLUSION

Findings of this study suggest that the combination of 4% hydroquinone cream with oral tranexamic acid is a more efficacious treatment option for melasma compared to topical 20% azelaic acid.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ZN & BM: Data acquisition, data analysis, critical review, approval of the final version to be published.

MAS & MH: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SA & MM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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