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ORIGINAL RESEARCH

Treatment of Melasma with Tranexamic Acid Essence Combined with Iontophoresis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Objective: This randomized, double-blind, placebo-controlled trial aimed to evaluate the efficacy of tranexamic acid essence combined with iontophoresis in treating melasma.

Methods: Thirty participants were recruited and randomly assigned to the experimental (Group A) or control group (Group B). Group A received tranexamic acid essence iontophoresis treatment twice weekly for three months, while Group B received placebo treatment. Melasma Area and Severity Index (MASI) scores and skin luminance (L) values were assessed at baseline and weeks 4, 8, and 12.

Results: No significant differences in baseline characteristics were observed between the groups. The mean MASI score reduction rate was significantly higher in Group A (−0.10±0.12%) compared to Group B (−0.02±0.09%) ($p<0.05$). Skin L values significantly increased in Group A from 61.32±3.53 to 63.32±1.78, while slightly decreasing in Group B ($p=0.037$).

Conclusion: Tranexamic acid essence combined with iontophoresis significantly improved MASI scores and skin luminance compared to placebo, demonstrating its effectiveness in treating melasma. Further research with larger sample sizes and longer follow-up is warranted to validate long-term effects and recurrence rates.

Keywords: tranexamic acid, iontophoresis, melasma, clinical trial

Background

Melasma is a common pigmentary disorder that significantly impacts the aesthetics and quality of life of patients.[1] It typically presents as irregular brown to gray-brown patches in areas exposed to sunlight. The pathogenesis of melasma involves multiple factors, including genetic predisposition, ultraviolet radiation, hormonal changes, and oxidative stress.[2] Despite the availability of various treatment methods, including topical medications, chemical peels, and laser therapy, the management of melasma remains a challenge, often characterized by incomplete responses and high recurrence rates.[3,4]

Tranexamic acid (TXA), a plasmin inhibitor with anti-inflammatory and whitening properties, has emerged as a promising option for the treatment of melasma.[5] Additionally, Iontophoresis, a non-invasive method that enhances the transdermal delivery of drugs through direct current, has been recognized for its application in the TXA treatment of melasma.[6] This technique potentially offers a targeted and efficient drug delivery method, minimizing the side effects associated with oral administration.

Besides improving pigmentation, tranexamic acid essence has also shown therapeutic effects on vascular dilation in melasma. Its anti-inflammatory properties help reduce the erythema and telangiectasia often associated with melasma, further contributing to the overall improvement of skin appearance. However, the effectiveness and safety of TXA Iontophoresis in treating melasma require further investigation to establish its role in the management of melasma. This study aims to evaluate the efficacy of tranexamic acid essence combined with Iontophoresis in the treatment of melasma through a randomized, double-blind, placebo-controlled trial.

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Materials and Methods

Clinical Research Ethics

The Ethics Committee of West China Hospital, Sichuan University, approved the trial protocol. This study was conducted in accordance with the principles of the Declaration of Helsinki (1964) and Good Clinical Practice guidelines. Patients were invited to participate in this study through social media announcements posted by the Department of Dermatology at West China Hospital, Sichuan University. Eligible and invited patients received a detailed information document describing the study's objectives, methods, benefits, and potential risks. A written informed consent form was distributed to all participants, with each recruited patient retaining a signed copy of the consent form. All eligible participants were recruited in September 2023 and underwent 3 months of tranexamic acid essence combined with Iontophoresis treatment until January 2024.

Inclusion and Exclusion Criteria

The study included 30 female participants aged 18–60 years, in generally good health, meeting the diagnostic criteria for melasma. Detailed medical history was collected, including current medications, history of hormonal disorders, and family history of melasma. Participants were excluded if they were pregnant, breastfeeding, had known allergies to the ingredients, or had used topical depigmenting agents within 2 weeks or oral tranexamic acid within 3 months prior to the study.

Inclusion criteria

Female patients aged 18–60 years; in good health condition; meeting the diagnostic criteria for melasma; agreeing to avoid sun exposure during the trial period; willing to comply with the trial requirements and complete the entire 3-month trial, capable of completing follow-up as required.

Exclusion criteria

Pregnant or breastfeeding women; known allergies to ingredients in daily chemical products, soaps, rubber, alcohol, lotion fragrances, or other cosmetics and drugs; skin diseases (eg, psoriasis, eczema, skin cancer), or significant erythema, sunburn, wounds in the test area or nearby; use of depigmenting agents within 2 weeks prior to the study, use of retinoids, tranexamic acid, chemical peels, injections, lasers within 3 months; participation in a similar clinical trial within the last 6 months; women on oral contraceptives; abnormal liver function, renal function or other systemic diseases; overly high expectations for treatment outcomes; patients who have had poor responses to conventional first-line treatments for melasma.

Withdrawal criteria

Participants can withdraw from the trial at any time for any reason; occurrence of serious adverse events or intolerable adverse events; appearance of any exclusion criteria during the study; the researcher can decide whether a participant should withdraw for medical reasons.

Elimination criteria

Serious violation of protocol inclusion, exclusion criteria, and requirements for withdrawal; poor compliance; lack of primary indicators, making it impossible to evaluate efficacy; use of prohibited drugs during the trial making it impossible to evaluate efficacy; patients who were randomized but did not use the drug or have any follow-up data.

Endpoint criteria

The endpoint of this study is "recovery"; if the result of any follow-up after treatment is evaluated as "recovery", the researcher may end the participant's treatment early; participants who end early will be included in the statistical analysis as completed cases.

Methods

Examic acid essence combined with Iontophoresis treatment on melasma. An efficacy target of 80% was set to ensure sufficient power to detect the presence of a treatment effect. Based on the alternative hypothesis, we assume the means of two independent samples are unequal ($\mu1 \neq \mu2$). A power analysis was conducted on this basis. At a significance level of $\alpha = 0.05$ (two-tailed), and expecting a mean difference (δ) of −0.6 with standard deviations ($\sigma1$ and $\sigma2$) of 0.5 for both groups, the calculated sample size required for each group is 13 participants (N1 = N2 = 13), with a total sample size of 26 (N = N1 + N2). Using the two-sample *t*-test (assuming unequal variances), the actual power calculation resulted in 81.93%. This exceeds our target efficacy of 80%, indicating that the sample size is sufficient to detect a difference in treatment effects. Considering potential participant dropout, we estimated a 10% dropout rate. To compensate for potential sample loss, we adjusted the sample size to ensure sufficient experimental power, even with sample attrition. Therefore, the sample size per group increased to 15 (N1' = N2' = 15), with a total adjusted sample size of 30 (N' = N1' + N2'). We expect 2 dropouts per group (D1 = D2 = 2), with a total of 4 anticipated dropouts (D = D1 + D2).[7,8] Through this power analysis and sample size estimation, adjusting for potential sample loss, we determined the required sample size and can be confident that the experimental design has sufficient statistical power to test the effect of tranexamic acid essence combined with Iontophoresis treatment on melasma compared to placebo.

Randomization and Blinding

Between August 2023 and September 2023, through recruitment advertisements posted by the Department of Dermatology at West China Hospital, Sichuan University, in clinics and on social media, we recruited 30 melasma patients who met the diagnostic criteria of the "Chinese Expert Consensus on the Diagnosis and Treatment of Melasma (2021 Edition)" and were eligible for the study. Through a computer-generated random sequence, each participant was assigned a random number. A comprehensive record of all procedures will be documented and preserved. Participants were randomized in a 1:1 ratio to either the experimental group (Group A) or the control group (Group B). Group A received tranexamic acid essence Iontophoresis treatment, while Group B received a placebo treatment without 3% tranexamic acid content. All participants, treatment providers, and outcome assessors were blinded to group assignments.

Intervention Measures

Group A patients received tranexamic acid essence Iontophoresis treatment twice a week for 3 months. Patients cleaned their skin before each treatment. During the treatment, tranexamic acid essence was penetrated into the skin through Iontophoresis, enhancing absorption at the treatment site. Iontophoresis treatments were conducted by professional medical personnel to ensure accuracy and safety. Group B patients received the same treatment procedure but with a placebo (base liquid ingredients) instead of tranexamic acid essence. Patients were advised to moisturize and apply sunscreen during the treatment period and to stop using other topical medications.

Materials: Iontophoresis treatment

Utilized the Derma-CR electromagnetic wave repair mode, typically at intensity level 6 (voltage 90–100 V, power 1.68–2.08 W). The treatment probe gently circled to infuse the essence into facial skin (Comfort Expert, model: Derma, input power: 400VA, produced by Chongqing Peninsula Medical Technology Co., Ltd); Treatment group essence ingredients: Bi-Zhan Mei tranexamic acid essence, containing water, butylene glycol, tranexamic acid (3%), pentylene glycol, glycerin, methyl gluceth-20, dipotassium glycyrrhizate, cyclodextrin, hydroxyacetophenone, isohexadecane, ethoxydiglycol, PCA, isostearic acid ester, acrylamidomethylpropane sulfonic acid ammonium/VP copolymer, sodium polyglutamate, sodium hyaluronate, Centella asiatica extract, disodium EDTA, oleyl alcohol, methylpropanediol, ethylhexylglycerin, hexylene glycol, produced by Sichuan Shengjia Technology Co., Ltd; Control group base liquid ingredients: Bi-Zhan Mei tranexamic acid essence base, containing water, butylene glycol, pentylene glycol, glycerin, methyl gluceth-20, dipotassium glycyrrhizate, cyclodextrin, hydroxyacetophenone, isohexadecane, ethoxydiglycol, PCA,

isostearic acid ester, acrylamidomethylpropane sulfonic acid ammonium/VP copolymer, sodium polyglutamate, sodium hyaluronate, Centella asiatica extract, disodium EDTA, oleyl alcohol, methylpropanediol, ethylhexylglycerin, hexylene glycol, produced by Sichuan Shengjia Technology Co., Ltd; The Melasma Area and Severity Index (MASI) scores were assessed before treatment, and at 4, 8, 12 weeks of treatment based on the subjective assessment of two dermatologists; simultaneously, the L values of cheeks and forehead (L value represents skin lightness, higher numbers indicate brighter skin) were measured using the CK multifunctional non-invasive skin testing device (CK-MPA10, manufactured by CK, Germany) as an objective indicator for this study.

Statistical Methods

The normality of data will be assessed using the Shapiro–Wilk test. For data that follow a normal distribution, paired sample *t*-tests will be used to compare the differences before and after treatment within groups, and independent samples *t*-tests will be used to compare differences between groups. For data not following a normal distribution, the Wilcoxon signed-rank test and Mann–Whitney *U*-test will be used for analysis. All statistical analyses will be conducted using SPSS-22.0 software, with a p-value < 0.05 considered statistically significant.

Results

Demographic Data

This study enrolled a total of 30 participants, with 15 in the experimental group (Group A) and 15 in the control group (Group B) after randomization. During the follow-up period, 4 participants dropped out, leaving 26 participants who completed the follow-up: 13 in Group A and 13 in Group B, aligning with the anticipated sample size for inclusion. The 26 participants included in the data analysis showed no significant differences at baseline in terms of age, total duration of melasma, average time exposed to natural light, PA/PFA values, average sleep duration, SPF values, and current clinical presentation of melasma, indicating comparability between the two groups at the start of the study. Differences in MASI baseline scores and skin L values at week 0 also did not reach statistical significance, further confirming the baseline consistency between the groups (Table 1).

Treatment Effectiveness

MASI scores at different time points: The Intraclass Correlation Coefficient (ICC) results indicated that the consistency of evaluations between Group A and B from week 0 to week 12 was moderately low, which might reflect subjective differences between evaluators or inconsistencies in scoring criteria (Table 2a). An analysis of the average MASI scores from evaluators A and B showed that the average reduction rate in MASI scores for Group A was (−0.10±0.12%), while for Group B, it was (−0.02±0.09%), with a statistically significant difference ($P<0.05$). This further confirmed the effectiveness of the treatment group in managing melasma (Table 2b).

Comparative results of skin L values measured by the CK multifunctional non-invasive skin testing device showed a more pronounced increase in L values in Group A during the treatment, rising from (61.32±3.53) to (63.32±1.78), while the L values in Group B slightly decreased from (63.50±2.73) to (62.44±1.84). This change reflected an improvement in skin brightness and a reduction in pigmentation in Group A. Repeated measures ANOVA revealed a statistically significant interaction between time and treatment group ($P=0.037$), indicating that tranexamic acid serum combined with Iontophoresis treatment significantly improved skin brightness (Table 2b and c).

The results of this study indicate that tranexamic acid essence Iontophoresis treatment can significantly improve MASI scores in patients with melasma, demonstrating its effectiveness compared to the control group. Despite some issues with evaluation consistency, the overall findings support the potential effectiveness of tranexamic acid essence Iontophoresis as a treatment for melasma. Future research needs to further explore its long-term effects and mechanisms of action and optimize evaluation methods to reduce the impact of subjective differences; all 26 patients experienced no exacerbation of symptoms or new discomfort during the treatment period (Figure 1a–d).

Table 1 Subject Demographics and Baseline Data

Group	Age (Year)	Melasma Spot Total Duration	Sunshine Exposure Time (h / Day)			PA/PFA			
			X≤1	1<X≤3	3<X≤5	++	+++	++++	
A	49.15±7.15	−40.15±6.58	7(53.85%)	5(38.46%)	1(7.69%)	5(38.46%)	7(53.85%)	1(7.69%)	
B	44.77±2.19	−34.85±7.48	6(46.15%)	6(46.15%)	1(7.70%)	2(15.38%)	10(76.92)	1(7.70%)	
t/χ^2/Z	1.483	−1.921		−0.344			−1.012		
P	0.151	0.067		0.731			0.270		
Group	**Mean sleep time (h / day)**		**SPF**			**Current clinical presentation of melasma**		**MASI-0W**	**L-0W**
	5<X≤6	**6<X≤8**	**15<X≤30**	**30<X≤50**	**X>50**	**Light brown**	**Puce**		
A	5(38.46%)	8(61.54%)	4(30.77%)	8(61.54%)	1(7.69%)	11(84.62%)	2(15.38%)	4.95±1.83	61.29±3.54
B	4(30.77%)	9(69.23%)	4(30.77%)	8(61.54%)	1(7.69%)	10(76.92%)	3(23.08%)	4.58±1.25	63.75±2.47
t/χ^2/Z	-			0		0		0.600	−2.055
P	>0.999			>0.999		>0.999		0.554	0.051

Notes: PA stands for Protection Grade of UVA and is indicated by "+" signs to show a product's ability to protect against long-wave ultraviolet rays. The PA rating is determined based on the Protection Factor of UVA (PFA value) of sunscreen cosmetics, reflecting the protective effect against tanning from long-wave ultraviolet rays. It is a protective indicator used to evaluate the ability of sunscreen cosmetics to prevent skin tanning. PA++ means very effective, potentially delaying by 4–8 times; PA+++ means highly effective, potentially delaying by 8–15 times; PA++++ can delay tanning by 16 times or more.

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Table 2 Experimental Result

a. Comparative consistency evaluation of MASI scores in both groups (ICC)					
Group		**0w**		**12w**	
		Individual measurements	**Mean measurement**	**Individual measurements**	**Mean measurement**
A		0.623	0.768	0.453	0.624
B		0.191	0.321	0.151	0.262
A+B		0.447	0.618	0.325	0.490
b. Analysis of mean MASI scores in two groups					
Group	**N**	**Not at the same time point comparison**		**D-value**	**Rate of decline (%)**
		0w	**12w**		
A	13	4.95±1.83	4.44±1.66	−0.50±0.52	−0.10±0.12
B	13	4.58±1.25	4.47±1.20	−0.10±0.44	−0.02±0.09
t		0.600	−0.054	−2.127	−1.903
P		0.554	0.957	0.044	0.069
c. Comparison of different point L values between the two groups					
Group	**N**	**Not at the same time point comparison**			
		0w	**4w**	**8w**	**12w**
A	13	61.32±3.53	61.98±3.32	62.19±2.34	63.32±1.78
B	13	63.50±2.73	63.09±2.53	63.13±1.65	62.44±1.84

Discussion

This randomized, double-blind, placebo-controlled trial demonstrated the efficacy of tranexamic acid essence combined with iontophoresis in treating melasma. The significant improvements in MASI scores and skin luminance in the treatment group, compared to the placebo group, provide evidence supporting this combination therapy as a promising treatment option for melasma.

The results align with previous studies that have reported the effectiveness of tranexamic acid in melasma treatment, attributed to its ability to inhibit plasminogen activation and reduce arachidonic acid release, thus decreasing melanocyte activity. The iontophoresis technique likely enhances the dermal delivery of tranexamic acid, allowing for more targeted and efficient treatment. Compared to conventional topical treatments, the combination of tranexamic acid essence and iontophoresis offers several advantages. It reduces the risk of systemic side effects associated with oral tranexamic acid while providing more controlled and localized delivery than manual topical application. The use of essence formulation also allows for easier application and better patient compliance compared to cream or lotion formulations.[9]

However, this study has some limitations. The relatively small sample size and short follow-up period limit the generalizability of the findings and the assessment of long-term efficacy and recurrence rates. The subjective nature of MASI scoring, as reflected by the moderate to low inter-rater consistency, highlights the need for more objective and standardized evaluation methods in future studies. Despite these limitations, the present study provides valuable insights into the potential of tranexamic acid essence combined with iontophoresis as a safe and effective treatment for melasma. Future research should involve larger sample sizes, longer follow-up periods, and more diverse participant demographics to further validate these findings and explore optimal treatment protocols.

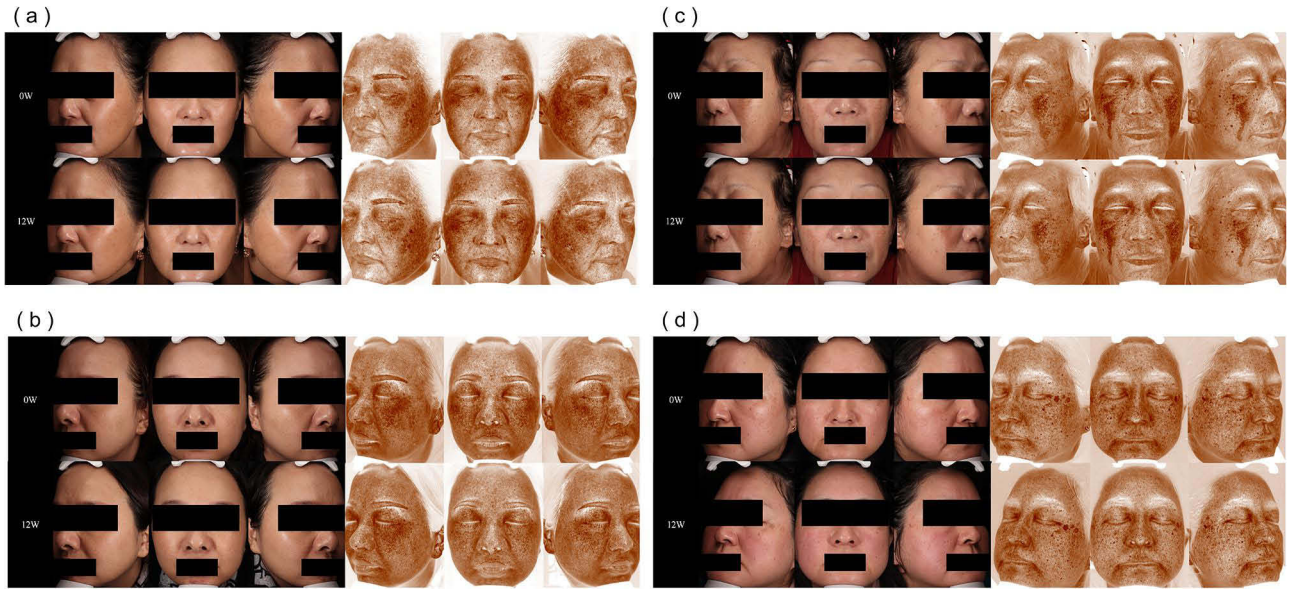

Figure 1 Clinical trial of Tranexamic Acid Essence in combination with Ion Introduction for the treatment of Melasma: Presentation of cases from the experimental group. (**a**) A 38-year-old female patient with Fitzpatrick skin type III and moderate melasma on the forehead and cheeks at baseline (0w), showing significant improvement after 12 weeks (12w) of treatment. (**b**) A 35-year-old female patient with Fitzpatrick skin type III and moderate melasma on the cheeks at baseline (0w), demonstrating substantial clearance of pigmentation after 12 weeks (12w) of treatment. (**c**) A 42-year-old female patient with Fitzpatrick skin type III and moderate melasma on the forehead and cheeks at baseline (0w), exhibiting marked reduction in the intensity and size of hyperpigmented patches after 12 weeks (12w) of treatment. (**d**) A 45-year-old female patient with Fitzpatrick skin type III and mild to moderate melasma on the cheeks at baseline (0w), showing notable improvement in skin uniformity and brightness after 12 weeks (12w) of treatment.

Conclusion

In conclusion, this randomized, double-blind, placebo-controlled trial demonstrates that tranexamic acid essence combined with iontophoresis is effective in treating melasma, as evidenced by significant improvements in MASI scores and skin luminance. This combination therapy offers a promising treatment modality for melasma, with the potential for better efficacy and patient compliance compared to conventional treatments. However, the limitations of this study, including the small sample size, short follow-up period, and inconsistencies in MASI scoring, warrant further research to validate these findings and optimize treatment protocols. Long-term studies with larger sample sizes and objective evaluation methods are needed to assess the durability of the treatment effects and recurrence rates.

For future clinical applications, it is recommended to develop standardized treatment guidelines, considering factors such as the optimal concentration of tranexamic acid essence, frequency and duration of iontophoresis sessions, and maintenance therapy for long-term management. Patient education on proper sun protection and avoidance of triggering factors should also be emphasized to minimize the risk of melasma recurrence. In summary, tranexamic acid essence combined with iontophoresis shows promise as a safe and effective treatment option for melasma. Further research and clinical experience will help refine this combination therapy and optimize its use in the management of this common and challenging skin condition.

Data Sharing Statement

De-identified participant data from this study (including text, tables, figures) will be made available upon request immediately following publication. Scientific researchers may submit reasonable requests for data usage to the corresponding author. Applicants will be required to sign a data access agreement. In addition to the raw data, the study protocol, statistical analysis plan, and informed consent form will also be available. The data will be accessible for 5 years after publication.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that there is no conflicts of interest in this work.

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