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Research Article

Effects of Masks Containing 0.5% Tranexamic Acid-Loaded Ethosomes on Melasma in the Asian Skin: A Randomized Controlled Clinical Trial

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Background. Tranexamic acid (TA) has emerged as a promising treatment for melasma without serious adverse effects. Ethosomes have been reported as the carriers for transdermal drug delivery systems to increase the amount of drug permeation through the skin. However, few studies of the local usage of TA-loaded ethosomes exist. *Objectives*. To evaluate the efficacy of a mask containing 0.5% TA-loaded ethosomes in the treatment of melasma in the Asian skin. *Methods*. In a double-blind, placebo-controlled, randomized, prospective study, 88 Asian participants with melasma were randomized 1 : 1 to two groups as follows: the TA or control. The TA group was treated with moisturizing masks with 0.5% TA-loaded ethosomes, and the control was treated with moisturizing masks only. Masks were applied once daily for the first two weeks and once every other day for the third and fourth weeks. The primary outcome was measured by the modified melasma area and severity index (mMASI) and a visual analog scale (VAS) for vessels. The secondary outcomes were VAS for skin texture and satisfaction. *Results*. The reduction of VAS vessel scores at the end of treatment in the TA group was significantly greater than that in the control group ($P < 0.001$). The mMASI scores and skin texture scores decreased over time in both groups, but no significant differences were found between the two groups ($P > 0.05$). The score of participant satisfaction in the TA group was significantly higher than that in the control group ($P < 0.01$). *Conclusions*. Masks containing TA-loaded ethosomes appear to be an effective treatment for Asian melasma in terms of angiogenesis and skin texture. It improves the pigmentation to some extent but has no significance. This trial is registered with ChiCTR1900024257.

1. Introduction

Melasma is a commonly acquired pigmentary disorder characterized by tan-brown macules that develops in the faces of Asian and Hispanic women. Although the pathogenesis of melasma remains unclear, certain risk factors are known, such as racial and genetic susceptibility, pregnancy, sun exposure, hormonal therapy (estrogen and progesterone), cosmetics, and some drugs. Melasma is asymptomatic, but it is a disfiguring skin disease that has a negative impact on the quality of life and self-esteem of affected individuals. Current treatments for melasma include oral and topical use of vitamin C, hydroquinone ointment, and laser treatment [1]. Tranexamic acid is a novel drug for treating melasma that is administered both topically and orally. TA is a plasmin inhibitor and an antifibrinolytic

agent used to prevent and treat hemorrhage. Although its mechanism of action has not been completely understood, TA seems to inhibit the synthesis of melanin by interfering with the interaction of melanocytes and keratinocytes. Moreover, TA can reverse the abnormal dermal changes induced by melasma, such as increased vasculature. The oral route, while convenient and pain-free, is often accompanied by adverse effects including abdominal bloating, headache, tinnitus, and menstrual irregularities. Moreover, some patients will refuse systemic medication due to side effects [2]. The topical use of TA has been widely used in clinics because of its high safety and acceptance, but its effect is unsatisfactory [3]. The dosage form of TA is limited to emulsion and cream, and there are few clinical studies on masks. In recent years, ethosomes have been found to allow hydrophilic drugs such as TA to cross the stratum corneum barrier and ultimately improve the bioavailability of the drug. Therefore, ethosome-based formulations have been widely used in a variety of skin pathologies (acne, psoriasis, atopic dermatitis, skin cancer, and skin infections) [4]. This randomized clinical trial aimed to evaluate the efficacy of topical use of a mask containing ethosomes with low concentrations of TA in the treatment of Asian skin melasma and to explore potential therapies for melasma.

2. Methods

The study was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (SH9H-2019-T67-1), and the Chinese Clinical Trial Registry (ChiCTR1900024257). All participants completed a written informed consent form before participation.

2.1. Study Design and Participants. A double-blind, single-center randomized clinical trial was conducted. From July 2019 to April 2020, a total of 88 participants were randomized 1 : 1 to 2 groups with 44 participants in each group: TA masks or control (moisturizing mask). No changes were made to the trial after its commencement. Participants older than 18 years who were Asians with melasma were eligible. Exclusion criteria included pregnancy or lactation, hormonal therapy or contraception, a history of coexisting endocrinopathies, allergy to TA, allergy to sunscreen ingredients, previous topical treatment for melasma within 2 weeks, systemic TA within 3 months, or oral retinoic acid derivatives within 1 year prior to the study.

2.2. Interventions. Participants in the TA group were treated with masks containing 0.5% TA-loaded ethosomes and moisturizers (moisturizers included hyaluronic acid, glycerol, and glycol propylene) for 20 minutes (Jiangsu LANCH Science & Technology Co., Ltd., Patent number: CN202210768790.2). Participants in the control group were treated with masks only containing moisturizers at the same time. The masks were applied before going to bed once a day for the first two weeks and once every two days for the third and fourth weeks. All participants must be instructed to avoid sun exposure and apply a standard broad-spectrum sunscreen. Participants returned for follow-up visits at weeks 4, 8, and 16.

2.3. Randomization and Blinding. Before the start of the trial, 88 participants were divided into 22 random groups of 4 participants per group according to the order of enrollment. The letters A-V were numbered. The order of each random group was numbered 1–4 (e.g., A1/B2/C3/D4). In each group, two participants were assigned to the experimental group and two to the control group so that the grouping results of each group would have six possible results and correspond to Roman numerals I–VI. A dice roll was used to determine the grouping of each group, which generated a random table of 88 people. Participants simply entered the prespecified randomization group according to the order in which they were recruited.

The outer packaging and inner texture of the masks used in the two groups were the same. Only the study leader and the specialist who distributes the masks knew the group situation. All the participants and evaluators did not know the grouping situation.

2.4. Outcomes. The primary outcome of this study was a reduction in melasma. The severity of melasma was evaluated by 2 approaches: the modified melasma area and severity index (mMASI) and a visual analog scale (VAS) for vessels. The mMASI is a reliable measure of melasma severity [5]. Areas of involvement and darkness are sufficient for accurate measurement of the severity of melasma, and homogeneity can be eliminated. The vessel was assessed using a VAS that ranged from 1 (no vessel) to 12 (extreme vessel) on a 12 cm line. All scores (mean ± SD) were evaluated by a total of 9 observers, including 5 independent dermatologists and 4 plastic surgeons, and averaged.

The secondary outcomes for this study were skin texture and patient satisfaction. Skin texture was measured after the procedure with a VAS. The VAS for skin texture was a 12 cm line ranging from very smooth, tender, and lustrous to very rough, loose, and dull. At week 16, patient satisfaction was assessed on a Likert scale of 1 to 5, ranging from very dissatisfied to very satisfied, and a score greater than 3 was considered satisfactory.

2.5. Sample Size and Statistical Analysis. The sample size was estimated according to the effectiveness test formula based on the ratio of the two samples. According to the previous data, the estimated effective rate in the treatment group and the control group was 55% and 25%, respectively, and the test efficiency was 0.8, alpha = 0.05 (bilateral). There would be a significant difference in 38 cases in each group. Considering the possibility of dropout, the sample size was expanded by 15% and the final sample size was determined to be 88 participants, with 44 participants in the treatment group and 44 participants in the control group.

Data are represented as the mean ± SD. SPSS 25.0 (IBM, US) was used for analysis. Scores on the mMASI VAS for skin texture and vessels were analyzed using one-way ANOVA and an independent-sample t test to assess the differences between the two groups. The patient satisfaction between the two groups was analyzed by the chi-square test. $P < 0.05$ was considered statistically significant.

3. Results

A total of 88 participants were randomized and included in the study, and 11 participants dropped out (5 from the TA group and 6 from the control group). No reason was given, and all were excluded from the final analysis. Thus, 77 participants completed the study and were analyzed for primary and secondary outcome measures (Figure 1). Demographics of participants were listed (Table 1). There were no reported adverse events during the 16-week follow-up.

The mMASI scores of both groups decreased gradually at four different time points, namely, baseline, week 4, week 8, and week 16. The scores of the TA group dropped from 4.84 ± 2.08 at the baseline to 4.69 ± 2.06 at week 4, 4.58 ± 1.86 at week 8, and 4.47 ± 1.97 at week 16 ($P = 0.87$). The scores of the control group dropped from 4.93 ± 2.25 at the baseline to 4.84 ± 1.94 at week 4, 4.82 ± 1.95 at week 8, and 4.80 ± 2.00 at week 16 ($P = 0.99$). The results of the two groups were not statistically different ($P = 0.47$) (Figures 2(a) and 3(a)).

The vessels were scored by VAS. The scores of the control group were only slightly decreased during the treatment period (6.47 ± 1.46 at the baseline and 6.43 ± 1.23 at week 4, $P = 0.82$), and the scores were increased after the treatment (6.86 ± 1.32 at week 8 and 7.23 ± 1.11 at week 16). In the TA group, there was a statistically significant reduction of the VAS vessel scores after treatment (4 weeks, 6.56 ± 1.43), 8 weeks (6.39 ± 1.39), and 16 weeks (6.31 ± 1.38) compared with the baseline values (7.25 ± 1.43, $P < 0.001$ for all). The VAS vessel scores in the TA group were significantly higher than those of the control group at the baseline ($P = 0.02$) and significantly lower than those of the control group at week 16 ($P = 0.002$) (Figures 2(b) and 3(b)).

The VAS skin texture scores decreased significantly after treatment in the TA group (6.80 ± 1.20 at the baseline and 6.24 ± 1.29 at week 4) ($P = 0.04$) and the control group (6.48 ± 1.19 at the baseline and 5.69 ± 1.16 at week 4) ($P = 0.008$). The results of the two groups were not statistically different (Figures 2(c) and 3(c)).

The overall satisfaction scores of masks in the TA group and the control group were 3.15 ± 0.96 and 2.53 ± 0.76, respectively ($P = 0.003$). The satisfaction rate (≥3) was 76.92% in the TA group and 52.63% in the control group, respectively ($\chi^2 = 4.99$ and $P < 0.05$) (Figure 2(d)).

4. Discussion

Although the pathogenesis of melasma remains unknown, it is generally known that melasma is an acquired chronic inflammatory skin disease with symmetrical hyperpigmentation. The volume and melanosome number of melanocytes increased in the epidermis. Melano phagocytes, inflammatory cell infiltration, and vascular proliferation were observed in the dermis [6]. A significant increase of both the number and size of dermal blood vessels in the lesional skin is one of the major findings in melasma. The increased vascularization is thought to increase local endothelial and inflammatory cells, which then promotes melanogenesis [7]. It has been reported that plasmin plays an important role in angiogenesis as it converts the extracellular matrix-bound vascular endothelial growth factor (VEGF) into freely diffusible forms [8]. UV irradiation induces the synthesis of plasminogen activators by keratinocytes, which results in the increased conversion of plasminogen to plasmin and then promotes angiogenesis and melanogenesis [9].

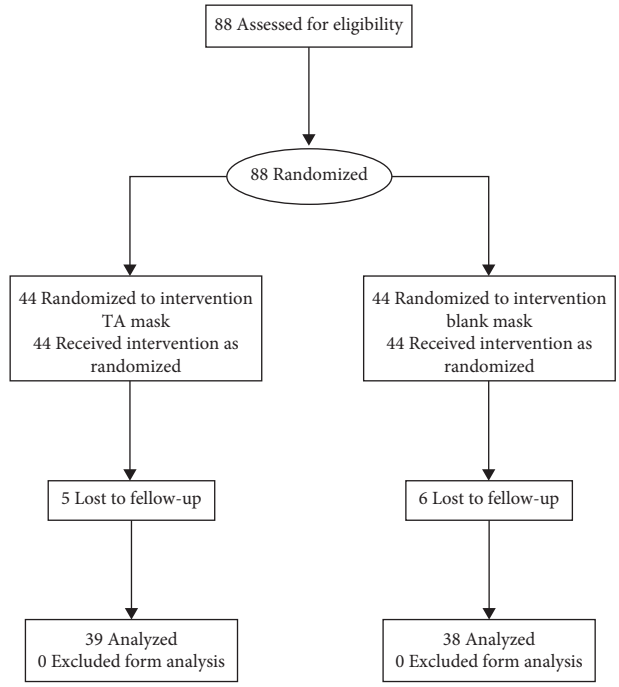


Figure 1: CONSORT diagram of participant recruitment and flow. TA indicates tranexamic acid.

TA, a plasmin inhibitor, can suppress UV-induced epidermal melanocyte tyrosinase activity by blocking the interaction of melanocytes and keratinocytes through the inhibition of the plasminogen/plasmin system [10]. TA also inhibits angiogenesis induced by the basic fibroblast growth factor (bFGF) and vascular endothelial growth factor [11]. Histopathological studies have shown that TA reversed melasma-related dermal changes, such as vascularization and increased mast cell numbers [12]. TA has been a useful therapeutic agent for the clinical treatment of abnormal bleeding and the improvement of melasma since 1979 [13]. As an initial therapy for melasma, TA can be applied orally, topically, or by local microinjection. Since it takes more than 3 months to observe efficacy and recurrence may occur after withdrawal, patients need long-term use of TA for melasma. Although the dose of oral TA for melasma is low, there are still risks such as deep vein thrombosis, massive pulmonary embolism, and acute myocardial infarction. Therefore, it is necessary to find a topical therapy for TA with remarkable

Table 1: Participant characteristics[a].

Characteristics	Total ($N = 77$)	Control group ($N = 38$)	TA group ($N = 39$)
Age, mean (SD), y	48.0 (6.0)	48.9 (5.8)	47.1 (6.1)
Sex, no. (%)			
Male	2 (2.6)	0 (0)	2 (5.1)
Female	75 (97.4)	38 (100)	37 (94.9)

[a]Data are presented as the number (percentage) of patients unless indicated.

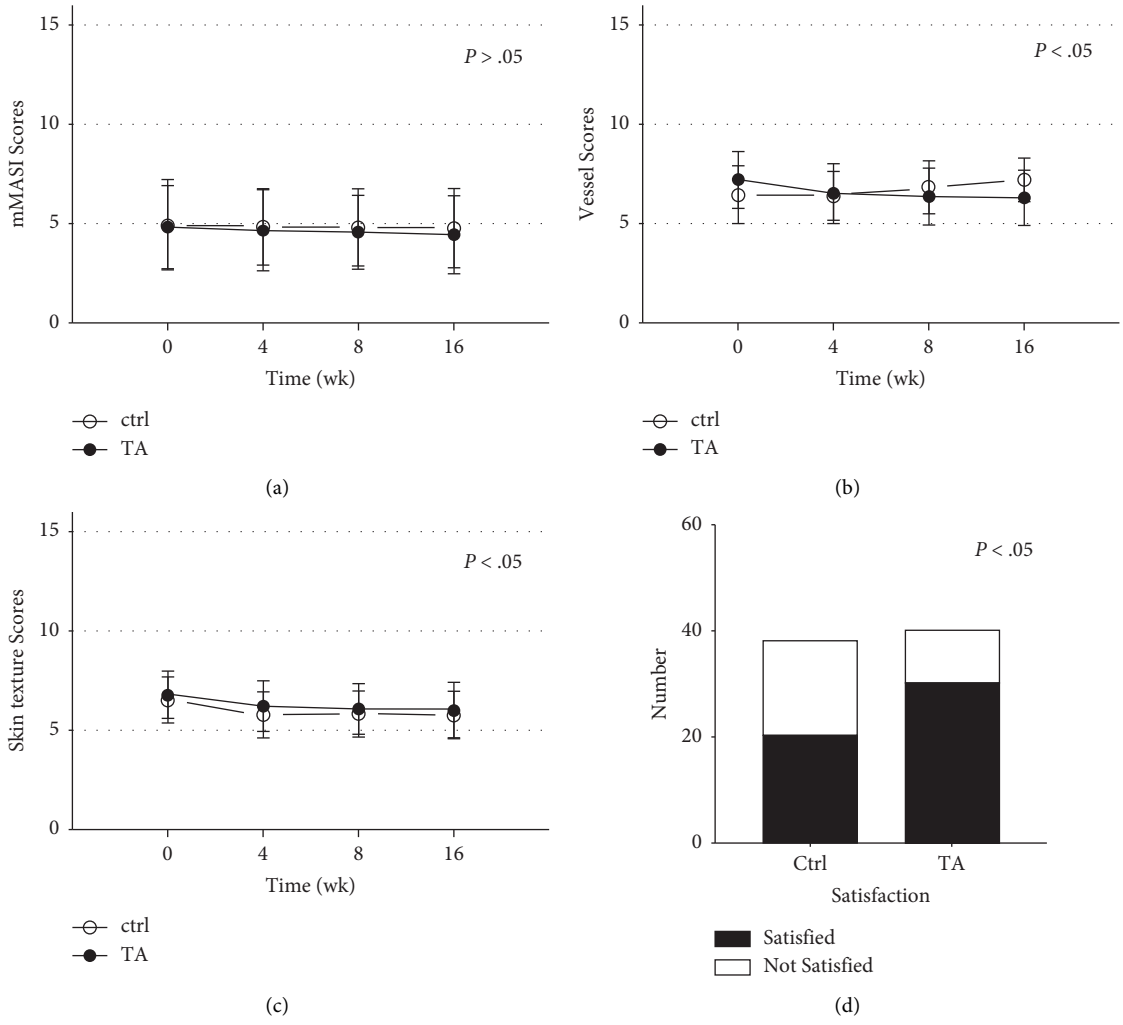
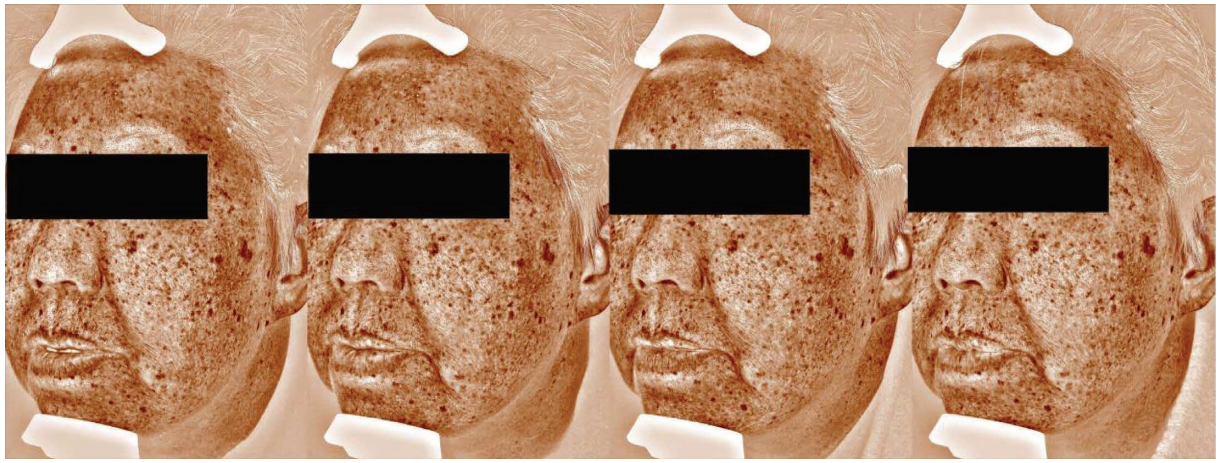


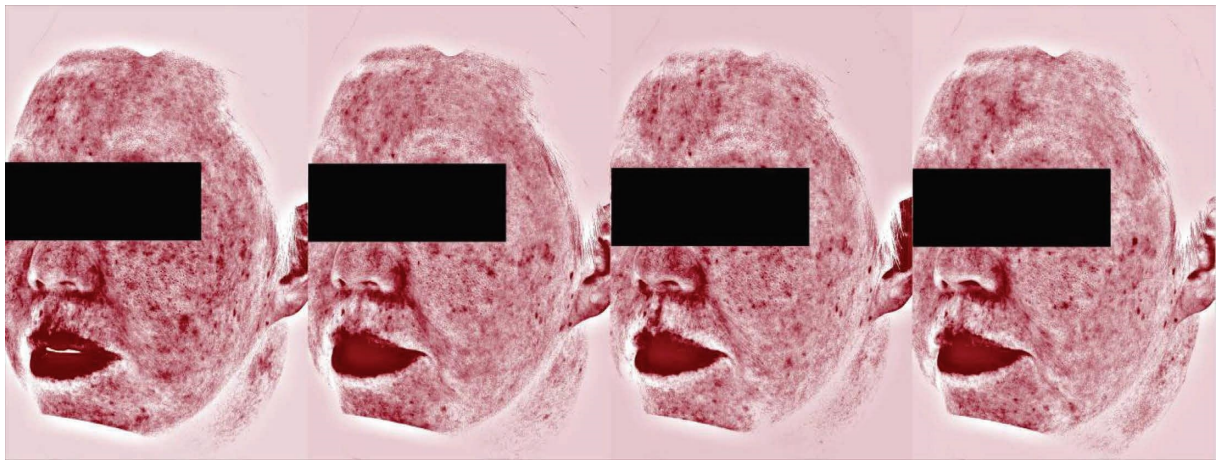
Figure 2: Efficacy and outcomes. (a) Improvement was seen in both groups at weeks 4, 8, and 16, but there were no significant differences either within or between the groups; TA, tranexamic acid. (b) Vessel scores were gradually decreased over time compared with the baseline in the TA group but rebounded at week 8 in the control group; TA, tranexamic acid. (c) Improvement was seen in both groups at weeks 4, 8, and 16, but no significant intergroup difference was observed. (d) The satisfaction rate (≥3) was 76.92% in the TA group and 52.63% in the control group, respectively; TA, tranexamic acid.

curative effects. Topical TA has been applied alone and in conjunction with intradermal injection, microneedling, fractionated CO_2 laser, and other ways to increase bioavailability. Topical treatment of TA is limited to emulsions and creams and is less effective than oral TA, which may be related to TA's difficulty in penetrating the stratum corneum as a hydrophilic substance [14].

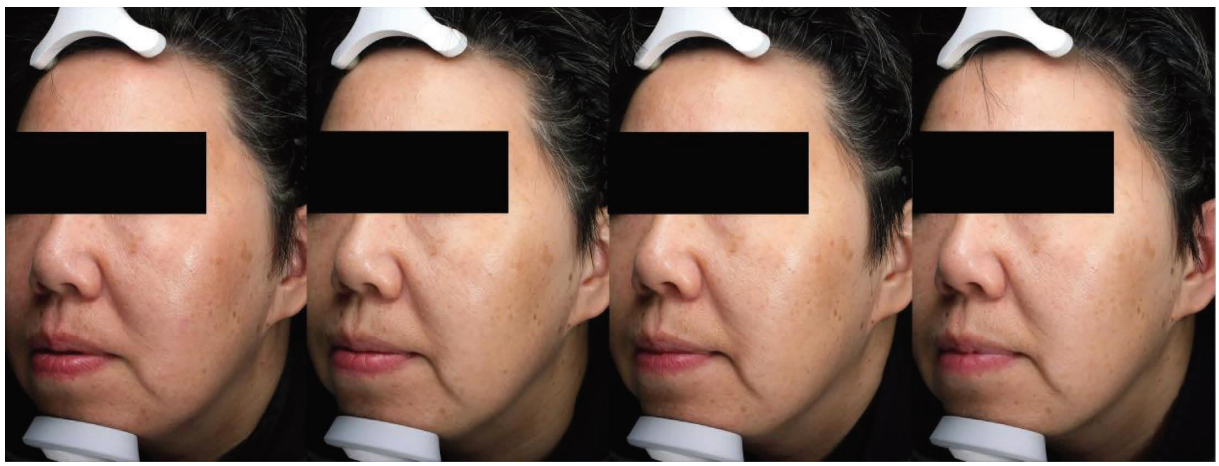
To solve the problem of low transdermal absorption caused by TA hydrophilicity, the test group used ethosomes to encapsulate TA. Ethosomes, which are modified liposomes, containing a relatively high concentration of ethanol, have been specifically designed to overcome the stratum corneum barrier in the intact skin. Kandil et al. found that ethosomes could improve the efficacy of topical ascorbic acid derivatives in the treatment of melasma [15]. Our results showed that masks containing TA significantly reduced vascularization in melasma lesions, compared with control subjects. Improved vascularization could further reduce



(a)



(b)



(c)

Figure 3: Clinical response of a representative female participant in the TA group. Pigmentation (a), angiogenesis (b), and skin texture (c) improved gradually compared with the baseline in group TA; TA, tranexamic acid.

VEGF stimulation of melanocytes and decrease melanin synthesis and secretion. At the end of treatment and 3 months later, the number of vessels in the TA group showed a continuous reduction, while an increase was observed in the control group 1 month later. In the two follow-up visits at week 8 and week 16, the VAS vessel scores in the control group increased, but the mMASI scores did not, suggesting that the increase in melanin synthesis and secretion may be lagging behind the angiogenesis [16].

It may be the effect of a moisturizer that improves skin texture in both groups, and short-term topical TA mask treatment can reduce facial mMASI scores. Moisturizers can keep the transepidermal water from leaking, maintain a stable internal environment for the epidermis and dermis, and relieve the damage to the skin barrier caused by ultraviolet exposure, dry weather, and unreasonable skin care [17]. Thus, the release of cytokines that promote melanogenesis and angiogenesis from keratinocytes and fibroblasts will decrease, the chronic inflammation of the skin will be corrected gradually, and the synthesis of melanin will be downregulated [18, 19]. In addition, a moist environment and a suitable pH value can accelerate the metabolism of epidermal cells and reduce the deposition of melanin in the epidermis. These results are consistent with our clinical experience that many participants show improvement in facial melasma by using antiultraviolet and moisturizing.

5. Limitations

Due to the high concentration of volatile ethanol in ethosomes, there may be a problem with ethosome-induced skin irritation. We shortened the duration of treatment to 1 month to avoid potential adverse effects. The treatment and follow-up time of this trial were relatively short, so it was only observed that the reduction of vascular scores in the TA group was more significant than that of the control group, but there was no marked difference in the mMASI scores between the two groups. Although a definite improvement was observed in the 0.5% TA group, the effect of different concentrations of TA was not evaluated in this study. Further trials may be needed to compare the efficacy of different concentrations and treatment times of TA to establish the safest and the most efficient treatment option. This trail experienced a process from spring to summer. Although the participants had adopted antiultraviolet measures strictly, the inevitable increase in ultraviolet exposure might have had an impact on the results.

6. Conclusions

Ethosomes with a 0.5% TA load on the mask appear to be an effective treatment for angiogenesis and skin texture in Asian melasma. It improves the pigmentation to a certain extent. This treatment has good compliance, no obvious side effects, and can be an option for the clinical treatment of melasma.

Data Availability

The data of this study are available from the corresponding author upon reasonable request.

Additional Points

Clinical trials number. This study is listed in the Chinese Clinical Trial Registry (https://chictr.org.cn) with (ChiCTR1900024257).

Ethical Approval

The study was approved by the independent Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (SH9H-2019-T67-1), and the study adhered to the Declaration of Helsinki principles.

Consent

Participants provided written informed consent to participation and publication of results.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

The tasks of study concept and design were conducted by Min Yao and Daorun Hu. The tasks of analysis and interpretation of data were performed by Qige Guo and Min Yan. Drafting of the manuscript was conducted by Qige Guo and Qing Pei. Critical revision of the manuscript for important intellectual content was carried out by Jiying Dong, Min Yao, and Shen Wang. Statistical analysis was performed by Qige Guo, Qing Pei, and Shen Wang. Study supervision was conducted by Min Yao, Jiying Dong, and Daorun Hu. Qige Guo and Daorun Hu contributed equally to this work and should be considered the co-first authors.

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