

Original Research Article

Effectiveness and safety of combined use of tranexamic acid and Xiyu dressing in chloasma therapy, and its effect on recurrence in patients

Xiaojian Chen, Lei Wu*, Jian Wu, Meihong Cai

Department of Dermatology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, China

*For correspondence: **Email:** wulei_szslyy@163.com

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Abstract

Purpose: To determine the effectiveness and safety of combined use of tranexamic acid (TA) and Xiyu dressing in chloasma patients.

Methods: Ninety female patients with moderate-to-severe melasma who were admitted to the Affiliated Suzhou Hospital of Nanjing Medical University (February 2020 - February 2021), were equally divided into 3 groups: A, B and C. Patients in group A were orally treated with TA, those in group B received oral TA and Xiyu dressing, while those in group C received Xiyu dressing only. Treatment effectiveness, Melasma Area and Severity Index (MASI) score, whole blood viscosity (WBV) and disease recurrence rate were assessed.

Results: General patient profile was comparable amongst the 3 groups ($p > 0.05$). Objective treatment effectiveness was higher in group B than in group A, and higher in group A than in group C ($p < 0.05$). At weeks 8, 16 and 20, the order of Melasma Area and Severity Index (MASI) scores was: $C > A > B$, with lower scores in group B than in group A, and lower in group A than in group C ($p < 0.05$). The whole blood viscosity (WBV) was highest in group B, while group C had the lowest WBV ($p < 0.05$). No notable differences occurred in disease recurrence rate amongst the 3 groups. Onset time of cure was shorter in group A than in group C, but was longer in group A than in group B ($p < 0.05$).

Conclusion: Treatment with TA and Xiyu dressing is more effective when combined than when using either of them alone; furthermore, disease recurrence rate is lowest with the combination therapy. Therefore, the combined therapy has potentials for use in the management of chloasma, but further clinical trials are required prior to application in clinical practice.

Keywords: Tranexamic acid, Xiyu chloasma dressing, Recurrence rate, Safety

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INTRODUCTION

Melasma is a chronic and treatment-resistant melanin pigmentation dermatosis with high degree of recurrence, and it severely affects the

appearance, quality of life and psychological status of patients [1-4]. At present, the pathogenesis of melasma is complex, and a single treatment often produces poor effectiveness or severe adverse effect.

Therefore, the use of combination regimens for melasma has become a consensus strategy in clinical practice.

Recently, better outcomes were obtained in China and elsewhere in treating melasma with orally taking tranexamic acid (TA) in combination with other methods [5-8]. *Xiyu* dressing has been applied in the treatment of melasma for more than 1 year, and reports from outpatient follow-ups indicate that it effectively alleviated melasma, with no obvious stimulus response [9,10]. There are limited studies on the effects of clinical application of *Xiyu* dressing. Therefore, this study was aimed at investigating the efficacy of combined use of TA and *Xiyu* on chloasma, with respect to alleviation of symptoms, recurrence rate and incidence of adverse effects.

METHODS

Subjects

Ninety female patients with moderate-to-severe melasma who were admitted to the Affiliated Suzhou Hospital of Nanjing Medical University for examination and treatment from February 2020 - February 2021 were selected. All cases were diagnosed by attending doctors or doctors from Department of Dermatology, Suzhou Municipal Hospital, The Affiliated Hospital of Nanjing Medical University. Before treatment, the facial features of the patients were photographed at frontal and lateral positions using a Canon 750D camera, and the images were saved and analyzed. All patients knew the purpose, associated risks and benefits, as well as potential complications, and they submitted signed informed consent. The study was approved by the ethics committee of Suzhou Municipal Hospital, The Affiliated Hospital of Nanjing Medical University (approval no. IEC-C-006-A19-V1.0), and it met the principles of the Declaration of Helsinki as revised in 2013 [11].

Grouping of patients

The patients were randomly and equally assigned to 3 groups: A, B and C. Patients in group A were orally treated with TA, those in group B received oral TA and *Xiyu* dressing and those in group C received *Xiyu* dressing only.

Inclusion criteria

The subjects included in this study were patients with MASI scores ≥ 10 points, and patients who met the disease diagnosis standards of Pigment Disease Group, Combination of Traditional and Western Medicine Dermatology [12]: light brown

and dark brown symmetrical patches with clear boundaries on the face, with no inflammation and scaling, and no obvious subjective symptoms. Moreover, patients who did not have hyperpigmentation caused by other diseases were included.

Exclusion criteria

Patients in the following categories were excluded: those having coagulation dysfunction or medical history of thrombosis, those who were allergic to TA, patients with severe endocrine diseases, subjects who used glucocorticoids and vitamin A acid drugs in the previous 1 month, patients who had skin lesions, and those who used laser, resurfacing and exfoliative freckle products prior to the study.

Drug specification

The drugs used in this study were Transamin[®] tranexamic acid tablets (CMIC CMO Co. Ltd., Shizuoka Plant; NMPA approval no. J20160092; specification: 0.25 g), *Xiyu* chloasma treatment dressing (Jiangsu Langqin Technology Co. Ltd; Registration Certificate no. 20180203), and sunscreen (SPF30, PA+++; Jilin Landing Luhe Science & Technology Co. Ltd.; name: FORENÉE repair type III).

Intervention methods

This study followed the principles of randomization, single-blind method, and placebo control. Patients in both groups were given 0.25 g of TA twice a day for 16 continuous weeks [13]. In addition, patients in group B were directed to clean their faces with normal saline, after which *Xiyu* dressing was evenly plastered on their faces for 20 min. Thereafter, their faces were cleaned with water, and lotion was applied. The dressing was used once daily for the first two weeks, and thereafter, once every two days, for a total of 16 weeks. The *Xiyu* dressing was applied in group C in the same way as in group B, but TA was not administered. All patients were asked to avoid direct sunlight, and were made to use the SPF30 physical and chemical sunscreen with pea-sized volume every morning, and this was repeated once every 2 - 3 h.

Clinical efficacy of treatment

Treatment effectiveness was determined in line with the *Criteria for Clinical Diagnosis and Efficacy of Chloasma* [14]. Under these criteria, treatment efficacy was classified into *cured* (> 90 % disappearance of area of hyperpigmented macule, with color basically absent); *markedly*

effective (> 60 % ≤ 90 % disappearance of area of hyperpigmented macule, or obvious fading away of patch color); *effective* (> 30 % ≤ 60 % disappearance of area of hyperpigmented macule, and fading away of patch color), and *ineffective* (< 30 % disappearance of area of hyperpigmented macule, and absence of any obvious change in patch color). Total effectiveness (TE) was calculated as shown in Eqn 1:

$$TE = \frac{(C + ME + E)}{T} \dots\dots\dots (1)$$

where TE = total effectiveness, C = number of cured patients, ME = number of *markedly effective* cases, E = number of *effective* cases, T = total number of patients.

Evaluation of parameters/indices

General patient information

General information such as age, duration of disease, disease type, severity, MASI scores, clinical type, area of pigmented spot, family medical history, and skin lesion type were analyzed and compared amongst the 3 groups.

MASI scores

The MASI scale was used to assess the severity of melasma at each stage of treatment. The area of melasma involvement was graded 0 - 6 points, with 0 for no involvement, 1 for less than 10 % involvement, 2 for 10 - 29 % involvement, 3 for 30 - 49 % involvement, 4 for 50 - 69 % involvement, 5 for 70 - 89 % involvement, and 6 for 90 - 100 % involvement. Homogeneity and skin darkening were graded from 0 to 4 points, with 0 for total unevenness, 1 for slight evenness, 2 for moderate evenness, 3 for obvious evenness, and 4 for complete evenness. Skin darkening was scored 1 for no darkening, 2 for slight darkening, 2 for general darkening, 3 for obvious darkening, and 4 for severe darkening. The total score in MASI was 48 points, which was positively correlated with the severity of melasma. Values of MASI were calculated as shown in Eq 2

$$MASI = F\{A (H + D) \times 0.3\} + R\{A (H + D) \times 0.3\} + L\{A (H + D) \times 0.3\} + C \{A (H + D) \times 0.1\} \dots\dots\dots (2)$$

where F = forehead, A = area of melasma involvement, R = right cheek, L = left cheek, C = chin, H = homogeneity of pigment distribution, D = darkening.

Whole blood viscosity (WBV)

The WBV was determined using a fully automated blood rheometer at the shear rates of 200, 30, and 1/sec. The instrument was pre-heated for 30 min, with temperature controlled at 37 ± 0.3 °C. Then, the anticoagulant vessel was placed on the turntable, and the measurement was completed automatically by the instrument.

Disease recurrence rate

The subjects were followed up for two months at the end of treatment, and during return visits. Recurrence was confirmed if patients presented with new lesions, or had expanded lesions with deeper color, with an increase ≥ 3 points in MASI score.

Patients' satisfaction

A satisfaction questionnaire was prepared on the actual conditions of patients to scientifically evaluate their satisfaction with the treatment process and outcomes, and the results were classified into 3 categories viz: *fully satisfied*, *satisfied* and *dissatisfied*. Satisfaction was calculated as shown in Eq 3:

$$SA = \frac{(FS + S)}{T} \dots\dots\dots (3)$$

where SA = satisfaction, FS = number of *fully satisfied* patients, S = number of *satisfied* patients, T = total number of patients.

Healing onset time and adverse reactions

Healing onset time and occurrence of adverse reactions in patients during treatment were recorded and compared.

Statistical analysis

Data were processed with SPSS21.0 software, while graphs were prepared with GraphPad Prism 7 (GraphPad Software, San Diego, USA). The results obtained comprised enumeration data and measurement data which were expressed as [n (%)] and mean ± SD, respectively. They were statistically analyzed using χ^2 test and *t*-test, respectively. Differences assumed to be statistically significant at $p < 0.05$.

RESULTS

General information on subjects

General information such as age, duration of disease and MASI scores were comparable

amongst the 3 groups of patients ($p > 0.05$; Table 1).

Treatment efficacy

The numbers of patients in whom treatment was effective in groups A, B and C, and effectiveness (in brackets) were 20 (66.67 %), 27 (90 %) and 10 (33.33 %), respectively (Figure 1). Thus, the order of effectiveness was: group B > group A ($\chi^2 = 4.8118, p = 0.028$) > group C ($\chi^2 = 6.6667, p = 0.010$).

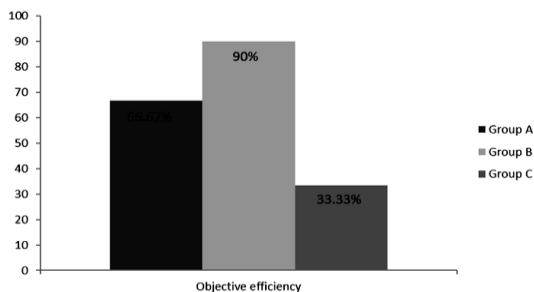


Figure 1: Comparison of clinical efficacy (%; n = 30)

MASI scores

At the 8th, 12th, 16th, and 20th weeks, the MASJ scores were $13.94 \pm 4.12, 12.01 \pm 3.25, 9.05 \pm 3.26$ and 8.16 ± 3.61 in group A; $12.16 \pm 2.73, 10.51 \pm 3.64, 6.32 \pm 3.18$ and 5.79 ± 3.07 in group B, and $14.63 \pm 4.16, 13.11 \pm 3.67, 11.82 \pm 3.40$ and 11.46 ± 3.39 in group C, respectively. The ranking of MASJ scores at the various

treatment time points was: group B < group A < group C, with group B lower than group C at the 8th week, group B lower than groups A and C at the 12th week, and notable differences amongst the groups at the 16th and 20th weeks ($p < 0.05$). These data are shown in Figure 2.

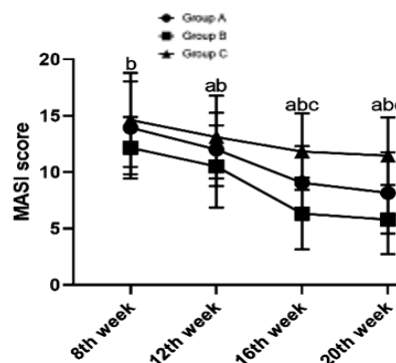


Figure 2: Comparison of MASJ scores. ^a $P < 0.05$, MASJ score in group A vs MASJ score in group B at the same period; ^b $p < 0.05$, MASJ score in group B vs MASJ score in group C at the same period; ^c $p < 0.05$, MASJ score in group A vs MASJ score in group C at the same period. Results are presented as mean ± SD

Whole blood viscosity (WBV)

As shown in Table 2, after treatment, WBV values of patients in the three groups differed significantly different, with group B better than group A, and group A better than group C ($p < 0.05$).

Table 1: General patient information

Parameter	Group A	Group B	Group C	P-value
Age (years)	36.24±3.55	37.19±3.68	35.86±3.37	>0.05
Duration of disease (years)	3.85±1.02	4.11±1.13	3.94±1.05	>0.05
MASJ score	15.98±2.17	16.05±2.26	16.13±2.34	>0.05
Clinical type				>0.05
Primary	6 (20)	4 (13.33)	6 (20)	
Secondary	24 (80)	26 (86.67)	24 (80)	
Area of melasma (cm ²)	4.35±1.83	4.49±1.87	4.52±1.84	>0.05
Patients with family medical history	3 (10)	2 (6.67)	2 (6.67)	>0.05
Type of skin lesion location				>0.05
Butterfly-like	10 (33.33)	12 (40)	9 (30)	
Upper side of the face	8 (26.67)	6 (20)	8 (26.67)	
Lower side of the face	6 (20)	7 (23.33)	7 (23.33)	
Generalized	6 (20)	5 (16.67)	6 (20)	

Table 2: Values of WBV in the 3 groups before and after treatment (mPa.s)

Shear rate/sec	Period	Group A	Group B	Group C
200	Before treatment	6.14±1.18	6.09±1.12	6.12±1.09
	After treatment	4.85±0.98*	4.13±1.02	5.79±1.16*#
30	Before treatment	7.23±1.14	7.19±1.11	7.16±1.08
	After treatment	5.62±0.78*	5.07±0.75	6.51±0.82*#
1	Before treatment	11.40±1.16	11.35±1.13	11.46±1.20
	After treatment	9.16±1.04*	8.25±1.24	10.12±1.28*#

* $P < 0.05$, vs group B; # $p < 0.05$, vs group A. Data are presented as mean ± SD

Onset time of healing and recurrence rate

The ranking of recurrence rate (from high to low) was group C > group A > group B, with no obvious differences amongst the groups ($p > 0.05$). The onset time of healing in group A was shorter than that in group C and longer than that in group B ($p < 0.05$). The results are shown in Table 3.

Table 3: Onset time and recurrence rate

Group	Cured	Relapsed	Onset time (days)
A	8	3 (37.5)	8.67±1.21*
B	14	1 (7.14)	6.49±1.05
C	5	2 (40)	10.35±1.32**

* $P < 0.05$, vs group B; # $p < 0.05$, vs group A

Safety

At the 8th, 12th and 16th weeks of treatment, there were no abnormalities in results of routine blood test, routine urinalysis, hepatic and kidney function tests, electrocardiogram (ECG), and prothrombin time (PT). Moreover, there were no marked changes in fibrinogen, fibrin degradation product (FDP), profibrinolytic activity, estradiol, progesterone and oxidative stress indicators. One patient in group A had mild diarrhea on the first day of menstruation, but her condition was alleviated after drinking warm water. One patient in group C felt slightly hot on the face after the first application of dressing. However, this resolved on its own without treatment. No allergies or other adverse reactions were observed during treatment.

Rating of patients' satisfaction

Satisfaction was higher in group B than in group A ($\chi^2 = 5.4545$, $p = 0.020$) and group C ($\chi^2 = 7.9365$, $p = 0.005$; Figure 3).

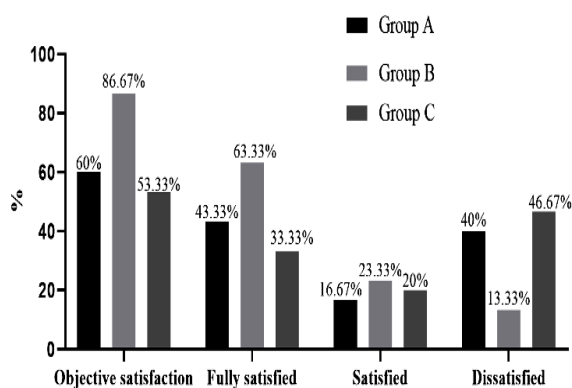


Figure 3: Degrees of patients' satisfaction in the 3 groups (%; n = 30)

DISCUSSION

At present, many therapeutic options with different safety and success rates have been used in the clinics for melasma. Treatment strategies such as TA, laser, topical drugs and chemical exfoliation are mostly used in combination therapy which has become the focus of attention in various medical units and scientific institutes [15]. Recently, the use of *Xiyu* dressing for chloasma treatment has resulted in some advantages such as better clinically-observed results and absence of adverse side effects. The core bioactive components of *Xiyu* dressing are vitamin C, TA, and arbutin. It was developed, produced and exclusively patented as a transdermal absorption formulation using bioactive components with enhanced potential for permeation through the skin [16].

Presently, there are very limited data from clinical studies on the effects of *Xiyu* dressing on melasma. Therefore, this study was carried out to investigate the efficacy of TA and *Xiyu* dressing on clinical treatment of melasma. The results obtained showed that objective treatment effectiveness was higher in group B than in group A, and higher in group A than in group C. The ranking of MASI scores (from high to low) at each period of treatment was: group C > group A > group B, with a lower score in group B than in group C at the 8th week, lower score in group B than in groups A and C at the 12th week, lower scores in group B than in group A at the 16th and 20th weeks, and lower scores in group A than in group C at the 16th and 20th weeks. These data suggest that the use of TA or *Xiyu* dressing alone did not produce significant effects at the early stage. However, TA in combination with *Xiyu* dressing resulted in better and preferable treatment efficacy at the 8th week, which was even better than the efficacy values due to use of *Xiyu* dressing alone in the middle and late periods. In addition, group B had better WBV than group A, while group C ranked last. These data are consistent with the results obtained in previous studies [17,18].

In recent years, several reports in China and elsewhere on the treatment of melasma have shown that the patients presented with abnormal hemorheology, although there were some variabilities in data reporting on each index, which may be related to factors such as age, disease course and symptom presentation of patients. Therefore, data from many clinical trials are required to obtain the hemorheological indices of patients. In this study, after analysis of WBV of patients with low, medium and high shear rates, it was concluded that the combined

therapy effectively reduced the WBV shear rates of melasma patients, with TA better in this regard than *Xiyu* dressing. The ranking of recurrence rate (from high to low) was: group C > group A > group B, with no obvious differences amongst the groups.

The onset time of healing in group A was shorter than that in group C, but longer than that in group B. Objective satisfaction was higher in group B than in groups A and C. There were no cases of allergies or other adverse reactions during treatment. These results indicate that all three treatments were safe, but the combined therapy had the fastest onset time of healing, followed by the TA treatment, with dressing treatment ranking last. Most patients were satisfied with the combined therapy. Although the recurrence rate was lowest in the combined therapy, no obvious differences were found in recurrence amongst the groups. However, this might be because of the small sample size used in the research.

Limitations of the study

The study has some shortcomings. First, TA is one of the hemostatic agents commonly used in the clinic, and it is contraindicated in patients receiving thrombin because of the susceptibility to adverse drug reactions. Second, the small sample size of this study might have largely affected the recurrence rates at follow-up, thereby resulting in variabilities in recurrence rates. Finally, due to the high cost of *Xiyu* dressing, many patients might have abandoned its use.

CONCLUSION

The combined use of TA and *Xiyu* dressing for the treatment of chloasma is more effective than the use of TA or *Xiyu* dressing alone. In terms of disease control and alleviation, the combined therapy is also superior to TA treatment, while TA treatment is better than the dressing. Besides, there is no incidence of allergies or other adverse reactions during treatment. Furthermore, patients who received TA in combination with *Xiyu* dressing exhibit the lowest recurrence rate. Therefore, However, there is need for further clinical trials to validate these findings.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Xiaojian Chen and Lei Wu conceived and designed the study, and drafted the manuscript. Xiaojian Chen, Lei Wu, Jian Wu and Meihong Cai collected, analyzed and interpreted the experimental data. Lei Wu and Jian Wu revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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