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Original Article

Clinical efficacy of self-designed Xiaoban Huoxue Prescription on chloasma derived from liver stagnation and blood stasis

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Abstract: Objective: To investigate the therapeutic effect and specific mechanism of self-designed Xiaoban Huoxue Prescription on chloasma derived from liver stagnation and blood stasis. Methods: This study retrospectively analyzed the clinical data of 94 patients with chloasma derived from liver stagnation and blood stasis. The patients were divided into a control group (treated with tranexamic acid tablets) and an experimental group (treated with self-designed Xiaoban Huoxue Prescription), with 47 cases in each group. Both groups were treated for 3 months, and the clinical efficacy was compared between the two groups. Results: The total response rate of the experimental group was higher than that of the control group ($P<0.05$). Compared with before treatment, the traditional Chinese medicine syndrome scores and Melasma area severity index scores in the two groups were lower 1, 2 and 3 months after treatment, and lower scores were seen in the experimental group than in the control group (all $P<0.001$); there was an opposite trend in the ITA° value (all $P<0.001$). Compared with before treatment, serum levels of estradiol, luteinizing hormone, follicle-stimulating hormone and tyrosinase absorbance in both groups were lower 3 months after treatment, and those in the experimental group were lower than those in the control group (all $P<0.001$). The experimental group had lower incidence of adverse reactions than the control group (2.13% vs. 12.77%, $P<0.05$). The satisfaction scores regarding pigmentation area regression, pigmentation regression and facial beauty in the experimental group were higher than those in the control group (all $P<0.001$). Conclusion: The self-designed Xiaoban Huoxue Prescription is safe and effective for chloasma derived from liver stagnation and blood stasis. Its mechanism may be related to the downregulation of serum sex hormone expressions and tyrosinase absorbance.

Keywords: Chloasma, liver stagnation and blood stasis syndrome, self-designed Xiaoban Huoxue Prescription, traditional Chinese medicine syndrome score, skin lesion score, sex hormone

Introduction

Chloasma is a common and frequently-occurring disease in dermatology. Although it does not endanger the life of patients, the disease can cause a great impact on the psychology and social interaction of patients due to its facial occurrence, and even induce mental disorders such as inferiority, anxiety and depression. Moreover, chloasma is easy to diagnose but difficult to treat with a long disease course, which poses a great threat to the physical and mental health of patients [1]. Tranexamic acid is a commonly used drug in the treatment of chloasma, but the overall effect is inferior to the clinical expectation, with frequently occurred drug dependence and easy relapse after drug withdrawal [2]. In recent years, more and more clinical attention has been paid to the role of traditional Chinese medicine (TCM) for the treatment of dermatological diseases [3, 4]. Modern TCM attributes chloasma to the category of blackish facial patch. It points out that women who are irritable and easy to worry can develop negative impact on liver, resulting in loss of liver qi, stagnation of fire and burning of Yin and blood, facial Qi and blood disharmony, stasis of meridians and collageness, thereby causing spots. Therefore, chloasma is commonly accompanied with the syndrome of liver stagnation and blood stasis, which should be treated by smoothing liver, regulating qi, promoting blood circulation and removing blood stasis [5, 6]. The self-designed Xiaoban Huoxue

Prescription is the cipher prescription of our hospital, which is composed of Scutellaria, Bupleurum, Gardenia jasminoides, Peppermin, Chinese angelica root-tip and other herbs. This prescription has the effect of smoothing liver, regulating qi, promoting blood circulation and removing blood stasis. However, there is no systematic study on the application value of self-designed Xiaoban Huoxue Prescription in treating chloasma derived from liver stagnation and blood stasis. Based on this, this study aimed to clarify the clinical value of this prescription and seek a safe and effective treatment program for patients with chloasma.

Materials and methods

Clinical information

Clinical data of 94 patients with chloasma derived from liver stagnation and blood stasis admitted to our hospital from December 2019 to December 2020 were retrospectively analyzed. According to different treatment methods, the patients were divided into two groups: the experimental group and control group, with 47 cases in each group. The control group was treated with tranexamic acid tablets, and the experimental group was treated with self-designed Xiaoban Huoxue Prescription.

Inclusion criteria: (1) Patients met the diagnostic criteria in *Clinical Diagnosis and Curative Effect Criteria for Chloasma (revised in 2003)* formulated by pigment epidemiology group of Dermatological and Venereal Diseases Professional Committee of Chinese Association of Integrated Traditional and Western Medicine [7]. Light brown to dark brown well-demarcated patches showed on patients' face with basically symmetrical distribution, without inflammation, scaling, and subjective physical discomfort. The symptom showed a certain seasonality, severer in summer and lighter in winter. (2) Female patients were aged 18 years old or above. (3) Patients had normal cognition, and had no communication or audio-visual obstacles. (4) Patients had normal liver and kidney function. (5) Patients did not use any freckle removing products within 3 months before inclusion. (6) Patients participated voluntarily and signed the informed consent for the study.

Exclusion criteria: (1) Patients had pigmentation caused by other diseases. (2) Patients had diseases in liver, endocrine system or blood system. (3) Patients had local skin exudation, erosion or inflammation. (4) Patients were pregnant or in lactation. (5) Patients had an allergic constitution. (6) Patients had mental illness and were unable to cooperate with the research.

This study was approved by the Medical Ethics Committee of our hospital (Approval No. 2018-ky-31).

Methods

The control group took 250 mg of tranexamic acid tablets (Sinopharm Group Tongjitang (Guizhou) Pharmaceuticals Co., Ltd.; SFDA approval number: H52020898; specification: 0.25 g/tablet), twice a day for 3 months orally. The experimental group was given self-designed Xiaoban Huoxue Prescription, including Scutellaria (9 g), Bupleurum (9 g), Gardenia jasminoides (9 g), Peppermin (9 g), Radix Paeoniae Rubra (9 g), Chinese angelica root-tip (9 g), Curcuma phaeocaulis (9 g), Carthamus tinctorius (9 g), Tangerine Peel (9 g) and Liquorice (6 g). All the traditional Chinese medicines were provided by the Pharmacy Department of our hospital and checked by the deputy chief pharmacist of traditional Chinese medicine). The above herbs were added to 500 mL of water and decocted to 300 mL, which were divided into 150 mL each for oral administration for 3 months.

Outcome measures

(1) Efficacy criteria: It was divided into four grades as basically cured, remarkably effective, improved and invalid. Basically cured: The color was basically faded, and the color spots were completely faded, or the fading area was equal to or over 90%. Remarkably effective: The color was significantly lighter, and the fading area of color spots was 60%-89%. Improved: The color became lighter, and the fading area of color spots was 30%-59%. Invalid: Failure to meet the above standards. Total response rate: Number of cases with (basically cured + remarkably effective + improved)/total number of cases *100% [7].

(2) Melasma area severity index (MASI): The evaluation was performed by three attending physicians, and the average value was taken to ensure the accuracy of the MASI score.

MASI=0.3 (DMR+HMR) AMR+0.3 (DF+HF) AF+0.3 (DML+HML) AML+0.1 (DC+HC) AC. A stands for the lesion area of chloasma, in which 0, 1, 2, 3, 4, 5 and 6 points respectively corresponds to chloasma area accounts for 0%, <10%, 10%-30%, 30%-50%, 51%-69%, 70%-89%, ≥90% of the skin area. H is the uniformity of the pigment in the lesion, in which scores of 0, 1, 2, 3 and 4 respectively correspond to extremely inconsistent, slightly consistent, moderately consistent, obviously consistent and almost completely consistent. D stands for the degree of color spot deepening, in which 0, 1, 2, 3 and 4 points respectively correspond to no deepening, slight deepening, general deepening, obvious deepening and severe deepening. F: forehead; ML: left cheek; MR: right cheek; C: lower jaw. The total score is 48 points, and lower score indicates lighter degree of chloasma.

(3) Criteria of TCM syndrome score: The primary symptoms include chloasma and deepened premenstrual macular color. The secondary symptoms involve chest and hypochondriac distention, bitter taste and anorexia, anxiety and irritability, premenstrual breast distension and dysmenorrhea with blood clots. Each symptom scored 0, 2, 4 and 6 points with no symptom, mild symptoms, moderate symptoms and severe symptoms, respectively, while tongue and pulse symptoms were not scored [8].

(4) ITA° value: The ITA° value at the lesions was measured by dermoscope to evaluate the overall change in skin chromaticity. L * value (reflecting the skin brightness), a * value (reflecting the skin red-green balance) and b * value (reflecting the skin yellow-blue balance) were measured by dermoscope, respectively. ITA° value was calculated according to the measurement results of L, a, and b. ITA° = (a(L-50)/b) *180°/3.14159. The ITA° value is inversely proportional to the skin color at the lesion. Namely, higher ITA° value indicates lighter color of the skin.

(5) Biochemical index levels: Fasting peripheral venous blood (3 mL) was collected from patients. Serum was collected by centrifugation. Serum levels of estradiol (E_2), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were detected by radioimmunoassay. The 723C spectrophotometer (Shanghai Xinmao Instrument Co., Ltd., China) was used to measure the concentration of tyrosinase.

(6) Incidence of adverse reactions: Adverse reactions were compared between the two groups, including nausea, vomiting, diarrhea and menstrual discomfort. Incidence of adverse reactions = number of cases with adverse reactions/total number of cases *100%.

(7) Treatment satisfaction: The self-made questionnaire of satisfaction with treatment of chloasma was used for evaluation, including satisfaction regarding pigmentation area regression, pigmentation regression and facial beauty. The score for each item ranged from 0 to 10 points, and higher score means higher satisfaction. The Cronbach's α value of the scale was 0.8134, which proved that the scale has a promising reliability and validity.

Statistical analysis

SPSS22.0 was used for data analysis and GraphPad Prism 7.0 software was used to draw statistical graphs. Measurement data were tested by Bartlett's test for homogeneity of variance and Kolmogorov-Smirnov normality test. Measurement data with homogeneity of variance and conforming to normal distribution were expressed as ($\bar{x}$±sd); independent sample t-test was performed for inter-group comparison, and paired t-test was performed for intra-group comparison between before and after treatment. Count data were represented by n (%). P<0.05 was considered statistically significant.

Results

Comparison of general information

There was no significant difference in the general information between the two groups (all P>0.05). See **Table 1**.

Comparison of clinical efficacy

The total response rate of the experimental group was higher than that of the control group (89.36% vs. 72.34%, P<0.05), as shown in **Table 2**.

Comparison of TCM syndrome score and MASI score

There was no significant difference in TCM syndrome score and MASI score between the two

Table 1. Comparison of general information ($\bar{x}$±sd)

Group	Sex (male/female)	Age (years old)	Smoking history (n)	BMI (kg/m^2)	Hypertension (n)
Experimental group (n=47)	24/23	39.1±5.1	4.56±1.18	23.29±3.19	9
Control group (n=47)	22/25	38.3±6.3	5.04±1.22	22.97±3.42	11
χ^2	0.170	0.677	0.151	0.498	0.254
P	0.680	0.500	0.697	0.619	0.614

Note: BMI: body mass index.

Table 2. Comparison of clinical efficacy (n, %)

Group	Basically cured	Remarkably effective	Improved	Invalid	Total response rate
Experimental group (n=47)	9 (19.15)	19 (40.43)	14 (29.79)	5 (10.64)	42 (89.36)
Control group (n=47)	5 (10.64)	16 (34.04)	13 (27.66)	13 (27.66)	34 (72.34)
χ^2					4.398
P					0.036

Table 3. Comparison of Chinese medicine syndrome score ($\bar{x}$±sd, point)

Group	Before treatment	One month after treatment	Two months after treatment	Three months after treatment
Experimental group (n=47)	35.04±6.33	24.28±5.69***	13.24±4.82***	6.51±1.28***
Control group (n=47)	34.72±7.12	29.71±5.74***	22.87±5.15***	17.52±3.58***
t	0.230	4.606	9.360	19.853
P	0.818	<0.001	<0.001	<0.001

Note: Compared with the same group before treatment, ***P<0.001.

Table 4. Comparison of MASI score ($\bar{x}$±sd, point)

Group	Before treatment	One month after treatment	Two months after treatment	Three months after treatment
Experimental group (n=47)	12.92±3.22	10.26±3.14*	8.05±3.08*	6.15±3.23*
Control group (n=47)	12.87±5.19	11.59±2.79*	9.72±3.88*	8.14±3.66*
t	0.056	2.171	2.311	2.795
P	0.955	0.033	0.023	0.006

Note: Compared with the same group before treatment, *P<0.001. MASI: melasma area severity index.

groups before treatment (all P>0.05). The two scores at 1, 2 and 3 months after treatment were lower than those before treatment (P< 0.001), and lower scores were seen in the experimental group (P<0.001). See **Tables 3** and **4**.

Comparison of ITA° value

There was no significant difference in ITA° value between the two groups before treatment (all P>0.05). The ITA° values at 1, 2 and 3 months after treatment were higher than those before treatment (P<0.001), and higher values were seen in the experimental group (P<0.001). See **Table 5**.

Comparison of serum biochemical indices

Before treatment, serum levels of E_2, LH and FSH and tyrosinase absorbance value were not significantly different between the two groups (all P>0.05); those at 3 months after treatment were lower than those before treatment, and lower values were found in the experimental group (all P<0.001). See **Figure 1**.

Comparison of adverse reactions

The incidence of adverse reactions in the experimental group was lower than that in the control group (2.13% vs, 12.77%, P<0.05), as shown in **Table 6**.

Table 5. Comparison of ITA° value ($\bar{x}\pm sd$)

Group	Before treatment	One month after treatment	Two months after treatment	Three months after treatment
Experimental group (n=47)	6.88±1.24	10.75±2.05***	14.11±2.63***	16.89±3.21***
Control group (n=47)	7.02±1.31	9.02±1.82***	10.82±1.95***	14.37±2.52***
t	0.532	4.326	6.889	4.233
P	0.596	<0.001	<0.001	<0.001

Note: Compared with the same group before treatment, ***P<0.001.

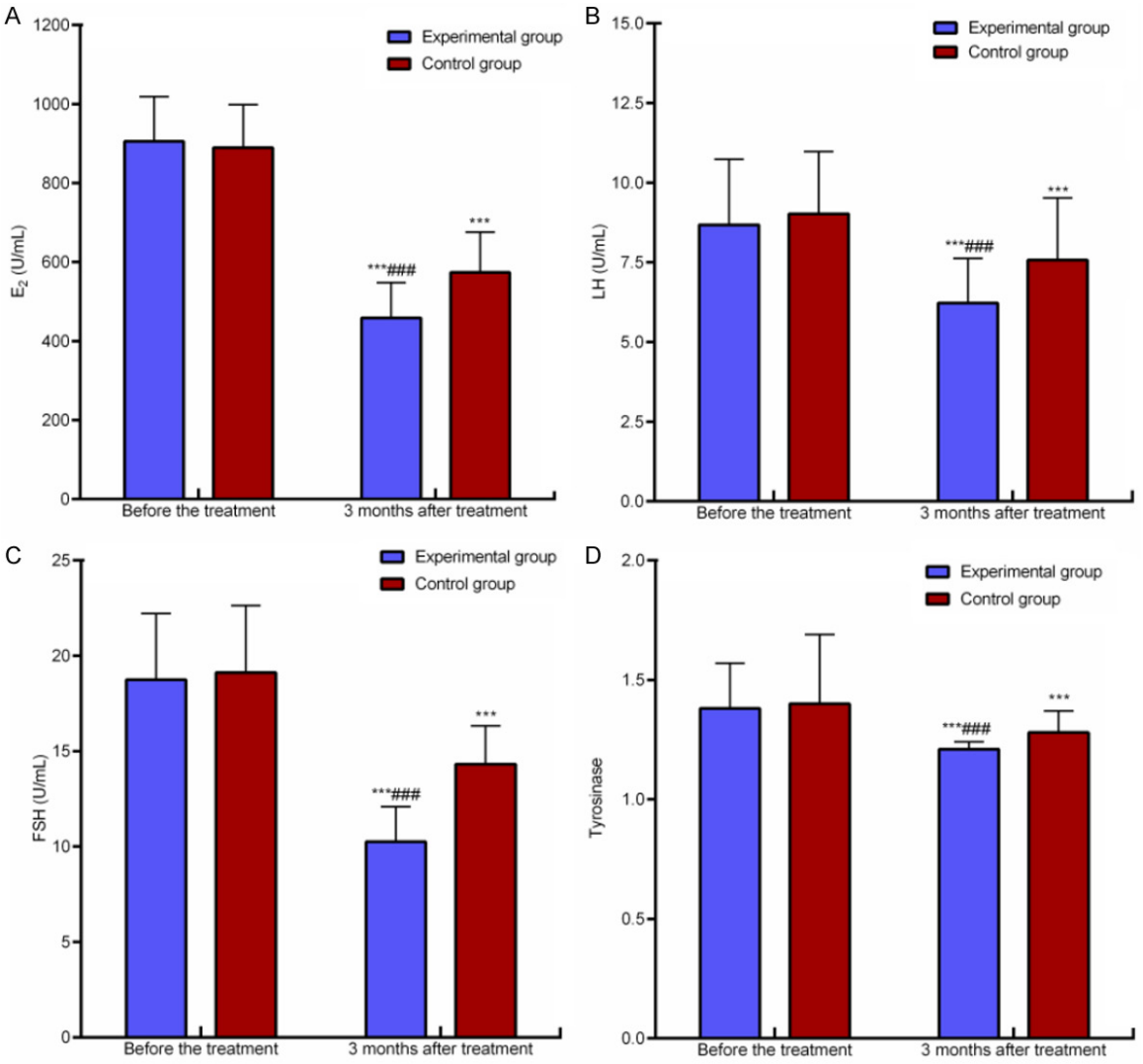

Figure 1. Comparison of serum E_2, LH, FSH and tyrosinase levels between the two groups. Self-designed Xiaoban Huoxue Prescription reduced serum E_2 (A), LH (B) and FSH (C) and tyrosinase (D) levels in patients with chloasma derived from liver stagnation and blood stasis. Compared with those before treatment, ***P<0.001; compared with the control group 3 months after treatment, ###P<0.001. E_2: estradiol; LH: luteinizing hormone; FSH: follicle-stimulating hormone.

Comparison of treatment satisfaction

The satisfaction scores regarding pigmentation area regression, pigmentation regression and facial beauty in the experimental group were all higher than those in the control group (all P<0.001). See **Table 7**.

Table 6. Comparison of adverse reactions (n, %)

Group	Nausea	Vomiting	Diarrhea	Menstrual discomfort	Total incidence
Experimental group (n=47)	1 (2.13)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.13)
Control group (n=47)	2 (4.26)	1 (2.13)	1 (2.13)	2 (4.26)	6 (12.77)
χ^2					3.859
P					0.049

Table 7. Comparison of treatment satisfaction ($\bar{x}$±sd, point)

Group	Pigmentation area regression	Pigmentation regression	Facial beauty
Experimental group (n=47)	89.52±8.24	87.35±9.31	90.41±7.53
Control group (n=47)	72.58±10.36	74.89±11.69	75.35±9.32
t	8.773	5.716	8.617
P	<0.001	<0.001	<0.001

Discussion

Chloasma is a common skin disease in women, with characteristics of high incidence and easy relapse [9-11]. Although the disease does not pose a threat to the patient's life, it can cause aesthetic impact on the patient's appearance because of its facial occurrence, which will cause negative emotions and even psychological issues, affecting the physical and mental health of the patients [12, 13]. Therefore, clinical prevention and treatment is important. Seeking a safe and effective treatment program has become the key research direction for clinical dermatologists.

In this study, tranexamic acid and self-designed Xiaoban Huoxue Prescription were respectively used to treat patients with chloasma derived from liver stagnation and blood stasis. The results showed that the related symptoms of the two groups were improved after treatment, but the clinical efficacy, TCM syndrome score, MASI score, ITA° value, incidence of adverse reactions and treatment satisfaction score of the experimental group were better than those of the control group. These results indicate that the self-designed Xiaoban Huoxue Prescription is safe and effective for chloasma derived from liver stagnation and blood stasis in improving the facial lesions, showing generally satisfied therapeutic effect. Scholars have found that the efficacy and safety of Shugan Huayu Decoction in the treatment of female chloasma derived from liver stagnation and blood stasis are basically consistent with the results of this study [13]. It suggests that the method of soothing liver, regulating qi, promoting blood circulation and removing blood stasis of TCM has a high application value in treating chloasma derived from liver stagnation and blood stasis. ATranexamic acid can inhibit the enzyme activator in the formation of the plasma, whose main target is keratinocyte. Also, it can inhibit the formation of fibrinolytic enzyme, so that tyrosinase cannot fully play its activity. Then keratinocytes cannot be converted into melanocytes, and the transport and transmission of melanin are inhibited, thereby desalting pigment spots [14-16]. However, clinical studies have pointed out that tranexamic acid alone is difficult to achieve ideal results, and increased drug dose will increase the risk of toxic and side reactions [17, 18].

Scutellaria, Bupleurum bupleurum, Gardenia jasminoides and Peppermin have the effect of dredging liver and regulating qi, and can clear liver meridian and suppress heat. Curcuma phaeocaulis, Chinese angelica root-tip, Carthamus tinctorius and Radix Paeoniae Rubra have the effect of promoting blood circulation, channeling and removing blood stasis. Tangerine Peel can adjust middle-jiao, regulate the flow of vital energy and remove obstruction. Moreover, Liquorice can moderate the property of herbs. The whole self-designed prescription plays the effect of dredging liver, regulating qi, promoting blood circulation and removing blood stasis. The smooth regulation of qi and blood will eliminate spots from the skin, which can effectively relieve the skin condition of patients with chloasma, and ultimately achieve the purpose of treatment.

This study also showed that after treatment, serum levels of E_2, LH and FSH and tyrosinase absorbance value in the experimental group were lower than those in the control group, suggesting that the self-designed Xiaoban Huoxue Prescription is beneficial to the downregulation

of serum sex hormone expression and tyrosinase absorbance value in patients with chloasma derived from liver stagnation and blood stasis. Researches indicate that the onset of chloasma is related to genetic and ultraviolet radiation factors, and changes in sex hormone levels are also one of the main causes of this disease [19, 20]. Abnormal changes in hormone levels can stimulate melanocytes to secrete melanin granules, and promote the transport and diffusion of melanin granules, thus inducing chloasma [21]. In addition, tyrosinase is the key enzyme for the synthesis of melanin. It oxidizes dopamine into dopa-quinone in the melanocytes, then oxidizes it into intermediates, and finally synthesizes melanin. Liu et al. found that the tyrosinase activity was significantly increased in patients with chloasma derived from liver qi stagnation, and Shugan Jieyu Pills could inhibit the production of this enzyme to reduce the formation of melanin, which could be used for the treatment of pigment-increasing skin diseases (chloasma) [22]. These results were consistent with the results of this study. Studies have shown that Angelica sinensis and Liquorice contain one or more plant sex hormone components, which can play a hormone-like bidirectional regulating effect to inhibit tyrosinase activity, and further prevent tyrosinase oxidation to form melanin, thereby promoting the regression of chloasma [23-25].

However, TCM treatment does not simply play its role through a single mechanism but it works due to synergistic a*ction of multiple* targets. This study only analyzed its influence on the expression of serum sex hormones. Therefore, there are some limitations in the mechanistic study. In addition, the study had a short follow-up and observation period without statistical analysis of disease recurrence. The sample size was small, which may lead to biased results. Thus, it is still necessary to extend the follow-up observation time and conduct multicenter, large-sample size and multi-mechanistic studies in the future, so as to provide more clinical evidence for the application value of self-designed Xiaoban Huoxue in treatment of chloasma derived from liver stagnation and blood stasis.

In conclusion, the self-designed Xiaoban Huoxue Prescription is safe and effective in treating chloasma derived from liver stagnation and blood stasis. It is beneficial to improve the facial lesions of patients. The mechanism may be related to the downregulation of sex hormone expression and tyrosinase absorbance value in the body, and the patients have high satisfaction with treatment.

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Disclosure of conflict of interest

None.

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