Original paper

Comparison of the efficacy of Hydroquinone cream versus Hydroquinone cream plus Danggui Shaoyao powder in the treatment of melasma

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Adv Dermatol Allergol 2024; XLI (1): 66–71
DOI: https://doi.org/10.5114/ada.2023.135613

Abstract

Introduction: Melasma is an acquired hypermelanosis and occurs in areas exposed to sunlight.
Aim: To investigate the effectiveness of Danggui Shaoyao powder (DSP) as a complementary drug in the treatment of melasma.
Material and methods: A total of 40 melasma patients over the age of 18 who met the inclusion criteria entered the study randomly in two DSP + Hydroquinone (DSP + H) and Hydroquinone (H) groups.
Results: At the beginning of the study, the average MASI score of the two groups of patients had no statistical difference (DSP + H: 15.79 ±1.01 vs. H: 15.37 ±1.17, $p = 0.23$). But from the eighth week of treatment, the MASI score of the patients decreased significantly and in the DSP + H group it decreased statistically significantly compared to the H group (DSP + H: 5.83 ±0.97 vs. H: 8.29 ±2.23, $p < 0.001$ for the eighth week and DSP + H: 3.60 ±0.58 vs. H: 5.52 ±1.73, $p < 0.001$ for the twelfth week of the treatment). It means after 12 weeks of treatment, the average MASI score of patients in the DSP + H group decreased by 77.26 ±2.70%, but in the grroup H, it decreased by 64.31 ±9.68% ($p < 0.001$). Dynamic PGA showed that excellent treatment occurred in 65% of the + H group H, but only 20% of the H group ($p = 0.01$).
Conclusions: Oral DSP for 12 weeks along with hydroquinone cream can significantly reduce the MASI score of melasma patients and increase the patients' recovery and satisfaction.

Key words: melasma, hydroquinone, Danggui Shaoyao powder, traditional Chinese medicine.

Introduction

Melasma is an acquired hypermelanosis and occurs in areas exposed to sunlight, it is common in Blacks and Asians, and also in women especially during childbearing age and the prevalence of this disease reported about 1% but can increase up to 50% in high risks persons [1–3]. Although the underlying cause of melasma is not yet known [4, 5]. Among several melasma-related factors, the contact of the sun is most associated, also ultraviolet radiation, hormones during pregnancy, oral contraceptive pills, glandular disorders such as thyroid dysfunction, family history of melasma, cosmetic products, and anti-epileptic drugs are related factors [6–8]. Melasma is divided into four clinical types: epidermal, dermal, mixed and unnamed type [9–11]. Melasma often causes obvious psychological problems such as depression in patients due to damage to the appearance and beauty of people in the form of facial spots so it reduces the quality of life [12, 13]. Treatment of melasma is difficult due to its resistant and recurrent nature [14]. Hydroquinone is the most common and effective topical anti-stain agent and a gold standard in the treatment of melasma [15, 16]. Although hydroquinone is the most widely-used melasma drug worldwide, due to the relapse of the disease and the dissatisfaction of patients with the treatment process, doctors are looking for a more effective way to treat melasma [17, 18]. Therefore many complementary methods and drugs have been studied to increase the effectiveness of treatment. But still, the methods used have failed to become an effective and reliable alternative to the main treatment regimen of these patients. Some new methods, such as using lasers, have many fans, but due to the complications or lack of trust of patients, it has still not been selected as an alternative method. In traditional Chinese medicine (TCM), pathogenesis of melasma described as qi stagnation blood

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Received: 13.10.2023, **accepted:** 19.11.2023, **online publication:** 28.02.2024.

stasis syndrome, weakness of liver, spleen, and stomach, and kidney deficiency. The treatment principles are to strengthen the spleen, activate the liver, activate the kidney, regulate qi, increase blood circulation and eliminate blood stasis [19]. Therefore, in addition to topical medicines, oral medicinal products have also been used to treat melasma from the past. Danggui Shaoyao powder (DSP) is one of newly recommended TCM drugs for dermatologic diseases like melasma. The original prescription is mainly composed of six TCM, namely, Radix Paeoniae alba, Angelica sinensis, Rhizoma Alismatis, Poria cocos, Rhizoma chuanxiong, and Rhizoma Atractylodis Macrocephalae [20]. Despite the widespread use of this drug in the East Asia, especially in China, few articles have been reported about the effectiveness of this drug, although in past studies, the effectiveness of this drug was reported for the treatment of gynaecological diseases, stroke, liver, etc., but rare reports are available on melasma disease, so the purpose of this study is to investigate the effectiveness of DSP as a complementary drug in the melasma treatment.

Material and methods

Study populations

A total of 40 melasma patients over the age of 18 who met the inclusion criteria entered the study randomly in two DSP + Hydroquinone (DSP + H) and Hydroquinone (H) groups. Exclusion criteria included: pregnant and lactating women, history of melasma treatment within a month before the intervention, the presence of sensitivity to the drugs in the study, facial warts, use of anticoagulant drugs and anticonvulsant drugs, and use of contraceptive drugs during the 12 months before the intervention and during the study. The wood lamp was used for patient examination and confirming the type of melasma.

Intervention

Patients in the DSP + H group took Danggui Shaoyao powder orally BID for twelve weeks and simultaneously used 4% hydroquinone cream topically twice a day. The H group used only 4% hydroquinone cream topically twice a day for 12 weeks.

Evaluation and follow-up

The follow-up of the patients was done by measuring the MASI score, which was done 4 times in total and also by The Physician Assessment (Dynamic PGA). The MASI score was measured and recorded at the beginning of the study, and 4, 8 and 12 weeks after starting intervention. The patients were followed up monthly for 3 months to evaluate the recurrence of melasma.

Measurement of Melasma Area and Severity Index (MASI)

The MASI score was calculated based on the involved area (A), and darkness (D) and homogeneity (H) of hyperpigmentation. The right side of the forehead, the right side of the cheek, and the right side of the chin were calculated as 15%, 30%, and 5% of the entire face, respectively, and the same areas on the left side were calculated in the same way, so that it finally includes 100% of the face. The evaluation score of A in each area was 0–6. The evaluation score of D and H was from 0 to 4. The MASI score was calculated by multiplying the score A by the sum of D and H for each of the 6 areas.

Measurement of Dynamic Physician Assessment (Dynamic PGA)

The overall evaluation by the doctor was done dynamically (Dynamic PGA) using the photos taken at the beginning and then at the end of the treatment. The degree of improvement of melasma was as follows: > 75% lighting (excellent), 51–75% (good), 26–50% (fair), and 0–25% (poor).

Statistical analysis

SPSS (v20) statistical software was used for data analysis. To describe the data, mean and standard deviation were used in quantitative variables and frequency and percentage were used in qualitative variables. First, the normality of data distribution was checked by the Kolmogorov-Smirnov test, and then parametric tests were used for normal data and non-parametric tests were used for non-normally distributed data, and in all tests, the significance level was less than 0.05.

Results

As mentioned in the method section, 40 patients in two groups (DSP + H: 20 and H: 20) were included in the study. There was no statistically significant difference between the demographic information and disease indicators of the two groups. The average age of patients in the DSP + H group was 35.15 ±5.47 years and in the H group was 37.40 ±4.73 years, and no significant difference was found between the two groups (p = 0.17). Also, examining the skin type of the patients showed that most of the patients in DSP + H and H groups were skin type 4 and there was no statistically significant difference between the skin types of the patients (50% vs. 55% respectively, p = 089). 60% of the patients in the DSP + H group and 55% of the patients in the H group had a positive family history, and there was no significant difference between the two groups. Predisposing factors of patients of the two groups include pregnancy and UV, in both groups, pregnancy was the highest factor without significant differences (70% vs. 75% respectively, p = 72). Although the studied patients had not been treated within a month before the study, 55% of the patients in the DSP + H group and 60% of the patients in the H group had a history of treatment before that (p = 0.74). Also, examining the affected area of the patients showed that most of the patients in DSP + H and H groups were affected at malar area and there was

Table 1. Comparison of patient characteristics in the DSP + H and H groups

Patient characteristics		DSP + H	H	*P*-value
Age		35.15 ±5.47	37.40 ±4.73	0.17
Skin type	1	0 (0%)	0 (0%)	0.89
	2	2 (10%)	2 (10%)	
	3	7 (35%)	6 (30%)	
	4	10 (50%)	11 (55%)	
	5	1 (5%)	1 (5%)	
Family history	Yes	12 (60%)	11 (55%)	0.34
	No	8 (40%)	9 (45%)	
Predisposing factor	Pregnancy	14 (70%)	15 (75%)	0.72
	UV	6 (30%)	5 (25%)	
Previous treatment	Yes	11 (55%)	12 (60%)	0.74
	No	9 (45%)	8 (40%)	
Area affected	Central	0 (0%)	1 (5%)	0.54
	Malar	14 (70%)	13 (65%)	
	Central Malar	6 (30%)	5 (25%)	
	Malar mandibular	0 (0%)	1 (5%)	
Melasma type	Mixed	7 (35%)	11 (55%)	0.20
	Epidermal	13 (65%)	9 (45%)	
	Dermal	0 (0%)	0 (0%)	

Table 2. MASI score of patients during treatment periods

Time	DSP + H	H	*P*-value
Baseline MASI	15.79 ±1.01	15.37 ±1.17	0.23
After 4 weeks	11.75 ±1.50	11.74 ±2.04	0.98
After 8 weeks	5.83 ±0.97	8.29 ±2.23	< 0.001
After 12 weeks	3.60 ±0.58	5.52 ±1.73	< 0.001

no significant difference between the affected area of the patients (70% vs. 65% respectively, $p = 54$). The type of melasma in the majority of the patients of the two groups was epidermal, and no significant difference was found between the types of melasma of the patients (65% vs. 55% respectively, $p = 54$) (Table 1).

The MASI score was used to evaluate the effectiveness of the drugs. At the beginning of the study, the average MASI score of the two groups of patients had no statistical difference (DSP + H: 15.79 ±1.01 vs. H: 15.37 ±1.17, $p = 0.23$). Also, in the first follow-up of the patients, which was done after 4 weeks from the start of the treatment, no statistically significant difference was found between the MASI score of the patients of the two groups (DSP + H: 11.75 ±1.50 vs. H: 11.74 ±2.04, $p = 0.98$). But from the eighth week of treatment, the MASI score of the patients decreased significantly and in the DSP + H group it decreased statistically significantly compared to the H group (DSP + H: 5.83 ±0.97 vs. H: 8.29 ±2.23, $p < 0.001$). Also, the follow-up of the patients in the twelfth week of the treatment showed a more downward trend in the MASI score of the patients in the DSP + H group, and the average MASI score of the patients was statistically significantly lower than in the H group (DSP + H: 3.60 ±0.58 vs. H: 5.52 ±1.73, $p < 0.001$). In general, after 12 weeks of treatment, the average MASI score of patients in the DSP + H group decreased by 77.26 ±2.70%, but in the H group, it decreased by 64.31 ±9.68%. Therefore, we have seen a statistically significant decrease in the DSP + H group compared to the H group ($p < 0.001$) (Tables 2 and 3).

To ensure the effectiveness of treatment, the overall evaluation by the doctor was done dynamically by PGA evaluation. Our analysis showed that excellent treatment occurred in 65% of the DSP + H group but only 20% of the H group ($p = 0.01$). Therefore, the expert evaluation of the patients also showed that the DSP + H group had a statistically significant improvement compared to the H group (Table 4).

Table 3. The percentage of patients' MASI score reduction in different stages of the follow-up

Time	DSP + H	H	*P*-value
After 4 weeks	25.78 ±6.36	23.86 ±9.92	0.47
After 8 weeks	63.23 ±4.68	46.43 ±12.18	< 0.001
After 12 weeks	77.26 ±2.70	64.31 ±9.68	< 0.001

Table 4. Patient satisfaction results from the study and results of Dynamic PGA

Outcome		DSP + H	H	*P*-value
Satisfaction	No	1 (5%)	5 (25%)	0.02
	Relative	7 (35%)	11 (55%)	
	Complete	12 (60%)	4 (20%)	
PGA	Excellent	13 (65%)	4 (20%)	0.01
	Good	5 (25%)	12 (60%)	
	Fair	2 (10%)	4 (20%)	
	Poor	0 (0%)	0 (0%)	

Since one of the main aspects of melasma treatment is increasing the quality of life of patients and patient satisfaction is the main pillar of treatment, in this study the satisfaction of patients was also examined and it was observed that in the DSP + H group, 60% of the patients were fully satisfied and 35% of the patients were partially satisfied, and only one person was dissatisfied, but in the H group, only 20% of the patients were fully satisfied, and although 55% were partially satisfied, but 25% of patients were dissatisfied, so according to this, the satisfaction of the patients in the DSP + H group was statistically significantly higher than in the H group ($p = 0.02$).

Discussion

Melasma is chronic disease as a result of increased symmetrical hyperpigmentation of the skin which presents in the form of light to dark brown macules and patches with regular borders [21–24]. Melasma is related to hyper-production of melanin in the face skin, but this pathogenesis has not been completely determined up to now. Some melasma risk factors include sunlight exposure, ultraviolet radiation, pregnancy hormones, oral contraceptive pills, endocrine disorders, such as and family history of melasma [25, 26]. The prevalence of melasma in the general population is 1% and may be up to 50% in risky populations [3]. The incidence of melasma in Asian women of reproductive years is still up to 30% [19]. In Chinese people, the prevalence of melasma is 3.23% to 13.61%, with 0.36% to 8.33% in men and 4.65% to 17.98% in women [27]. In spite of a powerful therapeutic demand, melasma treatment is facing recurrent relapse which is a big problem in managing these patients [28, 29]. Non systemic treatments are classically the usual approach for treating melasma, among which hydroquinone (H) is one of the effective depigmenting agent and is known as the gold standard for melasma treatment [30, 31]. However, numerous researches reported a wide range of side effects after treating by H. H has been related with repeatedly irritant dermatitis. Therefore, a novel strategy for the cure of this refractory skin disease is still urgently needed. DSP is a famous prescription in China, it was originally designed to treat women with abdominal pain during pregnancy and women with various abdominal diseases and pains. It is used by TCM to strengthen the spleen and relieve pain. But other studies showed that DSP can effectively remove free radicals in the body, increase the activity of superoxide dismutase in the body, inhibit cell apoptosis, and has a good protective effect on the central nervous system [32]. Recently, this drug has also received attention in the treatment of skin diseases, but few reports have been published in the literature. Therefore, in this study, we investigated the effect of DSP in the treatment of melasma patients. The results of our study showed that at the beginning of the study, the average MASI score of the two groups of patients had no statistical difference (DSP + H: 15.79 ±1.01 vs. H: 15.37 ±1.17, $p = 0.23$). This means the severity of disease in the two groups was the same. But from the eighth week of treatment, the MASI score of the patients decreased significantly and in the DSP + H group it decreased statistically significantly compared to the H group (DSP + H: 5.83 ±0.97 vs. H: 8.29 ±2.23, $p < 0.001$ for the eighth week and DSP + H: 3.60 ±0.58 vs. H: 5.52 ±1.73, $p < 0.001$ for the twelfth week of the treatment). It means after 12 weeks of treatment, the average MASI score of patients in the DSP + H group decreased by 77.26 ±2.70%, but in the H group, it decreased by 64.31 ±9.68%. Therefore, we have seen a statistically significant decrease in the DSP + H group compared to the H group ($p < 0.001$). We also evaluated effectiveness of treatment by dynamic PGA which showed that excellent treatment occurs in 65% of the DSP + H group but only 20% of the

H group (p = 0.01). Finally, satisfaction of patients was also examined and it was observed that in the DSP + H group, 60% of the patients were fully satisfied, but in the H group, only 20% of the patients were fully satisfied which means the satisfaction of the patients in the DSP + H group was statistically significantly higher than in the H group (p = 0.02). Although extensive studies have investigated DSP in various diseases, few studies have investigated the effect of DSP on the treatment of melasma, in which the effectiveness results have been reported in line with the present study. In the study of Chen *et al*., researchers studied the effect of DSP on the treatment of melasma and they reported that the clinical cure rate and total effective rate of the observation group were significantly higher than those of the control group (p < 0.05). They mentioned after 12 weeks of treatment, the spots area of the patients in the two groups and the colour significantly improved (p < 0.05), and the improvement in the observation group was more significant (p < 0.05) [33]. In another study by Luo *et al*. evaluating the efficacy of DSP in the treatment of melasma in women with blood deficiency and dampness syndrome, they reported that the total effective rate of the observation group was 89.7%, which was significantly higher than 43.6% of the control group (p < 0.05). The MASI index of the observation group after treatment was 8.21 ±3.25 points, which was significantly lower (19.57 ±3.14 points) compared with the control group (p < 0.05) [34]. Also another study conducted by Zhu evaluated the effect of DSP in the treatment of melasma; they showed that the total effectiveness of the test group was significantly higher than the control group (p < 0.05); after treatment the skin lesion scores of the two groups were significantly lower than those before treatment (p < 0.05) [35]. These studies statistically significantly showed that, like the present study, DSP has significant effectiveness in the treatment of melasma. In general, the results of this study show that in addition to topical drugs such as hydroquinone cream, effective treatment for melasma can also be achieved using systemic drugs, and since the side effects of TCM are less common than for other chemical drugs, therefore TCM can be used to treat melasma, and DSP is one of these drugs that, according to the findings of the present study, has been significantly effective in treating melasma.

Conclusions

Our results showed that the use of oral DSP for 12 weeks along with hydroquinone cream can significantly reduce the MASI score of melasma patients and increase the patients' recovery and satisfaction of the treatment. We suggest using different dosages of this drug in future studies and also using this product for treating other dermatologic diseases.

Acknowledgments

This research was supported by the National Natural Science Youth Foundation Project (H120382103739).

Yuan-Yuan Cheng and Rui-Rui Peng contributed equally.

Conflict of interest

The authors declare no conflict of interest.

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