

Efficacy and Safety of Tranexamic Acid Combined with Hydroquinone Cream in the Treatment of Chloasma

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Wu *et al.*: Treatment of Chloasma with Tranexamic Acid and Hydroquinone Cream

To study the efficacy and safety of tranexamic acid and hydroquinone cream with water light needle in the treatment of chloasma, and to provide clinical reference for the treatment of Chloasma is the main objective. A total of 230 patients with chloasma admitted to Fuyang Maternal and Child Health Hospital of Hangzhou from March 2019 to August 2022 were selected and divided into study group (n=115) and control group (n=115) according to the odd and even number of treatment. The study group received tranexamic acid injection with water-light needle and hydroquinone cream. In the control group, tranexamic acid was injected with water light needle and asiaticoside ointment was applied. After the treatment, the effective rate, melasma area and severity index, dermatology life quality index, recurrence rate and incidence of adverse drug reactions were compared between the two groups. After the treatment, the total effective rate of the study group was 94.78 %, which was significantly higher than 80.87 % of the control group ($p<0.05$). The melasma area and severity index and dermatology life quality index scores of the study group were lower than those of the control group ($p<0.05$), and the recurrence rate and adverse drug reaction rate of the study group were lower than those of the control group ($p<0.05$). Tranexamic acid and hydroquinone cream with water light needle in the treatment of melasma has obvious curative effect, high safety, low recurrence rate and high patient satisfaction, significantly enhance the quality of life and it is worthy of drug promotion.

Key words: Tranexamic acid, hydroquinone cream, asiaticoside ointment, melasma

Melasma is a kind of pigmented skin disease and there is no clinically specific treatment. The pathogenesis of melasma is mostly believed to be caused by the deposition of too many melanosomes by melanocytes^[1]. Histologically, it shows a significant increase in melanin in the epidermis, enhances cell activity and some of the diseased melanin can affect the dermis. Under electronic endoscopy, melanosomes produced by melanocytes showed dendritic structures and some patients showed endoplasmic reticulum structures such as mitochondria and golgi apparatus. At present, the treatment methods for melasma include drug therapy, oral vitamin, chemical exfoliation, traditional Chinese medicine therapy, laser and photon therapy, etc.

In the drug treatment of chloasma, the main drugs include Tranexamic Acid (TXA), hydroquinone cream, asiaticoside ointment, Huayu capsule, phenylalanine, acanthin extract and borosiloxane.

TXA is an antifibrinolytic drug, which mainly triggers the antifibrinolytic effect by blocking the lysine trigger point in the plasminogen molecule. This drug did not increase prothrombin activity and had no effect on coagulation parameters. The mode of administration is oral or intravenous injection. Studies have shown that TXA can inhibit the synthesis of melanin and has a good effect on the treatment of melasma^[2]. In view of this, TXA is a common drug for melasma in hospital hence it was included in this study. Hydroquinone cream is a white hydroquinone ointment with a cream type matrix and its main ingredient is hydroquinone. Its pharmacological action is to inhibit the metabolic process of melanocytes and produce a reversible skin fade effect, so it plays a role in the treatment of melasma. Studies have shown that the effect of hydroquinone cream alone is not good and the treatment effect is obvious when combined with TXA^[3]. Based on this, hydroquinone cream was used as one of the investigational drugs in this

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study. Asiaticoside is extracted from the umbrella-like plant *Centella asiatica*, which has the effect of clearing heat, detoxifying, swelling and dampness. Clinical studies have shown that asiaticoside can inhibit scar hyperplasia and repair skin damage^[4]. Its pharmacological mechanism is to inhibit the replication of scar fibroblasts, synthesis of collagen and plays a role in inhibiting scar hyperplasia. Asiaticoside is generally used as a complementary medicine for the treatment of melasma. It was used as a comparative study drug in this study.

MATERIALS AND METHODS

Research data:

The study data were collected from 230 patients with chloasma admitted to Fuyang Maternal and Child Health Hospital of Hangzhou from March 2019 to August 2022. Through the grouping method of odd and even outpatient numbers, the odd number was divided into the study group, and the even number was divided into the control group, with 115 patients in each group. Study group contains 26 males and 89 females with mean age (36.22 ± 2.46) y (range, 17 y-65 y). The disease duration was 1 y-11 y, with an average of (4.64 ± 1.32) y and Melasma Area and Severity Index (MASI) score was (2.35 ± 0.37). Control group contains 24 males and 91 females with mean age (36.62 ± 2.54) y (range, 18 y-66 y). The disease duration was 1 y-11 y, with an average of (4.56 ± 1.34) y and MASI score was 2.36 ± 0.38 . There was no significant difference in the data between the two groups ($p > 0.05$). All the enrolled patients were informed of the study and signed the informed consent.

Inclusion and exclusion criteria of study data:

Inclusion criteria: Meeting the inclusion criteria of Chinese Expert Consensus on the Treatment of melasma (2021 edition); no history of drug allergy and normal coagulation function.

Exclusion criteria: Hepatic and renal insufficiency, patients during pregnancy or lactation, allergic to TXA, hydroquinone cream, asiaticoside and patients who withdrew from the study.

Research methods:

All patients were given TXA compound injection by water light needle. Specific operation like using 40° warm water to clean the patients face, so that,

the face is completely exposed and then use the concentration of 0.5 % compound lidocaine to apply anesthesia and the anesthesia time is generally 40 min. After the anesthesia effect of patients was achieved, demineralized water and light injection instrument was used to inject drugs into the melasma area of patients and this process was strictly carried out in a sterile environment. Take 0.5 g TXA (TXA injection manufacturer: Yangzi Jiang Pharmaceutical Group Nanjing Haing Pharmaceutical Co., LTD., specification is 0.5 g, batch No. 20110411, Sinopuncture approval number: H20123004) dissolved in 10 ml normal saline and added with 0.6 g glutathione for injection (produced by Guangzhou Baiyunshan Mingxing Pharmaceutical Co., Ltd., Sinopuncture approval number: H20183335) and extracted with water optical needle and injected. After the injection, the patient area is iced with a medical mask for about 30 min. After the ice application, gel should also be applied. TXA should be injected once a month for a total of three times.

Patients in the study group were treated with hydroquinone cream once a day in the morning and evening (hydroquinone cream manufacturer: Guangdong Renkang Pharmaceutical Co., Ltd., specification 20 g: 0.4 g×1 pack/box, Chinese medicine approval number: H20040088). After application, it should be gently massaged for 5 min. Every Tuesday, Thursday and Saturday evening, ultrasound was used to introduce. Before the introduction, steam the face with a steam meter to open the facial pores, which is conducive to the better absorption of the hydroquinone cream. The introduction time is generally 20 min and the ultrasound is selected in the middle range. The whole course of treatment was 3 mo.

Patients in the control group were treated with asiaticoside ointment once a day in the morning, afternoon and evening (produced by Shanghai Modern Pharmaceutical Co., Ltd., 10 g: 0.25 g asiaticoside, Chinese medicine approved number: Z31020564). As in the study group, the patients received massage after application and ultrasound induction three times a week. The treatment cycle was 3 mo.

During the medication period, all patients were forbidden to drink alcohol, avoid eating spicy and irritating foods, and do a good job of sun and dust protection.

Observation indicators and judgment criteria:

The effective rates of the two groups were compared. According to the “Clinical Diagnosis and Efficacy Evaluation Criteria of melasma”, the therapeutic effect was divided into basic cure, marked effect, effective and ineffective, with effective rate=basic cure rate+marked efficiency. The standard of basic cure is that the area of the macroscopic stain is reduced by more than 90 % and the color is basically disappeared. The standard of obvious effect is that the area of the color spot visible to the naked eye is reduced by 60 % to 90 % and the color is obviously visible to the naked eye. The criterion for effectiveness was a 30 % to 60 % reduction in the area of pigmented spots visible to the naked eye and the color was lightened to the naked eye. The criterion for ineffectiveness was less than 30 % reduction in the area of the macroscopic stain and no significant change in the color of the macroscopic stain.

MASI scores before and after medications were compared between the two groups. The MASI score was used to evaluate the severity of melasma. According to the MASI scoring rule, the whole face is divided into four areas, the forehead, the right cheek, the left cheek and the lower jaw, which correspond to 30 %, 30 %, 30 % and 10 % of the face area, respectively. The severity of melasma was assessed using three variables-The extent of facial lesions (0 (no lesions) to 6 (90 % to 100 % lesions)), the depth of color (0 (no lesions) to 4 (blackest)) and the homogeneity of pigmentation (0 (lightest) to 4 (heaviest)). MASI total score is the sum of the above four regional scores.

Dermatology Life Quality Index (DLQI) scores before and after medication was compared between the two groups. The DLQI score sheet had 10 questions, mainly related to skin and life, study, work, dressing, social interaction and so on. DLQI scores of 2-5 were classified as mild, $6 \leq 10$ as moderate and $DLQI \geq 10$ as severe.

The recurrence rate after medication was compared between the two groups. All patients were followed up for 3 mo and the recurrence rate of the patients within 3 mo was recorded.

The adverse drug reactions during medication were compared between the two groups. During the medication, the adverse reactions of the two groups were recorded, including skin burning, rash, stomach discomfort, loss of appetite and skin itching.

Data processing methods:

Statistical Package for the Social Sciences (SPSS) 16.0 statistical software was used to process all data and t test was used to compare the two groups, $p < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

After treatment, the overall drug efficiency of the two groups was compared, it was more obvious. However, the total effective rate of the study group was 94.78 %, which was significantly higher than 80.87 % of the control group ($p < 0.05$) (Table 1).

Comparison of MASI scores between the two groups before and after treatment was shown in Table 2. Before treatment, there was no significant difference in MASI score between the two groups ($p > 0.05$). After treatment, the MASI scores were decreased in both groups, which indicated that both groups had some efficacy in the treatment of melasma. However, the MASI score of the study group was lower than that of the control group, indicating that the drug effect of the study group was better ($p < 0.05$) (Table 2).

Before treatment, there was no significant difference in DLQI score between the two groups ($p > 0.05$). After treatment, DLQI scores decreased substantially in both groups. This indicates that both groups of drugs have an effect on improving the quality of life of patients. However, the DLQI score of the study group was lower, indicating that the effect of medication in the study group on improving the quality of life of patients was more obvious ($p < 0.05$) (Table 3).

The recurrence rate is an important basis for judging the efficacy of drugs. In the process of skin cosmetic diagnosis and treatment, recurrence after drug withdrawal often occurs, this indicates that the effect of the drug is not durable and cannot fundamentally solve the disease. In this study, 1 case recurred in the study group and 6 cases recurred in the control group. This indicated that the relapse rate of the control group was higher ($p < 0.05$) (Table 4).

Comparison of adverse drug reactions between the two groups was shown in Table 5. During the treatment, there was 1 case of adverse drug reaction in the study group and 4 cases in the control group. The difference between the two groups was statistically significant ($p < 0.05$) (Table 5).

TABLE 1: DIFFERENT MEDICINES EFFECTIVE RATES ($\bar{x}\pm s$)

Group	n	Basic cure	Marked effect	Effective	Ineffective	Total effective rate
Research group	115	76 (66.09 %)	33 (28.69 %)	5 (4.35 %)	1 (0.87 %)	94.78 %
Control group	115	62 (53.91 %)	31 (26.96 %)	12 (10.43 %)	10 (8.69 %)	80.87 %
χ^2						5.46
p						<0.05

TABLE 2: COMPARISON OF MASI SCORES BETWEEN THE TWO GROUPS BEFORE AND AFTER TREATMENT ($\bar{x}\pm s$)

Group	n	MASI score	
		Before medication	After medication
Research group	115	5.27 \pm 1.26	1.56 \pm 0.28
Control group	115	5.18 \pm 1.28	2.12 \pm 0.38
t		0.18	6.29
p		>0.05	<0.05

TABLE 3: COMPARISON OF DLQI SCORES BETWEEN THE TWO GROUPS BEFORE AND AFTER TREATMENT ($\bar{x}\pm s$)

Group	n	DLQI score	
		Before medication	After medication
Research group	115	9.36 \pm 1.08	2.08 \pm 0.42
Control group	115	9.28 \pm 1.16	3.16 \pm 0.48
t		0.11	5.29
p		>0.05	<0.05

TABLE 4: COMPARISON OF RECURRENCE RATES BETWEEN THE TWO GROUPS AFTER TREATMENT ($\bar{x}\pm s$)

Group	n	Relapse	Rate of recurrence
Research group	115	1	0.87 %
Control group	115	6	5.22 %
t			9.72
p			<0.05

TABLE 5: COMPARISON OF ADVERSE DRUG REACTIONS BETWEEN THE TWO GROUPS ($\bar{x}\pm s$)

Group	n	Burning skin	Rash	Upset stomach	Loss of appetite	Itchy skin	Total occurrence probability
Research group	115	0	1	0	0	0	0.87 %
Control group	115	1	1	0	0	2	3.48 %
t							7.82
p							<0.05

Some scholars believe that the pharmacological mechanism of TXA in the treatment of chloasma is the cognition of chloasma dermal lesions^[5]. Plasmin plays an important role in the formation of new blood vessels. TXA is an anti-fibrinolytic drug, which can inhibit the formation of new blood vessels, thereby reducing the number of erythema and blood vessels. Facial mast cells are generally thought to correlate with variables of solar elastic fibers. Excessive Ultraviolet (UV) irradiation can increase the viability of facial mast cells, thereby increasing their number and tryptase. The presence of tryptase may be associated with the variables of basal cell fluid in melasma. The increment of mast cells can also produce vascular endothelial growth factor and promote the formation of neovascularization. The role of TXA in this process is to inhibit the number and activity of mast cells, thereby reducing the formation of melasma.

Some scholars also believe that the formation of chloasma is related to the obstruction of microcirculation in human tissue cells, cell lysis and black sludge^[6]. Once the superoxide dismutase in the human body is in an unstable state, the cell membrane in the human body will be oxidized, resulting in excessive toxic lipid peroxide production and a large amount of copper ions will be released. This process leads to accelerated pigment production and eventually pigmented spots. This study explains the pathogenesis of melasma. Experiments have found that the mechanism of chloasma is related to tyrosinase^[7]. TXA as a lysine synthetic derivative, its chemical structure is p-aminomethylcyclohexane carboxylic acid, which is similar to the chemical structure of tyrosine and contains carboxylic acid. Some studies have suggested that TXA can inhibit the synthesis of melanin by hindering the metabolic catalytic process of tyrosine by tyrosinase through competition with tyrosine^[8]. The effect of TXA is not directly against tyrosinase, but in the process of keratinocytes, it inhibits tyrosinase to catalyze Single-chain urokinase-type Plasminogen Activator (Sc-uPA) with enhanced effect, prevents the conversion of plasminogen to plasmin, blocks the conversion channel between melanocytes and keratinocytes, and reduces the conversion of melanin granules to keratinocytes and the formation of melanocytes. This process of inhibiting the expression of melanocytes has the effect of dilating the pigmentation.

The application of TXA is mainly divided into

oral, intravenous drip, water light needle injection, etc. Studies have shown that the onset time of intravenous drip therapy for melasma is faster than that of oral administration^[9]. Some studies have also shown that the effect of water light needle injection of TXA+glutathione compound drug is better than that of intravenous injection of TXA^[10]. In this study, water light needle injection therapy was used. From a clinical point of view, water light needle injection therapy directly targets the lesion area, which is safer and faster than oral injection through the gut and blood vessels.

Hydroquinone cream is one of the most common drugs for the treatment of melasma. 4 % hydroquinone is considered as the gold standard for the treatment of melasma. Hydroquinone can inhibit melanin evolved from tyrosine and further biosynthesis of melanin, thus reducing melanin deposition. Some studies have suggested that hydroquinone can inhibit the synthesis of Deoxyribonucleic Acid (DNA) and Ribonucleic Acid (RNA) in melanocytes, thus reducing the formation of melanin^[11]. In the process of tyrosinase, tyrosine is oxidized to Dihydroxyphenylalanine (DOPA) and dopamine, which are rearranged and then combined with proteins to form melanin. Tyrosinase has been identified as the only enzyme involved in melanin metabolism. The decolorization effect of hydroquinone cream is to inhibit the process of melanin synthesis, which prevents pigmentation and reduces the color of the pigment. Hydroquinone is a chemical in nature, but it can be extracted from many natural plants. Since its use in the 20th century, few adverse reactions have been reported. This would explain the low rate of adverse drug reactions in this study.

Asiaticoside is extracted from *Centella asiatica*. Through modern pharmacological analysis, the main components of *Centella asiatica* are triterpenoids, volatile oils, polyalkynes and flavonoids. Asiaticoside has the effect of inhibiting fibroblast replication and reducing the activity of tyrosinase. The therapeutic effect of asiaticoside on melasma is mainly due to its ability to reduce tyrosinase activity. Asiaticoside plays a role in skin repair by inhibiting the replication of scar fibroblasts and the synthesis of collagen. Its pharmacology may be related to the inhibition of hypertrophic scar formation by Suppressor of Mothers against Decapentaplegic (SMAD) protein family. Some scholars have shown that the main pharmacological effects of asiaticoside are anti-

proliferation of tumor cells, induction of tumor cell apoptosis, anti-inflammation, anti-Alzheimer's disease, anti-depression and blood glucose control^[12]. However, it has also been found to have a certain effect on skin repair in clinical practice. This explains the general performance of asiaticoside in this study. Asiaticoside can act on the nervous system, liver, kidneys, blood glucose and other aspects. The pharmacological effect of asiaticoside in combination with TXA is still unknown. In this study, there were 4 cases of adverse drug reactions in the asiaticoside control group, indicating that the safety of asiaticoside in the treatment of chloasma deserves further study.

In this study, water light needle injection of TXA compound drug, which is a new type of therapy, can accurately place, quantitatively and depth of the drug into the superficial and deeper layers in dermis of the lesion area, and the effect is more direct and rapid than traditional oral injection, intravenous injection, and microneedle injection. In this study, the hydroquinone cream was compared with asiaticoside, which confirmed that the hydroquinone cream group had better efficacy, higher safety and lower recurrence rate. In conclusion, TXA injection combined with hydroquinone cream is worth promoting in the treatment of chloasma.

Conflict of interests:

The authors declared no conflict of interest.

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