PIONEER
ACADEMIC PUBLISHING LIMITED

Current Research in Medical Sciences
ISSN 2958-0390
www.pioneerpublisher.com/crms
Volume 2 Number 1 March 2023

Clinical Efficacy of Spleen and Yin Prescription in the Treatment of Primary Sjogren Syndrome and Its Impact on Disease Activity

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doi:10.56397/CRMS.2023.03.02

Abstract

Objective: To study the clinical efficacy of primary Sjogren syndrome and the effect of disease activity. ***Methods:*** The 60 patients from January 2021 to January 2022 respectively, and divided into two groups according to random numbers, hydroxychloroquine sulfate, 30 patients, clinical effect combined with hydroxychloroquine sulfate, inflammatory index, complement levels, and immunoglobulins (ESR, RF, CRP, C3, C4, IgG, IgA, IgM), ESSDAI, ESSPRI, and adverse effects. ***Results:*** The total response rate of the two groups was 86.67% (26/30) and 73.33% (22/30), respectively, comparing with the treatment group (P <0.05). Comparison between groups found that no differences in CRP, C4, IgA, and IgM were significant (P>0.05). After treatment, peripheral ESR, RF, IgG decreased, complement C3 levels increased (P <0.05), the ESSDAI score and ESSPRI score of the two groups also decreased (P<0.05). On the Traditional Chinese medicine symptom integral, the treatment group had better results in improving dry mouth, dry throat, dry eyes, dry skin, five upset heat, and joint pain(P<0.05), and no adverse reactions were found in either group. ***Conclusion:*** The treatment group can effectively improve the clinical efficacy, reduce the level of inflammatory indicators and disease activity, and see no obvious adverse reactions, which can be effectively used in clinical practice.

Keywords: primary Sjogren's syndrome, Jian Pi Yang Yin Fang, hydroxychloroquine sulfate, disease activities

1. Introduction

Primary Sjogren's syndrome (pSS) is a chronic progressive autoimmune mediated disease, 1/3 patients can appear joints, lung, kidney, kidney, liver, spleen, peripheral nerve and vascular systemic damage, the most serious damage is the development of higher mortality of malignant Hodgkin's lymphoma, this damage often appear in the disease late (Boukadida K., 2019). The initial clinical manifestations of pSS are mucosal or non-specific dry symptoms, and it takes up to 8-10 years from the initial symptoms to the middle and late disease. Sjogren's syndrome can occur in all ages, including children, but it is more common in middle-aged women (female: male =16:1), with a

prevalence rate of 0.5% -1.0% (Zhang Q, Wang X, Chen H, et al., 2017). The prevalence of pSS in China is 0.29%~0.77% (Zhang Huan, Liu Chunhong & Wu Bin, 2020), and it is increasing year by year, with 30% of patients with autoimmune rheumatic diseases having secondary Sjogren's syndrome. The treatment of combined traditional Chinese and western medicine has gradually become the dominant choice, and pSS is included in the category of traditional Chinese medicine, and the treatment effect of TCM treatment is significant, which can avoid the deficiency of western medicine to a certain extent, and bring new opportunities for patients with Sjogren's syndrome. This study mainly studied the clinical efficacy, laboratory inflammation index, disease activity score and TCM syndrome score in the treatment of pSS.

2. Data and Methods

2.1 Basic Document

60 patients of pSS from January 2021 to January 2022 were selected and divided into two groups according to the study design, with 30 patients in the treatment group and 30 patients in the control group. Moreover, the gender of 60 patients with Sjogren's syndrome was female, and the mean age of the treatment group was (51.22 ± 13.20) years, and the mean duration was (5.02 ± 1.56) years; in the mean age of the control group, the value was (49.89 ± 11.09) years, and the mean duration of the disease was (5.41 ± 1.03) years.

2.2 Study Inclusion and Exclusion Criteria

(1) Inclusion criteria: meet the 2016 pSS international classification diagnostic criteria (Shiboski C H, Shiboski S C, Seror R, et al., 2017); meet the TCM spleen and Yin deficiency syndrome differentiation criteria; female patients aged from 18 to 65 years; be able to participate in the study.

(2) Exclusion criteria: patients with complicated severe systemic disease or recent severe infection or tuberculosis; patients with pathological confirmed tumor; patients who have participated in other clinical trials in a short period of time (within 3 months); patients allergic to Western medicine or Chinese medicine in this trial; Female patients during pregnancy or lactation; mental illness and no capacity for civil conduct; patients under 18 years old or over 65 years old; the investigator is not fit to participate in the clinical subject based on the safety assessment.

2.3 Method

Treatment group: the spleen nourishing Yin square Chinese medicine decoction combined with hydroxychloroquine sulfate; control group: hydroxychloroquine sulfate.

(1) Hydroxychloroquine sulfate (approval number: H19990263, manufacturer: Shanghai Shanghai Pharmaceutical Co., LTD.): 0.1g / tablet. Usage: 2 tablets / 1 time, 2 times / 1 day. Method: 0.2g / bid for 12 weeks.

(2) The basic components of spleen and Yin prescription: radix pseudostellariae, bighead atractylodes rhizome and rhizoma dioscoreae 15g each; poria cocos, radix glehniae, radix ophiopogonis, radices paeoniae alba,fresh dendrobium andsemen dolichoris 12g each; licorice 6g. (Decry, 1 dose/day, take twice). The treatment duration was 12 weeks, during which relevant indicator data were monitored before and after treatment.

2.4 Efficacy Evaluation and Criteria

(1) Clinical efficacy: According to relevant contents in (Zheng Xiaoyu, 2002) of Guiding Principles for Clinical Research of New Chinese Medicine.

(2) Traditional Chinese medicine syndrome points: According to the 2002 Guidelines for Clinical Research of New Chinese Medicine Drugs (Zheng Xiaoyu, 2002).

(3) Disease activity: Dry syndrome disease activity score, according to the ESSDAI score (Seror R, Ravaud P, Bowman S J, et al., 2010) rules developed in EUALAR 2009. Subjective score of patients with Sjogren's syndrome, according to the (Seror R, Theander E, Brun J G, et al., 2015) rules of ESSPRI score developed in EUALAR in 2015.

(4) IgG, IgA, IgM, C3, C4, and CRP were determined by immunoturbidimetry, and ESR was detected by the Wei assay.

(5) Glandular secretory function determination: including corneal fluorescence staining, tear film rupture time, salivary flow rate, specific determination method reference (Lim S A, Nam S, Kwok S K, et al., 2015).

(6) Adverse reactions, including abnormal laboratory indicators and patient self-sensory abnormalities, self-perception including nausea, vomiting, fatigue, loss of appetite, abdominal distension, diarrhea, etc.

2.5 Statistical Treatment

The data collected in this topic were summarized by Excel2016 software, and all statistical tests were two-sided, and the differences of the data tested for P <0.05 or P <0.01 were considered statistically significant. Mean and standard deviation are used for quantitative index; number and percentage of various cases are used for classification index. Paired t-test is used for within-group comparisons for quantitative indicators that meet the normal distribution, and independent t-test is used between groups; non-parametric tests are used between groups for quantitative indicators that do not meet the normal distribution. Within and between group rank indicators were compared with Wilcoxon rank sum test, statistical software version is SPSS23.0.

3. Result

3.1 Clinical Effects

The total clinical response rate of the two groups was 90.00% and 73.33%, respectively, which was higher in the treatment group compared with the control group (P <0.05). (Table 1)

Table 1. Comparison of clinical effects between treatment group and control grou

group	number	excellence	effective	ameliorate	invalid	total effective rate
treatment group	30	15(50.00%)	8(26.67%)	4(13.33%)	3(10.00%)	90.00%▼
control group	30	11(36.67%)	6(20/00%)	5(16.67%)	8(26.67%)	73.33%

Annotate: ▼<0.05

3.2 Laboratory Indicators

Comparing the two groups, immunoglobulin IgA, IgM levels, complement C4 expression and CRP levels (P> 0.05), within-group comparison found that both groups increased the peripheral complement C3 levels and decreased the IgG, RF, and ESR levels. The comparison between groups found that the increase of C3 in peripheral blood was higher than that of the control group (P <0.05), and the decrease of serum IgG, ESR and RF was more than that of the control group (P <0.05). (Table 2)

Table 2. Comparison of clinical laboratory indexes

	treatment group(n=30)		control group(n=30)	
index	pretherapy	post-treatment	pretherapy	post-treatment
IL-2(pg/ml)	9.86±1.39	30.57±5.27**▼▼	10.62±3.46	28.41±6.57**
IL-6(pg/ml)	21.10±3.29	11.54±3.01**▼▼	21.93±3.09	17.79±6.19**
ESR(mm/h)	58.58±14.23	19.13±8.04**▼	55.71±19.47	30.37±6.21**
RF(IU/ml)	37.33±10.45	18.90±2.69**▼	35.69±10.96	24.81±6.89**
CRP(mg/L)	9.47±4.80	8.86±1.96	10.09±3.48	8.09±1.18
IgG(g/L)	20.12±5.13	9.83±1.19**▼	18.33±5.79	13.90±7.84**
C3(mg/dL)	53.22±14.34	154.64±7.44**▼	53.14±13.29	96.28±25.08**

Annotate: Pretreatment comparison with the treatment group**<0.01,*<0.05;Pre-treatment comparison with the control group▼▼<0.01,▼<0.05

3.3 Adenal Secretion Function

Both groups can increase the rate of static salivary flow in the glands, increase the time of tear film rupture, and reduce the integration of corneal fluorescence staining (P<0.01or P<0.05); Comparison between the groups found no statistically significant differences in pretreatment tear film rupture time, static salivary flow rate and corneal fluorescence

staining integral between the two groups(P>0.05), after treatment, the treatment group was better than the control group(P<0.01). (Table 3)

Table 3. Comparison of oral and eye function tests before and after treatment in two groups of SS patients (`x ± s)

index	treatment group(n=30)		control group(n=30)	
	pretherapy	post-treatment	pretherapy	post-treatment
breakup time of tear film(S)	2.83±1.52	6.30±1.46**▼▼	2.57±0.98	6.06±1.89**
corneal fluorescence staining (integral)	6.63±1.31	3.68±0.93**▼▼	6.83±1.13	4.22±0.88**
static saliva flow rate(ml/10min)	0.57±0.07	1.98±0.43**▼▼	0.52±1.12	1.46±0.23**

Annotate: the same as above

3.4 Traditional Chinese Medicine Syndrome Points

Both groups were effective in improving the symptoms except for the tongue image, and the treatment group was better than the control group (P<0.05 or P<0.01), compared with the control group, the method was better in improving dry throat, dry eyes, dry skin, heat of five pains, and joint pain(P<0.05). (Table 4)

Table 4. Compared with TCM syndrome points in two groups of pretherapy and post-treatment of SS patients

index	treatment group(n=30)		control group(n=30)	
	pretherapy	post-treatment	pretherapy	post-treatment
Eyes dry (points)	6.83±1.92	2.47±1.16*▼	6.71±2.30	2.68±2.11*
Dry mouth and dry throat (points)	6.39±2.03	3.29±1.83**▼	6.22±2.46	3.48±2.11*
Xerosis cutis (points)	4.96±1.54	1.69±1.50*▼	4.88±1.82	2.85±1.44*
Exhaust (points)	4.36±1.38	1.41±1.32*	4.05±1.66	2.06±1.27*
dysphoria in chestpalms-soles (points)	4.32±1.48	1.33±1.07*▼	4.10±1.28	1.56±0.95*
Muscle wasting (points)	2.08±1.10	0.91±1.10*	1.96±1.10	1.13±0.97*
Joint pain (points)	3.32±1.95	1.62±1.26**▼	3.33±1.93	2.55±1.82*
Dry stool knot (points)	3.67±1.55	1.74±1.42*	3.60±1.37	2.14±1.26*
Dry cough (points)	1.62±1.01	0.74±0.95*	1.57±1.11	1.01±1.10*
Tongue picture (points)	4.36±1.38	2.32±1.85	5.39±2.15	3.20±2.05

Annotate: the same as above

3.5 Disease Activity Score

The intra-group comparison indicated that ESSPRI and ESSDAI integration between the two groups before treatment(P>0.05); after

treatment, SS patients decreased in both groups (P<0.01); The results of post-treatment group comparison showed that the treatment group was better than the control group in reducing ESSPRI and ESSDAI points(P<0.05). (Table 5)

Table 5. ESSDAI and ESSPRI integral comparisons

index	treatment group(n=30)		control group(n=30)	
	pretherapy	post-treatment	pretherapy	post-treatment
ESSPRI	4.38±0.98	1.56±1.10$^{**▼}$	4.54±1.40	2.60±1.03**
ESSDAI	4.37±1.40	1.15±0.42$^{**▼}$	4.58±2.13	2.34±0.93**

Annotate: the same as above

4. Discuss

Primary Sjogren's syndrome (pSS) is an autoimmune disease affected by genetic, immune, environmental and other factors. The clinical manifestations are that dry mouth and dry eyes first appear due to the reduction of gland secretion. If not controlled, the progression of the disease can cause the damage of the systemic system. In this study, pSS patients of spleen Yin deficiency, the treatment is "spleen and Yin" addition and decrease, by observing the changes in clinically relevant laboratory indicators, disease activity scores, and TCM syndrome points, the role of TCM is discussed from the theoretical mechanism.

The spleen and nourishing Yin square is composed of radix pseudostellariae, bighead atractylodes rhizome, rhizoma dioscoreae, poria cocos, radix glehniae, radix ophiopogonis, radices paeoniae alba, fresh dendrobium, semen dolichoris and licorice. Previous study (Fu Peng, 2021) also found that the treatment group with spleen and Yin nourishing side could improve the serum complement C3 of SS patients, reduce ESR, RF, and IgG levels, and reduce disease activity. The mechanism of the treatment of SS with spleen and Yin prescription may be to upregulate the level of IL-10 and IL-4 cytokines, and downregulate the expression of TNF-α and IL-6, indirectly regulate the imbalance of proinflammatory and antiinflammatory immunity in SS patients, suppress the production of gland inflammation, relieve clinical symptoms such as dryness, joint pain and other (Xiao Ruzhi, 2020); Or to upregulate the cytokine IL-10 expression, downregulate the serum BAFF/BLys and cytokine IL-21 levels, and balance the cytokine network level (Fu Peng, 2021).

Among them, radix pseudostellariae, strengthens the spleen, bighead atractylodes rhizome and rhizoma dioscoreae, takes into account the vitality of qi and nourishes the lungs, playing a leading role in traditional Chinese medicine; radix glehniae, radix ophiopogonisand fresh dendrobium, plays an important role in traditional Chinese medicine to clearing heat and produce fluid, to achieve the purpose of nourishing every dry organ; semen dolichoris, poria cocos and paeoniae radix alba, its help other drugs work, while balancing drug interactions; licorice, mainly to reconcile the performance of all drugs, to achieve the cure does not hurt and healthy qi. The whole party played the qi of the viscera, nourishing the spleen, nourishing the body fluid, while taking into account the main symptom, taking into account the pSS patients Yin deficiency is easy to produce dry heat, this side in the treatment of the original at the same time and treat the symptoms, is more flexible in its clinical application. This study found that the treatment group with the spleen-nourishing side had more ESSDAI scores and ESSPRI scores in reducing disease activity in pSS patients than in the control group(P<0.05), it was also found that the expression levels of clinical laboratory indicators IgG, ESR and RF were downregulated, and the regulation of complement C3 was better than that of the control group (P<0.01 or P<0.05), the total clinical response rate was higher in the treatment group (P<0.05). This study also further shows that the combination of traditional Chinese and western medicine for pSS is expected to become a new target. Our future research group will push forward to animal experiments, cell molecules and genes to further seek theoretical support.

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