Original Article

Long-term hydroxychloroquine therapy improves the quality of sleep in patients with primary Sjögren's syndrome: a real-world study

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Background: Patients with primary Sjögren's syndrome (pSS) often suffer from sleep disturbance. Studies suggest it may be related to symptoms, including xerostomia and dry eyes. Clinical studies have confirmed that hydroxychloroquine (HCQ) has a definite effect on pSS, but there is no clear report about its effect on sleep disorders in pSS patients.

Methods: A total of 383 pSS patients were enrolled and followed up. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the sleep quality of the patients, and the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) scale was used to evaluate the quality of life (QoL) of patients. The European League assessed the patient's condition against Rheumatism Sjögren's syndrome patients reported index (ESSPRI). According to PSQI, patients were divided into two groups: good sleep group (GSG) and poor sleep group (PSG). The risk factors of sleep disorder are analyzed by univariate and multivariate analysis. The patients were further divided into HCQ-administered group and non-administered group, and the differences of baseline characteristics and outcome in follow-up between the two groups were compared.

Results: There were 208 patients with PSG (54.3%) and 175 patients with GSG (45.7%). Further, there is no statistical difference between the two groups in baseline data. Also, there were 112 cases (53.8%) and 118 cases (67.4%) taking HCQ in the two groups, respectively, P=0.007. Univariate and multivariate analysis showed that long-term use of HCQ, menopause, and income were related to sleep quality. The patients were divided into the HCQ-administered group (n=230) and non-administered group (n=153) according to whether they took HCQ. One hundred eighteen patients (51.3%) in the HCQ-administered group had a good sleep, and 58 patients in the non- administered group had a good sleep (37.9%), P<0.05. At follow-up, the PSQI of the two groups were 7.3±2.1 *vs.* 8.1±2.4, respectively, P<0.05 and the ESSPRI were 4.9±1.1 *vs.* 5.4±1.3, P<0.05. The QoL of the two groups of patients was statistically different in all four dimensions, P<0.05.

Conclusions: Long-term use of HCQ can reduce the risk of sleep disturbance in patients with primary Sjögren's syndrome.

Keywords: Hydroxychloroquine (HCQ); primary Sjögren's syndrome (pSS); sleep disturbance

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Introduction

Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease that affects the exocrine glands. Its key features are dry mouth, dry eyes, and other multi-system damage including fatigue, fever, vasculitis, joint pain and kidney injury. The global prevalence rate is about 0.04% to 4.8%, the prevalence in China is 0.29% to 0.77% (1,2). Progress in treating pSS includes biological agents, combination of steroids immunosuppressive agents (1,2). The disease affects middle-aged women aged 40 to 50 years old. In addition to reducing the secretion of exocrine glands, the disease can also cause symptoms, including weakness and pain. These discomforts will eventually lead to a decrease in the quality of life (QoL) of the patient, especially the deterioration of sleep quality, mainly manifested as nighttime sleep disturbance and excessive daytime sleep, and a higher prevalence of obstructive sleep apnea syndrome. Clinical studies have found that sleep disorders are more common in patients with pSS (3,4). The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate patients' sleep quality in a study, and the researchers found that among Chinese pSS patients, 57.5% of patients have sleep disorders (4). Modern medicine believes that sleep is closely related to many diseases, such as coronary heart disease, hypertension and stroke, and also affects mental and psychological health, including increasing the risk of anxiety, depression, and dementia (5,6). However, it is still unclear what the main mechanism of pSS associated sleep disorders are, which may be related to dry mouth, dry eyes, and weakness. The current research focuses on the influencing factors of sleep disorders in patients with pSS. And there are few studies focused on the effect of different treatments on the sleep quality of these patients.

The main evaluation parameters of most intervention studies look at the function of exocrine glands, and disease activity indexes, including the European League Against Rheumatism Sjögren's Syndrome Patients Reported Index (ESSPRI). There was no comparison of sleep quality before and after treatment or during follow-up. Hydroxychloroquine (HCQ) has been widely used in rheumatic diseases. Some pSS patients are also receiving HCQ treatment. Studies have shown HCQ can significantly alleviate the symptoms of dry mouth, dry eyes, and joint pain in pSS patients and can also reduce circulating inflammatory factors. Simultaneously, it has excellent safety (7). Whether the patient's condition improves can also improve sleep quality is still lacking related research. In this study, we evaluated the sleep quality of patients through follow-up and retrospectively analyzed the effects of different treatment methods on patients' sleep quality.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1380).

Methods

The research subjects included pSS patients who were treated in our hospital from January 2015 to December 2019. According to the inclusion and exclusion criteria, a total of 383 patients were enrolled in the final analysis. Among these patients, 208 patients had poor sleep (poor sleep group, PSG) and 175 patients had good sleep quality (good sleep group, GSG). Inclusion criteria: (I) ≥18 years old; (II) the diagnosis of pSS is confirmed according to China's Sjögren's Syndrome Diagnosis and Treatment Guidelines (2) and the American Rheumatology Society's diagnostic criteria (8); (III) receiving anti-pSS treatment when enrolled. Exclusion criteria: (I) diagnosed with malignant tumor; (II) complicated with severe heart failure; (III) complicated with other diagnosed systemic autoimmune diseases; (IV) complicated with other diseases that affect sleep; (V) subjects who have been diagnosed with mental and mental illness before a diagnosis of pSS; (VI) long-term history of alcoholism; (VII) those who cannot complete the questionnaire survey. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Guangzhou Chest Hospital. and informed consent was taken from all the patients.

Data collection

Enrolled patients were followed up and evaluated. Patients' clinical information was collected from hospital records and clinic records. The main parameters include age, gender, marital status, education level, employment status, income level, life habits, underlying diseases, and medication. Sleep quality assessment: the PSQI Scale is used to assess the sleep quality of patients in the past month. Each part is scored on a scale of 0–3, with a total score of 21 points. The scale was revised in 1996 by experts, including Liu Xianchen and other experts (9), and the PSQI score >7 was used as the cut-off value for dividing good and poor sleep quality. Both

reliability and validity are high, which is suitable for the Chinese population. This study also uses the score >7 points that are judged as sleep disorders. QoL assessment: The World Health Organization Quality of Life Brief Version (WHOQOL-BREF) was used for QoL assessment. The form was simplified by WHOQOL-100 and contained 26 questions in four areas. Evaluation of Sjögren's Syndrome: The European League Against Rheumatism Sjögren's Syndrome Patients Reported Index (ESSPRI) was used for evaluation.

Grouping of patients

According to the results of PSQI assessment, patients were divided into good sleep group (GSG) and poor sleep group (PSG). Univariate and multivariate analysis is used to find factors related to sleep disorders. According to whether the patients take HCQ, they are further divided into the HCQ-administered group, and non-administered group and the prognosis and sleep quality of the two groups is compared.

Statistical analysis

SPSS17.0 software was used for statistical processing. Quantitative data were evaluated for normal homogeneity. Data that conformed to the normal distribution were expressed as mean ± standard deviation, and the student *t*-test was used for comparison between groups; medians were used for non-compliant distribution, and the rank-sum test was used for comparison between groups. Qualitative data are expressed in numerical values and percentages, and comparison between groups is performed using the X^2 test or Fisher's exact test. Logistic univariate and multivariate analysis were used to find factors related to sleep disorders in pSS patients. P<0.05 was considered statistically significant.

Results

Baseline data

From January 1, 2015, to December 31, 2019, 517 patients with pSS were treated in our hospital. According to the inclusion and exclusion criteria, a total of 383 patients were enrolled in the final analysis. The patients ranged in age from 27 to 71 years old, with an average of 47.6±12.8 years old and a disease course of 5.1±2.7 years. There were 23 males (6.0%) and 360 females (94.0%). A total of 208 (54.3%) patients had PSQI ≥7 points (that is, sleep disorders), and a total of 175 (45.7%) patients with PSQI <7 points (good sleep quality). The baseline data of patients are shown in *Table 1*. There are statistical differences between the two groups in marital status, menopause, education, income, and long-term use of HCQ. Among all patients, 230 patients (60.1%) took HCQ for a long time, and 153 patients (39.9%) did not take HCQ. In this group of patients, the dosage of HCQ is 200–400 mg/day. HCQ treatment duration is from 4 months to 41 months, and the total dose is 24.8 to 371.4 g.

Factors related to sleep quality in patients with pSS

Univariate analysis showed that divorce, menopause, low income, low education, and long-term use of HCQ and ESSPRI all have a specific relationship with pSS patients' sleep quality. Further multivariate analysis showed that menopause, low income, long-term use of HCQ, and ESSPRI were associated with sleep quality in patients with pSS. See *Table 2* for details.

The effect of long-term HCQ treatment on the pSS condition and QoL of patients

We conducted a pSS condition assessment on all patients and found the ESSPRI of patients taking HCQ was significantly lower than those who did not (P<0.05). See *Table 3* for details. The QoL assessment analysis showed that the QoL of the patients in the long-term HCQ-administrated group was higher than that in the non-administrated group. The specific performance is that the patients in the long-term HCQ-administrated group have better scores in the physiological, psychological, social relationship, and environmental fields than the non-administrated group. Further analysis found that the QoL of patients with sleep quality disorders was lower than patients without sleep disorders.

Discussion

In this study, we conducted a survey and analysis of pSS patients in the real world and found that compared with patients who did not take HCQ in the past three months, patients who took HCQ for a long time not only significantly improved the condition index ESSPRI of pSS but also decrease their sleep quality index PSQI. The WHOQOL-100 score of QoL in patients with long-term

Table 1 Baseline characteristics between poor sleep group and good sleep group.

Items	General (n=383)	PSG (n=208)	GSG (n=175)	P value
Age (yrs)	47.6±12.8	47.3±12.9	48.1±13.2	<0.05
Female (n, %)	360 (94.0)	193 (92.8)	167 (95.4)	>0.05
Marriage				>0.05
Yes	348 (90.9)	186 (89.4)	162 (92.6)	
No	35 (9.1)	22 (10.4)	13 (7.4)	
Divorce	59 (15.4)	46 (22.1)	13 (7.4)	<0.05
Lost	21 (5.5)	10 (4.8)	11 (6.3)	>0.05
Education				<0.05
≤High school	188 (49.1)	134 (64.4)	54 (30.9)	
College	167 (43.6)	61 (29.3)	106 (60.6)	
Postgraduate	28 (7.3)	13 (6.3)	15 (8.6)	
Income (yuan, monthly)				<0.05
<5,000	173 (41.2)	112 (53.5)	61 (34.9)	
5,000–10,000	139 (36.3)	71 (34.1)	68 (38.9)	
>10,000	71 (18.5)	25 (12.0)	46 (26.3)	
Smoke	21 (5.5)	11 (5.3)	10 (5.7)	>0.05
Alcohol	47 (12.3)	27 (13.0)	20 (11.4)	>0.05
Menopause	83 (23.1)	57 (29.8)	26 (15.4)	<0.05
ALT (U/L)	24.8±7.9	24.5±8.4	25.2±8.7	>0.05
Cr (μmol/L)	71.6±17.5	70.2±18.1	73.3±19.7	>0.05
Long term HCQ	230 (60.1)	112 (53.8)	118 (67.4)	<0.05

PSG, poor sleep group; GSG, good sleep group; HCQ, hydroxychloroquine; ESSPRI, European League Against Rheumatism Sjögren's syndrome patients reported index.

Table 2 Univariate and multivariate analysis of factors related to sleep disorders in patients with primary Sjögren's syndrome

Items	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Menopause	1.368 (1.073–1.729)	0.015	1.411 (1.108–1.835)	0.012
Low income	1.107 (0.922–1.406)	0.194	1.173 (0.946–1.630)	0.188
Long term HCQ	0.626 (0.413–0.861)	0.017	0.644 (0.439–0.885)	0.036
Low education	1.325 (1.061–1.733)	0.010	1.387 (1.108–1.822)	0.024
ESSPRI	1.659 (1.125–2.016)	0.024	1.528 (1.132–1.908)	0.035
Divorce	1.373 (1.101–1.712)	0.009	1.435 (1.116–1.829)	0.015

HCQ, hydroxychloroquine; ESSPRI, European League Against Rheumatism Sjögren's syndrome patients reported index.

Table 3 Influence of long-term HCQ therapy on quality of life in patients with pSS

Domains	HCQ (n=230)	Non-HCQ (n=153)	P value
Physical health	64.3±12.7	56.9±12.1	<0.05
Psychological health	61.1±11.8	53.6±11.2	<0.05
Social relationships	54.4±11.7	45.5±10.8	<0.05
Environmental health	57.5±11.4	51.8±10.6	<0.05
ESSPRI	4.9±1.1	5.4±1.3	<0.05
PSQI	7.3±2.1	8.1±2.4	<0.05
PSG	112 (48.7)	96 (62.7)	<0.05
GSG	118 (51.3)	58 (37.9)	

HCQ, hydroxychloroquine; pSS, primary Sjögren's syndrome; ESSPRI, European League Against Rheumatism Sjögren's syndrome patients reported index; PSQI, Pittsburgh Sleep Quality Index; PSG, poor sleep group; GSG, good sleep group.

HCQ therapy was significantly higher than that in patients without HCQ therapy in the past three months. With this result, we believe that long-term use of HCQ cannot only improve the pSS condition, but also significantly improve the sleep quality of pSS patients, and may lead to an improvement in the QoL. According to the literature search, this is the first real-world study on the sleep quality of pSS patients taking long-term HCQ.

In addition to involving the secretion of salivary glands and lacrimal glands, pSS also has some extra-glandular manifestations, including weakness, pain, depression, etc. (10). Decreased sleep quality is a widespread problem in patients with pSS. The main reason is that pSS affects exocrine glands, including salivary glands and lacrimal glands, to cause dry mouth and dry eyes. It also affects joint muscles and causes pain in the motor system. It is also a secondary cause of psychological problems caused by diseases (3,11). If the condition of pSS is controlled and the secretory function of the exocrine glands is improved, the quality of sleep will often be improved (12,13) in some patients. When the severity of the patient's condition is different, and the organs and tissues involved are different, there are often different treatment options, including simple symptomatic treatment, immunosuppressive treatment and device-assisted treatment, which can be selected according to the specific situation of the patient (14). However, is there any difference that exists between different medications to improve sleep quality? There has been no explicit study to discuss this issue. Secondly, besides, to improve the control of pSS, is there any other possibility to improve sleep? Also, because there are many reasons for the decline in sleep quality, some symptomatic methods may improve sleep. For example, Cognitive Behavioral Therapy for Insomnia (CBT-I) is aimed at patients with underlying diseases, especially some patients with long-term chronic pain or other discomfort (15,16). Symptomatic relief from dry mouth and dry eyes may also help improve sleep quality, but this method may be more limited to mild patients, and for those with more severe dry mouth and dry eye symptoms, it may not be effective (17,18) as usual. For patients with limb pain, proper administration of analgesic drugs can effectively relieve pain, especially the reduction of pain at night, which is conducive to sleep improvement (19,20). When the patient develops nocturnal obstructive apnea syndrome, continuous positive airway pressure may improve the patient's breathing, thereby improving sleep quality and QoL (21). In terms of systemic treatment, currently mainly used drugs include glucocorticoids, immunosuppressants and bio-targeted drugs, but the impact of these drugs on the sleep quality of pSS patients is currently unclear. HCQ is an established drug widely used in rheumatic diseases in recent years. Several studies have supported HCQ in systemic lupus erythematosus (22), systemic vasculitis (23) and rheumatoid arthritis (24), and other diseases, and there are still some studies suggesting that HCQ is relatively safe for long-term use, especially at a lower dosage (25,26). However, many studies have found that HCQ has certain retinal toxicity (27) and cardiotoxicity (28). During HCQ therapy, these toxicities should be closely monitored. When cardiotoxicity occurs, it can recover by itself after stopping the drug in time (29). There are few reports on the effects of long-term use of HCQ on sleep. Earlier, Manzo *et al.* reported an elderly female patient who experienced psychomotor agitation after taking HCQ. The authors analyzed that HCQ can cause irritability, nervousness, emotional changes and nightmares (30). Once the patient occurs, spiritual agitation and sleep disturbances can hurt family members living together, and further reduce the QoL through various mechanisms (31). However, there is no relationship between this phenomenon and the sleep of such patients. Since there are few confirmed cases, there is no relevant research.

The results of this study show that compared with patients who do not use HCQ, the risk of sleep disturbance in patients who take HCQ for a long time is significantly

reduced. The average sleep quality of patients with long-term HCQ therapy is better than those who do not take it, and this effect is independent of the improvement of the disease condition. However, few studies focus on the relationship between HCQ and sleep quality. It is inconsistent with the earlier research results (30,32). As for a reason, there are few cases of mental side effects of HCQ that are reported until now. The relationship between this side effect and sleep is currently unclear. Our research shows that the pSS condition of this group of patients is effectively controlled, and the symptoms of dry mouth and dry eyes are significantly alleviated. During the follow-up, no patients showed typical agitation and various levels of mental excitement. Through a literature search, only 4 cases of HCQ related to psychiatric symptoms have been reported in China. Foreign scholars have integrated relevant literature and believe that the main risk factors for mental changes in patients taking HCQ include drug interactions, alcohol consumption during medication, family history of mental illness, women, and concurrent use of low-dose glucocorticoids (32). When psychiatric symptoms occur, symptomatic treatment or withdrawal of HCQ can effectively reverse this side effect.

In this study, the long-term daily dose of HCQ was 200–400 mg/d. The duration of HCQ therapy was 4 to 41 months; the total dose was 24.8–371.4 g, which was low. During the period of medication, these patients used fewer types of drugs, with an average of 2–3 types. No obvious drug interaction was found, and only a few patients had drunk a small amount of alcohol during the period of HCQ therapy. There was no clear family history of mental illness. Some patients were taking small doses of prednisone together, so no clear mental changes were found in this group of patients. Therefore, the possibility of sleep quality decrease due to mental changes was slight in this study. According to results from previous studies and our research, HCQ caused mental changes only in specific individual patients and did not affect most of the patient's sleep quality. Secondly, the selective use of HCQ can significantly reduce the incidence of mental disorders.

Concurrently, no new onset eye diseases or diagnosed retinopathy were reported in all patients. The 2008 American College of Rheumatology recommended that when the total dose of HCQ exceeds 1,000 g, the risk of retinal toxicity increases significantly (33). Most of the high-risk factors of retinal toxicity have been excluded from the prescription of HCQ in this group of patients, including severe liver and kidney disease, advanced age, existing retinal or macular degeneration, cataracts, and significant obesity. However, with the prolonged use of drugs and the increase of cumulative doses, the risk of retinal toxicity of patients also increases. Therefore, it is necessary to conduct regular retinal examinations for patients who receive long-term and high dosage HCQ therapy. In terms of cardiotoxicity, there are no clearly diagnosed cases in this group of patients. Individual patients with reduced cardiac function have basic coronary heart disease, and HCQ has not aggravated related symptoms.

Limitations of this study: this study did not further evaluate the psychiatric scale of patients with sleep disorders. Only some patients were treated symptomatically. Although it is indirectly proved that long-term use of HCQ can improve the sleep quality of pSS patients, the study is not in-depth enough, failing to analyze the specific mechanism of HCQ to improve the sleep of patients with pSS. And, because this is a retrospective study, we didn't collet blood sample at baseline for related cytokines test. Future research can be targeted for relevant examinations, including sleep polysomnography, psychiatric scale evaluation, some cytokines and can also assess the effects of related drugs on sleep-related factors, including whether HCQ affects depression in pSS patients.

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Footnote

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in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Guangzhou Chest Hospital and informed consent was taken from all the patients.

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