Efficacy and Safety of Qinggan Jieyu Herbal Formula Granule on Insomnia: A Prospective Randomized Controlled Trial

Fang Han (✉ hftcmdoctor@mail.ccmu.edu.cn)

Beijing Hospital of Traditional Chinese Medicine

Luda Feng

Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital

Kegang Cao

Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital

Huanqin Li

Beijing Hospital of Traditional Chinese Medicine

Ying Gao

Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital

---

Abstract

Background:

Traditional Chinese Medicine (TCM) is widely used in China for insomnia treatment. The objective of this study was to evaluate the efficacy and safety of QingganJieyu (QGJY)Herbal Formula Granule for insomnia patients with liver depression of heat syndrome.

Methods:

In this randomized controlled clinical trial, 60patients were randomly assigned into the treatment group and the control group in a 1:1 ratio. Participants received QGJYHerbal Formula GranuleandWuling capsulerespectively for 4 weeksand were followed for another 4 weeks. The primary outcomes weresyndrome integral changes according to theliver depression of heat syndrome evaluation scaleand global and subscale score changes according to the Pittsburgh Sleep Quality Index (PSQI). The secondary outcome wasquality of life assessed by the Short-form 36 Questionnaire (SF-36). A correlation analysis was also done between syndrome integral and PSQI global score and subscale score.

Results:

Compared with pretreatment baseline, patients in both groups showed a decreasedtrend in TCM syndrome integral scores, especially for the main syndrome.There were significant differences in the total score of syndrome integral between the two groups at 2, 3, 4 weeks, and follow-up period (all Ps<0.05)).During the treatment period, patients in both groups experienced a lower trend and the differences in PSQI global score, sleep disturbance, sleep duration, and use of sleep medication between the two groups were statistically significant (all Ps<0.05).Concerning secondary outcome measure, quality of life was improved for patients in both groups and mental health on the SF-36 questionnaire improvement was significantly better for the treatment group (P<0.05). Additionally, a significant, positive correlation was found between sleep disorders and TCM syndrome integral change (Pearson r = 0.340, P < 0.001).

Conclusions:

Results of our study suggested that QGJY Herbal Formula Granule not only improved the liver depression of heat syndrome(syndrome) but also sleep disturbance, sleep duration, and use of sleep medication(disease). Additionally, QGJY Herbal Formula Granule promotes psychological health better. Considering therelationship between insomnia and adverse mental health, our findings may have important implications for the management of insomnia in the long run.

Trial registration:

ChiCTR, ChiCTR-TRC-14004469, Registered 24 January 2014- Retrospectively registered, http://www.chictr.org.cn/showproj.aspx?proj=5101.

1. Background

Insomnia, characterized by difficulty initiating sleep, maintaining sleep, repeatedly early-morning awakening, and daytime dysfunction, is the most common type of sleep disorder[1]. It is associated with diurnal symptoms such as fatigue, sleepiness, concentration problems, mood disturbance, and impaired social or occupational performance. As many as 50% of older adults complain about difficulty initiating or maintaining sleep[2]. Insomnia has brought great burden individually and socially, thus becoming a more and more prevalent public health concern. For individuals, insomnia was associated with many adverse health outcomes such as the increased risk for depression[3], cardiovascular disease[4], Alzheimer's disease[5, 6], diabetes mellitus[7], et al. Insomnia was also an independent risk factor of suicidality and mortality[8–10]. On the other hand, insomnia imposes substantial economic burdens on society. It was estimated that the aggregate total of direct and indirect insomnia healthcare costs could be as high as 100 billion dollars per year[11]. Compared to people with no insomnia, the mean total healthcare costs for those moderate and severe insomnia populations were 75% higher[12]. The goal of insomnia treatment is to improve sleep quality and/or quantity and reduce distress dysfunction[13]. According to the American Academy of Sleep Medicine Clinical Practice Guideline, cognitive-behavioral therapies for insomnia (CBT-I) and pharmacotherapy are two major approaches to insomnia treatment, and CBT-I was identified as the recommended first-line treatment [14, 15]. Whilst there are favorable benefits for CBT-I, not all insomniacs can derive benefits from this treatment because of unaccessible, high costs, unwillingness, or non-responsiveness in the real world[16, 17]. Current pharmacologic options for insomniacs include benzodiazepine receptor agonists, melatonin receptor agonists, dual orexin receptor antagonists, sedating antidepressants, and sedating antihistamines[18]. Considering the potential undesirable adverse effects such as dizziness, addiction, memory impairment, decreased motor skills, withdrawal reaction, lethargy, hangover, and tolerance[19–21], a considerable number of insomniacs were dissatisfied with long-term use of hypnotics[22].

In recent years, TCM has gained growing interest and wide acceptance which promotes its internationalization greatly[23]. Chinese medicinal herbs and formulas have been extensively utilized in the treatment of insomnia for more than 2000 years with the advantages of economic, high efficacy, easy access, and good population basis[24]. Previous studies have found that when used as a monotherapy or an adjunct to conventional therapies, Chinese herbal medicine has shown significant improvements in different aspects of sleep in insomniacs [25–27].Based on clinical symptoms and signs collected through inspection, auscultation, olfaction, interrogation, and pulse palpation, TCM syndromes were finally determined on which the clinicians based to choose suitable treatments. According to the theory of TCM, the liver is responsible for blood storage and catharsis. If the storage function is damaged, the catharsis would become dysfunctional, resulting in stagnation of liver-Qi and the subsequent liver-heat syndrome[28]. In the present study, we assessed the efficacy and safety of QGJY Herbal Formula Granule for patients with liver depression of heat syndrome.

2. Methods

2.1 study design

This current study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guideline for randomized controlled trials. It was a randomized, 2-arm, parallel, assessor-masked, positive controlled clinical trial conducted in a single center in Beijing. The study protocol was approved by the Research Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (The approved No. of the ethic committee was ECPJ-BDY-2013-28), conducted per the principle of the Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki [29].

2.2 Participants

2.2.1 Inclusion criteria

Participants were eligible for this study if they were aged between 18–65 years, of either sex, were diagnosed as non-organic insomnia according to the Diagnostic and Statistical Manual of mental disorders (4th edition) (DSM-4)[30], to be considered with liver depression of heat syndrome according to liver depression of heat syndrome diagnosis scale, and signed the written informed consents.

2.2.2 Exclusion criteria

Participants will be excluded if they met any of the following criteria: (1) were combined with another obvious syndrome, (2) were using other interventions for insomnia, (3) suffered from primary diseases of cardiovascular, liver, brain, kidney, and hematopoietic system, and psychiatric system, (4) were pregnant or during lactation, (5) were allergic to any of the ingredient of the QGJY Herbal Formula Granule, (6) had participated other clinical studies in last 3 months.

2.2.3 Diagnosis of insomnia

Diagnostic criteria for non-organic insomnia refer to the DSM-4[30]. The chief complaint is either difficulty falling asleep, difficulty maintaining sleep, or poor sleep quality. Such a sleep disorder occurs at least three times a week and lasts for more than a month. Patients are always obsessively worried about the consequences of insomnia day and night, such that dissatisfaction with the amount and/or quality of sleep causes significant distress or affects social and occupational functioning.

2.2.4 Diagnosis of liver depression of heat syndrome

The diagnosis of liver depression of heat syndrome was made according to the liver depression of heat syndrome diagnosis scale[31]. It was formed by 8 items including the dysphoric mood, bitter taste, distending pain in the hypochondrium, dry eyes, poor sleep, red tongue, yellow tongue coating, and stringy pulse. The threshold to make a diagnosis of liver depression of heat syndrome is 30. The sensitivity of the scale is 93.91%, the specificity is 92.94%, the accuracy rate is 93.50%, and the positive likelihood ratio is 13.30, and the negative likelihood ratio is 0.065.

2.3 Randomization and allocation

The Clinical Evaluation Center of Dongzhimen Hospital of Beijing University of Chinese Medicine was responsible for the design of the randomization scheme. The randomization sequence was generated by an independent investigator, ensuring that allocation wouldn't be influenced by the research team. Participants were recruited through advertising via hospital notice boards. After screening, sixty eligible participants were randomly allocated to the treatment group or control group with an allocation ratio of 1:1. Randomization numbers were sealed in opaque envelopes, with patients' sequence numbers printed outside. All envelopes were numbered consecutively.

2.4 Intervention

Participants in the treatment group will receive 7 dosages of QGJY Herbal Formula Granule (orally, twice daily) for 4 weeks per study protocol. It was composed of seven kinds of Chinese herbal medicines (Table 1) and was manufactured and supplied by Kangrentang Pharmaceutical Co. Ltd., Beijing, China. Participants in the control group will receive Wuling Capsule (orally, three times a day) for 4 weeks and it was manufactured by Zhejiang Zuoli Pharmaceutical Co. Ltd., Zhejiang, China. After the 4-week treatment, all participants will enter an additional 4-week follow-up period.

Table 1
Information of components of QGJY Herbal Formula Granule

Chinese pinyin name	Chinese name	English name	Latin name	Amount(g)
Chaihu	柴胡	Chinese Thorowax Root	Radix Bupleuri	9g
Huanglian	黄连	Golden Thread	Rhizoma Coptidis	6g
Qingbanxia	清半夏	Prepared Rhizoma Pinelliae	Rhizoma Pinelliae Concisum	9g
Dannanxing	胆南星	Bile Arisaema	Arisaema Cum Bile	6g
Yujin	郁金	Turmeric Root Tuber	Radix Curcumae	9g
Jiangcan	僵蚕	Silkworm	Bombyx Batryticatus	6g
Chaomaiya	炒麦芽	Fried Germinated Barley	Fructus Hordei Germinatus	9g

2.5 Sample size estimation

Since there were no previous studies designed specifically for liver depression of heat syndrome efficacy, the present study will be a pilot study. For practical reasons, a sample size of 30 per group and a total number of 60 participants will be recruited for the current study. This sample was already larger than the minimum number recommended for pilot studies[32] and could provide more accurate parameters for formal trials in the future[33].

2.6 Outcome measures

2.6.1 Primary outcomes

One of the primary outcome measures was TCM syndrome integral change at post-treatment according to the liver depression of heat syndrome evaluation scale[34]. The scale including primary syndromes and secondary syndromes. The primary syndromes are composed of thirteen items, each item is divided into four grades with a score that ranges from 0 to 6, namely none (0), mild (2), moderate (4), and severe (6). The secondary symptoms included 5 items which are also divided into four grades, namely none (0), mild (1), moderate (2), and severe (3). The scores of main syndromes and secondary syndromes would be summed to yield a global score. TCM syndrome evaluation was carried out at 6 visit time points, including baseline, week 1(after 7 days of administration), week 2(after 14 days of administration), week 3(after 21 days of administration), week 4(after 28 days of administration) and at follow-up when the participants withdrew administration for 28 days.

The Pittsburgh Sleep Quality Index (PSQI) was another primary outcome measurement that was assessed at baseline and post-treatment. PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval[35]. It is composed of 19 items weighted on a 0 (no difficulty) − 3 (severe difficulty) interval scale. The items of the PSQI are divided into seven components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. A global score is calculated by totaling the seven component scores providing an overall score ranging from 0 to 21, with lower scores reflecting a better quality of sleep and higher scores denote a worsen sleep. A score of 5 or more usually suggests poor sleep quality.

2.6.2 Secondary outcome

The Short-Form Health Survey (SF-36) is a widely used self-report questionnaire that consists of 36 items[36]. It assesses Health-Related Quality of Life (HRQOL) in eight domains: Mental Health (MH), Role Emotional (RE), Social Functioning (SF), Vitality (VT), General Health (GH), Body Pain (BP), Role Physical (RP), Physical Functioning (PF). Scores range from 0 to 100, with higher scores indicating better HRQOL. SF-36 were measured at baseline and post-intervention after 4 weeks of administration.

2.6.3 Safety outcomes

The routine blood test, routine urine test, renal function test, liver function test, and electrocardiogram were evaluated baseline and after 4-weeks' intervention as safety evaluation endpoints. All participants were monitored and ascertained for adverse events (AE) at each visit. Serious adverse events (SAE) were defined as those that were fatal, were life threatening, were severely incapacitating, were permanently disabling or required prolonged inpatient hospital stay. Participants could report AEs to researchers at any time during the study period.

2.7 Statistical analysis

A per-protocol analysis was employed in the current study. Categorical variables were displayed as percentages. Continuous variables were presented as mean ± standard deviations if the data fit a normal distribution in 2 groups, otherwise, the data would be presented as median (interquartile range). Paired T test was used for comparison within-group and independent-sample T test was used to compare the differences between groups. Nonparametric test was used for abnormal distribution with the Mann–Whitney U tests. The comparisons for categorical data will be compared using the chi-squared test. A correlation analysis was done between syndrome integral change and PSQI global and subscale score. All analyses were performed using the SPSS 23. Statistical significance was accepted in two-sided tests at $p < 0.05$.

2.8 Ethics approval

The study protocol follows the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Dongzhimen Hospital Affiliated with Beijing University of Chinese Medicine (ECPJ-BDY-2013-28). The study was registered with http://www.chictr.org.cn/index.trial (ChiCTR-TRC-14004469). All study participants provided written informed consent before the commencement of the trial.

3. Results

Of 60 participants included in the current study, 30 were randomized to the treatment group and 30 were randomized to the control group. During the trial period, 3 cases were lost during the follow-up period (1 case in the experimental group and 2 cases in the control group). Finally, 57 cases entered the per-protocol set (PPS), 29 cases in the experimental group, and 28 cases in the control group. In the experimental group, there were 10 males and 19 females, with an average age of 53.35 years and an average course of 23.23 ± 30.81 months. In the control group, there were 5 males and 23 females, with an average age of 51 years and an average course of 27.93 ± 32.55 months. For baseline demographics, the two groups were balanced.

3.1 Primary outcomes

3.1.1 The liver depression of heat syndrome

At baseline, there was no significant difference between the two groups in the scores of liver depression of heat syndrome, which were comparable ($P > 0.05$). After 4 weeks' administration of QGJY Herbal Formula Granule or Wuling Capsule, the total and subscale scores were decreased in both groups, from 40.55 to 10.06 in the QGJY group and from 39.69 to 15.21 in the Wuling group. There were significant differences in total syndrome scores between the two groups at 2, 3, 4 weeks and follow-up visit (all Ps < 0.05)), and the main syndrome score of the experimental group was significantly decreased compared with that of the control group. (Table 2)

Table 2
The comparison of TCM syndrome integral change between groups

Time points	Group	Total syndrome integral	Main syndrome integral	Secondary syndrome integral
Baseline	Treatment group	40.55 ± 8.64	34.13 ± 7.33	6.42 ± 2.80
	Control group	39.69 ± 8.82	32.76 ± 7.93	6.93 ± 2.49
Week 1	Treatment group	32.48 ± 9.12	27.55 ± 7.55	4.94 ± 2.36
	Control group	34.72 ± 8.17	28.69 ± 6.81	6.03 ± 2.54
Week 2	Treatment group	23.81 ± 9.63	20.26 ± 8.02	3.55 ± 2.29
	Control group	29.72 ± 6.05	24.45 ± 5.12	5.28 ± 2.51
Week 3	Treatment group	17.77 ± 8.08	15.00 ± 6.77	2.77 ± 2.01
	Control group	25.28 ± 5.86	20.83 ± 4.79	4.45 ± 2.38
Week 4	Treatment group	12.71 ± 6.92	10.48 ± 5.42	2.23 ± 1.89
	Control group	19.45 ± 5.07	16.07 ± 4.16	3.38 ± 1.92
Follow up	Treatment group	10.06 ± 5.17	8.55 ± 4.16	1.52 ± 1.45
	Control group	15.21 ± 4.27	12.76 ± 3.64	2.45 ± 1.72

3.1.2 Pittsburgh Sleep Quality Index

Before treatment, the tests for between-group comparisons of PSQI global score, subjective sleep quality, sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency and use of sleep medication were all non-significant (all Ps > 0.05). After 4-week treatment, the global scores of PSQI were decreased in both groups, from 13.42 to 10.45 in the QGJY group and from 14.90 to 12.83 in the Wuling group. There were significant intergroup differences in PSQI global score, sleep disturbance, sleep duration, and use of sleep medication (all Ps < 0.05). (Table 3)

Table 3
The comparison of PSQI between two groups

	The treatment group		The control group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
global score	13.42 ± 4.38	10.45 ± 2.26	14.90 ± 3.14	12.83 ± 3.08
subjective sleep quality	2.17 ± 0.47	1.52 ± 0.51	2.29 ± 0.58	1.18 ± 0.55
sleep duration	2.10 ± 0.77	1.73 ± 0.80	2.23 ± 0.81	1.29 ± 0.66
sleep disturbance	1.31 ± 0.47	1.03 ± 0.18	1.74 ± 0.57	1.29 ± 0.46
sleep latency	2.11 ± 0.92	1.97 ± 0.82	2.68 ± 0.55	2.52 ± 0.91
daytime dysfunction	2.52 ± 0.78	1.85 ± 0.52	2.58 ± 0.76	1.86 ± 0.65
sleep efficiency	1.59 ± 1.21	1.66 ± 0.89	1.97 ± 1.11	1.71 ± 0.94
sleep medication	0.72 ± 1.03	0.31 ± 0.54	1.42 ± 1.36	1.00 ± 1.05

3.2 Secondary outcome

At 4-week follow-up assessment, the quality of life for patients in both groups was improved compared with baseline. The improvement in mental health was significantly better in the treatment group than in the control group($P < 0.05$). (Table 4)

Table 4
The comparison of SF-36 between groups

	The treatment group		The control group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
PF	93.05 ± 6.32	97.16 ± 3.83	93.13 ± 7.58	95.31 ± 6.23
RP	45.45 ± 41.26	78.86 ± 34.26	51.52 ± 39.21	79.69 ± 35.83
BP	58.36 ± 16.38	73.56 ± 15.52	61.18 ± 17.42	76.18 ± 16.21
GH	43.28 ± 15.37	61.13 ± 15.56	46.32 ± 13.19	59.25 ± 12.78
VT	53.57 ± 16.15	70.25 ± 13.36	56.23 ± 11.64	69.48 ± 12.31
SF	66.14 ± 19.47	76.13 ± 14.35	64.65 ± 15.85	79.27 ± 13.65
RE	41.23 ± 40.17	69.16 ± 32.23	45.38 ± 35.46	70.37 ± 32.58
MH	52.01 ± 10.52	71.23 ± 12.14	50.60 ± 11.86	61.06 ± 12.64

3.3 The correlation between PSQI and TCM syndrome

A correlation analysis was made between syndrome integral change and the changes of PSQI global score and each of the subscale scores. It shows that there was a significant positive correlation between sleep disorders and syndrome integral change (Pearson r = 0.340, P < 0.001), indicating that the improvement of liver depression of heat syndrome can impact sleep, especially in sleep disorders. (Table 5)

Table 5
The correlation between syndrome integral and PSQI

Item	rho	P-value
syndrome integral change		
PSQI global score	0.219	0.093
subjective sleep quality	0.162	0.218
sleep latency	0.177	0.176
sleep duration	0.128	0.331
sleep efficiency	0.067	0.611
sleep disturbance	0.340	0.008
sleep medication	0.075	0.568
daytime dysfunction	0.131	0.317

3.4 Safety and tolerability

After 4-week treatment, results of blood routine, liver function, kidney function, and ECG examination in the two groups were rechecked, and no clinically significant abnormal changes were found. Four patients (3 in the QGJY group and 1 in the Wuling group) reported AEs during the 8 weeks. Two patients from the QGJY group complained of itchy skin sensation, and one reported a loose stool. The other 1 patients in the Wuling group described experiencing a dry throat. All AEs were mild and none of them required special medical interventions. During the study period, no SAEs was reported in patients of both groups.

4. Discussion

In the current randomized controlled trial of QGJY Herbal Formula Granule for insomniacs with liver depression of heat syndrome, QGJY showed promising effect for insomnia after 4 weeks' administration.

In the meantime, the effect of QGJY Herbal Formula Granule on patients' mental health was significantly better.

We found that QGJY Herbal Formula Granule improved both the disease and syndrome. Previous studies have explored the effect of Chinese medicinal herbs and formulas in insomnia treatment. Zeng et al conducted an RCT to explore the efficacy and safety of Jiao-tai-wan for ameliorating insomnia symptoms caused by disharmony of the heart and kidney. In this study, Disharmony of Heart and Kidney Scoring System was used to evaluate the syndrome at the baseline and the end of drug intervention [37]. However, they didn't distinguish syndrome diagnosis and evaluation scale and the validity and reliability of this questionnaire was not identified. In the study conducted by Liu et al, researchers evaluated the efficacy and safety of Chaihuguizhiganjiang-suanzaoren granule in patients with primary insomnia. Insomniacs were required to meet the diagnostic criteria of spleen deficient and liver heat syndrome. However, syndrome integral change was not evaluated in that study [38]. Another study conducted by Ye et al. recruited insomniacs with Qi-deficiency of heart and gallbladder syndrome and included PSQI and syndrome score as outcome measures[39]. However, the clinical efficacy of Zhenjingdingzhi decoction was assessed by effective rate, which is a composite outcome indicator and could not reflect the true effect of TCM intervention[40]. Additionally, in the Self-Designed Ningxin Anshen Formula for Treatment of Post-ischemic Stroke Insomnia study, patients with blood-deficient and liver-heat syndrome were recruited and the scores of TCM Syndromes were included in the secondary outcomes though it was not validated[41]. Appropriate outcome measures are important for clinical trial design. In clinical trials of TCM, objective indexes of Western medicine were usually employed as the primary outcome measures, while some indexes with TCM characteristics such as syndrome, patient report outcomes were seen as secondary outcome measures as in the Ningxin Anshen Formula study[42]. TCM is a syndrome-oriented holistic medical system and different from Western medicine counterpart. In clinical trial of Chinese medicine, outcome measures evaluating the efficacy of Chinese medicine interventions are often incompatible with the theory and clinical practice of TCM, which was inappropriate[43]. As was suggested by Run Qiu Chen et al, the development of TCM syndrome-specific outcome measures is needed for the evaluation of TCM syndrome-specific therapies[44].

Improvements in the mental health domain of quality of life were also found. Recent studies had explored relations between sleep disorders and mental well-being, suggesting that poor sleep was associated with negative psychological well-being[45–47]. Sun-Young Kim and colleagues recruited participants in the Korean National Health and Nutrition Examination Survey and suggested that shorter or longer sleep durations were both associated with a higher risk of suicidal ideation[48]. Ko Y et al. found that short sleep duration was particularly closely related with an increased risk for suicide attempt in Korean Adults[49]. QGJY Herbal Formula Granule had unique advantages not only improving sleep but also promoting particitants' psychological health. This may helps explain the mechanisms of QGJY Herbal Formula Granule in insomnia treatment in the future.

Our research is clinically required which followed the Evidence-based traditional Chinese medicine research: Beijing Declaration [50]. One merit of the present study was the use of multiple primary

endpoints based on the combination of diseases and syndromes[42]. It was recommended by ICH E9 that there should be one primary endpoint in clinical trials[51], which usually serves as the basis for sample size determination, interim data monitoring, final analyses, and the reporting of the trial result[52]. However, the interventional effects of Chinese herbs and formulas are usually multidimensional and cannot be reflected by a single primary outcome measure. The concept of syndromes (zhengs) is unique to TCM and difficult to measure[53]. Syndrome differentiation is an important concept and has its particular advantage in TCM clinical practice. It's not uncommon that only outcome measures of Western medicine were employed as the main indexes in TCM clinical trials. Hence it's unable to reflect the advantages of characteristic treatment of TCM comprehensively and objectively. TCM and western medicine outcomes should be treated equally, and the results of curative effect of "disease" and "syndrome" should be combined to evaluate the interventional effect of TCM methods. Second, different scales for diagnosis and evaluation of syndrome were utilized in the current study. Being the core concept of TCM, Syndrome (*Zheng*) is a characteristic outcome indicator in the evaluation system of TCM, however, syndrome efficacy is frequently absent in clinical trial design. As a reporting specification of Chinese herbal formulae, the Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations,Explanation and Elaboration (SPIRIT-TCM 2018) introduced the concept of TCM syndrome[54]. Chinese herbal formulae are one of the most commonly used and representative TCM interventions in clinical practice and research. Syndrome diagnosis and evaluation are two distinct concepts in TCM that should be treated differently. In 2018, the Drug Evaluation Center of China Food and Drug Administration issued the Technical Guiding Principles for Clinical Research of Syndromes and New Chinese Drugs in which the "syndrome diagnosis" and "syndrome evaluation" were detailed[55]. The purpose of the diagnostic scale is to judge the presence or absence of syndromes, that is to say, the question of "yes or no". When the syndrome is confirmed, we would measure the degree of severity, that is, the problem of "how much". In clinical trials evaluating syndrome-specific therapies, syndrome is not only a diagnostic criterion but also an evaluation index. It is of great significance to explore a research model that is syndrome-centered and in line with the diagnosis and treatment model of TCM. Our research has set a good example for others by including syndrome-specific outcome measure as one of the primary outcome measures.

The results of our study should be considered in the context of several limitations. The first limitation derives from the study design of RCT, which has pre-specified fixed interventions and cannot capture the subtle dynamic changes of the syndrome. This was not complied with the clinical practice guidelines when the syndrome changes there will be corresponding adjustment in the Chinese herbal prescriptions. However, we can still capture the trajectory of syndrome changes throughout the trial. Second, we didn't use a sleep diary for tracking the sleep/wake pattern prospectively in the current study. Sleep diary reflects a subjective global appraisal of each night's sleep based on important information such as bedtime, wake-up time, sleep duration, sleep onset latency, and night awakenings. It can provide reliable source of sleep parameters and will be included as one of the sleep outcomes in our future study. Third, the sample size was small and may lead to statistical bias in outcome assessment. A study with larger sample and more strictly design was warranted in the future. Additionally, we didn't employ objective

tools such as polysomnography (PSG) for sleep evaluation in the current study although it may help rule out some other sleep disorders. As the gold standard of sleep evaluation, PSG monitoring is the most basic, the most important, and the most extensive evaluation index in the existing sleep medicine evaluation technology[56]. However, the utilization of PSG is limited by drawbacks such as high cost and space limitation.

5. Conclusions

To summarize, four weeks' administration of QGJY Herbal Formula Granule showed promising effects in improving the liver depression of heat syndrome and subjective sleep parameters of sleep disturbance, sleep duration, and sleep medication. QGJY Herbal Formula Granule could improve patients' mental health significantly. These findings indicate that QGJY Herbal formula granule improved both disease and syndrome, lending further weight to the clinical guideline recommendation of TCM as one of the treatment choices for insomnia.

6. Abbreviations

QGJY: QingganJieyu Herbal Formula Granule; TCM: Traditional Chinese Medicine; PSQI: Pittsburgh Sleep Quality Index; CONSORT: Consolidated Standards of Reporting Trials; GCP: Good Clinical Practice; CBT-I: Cognitive-Behavioral Therapy for Insomnia; DSM-4: Diagnostic and Statistical Manual of mental disorders (4th edition); HRQOL: health-related quality of life; SF-36: Short-form 36 Questionnaire; MH: Mental Health; RE: Role Emotional; SF: Social Functioning; VT: Vitality; GH: General Health; BP: Body Pain; RP: Role Physical; PF: Physical Functioning; SPIRIT-TCM 2018: the Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018; AE: adverse events; SAE: Serious adverse events.

7. Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all study participants before enrollment. This trial was approved by the Institutional Review Board at the Dongzhimen Hospital, Beijing University of Chinese Medicine (The approved No. was ECPJ-BDY-2013-28).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

8. References

1. Association AP: Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.

2. Crowley K: Sleep and sleep disorders in older adults. Neuropsychology review 2011, 21(1):41-53.

3. Fang H, Tu S, Sheng J, Shao A: Depression in sleep disturbance: a review on a bidirectional relationship, mechanisms and treatment. Journal of cellular and molecular medicine 2019, 23(4):2324-2332.

4. Zheng B, Yu C, Lv J, Guo Y, Bian Z, Zhou M, Yang L, Chen Y, Li X, Zou J: Insomnia symptoms and risk of cardiovascular diseases among 0.5 million adults: A 10-year cohort. Neurology 2019, 93(23):e2110-e2120.

5. Sadeghmousavi S, Eskian M, Rahmani F, Rezaei N: The effect of insomnia on development of Alzheimer's disease. Journal of Neuroinflammation 2020, 17(1):1-20.

6. Sindi S, Kåreholt I, Johansson L, Skoog J, Sjöberg L, Wang HX, Johansson B, Fratiglioni L, Soininen H, Solomon A: Sleep disturbances and dementia risk: a multicenter study. Alzheimer's & Dementia 2018, 14(10):1235-1242.

7. Zhang Y, Lin Y, Zhang J, Li L, Liu X, Wang T, Gao ZA-O: Association between insomnia and type 2 diabetes mellitus in Han Chinese individuals in Shandong Province, China. (1522-1709 (Electronic)).

8. Liu B-P, Wang X-T, Liu Z-Z, Wang Z-Y, Liu X, Jia C-X: Stressful life events, insomnia and suicidality in a large sample of Chinese adolescents. Journal of affective disorders 2019, 249:404-409.

9. Lopez-Castroman J, Jaussent I: Sleep disturbances and suicidal behavior. 2020.

10. Merlino G, Lorenzut S, Gigli GL, Del Negro I, Tereshko Y, Smeralda C, Piani A, Valente M: Insomnia and daytime sleepiness predict 20-year mortality in older male adults: data from a population-based study. Sleep medicine 2020, 73:202-207.

11. Taddei-Allen P: Economic burden and managed care considerations for the treatment of insomnia. Am J Manag Care 2020, 26(4 Suppl):S91-s96.

12. Sarsour K, Kalsekar A, Swindle R, Foley K, Walsh JK: The association between insomnia severity and healthcare and productivity costs in a health plan sample. Sleep 2011, 34(4):443-450.

13. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD: Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2016, 165(2):125-133.

14. Abad VC, Guilleminault C: Insomnia in Elderly Patients: Recommendations for Pharmacological Management. Drugs Aging 2018, 35(9):791-817.

15. Voelker R: New Warnings for Insomnia Drugs. Jama 2019, 321(21):2066.

16. Buenaver LF, Townsend D, Ong JC: Delivering Cognitive Behavioral Therapy for Insomnia in the Real World: Considerations and Controversies. Sleep Med Clin 2019, 14(2):275-281.

17. Ong JC: Delivering Cognitive Behavioral Therapy for Insomnia in the Real World. Cognitive-Behavioral Therapies for Insomnia, An Issue of Sleep Medicine Clinics, Ebook 2019, 14(2):275-281.

18. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL: Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017, 13(2):307-349.

19. Brewster GS, Riegel B, Gehrman PR: Insomnia in the Older Adult. Sleep medicine clinics 2018, 13(1):13-19.

20. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society 2019, 67(4):674-694.

21. Akram M, Daniyal M, Munir N, Mohiuddin E, Sultana S: Medicinal Plants Combating Against Insomnia: A Green Anti-Insomnia Approach. The Journal of nervous and mental disease 2019, 207(11):927-935.

22. Krakow B, Ulibarri VA, Romero E: Persistent insomnia in chronic hypnotic users presenting to a sleep medical center: a retrospective chart review of 137 consecutive patients. J Nerv Ment Dis 2010, 198(10):734-741.

23. Lin AX, Chan G, Hu Y, Ouyang D, Ung COL, Shi L, Hu H: Internationalization of traditional Chinese medicine: current international market, internationalization challenges and prospective suggestions. Chin Med 2018, 13:9.

24. Singh A, Zhao K: Treatment of Insomnia With Traditional Chinese Herbal Medicine. Int Rev Neurobiol 2017, 135:97-115.

25. Ni X, Shergis JL, Zhang AL, Guo X, Lu C, Li Y, Xue CC: Traditional Use of Chinese Herbal Medicine for Insomnia and Priorities Setting of Future Clinical Research. (1557-7708 (Electronic)).

26. Zhou QH, Zhou XL, Xu MB, Jin TY, Rong PQ, Zheng GQ, Lin Y: Suanzaoren Formulae for Insomnia: Updated Clinical Evidence and Possible Mechanisms. (1663-9812 (Print)).

27. Birling Y, Jia M, Li G, Sarris J, Bensoussan A, Zhu X: Zao Ren An Shen for insomnia: a systematic review with meta-analysis. (1878-5506 (Electronic)).

28. Dai N, Li Y, Sun J, Li F, Xiong H: Self-Designed Ningxin Anshen Formula for Treatment of Post-ischemic Stroke Insomnia: A Randomized Controlled Trial. Front Neurol 2020, 11:537402.

29. Ni X, Shergis JL, Zhang AL, Guo X, Lu C, Li Y, Xue CC: Traditional Use of Chinese Herbal Medicine for Insomnia and Priorities Setting of Future Clinical Research. Journal of alternative and complementary medicine (New York, NY) 2019, 25(1):8-15.

30. Do LJSU: American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 2011.

31. Guo Shengnan, Liu Qiang, Wang Shaoqing, Chen Sheng, Zhu Wenhao, Gao Ying. Development of liver depression of heat syndrome diagnosis scale. Journal of Traditional Chinese Medicine, 2014,55(14):1219-1222..

32. Julious SJPS: Sample size of 12 per group rule of thumb for a pilot study. 2005, 4.

33. Zhang Ying, Wang Junhui, Hu Yeyin, Shao Baoyi, Fu Zhanju, Liu Jianping. Determination of sample size in pilot study of traditional Chinese medicine. Journal of Traditional Chinese Medicine. 201,62(04):307-311.

34. Guo Shengnan, Liu Qiang, Wang Shaoqing, Gao Ying. Development of liver depression of heat syndrome evaluation scale. Journal of Basic Chinese Medicine, 2017, 23(03):351-353.

35. Buysse DJ, Reynolds Cf 3rd Fau - Monk TH, Monk Th Fau - Berman SR, Berman Sr Fau - Kupfer DJ, Kupfer DJ: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. (0165-1781 (Print)).

36. McHorney CA, Ware Je Jr Fau - Raczek AE, Raczek AE: The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. (0025-7079 (Print)).

37. Zeng C, Liu X, Hu L, Feng Y, Xia N, Zeng H, Luo L, Ye R, Yuan Z: Jiao-tai-wan for insomnia symptoms caused by the disharmony of the heart and kidney: a study protocol for a randomized, double-blind, placebo-controlled trial. (1745-6215 (Electronic)).

38. Liu QQ, Zhang J, Guo RJ, Xie YZ, Fu QN, He T, Zhu XQ, Du J, Yang J, Wang JL et al: Efficacy and safety of the Chaihuguizhiganjiang-suanzaoren granule on primary insomnia: study protocol for a randomised controlled trial. (2044-6055 (Electronic)).

39. Ye Q Fau - Zhou J, Zhou J Fau - Yuan X, Yuan X Fau - Yuan C, Yuan C Fau - Yang X, Yang X: Efficacy of Zhenjingdingzhi decoction in treating insomnia with Qi-deficiency of heart and gallbladder: a randomized, double-blind, controlled trial. (0255-2922 (Print)).

40. Zhang Ying-ying，Shen Chen，Zhang Ying，Liu Jian-ping. Misunderstandings in Using 《Total Effective Rate》 As an Index for Evaluating the Therapeutic Effect of Traditional Chinese Medicine[J].Chinese Journal of Drug Evaluation,2020,37(5):337-340..

41. Dai N, Li Y, Sun J, Li F, Xiong H: Self-Designed Ningxin Anshen Formula for Treatment of Post-ischemic Stroke Insomnia: A Randomized Controlled Trial. (1664-2295 (Print)).

42. Hu Jing, Liu Weihong, Zhang Huina, Li Bo, Zhang Xiaoyu，Shang Hongcai. Application of Evaluation of Multiple Primary Endpoints Based on Combination of Diseases and Symptoms in TCM Clinical Trials. World Chinese Medicine, 2017, 12(06):1214-1217.

43. Yan J, Engle Vf Fau - He Y, He Y Fau - Jiao Y, Jiao Y Fau - Gu W, Gu W: Study designs of randomized controlled trials not based on Chinese medicine theory are improper. (1749-8546 (Electronic)).

44. Chen RQ, Wong Cm Fau - Lam TH, Lam TH: Construction of a traditional Chinese medicine syndrome-specific outcome measure: the Kidney Deficiency Syndrome Questionnaire (KDSQ). (1472-6882 (Electronic)).

45. Littlewood DL, Kyle SD, Carter LA, Peters S, Pratt D, Gooding PJPM: Short sleep duration and poor sleep quality predict next-day suicidal ideation: an ecological momentary assessment study. 2018:1-9.

46. Zhai K, Gao X, Wang GJIJoER, Health P: The Role of Sleep Quality in the Psychological Well-Being of Final Year UndergraduateStudents in China. 2018, 15(12).

47. Zou P, Wang X, Sun L, Liu K, Chen QJJoPR: Poorer sleep quality correlated with mental health problems in college students: A longitudinal observational study among 686 males. 2020, 136.

48. Jae-Hyun K, Eun-Cheol P, Woo-Hyun C, Jong-Yeon P, Won-Jung C, Hoo-Sun CJS: Association between total sleep duration and suicidal ideation among the Korean general adult population. (10):1563.

49. Ko Y, Ji EM, Han S: Sleep Duration is Closely Associated with Suicidal Ideation and Suicide Attempt in Korean Adults: A Nationwide Cross-sectional Study. 2021.

50. Zhang J, Li Y, Zhang B, Chen K, Wang Q, Li Z, Sun S, Tian J, Sun X, Yao C et al: Evidence-based traditional Chinese medicine research: Beijing Declaration. (1756-5391 (Electronic)).

51. Lewis JA: Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. (0277-6715 (Print)).

52. Hamasaki TA-O, Evans SR, Asakura K: Design, data monitoring, and analysis of clinical trials with co-primary endpoints: A review. (1520-5711 (Electronic)).

53. Wang XN, Zhou V, Liu Q, Gao Y, Zhou XH: Evaluation of the accuracy of diagnostic scales for a syndrome in Chinese medicine in the absence of a gold standard. (1749-8546 (Print)).

54. Dai L, Cheng CW, Tian R, Zhong LL, Li YP, Lyu AP, Chan AW, Shang HC, Bian ZX: Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation and Elaboration (SPIRIT-TCM Extension 2018). (1672-0415 (Print)).

55. Ma Lian, Wang Kebin, Wu Shengxian. Discussion on the development of new TCM drugs in perspective of theoretical innovation. China Journal of Chinese Materia Medica, 2020,45(20):5048-5056.

56. Rundo JV, Downey R, 3rd: Polysomnography. (0072-9752 (Print)).