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Research Article

Efficacy and Safety of a Traditional Chinese Medicine Formula, Suanzaorentang, on Primary Insomnia: A Double-Blind Randomized Placebo-Controlled Study

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Abstract

Despite widely used as one of the commonest over-the-counter treatments of insomnia, the efficacy and safety of suanzaorentang, a composite Traditional Chinese Medicine (TCM) formulae, are poorly understood. We aimed to evaluate the efficacy and safety of suanzaorentang on primary insomnia over a period of four weeks with both subjective and objective sleep measurements. A randomized, double-blind, placebo-controlled trial (RCT) involving 162 primary insomniac subjects (mean age 46.5 years, range 21 to 64 years; female: 68.5%) treated at 2 university affiliated sleep centers in Hong Kong. Among 162 subjects, 86% (n=139) completed the whole trial. Participants received either four weeks Chinese herbal formula (suanzaorentang group) or placebo by block randomization. After 4-week treatment, the treatment group showed more improvement in subjective sleep quality in the perceived depth of sleep (Visual analog scale, mean differences (95%CI) = -16.0 (-22.1 to -9.9) v.s. -7.1 (-13.3 to -1.0), $p<0.05$) and refreshing sleep (mean differences (95%CI) = -12.0 (-18.2 to -5.8) v.s. -2.2 (-8.9 to 4.5), $p<0.05$) than placebo group. However, the two groups did not have any differences over the objective measures and the Insomnia Severity Index total scores. No difference in overall adverse events was found between groups. The study showed that 4-weeks treatment of suanzaorentang improved perceived sleep quality but not subjective sleep difficulty or objective sleep parameters. In particular, suanzaorentang had good safety profile and tolerability.

INTRODUCTION

Being one of the commonest sleep disorders, the prevalence of insomnia is about 10-20% in general population with a much higher rate in clinical populations [1-3]. Insomnia tends to run a chronic and persistent course [4-6] and is associated with a constellation of physical, pain and mental consequences [4, 7-9]. Insomnia also results in marked personal distress, and impairs personal functioning including higher rates of absenteeism and a lower productivity at work [10,11]. Understandably, insomnia has a huge impact on healthcare cost of the society [12].

Thus, early management of insomnia is implicated, but less than one fourth of patients had medical consultations about their sleep problems [13]. Instead, they commonly used complementary and alternative medicine (CAM) for management of their sleep problems. CAM covers a range of therapies such as over-the-counter (OTC) medication of natural products and herbal supplements, acupuncture, and aromatherapy [13-15]. Among all options, OTC medication (herbal and folk medicine) is the commonest choice [16]. A survey of the use of OTC sleeping pills in Hong Kong found that a significant proportion of the OTC sleep aids were composed of Traditional Chinese Medicine (TCM) and Western herbal agents [17]. The TCM formula, Suanzaorentang, was the most commonly used ingredient sampled in the study [17]. Suanzaorentang is a popular and one of the oldest TCM formulae that was first recorded in the Han dynasty classical text, the "Golden Chest", in China [18,19]. The herbal formula composes of 6 herbal components including semen ziziphi spinosae, caulis polygoni multiflori, poria cum radix pini, fructus tritici levis, rhizoma anemarrhenae and radix polygalae (Wing, 2001) [18]. The key component, semen ziziphi spinosae, is the seed of a plant called "wild jujube" and has been proposed to exert its sedative effect via 5HT1a, 5HT2 and GABA receptors [20, 21], which leads to its hypnotic effect in rats [22, 23]. Some clinical case series suggested that suanzaorentang could improve sleep [24,25]. However, the existing evidence on its efficacy in treatment of insomnia remains weak. A recent review concluded that only a few studies have tested the efficacy of suanzaorentang

with randomized-controlled design [26]. However, there were many shortcomings from previous drug trials in suanzaorentang which included insufficient information about randomization generation, absence of allocation concealment, lack of blinding and placebo control, absence of intention-to-treat analysis, lack of follow-up, and small sample sizes [26, 27]. Furthermore, most of the previous studies did not exclude other comorbid sleep disorders such as sleep apnea syndrome and periodic limb movement disorder, which could have contributed to sleeping difficulty. In addition, neurotoxic serotonin syndrome has resulted from a combination of venlafaxine and suanzaorentang [28]. In view of the easy accessibility of CAM and popular usage of suanzaorentang, its efficacy and safety will need to be addressed in a well-conducted study. Thus, we conducted a randomized, double-blind, case controlled study to look into the efficacy of suanzaorentang in the treatment of insomnia with both subjective and objective outcomes as well as its safety profile.

METHODOLOGY

This was a 4-week, two-sites, randomized double-blind, placebo-controlled study carried out at two university-based sleep centers in Hong Kong with the approval of the protocol by respective site's Institutional Review Board in 2006-2009. The study was conducted according to the International Conference for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice. The reporting of this RCT followed the suggestions of the CONSORT 2010 statement [29].

Subject selection

Participants were recruited through advertisements from the community. Inclusion criteria were those of aged 18-65, Chinese, having a diagnosis of insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (Text revision) (DSM-IV-TR) as follows: 1) A predominant complaint of difficulty initiating sleep (DIS) or maintaining sleep (DMS) or early morning awakening (EMA) for at least 1 month; 2) The insomnia causes significant distress or impairment in social, occupational, and/or other important areas of functioning. Exclusion criteria were 1) Any lifetime/ current psychotic disorder, affective or anxiety disorders, substance use disorder as defined by DSM-IV criteria (Structural Clinical Interview for DSM-IV); 2) General medical condition that directly related to onset and course of insomnia; 3) Pregnancy; 4) Concurrent treatment with other TCM or herbal medications; 5) Intake of any benzodiazepines or other psychotropics during the 2 weeks period prior to entry; 6) Obstructive sleep apnea syndrome (OSA) of moderate degree or above, defined by a apnea-hypneic index (AHI) cutoff of > 15/hour at baseline polysomnography (PSG); 7) Periodic limb movement during sleep (PLMS) as defined by a periodic limb movement index > 15 /hour at baseline PSG; 8) Any disease state which, judged by the investigator, could interfere with study participation or study evaluation; 9) Participation in any other clinical trial investigational products within 30 days of baseline assessment.

A summary of participant flow is shown in Figure (1). Of the 1090 individuals who completed telephone screening for eligibility assessment, 413 subjects underwent subsequent face-to-face clinical interview screening, and overnight PSG to exclude subjects with prominent OSA and PLMS. After the screening, 251 persons were excluded for various reasons and 162 subjects were eligible for the randomization (Figure 1).

Study design

Subjects were randomly assigned to either treatment group or placebo group for 4-week treatment. Block randomization method was used to randomize participants into treatment and placebo groups. Every ten number was allocated into 1 block [30]. Equal number was randomly assigned into treatment and placebo group in the block. This procedure resulted in equal participants in both treatment and placebo groups in each center. Participants and the clinicians responsible for clinical interviews and assessment were blind to the randomization result throughout the trial period. The participants were scheduled to have 4 clinical assessments at baseline (visit 1), 2nd week (visit 2), 4th week (visit 3) of treatment and 1-week post study (visit 4). During all visits, subjects were instructed to complete a set of standardized questionnaires and 3-days actigraphy and sleep diary. At visits 1, 3 and 4, subjects also completed 2-nights PSG (1 night PSG at visit 4). Telephone follow-up were also scheduled on the 1st and the 3rd week for safety check-up.

Assessments and Outcome Measures

1. Primary outcomes: The two designated primary outcome measures included the Chinese version of Insomnia Severity Index (ISI) and visual analogue scales (VAS), which were used to measure insomnia severity and perceived sleep quality, respectively. ISI is a 7-item questionnaire assessing the subtype, severity, and impact of sleep difficulties by a 5-point scale with satisfactory psychometric properties and sensitivity to measure treatment response [31]. The Chinese version of ISI has been validated and was found to have good psychometric properties [32]. A total score of ISI less than 7 and a decrease of 30% in ISI at week 4 reference to baseline was considered as remission and improvement respectively.

Apart from the quantification of insomnia symptoms severity by ISI, the subjective measurement of various domains of perceived sleep quality was further assessed by VAS. In TCM concept, insomnia is regarded as a disease state of imbalance of Yin and Yang, a disharmony between the Heart and the Kidney [33,34]. Indeed, insomniac patients commonly complain of non-restoring, dreamy and restless sleep [33,34]. Hence, we employed VAS (ranging from 0-100 mm) to quantify four domains of sleep quality, including the perceived depth of sleep (deep to light sleep), dreams (dreamless to lots of dreams), calmness (calm to restless sleep), and degree of refreshment (refreshing to non-refreshing upon awakening). The lower the score, the better is the sleep quality.

2. Secondary outcomes: Objective sleep measures by means of actigraphy and overnight PSG were used as secondary outcomes. Wrist actigraphy was measured with Actiwatch 16 (Mini Mitter Company, Inc) and was worn for 3 consecutive days at baseline, 2nd week, 4th week and 1-week post-treatment, concurrently with the collection of sleep diary data. Data was collected in 1-min/epoch and analyzed with the Actiware software program. Outcome variables included sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST) and sleep efficiency (SE).

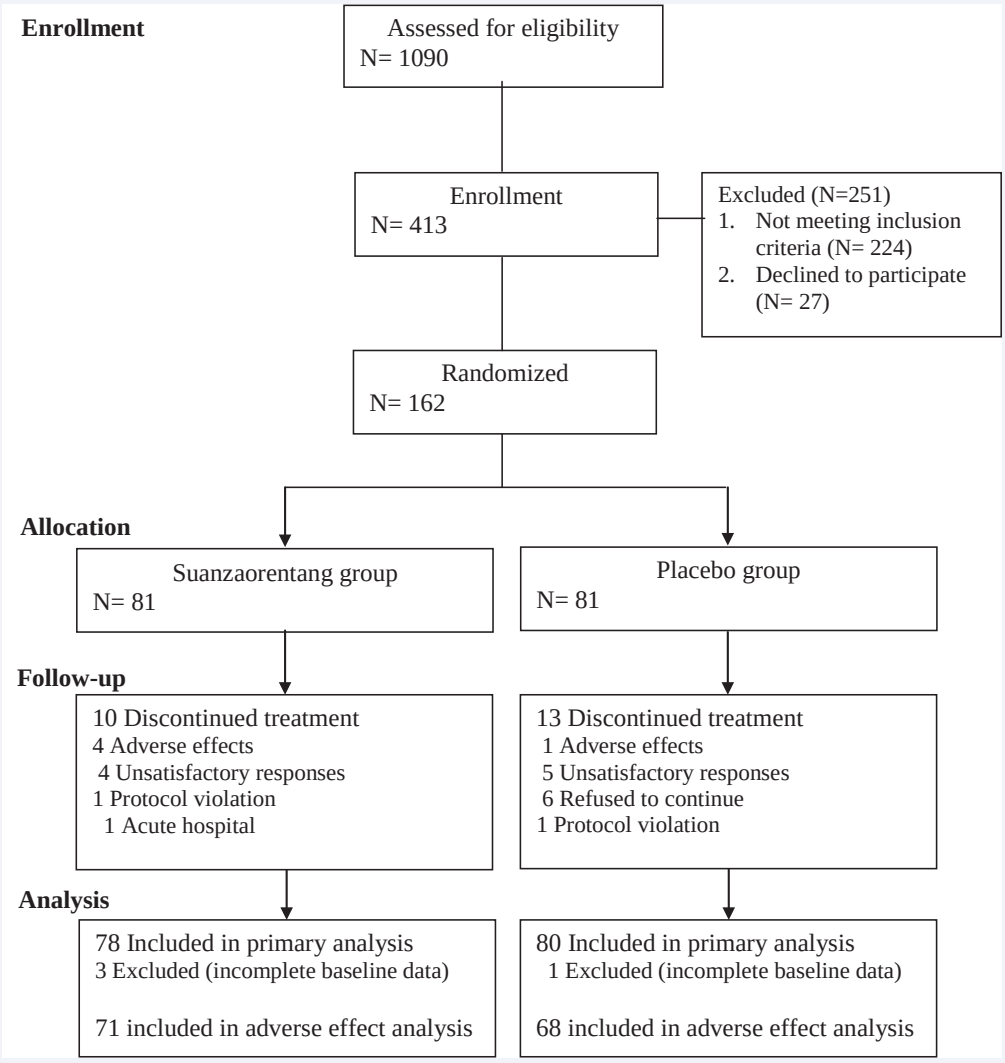

Figure 1 Participant flow.

Figure 2 Identical packing and appearance of Suanzaorentang and Placebo granules.

PSG assessment includes the measurements of EEG activity from central leads (C3-A2, C4-A1), EMG activity of mentalis and bilateral anterior tibalis, and bilateral electrooculogram (EOG) activity. ECG and heart rate were continuously recorded from two anterior chest leads. The nasal pressure as measured via nasal cannula monitors both the airflow. Respiratory effort was measured using the abdominal and thoracic strain gauges. An oximeter with finger probe was used to measure the SaO_2. All parameters were recorded with the P-1000 or Alice 5 PSG machines. All PSG data were further edited manually with the criteria of the Rechtschaffen and Kales by blinded experienced technologists and [35]. A total of 5 PSG nights were recorded (2 nights at baseline, 2 nights at week 4, 1 night at 1 week post treatment). Outcome variables included SOL, WASO, TST, SE and percentages of sleep stages, and they were calculated by averaging the 2 nights' data for baseline and week 4.

Measurements on adverse events and treatment adherence: Adverse effects were measured with Treatment Emergent Side effect Scale (TESS) [36]. For checking of treatment adherence, during each visit, study subjects were given with exact amount of medications and they were instructed to return all the packages (used/ unused) at the next scheduled visit for adherence checking. The adherence rate was calculated by dividing the number of empty bags returned by the number of bags of medication prescribed in each group.

Interventions

For the treatment group, suanzaorentang was used. The herbal formula composes of 6 herbal components in the following proportions: 1) Semen ziziphi spinosae 15 gram; 2) Caulis polygoni multiflori 15 gram; 3) Poria cum radix pini 15 gram; 4) Fructus tritici levis 30 gram; 5) Rhizoma anemarrhenae 10 gram; and 6) Radix polygalae 10 gram. The herbs were formulated and processed by the National Engineering Research Center for Modernization of Traditional Chinese Medicine, Zhuhai, People's Republic of China. The raw herbs and the sachets including the placebo prepared for clinical use underwent all the relevant safety tests. The preparation was in the form of brownish granules. The placebo agent was also made into the form of granules with very similar color and taste (Figure 2).

During the 4-week treatment, participants were instructed to take the medication (2 packages) nightly, about 30 minutes before bed time. Upon completion of the 4-week treatment period, the medication was stopped. A safety follow-up was scheduled to assess for any rebound of the sleep symptoms and adverse effect at 7-14 days after the last dose of medication.

STATISTICAL ANALYSIS

Sample size calculation: As there was no well-designed randomized controlled trial for this particular formula previously, we calculated the sample size based on a power analysis with effect size estimated from our previous open label trial. Assuming the treatment difference of 20 minutes in sleep onset latency (SOL) between treatment and placebo group were significant with standard deviation of 36.5 minutes. The sample size for a 2-sided significance level of 5% with power 90% was about 70 subjects in each group.

Statistical Package for Social Science 17.0 (SPPSS, Chicago, IL, USA) was used for the data analysis. Comparisons of demographic and clinical characteristics between treatment groups are conducted by independent student's t test and Mann-Whitney U test for continuous variables, and Pearson χ^2 test or Fisher's exact test for discrete categorical variables. For the primary and secondary treatment outcomes, the analyses were based on intent-to-treat model. If a patient's data were incomplete, a last observation carried forward (LOCF) approach was used to impute values. Linear mixed models were used to test group, time, and interaction effects. Linear mixed models were used to test group, time, and interaction effects for continuous dependent variables. Pearson χ^2 test was used to compare the remission rate and response rate between groups. Statistical significance is noted if $p<0.05$ using two-sided tests.

RESULTS

Participants and treatment adherence

The participant flow is shown in figure 2. One hundred and sixty-two subjects were finally randomized to receive suanzaorentang or placebo (81 subjects in each group). A total of 139 subjects completed the trial and the overall attrition rate was 14.2% and there was no significant difference in the attrition rate between the treatment and placebo groups. Ten subjects in suanzaorentang group and 13 subjects in the placebo group dropped out of treatment. In the treatment arm, 4 had symptoms possibly related to suanzaorentang (headache, muscle ache and urine retention), 4 withdrew due to unsatisfactory response, 1 took other herbal medication and violated the protocol and 1 was hospitalized because of blurred vision and was suspected to have transient ischemic attack on Day 19 of treatment, which was unlikely to be related to the formula. For the placebo group, 1 withdrew due to generalized physical discomfort, 5 reported unsatisfactory response and 6 refused to continue the study with no clear reason stated and 1 violated the protocol by taking other herbal medication. All the adverse effects experienced by suanzaorentang and placebo groups were mild and resolved after stopping the medication.

Baseline characteristics of the TCM treatment and placebo groups

For final analysis, due to incomplete baseline data, 4 subjects were excluded and hence data of 158 subjects were analyzed (78 from suanzaorentang group, 80 from placebo group) and presented in this paper. The subjects (32.3% male) had a mean age of 46.5 years (SD 10.0) (Table 1). The mean duration of insomnia was 10 years (SD 8.17). The most frequent insomniac complaint DIS (69.6%) followed by DMS (68.4%) and EMA (50%). Majority of them reported mixed insomnia symptoms (67.1%). Adherence to the medication regimen was 97% and 95% for the suanzaorentang and placebo group respectively. The two groups had similar demographic profiles (Table 1). They also had comparable insomnia symptoms subtypes and severity (in terms of ISI score). However, suanzaorentang group had longer duration of insomnia (suanzaorentang: 11.4 years vs Control: 8.6 years). There was no significant difference over the PSG parameters between the two groups.

Outcome measures between suanzaorentang treatment and placebo groups

The means, changes in scores, and Cohen *d* values of the subjective sleep parameters are displayed at Table (2). After 4 weeks of treatment, both suanzaorentang (-3.4, 95% CI -4.3 to -2.5) and placebo (-2.3, 95% CI -3.3 to -1.4) groups showed similar degree of improvement in ISI. The remission rates as defined by ISI less than 7 at week 4 was 13.8% for placebo and 11.5% for suanzaorentang group (p > 0.05).). The improvement rates as defined by a 30% decrease of ISI at week 4 as referenced to baseline was 21.1% for placebo and 26.9% for suanzaorentang group (p > 0.05). For the perception of depth of sleep, suanzaorentang group (-16.3, 95% CI -22.1 to -9.9; *d* = -0.685) showed a significant and greater improvement than the placebo group (-7.1, 95% CI -13.3 to -1.0; *d* = -0.305; p value for group by time interaction <0.05). Suanzaorentang group (-12.0, 95% CI -18.2 to -5.8; *d* = -0.447) also reported more refreshing sleep than the placebo group at week 4 (-2.2, 95% CI -8.9 to 4.5; *d* = -0.056; p value for group by time interaction <0.05). Regarding the objective measures by PSG and actigraphy, both groups did not have any significant changes at week 4 when compared to baseline (Table 3). There were no differences in the changes between suanzaorentang group and placebo group.

Adverse effects

For those who have completed the trial (n=138), the common adverse effects are listed in Table (4). A total of 25 subjects reported adverse effects and there was no significant difference between the two groups (p= 0.59). The most frequently occurring adverse events were drowsiness (8.7%), dry mouth (5.8%), lack of concentration (3.6%), and headache (2.9%). Placebo group had a higher rate of complaint of a lack of concentration but marginally lower rate of headache than treatment group. Overall, the severity of these adverse events was mild and none of them needed medical intervention.

DISCUSSION

To our knowledge, this is the first randomized double-blind placebo-controlled trial of a typical TCM herbal formula, suanzaorentang, for primary insomnia using a stringent screening process, careful exclusion of comorbid sleep and mental disorders, as well as both subjective and objective sleep outcome measures. The study showed that a short term (4 weeks) treatment of suanzaorentang improved insomnia in subjective sleep quality but not objective sleep measures. This formula also had good safety profile and tolerability.

This study result suggested that suanzaorentang had modest effects in improving the perceived sleep quality. The

Table 1: Baseline Demographic and clinical characteristics of the randomized population.

	All (N= 158)	Suanzaorentang (N= 78)	Placebo (N=80)	p value
Age, mean (SD), year	46.5 (10.0)	46.9 (10.5)	46.1 (9.5)	NS
Gender, Male (%)	51 (32.3)	25 (32.1)	26 (32.5)	NS
Marital status (%) Married Single Divorced/ Widowed	 108 (68.4) 40 (25.3) 10 (6.3	 51 (65.4) 21 (26.9) 6 (7.7)	 57 (71.2) 19 (23.8) 4 (5)	NS
Education (%) Primary or less Secondary Tertiary or above	 19 (12.0) 84 (53.2) 55 (34.8)	 12 (15.4) 39 (50.0) 27 (34.6)	 7 (8.8%) 45 (56.2%) 28 (35.0%)	NS
Occupation (%) Employed/ Student Homemaker Retired Unemployed	 106 (67.1) 30 (19) 6 (3.8) 16 (10.1)	 53(67.9) 14 (17.9) 3 (3.8) 8 (10.3)	 53 (66.2) 16 (20.0) 3 (3.8) 8 (10.0)	NS
Insomnia duration, mean (SD), year	10.0 (8.17)	11.4 (9.3)	8.6 (6.7)	< 0.05
Types of insomnia: DIS (%) DMS (%) EMA (%) Mixed types (%)	 110 (69.6) 108 (68.4) 79 (50.0) 106 (67.1)	 52 (66.7) 52 (66.7) 39 (50.0) 49 (62.8)	 58 (72.5) 56 (70.0) 40 (50.0) 57 (71.2)	 NS NS NS NS
ISI total score, mean (SD)	16.6 (4.6)	17.1 (4.8)	16.1 (4.4)	NS
PSG (average of 1st and 2nd night)				
Total sleep time, mean (SD), min	361.3 (55.9)	365.4 (59.2)	357.4 (52.6)	NS
Sleep efficiency, mean (SD), %	75.6 (11.5)	76.4 (12.1)	74.7 (10.9)	NS
Sleep onset latency, mean (SD), min	40.6 (37.2)	39.6 (36.9)	41.6 (37.7)	NS
WASO, mean (SD), min	70.24 (42.5)	64.4 (40.9)	75.9 (43.4)	NS

Abbreviations: DIS: Difficulty Initiating Sleep ; DMS: Difficulty Maintaining Sleep ; EMA: Early Morning Awakening
ISI: Insomnia Severity Index; WASO: Wake After Sleep Onset

Table 2: Outcomes: Subjective sleep parameters.

	Mean (SE)		Change from baseline to week-4, Mean (95%CI)	*d*	p value*
	Baseline	Week 4			
ISI total score					
Suanzaorentang (N= 78)	17.1 (0.51)	13.7 (0.54)	-3.4 (-4.3 to -2.5)	-0.70	NS
Placebo (N= 80)	16.1 (0.51)	13.7 (0.53)	-2.3 (-3.3 to -1.4)	-0.54	
VAS for sleep – Deep/Light (mm)					
Suanzaorentang(N= 78)	72.8 (2.60)	56.4 (2.8)	-16.0 (-22.1 to -9.9)	-0.69	<0.05
Placebo (N= 80)	64.0 (2.57)	52.3 (2.73)	-7.1 (-13.3 to -1.0)	-0.31	
VAS for sleep – Dreamless/Lots of dreams (mm)					
Suanzaorentang(N= 78)	40.9 (3.94)	39.1 (3.52)	-1.9 (-10.1 to -6.4)	-0.05	NS
Placebo (N= 80)	31.2 (3.91)	33.2 (3.48)	2.9 (-2.7 to 8.5)	0.05	
VAS for sleep – Calmness / Restless (mm)					
Suanzaorentang(N= 78)	54.9 (3.3)	47.1 (3.1)	-7.2 (-15.1 to 0.7)	-0.25	NS
Placebo (N= 80)	49.5 (3.3)	50.5 (3.1)	0.4 (-6.6 to 7.4)	0.04	
VAS for sleep – Refreshing /non-refreshing (mm)					
Suanzaorentang(N= 78)	69.4 (2.8)	57.7 (2.8)	-12.0 (-18.2 to -5.8)	-0.45	<0.05
Placebo (N= 80)	59.2 (2.8)	57.9 (2.8)	-2.2 (-8.9 to 4.5)	-0.06	

* p value for group by time interaction using linear mixed-effects models.

Table 3: Objective sleep parameters.

	Mean (SE)		Change from baseline to week-4, Mean (95%CI)	*d*	p value*
	Baseline	Week 4			
PSG - Total sleep time (min)					
Suanzaorentang(N= 78)	365.4 (6.3)	363.9 (6.7)	-2.1 (-11.7 to 7.4)	-0.002	NS
Placebo (N= 80)	357.4 (6.3)	358.8 (6.6)	1.5 (-11.0 to 13.8)	0.03	
PSG – Sleep efficiency (%)					
Suanzaorentang(N= 78)	76.4 (1.3)	77.6 (1.3)	-1.13 (-3.2 to 1.0)	0.09	NS
Placebo (N= 80)	74.7 (1.3)	76.4 (1.3)	-1.6 (-4.0 to 0.8)	0.15	
PSG – Sleep onset latency (min)					
Suanzaorentang(N= 78)	39.6 (4.2)	36.4 (4.1)	-3.6 (-7.8 to 0.7)	-0.009	NS
Placebo (N= 80)	41.6 (4.2)	39.3 (4.0)	-2.4 (-7.7 to 2.8)	-0.006	
PSG – WASO (min)					
Suanzaorentang(N= 78)	64.4 (4.8)	67.0 (5.8)	3.4 (-6.0 to 12.7)	0.06	NS
Placebo (N= 80)	75.9 (4.7)	69.3 (5.7)	-7.0 (-18.6 to 4.6)	0.12	
Actiwatch – Total sleep time (min)					
Suanzaorentang(N= 78)	400.3 (6.8)	411.6 (6.3)	10.1 (-3.2 to 23.4)	0.20	NS
Placebo (N= 80)	396.7 (6.6)	404.1 (6.2)	6.1 (-9.8 to 22.0)	0.13	
Actiwatch – Sleep efficiency (%)					
Suanzaorentang(N= 78)	87.3 (1.1)	87.8 (0.9)	0.4 (-1.2 to 2.0)	0.08	NS
Placebo (N= 80)	86.6 (1.0)	88.5 (0.9)	2.2 (-0.3 to 4.7)	0.17	
Actiwatch – Sleep onset latency (min)					
Suanzaorentang(N= 78)	20.0 (2.7)	20.9 (2.7)	1.3 (-2.9 to 5.4)	0.04	NS
Placebo (N= 80)	20.9 (2.5)	21.1 (2.7)	-1.2 (-9.0 to 6.6)	0.02	
Actiwatch – WASO (min)					
Suanzaorentang(N= 78)	26.7 (2.8)	28.9 (2.4)	2.2 (-2.0 to 6.4)	0.09	NS
Placebo (N= 80)	26.3 (2.7)	25.8 (2.4)	-0.8 (-5.1 to 3.6)	-0.02	

PSG – Stage N1 (% of Total Sleep Time)					
Suanzaorentang(N= 78)	14.1 (1.1)	13.4 (1.1)	0.7 (-0.5 – 1.9)	0.24	NS
Placebo (N= 80)	15.6 (1.1)	15.2 (1.1)	0.38 (-1.3 – 2.0)	0.03	
PSG – Stage N2 (% of Total Sleep Time)					
Suanzaorentang(N= 78)	63.5 (0.8)	64.8 (0.8)	-1.3 (-2.7 – 0.2)	-0.28	NS
Placebo (N= 80)	61.9 (0.9)	62.2 (1.0)	-0.4 (-1.6 – 0.9)	-0.04	
PSG – Stage N3 (% of Total Sleep Time)					
Suanzaorentang(N= 78)	2.3 (0.4)	2.4 (0.4)	-0.1 (-0.6 – 0.5)	-0.03	NS
Placebo (N= 80)	2.7 (0.5)	2.9 (0.5)	-0.2 (-0.6 – 0.3)	-0.04	
PSG – Stage R (% of Total Sleep Time)					
Suanzaorentang(N= 78)	20.3 (0.7)	19.7 (0.7)	0.6 (-0.4 – 1.7)	0.10	NS
Placebo (N= 80)	19.9 (0.7)	19.7 (0.7)	0.2 (-0.9 – 1.2)	0.03	
Abbreviations: WASO: Wake after Sleep Onset * p value for group by time interaction using linear mixed-effects models.					

Table 4: Common adverse events, n (%), reported by subjects completed the trial.

Adverse effect	All (N= 139)	Suanzaorentang(N= 71)	Placebo (N=68)	P value
Any adverse effect	25 (18.0)	11 (15.5)	14 (20.6)	NS
Drowsiness	12 (8.6)	6 (8.5)	6 (8.8)	NS
Dry mouth	8 (5.6)	3 (4.2)	5 (7.4)	NS
Lack of concentration	5 (3.6)	0	5 (7.4)	0.026[&]
Headache	4 (2.9)	4 (5.6)	0	0.055[&]
Stiffness of nose	4 (2.9)	2 (2.8)	2 (2.9)	NS
Muscle Stiffness	3 (2.2)	2 (2.8)	1 (1.5)	NS
Constipation	3 (2.2)	2 (2.8)	1 (1.5)	NS
Depressed mood	3 (2.2)	1 (1.4)	2 (2.9)	NS
[&] Fisher's exact test				

changes in sleep quantity, in terms of PSG and actigraphic measures, however, were not conspicuous. The improvement in subjective, rather than objective outcomes could possibly be explained by the following reasons. Firstly, discrepancy between subjective and objective measures in insomnia trial is commonly encountered. Therefore, it has been suggested that subjective measures could be an even better index for gauging the magnitude of improvement in the treatment of insomnia [37]. A recent study also showed that quantitative PSG-based selection criteria exclude a large proportion of patients meeting insomnia diagnostic criteria [38]. Reviewing the literature, similar results had been found in randomized-controlled trials of CAM for western herbal medicine [39,40]. For example, Morin et al reported that a combination of valerian-hops improved sleep in subjective measures but not in PSG parameters [40]. Second, our findings could be limited by the study design of a fixed dosage of trial medication and the relatively short treatment period. A longer treatment period and a titrating dosage may be able to show progressive change in objective parameters.

Regarding the subjective improvement, suanzaorentang showed more prominent result in depth of sleep and feeling of refreshment upon awakening but not the ISI total score. Although the ISI score also showed improvement, however, it was not superior to placebo effect. While ISI focuses on insomnia subtypes (DIS, DMS or EMA) and the consequences of insomnia, the VAS questions additionally measured the perceived sleep quality. Insomniac patients often complain of non-restoring, dreamy and restless sleep. The concept is comparable to nonrestorative sleep (NRS). The concept of NRS is based on the restorative theory, at which sleep is regarded as a process for replenishing the body and mind for daily functioning. While NRS is commonly co-morbid with other subtypes of insomnia (sleep difficulty), it is regarded as a distinctive type of insomnia [41-43]. A recent study revealed that the sleep architecture of NRS appeared polysomnographically normal on the basis of sleep parameters such as TST, WASO, SOL and sleep stages [41]. However, subjects of NRS had more EEG arousal and cyclic alternating pattern (CAP), suggesting a possible theory of hyperarousal, or a hyper-vigilant state during sleep [42]. Other than the hyperarousal concept, the understanding of pathophysiological mechanisms and the treatment modality of NRS remains sparse. Our study found that 4-week treatment of suanzaorentang improved NRS symptoms. Interestingly, the lack of concentration, which was considered as an adverse effect of treatment, was less likely in suanzaorentang when compared with placebo group. This result was consistent with the finding that suanzaorentang improved NRS symptoms. Its efficacy on NRS warrants further studies to replicate its effect and to look into its long-term effect on NRS. The detailed mechanisms underlying our observation are

unclear. It seems unlikely that suanzaorentang exerts its effect on improving NRS symptom by increasing slow wave sleep as we did not find any differences in sleep architecture between groups. Future quantitative measures with power spectrum analysis of sleep EEG and further research on the detailed pharmacological actions of suanzaorentang will be needed.

Although it has been reported that suanzaorentang might induce serotonin syndrome when being used in combination with venlafaxine in a patient our study suggests that suanzaorentang has good safety profile and tolerability, which is consistent with the conclusion from a recent review. In addition, we did not observe any rebound of insomnia symptoms, which is commonly reported in abrupt cessation of benzodiazepines [45]. Nonetheless, superior efficacy trials are warranted to compare the efficacy, safety, and cost with other well-established treatments of insomnia (e.g.; benzodiazepines and cognitive behavior therapy).

LIMITATIONS

This study had some limitations. Firstly, this is a relatively short-term study (4 weeks) with a fixed dosage design on subjects with chronic insomnia (mean duration of 10 years). The findings of a modest effect in subjective measurements could be limited by a fixed dosage design and a rather short treatment period of 4 weeks. Thus, it remains unclear whether suanzaorentang could have better efficacy in higher dosage and longer treatment period. Given its short term effect on insomnia, further trials could be conducted to explore the effect of higher dosage and its long-term efficacy. Second, this study adopted a stringent diagnostic, monitoring, and evaluation process to include primary insomnia subjects free of other comorbid major sleep disorders and mental disorders. As insomnia is a common co-morbidity in various physical, mental and sleep disorders, the exclusion of other co-morbidities may limit its generalizability to insomnia in other clinical populations.

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