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CLINICAL STUDY

Efficacy of Huadananshen mistura on insomnia: a randomized, double-blind, placebo-controlled, and multi-center clinical trial

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Abstract

OBJECTIVE: To evaluate the effect of Huadananshen mistura in clinical treatment of Chinese patients with insomnia.

METHODS: In this randomized, double-blind, placebo-controlled, multi-center study, 244 patients with insomnia were randomly assigned to a placebo group, a low-dose (10 mL/day), or a high-dose (20 mL/day) mistura group. Efficacy was assessed by using the sleep dysfunction rating scale (SDRS) and Clinical Global Impression-Improvement (CGI-I) scores. Safety and tolerability assessments included emergent adverse events, laboratory tests, and electrocardiograms.

RESULTS: Total SDRS scores decreased in all three groups, and there were significant differences between the placebo group and the low- and high-dose mistura groups (P=0.000). CGI-I ratings in the low- and high-dose mistura groups were significantly better than that of the placebo group (P=0.000). Incidences of rebound insomnia were similar in all three groups (placebo group: 6.94% , low-dose mistura group: 12.99% , and high-dose mistura group: 10.96% ; P=0.475). The efficacy of Huadananshen mistura in the low- or high-dose group was significantly better than that of the placebo group (P=0.000), but with no significant difference found between the low- and high-dose mistura groups (P=0.887). The rates of adverse events were similar in the three groups (placebo 2.44% , low-dose mistura 0% , and high-dose mistura 5% ; P=0.088).

CONCLUSION: Huadananshen mistura is an effective and generally well-tolerated hypnotic medicine for the treatment of Chinese patients with insomnia.

Key words: Sleep initiation and maintenance disorders; Medicine, Chinese traditional; Randomized controlled trials; Double-blind method; Huadananshen mistura

INTRODUCTION

Insomnia is the most common sleeping problem in the general population, with a prevalence of about 13%-45% depending on the criteria used.[1-3] With social and economic development, more people suffer from insomnia, especially women and the elderly. Many western hypnotics have been developed in recent years, such as benzodiazepine derivatives, non-benzodiazepine hypnotics, and z-drugs like zolpidem, zopiclone, eszopiclone and zaleplon.[4,5] Each drug acts on

neurotransmitters or receptors to produce sedative and hypnotic effects. However, the medications have short durations of action, and some have a risk of tolerance or abuse.[6] They may also cause impairments in memory and cognitive function, especially benzodiazepine derivatives.[7]

Huadananshen mistura (Mind-tranquilizing Mixture of Huadan Brand, mistura) is a modern Traditional Chinese Medicine. The main ingredients are the twigs and leaves of the peanut and Danshen (*Radix Salviae Miltiorrhizae*). Huadananshen mistura was developed by the Shanghai Science and Technology Commission from December 2000 to December 2002. The peanut plant opens its leaves in the daytime and closes them in the evening, just like normal people work in the daytime and sleep at night. This indicates that the peanut leaf possibly contains sleep-promoting substances.[8-12] Toxicological study[9] found that the LD 50 was 141.75 g/kg, or 283 times the clinical dosage. Long-term toxicity tests[9] showed that there were no significant changes in blood indexes and biochemical parameters of rats taking Huadananshen mistura for 3 months. Only the clotting time was prolonged in male rats in the medication group. Pre-clinical trials[10-12] demonstrated that Huadananshen mistura can improve sleep, and adverse reactions are similar to the placebo.

Huadananshen mistura was approved as a hypnotic medicine by the State Food and Drug Administration (SFDA) of China in September 2004 (File No. 2004L03248, Chinese Traditional Medicine Category Six). We conducted this randomized controlled trial (RCT) to evaluate the efficacy and safety of Huadananshen mistura in the clinical treatment of insomnia, and observe rebound insomnia after medication end.

METHODS

This randomized double-blind, placebo-controlled multi-center clinical trial was designed to evaluate the efficacy and safety of low- or high-dose Huadananshen mistura in the clinical treatment of insomnia.

Subjects

Patients that were aged 18 to 65 years, had been admitted to hospital, and met the DSM-IV criteria for insomnia were recruited into the study. The exclusion criteria were: (a) alcoholics, drug addicts, or pregnant or lactating women; (b) insomnia caused by drugs, alcohol, or physical and mental illness; (c) patients undergoing regular antipsychotic or antidepressant treatment 4 weeks before the enrollment; (d) patients with significant heart, liver, kidney or other major diseases; (e) laboratory tests and electrocardiogram (ECG) indicating significant abnormalities, with AST or ALT more than 1.5 times the normal upper limit; (f) allergies to Huadananshen mistura; (g) Hamilton anxiety rating scale (HAM-A) score ≥14, or Hamilton depression rating scale (HDRS) score ≥18; or (h) undergoing other clinical trials within 30 days of the study.

Study design

This trial was conducted in three hospitals (Shanghai Mental Health Center, Shanghai Huashan Hospital, and Shanghai Yueyang Hospital) from March 2005 to December 2006. According to the sample size, the table of random numbers was produced by statistical software SAS 6.12 (SAS Institute Inc., Cary, NC, USA). All patients were randomly assigned to the low-dose mistura, high-dose mistura, or placebo group. Patients took 10 or 20 mL of Huadananshen mistura, or the placebo, orally every night for 2 weeks. There was a 1-week follow-up observation for rebound insomnia. The study protocol was reviewed and approved by the Institutional Review Board of Shanghai Mental Health Center, and the study was approved by the Ethic Committee of Shanghai Mental Health Center. Written informed consent was signed by all subjects before any study-related activities.

Medication and administration

Patients took Huadananshen mistura oral liquid (10 or 20 mL every night) or placebo for 2 weeks. They were asked to suspend all other hypnotics during the trial. Any psychiatric medications, including antipsychotics, antidepressants, anxiolytics, were forbidden.

The Huadananshen mistura oral liquid and the placebo were similar in appearance and taste and were produced by Shanghai Baolong Pharmaceutical Corporation (Shanghai, China) (Batch No. 050401 and 050101). Personnel involved in the manufacturing and packaging of the medications were not allowed to contact the subjects or the research personnel.

For all subjects, a physical examination, an ECG, and blood tests including serum creatinine, aspartate aminotransferase, alanine aminotransferase, and urea nitrogen were performed. Laboratory tests were done at the beginning and end of the 2-week trial. Investigators documented and recorded adverse events and concomitant medications. Finally, the medication containers and remaining drugs were withdrawn from all subjects.

Efficacy evaluation

Efficacy evaluations were made according to the baseline at the end of 1- and 2-weeks, based primarily on changes in the total sleep dysfunction rating scale (SDRS) scores. Secondary efficacy measures included the reduction rate of SDRS scores and changes Clinical Global Impression-Improvement (CGI-I) scores. Clinical recovery was defined as a reduction rate ≥80%. If the reduction rate was between 50% and 79%, then the clinical efficacy was markedly effective. If the reduction rate was between 30% and 49%, then it was effective. Recovery was invalid if the reduction rate was less than 30%. The effective rate was the sum of the clinical recovery and marked effect.

Safety evaluation

Spontaneous reports about emergent adverse events (AEs) were collected daily. AEs were defined as untoward medical events occurring during the clinical trial, regardless of whether or not there was a close relation with Huadananshen mistura. AEs included: (a) all the drug's suspected adverse reactions; (b) the allergic or toxic reaction due to overdose or abuse; (c) worsening of unrelated diseases; (d) injury or accident; (e) abnormalities found by physical examination or laboratory tests, needing further investigation or clinical treatment. When the investigator recorded the CRF of adverse events, they used three grades (mild, moderate, and severe) to describe the condition of adverse events.

Statistical analysis

The study was analyzed with the principle of intention to treat (ITT). The primary analysis of efficacy endpoints was performed for the full analysis set (FAS) population, including all patients who were randomly assigned to treatment, who received at least one dose of the study medication, and who had at least a baseline and one post-baseline assessment. The endpoint was defined as the last observation carried forward . Secondary analyses were also carried out for the per-protocol set (PPS), which included all FAS patients who had good compliance, did take prohibited medication, and had a clinical observation duration of more than 2 weeks. Safety evaluation proceeded according to the safety set (SS), which included all randomized subjects who received at least one dose of the study medication.

T-tests were used to compare the quantitative parameters of normal distributions and the Wilcoxon rank-sum test was used to compare the quantitative parameters of non-normal distributions by SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Cochran Mantel-Haenszel *Chi*-squared test was used to analyze the differences in ordinal segment parameters between groups. An analysis of covariance was used to analyze the difference in qualitative parameters between groups, which included the baseline score and gender as the covariates, and the treatment center as a random effect. All the statistical tests were two-tailed, and the significance was set to $P<0.05$.

RESULTS

The 252 patients recruited to participate in this trial were from three hospitals in Shanghai, and were randomly divided into three groups. Twenty-five patients dropped out because of adverse events, invalid effects, lost follow-up, or revocation of informed consent. Eight patients (two in the placebo group, two in low-dose mistura group and four in high-dose mistura group) that could not enter into any analysis sets were removed. 244 patients were included in the FAS, 229 in the PPS, and 244 in the SS. The baseline demographic characteristics are shown in Table 1. There were no significant differences between the three groups at the baseline in terms of demographic variables ($P>0.05$).

Efficacy of Huadananshen mistura for treating insomnia

All patients showed improvements in quality of sleep and total SDRS scores gradually decreased in the three groups during the 2-week clinical trial (Figure 1). Comparing the total scores of SDRS before and after treatment, the score at the baseline was 26±6 in the placebo group, 27±6 in the low-dose mistura group, and 26±6 in the high-dose mistura group. After a 2-week treatment, the score was 18±9 in the placebo group, 13±6 in the low-dose mistura group and 13 ± 7 in the high-dose mistura group. There were significant differences at each measured time point during the treatment between the placebo group and the low- and high-dose mistura groups ($P=0.000$). However, there were no significant differences between the low-dose mistura group and the high-dose mistura group. The SDRS scores in the 2-week and 3-week treatment showed no significant differences among the three groups ($P=0.319$).

According to the CGI-I scores, there were no statistically significant differences among the three groups at the baseline (placebo group: 4.5 ± 1.0, low-dose mistura group: 4.6±1.0, and high-dose mistura group: 4.4±0.9; $P=0.635$). Throughout the study, the mean scores gradually decreased in the three groups, and the changes were statistically significant at week 1 (placebo group: 3.7 ± 1.1, low-dose mistura group: 3.4 ± 1.1, and high-dose mistura group: 3.2 ± 1.0; $P=0.024$), and at the end of the 2-week treatment (placebo group: 3.6± 1.1, low-dose mistura group: 2.8 ± 1.1, and high-dose mistura group: 2.6 ± 1.4; $P=0.000$). The improvements in CGI-I scores were statistically significant at week 1 ($P=0.032$) and week 2 ($P=0.000$) in all three groups. The improvement of CGI-I in the low- or high-dose mistura group was significantly better than that of the placebo group ($P=0.000$). However, there were no significant differences between the low- and high-dose mistura groups ($P=0.920$ at week 1 and $P=0.839$ at week 2).

We also observed the incidence of rebound insomnia after medication cessation at the end of the 2-week treatment. The occurrence rates of rebound insomnia were 6.94%, 12.99%, and 10.96%, respectively, in the placebo, low-dose mistura, and high-dose mistura groups. There were no significant differences among the three groups ($P=0.475$). However, the duration of rebound insomnia was similarly about 2-3 days in the three groups ($P=0.376$).

Adverse events

In the safety analysis of 82 patients in the placebo

Table 1 Baseline demographic characteristics of insomnia patients

Variable		Placebo (*n*=82)	Low-dose (*n*=82)	High-dose (*n*=80)	*P*
Age (year)		47±11	47±12	48±12	0.652
Gender	Male (%)	26 (31.71)	25 (30.49)	19 (23.75)	0.485
	Female (%)	56 (68.29)	57 (69.51)	61 (76.25)	
Marriage status	Married [*n* (%)]	75 (91.46)	74 (90.24)	74 (92.50)	0.873
	Divorced or separated [*n* (%)]	1 (1.22)	2 (2.44)	0 (0.00)	
	Unmarried [*n* (%)]	6 (7.32)	6 (7.32)	6 (7.50)	
Family status	Spouse [*n* (%)]	74 (90.24)	74 (90.24)	72 (90.00)	0.819
	Parents [*n* (%)]	5 (6.10)	2 (2.44)	3 (3.75)	
	Solitary [*n* (%)]	1 (1.22)	1 (1.22)	2 (2.50)	
	Others [*n* (%)]	2 (2.44)	5 (6.10)	3 (3.75)	
Insomnia status	First episode [*n* (%)]	32 (39.02)	19 (23.17)	22 (27.50)	0.133
	Recurrence [*n* (%)]	23 (28.05)	27 (32.93)	32 (40.00)	
	Chronic [*n* (%)]	27 (32.93)	36 (43.90)	26 (32.50)	
Causing factor	No factors [*n* (%)]	36 (43.90)	30 (36.59)	32 (40.00)	0.961
	Physical illness [*n* (%)]	1 (1.22)	2 (2.44)	2 (2.50)	
	Psycho-social pressure [*n* (%)]	13 (15.85)	16 (19.51)	16 (20.00)	
	Physical illness and pressure [*n* (%)]	0 (0.00)	1 (1.22)	0 (0.00)	
	Unclear factors [*n* (%)]	32 (39.02)	33 (40.24)	30 (37.50)	
Previous treatment	No any treatment [*n* (%)]	54 (65.85)	55 (67.07)	55 (68.75)	0.927
	Have been treated [*n* (%)]	28 (34.15)	27 (32.93)	25 (31.25)	
Duration of the disease (month)		8±15	10±14	8±11	0.472
Total duration of the disease (month)		36±70	42±69	37±65	0.446
Combined drug usage [*n* (%)]		11 (13.41)	8 (9.76)	8 (10.00)	0.763
Total score of HAMA		5±3	5±3	5±3	0.613
Total score of HDRS		6±2	6±2	6±3	0.935

Notes: placebo group: similar appearance liquid; low-dose group: 10 mL/day mistura; high-dose group: 20 mL/day mistura. HAMA: hamilton anxiety rating scale; HDRS: hamilton depression rating scale.

group, 82 patients in the low-dose mistura group, and 80 patients in the high-dose mistura group, the incidence of the possible study drug-related AEs generally reflected the known safety profiles of Huadananshen mistura. The overall incidence of AEs was 2.44% in the placebo group, 5% in the high-dose mistura group, while no AEs were found in the low-dose mistura group. There were no significant differences in the incidence of AEs among the three groups (*P*=0.088). Most AEs were nausea, vomiting, and gastrointestinal reactions. One of the AEs in the placebo group was moderate bronchiectasis complicated by hemoptysis, but the patient had a previous history, not related to Huadananshen mistura.

DISCUSSION

This randomized, double-blind, placebo-controlled clinical study followed Good clinical practice (GCP) management specifications for China. The study was performed in three hospitals to evaluate the efficacy and safety of Huadananshen mistura in patients with insomnia. The findings from the primary endpoints demonstrated that 10 and 20 mL/day Huadananshen mistura were more effective than the placebo for treating insomnia.

The results from the present study are supported by the other studies,[13,14] demonstrating that Huadananshen mistura has efficacy in the treatment of insomnia. For example, Wang *et al* [13] observed the clinical efficacy

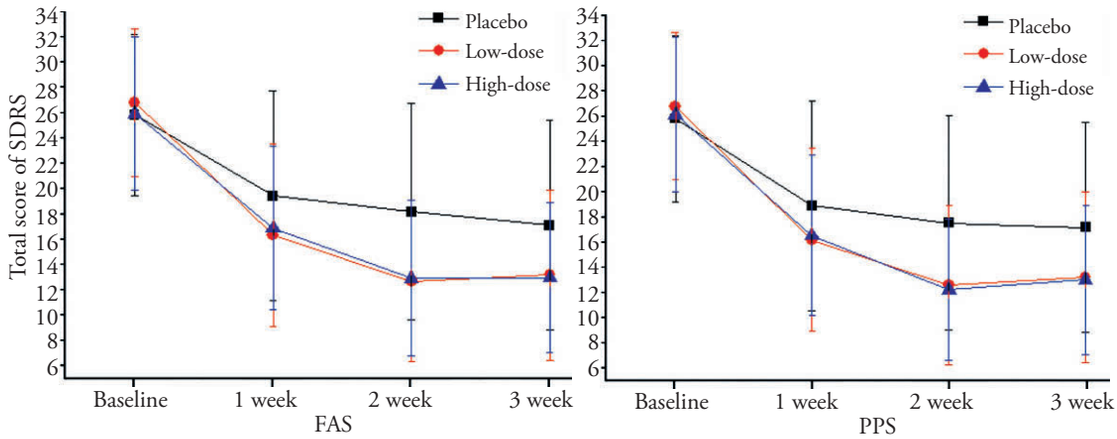

Figure 1 Changes in the total SDRS scores at multiple time points (FAS and PPS)
Placebo group: similar appearance liquid; Low-dose group: 10 mL/day mistura; High-dose group: 20 mL/day mistura. SDRS: Sleep dysfunction rating scale; FAS: full analysis set; PPS: per-protocol set. At the end of 2 weeks' treatment, the clinical recovery rate and effective rate were 6.10% and 26.83% in the placebo group, respectively. In the low-dose mistura group, the rates were 8.54% and 68.29%, respectively. In the high-dose mistura group, the rates were 5.00% and 70.00%, respectively. The efficacy of Huadan-anshen mistura in the low- or high-dose was significantly better than that of placebo (P=0.000), but there was no significant difference between the low-dose and high-dose mistura groups (P=0.887).

of peanut twigs and leaves in a controlled study of 458 patients with insomnia, and found that the total effective rate was 96% in the treatment group of 100 cases. Another randomized, double-blind, and placebo-controlled clinical trial had a total effective rate of 73.6% in a peanut preparation group, but 43.2% in the placebo group.[14]

The clinical efficacies of benzodiazepine derivatives and non-benzodiazepine hypnotics have been recognized, but their use may induce many side effects, such as rebound insomnia and residual sedation.[15] Rebound insomnia often aggravates clinical symptoms, especially after withdrawal of a short-term treatment. In the present study, the occurrence rates of rebound insomnia were 6.94% , 12.99% , and 10.96% in the placebo, low-dose, and high-dose mistura groups, respectively, within 1 week following an abrupt discontinuation of the medication, with no significant differences among the three groups. No unexpected adverse events or serious adverse events appeared in the low- or high-dose mistura groups. To sum up, Huadananshen mistura is effective for treating insomnia and the dose of mistura is well tolerated and safe.

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