JoP Journal of Pharmacopuncture
Journal of Pharmacopuncture 2024;27(4):322-331
pISSN: 2093-6966 • eISSN: 2234-6856
https://doi.org/10.3831/KPI.2024.27.4.322
Original Article
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Effect of Herbal Medicine (Hwanglyeonhaedok-tang) on Insomnia Patients with Bedtime Procrastination: study protocol for a randomized controlled trial

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Received July 29, 2024
Reviewed August 12, 2024
Accepted September 20, 2024

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Objectives: Insomnia, characterized by difficulty initiating or maintaining sleep, affects a significant portion of the global population. Bedtime procrastination, which is a voluntary delay in going to bed, is a major contributing factor to the prevalence of sleep deprivation in modern societies. Hwanglyeonhaedok-tang (HJD decoction) has shown promise in improving the symptoms of insomnia. This study aimed to evaluate the efficacy of HJD decoction in patients with insomnia and bedtime procrastination.
Methods: This study employs a parallel-group design, comparing HJD decoction to usual care in a 1:1 ratio. Sixty participants with insomnia and bedtime procrastination will be enrolled. The experimental group will receive HJD decoction for 4 weeks, while both groups will undergo a brief behavioral treatment for insomnia. The primary outcome will be the change in the Insomnia Severity Index score (ISI) from baseline to 4 weeks. Secondary outcomes include sleep diary metrics, the Pittsburgh Sleep Quality Index (PSQI), and Bedtime Procrastination Scale (BPS). The exploratory outcomes include perceived stress, anxiety, smartphone use, and heart rate variability.
Conclusion: This trial examines the role of herbal medicine in treating a specific type of insomnia that is increasingly common in modern society. The combination of HJD decoction with behavioral intervention offers a comprehensive approach to treating insomnia complicated by bedtime procrastination. The results will provide valuable insights into integrative treatment strategies for sleep disorders in the digital age.

Keywords: bedtime procrastination, clinical protocols, Huanglian-jie-du decoction, Hwanglyeonhaedok-tang, oren gedoku to, sleep initiation and maintenance disorders

INTRODUCTION

Insomnia, characterized by difficulty in initiating or maintaining sleep or experiencing early morning awakenings [1], impacts a significant portion of the population. In Korea, 17% of individuals encounter insomnia symptoms more than three times a week, and 5% fulfill the diagnostic criteria for insomnia [2, 3]. Globally, population-based data suggest that 30-36% of people experience nocturnal insomnia symptoms, with 10-15% reporting daytime difficulties due to insomnia and 6-10% meeting the diagnostic criteria for insomnia disorder [4]. Insomnia is highly heterogeneous due to its numerous contributing factors [5, 6]. Bedtime procrastination, the voluntary delay of going to bed despite the absence of external elements, is a critical factor contributing to sleep deprivation in contemporary society [7-9]. This behavior is associated with poor sleep quality and duration, resulting in chronic sleep deprivation [10]. Psychological counseling programs aimed at improving bedtime procrastination have demonstrated significant improvements in Insomnia Severity Index (ISI) scores compared with control

groups [11].

Hwanglyeonhaedok-tang (Huanglian-jie-du decoction in Chinese, Oren gedoku to in Japanese, HJD decoction), a composition of *Coptidis Rhizoma*, *Scutellariae Radix*, *Phellodendri Cortex*, and *Gardeniae Fructus*, has demonstrated significant effects in improving insomnia symptoms, as evidence in three clinical trials [12-14] and two case reports [15, 16]. In a clinical trial involving patients with Hwa-Byung, the group taking HJD decoction for 7 days exhibited a notable reduction in ISI scores compared to the placebo group [13]. Another trial involving insomnia patients demonstrated significant reductions in the ISI and Pittsburgh Sleep Quality Index (PSQI) scores following a 3-week regimen with HJD decoction. This trial compared the effect of HJD decoction with another herbal medicine, Gamiguibi-tang [14]. Additionally, a trial conducted on patients with schizophrenia and other psychoses revealed a decrease in sleep medication use in the group treated with HJD decoction [12]. Case studies have also highlighted the efficacy of HJD decoction, with two patients lowering their sleep medication dosage and enhancing ISI scores after a 2-week treatment [16] and another patient with severe insomnia demonstrated clinical improvement after a 4-week combination treatment with HJD decoction [15]. However, to date, no clinical trial has evaluated the efficacy of the HJD decoction in improving insomnia symptoms compared to a control group (placebo or usual care), specifically in patients diagnosed with primary insomnia. Previous studies have focused primarily on insomnia associated with other conditions or compared HJD to other herbal medicines.

This study aimed to assess the efficacy of HJD decoction in patients with insomnia and bedtime procrastination. Both the experimental and control groups will receive brief behavioral treatment for insomnia [17], with the experimental group additionally receiving HJD decoction as an add-on treatment. The primary objective of this study is to evaluate the efficacy of HJD decoction on insomnia symptoms compared to standard care. The secondary objective of this study is to determine the effects of HJD decoction on bedtime procrastination and its safety profile in comparison with usual care. This study utilized a parallel-group design to compare the impact of HJD decoction with usual care, with an allocation ratio of 1:1, aiming for superiority.

MATERIALS AND METHODS

1. Study setting

This study will be conducted at a Korean medicine university hospital in the Republic of Korea. This trial was registered at Clinical Research Information Service (KCT0009329) on April 12, 2024.

2. Eligibility criteria

1) Inclusion criteria

The inclusion criteria for this study are as follows: participants must be adults aged 19-59 years of either sex. They must have a diagnosis of insomnia disorder according to the DSM-5 criteria [1] and an ISI score between 15 and 28 [18, 19], indicating moderate to severe insomnia. Additionally, participants must score between 33 and 45 on the Bedtime Procrastination Scale (BPS) [10, 20], targeting individuals with insomnia and bedtime procrastination behaviors. A Beck Anxiety Inventory (BAI) score between 8 and 26 [21, 22] is required to include participants with anxiety symptoms consistent with the indications for HJD decoction. Participants must also score 3-5 points on item 13 of the Cold-Heat Pattern Identification questionnaire [23], which measures facial redness, an additional symptom of HJD. Finally, participants were required to voluntarily provide written consent to participate in the clinical trial.

2) Exclusion criteria

The exclusion criteria for this study are as follows: participants with a history of major psychiatric disorders within the past two years are excluded. Those who have recently used medications, such as antipsychotics, antidepressants, mood stabilizers, benzodiazepines, or Z-drugs, within four weeks leading up to screening will be excluded. Participants suspected of having major depressive disorder, panic disorder, generalized anxiety disorder, binge-eating disorder, bulimia nervosa, or alcohol use disorder, as indicated by the Patient Health Questionnaire [24], are excluded to focus on primary insomnia without major psychiatric comorbidities. Individuals with thyroid disorders or abnormal TSH levels will be excluded to avoid insomnia associated with thyroid dysfunction. Elevated liver enzymes or creatinine levels indicate liver or kidney dysfunction, necessitating exclusion. Additional details regarding the inclusion and exclusion criteria can be found in the clinical trial registration

information provided by the Clinical Research Information Service (registration number: KCT0009329).

3. Intervention

1) HJD decoction

In the experimental group, the participants will be given HJD decoction for four weeks. The decoction will be taken twice daily, once in the morning and once in the evening, either before or between meals, with each dose consisting of one packet (3 g). HJD is a fine, yellowish-brown granule administered orally with water. It is manufactured by Kracie Pharma, Ltd., and the composition and dosage of the HJD decoctions are summarized in Table 1.

Unless the participants experience side effects that warrant discontinuation, all participants in the experimental group will receive the same dose of HJD decoction without any modifications. HJD will be administered every two weeks, with adherence monitored by counting the remaining packets and those consumed at each visit. Participants will be instructed to take the medication twice daily as prescribed.

2) Brief behavioral treatment of insomnia

Starting from the time of randomization, all participants in both the experimental and usual care groups will receive Brief Behavioral Treatment for Insomnia (BBTI) [17]. BBTI is a short-term program that emphasizes behavioral aspects, focusing less on cognitive elements than traditional cognitive behavioral therapy for insomnia. Primarily, it involves sleep restriction and stimulus control therapies [17, 25].

During the second visit, participants will receive an explanation of the two processes that regulate sleep, review their sleep diaries, and establish a sleep plan. During the third and fourth visits, sleep diaries will be reviewed, and participants' sleep quality, daytime functionality, and compliance with the sleep plan will be assessed. Sleep plans will be adjusted as needed.

3) Recommendations on smartphone use

In addition to the BBTI, participants will be instructed to abstain from using smartphones starting 30 minutes prior to their planned bedtime. Participants will also review their smartphone usage logs over a seven-day period to assess daily usage and plan to limit daily smartphone use to a specified duration.

4) Prohibited or permitted concomitant medications

The use of antipsychotics, antidepressants, mood stabilizers, benzodiazepines, and Z-drugs (zolpidem, zaleplon, and zopiclone) will be prohibited throughout the clinical trial. Other medications deemed not to influence the outcomes of the clinical trial outcomes and are required for the treatment or examination of different conditions may be permitted at the discretion of the investigator. Information on any concomitant medications used during the trial to treat other conditions or adverse reactions will be documented on a case report form.

4. Outcomes

1) Primary outcome

The primary outcome focuses on the ISI total score [18, 19], which measures the change from baseline, assessed at 4 weeks. This self-report scale consists of seven items, each rated on a 0-4 scale, with a total score that ranges from 0-28. Higher scores signify increased severity of insomnia symptoms.

2) Secondary outcomes

Secondary outcomes encompass various sleep diary metrics, such as Total Sleep Time (TST), Sleep Efficiency (SE), Sleep Onset Latency (SOL), Wake After Sleep Onset (WASO), and Bedtime Procrastination Duration (BPD). These metrics will be recorded daily for seven days prior to each visit and then averaged. Additionally, the Pittsburgh Sleep Quality Index (PSQI) will be used to evaluate subjective sleep quality, with changes from baseline measured at 4 weeks [26, 27]. A lower PSQI score

Table 1. Name and dosages of herbal substance for 3 g of HJD decoction

Herbal name	Botanical name	Part used	Dosage (g)
Coptidis Rhizoma	Coptis chinensis Franch. [Ranunculaceae]	Rhizome	0.75
Scutellariae Radix	Scutellaria baicalensis Georgi. [Lamiaceae]	Root	1.5
Phellodendri Cortex	Phellodendron amurense Rupr. [Rutaceae]	Bark	0.75
Gardeniae Fructus	Gardenia jasminoides J.Ellis. [Rubiaceae]	Fruit	1.0

The total dosage presented in the table is 4 g, which represents the amount of raw herbal materials. These raw materials are subjected to water extraction to produce 3 g of granules.

 https://doi.org/10.3831/KPI.2024.27.4.322

indicates better sleep quality. The BPS measures the extent of delayed bedtime, with changes from baseline evaluated at 4 weeks [10, 20]. Lower BPS scores signify a decrease in bedtime procrastination. The Patients' Global Impression of Change (PGIC) will assess patients' perceptions of improvement in insomnia and bedtime procrastination symptoms, with the proportion of patients reporting improvement calculated at 4 weeks.

3) Exploratory outcomes

Exploratory outcomes include the Perceived Stress Scale (PSS), which quantifies perceived stress levels, with a total score ranging from 0 to 40 [28, 29]. Changes from baseline will be assessed at 4 weeks, with lower scores indicating decreased stress. The Beck Anxiety Inventory (BAI) measures anxiety levels, with changes from baseline measured at 4 weeks [21, 22, 30]. Lower BAI scores suggest a decrease in anxiety. The Cold-Heat Pattern Identification (CHPI) questionnaire will assess traditional medicine patterns, with changes from baseline evaluated at 4 weeks [23]. Higher scores reflect stronger cold or heat symptoms.

Smartphone usage time will be recorded daily for seven days prior to each visit, and the mean daily usage time will be calculated. Additionally, adherence to daily smartphone usage goals and the restriction of smartphone use 30 minutes before bedtime will be evaluated, and the proportion of days meeting these goals will be calculated. The Smartphone Addiction Scale Short Version (SAS-SV) evaluates problematic smartphone usage, with changes from baseline assessed at four weeks [31, 32]. Lower SAS-SV scores imply a decrease in addiction.

Finally, heart rate variability (HRV) will be measured to indicate the autonomic nervous system balance. Metrics such as Low Frequency (LF), High Frequency (HF), and LF/HF ratio will be evaluated based on changes from baseline measured at 4 weeks.

5. Participant timeline

After providing informed consent, the participants will un-

	STUDY PERIOD				
	Enrollment	Allocation	Post-allocation		Close-out
TIMEPOINT	-2W±7days	0W	2W±5days	4W±5days	8W±7days
ENROLLMENT:					
Informed consent	O				
Eligibility screen	O				
Diagnosis of insomnia disorder	O				
Allocation		O			
INTERVENTIONS:					
HJD decoction		←	—	→	
BBTI (both groups)		←	—	→	
ASSESSMENTS:					
ISI, BPS	O	O	O	O	O
Sleep diary		O	O	O	O
PSQI		O		O	O
PGIC			O	O	O
PSS		O		O	O
CHPI, BAI	O			O	O
Smartphone use diary		O	O	O	O
SAS-SV, HRV		O		O	O

Figure 1. Schedule of enrollment, interventions, and assessments. HJD decoction, Hwanglyeonhaedok-tang; BBTI, Brief Behavioral Treatment of Insomnia; ISI, Insomnia Severity Index; BPS, Bedtime Procrastination Scale; PSQI, Pittsburgh Sleep Quality Index; PGIC, Patients' Global Impression of Change; PSS, Perceived Stress Scale; CHPI, Cold-Heat Pattern Identification; BAI, Beck Anxiety Inventory; SAS-SV, Smartphone Addiction Scale Short Version; HRV, heart rate variability.

dergo a screening test (visit 1) to assess their eligibility based on the inclusion and exclusion criteria. Within 7-21 days, eligible participants will attend a baseline evaluation (visit 2), where they will be assigned randomly to either the experimental group receiving the HJD decoction for 4 weeks or the control group not receiving the treatment. Both groups will receive brief behavioral treatments for insomnia. Symptoms of insomnia will be evaluated at baseline (week 0), after treatment (week 4), and 4 weeks after treatment completion (week 8). A schematic of the participants' timelines is depicted in Fig. 1.

6. Sample size and recruitment

The primary efficacy endpoint of this clinical trial will be the change in the total ISI score from baseline to 4 weeks post-treatment. Due to a lack of substantial evidence concerning the effect size of the HJD decoction relative to the usual care group on the change in the ISI total score from baseline to 4 weeks, the sample size was determined based on the results of a previous study. In a randomized controlled trial comparing HJD decoction with placebo in patients with Hwa-byung, the ISI total score at 1 week was reported as 9.05 ± 3.88 in the treatment group and 13.1 ± 5.95 in the control group [13]. Based on this, assuming a difference of 4.05 between the two groups and a common standard deviation of 5.02, the required sample size per group was calculated to be 25 utilizing the following formula:

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2}{\eta^2} = \frac{2(1.956 + 0.842)^2}{(4.05/5.02)^2} \approx 25$$

Consequently, the final sample size is N = 50. Considering a dropout rate of 15% for this clinical trial, the final sample size was 30 participants per group, for a total of 60 participants.

To achieve adequate participant enrollment, IRB-approved recruitment notices will be posted on bulletin boards, both inside and outside the trial institution. Furthermore, online and local advertisements, such as those on subway stations, buses, and apartment bulletin boards, may be used to enhance participant recruitment.

7. Randomization and allocation concealment

An independent statistician created a computer-generated randomization table using SAS (Version 9.4 or higher) with a 1:1 allocation ratio and block randomization. The stratification factors will be applied. The allocation sequence will be uploaded to a secure electronic randomization system and concealed until interventions have been assigned.

Upon providing written consent, participants will receive a screening number. Those who meet the inclusion/exclusion criteria will be assigned a unique randomization number in order of enrollment. The investigator will access the electronic system to disclose the group allocation for each randomization number using the investigator's name, date, and time recorded in the system. Allocation concealment is preserved, as group allocations remain unknown until disclosure.

8. Blinding

This open-label study utilizes usual care as the control; no blinding methods will be implemented.

9. Data collection and management

Data will be collected in Korea using standardized questionnaires. To maintain data quality and uniformity, the investigators will undergo training in administering questionnaires adhering to the study's standard operating procedures. They will provide clear explanations to participants, ensuring each individual fully understands the content before responding.

Participants will complete sleep and smartphone use diaries seven days prior to each visit. The investigators will confirm the accuracy of the entries at each visit. To minimize the impact of outliers, the minimum and maximum values from the 7-day sleep and smartphone use diaries will be excluded, and the average of the remaining five days will be computed.

Text message reminders will be dispatched the day before each visit to promote participant retention and compliance with the clinical trial schedule. If a participant discontinues the trial, efforts will be made to perform all safety assessments scheduled for the post-treatment visit.

Data will be entered into an electronic case report form (eCRF) system, which includes preset ranges for data input values to enable additional verification and prevent data entry errors. To ensure data quality, the clinical monitor will conduct full-source data verification during regular monitoring visits, which are planned to occur after every 3-4 enrolled participants. This process identifies and resolves discrepancies between the source documents and the eCRF.

10. Statistical methods

1) Definition of analysis set

The primary population for efficacy analysis will be the full analysis set (FAS), including all randomized participants who have undergone at least one post-baseline efficacy assessment. The per-protocol set (PPS) will be used for sensitivity analyses and will consist of participants in the FAS who do not meet any of the following exclusion criteria: violation of inclusion/exclusion criteria, use of prohibited concomitant medications, absence of ISI assessment results at baseline (visit 2) and end of treatment (visit 4), randomization error resulting in the experimental group not receiving the HJD decoction or the usual care group receiving the HJD decoction prior to the follow-up visit, or HJD decoction compliance below 70% in the experimental group. In addition, participants deemed to have deviated from the planned study protocol will be extensively evaluated through a blinded meeting before the database lock to determine their exclusion from the PPS based on their influence on the study. Safety analyses will be conducted using a Safety Analysis Set (SAS), including all randomized participants.

2) Statistical methods for analyzing primary outcome

The primary efficacy endpoint, defined as the change in the ISI total score from baseline to week 4, will be analyzed using a mixed-effects model for repeated measures (MMRM), with the experimental group and visit as fixed factors, the participant as a random factor, and the interaction between the treatment group and visit. If there are significant differences between the groups in baseline characteristics that could impact the treatment effect, these variables will be incorporated as fixed factors in the model. If there are significant differences in baseline values between groups, an analysis of covariance (ANCOVA) using baseline value as a covariate will be performed as a supportive analysis. The results will be presented as means with 95% confidence intervals (CIs) and p-values. Additional within-group analyses will be performed using a multilevel linear model for repeated measures to evaluate trends over time in each treatment group.

3) Statistical methods for analyzing secondary outcomes

Secondary and exploratory continuous efficacy endpoints will be evaluated using the same MMRM approach as the primary endpoint. For binary endpoints, the number and percentage of participants achieving or not achieving the endpoint at the end of treatment will be reported by group. Logistic regression analysis will be employed for between-group comparisons, with odds ratios and 95% confidence intervals (CIs) provided.

4) Statistical methods for safety outcomes

Safety analyses will encompass the incidence and number of adverse events (AEs) summarized by type, severity, and relationship with the study treatment. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), System Organ Class (SOC), and Preferred Term (PT). Laboratory tests and vital signs will be summarized using descriptive statistics, with continuous variables presented as mean and standard deviation and categorical variables as frequency and percentage, by visit and treatment group.

5) Statistical methods to handle missing data

Missing data for the primary endpoint will be managed utilizing the MMRM approach, compensating for missing data using maximum likelihood estimation without explicit imputation. For supportive analyses of continuous variables, such as analysis of covariance (ANCOVA) or repeated-measures ANOVA, multiple imputation will be applied to address missing data. Missing data for binary variables will not be subject to imputation.

11. Data monitoring

This study does not require a Data Monitoring Committee, as investigational herbal medicine is being used within its approved indication. No interim analyses are anticipated. However, the trial may be terminated prematurely if there are unacceptable or unforeseen risks to participants due to the investigational medicinal product, if moderate or severe adverse reactions occur in more than 25% of the participants, or if the required number of participants are not recruited despite a sufficient recruitment period.

The adverse events will be vigilantly monitored and identified via both interviews and examinations at each visit. For each adverse event, the following information will be reported: name, duration, severity, causal relationship with the investigational medicinal product, actions taken, outcome, corrective treatment, and seriousness. The expected adverse reactions include rash, urticaria, loss of appetite, epigastric discomfort, nausea, vomiting, abdominal pain, and diarrhea. Fever, cough, dyspnea, and AST/ALT elevation may occur in rare cases. The severity

of these expected adverse reactions will be evaluated according to pre-established criteria (mild, moderate, and severe), and the investigator will analyze the causal relationship between the adverse events and the investigational medicinal product.

No separate auditing is planned other than monitoring; however, the conducting institution or the Ministry of Food and Drug Safety retains the option to carry out independent auditing. Regular monitoring will be implemented to ensure proper informed consent, protocol compliance, and adherence to Good Clinical Practice.

ETHICS AND DISSEMINATION

1. Research ethics approval

The study protocol was approved by the Institutional Review Board of Daejeon University Daejeon Korean Medicine Hospital (DJDSKH-24-DR-01). Any necessary protocol modifications will be applied after receiving approval from the IRB. The current version of the protocol is V 1.3 (date: 19 March 2024).

2. Consent

Investigators delegated by the principal investigator will obtain written informed consent from potential trial participants using informed consent forms approved by the IRB. The investigators will thoroughly elucidate the clinical trial to the participants and obtain written informed consent prior to executing any trial-associated procedures. The original signed consent form will be stored in the investigator's file, and a copy will be provided to each participant.

3. Confidentiality and access to data

Participants' personal information will be managed following relevant regulations to ensure confidentiality. Records that can identify participants will be kept confidential, and participants will be managed and assessed via a unique screening number and initials allocated at the start of the study. Authorized individuals or institutions, including the monitor, inspector, IRB, or head of the Ministry of Food and Drug Safety, may access participants' medical records and trial-related data to confirm trial conduct and data reliability in accordance with relevant regulations without compromising subject confidentiality. Trial-related documents and data will be securely stored in a locked computer with restricted access. Access to the final trial dataset will be restricted to a limited number of researchers, including statisticians.

4. Ancillary and post-trial care

Investigators will diligently monitor participants for possible adverse events and take appropriate measures should any adverse events occur. Adverse events that occur during the clinical trial will be followed up until they resolve, show stable results, or the participant is lost to follow-up. If medical issues directly related to trial procedures arise, the best possible medical care will be provided. In cases of direct injury or health damage caused by the investigational medicinal product during participation in this clinical trial, compensation will be offered through the 'Compensation Agreement' and clinical trial insurance.

5. Dissemination policy

The findings of this investigator-initiated clinical trial will be published in a peer-reviewed journal and will be presented at a conference. Once the clinical trial is completed, the data anonymized by removing the participants' personal identification information will be registered in the Korean Medicine Data Repository (KMDR; https://kmdr.kiom.re.kr) [33].

DISCUSSION

This study investigates the impact of HJD decoction on insomnia patients with bedtime procrastination. Bedtime procrastination has a bidirectional relationship with problematic smartphone use [34-36], which is an increasingly relevant issue in contemporary society [8]. Our approach merges HJD decoction with BBTI and smartphone use guidelines, thereby presenting a comprehensive treatment strategy. The usual care group receives BBTI and smartphone use guidelines without HJD decoction, enabling us to evaluate the specific contribution of HJD to this comprehensive methodology. To assess efficacy, we included exploratory outcomes related to smartphone use, which used 30 minutes prior to bedtime, total usage time, and scores on the SAS-SV. This enables us to evaluate the effect of our intervention on both sleep and smartphone-related behaviors.

However, this study possesses certain limitations. First, be-

ing an open-label trial, it lacks blinding, which may introduce bias in subjective outcome measures such as the ISI and PSQI. Second, the comparison to usual care rather than a placebo makes it challenging to differentiate the specific effects of HJD decoction from placebo effects. Lastly, the inclusion criteria are highly specific, requiring moderate to severe insomnia, bedtime procrastination, anxiety symptoms, and facial redness, as per the indications for HJD decoction. This may limit the generalizability of our findings to the broader insomnia population.

Despite these limitations, this trial will yield significant information on the efficacy and safety of HJD decoction for insomnia related to bedtime procrastination when paired with behavioral interventions and lifestyle recommendations.

CONCLUSION

This study protocol describes a randomized controlled trial that will evaluate the efficacy of HJD decoction for insomnia patients with bedtime procrastination. Despite the limitations of the open-label design, this study will examine the role of herbal medicine in treating a specific type of insomnia that is increasingly common in modern society. The results will provide valuable insights into integrative treatment strategies for sleep disorders in the digital age.

AUTHORS' CONTRIBUTIONS

Conceptualization: Yujin Choi, Pyung-Wha Kim, In-Chul Jung, Hyungjun Kim, Kyung-Min Shin; Methodology: Hyo-Ju Park, So-Young Jung, Ojin Kwon; Investigation: Yujin Choi, Pyung-Wha Kim, Hyo-Ju Park; Writing – Original Draft: Yujin Choi; Writing – Review & Editing: Pyung-Wha Kim, Hyo-Ju Park, So-Young Jung, Ojin Kwon, In-Chul Jung, Hyungjun Kim, Kyung-Min Shin.

ETHICAL APPROVAL

This research was reviewed and approved by the Institutional Review Board (IRB) of Daejeon University Daejeon Korean Medicine Hospital (registration number DJDSKH-24-DR-01, approval date 2024.01.26). Informed consent will be obtained from all participants.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

FUNDING

This research was supported by the Korea Institute of Oriental Medicine (KSN2213010).

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