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Electroacupuncture for treating insomnia in cancer patients: a study protocol for a randomised pilot clinical trial

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Abstract

Introduction: Although insomnia is one of the most prevalent and disturbing symptoms among cancer patients, it has not been properly managed. Electroacupuncture (EA) has received attention as a promising intervention for insomnia, and a few previous studies have reported that this intervention may be beneficial for treating insomnia in cancer patients. The aim of this study is to explore the safety and therapeutic effect of EA on the sleep disturbance of cancer patients with insomnia using a subjective method, patient-reported questionnaires and an objective tool, actigraphy to measure the quality of sleep.

Methods and analysis: This is a study protocol for a randomised, three-arm, multi-centre, pilot clinical trial. A total of 45 cancer patients who have continuous insomnia related to cancer treatment or cancer itself will be randomly allocated to an EA group, sham EA group, or usual care group in equal proportions. The EA group will receive 10 sessions of EA treatment over 4 weeks. The sham EA group will receive sham EA at non-acupoints using nonpenetrating Streitberger placebo acupuncture needles with mock EA. The usual care group will not receive EA treatment. All participants will be provided a brochure on the management of sleep disorders regardless of their group assignment. The primary outcome measure is the mean change in the insomnia severity index from the baseline to week 5. Information related to sleep quality will also be obtained through the Pittsburgh sleep quality index, a sleep diary, and actigraphy. Participants will complete the trial by visiting the research centre at week 9 for follow-up assessment.

Ethics and dissemination: This study protocol was approved by the institutional review boards of each research centres. Written informed consent will be obtained from all participants. The result of this study will be published in peer-reviewed journals or presented at academic conferences.

Trial registration number: Clinical Research Information Service KCT0002162.

Strengths and limitations of this study

1. This randomised, multi-centre, clinical trial is the first study in South Korea exploring the effect and safety of electroacupuncture on the sleep disturbance of cancer patients suffering from insomnia.

2. The study will use actigraphy to acquire objective outcomes reflecting the quality of sleep as well as the patient-reported outcomes.

3. The study will measure the level of cortisol and melatonin in saliva as biomarkers reflecting the circadian rhythm of the body related to sleep and arousal.

4. Polysomnography needs to be included in future research to investigate the sleep architecture and the cause of sleep disorders in various ways.

5. Because of the unique nature of electroacupuncture and the design of this study including a usual care group, it is impossible to completely blind the practitioners and all participants.

6. The study adopts a nonpenetrating placebo needling at non-acupoints as a placebo comparator for acupuncture, however, a perfect placebo intervention for real acupuncture that has no physiologic effects while maintaining patient blinding has not been developed yet.

INTRODUCTION

Insomnia is one of the most common afflictions among the general population, and the prevalence of insomnia is known to be twice as high as in cancer patients compared to healthy adults.[1] Complex interactions of various factors such as adverse reactions to chemotherapy,[1] circadian disruption,[2] inflammation,[3] and tumour growth[3] seem to be the reasons why cancer patients are especially susceptible to insomnia. Insomnia has a profound effect on the overall quality of life,[4] energy,[5] emotion,[6] memory,[7] and immune system[8] of cancer patients. In addition, insomnia is also known to be associated with decreased survival[9] and tumour worsening.[10] Although insomnia is such a common and important problem among cancer patients, it is not easily cured or well managed.[1 11]

The most commonly used therapy for the management of insomnia in cancer patients is pharmacotherapy.[12] According to Moore et al., approximately half of breast cancer patients are prescribed sleeping pills.[13] Long-term use of sleeping pills is known to be associated with continued sleep disturbance, decreased ability to perform daily activities, memory impairment, traffic accidents, falls, etc.[12] Thus, pharmacotherapy should be used only for a short-term period; however, approximately 30% of cancer patients are receiving sleeping pills even one year after the end of chemotherapy.[13]

In addition to pharmacotherapy, cognitive behavioural therapy has been recommended as a standard therapy for the improvement of insomnia.[3] However, there are some limitations to this therapy in that the compliance rate to the therapy is low because the therapeutic response does not appear immediately, and patient access to the therapy is low due to the high cost of the therapy.[14] Moreover, experienced therapists are rare, and the effect of therapy varies widely depending on the proficiency of the therapist.[14]

For this reason, there is a growing demand for complementary alternative medicine (CAM) in the field of sleep management. Acupuncture is one of the most commonly used therapeutic interventions in CAM. Acupuncture is a treatment that punctures and stimulates the skin at acupoints using acupuncture needles. Electroacupuncture (EA) refers to a method that supplies a constant physical stimulus to acupoints through the inserted acupuncture needle connected to a microcurrent stimulator.

Previous systematic reviews on the effect of acupuncture for insomnia have revealed that

acupuncture is significantly more effective to improve sleep disturbance in insomniacs than no treatment[15] and sham acupuncture.[15-17] Insomnia has also been reported to be as effective as pharmacotherapy[15] or even superior to sleeping pills[15 17] and provides additional benefit to patients who are undergoing pharmacotherapy to improve insomnia.[15 16]

The effect of acupuncture for the improvement of sleep disorders has also been identified in studies targeting cancer patients. A survey conducted at a major cancer centre in the United States showed that acupuncture significantly improved the quality of sleep in cancer patients.[18] Garland et al. also determined that 8-week EA was more effective than pharmacotherapy to attenuate sleep disturbance from a recently published randomised controlled trial including breast cancer patients suffering from hot flush.[19] Choi et al. systematically investigated the clinical studies on the effect of acupuncture for insomnia in cancer patients and indicated that acupuncture may be superior to sham acupuncture or pharmacotherapy.[20] However, these authors could not draw any firm conclusions because the level of evidence in the included studies was low overall, the effect size of the studies was too small to confirm their clinical significance, and there were few studies strictly designed and performed.[20]

Subjective measurement tools such as self-reported questionnaires or sleep diaries are the most commonly used type of outcome measures for the assessment of sleep quality. This is because these tools are relatively simple to measure and have the advantage of not interfering with daily life or sleeping; however, one limitation of this approach is that the results of these measurements are entirely up to the decisions of participants and are unable to objectively measure the pattern of sleep.[21] Polysomnography and actigraphy are the two main methods to objectively measure sleep quality.[21]

Polysomnography is a gold standard method for the objective measurement of sleep,[3 21] because it can demonstrate the sleep structure and the cause of sleep disorders in various ways including electroencephalogram, electromyogram, electrocardiogram, respiration and oxygen saturation, etc.[22] However, one disadvantage is that polysomnography requires an expensive device and an expert capable of interpreting the results.[21]

To overcome these shortcomings, actigraphy has been investigated.[23] Actigraphy is a noninvasive means of measuring the motion of the body using an actigraph, a piezoelectric

accelerometer.[23] Actigraphy has been widely used in the field of sleep research because it can detect sleep, activity, and movement without disturbing the daily lives of the subjects who are only required to wear a small, watch-shaped device on the wrist.[23] Studies on the similarities and differences between the sleep quality measured by polysomnography, actigraphy, and subjective assessment tools have been pulished.[23] It is recommended to use both objective and subjective measurement methods to assess sleep quality in the field of sleep research.[24]

A few acupuncture researchers have reported the positive effect of acupuncture using objective measurement tools such as polysomnography[25-27] or actigraphy.[28 29] However, there remain conflicting results regarding whether acupuncture has the same effect on both subjective and objective aspects of sleep. Some researchers argued that the effect of acupuncture was approved via both objective and subjective measurement tools[25-27], while others reported that acupuncture seemed to affect the subjective outcomes only, not the result of polysomnography[30 31] or actigraphy.[32-34]

The aim of this study is to explore the therapeutic effect and safety of EA on the sleep disturbance of cancer patients with insomnia using both subjective questionnaires and objective actigraphy.

METHODS AND ANALYSIS

Study design

This is a study protocol for a randomised, three-arm, multi-centre, pilot clinical trial. Forty-five cancer patients with insomnia will be randomly assigned to an EA group, sham EA group, or usual care group at a 1:1:1 ratio. The schedule of enrolment, interventions, and assessments is summarised in Table 1, and the flow diagram of the study is presented in Figure 1.

Table 1 Schedule of enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrolment	Allocation	Treatment			Follow-up	
TIMEPOINT	***-wk1***	***wk$_0$***	***wk$_1$***	***wk$_3$***	***wk$_4$***	***wk$_5$***	***wk$_9$***
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS							
EA			←	—	→		
Sham EA			←	—	→		
Usual care			←	—	→		
ASSESSMENTS							
ISI	X	X		X		X	X
PSQI		X		X		X	X
Sleep diary	←	— →	←	—	—	—	— →
Actigraphy	←	— →	←	— →	←	— →	
FACT-F		X				X	
MoCA		X				X	
BDSS		X					
Salivary hormone test		X				X	
Blinding/credibility test[a]			X		X		
Adverse event			X	X	X	X	X

Laboratory test[b]	X	X

EA, Electroacupuncture; ISI, Insomnia Severity Inventory; PSQI, Pittsburgh Sleep Quality Index; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; MoCA, The Montreal Cognitive Assessment; BDSS, Blood Deficiency Scoring System.

[a]Only EA and sham EA groups will undergo blinding and credibility tests.

[b]The laboratory test includes complete blood count and differential count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, albumin, erythrocyte sedimentation rate, thyroid-stimulating hormone, free thyroxine, and human chorionic gonadotropin urine test (only for women in their childbearing years at the screening visit).

Recruitment

Two clinical research centres in South Korea will conduct this trial: Daejeon Oriental Hospital of Daejeon University and Dong-eui University Korean Medical Hospital in Busan. We will do our best to secure enough participants in this study using online and offline advertisement boards inside and outside the hospitals and by releasing flyers to daily local newspapers.

Inclusion criteria

1. Patients aged 19 years or over but under 80 years

2. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

3. Cessation of cancer-related treatments (e.g., surgery, radiotherapy, chemotherapy, immunotherapy) at least 12 weeks before the trial (ongoing hormone therapy, which must have been initiated at least 3 weeks prior to enrolment, is allowed)

4. Continuous insomnia related to cancer treatment or cancer itself for at least 3 months, with fulfilment of The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for insomnia disorder

5. Total score in the Insomnia Severity Index (ISI) ≥ 15 points

6. Willingness to participate in the trial and having provided written consent

Exclusion criteria

1. Having experienced the current level of sleep disorder prior to the diagnosis of cancer

2. Severe anaemia (platelet count < 60,000/μL, haemoglobin < 8 g/dL, or absolute neutrophil count < 1,000/μL)

3. A diagnosis of major depressive disorder, anxiety disorder, panic disorder, or other psychiatric disorder; caffeine, alcohol, or drug addiction; or a subscale of either anxiety or depression in Hamilton Anxiety and Depression Scale (HADS) score ≥ 11 points

4. Level of cancer pain measured by the numeric rating scale ≥ 4

5. An estimated life expectancy of six months or less

6. A plan for surgery, chemotherapy, or radiotherapy during the study

7. A recent change of regular medication to alleviate insomnia within 4 weeks of the beginning of the trial

8. Having taken sleeping pills as required within 2 weeks of the beginning of the trial

9. Having undergone Korean medical treatment (e.g., acupuncture, moxibustion, cupping, herbal medicine) within 4 weeks of the beginning of the trial

10. Initiation or a change in dietary supplement regimen or non-pharmacologic therapies (e.g., cognitive behavioural therapy, exercise, etc.) for alleviating insomnia during the trial or within 4 weeks of the beginning of the trial

11. Working shifts or changes in day/night work schedule that could impact circadian rhythm

12. Suffering from pain severe enough to cause sleep disturbance or presence of any disease that could cause insomnia

13. Taking haemostatic agents (e.g., Greenmono, Advate, Monoclate-P, Facnyne, BeneFix) because of haemostatic disorders

14. Abnormal findings in thyroid function test (abnormal level of free thyroxine [free T4] and thyroid stimulating hormone [TSH] < 0.1 uIU/ml or TSH > 5.1 uIU/ml)

15. History of hypersensitivity reactions to acupuncture or inability to cooperate with acupuncture therapy

16. The presence of implants that could interfere with EA or a history of hypersensitivity reactions to electrostimulation

17. Pregnancy, lactation, or planning to become pregnant

18. Having participated in other clinical trials within 4 weeks of the beginning of the trial

19. Difficulty complying with the study protocol

Randomisation and allocation concealment

Fifteen subjects will be allocated to each group according to a randomisation schedule generated by an independent statistician using SAS (Version 9.4, SAS institute Inc., Cary, NC). A stratified randomisation method will be used with the research centre and the standard therapies for insomnia (regular sleep medications or cognitive behavioural therapy for insomnia) as stratification factors. The statistician will seal the randomisation codes in sequentially numbered opaque envelopes and send them to the research centres. These envelopes will be kept in double-locked cabinets at the centres. Each envelope will be opened by a practitioner to assign the participant to one of the three groups after acquiring informed consent and eligibility screening.

Blinding

Participant blinding will be limited to the participants in the EA and sham EA groups. Complete participant blinding is not possible because the subjects in the usual care group

cannot help but notice their allocated group. Practitioner blinding cannot be achieved because of the unique nature of EA treatment. The assessor blinding will be maintained by separating the staff members who perform EA and who measure the outcomes.

Interventions

All participants of this trial will be educated with a brochure on the management of sleep disorders regardless of the assigned groups.

EA group

Participants in the EA group will receive acupuncture treatment at GV20, EX-HN3, bilateral HT7, PC6, BL63, and KI4 using sterilised stainless steel acupuncture needles (Asiamed GmbH & Co., 0.25 × 25 mm) (Figure 2). In addition to these 10 acupoints, up to 4 more points can be optionally added according to the symptoms of the patients. If participants with lymphatic oedema refuse to be treated with the acupoints on the affected site, the acupoints near the oedema site can be omitted. After inducing *deqi* by twisting the acupuncture needles, electric stimulation using an EA device (ES-160, Ito Co Ltd, Tokyo, Japan) will be applied with a 4-Hz frequency, at an intensity that the participant can notice but feel comfortable with. The EA treatment will be performed for 30 min per time, with a total of 10 times over 4 weeks. Details of the EA treatment based on the standards for reporting interventions in clinical trials of the acupuncture checklist are tabulated in Supplementary File 1.

Sham EA group

Participants in the sham EA group will receive sham acupuncture using nonpenetrating Streitberger placebo acupuncture needles (Asiamed GmbH & Co.). Unlike the real acupuncture needle that is inserted into the skin, the tip of the Streitberger placebo acupuncture needle is so blunt that it cannot penetrate the skin. The needles will be fixed by medical skin tape on the skin at non-acupoints unrelated to the management of sleep disorders in Korean traditional medicine as follows: upper limb 1 (1 cm lateral and 5 cm

proximal points from cubital creases of bilateral arms); upper limb 2 (2 cm above the upper limb 1 point); lower limb 1 (1.5 cm above the depression at the midpoint of the upper border of the bilateral patella); lower limb 2 (area 1/3 above the medial part of the bilateral tibia); and lower limb 3 (1.5 cm above the lower limb 2 point). The same EA device will be applied to the placebo needles, with an identical beeping sound and light signals as for the EA group. However, the electric current will not be delivered.

Usual care group

Participants in the usual care group will not receive EA treatment. These subjects will maintain the usual treatment and self-care but cannot begin any additional treatment to improve their insomnia during the study period.

Prohibited and permitted concomitant treatment

The participants will be prohibited from any Korean traditional medical treatment such as acupuncture, moxibustion, cupping, or herbal drugs to attenuate their insomnia symptoms except for the EA provided by the trial. If the participants remained on regular medication to improve insomnia at least 4 weeks prior to the beginning of the trial, they will be allowed to maintain the medication. However, if the type or dosage of the sleeping pill is changed during the trial, the subjects will be withdrawn from the study. If the subjects are receiving standard nonpharmacological treatment, such as cognitive behavioural therapy, or taking any dietary supplements to attenuate insomnia from at least 4 weeks prior to the beginning of the trial, they will be allowed to maintain these treatments. However, their regimens cannot be changed during the trial.

The participants will be trained to report all treatments newly received after the beginning of the trial to the staff members, and their treatment history will be recorded on the case report form (CRF). When participants are found to have received a prohibited treatment during the study period, they will be withdrawn from the trial.

Outcomes

Primary outcome measure

The primary outcome measure of this study will be the mean change in the ISI from the baseline to the end of the 4-week intervention. The ISI is a 7-item questionnaire devised to diagnose and assess the severity of the insomnia. The total score of the ISI ranges from 0 to 28 points, and it can categorise insomniacs according to scores of 0–7 (no clinically significant insomnia), 8–14 (subthreshold insomnia), 15–21 (clinical insomnia, moderate severity), and 22–28 (clinical insomnia, severe).[35]

Secondary outcome measures

The secondary outcome measures of this study will include the mean changes in the total score of the ISI from baseline to week 3 and week 9 and changes in the scores of the Pittsburgh Sleep Quality Index (PSQI), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), and Montreal Cognitive Assessment (MoCA); the level of the salivary hormones including cortisol and melatonin; and the quality of sleep measured by a sleep diary and actigraphy before and after the intervention.

The PSQI is a self-reported questionnaire to assess the quality of sleep over the past month. This scale comprises of 7 components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping pills, and daytime dysfunction. The global PSQI score ranges from 0 to 21, and a higher score represents poorer quality of sleep.[36] The change of the global score in the PSQI will be assessed at baseline, week 3, week 5, and week 9.

The FACT-F is a questionnaire devised to determine the level of fatigue of cancer patients. This instrument consists of 40 items in 5 domains including physical well-being, social/family well-being, emotional well-being, functional well-being, and fatigue. The total score of the FACT-F ranges from 0 to 160, where higher points denote a higher level of fatigue that disturbs the daily life of the patients.[37] This score will be assessed at baseline and week 5.

The MoCA is a one-page 30-point test originally devised to screen mild cognitive impairment in the geriatric population and can also be applied to evaluate the level of cognition of cancer survivors.[38] The MoCA will be assessed at baseline and week 5 by the assessors who will be blinded to the group allocation.

The change in the level of cortisol and melatonin in saliva will be measured before and after the intervention. These levels are known to reflect the circadian rhythm of the human body. The level of cortisol usually surges in the morning, while melatonin release increases at night in normal conditions, and the constant change of these hormones is known to be closely related to arousal and sleep.[39 40] We will check whether this type of rhythmical change in these hormones differs before and after the intervention.

To understand the details of the sleep status of the participants, a sleep diary will be provided to each participant. The subjects will be educated to write down their bedtime, final awakening time, sleep latency, number and duration of awakenings, perceived sleep duration, midday nap, and use of sleeping pills throughout the study period.[41]

To objectively measure the sleep patterns of the participants, actigraphy will be used in this trial. The candidate participants will wear a watch-type, physical activity monitoring device (ActiGraph™ wGT3X-BT, MTI Health Services Company, Pensacola, FL, USA) on their nondominant wrists for at least one week during the screening period. The subjects who meet all eligibility criteria will keep wearing the device during the 4 weeks of the intervention period to record their sleep and activity. Using this method, we can acquire objective data on the participants' sleep quality including the total time in bed, sleep latency, wake after sleep onset, total sleep time, and sleep efficiency.[23]

Blinding test and credibility test

The participants in the EA and sham EA groups will participate in the blinding test and credibility test after the first and last treatments. The purpose of these tests is to check whether the participant blinding was maintained for these groups. The blinding test will ask the participants which type of acupuncture they think has been received, real EA, sham EA, or unknown. The credibility test assesses the level of confidence in the treatment they have

received. The score of this test ranges from 0 to 6, where a higher score reflects higher confidence in the treatment.[42]

Safety assessment

For the safety assessment, the investigators will ask the participants on each visit if they have experienced any adverse events (AE). Laboratory tests will also be performed at baseline and week 5 to detect AEs. This test includes a complete blood count and differential count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, albumin, erythrocyte sedimentation rate, thyroid-stimulating hormone, free thyroxine, and human chorionic gonadotropin urine tests (only for women in their childbearing years at the screening visit).

The severity of AEs will be primarily assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.[43] When the NCI-CTCAE is not applicable, Spilker's three level criteria will be used instead.[44] The type of AE and its severity will be recorded to the CRF regardless of the relationship with the intervention provided in this study. The relationship between the treatment and the AE will be recorded as definitely related, probably related, possibly related, probably not related, definitely not related, or unknown.

Study feasibility outcomes

To see whether a full-scale randomised clinical trial for this issue is feasible, the recruitment rate and completion rate will be calculated. The overall rate of adherence to the planned intervention will also be obtained.

Data collection and management

Data will be collected after acquiring the signed consent from the participants. The collected data will be recorded on the CRF by certificated clinical research coordinators. The whole process of the trial will be regularly monitored to ensure the quality of the trial. Periodic

monitoring will confirm that the data in the CRF match the source document and that the procedures of the recruitment, intervention and assessment follow the protocol.

To guarantee the consistency of the procedures of the intervention and assessment between research centres, a standard operating procedure will be set and provided to the investigators. The practitioners are limited to licensed doctors of Korean medicine who have at least 2 years of clinical experience, and all investigators are required to take training courses for good clinical practice.

Sample size

The purpose of this pilot clinical trial is to explore the potential efficacy and safety of EA for insomnia in cancer patients. Therefore, a prospective sample size calculation was not performed. The result of this study will serve as the basis for sample size calculation for a full-scale trial on this theme in the future. An opinion from an expert in medical statistics recommended that the minimal number of people per group be 12 for a pilot study,[45] and assuming a dropout rate of 20%, 15 participants in each group or a total of 45 participants will be deemed appropriate for this research setting.

Statistical analysis

A full analysis set (FAS), which realises the intention-to-treat ideal as closely as possible,[46] will be the main set for primary analysis. The FAS includes all participants initially allocated to one of the three groups of the study; however, it excludes the data from participants who do not meet the eligibility criteria, who never received the intervention in this study, or who never provided any outcome value in this study. A per-protocol (PP) set will be used for sensitivity analysis to compare the results from the FAS. The PP set comprises the

participants who completed the trial without major violation of the protocol, with having received at least 70% of the planned intervention and provided all outcome values.

A two-sided significance level will be set at 5%, and the multiple imputation method will be adopted for missing data. SAS® Version 9.4 (SAS institute. Inc., Cary, NC) will be used for statistical analysis.

Demographic characteristics and baseline measurements of the variables of each group will be summarised. Continuous data will be expressed as the mean ± standard deviation. Analysis of variance (ANOVA) or the Kruskal–Wallis test will performed to compare the continuous data from each group. A 95% confidence interval can be presented as needed. For dichotomous or categorical data, frequency and percentile will be presented, and the difference between groups will be compared using a chi-square test or the Fisher's exact test.

The mean change of the ISI score from baseline to week 5 is the primary outcome measure of this study. To identify statistically significant differences in the primary outcome measure between groups, two sets of hypotheses are assumed as described below.

Set 1

The null hypothesis (H_{01}): There is no difference in the mean change of the ISI before and after treatment between the EA group and the usual care group.

The alternative hypothesis (H_{11}): There is a difference in the mean change of the ISI before and after treatment between the EA group and the usual care group.

Set 2

The null hypothesis (H_{02}): There is no difference in the mean change of the ISI before and after treatment between the EA group and the sham EA group.

The alternative hypothesis (H_{12}): There is a difference in the mean change of the ISI before and after treatment between the EA group and the sham EA group.

If H_{01} is rejected and H_{11} is adopted in the statistical analysis for set 1, the test for the hypotheses of set 2 will be verified. However, if H_{01} is adopted in the test for the set 1 hypotheses, no further validation for the set 2 hypotheses will be required.

To validate the hypotheses, an analysis of covariance (ANCOVA) will be performed with the baseline value as a covariate and each group as a fixed factor. If there is any significant difference between groups among the demographic characteristics or baseline measurements of the variables, it will be adjusted according to its covariance. The problem of multiple comparison will be solved using the fixed sequence method.[47]

The secondary outcome measures will be analysed via the same methods used for the primary outcome measure analysis. The change of the outcome measures before and after the intervention within a group will be analysed using Student's paired t-test or Wilcoxon signed-rank test. Repeated measures ANOVA with post-hoc Dunnett's procedure will be used to validate the differences in the trends per visit.

Subgroup analysis will be conducted to determine whether the severity of insomnia, significant blood deficiency pattern according to a blood deficiency scoring system, or level of expectancy to the EA treatment at baseline affects the clinical response to EA. The correlation of the sleep-related variables extracted from an objective source (actigraphy) and a subjective source (patient-reported questionnaires) will be evaluated.

Ethics and dissemination

Licensed doctors of Korean medicine will obtain informed consent at each research centre. Only the participants who sign the informed consent form will be included in the study. The study protocol has been approved by the institutional review boards (IRBs) of the participating research centres; Daejeon Oriental Hospital of Daejeon University and Dong-eui University Korean Medical Hospital in Busan. The approved protocol was registered with the Clinical Research Information Service (CRIS) of South Korea (CRIS-KCT0002162).

Any modification to the protocol will be re-approved by the IRBs, documented in the online registry of CRIS, and reflected in the explanation for the participants. An amended consent form reflecting the revised protocol must be obtained from the participants.

The result of this study will be published in peer-reviewed journals or academic conferences.

DISCUSSION

Despite the high prevalence and enormous impact of insomnia in cancer patients, its importance has been overlooked.[1] The National Cancer Institute and National Comprehensive Cancer Network have strongly recommended evaluation and appropriate treatment of the sleep disturbance of cancer survivors during routine survivorship care.[11] Nevertheless, it seems that most of the hospitals and cancer centres are not properly managing the insomnia of cancer patients.[11]

Insomnia is one of the areas in which acupuncture-related publications have been most commonly focused for the last 20 years.[48] Previous researches have shown that acupuncture is an effective intervention for insomnia. Acupuncture also appears to be effective for the sleep disorders of cancer patients, but its effect on the cancer population has been studied relatively less than in general insomniacs. Thus, we expect that the results of this study will contribute to increasing the insufficient evidence in this area of research.

Reviewing previous studies, we found that acupuncture may have only a short-term effect on the insomnia of cancer patients. Mao et al. reported that the sleep quality of the EA group was significantly better than that of control group immediately after an 8-week intervention period, but this difference between groups disappeared after 4 weeks.[49] Another study by Otte et al. also showed a similar pattern that the effect of a 2-week acupuncture treatment vanished after a 4-week follow-up period.[28]

However, according to the opinion of Choi et al., the effect of acupuncture seems to be strengthened over time.[20] These authors found that acupuncture was as good as conventional therapy and became better at follow-up visits 3 weeks after final treatment.[20] We will record

the trend change of the effect of EA over time by assessing the response of the participants at baseline; week 3, a midpoint of the 4-week intervention; week 5, immediately after the end of the final intervention; and week 9, the final follow-up assessment. We expect the results of this study to contribute to solving the disagreement among the existing studies on the timing and duration of the effect of acupuncture on sleep disturbance in cancer patients.

In addition to time duration, there are many factors that can influence the effectiveness of acupuncture. Among them, we will try to determine whether a certain pattern identified according to the theory of Korean traditional medicine, blood deficiency, is an important variable that can affect the response to acupuncture. Blood deficiency is one of the main patterns of insomnia in Korean traditional medicine, and this study will investigate how many patients are categorised with a blood deficiency pattern using a blood deficiency scoring system[50] and whether their treatment response is different from the non-blood deficiency group.

In insomnia clinical trials, the placebo effect is very commonly observed.[51] The characteristics of insomnia—that it is intermittent and tends to maintain or even reinforce the therapeutic effect of specific treatment over long periods—seems to explain such a placebo effect.[51] This is the reason why the inclusion of a placebo control is generally recommended in insomnia clinical trials.[51] Thus, this study also included a sham EA group as a placebo control.

The sham EA group will receive sham acupuncture therapy at non-acupoints unrelated to insomnia using a Streitberger placebo needle. This placebo needle was devised by Streitberger and Kleinhenz in 1998.[52] Its appearance is the same as real acupuncture needles, but the needle does not penetrate the skin. The suitability of this device as a placebo comparator for acupuncture needles has been validated,[52] and it has been used as a control intervention in several acupuncture clinical studies.[53]

The Streitberger placebo needle is one of the two most commonly used and commercially available placebo devices in acupuncture clinical studies along with the Park sham placebo device.[53] Nevertheless, approximately half of the clinical studies using these placebo acupuncture needles have concluded that the effects of real acupuncture and placebo needles were not significantly different.[53] Generally, a placebo pill is used on the assumption that it

has no pharmacological effect and is harmless.[54] However, it has been repeatedly shown that placebo acupuncture needles seem to have a significant physiological effect in many studies so far.[54] Thus, the development of a new placebo device as a perfect comparator for real acupuncture that has no physiologic effects while maintaining patient blinding is still a significant challenge for acupuncture researchers. However, we currently have no choice but to use one of these available placebo devices considering their limitations.

It is known that the proportion of the placebo effect is not inconsiderable in acupuncture treatment.[54] Thus, a study design that directly compares acupuncture and placebo acupuncture is likely to produce a false negative result, failing to detect the whole characteristic effect of acupuncture.[54] Moreover, as we have seen, patients with insomnia tend to respond strongly to placebo treatment. Therefore, we designed a three-arm parallel study including the usual care group as well as a placebo control group.

The strength of this study is that it will acquire objective outcomes reflecting sleep quality and the related circadian rhythm. First, we will obtain both subjective and objective outcomes showing sleep quality using patient-reported questionnaires and actigraphy. Most of the acupuncture studies on insomnia have used only patient-reported outcomes; furthermore, even a small number of studies using objective outcomes such as polysomnography or actigraphy failed to show consistent results on the effect of acupuncture for each outcome.[30-34] Based on the results of this study, we expect that we will be able to compare the difference between the subjective and objective outcomes and contribute to solving the conflict on this issue. Only actigraphy is used for objective outcome measures at this time; however, polysomnography, a gold standard method for insomnia diagnosis, should be included in future research.

Second, the difference in the levels of cortisol and melatonin in saliva between the groups will be compared as biomarkers reflecting the circadian rhythm of the body that affects the pattern of sleep. It is known that acupuncture modulates various neurotransmitters and hormones such as endorphin, serotonin, norepinephrine, cortisol and melatonin.[39 40] Among them, changes of the cortisol surge in the morning or melatonin increase at night time are known to be closely related to arousal and sleep.[39 40] Previous studies have reported that acupuncture can improve insomnia by affecting the pattern of cortisol[55 56] or melatonin[27]

release. Based on these results, we will investigate the changes in salivary cortisol and melatonin in addition to the sleep quality of the participants.

Trial status

This trial is currently recruiting participants.

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Contributors

MK and JHK conceived the study. MK drafted the protocol. JEK, HYL, ARK, and HJP participated in the design of the study and contributed to the refinement of the protocol. OJK was responsible for the statistical design of the study. BKK and JHC provided clinical advice and made critical revisions. JHK is a principal investigator of the study and has the final responsibility for the decision to submit this manuscript for publication. All authors approved the final manuscript.

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Competing interests

None declared.

Patient consent

Will be obtained.

Ethics approval

Daejeon Oriental Hospital of Daejeon University IRB (djomc-140-1); Dong-eui University Korean Medical Hospital IRB (2016-04)

Provenance and peer review

Not commissioned; this study was peer reviewed for ethics and funding approval prior to submission.

Data sharing statement

Requested data for public purpose or research transparency will be provided (please contact the corresponding author).

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Table (in the main text)

Table 1 Schedule of enrolment, interventions, and assessments

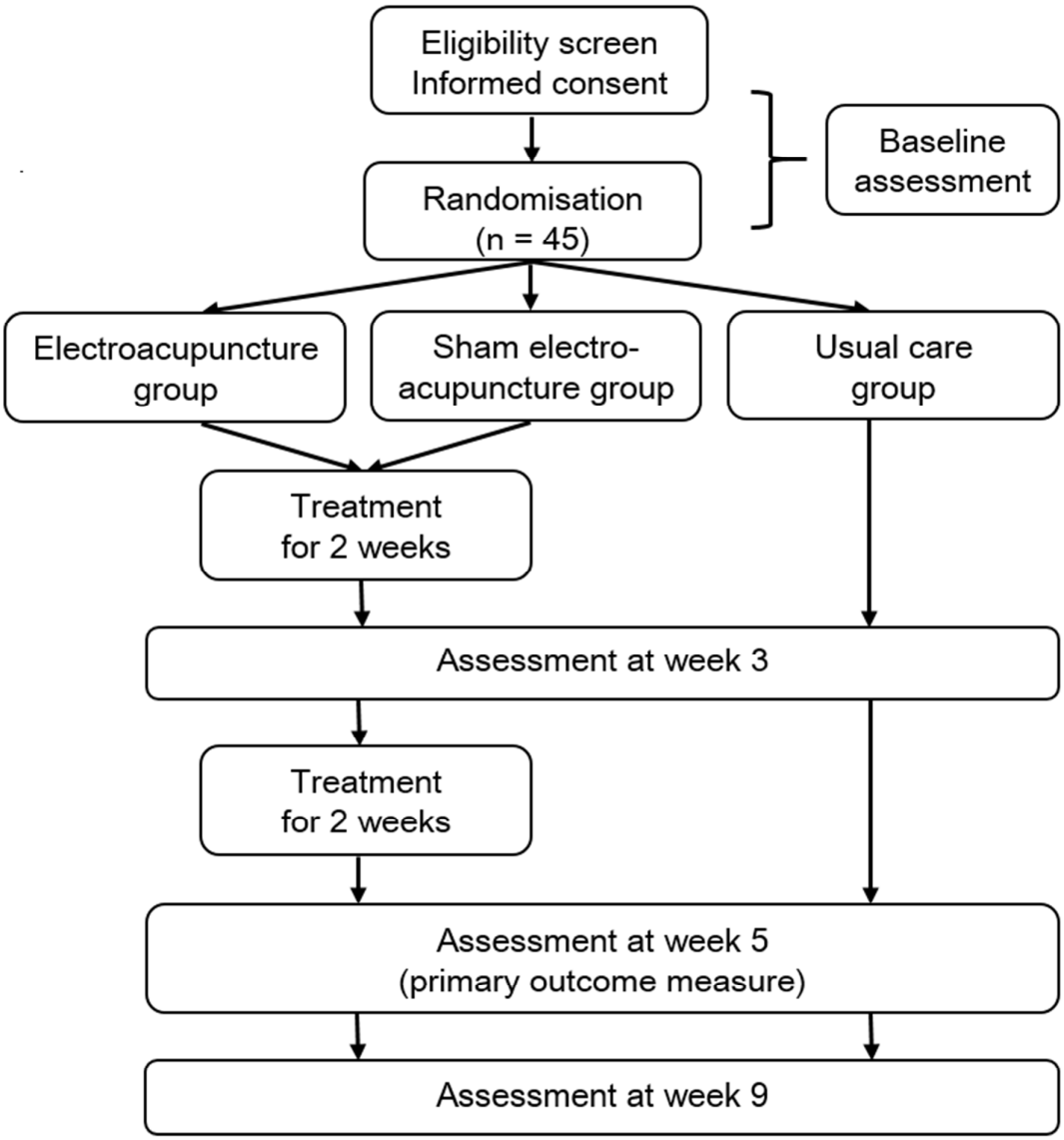
Figure titles

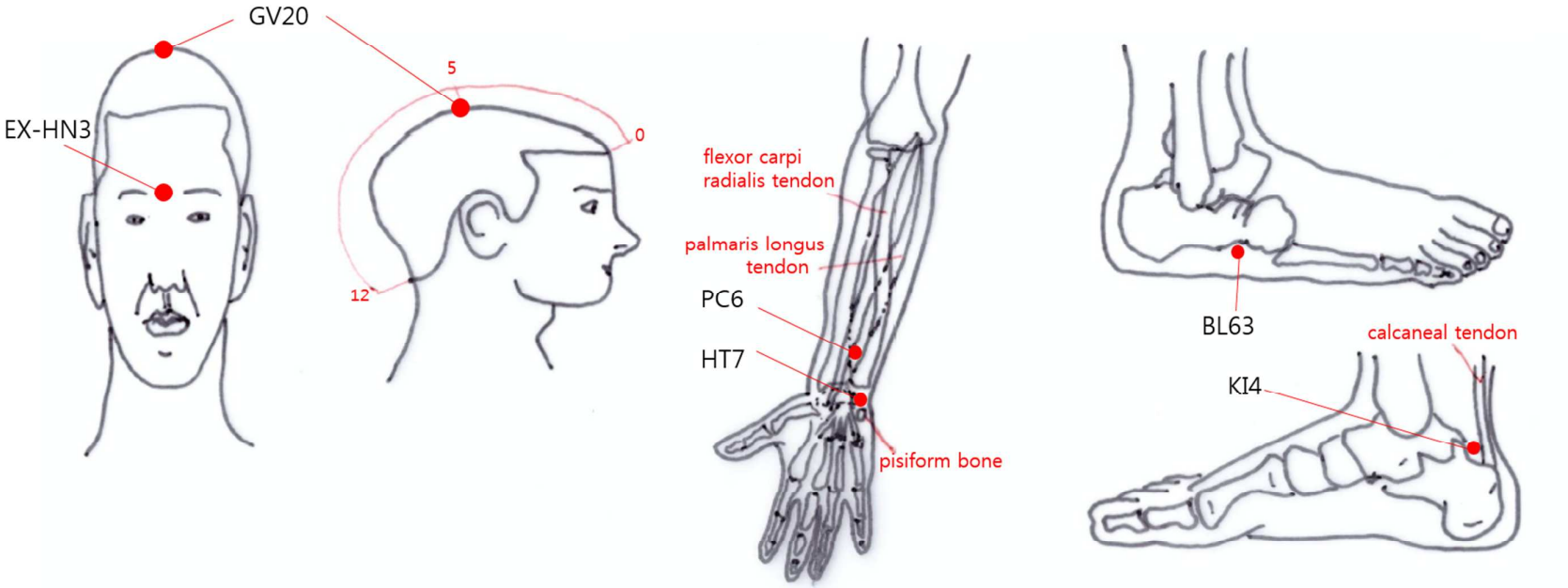
Figure 1 Flow diagram of the study

Figure 2 The points used for the electroacupuncture group

Supplementary file

Supplementary File 1 Details of the electroacupuncture (EA) and sham EA treatment based on the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist





Supplementary file 1 Details of the electroacupuncture (EA) and sham EA treatments based on the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist

Item	Detail	Description
1. Acupuncture rationale	1a) Style of acupuncture	Electroacupuncture based on traditional Korean acupuncture
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	Related papers[15-20,25-29,31-34] and expert (doctors of Korean medicine) consensus
	1c) Extent to which treatment was varied	Standardized treatment (option: up to 2 bilateral acupoints can be added according to the chief complaints of the participants)
2. Details of needling	2a) Number of needle insertions per subject per session	Standardized regimen: 10 (10 to 14, when considering addition of optional acupoints)
	2b) Names of points used	GV 20, EX-HN-3, bilateral HT7, PC6, BL63, KI4
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	0.6 – 4.5 cm
	2d) Response sought	Acupuncture: *de qi* (sense of soreness, numbness, heaviness, or distension) EA: cognition of stimulation and comfortable feeling
	2e) Needle stimulation	Manual stimulation: twisting-needling 3-5 times Electrical stimulation: 4 Hz
	2f) Needle retention time	30 minutes
	2g) Needle type (diameter, length, and manufacturer or material)	Acupuncture (diameter: 0.25 mm, length: 25 mm, manufacturer: Asiamed GmbH & Co., material: sterilized stainless steel)
3. Treatment regimen	3a) Number of treatment sessions	10
	3b) Frequency and duration of treatment sessions	10 sessions for 4 weeks (average 2.5 times per week)
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group	- All the three groups will be educated with a brochure about the management of sleep disorder - No additional Korean traditional medical treatment regarding insomnia is allowed except for what is given for the study - The interventions other than Korean traditional medical treatment to manage insomnia that have been steadily received for more than 4 weeks before the screening visit are allowed to continue during the study, but no additional treatment is allowed after the beginning of the trial (even sleeping pills are allowed)
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	- Setting: clinical trial centers in university hospitals - Unnecessary conversation will be limited between the acupuncturists and patients during the treatment.
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)	Licensed Korean medical doctors with at least 2 years of clinical experience
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice	Sham acupuncture: previous researches validating the nonpenetrating sham acupuncture device, Streitberger acupuncture needle[52] Mock electroacupuncture: previous researches with control intervention with no electrical stimulation with beeping sound and lighting[29,32-34,49]

	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.	1. rationale of sham acupuncture Use non-penetrating Streitberger acupuncture needles at 10 non-acupoints and connect electrostimulator in switch-off state on to the needles 2. points used for sham EA - Upper limb 1: 1 cm lateral and 5 cm proximal points from cubital creases of bilateral arms - Upper limb 2: 2 cm above the upper limb 1 point - Lower limb 1: 1.5 cm above the depression at the midpoint of the upper border of the bilateral patella - Lower limb 2: area 1/3 above the medial part of the bilateral tibia - Lower limb 3: 1.5 cm above the lower limb 2 point 3. number of needle insertions per subject per session: 10 4. needle type Sham acupuncture (Streitberger needle, Asiamed GmbH & Co., sterilized stainless steel) 5. Treatment duration, frequency, period: the same as the treatment group

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___title page___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_at the end of the abstract_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____-_____
Protocol version	3	Date and version identifier	_____-_____
Funding	4	Sources and types of financial, material, and other support	_____19_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____19_____
	5b	Name and contact information for the trial sponsor	_____-_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____-_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____-_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
	6b	Explanation for choice of comparators	8-9
Objectives	7	Specific objectives or hypotheses	3, 14
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-7, 13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4, table 1, figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7-8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	-
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Electroacupuncture for treating insomnia in cancer patients: a study protocol for a randomised pilot clinical trial

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Electroacupuncture for treating insomnia in cancer patients: a study protocol for a randomised pilot clinical trial

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Abstract

Introduction: Although insomnia is one of the most prevalent and disturbing symptoms among cancer patients, it has not been properly managed. Electroacupuncture (EA) has received attention as a promising intervention for insomnia, and a few previous studies have reported that this intervention may be beneficial for treating insomnia in cancer patients. The aim of this study is to explore the safety and therapeutic effect of EA on the sleep disturbance of cancer patients with insomnia using a subjective method, patient-reported questionnaires and an objective tool, actigraphy to measure the quality of sleep.

Methods and analysis: This is a study protocol for a randomised, three-arm, multi-centre, pilot clinical trial. A total of 45 cancer patients who have continuous insomnia related to cancer treatment or cancer itself will be randomly allocated to an EA group, sham EA group, or usual care group in equal proportions. The EA group will receive 10 sessions of EA treatment over 4 weeks. The sham EA group will receive sham EA at non-acupoints using nonpenetrating Streitberger acupuncture needles with mock EA. The usual care group will not receive EA treatment. All participants will be provided a brochure on the management of sleep disorders regardless of their group assignment. The primary outcome measure is the mean change in the insomnia severity index from the baseline to week 5. Information related to sleep quality will also be obtained through the Pittsburgh Sleep Quality Index, a sleep diary, and actigraphy. Participants will complete the trial by visiting the research centre at week 9 for follow-up assessment.

Ethics and dissemination: This study protocol was approved by the institutional review boards of each research centres. Written informed consent will be obtained from all participants. The result of this study will be published in peer-reviewed journals or presented at academic conferences.

Trial registration number: Clinical Research Information Service KCT0002162.

Strengths and limitations of this study

1. This randomised, multi-centre clinical trial is the first study in South Korea exploring the effect and safety of electroacupuncture as a treatment for sleep disturbance in cancer patients with insomnia.

2. In addition to patient-reported outcomes, the study will use actigraphy to acquire objective outcomes reflecting the quality of sleep.

3. The study will measure the levels of cortisol and melatonin in saliva as biomarkers reflecting the circadian rhythm of the body related to sleep and arousal.

4. Polysomnography needs to be included in future research to investigate sleep architecture and the various causes of sleep disorders.

5. Because of the unique nature of electroacupuncture and the design of this study, which includs a usual care group, it is impossible to completely blind the practitioners and all participants.

6. The study adopts nonpenetrating needling at non-acupoints as a sham comparator for acupuncture; however, a perfect placebo intervention for real acupuncture that exerts no physiologic effects while maintaining patient blinding has not been developed yet.

INTRODUCTION

Insomnia is one of the most common afflictions among the general population, and the prevalence of insomnia is known to be twice as high as in cancer patients compared to healthy adults.[1] Complex interactions of various factors such as adverse reactions to chemotherapy,[1] circadian disruption,[2] inflammation,[3] and tumour growth[3] seem to be the reasons why cancer patients are especially susceptible to insomnia. Insomnia has a profound effect on the overall quality of life,[4] energy,[5] emotion,[6] memory,[7] and immune system[8] of cancer patients. In addition, insomnia is also known to be associated with decreased survival[9] and tumour worsening.[10] Although insomnia is such a common and important problem among cancer patients, it is not easily cured or well managed.[1 11]

The most commonly used therapy for the management of insomnia in cancer patients is pharmacotherapy.[12] According to Moore et al., approximately half of breast cancer patients are prescribed sleeping pills.[13] Long-term use of sleeping pills is known to be associated with continued sleep disturbance, decreased ability to perform daily activities, memory impairment, traffic accidents, falls, etc.[12] Thus, pharmacotherapy should be used only for a short-term period; however, approximately 30% of cancer patients are receiving sleeping pills even one year after the end of chemotherapy.[13]

In addition to pharmacotherapy, cognitive behavioural therapy has been recommended as a standard therapy for the improvement of insomnia.[3] However, there are some limitations to this therapy in that the compliance rate to the therapy is low because the therapeutic response does not appear immediately, and patient access to the therapy is low due to the high cost of the therapy.[14] Moreover, experienced therapists are rare, and the effect of therapy varies widely depending on the proficiency of the therapist.[14]

For this reason, there is a growing demand for complementary alternative medicine (CAM) in the field of sleep management. Acupuncture is one of the most commonly used therapeutic interventions in CAM. Acupuncture is a treatment that punctures and stimulates the skin at acupoints using specialisedneedles. Electroacupuncture (EA) refers to a method that supplies a constant physical stimulus to acupoints through the inserted acupuncture needle connected to a microcurrent stimulator.

Previous systematic reviews on the effect of acupuncture for insomnia have revealed that

acupuncture is significantly more effective to improve sleep disturbance in insomniacs than no treatment[15] and sham acupuncture.[15-17] Insomnia has also been reported to be as effective as pharmacotherapy[15] or even superior to sleeping pills[15 17] and provides additional benefit to patients who are undergoing pharmacotherapy to improve insomnia.[15 16]

The effect of acupuncture for the improvement of sleep disorders has also been identified in studies targeting cancer patients. A survey conducted at a major cancer centre in the United States showed that acupuncture significantly improved the quality of sleep in cancer patients.[18] Garland et al. also determined that 8-week EA was more effective than pharmacotherapy to attenuate sleep disturbance from a recently published randomised controlled trial including breast cancer patients suffering from hot flush.[19] Choi et al. systematically investigated the clinical studies on the effect of acupuncture for insomnia in cancer patients and indicated that acupuncture may be superior to sham acupuncture or pharmacotherapy.[20] However, these authors could not draw any firm conclusions because the level of evidence in the included studies was low overall, the effect size of the studies was too small to confirm their clinical significance, and there were few studies strictly designed and performed.[20]

Subjective measurement tools such as self-reported questionnaires or sleep diaries are the most commonly used type of outcome measures for the assessment of sleep quality. This is because these tools are relatively simple to measure and have the advantage of not interfering with daily life or sleeping; however, one limitation of this approach is that the results of these measurements are entirely up to the decisions of participants and are unable to objectively measure the pattern of sleep.[21] Polysomnography and actigraphy are the two main methods to objectively measure sleep quality.[21]

Polysomnography is a gold standard method for the objective measurement of sleep,[3 21] because it can demonstrate the sleep structure and the cause of sleep disorders in various ways including electroencephalogram, electromyogram, electrocardiogram, respiration and oxygen saturation, etc.[22] However, one disadvantage is that polysomnography requires an expensive device and an expert capable of interpreting the results.[21]

To overcome these shortcomings, actigraphy has been investigated.[23] Actigraphy is a noninvasive means of measuring the motion of the body using an actigraph, a piezoelectric

accelerometer.[23] Actigraphy has been widely used in the field of sleep research because it can detect sleep, activity, and movement without disturbing the daily lives of the subjects who are only required to wear a small, watch-shaped device on the wrist.[23] Studies on the similarities and differences between the sleep quality measured by polysomnography, actigraphy, and subjective assessment tools have been published.[23] It is recommended to use both objective and subjective measurement methods to assess sleep quality in the field of sleep research.[24]

A few acupuncture researchers have reported the positive effect of acupuncture using objective measurement tools such as polysomnography[25-27] or actigraphy.[28 29] However, there remain conflicting results regarding whether acupuncture has the same effect on both subjective and objective aspects of sleep. Some researchers argued that the effect of acupuncture was approved via both objective and subjective measurement tools[25-27], while others reported that acupuncture seemed to affect the subjective outcomes only, not the result of polysomnography[30 31] or actigraphy.[32-34]

The aim of this study is to explore the therapeutic effect and safety of EA on the sleep disturbance of cancer patients with insomnia using both subjective questionnaires and objective actigraphy.

METHODS AND ANALYSIS

Study design

This is a study protocol for a randomised, three-arm, multi-centre, pilot clinical trial. Forty-five cancer patients with insomnia will be randomly assigned to an EA group, sham EA group, or usual care group at a 1:1:1 ratio. The schedule of enrolment, interventions, and assessments is summarised in Table 1, and the flow diagram of the study is presented in Figure 1.

Table 1 Schedule of enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrolment	Allocation	Treatment			Follow-up	
TIMEPOINT	$-wk_1$	wk_0	wk_1	wk_3	wk_4	wk_5	wk_9
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS							
EA			◆—	—	—◆		
Sham EA			◆—	—	—◆		
Usual care			◆—	—	—◆		
ASSESSMENTS							
ISI	X	X		X		X	X
PSQI		X		X		X	X
Sleep diary	◆—	—◆	◆—	—	—	—	—◆
Actigraphy	◆—	—◆	◆—	—◆	◆—	—◆	
FACT-F		X				X	
MoCA		X				X	
BDSS		X					
Salivary hormone test		X				X	
Blinding/credibility test[a]			X		X		
Adverse event			X	X	X	X	X

Laboratory test[b]	X		X

EA, Electroacupuncture; ISI, Insomnia Severity Inventory; PSQI, Pittsburgh Sleep Quality Index; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; MoCA, The Montreal Cognitive Assessment; BDSS, Blood Deficiency Scoring System.

[a]Only EA and sham EA groups will undergo blinding and credibility tests.

[b]The laboratory test includes complete blood count and differential count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, albumin, erythrocyte sedimentation rate, thyroid-stimulating hormone, free thyroxine, and human chorionic gonadotropin urine test (only for women in their childbearing years at the screening visit).

Recruitment

Two clinical research centres in South Korea will conduct this trial: Daejeon Oriental Hospital of Daejeon University and Dong-eui University Korean Medical Hospital in Busan. We will do our best to secure enough participants in this study using online and offline advertisement boards inside and outside the hospitals and by releasing flyers to daily local newspapers.

Inclusion criteria

1. Patients aged 19 years or over but under 80 years

2. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

3. Cessation of cancer-related treatments (e.g., surgery, radiotherapy, chemotherapy, immunotherapy) at least 12 weeks before the trial (ongoing hormone therapy, which must have been initiated at least 3 weeks prior to enrolment, is allowed)

4. Continuous insomnia related to cancer treatment or cancer itself for at least 3 months, with fulfilment of The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for insomnia disorder

5. Total score in the Insomnia Severity Index (ISI) ≥ 15 points

6. Willingness to participate in the trial and having provided written consent

Exclusion criteria

1. Having experienced the current level of sleep disorder prior to the diagnosis of cancer

2. Severe anaemia (platelet count < 60,000/μL, haemoglobin < 8 g/dL, or absolute neutrophil count < 1,000/μL)

3. A diagnosis of major depressive disorder, anxiety disorder, panic disorder, or other psychiatric disorder; caffeine, alcohol, or drug addiction; or a subscale of either anxiety or depression in Hamilton Anxiety and Depression Scale (HADS) score ≥ 11 points

4. Level of cancer pain measured by the numeric rating scale ≥ 4

5. An estimated life expectancy of six months or less

6. A plan for surgery, chemotherapy, or radiotherapy during the study

7. A recent change of regular medication to alleviate insomnia within 4 weeks of the beginning of the trial

8. Having taken sleeping pills as required within 2 weeks of the beginning of the trial

9. Having undergone Korean medical treatment (e.g., acupuncture, moxibustion, cupping, herbal medicine) within 4 weeks of the beginning of the trial

10. Initiation or a change in dietary supplement regimen or non-pharmacologic therapies (e.g., cognitive behavioural therapy, exercise, etc.) for alleviating insomnia during the trial or within 4 weeks of the beginning of the trial

11. Working shifts or changes in day/night work schedule that could impact circadian rhythm

12. Suffering from pain severe enough to cause sleep disturbance or presence of any disease that could cause insomnia

13. Taking haemostatic agents (e.g., Greenmono, Advate, Monoclate-P, Facnyne, BeneFix) because of haemostatic disorders

14. Abnormal findings in thyroid function test (abnormal level of free thyroxine [free T4] and thyroid stimulating hormone [TSH] < 0.1 μIU/ml or TSH > 5.1 μIU/ml)

15. History of hypersensitivity reactions to acupuncture or inability to cooperate with acupuncture therapy

16. The presence of implants that could interfere with EA or a history of hypersensitivity reactions to electrostimulation

17. Pregnancy, lactation, or planning to become pregnant

18. Having participated in other clinical trials within 4 weeks of the beginning of the trial

19. Difficulty complying with the study protocol

Randomisation and allocation concealment

Fifteen subjects will be allocated to each group according to a randomisation schedule generated by an independent statistician using SAS (Version 9.4, SAS institute Inc., Cary, NC). A stratified randomisation method will be used with the research centre and the standard therapies for insomnia (regular sleep medications or cognitive behavioural therapy for insomnia) as stratification factors. The statistician will seal the randomisation codes in sequentially numbered opaque envelopes and send them to the research centres. These envelopes will be kept in double-locked cabinets at the centres. Each envelope will be opened by a practitioner to assign the participant to one of the three groups after acquiring informed consent and eligibility screening.

Blinding

Participant blinding will be limited to the participants in the EA and sham EA groups. Complete participant blinding is not possible because the subjects in the usual care group

cannot help but notice their allocated group. Practitioner blinding cannot be achieved because of the unique nature of EA treatment. The assessor blinding will be maintained by separating the staff members who perform EA and who measure the outcomes.

Interventions

All participants of this trial will be educated with a brochure on the management of sleep disorders regardless of the assigned groups.

EA group

Participants in the EA group will receive acupuncture treatment at GV20, EX-HN3, bilateral HT7, PC6, BL63, and KI4 using sterilised stainless steel acupuncture needles (Asiamed GmbH & Co., 0.25 × 25 mm) (Figure 2). In addition to these 10 acupoints, up to 4 more points can be optionally added according to the symptoms of the patients. If participants with lymphatic oedema refuse to be treated with the acupoints on the affected site, the acupoints near the oedema site can be omitted. After inducing *deqi* by twisting the acupuncture needles, electric stimulation using an EA device (ES-160, Ito Co Ltd, Tokyo, Japan) will be applied with a 4-Hz frequency, at an intensity that the participant can notice but feel comfortable with. The EA treatment will be performed for 30 min per time, with a total of 10 times over 4 weeks. This regimen was decided by consensus among experts traditional Korean medicine based on previous research.[15-20 25-29 31 32 34] Details of the EA treatment based on the standards for reporting interventions in clinical trials of the acupuncture checklist are tabulated in Supplementary File 1.

Sham EA group

Participants in the sham EA group will receive sham acupuncture using nonpenetrating Streitberger acupuncture needles (Asiamed GmbH & Co.). Unlike the real acupuncture needle that is inserted into the skin, the tip of the Streitberger acupuncture needle is so blunt that it cannot penetrate the skin. The needles will be fixed by medical skin tape on the skin at

non-acupoints unrelated to the management of sleep disorders in Korean traditional medicine as follows: upper limb 1 (1 cm lateral and 5 cm proximal points from cubital creases of bilateral arms); upper limb 2 (2 cm above the upper limb 1 point); lower limb 1 (1.5 cm above the depression at the midpoint of the upper border of the bilateral patella); lower limb 2 (area 1/3 above the medial part of the bilateral tibia); and lower limb 3 (1.5 cm above the lower limb 2 point). The same EA device will be applied to the Streitberger acupuncture needles, with an identical beeping sound and light signals as for the EA group. However, the electric current will not be delivered.

Usual care group

Participants in the usual care group will not receive EA treatment. These subjects will maintain the usual treatment and self-care but cannot begin any additional treatment to improve their insomnia during the study period.

Prohibited and permitted concomitant treatment

The participants will be prohibited from any Korean traditional medical treatment such as acupuncture, moxibustion, cupping, or herbal drugs to attenuate their insomnia symptoms except for the EA provided by the trial. If the participants remained on regular medication to improve insomnia at least 4 weeks prior to the beginning of the trial, they will be allowed to maintain the medication. However, if the type or dosage of the sleeping pill is changed during the trial, the subjects will be withdrawn from the study. If the subjects are receiving standard nonpharmacological treatment, such as cognitive behavioural therapy, or taking any dietary supplements to attenuate insomnia from at least 4 weeks prior to the beginning of the trial, they will be allowed to maintain these treatments. However, their regimens cannot be changed during the trial.

The participants will be trained to report all treatments newly received after the beginning of the trial to the staff members, and their treatment history will be recorded on the case report form (CRF). When participants are found to have received a prohibited treatment during the

study period, they will be withdrawn from the trial. Despite withdrawal from the trial, the recordings of the participants will continue if the subjects have already randomised. To realise the intention-to-treat principle, the data from the withdrawn participants will also be included in the analysis set and recorded in the results.

Outcomes

Primary outcome measure

The primary outcome measure of this study will be the mean change in the ISI from the baseline to the end of the 4-week intervention. The ISI is a 7-item questionnaire devised to diagnose and assess the severity of the insomnia. The total score of the ISI ranges from 0 to 28 points, and it can categorise insomniacs according to scores of 0–7 (no clinically significant insomnia), 8–14 (subthreshold insomnia), 15–21 (clinical insomnia, moderate severity), and 22–28 (clinical insomnia, severe).[35] The Korean version of the ISI validated by Cho et al. will be used in this study.[36]

Secondary outcome measures

The secondary outcome measures of this study will include the mean changes in the total score of the ISI from baseline to week 3 and week 9 and changes in the scores of the Pittsburgh Sleep Quality Index (PSQI), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), and Montreal Cognitive Assessment (MoCA); the level of the salivary hormones including cortisol and melatonin; and the quality of sleep measured by a sleep diary and actigraphy before and after the intervention.

The PSQI is a self-reported questionnaire to assess the quality of sleep over the past month. This scale comprises of 7 components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping pills, and daytime dysfunction. The global PSQI score ranges from 0 to 21, and a higher score represents poorer quality of sleep.[37] The Korean version of the PSQI validated by Sohn et al. will be used in this study.[38]

The change of the global score in the PSQI will be assessed at baseline, week 3, week 5, and week 9.

The FACT-F is a questionnaire devised to determine the level of fatigue of cancer patients. This instrument consists of the FACT-general (G) and the fatigue subscale. The FACT-G is composed of 27 items in 4 domains including physical well-being, social/family well-being, emotional well-being, and functional well-being. The fatigue subscale has 13 items assessing the level of fatigue. The total score of the FACT-F ranges from 0 to 160, where higher points denote a higher level of fatigue that disturbs the daily life of the patients.[39] Lee et al. validated the Korean version of the FACT-G.[40] Jeong et al. have translated and validated the Korean version of the fatigue subscale and also used it with Lee's Korean version of the FACT-G among patients with cancer-related fatigue.[41] In other words, the Korean version of the complete FACT-F has been used to measure the level of fatigue among cancer patients in Korea.[41] FACT-F scores will be assessed at baseline and week 5.

The MoCA is a one-page, 30-point test originally devised to screen for mild cognitive impairment in the geriatric population and can also be applied to evaluate the level of cognition of cancer survivors.[42] The validated Korean version of the MoCA will be used in this study.[43] The MoCA will be assessed at baseline and week 5 by the assessors who will be blinded to the group allocation

The change in the level of cortisol and melatonin in saliva will be measured before and after the intervention. These levels are known to reflect the circadian rhythm of the human body. The level of cortisol usually surges in the morning, while melatonin release increases at night in normal conditions, and the constant change of these hormones is known to be closely related to arousal and sleep.[44 45] We will check whether this type of rhythmical change in these hormones differs before and after the intervention.

To understand the details of the sleep status of the participants, a sleep diary will be provided to each participant. The subjects will be educated to write down their bedtime, final awakening time, sleep latency, number and duration of awakenings, perceived sleep duration, midday nap, and use of sleeping pills throughout the study period.[46]

To objectively measure the sleep patterns of the participants, actigraphy will be used in this trial. The candidate participants will wear a watch-type, physical activity monitoring device (ActiGraph™ wGT3X-BT, MTI Health Services Company, Pensacola, FL, USA) on their nondominant wrists for at least one week during the screening period. The subjects who meet all eligibility criteria will keep wearing the device during the 4 weeks of the intervention period to record their sleep and activity. Using this method, we can acquire objective data on the participants' sleep quality including the total time in bed, sleep latency, wake after sleep onset, total sleep time, and sleep efficiency.[23]

Blinding test and credibility test

The participants in the EA and sham EA groups will participate in the blinding test and credibility test after the first and last treatments. The purpose of these tests is to check whether the participant blinding was maintained for these groups. The blinding test will ask the participants which type of acupuncture they think has been received, real EA, sham EA, or unknown. The credibility test assesses the level of confidence in the treatment they have received. The score of this test ranges from 0 to 6, where a higher score reflects higher confidence in the treatment.[47]

Safety assessment

For the safety assessment, the investigators will ask the participants on each visit if they have experienced any adverse events (AE). Laboratory tests will also be performed at baseline and week 5 to detect AEs. This test includes a complete blood count and differential count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, albumin, erythrocyte sedimentation rate, thyroid-stimulating hormone, free thyroxine, and human chorionic gonadotropin urine tests (only for women in their childbearing years at the screening visit).

The severity of AEs will be primarily assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.[48] When the NCI-CTCAE is not applicable, Spilker's three level criteria will be used instead.[49] The type of AE and its severity will be recorded to the CRF regardless of the relationship with the intervention provided in this study. The relationship between the treatment and the AE will be

recorded as definitely related, probably related, possibly related, probably not related, definitely not related, or unknown.

Study feasibility outcomes

To see whether a full-scale randomised clinical trial for this issue is feasible, the recruitment rate and completion rate will be calculated. The overall rate of adherence to the planned intervention will also be ascertained.

Data collection and management

Data will be collected after acquiring the signed consent from the participants. The collected data will be recorded on the CRF by certificated clinical research coordinators. The whole process of the trial will be regularly monitored to ensure the quality of the trial. Periodic monitoring will confirm that the data in the CRF match the source document and that the procedures of the recruitment, intervention and assessment follow the protocol.

To guarantee the consistency of the procedures of the intervention and assessment between research centres, a standard operating procedure will be set and provided to the investigators. The practitioners are limited to licensed doctors of Korean medicine who have at least 2 years of clinical experience, and all investigators are required to take training courses for good clinical practice.

To promote participant retention and prevent follow-up loss, the researchers will make phone calls to participants prior to follow-up sessions. We will also inquire the participants failing to attend follow-up or treatment sessions about the reasons for absence and encourage compliance by telephone.

Sample size

The purpose of this pilot clinical trial is to explore the potential efficacy and safety of EA for insomnia in cancer patients. Therefore, a prospective sample size calculation was not performed. The result of this study will serve as the basis for sample size calculation for a full-scale trial on this theme in the future. An opinion from an expert in medical statistics recommended that the minimal number of people per group be 12 for a pilot study,[50] and assuming a dropout rate of 20%, 15 participants in each group or a total of 45 participants will be deemed appropriate for this research setting.

Statistical analysis

A full analysis set (FAS), which realises the intention-to-treat ideal as closely as possible,[51] will be the main set for primary analysis. The FAS includes all participants initially allocated to one of the three groups of the study; however, it excludes the data from participants who do not meet the eligibility criteria, who never received the intervention in this study, or who never provided any outcome value in this study. A per-protocol (PP) set will be used for sensitivity analysis to compare the results from the FAS. The PP set comprises the participants who completed the trial without major violation of the protocol, with having received at least 70% of the planned intervention and provided all outcome values.

A two-sided significance level will be set at 5%, and the multiple imputation method will be adopted for missing data. SAS® Version 9.4 (SAS institute. Inc., Cary, NC) will be used for statistical analysis.

Demographic characteristics and baseline measurements of the variables of each group will be summarised. Continuous data will be expressed as the mean ± standard deviation. Analysis of variance (ANOVA) or the Kruskal–Wallis test will performed to compare the continuous data from each group. A 95% confidence interval can be presented as needed. For dichotomous or categorical data, frequency and percentile will be presented, and the difference between groups will be compared using a chi-square test or the Fisher's exact test.

The mean change of the ISI score from baseline to week 5 is the primary outcome measure of this study. To identify statistically significant differences in the primary outcome measure between groups, two sets of hypotheses are assumed as described below.

Set 1

The null hypothesis (H_{01}): There is no difference in the mean change of the ISI before and after treatment between the EA group and the usual care group.

The alternative hypothesis (H_{11}): There is a difference in the mean change of the ISI before and after treatment between the EA group and the usual care group.

Set 2

The null hypothesis (H_{02}): There is no difference in the mean change of the ISI before and after treatment between the EA group and the sham EA group.

The alternative hypothesis (H_{12}): There is a difference in the mean change of the ISI before and after treatment between the EA group and the sham EA group.

If H_{01} is rejected and H_{11} is adopted in the statistical analysis for set 1, the test for the hypotheses of set 2 will be verified. However, if H_{01} is adopted in the test for the set 1 hypotheses, no further validation for the set 2 hypotheses will be required.

To validate the hypotheses, an analysis of covariance (ANCOVA) will be performed with the baseline value as a covariate and each group as a fixed factor. If there is any significant difference between groups among the demographic characteristics or baseline measurements of the variables, it will be adjusted according to its covariance. The problem of multiple comparison will be solved using the fixed sequence method.[52]

The secondary outcome measures will be analysed via the same methods used for the primary outcome measure analysis. The change of the outcome measures before and after the intervention within a group will be analysed using Student's paired t-test or Wilcoxon signed-rank test. Repeated measures ANOVA with post-hoc Dunnett's procedure will be used to validate the differences in the trends per visit.

Subgroup analysis will be conducted to determine whether the severity of insomnia, significant blood deficiency pattern according to a blood deficiency scoring system, or level of expectancy to the EA treatment at baseline affects the clinical response to EA. The correlation of the sleep-related variables extracted from an objective source (actigraphy) and a subjective source (patient-reported questionnaires) will be evaluated.

Ethics and dissemination

Licensed doctors of Korean medicine will obtain informed consent at each research centre. Only the participants who sign the informed consent form will be included in the study. The study protocol has been approved by the institutional review boards (IRBs) of the participating research centres; Daejeon Oriental Hospital of Daejeon University and Dong-eui University Korean Medical Hospital in Busan. The approved protocol was registered with the Clinical Research Information Service (CRIS) of South Korea (CRIS-KCT0002162).

Any modification to the protocol will be re-approved by the IRBs, documented in the online registry of CRIS, and reflected in the explanation for the participants. An amended consent form reflecting the revised protocol must be obtained from the participants.

The result of this study will be published in peer-reviewed journals or academic conferences.

DISCUSSION

Despite the high prevalence and enormous impact of insomnia in cancer patients, its importance has been overlooked.[1] The National Cancer Institute and National Comprehensive Cancer Network have strongly recommended evaluation and appropriate treatment of the sleep disturbance of cancer survivors during routine survivorship care.[11] Nevertheless, it seems that most hospitals and cancer centres are not properly managing the insomnia of

cancer patients.[11]

Insomnia is one of the areas in which acupuncture-related publications have been most commonly focused for the last 20 years.[53] Previous researches have shown that acupuncture is an effective intervention for insomnia. Acupuncture also appears to be effective for the sleep disorders of cancer patients, but its effect on the cancer population has been studied relatively less than in general insomniacs. Thus, we expect that the results of this study will contribute to increasing the insufficient evidence in this area of research.

Reviewing previous studies, we found that acupuncture may have only a short-term effect on the insomnia of cancer patients. Mao et al. reported that the sleep quality of the EA group was significantly better than that of control group immediately after an 8-week intervention period, but this difference between groups disappeared after 4 weeks.[54] Another study by Otte et al. also showed a similar pattern that the effect of a 2-week acupuncture treatment vanished after a 4-week follow-up period.[28]

However, according to the opinion of Choi et al., the effect of acupuncture seems to be strengthened over time.[20] These authors found that acupuncture was as good as conventional therapy and became better at follow-up visits 3 weeks after final treatment.[20] We will record the trend change of the effect of EA over time by assessing the response of the participants at baseline; week 3, a midpoint of the 4-week intervention; week 5, immediately after the end of the final intervention; and week 9, the final follow-up assessment. We expect the results of this study to contribute to solving the disagreement among the existing studies on the timing and duration of the effect of acupuncture on sleep disturbance in cancer patients.

In addition to time duration, there are many factors that can influence the effectiveness of acupuncture. Among them, we will try to determine whether a certain pattern identified according to the theory of Korean traditional medicine, blood deficiency, is an important variable that can affect the response to acupuncture. Blood deficiency is one of the main patterns of insomnia in Korean traditional medicine, and this study will investigate how many patients are categorised with a blood deficiency pattern using a blood deficiency scoring system[55] and whether their treatment response is different from that of the non-blood deficiency group.

In insomnia clinical trials, the placebo effect is very commonly observed.[56] The characteristics of insomnia—that it is intermittent and tends to maintain or even reinforce the therapeutic effect of specific treatment over long periods—seems to explain such a placebo effect.[56] This is the reason why the inclusion of a placebo control is generally recommended in insomnia clinical trials.[56] Thus, this study also included a sham EA group as a placebo control.

The sham EA group will receive sham acupuncture therapy at non-acupoints unrelated to insomnia using a Streitberger acupunctureneedle. This sham needle was devised by Streitberger and Kleinhenz in 1998.[57] Its appearance is the same as real acupuncture needles, but the needle does not penetrate the skin. The suitability of this device as a placebo comparator for acupuncture needles has been validated,[57] and it has been used as a control intervention in several acupuncture clinical studies.[58]

The Streitberger acupuncture needle is one of the two most commonly used and commercially available placebo devices in acupuncture clinical studies along with the Park sham device.[58] Nevertheless, approximately half of the clinical studies using these sham devices have concluded that the effects of real acupuncture and sham needles were not significantly different.[58] Generally, a placebo pill is used on the assumption that it has no pharmacological effect and is harmless.[59] However, it has been shown in many studies to date that sham acupuncture needles seem to have a significant physiological effect.[59] Thus, the development of a new placebo device as a perfect comparator for real acupuncture that has no physiologic effects while maintaining patient blinding is still a significant challenge for acupuncture researchers. However, we currently have no choice but to use one of these available sham devices while considering their limitations.

It is known that the proportion of the placebo effect is not inconsiderable in acupuncture treatment.[59] Moreover, as we have seen, patients with insomnia tend to respond strongly to placebo treatment. In addition, the response to sham acupuncture such as the skin sensation of pressure or tingling, may be akin to the response to acupressure, which is also known to be effective for insomnia.[16] Thus, a study design that directly compares acupuncture and sham acupuncture is likely to produce a false negative result, failing to detect the whole characteristic effect of acupuncture.[59] Therefore, we designed a three-arm parallel study

including the usual care group as well as a sham control group.

The strength of this study is that it will acquire objective outcomes reflecting sleep quality and the related circadian rhythm. First, we will obtain both subjective and objective outcomes showing sleep quality using patient-reported questionnaires and actigraphy. Most of the acupuncture studies on insomnia have used only patient-reported outcomes; furthermore, even a small number of studies using objective outcomes such as polysomnography or actigraphy failed to show consistent results on the effect of acupuncture for each outcome.[30-34] Based on the results of this study, we expect that we will be able to compare the difference between the subjective and objective outcomes and contribute to solving the conflict on this issue. Only actigraphy is used for objective outcome measures at this time; however, polysomnography, a gold standard method for insomnia diagnosis, should be included in future research.

Second, the difference in the levels of cortisol and melatonin in saliva between the groups will be compared as biomarkers reflecting the circadian rhythm of the body that affects the pattern of sleep. It is known that acupuncture modulates various neurotransmitters and hormones such as endorphin, serotonin, norepinephrine, cortisol and melatonin.[44 45] Among them, changes of the cortisol surge in the morning or melatonin increase at night time are known to be closely related to arousal and sleep.[44 45] Previous studies have reported that acupuncture can improve insomnia by affecting the pattern of cortisol[60 61] or melatonin[27] release. Based on these results, we will investigate the changes in salivary cortisol and melatonin in addition to the sleep quality of the participants.

Trial status

This trial is currently recruiting participants.

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Contributors

MK and JHK conceived the study. MK drafted the protocol. JEK, HYL, ARK, and HJP participated in the design of the study and contributed to the refinement of the protocol. OJK was responsible for the statistical design of the study. BKK and JHC provided clinical advice and made critical revisions. JHK is a principal investigator of the study and has the final responsibility for the decision to submit this manuscript for publication. All authors approved the final manuscript.

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Competing interests

None declared.

Patient consent

Will be obtained.

Ethics approval

Daejeon Oriental Hospital of Daejeon University IRB (djomc-140-1); Dong-eui University Korean Medical Hospital IRB (2016-04)

Provenance and peer review

Not commissioned; this study was peer reviewed for ethics and funding approval prior to submission.

Data sharing statement

Data requested for public purposes or research transparency will be provided (please contact the corresponding author).

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Table (in the main text)

Table 1 Schedule of enrolment, interventions, and assessments

Figure titles

Figure 1 Flow diagram of the study

Figure 2 The points used for the electroacupuncture group

Supplementary file

Supplementary File 1 Details of the electroacupuncture (EA) and sham EA treatment based on the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist

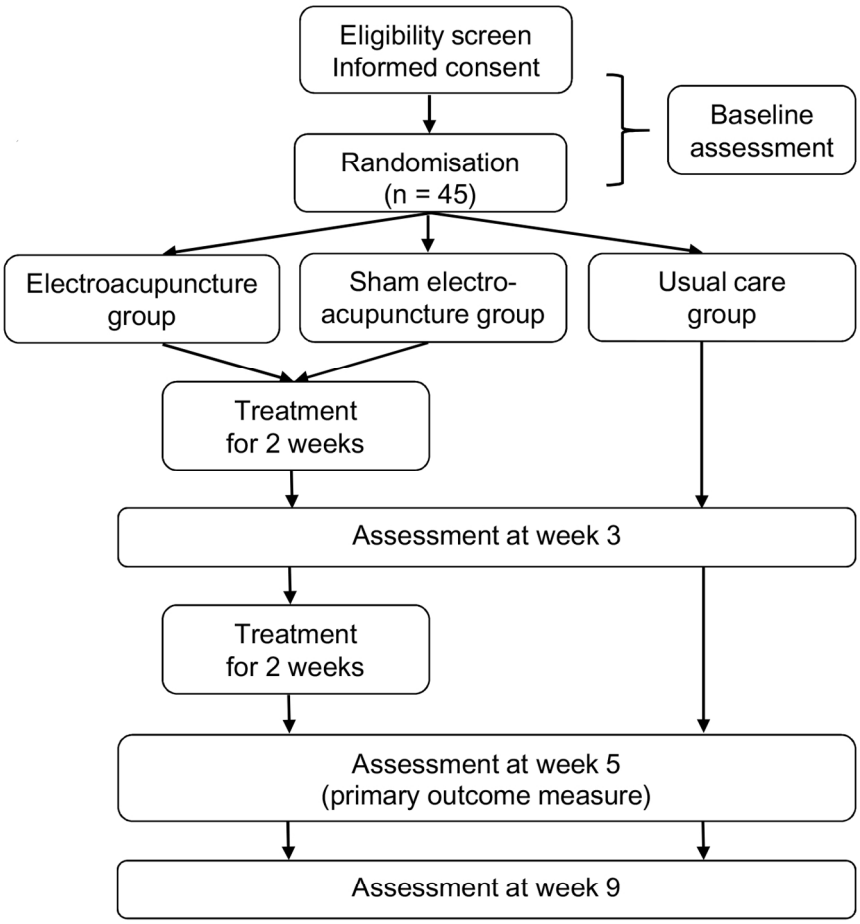

Figure 1 Flow diagram of the study

137x141mm (300 x 300 DPI)

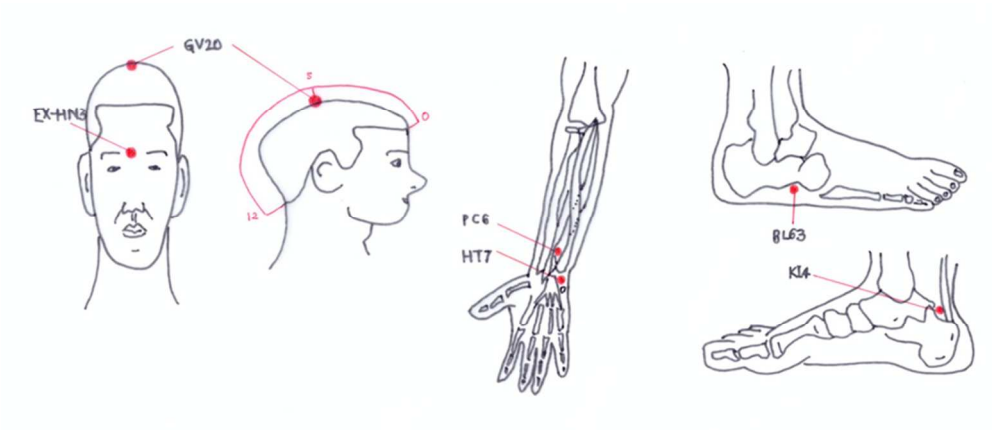

Figure 2 The points used for the electroacupuncture group

73x31mm (300 x 300 DPI)

Supplementary file 1 Details of the electroacupuncture (EA) and sham EA treatments based on the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist

Item	Detail	Description
1. Acupuncture rationale	1a) Style of acupuncture	Electroacupuncture based on traditional Korean acupuncture
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	Related papers[15-20,25-29,31-34] and expert (doctors of Korean medicine) consensus
	1c) Extent to which treatment was varied	Standardized treatment (option: up to 2 bilateral acupoints can be added according to the chief complaints of the participants)
2. Details of needling	2a) Number of needle insertions per subject per session	Standardized regimen: 10 (10 to 14, when considering addition of optional acupoints)
	2b) Names of points used	GV 20, EX-HN-3, bilateral HT7, PC6, BL63, KI4
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	0.6 – 4.5 cm
	2d) Response sought	Acupuncture: *de qi* (sense of soreness, numbness, heaviness, or distension) EA: cognition of stimulation and comfortable feeling
	2e) Needle stimulation	Manual stimulation: twisting-needling 3-5 times Electrical stimulation: 4 Hz
	2f) Needle retention time	30 minutes
	2g) Needle type (diameter, length, and manufacturer or material)	Acupuncture (diameter: 0.25 mm, length: 25 mm, manufacturer: Asiamed GmbH & Co., material: sterilized stainless steel)
3. Treatment regimen	3a) Number of treatment sessions	10
	3b) Frequency and duration of treatment sessions	10 sessions for 4 weeks (average 2.5 times per week)
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group	- All the three groups will be educated with a brochure about the management of sleep disorder - No additional Korean traditional medical treatment regarding insomnia is allowed except for what is given for the study - The interventions other than Korean traditional medical treatment to manage insomnia that have been steadily received for more than 4 weeks before the screening visit are allowed to continue during the study, but no additional treatment is allowed after the beginning of the trial (even sleeping pills are allowed)
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	- Setting: clinical trial centers in university hospitals - Unnecessary conversation will be limited between the acupuncturists and patients during the treatment.
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)	Licensed Korean medical doctors with at least 2 years of clinical experience
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice	Sham acupuncture: previous researches validating the nonpenetrating sham acupuncture device, Streitberger acupuncture needle[52] Mock electroacupuncture: previous researches with control intervention with no electrical stimulation with beeping sound and lighting[29,32-34,49]

	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.	1. rationale of sham acupuncture Use non-penetrating Streitberger acupuncture needles at 10 non-acupoints and connect electrostimulator in switch-off state on to the needles 2. points used for sham EA - Upper limb 1: 1 cm lateral and 5 cm proximal points from cubital creases of bilateral arms - Upper limb 2: 2 cm above the upper limb 1 point - Lower limb 1: 1.5 cm above the depression at the midpoint of the upper border of the bilateral patella - Lower limb 2: area 1/3 above the medial part of the bilateral tibia - Lower limb 3: 1.5 cm above the lower limb 2 point 3. number of needle insertions per subject per session: 10 4. needle type Sham acupuncture (Streitberger needle, Asiamed GmbH & Co., sterilized stainless steel) 5. Treatment duration, frequency, period: the same as the treatment group

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___title page___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_at the end of the abstract_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____-_____
Protocol version	3	Date and version identifier	_____-_____
Funding	4	Sources and types of financial, material, and other support	_____24_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____24_____
	5b	Name and contact information for the trial sponsor	_____-_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____-_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____-_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	12-13
Objectives	7	Specific objectives or hypotheses	7,19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-11, 17
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-16

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, table 1, figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17-18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-17

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14, 18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	-
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Electroacupuncture for treating insomnia in cancer patients: a study protocol for a randomised pilot clinical trial

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Electroacupuncture for treating insomnia in cancer patients: a study protocol for a randomised pilot clinical trial

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Abstract

Introduction: Although insomnia is one of the most prevalent and disturbing symptoms among cancer patients, it has not been properly managed. Electroacupuncture (EA) has received attention as a promising intervention for insomnia, and a few previous studies have reported that this intervention may be beneficial for treating insomnia in cancer patients. The aim of this pilot study is to explore the feasibility and preliminary effectiveness of EA on the sleep disturbance of cancer patients with insomnia using a subjective method, patient-reported questionnaires and an objective tool, actigraphy to measure the quality of sleep.

Methods and analysis: This is a study protocol for a randomised, three-arm, multi-centre, pilot clinical trial. A total of 45 cancer patients who have continuous insomnia related to cancer treatment or cancer itself will be randomly allocated to an EA group, sham EA group, or usual care group in equal proportions. The EA group will receive 10 sessions of EA treatment over 4 weeks. The sham EA group will receive sham EA at non-acupoints using nonpenetrating Streitberger acupuncture needles with mock EA. The usual care group will not receive EA treatment. All participants will be provided a brochure on the management of sleep disorders regardless of their group assignment. The primary outcome measure is the mean change in the insomnia severity index from the baseline to week 5. Information related to sleep quality will also be obtained through the Pittsburgh Sleep Quality Index, a sleep diary, and actigraphy. Participants will complete the trial by visiting the research centre at week 9 for follow-up assessment.

Ethics and dissemination: This study protocol was approved by the institutional review boards of each research centres. Written informed consent will be obtained from all participants. The result of this study will be published in peer-reviewed journals or presented at academic conferences.

Trial registration number: Clinical Research Information Service KCT0002162.

Strengths and limitations of this study

1. This randomised, multi-centre clinical trial is the first study in South Korea exploring the effect and safety of electroacupuncture as a treatment for sleep disturbance in cancer patients with insomnia.

2. In addition to patient-reported outcomes, the study will use actigraphy to acquire objective outcomes reflecting the quality of sleep.

3. The study will measure the levels of cortisol and melatonin in saliva as biomarkers reflecting the circadian rhythm of the body related to sleep and arousal.

4. Polysomnography needs to be included in future research to investigate sleep architecture and the various causes of sleep disorders.

5. Because of the unique nature of electroacupuncture and the design of this study, which includs a usual care group, it is impossible to completely blind the practitioners and all participants.

6. The study adopts nonpenetrating needling at non-acupoints as a sham comparator for acupuncture; however, a perfect placebo intervention for real acupuncture that exerts no physiologic effects while maintaining patient blinding has not been developed yet.

7. The sample size of this pilot study is 15 per each group, which may be underpowered to draw a definitive conclusion of the effectiveness of the intervention.

INTRODUCTION

Insomnia is one of the most common afflictions among the general population, and the prevalence of insomnia is known to be twice as high as in cancer patients compared to healthy adults.[1] Complex interactions of various factors such as adverse reactions to chemotherapy,[1] circadian disruption,[2] inflammation,[3] and tumour growth[3] seem to be the reasons why cancer patients are especially susceptible to insomnia. Insomnia has a profound effect on the overall quality of life,[4] energy,[5] emotion,[6] memory,[7] and immune system[8] of cancer patients. In addition, insomnia is also known to be associated with decreased survival[9] and tumour worsening.[10] Although insomnia is such a common and important problem among cancer patients, it is not easily cured or well managed.[1 11]

The most commonly used therapy for the management of insomnia in cancer patients is pharmacotherapy.[12] According to Moore et al., approximately half of breast cancer patients are prescribed sleeping pills.[13] Long-term use of sleeping pills is known to be associated with continued sleep disturbance, decreased ability to perform daily activities, memory impairment, traffic accidents, falls, etc.[12] Thus, pharmacotherapy should be used only for a short-term period; however, approximately 30% of cancer patients are receiving sleeping pills even one year after the end of chemotherapy.[13]

In addition to pharmacotherapy, cognitive behavioural therapy has been recommended as a standard therapy for the improvement of insomnia.[3] However, there are some limitations to this therapy in that the compliance rate to the therapy is low because the therapeutic response does not appear immediately, and patient access to the therapy is low due to the high cost of the therapy.[14] Moreover, experienced therapists are rare, and the effect of therapy varies widely depending on the proficiency of the therapist.[14]

For this reason, there is a growing demand for complementary alternative medicine (CAM) in the field of sleep management. Acupuncture is one of the most commonly used therapeutic interventions in CAM. Acupuncture is a treatment that punctures and stimulates the skin at acupoints using specialisedneedles. Electroacupuncture (EA) refers to a method that supplies a constant physical stimulus to acupoints through the inserted acupuncture needle connected to a microcurrent stimulator.

Previous systematic reviews on the effect of acupuncture for insomnia have revealed that

acupuncture is significantly more effective to improve sleep disturbance in insomniacs than no treatment[15] and sham acupuncture.[15-17] Insomnia has also been reported to be as effective as pharmacotherapy[15] or even superior to sleeping pills[15 17] and provides additional benefit to patients who are undergoing pharmacotherapy to improve insomnia.[15 16]

The effect of acupuncture for the improvement of sleep disorders has also been identified in studies targeting cancer patients. A survey conducted at a major cancer centre in the United States showed that acupuncture significantly improved the quality of sleep in cancer patients.[18] Garland et al. also determined that 8-week EA was more effective than pharmacotherapy to attenuate sleep disturbance from a recently published randomised controlled trial including breast cancer patients suffering from hot flush.[19] Choi et al. systematically investigated the clinical studies on the effect of acupuncture for insomnia in cancer patients and indicated that acupuncture may be superior to sham acupuncture or pharmacotherapy.[20] However, these authors could not draw any firm conclusions because the level of evidence in the included studies was low overall, the effect size of the studies was too small to confirm their clinical significance, and there were few studies strictly designed and performed.[20]

Subjective measurement tools such as self-reported questionnaires or sleep diaries are the most commonly used type of outcome measures for the assessment of sleep quality. This is because these tools are relatively simple to measure and have the advantage of not interfering with daily life or sleeping; however, one limitation of this approach is that the results of these measurements are entirely up to the decisions of participants and are unable to objectively measure the pattern of sleep.[21] Polysomnography and actigraphy are the two main methods to objectively measure sleep quality.[21]

Polysomnography is a gold standard method for the objective measurement of sleep,[3 21] because it can demonstrate the sleep structure and the cause of sleep disorders in various ways including electroencephalogram, electromyogram, electrocardiogram, respiration and oxygen saturation, etc.[22] However, one disadvantage is that polysomnography requires an expensive device and an expert capable of interpreting the results.[21]

To overcome these shortcomings, actigraphy has been investigated.[23] Actigraphy is a noninvasive means of measuring the motion of the body using an actigraph, a piezoelectric

accelerometer.[23] Actigraphy has been widely used in the field of sleep research because it can detect sleep, activity, and movement without disturbing the daily lives of the subjects who are only required to wear a small, watch-shaped device on the wrist.[23] Studies on the similarities and differences between the sleep quality measured by polysomnography, actigraphy, and subjective assessment tools have been published.[23] It is recommended to use both objective and subjective measurement methods to assess sleep quality in the field of sleep research.[24]

A few acupuncture researchers have reported the positive effect of acupuncture using objective measurement tools such as polysomnography[25-27] or actigraphy.[28 29] However, there remain conflicting results regarding whether acupuncture has the same effect on both subjective and objective aspects of sleep. Some researchers argued that the effect of acupuncture was approved via both objective and subjective measurement tools[25-27], while others reported that acupuncture seemed to affect the subjective outcomes only, not the result of polysomnography[30 31] or actigraphy.[32-34]

The aim of this pilot study is to explore the feasibility and preliminary effectivenessof EA on the sleep disturbance of cancer patients with insomnia using both subjective questionnaires and objective actigraphy.

METHODS AND ANALYSIS

Study design

This is a study protocol for a randomised, three-arm, multi-centre, pilot clinical trial. Forty-five cancer patients with insomnia will be randomly assigned to an EA group, sham EA group, or usual care group at a 1:1:1 ratio. The schedule of enrolment, interventions, and assessments is summarised in Table 1, and the flow diagram of the study is presented in Figure 1.

Table 1 Schedule of enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrolment	Allocation	Treatment			Follow-up	
TIMEPOINT	$-wk_1$	wk_0	wk_1	wk_3	wk_4	wk_5	wk_9
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS							
EA			◆—	—	—◆		
Sham EA			◆—	—	—◆		
Usual care			◆—	—	—◆		
ASSESSMENTS							
ISI	X	X		X		X	X
PSQI		X		X		X	X
Sleep diary	◆—	—◆	◆—	—	—	—	—◆
Actigraphy	◆—	—◆	◆—	—◆	◆—	—◆	
FACT-F		X				X	
MoCA		X				X	
BDSS		X					
Salivary hormone test		X				X	
Blinding/credibility test[a]			X		X		
Adverse event			X	X	X	X	X

Laboratory test[b]	X		X

EA, Electroacupuncture; ISI, Insomnia Severity Inventory; PSQI, Pittsburgh Sleep Quality Index; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; MoCA, The Montreal Cognitive Assessment; BDSS, Blood Deficiency Scoring System.

[a]Only EA and sham EA groups will undergo blinding and credibility tests.

[b]The laboratory test includes complete blood count and differential count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, albumin, erythrocyte sedimentation rate, thyroid-stimulating hormone, free thyroxine, and human chorionic gonadotropin urine test (only for women in their childbearing years at the screening visit).

Recruitment

Two clinical research centres in South Korea will conduct this trial: Daejeon Oriental Hospital of Daejeon University and Dong-eui University Korean Medical Hospital in Busan. We will do our best to secure enough participants in this study using online and offline advertisement boards inside and outside the hospitals and by releasing flyers to daily local newspapers.

Inclusion criteria

1. Patients aged 19 years or over but under 80 years

2. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

3. Cessation of cancer-related treatments (e.g., surgery, radiotherapy, chemotherapy, immunotherapy) at least 12 weeks before the trial (ongoing hormone therapy, which must have been initiated at least 3 weeks prior to enrolment, is allowed)

4. Continuous insomnia related to cancer treatment or cancer itself for at least 3 months, with fulfilment of The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for insomnia disorder

5. Total score in the Insomnia Severity Index (ISI) ≥ 15 points

6. Willingness to participate in the trial and having provided written consent

Exclusion criteria

1. Having experienced the current level of sleep disorder prior to the diagnosis of cancer

2. Severe anaemia (platelet count < 60,000/μL, haemoglobin < 8 g/dL, or absolute neutrophil count < 1,000/μL)

3. A diagnosis of major depressive disorder, anxiety disorder, panic disorder, or other psychiatric disorder; caffeine, alcohol, or drug addiction; or a subscale of either anxiety or depression in Hamilton Anxiety and Depression Scale (HADS) score ≥ 11 points

4. Level of cancer pain measured by the numeric rating scale ≥ 4

5. An estimated life expectancy of six months or less

6. A plan for surgery, chemotherapy, or radiotherapy during the study

7. A recent change of regular medication to alleviate insomnia within 4 weeks of the beginning of the trial

8. Having taken sleeping pills as required within 2 weeks of the beginning of the trial

9. Having undergone Korean medical treatment (e.g., acupuncture, moxibustion, cupping, herbal medicine) within 4 weeks of the beginning of the trial

10. Initiation or a change in dietary supplement regimen or non-pharmacologic therapies (e.g., cognitive behavioural therapy, exercise, etc.) for alleviating insomnia during the trial or within 4 weeks of the beginning of the trial

11. Working shifts or changes in day/night work schedule that could impact circadian rhythm

12. Suffering from pain severe enough to cause sleep disturbance or presence of any disease that could cause insomnia

13. Taking haemostatic agents (e.g., Greenmono, Advate, Monoclate-P, Facnyne, BeneFix) because of haemostatic disorders

14. Abnormal findings in thyroid function test (abnormal level of free thyroxine [free T4] and thyroid stimulating hormone [TSH] < 0.1 μIU/ml or TSH > 5.1 μIU/ml)

15. History of hypersensitivity reactions to acupuncture or inability to cooperate with acupuncture therapy

16. The presence of implants that could interfere with EA or a history of hypersensitivity reactions to electrostimulation

17. Pregnancy, lactation, or planning to become pregnant

18. Having participated in other clinical trials within 4 weeks of the beginning of the trial

19. Difficulty complying with the study protocol

Randomisation and allocation concealment

Fifteen subjects will be allocated to each group according to a randomisation schedule generated by an independent statistician using SAS (Version 9.4, SAS institute Inc., Cary, NC). A stratified randomisation method will be used with the research centre and the standard therapies for insomnia (regular sleep medications or cognitive behavioural therapy for insomnia) as stratification factors. The statistician will seal the randomisation codes in sequentially numbered opaque envelopes and send them to the research centres. These envelopes will be kept in double-locked cabinets at the centres. Each envelope will be opened by a practitioner to assign the participant to one of the three groups after acquiring informed consent and eligibility screening.

Blinding

Participant blinding will be limited to the participants in the EA and sham EA groups. Complete participant blinding is not possible because the subjects in the usual care group

cannot help but notice their allocated group. Practitioner blinding cannot be achieved because of the unique nature of EA treatment. The assessor blinding will be maintained by separating the staff members who perform EA and who measure the outcomes.

Interventions

All participants of this trial will be educated with a brochure on the management of sleep disorders regardless of the assigned groups.

EA group

Participants in the EA group will receive acupuncture treatment at GV20, EX-HN3, bilateral HT7, PC6, BL63, and KI4 using sterilised stainless steel acupuncture needles (Asiamed GmbH & Co., 0.25 × 25 mm) (Figure 2). In addition to these 10 acupoints, up to 4 more points can be optionally added according to the symptoms of the patients. If participants with lymphatic oedema refuse to be treated with the acupoints on the affected site, the acupoints near the oedema site can be omitted. After inducing *deqi* by twisting the acupuncture needles, electric stimulation using an EA device (ES-160, Ito Co Ltd, Tokyo, Japan) will be applied with a 4-Hz frequency, at an intensity that the participant can notice but feel comfortable with. The EA treatment will be performed for 30 min per time, with a total of 10 times over 4 weeks. This regimen was decided by consensus among experts traditional Korean medicine based on previous research.[15-20 25-29 31 32 34] Details of the EA treatment based on the standards for reporting interventions in clinical trials of the acupuncture checklist are tabulated in Supplementary File 1.

Sham EA group

Participants in the sham EA group will receive sham acupuncture using nonpenetrating Streitberger acupuncture needles (Asiamed GmbH & Co.). Unlike the real acupuncture needle that is inserted into the skin, the tip of the Streitberger acupuncture needle is so blunt that it cannot penetrate the skin. The needles will be fixed by medical skin tape on the skin at

non-acupoints unrelated to the management of sleep disorders in Korean traditional medicine as follows: upper limb 1 (1 cm lateral and 5 cm proximal points from cubital creases of bilateral arms); upper limb 2 (2 cm above the upper limb 1 point); lower limb 1 (1.5 cm above the depression at the midpoint of the upper border of the bilateral patella); lower limb 2 (area 1/3 above the medial part of the bilateral tibia); and lower limb 3 (1.5 cm above the lower limb 2 point). The same EA device will be applied to the Streitberger acupuncture needles, with an identical beeping sound and light signals as for the EA group. However, the electric current will not be delivered.

Usual care group

Participants in the usual care group will not receive EA treatment. These subjects will maintain the usual treatment and self-care but cannot begin any additional treatment to improve their insomnia during the study period.

Prohibited and permitted concomitant treatment

The participants will be prohibited from any Korean traditional medical treatment such as acupuncture, moxibustion, cupping, or herbal drugs to attenuate their insomnia symptoms except for the EA provided by the trial. If the participants remained on regular medication to improve insomnia at least 4 weeks prior to the beginning of the trial, they will be allowed to maintain the medication. However, if the type or dosage of the sleeping pill is changed during the trial, the subjects will be withdrawn from the study. If the subjects are receiving standard nonpharmacological treatment, such as cognitive behavioural therapy, or taking any dietary supplements to attenuate insomnia from at least 4 weeks prior to the beginning of the trial, they will be allowed to maintain these treatments. However, their regimens cannot be changed during the trial.

The participants will be trained to report all treatments newly received after the beginning of the trial to the staff members, and their treatment history will be recorded on the case report form (CRF). When participants are found to have received a prohibited treatment during the

study period, they will be withdrawn from the trial. Despite withdrawal from the trial, the recordings of the participants will continue if the subjects have already randomised. To realise the intention-to-treat principle, the data from the withdrawn participants will also be included in the analysis set and recorded in the results.

Outcomes

Study feasibility outcomes

To see whether a full-scale randomised clinical trial for this issue is feasible, the recruitment rate and completion rate will be calculated. The overall rate of adherence to the planned intervention will also be ascertained.

Primary outcome measure

The primary outcome measure of this study will be the mean change in the ISI from the baseline to the end of the 4-week intervention. The ISI is a 7-item questionnaire devised to diagnose and assess the severity of the insomnia. The total score of the ISI ranges from 0 to 28 points, and it can categorise insomniacs according to scores of 0–7 (no clinically significant insomnia), 8–14 (subthreshold insomnia), 15–21 (clinical insomnia, moderate severity), and 22–28 (clinical insomnia, severe).[35] The Korean version of the ISI validated by Cho et al. will be used in this study.[36]

Secondary outcome measures

The secondary outcome measures of this study will include the mean changes in the total score of the ISI from baseline to week 3 and week 9 and changes in the scores of the Pittsburgh Sleep Quality Index (PSQI), Functional Assessment of Cancer Therapy-Fatigue (FACT-F), and Montreal Cognitive Assessment (MoCA); the level of the salivary hormones including cortisol and melatonin; and the quality of sleep measured by a sleep diary and actigraphy before and after the intervention.

The PSQI is a self-reported questionnaire to assess the quality of sleep over the past month. This scale comprises of 7 components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping pills, and daytime dysfunction. The global PSQI score ranges from 0 to 21, and a higher score represents poorer quality of sleep.[37] The Korean version of the PSQI validated by Sohn et al. will be used in this study.[38]

The change of the global score in the PSQI will be assessed at baseline, week 3, week 5, and week 9.

The FACT-F is a questionnaire devised to determine the level of fatigue of cancer patients. This instrument consists of the FACT-general (G) and the fatigue subscale. The FACT-G is composed of 27 items in 4 domains including physical well-being, social/family well-being, emotional well-being, and functional well-being. The fatigue subscale has 13 items assessing the level of fatigue. The total score of the FACT-F ranges from 0 to 160, where higher points denote a higher level of fatigue that disturbs the daily life of the patients.[39] Lee et al. validated the Korean version of the FACT-G.[40] Jeong et al. have translated and validated the Korean version of the fatigue subscale and also used it with Lee's Korean version of the FACT-G among patients with cancer-related fatigue.[41] In other words, the Korean version of the complete FACT-F has been used to measure the level of fatigue among cancer patients in Korea.[41] FACT-F scores will be assessed at baseline and week 5.

The MoCA is a one-page, 30-point test originally devised to screen for mild cognitive impairment in the geriatric population and can also be applied to evaluate the level of cognition of cancer survivors.[42] The validated Korean version of the MoCA will be used in this study.[43] The MoCA will be assessed at baseline and week 5 by the assessors who will be blinded to the group allocation

The change in the level of cortisol and melatonin in saliva will be measured before and after the intervention. These levels are known to reflect the circadian rhythm of the human body. The level of cortisol usually surges in the morning, while melatonin release increases at night in normal conditions, and the constant change of these hormones is known to be closely related to arousal and sleep.[44 45] We will check whether this type of rhythmical change in these hormones differs before and after the intervention.

To understand the details of the sleep status of the participants, a sleep diary will be provided to each participant. The subjects will be educated to write down their bedtime, final awakening time, sleep latency, number and duration of awakenings, perceived sleep duration, midday nap, and use of sleeping pills throughout the study period.[46]

To objectively measure the sleep patterns of the participants, actigraphy will be used in this trial. The candidate participants will wear a watch-type, physical activity monitoring device (ActiGraph™ wGT3X-BT, MTI Health Services Company, Pensacola, FL, USA) on their nondominant wrists for at least one week during the screening period. The subjects who meet all eligibility criteria will keep wearing the device during the 4 weeks of the intervention period to record their sleep and activity. Using this method, we can acquire objective data on the participants' sleep quality including the total time in bed, sleep latency, wake after sleep onset, total sleep time, and sleep efficiency.[23]

Blinding test and credibility test

The participants in the EA and sham EA groups will participate in the blinding test and credibility test after the first and last treatments. The purpose of these tests is to check whether the participant blinding was maintained for these groups. The blinding test will ask the participants which type of acupuncture they think has been received, real EA, sham EA, or unknown. The credibility test assesses the level of confidence in the treatment they have received. The score of this test ranges from 0 to 6, where a higher score reflects higher confidence in the treatment.[47]

Safety assessment

For the safety assessment, the investigators will ask the participants on each visit if they have experienced any adverse events (AE). Laboratory tests will also be performed at baseline and week 5 to detect AEs. This test includes a complete blood count and differential count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, total bilirubin, blood urea nitrogen, creatinine, albumin, erythrocyte sedimentation rate, thyroid-stimulating hormone, free thyroxine, and human chorionic gonadotropin urine tests (only for women in their childbearing years at the screening visit).

The severity of AEs will be primarily assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.[48] When the NCI-CTCAE is not applicable, Spilker's three level criteria will be used instead.[49] The type of AE and its severity will be recorded to the CRF regardless of the relationship with the intervention provided in this study. The relationship between the treatment and the AE will be recorded as definitely related, probably related, possibly related, probably not related, definitely not related, or unknown.

Data collection and management

Data will be collected after acquiring the signed consent from the participants. The collected data will be recorded on the CRF by certificated clinical research coordinators. The whole process of the trial will be regularly monitored to ensure the quality of the trial. Periodic monitoring will confirm that the data in the CRF match the source document and that the procedures of the recruitment, intervention and assessment follow the protocol.

To guarantee the consistency of the procedures of the intervention and assessment between research centres, a standard operating procedure will be set and provided to the investigators. The practitioners are limited to licensed doctors of Korean medicine who have at least 2 years of clinical experience, and all investigators are required to take training courses for good clinical practice.

To promote participant retention and prevent follow-up loss, the researchers will make phone calls to participants prior to follow-up sessions. We will also inquire the participants failing to attend follow-up or treatment sessions about the reasons for absence and encourage compliance by telephone.

Sample size

The purpose of this pilot clinical trial is to explore the potential efficacy and safety of EA for insomnia in cancer patients. Therefore, a prospective sample size calculation was not performed. The result of this study will serve as the basis for sample size calculation for a full-scale trial on this theme in the future. An opinion from an expert in medical statistics recommended that the minimal number of people per group be 12 for a pilot study,[50] and assuming a dropout rate of 20%, 15 participants in each group or a total of 45 participants will be deemed appropriate for this research setting.

Statistical analysis

A full analysis set (FAS), which realises the intention-to-treat ideal as closely as possible,[51] will be the main set for primary analysis. The FAS includes all participants initially allocated to one of the three groups of the study; however, it excludes the data from participants who do not meet the eligibility criteria, who never received the intervention in this study, or who never provided any outcome value in this study. A per-protocol (PP) set will be used for sensitivity analysis to compare the results from the FAS. The PP set comprises the participants who completed the trial without major violation of the protocol, with having received at least 70% of the planned intervention and provided all outcome values.

A two-sided significance level will be set at 5%, and the multiple imputation method will be adopted for missing data. SAS® Version 9.4 (SAS institute. Inc., Cary, NC) will be used for statistical analysis.

Demographic characteristics and baseline measurements of the variables of each group will be summarised. Continuous data will be expressed as the mean ± standard deviation. Analysis of variance (ANOVA) or the Kruskal–Wallis test will performed to compare the continuous data from each group. A 95% confidence interval can be presented as needed. For dichotomous or categorical data, frequency and percentile will be presented, and the difference between groups will be compared using a chi-square test or the Fisher's exact test.

The mean change of the ISI score from baseline to week 5 is the primary outcome measure of this study. To identify statistically significant differences in the primary outcome measure between groups, two sets of hypotheses are assumed as described below.

Set 1

The null hypothesis (H_{01}): There is no difference in the mean change of the ISI before and after treatment between the EA group and the usual care group.

The alternative hypothesis (H_{11}): There is a difference in the mean change of the ISI before and after treatment between the EA group and the usual care group.

Set 2

The null hypothesis (H_{02}): There is no difference in the mean change of the ISI before and after treatment between the EA group and the sham EA group.

The alternative hypothesis (H_{12}): There is a difference in the mean change of the ISI before and after treatment between the EA group and the sham EA group.

If H_{01} is rejected and H_{11} is adopted in the statistical analysis for set 1, the test for the hypotheses of set 2 will be verified. However, if H_{01} is adopted in the test for the set 1 hypotheses, no further validation for the set 2 hypotheses will be required.

To validate the hypotheses, an analysis of covariance (ANCOVA) will be performed with the baseline value as a covariate and each group as a fixed factor. If there is any significant difference between groups among the demographic characteristics or baseline measurements of the variables, it will be adjusted according to its covariance. The problem of multiple comparison will be solved using the fixed sequence method.[52]

The secondary outcome measures will be analysed via the same methods used for the primary outcome measure analysis. The change of the outcome measures before and after the intervention within a group will be analysed using Student's paired t-test or Wilcoxon signed-rank test. Repeated measures ANOVA with post-hoc Dunnett's procedure will be used to validate the differences in the trends per visit.

Subgroup analysis will be conducted to determine whether the severity of insomnia, significant blood deficiency pattern according to a blood deficiency scoring system, or level of expectancy to the EA treatment at baseline affects the clinical response to EA. The correlation of the sleep-related variables extracted from an objective source (actigraphy) and a subjective source (patient-reported questionnaires) will be evaluated.

Ethics and dissemination

Licensed doctors of Korean medicine will obtain informed consent at each research centre. Only the participants who sign the informed consent form will be included in the study. The study protocol has been approved by the institutional review boards (IRBs) of the participating research centres; Daejeon Oriental Hospital of Daejeon University and Dong-eui University Korean Medical Hospital in Busan. The approved protocol was registered with the Clinical Research Information Service (CRIS) of South Korea (CRIS-KCT0002162).

Any modification to the protocol will be re-approved by the IRBs, documented in the online registry of CRIS, and reflected in the explanation for the participants. An amended consent form reflecting the revised protocol must be obtained from the participants.

The result of this study will be published in peer-reviewed journals or academic conferences.

DISCUSSION

Despite the high prevalence and enormous impact of insomnia in cancer patients, its importance has been overlooked.[1] The National Cancer Institute and National Comprehensive Cancer Network have strongly recommended evaluation and appropriate treatment of the sleep disturbance of cancer survivors during routine survivorship care.[11] Nevertheless, it seems that most hospitals and cancer centres are not properly managing the insomnia of

cancer patients.[11]

Insomnia is one of the areas in which acupuncture-related publications have been most commonly focused for the last 20 years.[53] Previous researches have shown that acupuncture is an effective intervention for insomnia. Acupuncture also appears to be effective for the sleep disorders of cancer patients, but its effect on the cancer population has been studied relatively less than in general insomniacs. Thus, we expect that the results of this study will contribute to increasing the insufficient evidence in this area of research.

Reviewing previous studies, we found that acupuncture may have only a short-term effect on the insomnia of cancer patients. Mao et al. reported that the sleep quality of the EA group was significantly better than that of control group immediately after an 8-week intervention period, but this difference between groups disappeared after 4 weeks.[54] Another study by Otte et al. also showed a similar pattern that the effect of a 2-week acupuncture treatment vanished after a 4-week follow-up period.[28]

However, according to the opinion of Choi et al., the effect of acupuncture seems to be strengthened over time.[20] These authors found that acupuncture was as good as conventional therapy and became better at follow-up visits 3 weeks after final treatment.[20] We will record the trend change of the effect of EA over time by assessing the response of the participants at baseline; week 3, a midpoint of the 4-week intervention; week 5, immediately after the end of the final intervention; and week 9, the final follow-up assessment. We expect the results of this study to contribute to solving the disagreement among the existing studies on the timing and duration of the effect of acupuncture on sleep disturbance in cancer patients.

In addition to time duration, there are many factors that can influence the effectiveness of acupuncture. Among them, we will try to determine whether a certain pattern identified according to the theory of Korean traditional medicine, blood deficiency, is an important variable that can affect the response to acupuncture. Blood deficiency is one of the main patterns of insomnia in Korean traditional medicine, and this study will investigate how many patients are categorised with a blood deficiency pattern using a blood deficiency scoring system[55] and whether their treatment response is different from that of the non-blood deficiency group.

In insomnia clinical trials, the placebo effect is very commonly observed.[56] The characteristics of insomnia—that it is intermittent and tends to maintain or even reinforce the therapeutic effect of specific treatment over long periods—seems to explain such a placebo effect.[56] This is the reason why the inclusion of a placebo control is generally recommended in insomnia clinical trials.[56] Thus, this study also included a sham EA group as a placebo control.

The sham EA group will receive sham acupuncture therapy at non-acupoints unrelated to insomnia using a Streitberger acupunctureneedle. This sham needle was devised by Streitberger and Kleinhenz in 1998.[57] Its appearance is the same as real acupuncture needles, but the needle does not penetrate the skin. The suitability of this device as a placebo comparator for acupuncture needles has been validated,[57] and it has been used as a control intervention in several acupuncture clinical studies.[58]

The Streitberger acupuncture needle is one of the two most commonly used and commercially available placebo devices in acupuncture clinical studies along with the Park sham device.[58] Nevertheless, approximately half of the clinical studies using these sham devices have concluded that the effects of real acupuncture and sham needles were not significantly different.[58] Generally, a placebo pill is used on the assumption that it has no pharmacological effect and is harmless.[59] However, it has been shown in many studies to date that sham acupuncture needles seem to have a significant physiological effect.[59] Thus, the development of a new placebo device as a perfect comparator for real acupuncture that has no physiologic effects while maintaining patient blinding is still a significant challenge for acupuncture researchers. However, we currently have no choice but to use one of these available sham devices while considering their limitations.

It is known that the proportion of the placebo effect is not inconsiderable in acupuncture treatment.[59] Moreover, as we have seen, patients with insomnia tend to respond strongly to placebo treatment. In addition, the response to sham acupuncture such as the skin sensation of pressure or tingling, may be akin to the response to acupressure, which is also known to be effective for insomnia.[16] Thus, a study design that directly compares acupuncture and sham acupuncture is likely to produce a false negative result, failing to detect the whole characteristic effect of acupuncture.[59] Therefore, we designed a three-arm parallel study

including the usual care group as well as a sham control group.

The sample size of this pilot study is 15 per each group, which may be underpowered to confirm the hypothesis of the study. Further study will be required to draw a definitive conclusion of the effectiveness of EA for improving insomnia in cancer patients. The result of this preliminary study will become a basis to design a full-scale RCT to conclude this issue.

The strength of this study is that it will acquire objective outcomes reflecting sleep quality and the related circadian rhythm. First, we will obtain both subjective and objective outcomes showing sleep quality using patient-reported questionnaires and actigraphy. Most of the acupuncture studies on insomnia have used only patient-reported outcomes; furthermore, even a small number of studies using objective outcomes such as polysomnography or actigraphy failed to show consistent results on the effect of acupuncture for each outcome.[30-34] Based on the results of this study, we expect that we will be able to compare the difference between the subjective and objective outcomes and contribute to solving the conflict on this issue. Only actigraphy is used for objective outcome measures at this time; however, polysomnography, a gold standard method for insomnia diagnosis, should be included in future research.

Second, the difference in the levels of cortisol and melatonin in saliva between the groups will be compared as biomarkers reflecting the circadian rhythm of the body that affects the pattern of sleep. It is known that acupuncture modulates various neurotransmitters and hormones such as endorphin, serotonin, norepinephrine, cortisol and melatonin.[44 45] Among them, changes of the cortisol surge in the morning or melatonin increase at night time are known to be closely related to arousal and sleep.[44 45] Previous studies have reported that acupuncture can improve insomnia by affecting the pattern of cortisol[60 61] or melatonin[27] release. Based on these results, we will investigate the changes in salivary cortisol and melatonin in addition to the sleep quality of the participants.

Trial status

This trial is currently recruiting participants.

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Contributors

MK and JHK conceived the study. MK drafted the protocol. JEK, HYL, ARK, and HJP participated in the design of the study and contributed to the refinement of the protocol. OJK was responsible for the statistical design of the study. BKK and JHC provided clinical advice and made critical revisions. JHK is a principal investigator of the study and has the final responsibility for the decision to submit this manuscript for publication. All authors approved the final manuscript.

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Competing interests

None declared.

Patient consent

Will be obtained.

Ethics approval

Daejeon Oriental Hospital of Daejeon University IRB (djomc-140-1); Dong-eui University Korean Medical Hospital IRB (2016-04)

Provenance and peer review

Not commissioned; this study was peer reviewed for ethics and funding approval prior to submission.

Data sharing statement

Data requested for public purposes or research transparency will be provided (please contact the corresponding author).

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Table (in the main text)

Table 1 Schedule of enrolment, interventions, and assessments

Figure titles

Figure 1 Flow diagram of the study

Figure 2 The points used for the electroacupuncture group

Supplementary file

Supplementary File 1 Details of the electroacupuncture (EA) and sham EA treatment based on the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist

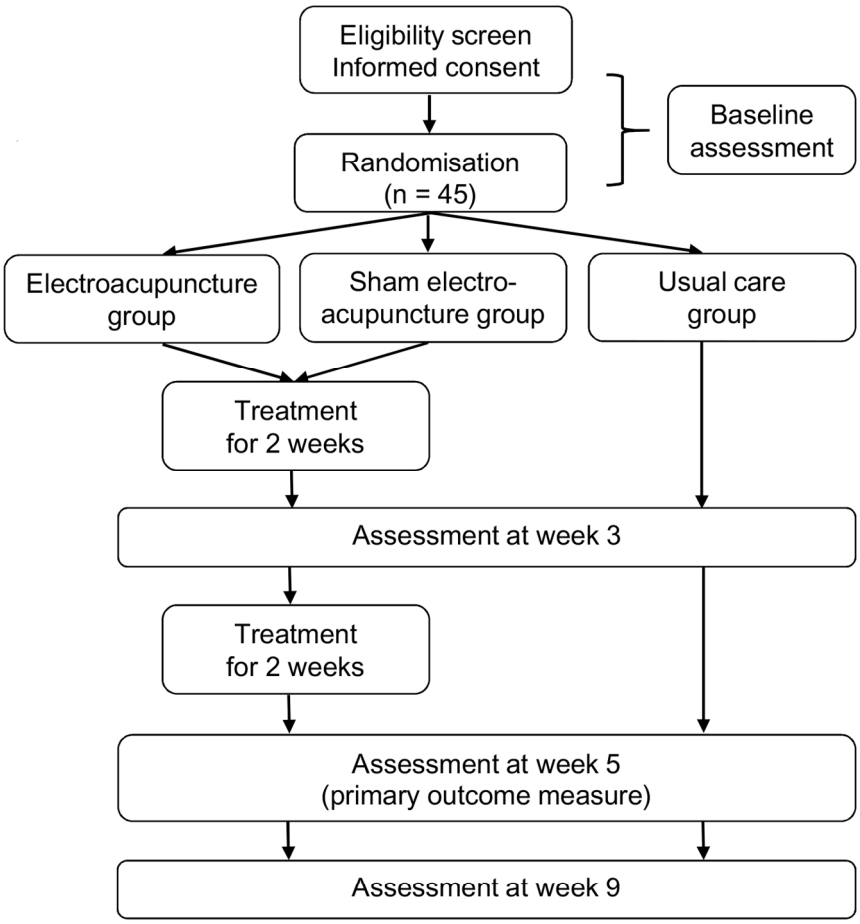

Figure 1 Flow diagram of the study

137x141mm (300 x 300 DPI)

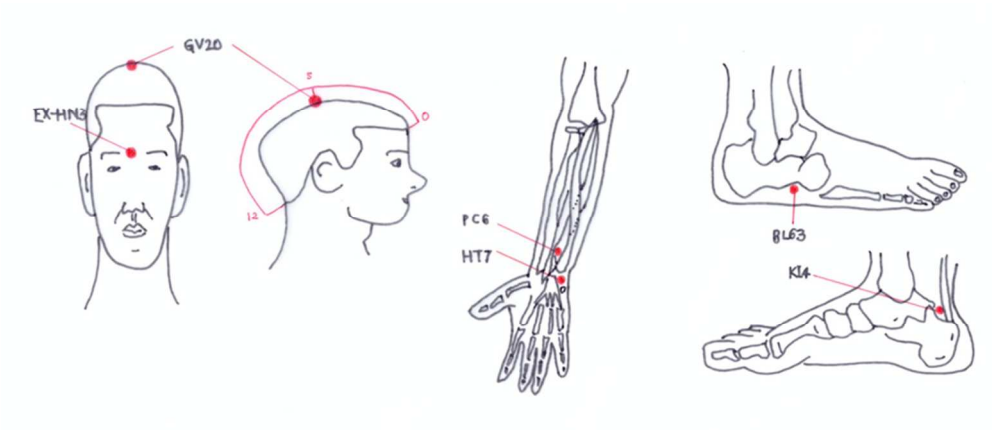

Figure 2 The points used for the electroacupuncture group

73x31mm (300 x 300 DPI)

Supplementary file 1 Details of the electroacupuncture (EA) and sham EA treatments based on the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist

Item	Detail	Description
1. Acupuncture rationale	1a) Style of acupuncture	Electroacupuncture based on traditional Korean acupuncture
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	Related papers[15-20,25-29,31-34] and expert (doctors of Korean medicine) consensus
	1c) Extent to which treatment was varied	Standardized treatment (option: up to 2 bilateral acupoints can be added according to the chief complaints of the participants)
2. Details of needling	2a) Number of needle insertions per subject per session	Standardized regimen: 10 (10 to 14, when considering addition of optional acupoints)
	2b) Names of points used	GV 20, EX-HN-3, bilateral HT7, PC6, BL63, KI4
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	0.6 – 4.5 cm
	2d) Response sought	Acupuncture: *de qi* (sense of soreness, numbness, heaviness, or distension) EA: cognition of stimulation and comfortable feeling
	2e) Needle stimulation	Manual stimulation: twisting-needling 3-5 times Electrical stimulation: 4 Hz
	2f) Needle retention time	30 minutes
	2g) Needle type (diameter, length, and manufacturer or material)	Acupuncture (diameter: 0.25 mm, length: 25 mm, manufacturer: Asiamed GmbH & Co., material: sterilized stainless steel)
3. Treatment regimen	3a) Number of treatment sessions	10
	3b) Frequency and duration of treatment sessions	10 sessions for 4 weeks (average 2.5 times per week)
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group	- All the three groups will be educated with a brochure about the management of sleep disorder - No additional Korean traditional medical treatment regarding insomnia is allowed except for what is given for the study - The interventions other than Korean traditional medical treatment to manage insomnia that have been steadily received for more than 4 weeks before the screening visit are allowed to continue during the study, but no additional treatment is allowed after the beginning of the trial (even sleeping pills are allowed)
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	- Setting: clinical trial centers in university hospitals - Unnecessary conversation will be limited between the acupuncturists and patients during the treatment.
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)	Licensed Korean medical doctors with at least 2 years of clinical experience
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice	Sham acupuncture: previous researches validating the nonpenetrating sham acupuncture device, Streitberger acupuncture needle[52] Mock electroacupuncture: previous researches with control intervention with no electrical stimulation with beeping sound and lighting[29,32-34,49]

	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.	1. rationale of sham acupuncture Use non-penetrating Streitberger acupuncture needles at 10 non-acupoints and connect electrostimulator in switch-off state on to the needles 2. points used for sham EA - Upper limb 1: 1 cm lateral and 5 cm proximal points from cubital creases of bilateral arms - Upper limb 2: 2 cm above the upper limb 1 point - Lower limb 1: 1.5 cm above the depression at the midpoint of the upper border of the bilateral patella - Lower limb 2: area 1/3 above the medial part of the bilateral tibia - Lower limb 3: 1.5 cm above the lower limb 2 point 3. number of needle insertions per subject per session: 10 4. needle type Sham acupuncture (Streitberger needle, Asiamed GmbH & Co., sterilized stainless steel) 5. Treatment duration, frequency, period: the same as the treatment group

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___title page___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_at the end of the abstract_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____-_____
Protocol version	3	Date and version identifier	_____-_____
Funding	4	Sources and types of financial, material, and other support	_____24_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____24_____
	5b	Name and contact information for the trial sponsor	_____-_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____-_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____-_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	12-13
Objectives	7	Specific objectives or hypotheses	7,19
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-11, 17
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8, table 1, figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17-18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14, 18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16-17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	-
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.