Study Protocol

Cognitive improvement effects of Tian Wang Bu Xin Dan (Cheonwangbosimdan) in patients with mild cognitive impairment: protocol for a randomized placebo-controlled pilot clinical trial

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Background: It is important to develop effective treatments to prevent the progress of mild cognitive impairment to Alzheimer's disease. Cheonwangbosimdan has been widely prescribed for palpitation, anxiety, insomnia, and memory decline. We aimed to obtain clinical trial data concerning the safety and efficacy of Cheonwangbosimdan for mild cognitive impairment.

Methods: This clinical trial would be a single-center, double-blinded, parallel-arm, prospective, randomized controlled trial. Forty-eight participants with mild cognitive impairment would be randomly allocated evenly to the placebo or Cheonwangbosimdan groups. Participants will be educated on self-management and exercise at baseline and will receive the trial medication (Cheonwangbosimdan group, Cheonwangbosimdan; placebo group, placebo) once daily for 24 weeks. Primary outcome would include the changes in the Montreal Cognitive Assessment scale scores at the end of the intervention. Secondary outcomes would include the changes in the Montreal Cognitive Assessment scale scores at 12 weeks following the first intervention and changes in the scores of the Alzheimer's Disease Assessment Scale-cognitive subscale-3, the European Quality of Life Five Dimension Five Level scale, Korean Instrumental Activities of Daily Living, Korean Activities of Daily Living, and Geriatric Depression Scale at 12 and 24 weeks following the first intervention.

Discussion: The results of our trial would provide clinical trial data concerning the usefulness, safety, and efficacy of Cheonwangbosimdan in the management of mild cognitive impairment.

Trial Registration: Clinical Research Information Service (Date: November 26, 2021; Registration No. KCT0006787; https://cris.nih.go.kr/cris/search/detailSearch.do?search_lang=E&search_page=M&pageSize=10&page=undefined&seq=20869&status=5&seq_group=20869).

Keywords: Mild cognitive impairment (MCI); cheonwangbosimdan; Tian Wang Bu Xin Dan; Tennohosintan; randomized controlled trial (RCT)

Introduction

Mild cognitive impairment (MCI) is a transitional state between normal cognition and early Alzheimer's disease (AD). Elderly people with MCI (I) have self- or informant-reported cognitive decline, (II) have preserved daily living, (III) have impairment in one or more of the six cognitive domains, (IV) do not meet the criteria for AD, and (V) do not experience MCI in the context of depression or delirium (1-3). MCI is clinically important since patients with MCI are at high risk of developing AD (4,5). In elderly people aged ≥65 years, 46% of the elderly with MCI develop AD, whereas 3% of healthy elderly develop AD within 3 years (6). Not all the cases of MCI are progressive and precursors to AD. Fortunately, many patients revert to the normal range of cognition (7). Thus, early detection and management of MCI is important for preventing or delaying the progress of MCI to AD (8,9).

Currently, no pharmacologic treatments for MCI have been approved; however, lifestyle modifications or nonpharmacological therapies, such as cognitive stimulation and regular exercise, could be effective in reducing the rate of progression of MCI to AD (7,8,10,11). Nine of the 13 guidance documents (nine consensus statements and four guidelines) cover the management and treatment of MCI, the recommendations for which are classified into four categories: non-pharmacologic interventions, pharmacologic interventions, intervention for risk reduction, and counseling. Three guidelines have not recommended pharmacological intervention. Non-pharmacologic interventions, including acupuncture, physical activity, and nutritional, dietary, and cognitive interventions, have been recommended in seven guidance documents (12).

Many randomized controlled trials (RCTs) (13-15) and systematic reviews (16-18) on Chinese herbal medicines (CHMs) for MCI treatment have been conducted. Conventional pharmacological treatments for MCI typically act on a single pharmacological target rather than multiple pathologies of MCI (19). However, CHMs, including Cheonwangbosimdan (CWBSD), contain various effective ingredients and have several beneficial effects on multiple targets and pathways, thereby improving cognition. A lot of studies have demonstrated that CHMs are capable of improving cognitive function by protecting against hippocampal neuronal apoptosis, reducing nerve fiber tangling and Aβ deposition, improving hippocampal neuronal mitochondrial function and brain microcirculation,

adjusting central cholinergic abnormalities, and protecting cerebral blood vessels (20).

The herbal remedy, known as CWBSD in Korea, Tian Wang Bu Xin Dan in China, and Tennohosintan in Japan, is often used to treat palpitation, anxiety, and insomnia by stabilizing the patients' minds and providing energy (21-23). CWBSD comprises 15 medicinal herbs: Rehmanniae Radix, Coptidis Rhizoma, Angelicae Gigantis Radix, Asparagi Tuber, Liriopis seu Ophiopogonis Tuber, Zizyphi Semen, Thujae Semen, Schisandrae Fructus, Ginseng Radix, Poria Sclerotium, Platycodonis Radix, Acori Graminei Rhizoma, Polygalae Radix, Salviae Miltiorrhizae Radix, and Scrophulariae Radix. In recent experimental animal studies, CWBSD has been shown to have neuroprotective (24) and vasorelaxant and hypotensive (25) effects and effects against AD (26,27).

Although CWBSD demonstrated significant effects on AD in experimental animal studies, to the best of our knowledge, no RCT has been performed to investigate its efficacy and safety in MCI. Thus, we designed a parallel-arm, double-blinded, randomized, controlled clinical trial to investigate the safety and efficacy of CWBSD for the management of MCI. The findings of our trial would provide clinical trial data concerning the usefulness, safety, and efficacy of CWBSD in the management of MCI. We present our protocol in accordance with the SPIRIT reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-701/rc) (28).

Methods/design

Aims

We intend to investigate the cognitive improvement effects of CWBSD in patients with MCI.

Hypothesis

We hypothesized that CWBSD will show significant cognitive improvement effects in patients with MCI.

Study design and setting

Our study was approved by the Ministry of Food and Drug Safety (approval No. 32007) and was registered with the Clinical Research Information Service (registration No. KCT0006787). Our study complies with the Korean Good Clinical Practice guidelines and the principles of the

Declaration of Helsinki (revised in 2013).

This clinical trial will be a single-center, double-blind, parallel-arm, prospective, RCT. Forty-eight eligible participants will be randomly allocated evenly to the CWBSD or placebo group. Dementia and MCI share similar, modifiable risk factors, including heart and cerebrovascular disease, hyperlipidemia, diabetes, hypertension, independent living, rural residence, smoking, and lower education. The management of these risk factors is crucial for preventing MCI progression (9). In patients with MCI, exercise is likely to improve the cognitive function (11); hence, all the participants will be educated on self-management of modifiable risk factors and exercise to prevent MCI progression at baseline and will receive the trial medication (CWBSD group, CWBSD; placebo group, placebo) once daily for 24 weeks.

Primary outcome will include the changes in the Korean Montreal Cognitive Assessment scale (MoCA-K) scores at 24 weeks following the first intervention. The secondary outcomes will include the changes in the MoCA-K scores at 12 weeks following the first intervention and changes in the scores of the Korean Alzheimer's Disease Assessment Scale-cognitive subscale-3 (ADAS-K-cog-3), Korean Instrumental Activities of Daily Living (K-IADL), Korean Activities of Daily Living (K-ADL), the European Quality of Life Five Dimension Five Level scale (EQ-5D-5L), and Geriatric Depression Scale (GDS) at 12 and 24 weeks after the first intervention. The trial design is presented in *Table 1* and *Figure 1*.

Recruitment

We will recruit participants from the Dongshin University Gwangju Korean Medicine Hospital in Republic of Korea via the internet, posters, and local newspapers in hospitals and communities. Interested individuals will receive an explanation of this trial from the clinical research coordinator (CRC) upon their visit at the clinical research center at the hospital and will voluntarily provide written informed consent before participation. All the recruited individuals will be screened using the Global Deterioration Scale, GDS, MoCA-K, and the Korean Mini-Mental State Examination (K-MMSE).

Whenever the participants visit, the CRC will explain the next visit schedule and will remind the visit schedule by phone call a day prior to the visit. The CRC will adjust the evaluation and visit schedules for each participant to facilitate participation.

Inclusion criteria

(I)   Adults aged between 55 and 85 years;
(II) Memory disorder for at least three months preceding screening with fulfillment of the diagnostic criteria for MCI (1-3) (i.e., self- or informant-reported cognitive decline, preserved daily living, impairment in one or more of the six cognitive domains, do not meet the criteria for AD, and do not experience MCI in the context of depression or delirium);
(III) MoCA-K scale score of 0–22;
(IV) K-MMSE score of 20–23;
(V)   Global Deterioration scale score of 2 or 3;
(VI) GDS score of 0–18;
(VII) Adequate Korean language proficiency for reliable outcome measurements;
(VIII) Voluntary consent for participation.

Exclusion criteria

(I)   Diagnosis of AD according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association) criteria or diagnosis of vascular dementia according to the NINDS-AIREN (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences) criteria;
(II) A history of structural brain diseases that could cause cognitive decline, such as congenital mental retardation, intracranial space-occupying lesions, stroke, or traumatic brain injury;
(III) A history of brain lesions confirmed on brain computed tomography or magnetic resonance imaging within 12 months;
(IV) Presence of a serious disease (e.g., multiple sclerosis, liver, kidney, central nervous system and cardiovascular diseases, Parkinson's and Huntington disease, and cancer);
(V)   History of treatment for mental illness (depression, serious anxiety, or schizophrenia) or drug/alcohol dependency in the 6 months preceding screening;
(VI) Current management for MCI, such as cognitive training, medication, or Korean medicine treatment within 4 weeks before screening;
(VII) Difficulties in undergoing outcome measurement

Table 1 Standard protocol items: recommendations for interventional trials statement

Timepoint	Enrollment	Allocation	Post-allocation				Close-out
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
			Week 0	Week 6	Week 12	Week 18	Week 24
Enrollment							
Informed consent	X						
Sociodemographic profile	X						
Medical history	X						
Vital signs	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X						
Allocation		X					
Global Deterioration scale	X						
Korean Mini-Mental State Examination	X						
Korean Montreal Cognitive Assessment	X						
Geriatric Depression Scale	X						
Interventions							
Trial medication (CWBSD or placebo)							
Education on self-management and exercise			X	X	X	X	
Assessments							
Change of medical history			X	X	X	X	X
Incidence of AEs and SAEs			X	X	X	X	X
Clinical laboratory test	X				X		X
MoCA-K			X		X		X
ADAS-K-cog-3			X		X		X
GDS			X		X		X
K-IADL, K-IDL			X		X		X
EQ-5D-5L			X		X		X

X means that the action is carried out at that time. CWBSD, Cheonwangbosimdan; AEs, adverse events; SAEs, serious adverse events; MoCA-K, Korean Montreal Cognitive Assessment scale; ADAS-K-cog-3, Korean Alzheimer's Disease Assessment Scale-cognitive subscale-3; GDS, Geriatric Depression Scale; K-IADL, Korean Instrumental Activities of Daily Living; K-ADL, Korean Activities of Daily Living; EQ-5D-5L, European Quality of Life Five Dimension Five Level scale.

attributed to hearing and visual impairments;

(VIII) Impaired hepatic function (alanine aminotransferase or aspartate aminotransferase level at least twice the normal upper limit);

(IX) Impaired renal function (creatinine at least twice the normal upper limit);

(X) Presence of hypertension (170/100 mmHg or greater) or diabetes (over 180 mg/dL of fasting blood glucose);

(XI) A history of gastrointestinal diseases, anorexia, nausea, and vomiting that could affect the absorption of the CWBSD or placebo;
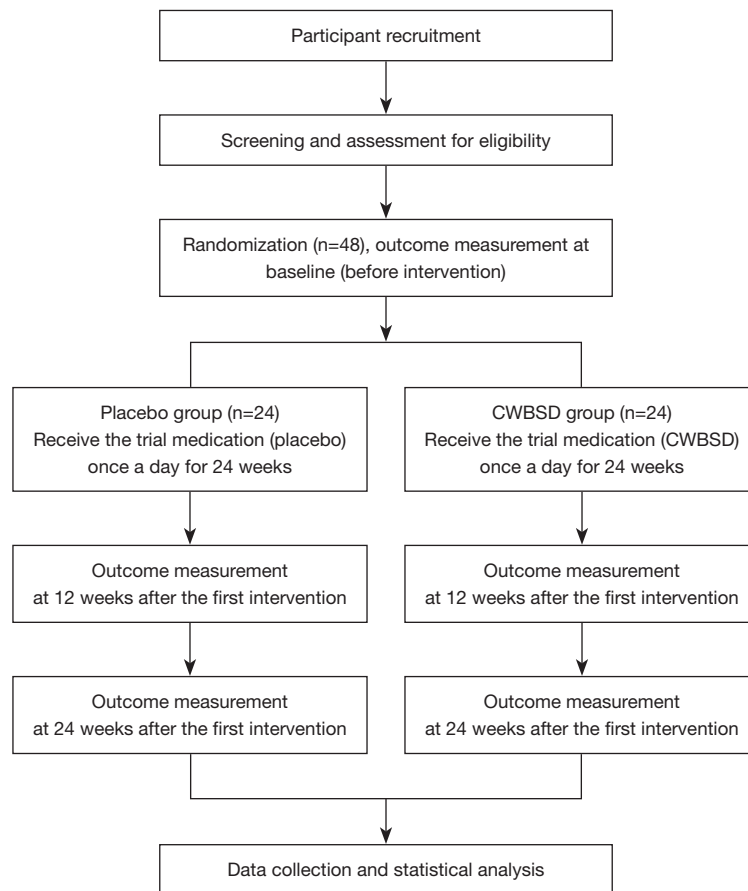
Figure 1 Study design flow chart. CWBSD, Cheonwangbosimdan.

(XII)   Pregnancy or breastfeeding;
(XIII)   A history of hypersensitivity to the composition of
         the CWBSD or placebo;
(XIV)   A person participating in other clinical trials or who
         has participated in other clinical trials within 4 weeks
         of screening for this study.

Dropout and violation criteria

The dropout criteria will be as follows: (I) withdrawal of
consent for participating in the clinical trial, (II) incomplete
data that can affect the results of the trial, (III) occurrence of
a serious adverse event (SAE), or (IV) decision to terminate
an individual's participation in the trial by the institutional
review board (IRB) or principal investigator (PI).

Those who meet the dropout criteria will stop
participating in this study.

The violation criteria will be as follows: (I) less than 135
of 168 total doses (<80% compliance with the intervention

protocol) and (II) critical error in the protocol or serious
deviation in implementation.

Those who meet the dropout and violation criteria will
be excluded from the per-protocol set (PPS) analysis.

Ethics

This protocol (version 1.1) was approved by the IRB
of Dongshin University Gwangju Korean Medicine
Hospital (date: November 19, 2021; approval No.
DSUOH-2021-004). The CRC will explain the purpose and
risk of this trial to the participants and their companions.
All the participants provided written informed consent
before participation.

Randomization and allocation

After a screening interview by the investigator, the
assessor will conduct baseline evaluations for the eligible

Table 2 Components of CWBSD

Chinese name	Botanical name	Amount (mg)
Shengdihuang	Rehmanniae Radix	500
Huanglian	Coptidis rhizoma	250
Danggui	Angelicae Gigantis Radix	125
Tianmendong	Asparagi Tuber	125
Wuweizi	Schisandrae Fructus	125
Baiziren	Thujae Semen	125
Suanzaoren	Zizyphi Semen	125
Maimendong	Liriopis seu Ophiopogonis Tuber	125
Renshen	Ginseng Radix	62.5
Jiegeng	Platycodonis Radix	62.5
Yuanzhi	Polygalae Radix	62.5
Xuanshen	Scrophulariae Radix	62.5
danshen	Salviae Miltiorrhizae Radix	62.5
Fuling	Poria sclerotium	62.5

CWBSD, Cheonwangbosimdan.

participants. Forty-eight enrolled participants will be randomly allocated evenly to the CWBSD or placebo groups. The randomization sequence will be generated using the SPSS version 21 software (IBM Corp., USA). The randomization number will be sealed in opaque and sequential envelopes and stored in a double-locked cabinet.

Implementation

The CRC will perform the allocation sequence generation, participant enrolment, group assignment, and participant management.

Blinding

All the investigators, participants, and outcome assessors of this trial will be blinded until the end of study. However, if necessary, such as in the case of the occurrence of SAE, unblinding will be permitted under IRB approval. Randomized labeled and prepacked placebo and CWBSD, which will be identical in taste, smell, and appearance, will be provided by the pharmaceutical company. Randomization and uncovering will be carried out by a statistician with no conflict of interest.

Interventions

The trial medications will be placebo and CWBSD pellets, which will be identical in smell, taste, and appearance. The small, brown pellets will be produced by Hanpoong Pharm & Food Co., Ltd. (Seoul, Republic of Korea). The detailed composition is shown in *Table 2*. The production process for the CWBSD is as follows: each component is washed; chopped to a proper small size, and crushed into powder form, followed by mixing of the powders, excipients, and binders. Then, the mixture is converted into pellets, dried, coated, and packed. Both the medications will be administered once daily (total daily dosage, 3 g) for 24 weeks. The participants will visit every 6 weeks and receive a 6-week dose of trial medication packed in a sealed box. Each time the participant visits, the CRC will check the medical conditions of the participants and the participant will return their trial medication boxes to evaluate the compliance to improve their adherence to the protocol.

During the study period, the participants will not be allowed to receive other treatment for improving MCI symptoms or use the following drugs: donepezil, rivastigmine, galantamine, memantine, or drugs containing any ingredient of CWBSD. All the participants will receive education on exercise and self-management to improve their cognitive function at each visit. They will be allowed to use pharmacological and non-pharmacological treatment for improving other symptoms that may not affect the results of this study.

Outcome measures

The primary outcome will include improvements in the cognition evaluated using the MoCA-K at the end of the intervention. The secondary outcomes will include the changes in the MoCA-K scores at 12 weeks following the first intervention and changes in the scores of the ADAS-K-cog-3, K-IADL, K-ADL, EQ-5D-5L, and GDS at 12 and 24 weeks following the first intervention.

The MoCA scale is a brief, validated, and clinician-friendly instrument with high specificity and sensitivity for MCI detection (29).

The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)-3 (word recognition, word recall, and orientation) was developed after removing eight tasks demonstrating ceiling effects in MCI from the ADAS-cog-11 to assess only the memory (30).

The GDS was developed as a screening tool to

distinguish the symptoms of depression from those of dementia in the elderly (31). The GDS has a simple format that efficiently and accurately assesses the symptoms of depression, aged from 65 to 85 years. The GDS can be applied to sample cases of younger individuals; however, it may not be the best choice (32).

The K-IADL and K-ADL scales are used to evaluate the physical function of the elderly. The K-IADL scale is used to evaluate complex activities necessary for independent daily life and the K-ADL scale is used to estimate basic activities for daily living (33).

The EQ-5D-5L is a widely used generic patient-reported outcome questionnaire for evaluating the health-related quality of life (34).

Safety assessment

A safety assessment will be carried out by comparing the incidence of adverse events (AEs) and SAEs, changes in the pulse rate, blood pressure, and items of the clinical laboratory test between the two groups.

AEs that could occur in this trial include diarrhea, anorexia, nausea, vomiting, stomach discomfort, itching, skin irritation, and urticaria. All the AEs and SAEs will be recorded in detail, including the degree of severity, potential causal relationships between the AE and trial medication, time of occurrence, and treatment for the improvement of AE by the CRC. They will be reported to the IRB and the IRB will take appropriate action. AEs and SAEs associated with trial medication will be compensated according to the relevant regulations.

Quality control

This study protocol has been developed and reviewed by experts in herbal medicine, MCI, clinical trial, and statistics. Prior to the trial, all the investigators will be trained several times to fully understand the standard operating procedures (SOPs) of this trial and the protocol. An independent clinical research associate will monitor our study and ensure that our clinical trial is carried out in accordance with the SOPs and protocol. The revisions of this protocol will be reviewed by the IRB of Dongshin University Gwangju Korean Medicine Hospital.

Sample size

No adequate preliminary study was conducted upon which

the sample size estimation could be based. Thus, a pilot study design was adopted considering the recruitment opportunities, limited funds, and study period. The appropriate sample size for the pilot study is >12 (35). According to a previous study that demonstrated the effects of CHMs on MCI (36), we set the number of groups to 2, effect size to 1.252, two-sided alpha level to 0.05, statistical power to 0.95, and a maximum dropout rate to 25%. Based on these parameters, 48 participants (24 in each group) will be required. Since our trial is a pilot RCT, the sample size will be insufficient to determine the safety and efficacy of CWBSD for MCI. The results of our study would provide clinical trial data concerning the safety, efficacy, and usefulness of CWBSD in patients with MCI.

Statistical analysis

The final data will be analyzed by a statistician with no conflict of interest. The primary analysis population for assessing the efficacy will be a full analysis set (FAS) and a supplementary PPS. The results of the analyses between the FAS and PPS will be compared and reflected in the efficacy evaluation. The last observation carried forward method will be used to obtain the missing values. Interim analyses will not be carried out. All the analyses will be carried out at the 5% (two-sided) significance level using the SPSS version 21 software (IBM Corp., USA).

Baseline variables and characteristics will be compared between the two groups for homogeneity test. Categorical data will be compared using the Fisher's exact test or chi-square test. Continuous data will be compared using the Wilcoxon's rank-sum test or independent t-test.

Within each group, changes in the MoCA-K, ADAS-K-cog-3, K-IADL, K-ADL, EQ-5D-5L, and GDS scores at 12 and 24 weeks following the first intervention, relative to the baseline, will be evaluated using a Friedman test or one-way repeated measures analysis of variance (RMANOVA) and Wilcoxon's signed rank test or a paired t-test. The degrees of change in the MoCA-K, ADAS-K-cog-3, K-IADL, K-ADL, EQ-5D-5L, and GDS scores between the two groups will be compared using the analysis of covariance (ANCOVA) with baseline scores as covariates and independent t-test or Wilcoxon rank sum test. Sub-analyses will be carried out in accordance with the participants' age (<70 and ≥70 years).

The incidence of SAEs and AEs will be compared between two groups using the Fisher's exact or chi-square

test. Within each group, changes in the blood pressure, pulse rate, and items of the clinical laboratory test at 24 weeks relative to the baseline will be evaluated using a Wilcoxon signed rank or paired t-test. The degree of these changes between two groups will be compared using Wilcoxon rank sum test or independent t-test.

Data management and confidentiality

All the documents will not reveal the names and will be labeled and recorded using identification codes. All the identification records will be kept confidential and will not be accessible without IRB approval.

At the end of the study, electronic data recorded by the CRC will be stored on a personal password-protected computer and those who are not authorized by the IRB will not allowed to access the data. The case report forms will be kept in a cabinet until three years after the clinical trial ends. The participants will voluntarily provide written informed consent for the publication of individual details.

Discussion

AD including MCI, is a heterogeneous syndrome with a complex pathophysiology (19). CHMs may have advantages in multitarget regulation, compared to a single target antagonist, such as a cholinesterase inhibitor (37). CHMs, such as the Bushen capsule (13), Shenwu capsule (14), and Qinggongshoutao (15), have demonstrated a significant improvement in memory and cognition in patients with amnestic MCI.

CWBSD is one of the CHMs most frequently used by Chinese medicine doctors to treat diseases of the nervous system and mental disorders in patients with AD in Taiwan. It is widely prescribed for psychological and behavioral symptoms of dementia related to AD (38). RCTs have been carried out to investigate the efficacy of CWBSD for insomnia (21-23). To the best of our knowledge, our study is the first RCT to investigate the cognitive improvement effects of CWBSD in patients with MCI.

In accordance with the objectives, changes in the MoCA-K scores will be the primary outcome. The MoCA is an important assessment tool for investigating the efficacy of CHMs in patients with MCI (18).

However, our protocol has some limitations. First, we intend to administer a single dose of the trial medication; thus, we cannot investigate the relationships between dose, efficacy, and side effects. Second, owing to the limited funds and lack of preliminary studies, we adopted a pilot clinical trial design with a small sample size.

Nevertheless, this study will provide a foundation for future studies on the safety and efficacy of CWBSD for the management of MCI.

Dissemination

The final data will be submitted to the IRB of Dongshin University Gwangju Korean Medicine Hospital in Republic of Korea. The results of this study will be published in the peer-reviewed journal.

Trial status

This clinical trial (protocol version 1.3; approved on May 09, 2022) is ongoing. The first participant was recruited on May 16, 2022.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://apm.amegroups. com/article/view/10.21037/apm-22-701/rc

Peer Review File: Available at https://apm.amegroups.com/ article/view/10.21037/apm-22-701/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm. amegroups.com/article/view/10.21037/apm-22-701/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study has been conducted in accordance with the Declaration of Helsinki (revised in 2013). Our study was approved by the Ministry of Food and Drug Safety (approval No. 32007) and was registered with the Clinical Research Information Service (registration No. KCT0006787). All the participants will provide and have provided written informed consent before participation.

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