Peer Review File

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Reviewer A

The aim of the study entitled Cognitive improvement effects of Cheonwangbosimdan (Tian Wang Bu Xin Dan) in patients with mild cognitive impairment: a study protocol for a randomized placebo-controlled trial by Kim et al., was to evaluate the efficacy and safety of Cheonwangbosimdan for the treatment of mild cognitive impairment. Overall, this is a potentially very interesting document. However, the general presentation lacks some information and details.

Comments 1 :
(Page 1, Line 1-3)
As authors declared the pilot study in the sample size and discussion section the title should present a 'pilot' or 'preliminary' study.
Reply 1:
Thank you for your valuable comment. We have revised the title as advised (See Page 1, line 1-3)
Changes in the text:
Cognitive improvement effects of Cheonwangbosimdan (Tian Wang Bu Xin Dan) in patients with mild cognitive impairment: a study protocol for a pilot randomized placebo-controlled trial (Page 1, line 1-3)

Comments 2:
(Page 2, Line 40-42)
Since the inclusion criteria stated in the main body, there is no need to list "i.e., fulfilling the Peterson diagnostic criteria…, and Geriatric Depression Scale scores of 0-18" in the abstract. I would suggest the author delete the sentences.
Reply 2:
Thank you for your valuable comment. As advised, we have deleted this sentence (See Page 2, line 35-36)
Changes in the text:
A total of 48 participants with mild cognitive impairment will be randomly divided in equal numbers into the placebo or Cheonwangbosimdan group. (Page 2, line 35-36)

Comments 3:
(Page 3, Line 83-86)
Scientific names are always italicized, e.g. Rehmannia glutinosa. However, botanical names (Latin) should not be italicized, e.g. Rehmanniae Radix. The author should correct this in line 83-86 and table 2

Reply 3:

Thank you for your valuable comment. We have corrected the botanical names in the introduction section and Table 2 as advised (See Page 4, line 93-96 and Table 2).

Changes in the text:

Rehmanniae Radix, Coptidis Rhizoma, Acori Graminei Rhizoma, Ginseng Radix, Angelicae Gigantis Radix, Schisandrae Fructus, Asparagi Tuber, Liriopis seu Ophiopogonis Tuber, Thujae Semen, Zizyphi Semen, Scrophulariae Radix, Poria Sclerotium, Salviae Miltiorrhizae Radix, Platycodonis Radix, and Polygalae Radix. (Page 4, line 93-96)

Table 2. Composition 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

Comments 4 :

(Page 4, Line 99)

The aims of this study should include the safety of CWBSD as well as the efficacy.

Reply 4:

Thank you for your valuable comment. We have revised the aims subsection as advised (See Page 5, line 110-111)

Changes in the text:

We plan to investigate the safety and efficacy of CWBSD for improvement of cognitive function in patients with MCI. (Page 5, line 110-111)

Comments 5:

(Page 4, Line 107)

The registration date and URL except the registration number of CRIS can be deleted.

Reply 5:

Thank you for your valuable comment. We have deleted the registration date and URL, as advised (See Page 5, line 121)

Changes in the text:

The trial was registered with the Clinical Research Information Service (Registration No. KCT0006787). (Page 5, line 121)

Comments 6:

(Page 4, Line 114)

All participants will be educated on self-management and exercise at baseline. The purpose of the education and the specific description of self-management should be provided.

Reply 6:

Thank you for your valuable comment. MCI and dementia share similar, modifiable risk factors including rural residence, lower education, living alone, smoking, hypertension, hyperlipidemia, diabetes, and heart and cerebrovascular disease. The determination and management of these risk factors are crucial for MCI progression (9). In patients with MCI, exercise training (6 months) is likely to improve cognitive measures (11); hence, all participants will be educated on self-management of modifiable risk factors and exercise to prevent MCI progression at baseline. We have revised the study design and setting subsection as advised. (See Page 6, line 126-131)

Changes in the text:

MCI and dementia share similar, modifiable risk factors including rural residence, lower education, independent living, smoking, hypertension, hyperlipidemia, diabetes, and heart and cerebrovascular disease. The determination and management of these risk factors are crucial for MCI progression (9). In patients with MCI, exercise training (6 months) is likely to improve cognitive measures (11); hence, all 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 a day for 24 weeks. (Page 6, line 126-131)

Comments 7:

(Page 4, Line 119)

The age of participants will be varied from 55 to 85. Hence, the Geriatric Depression Scale (GDS) seems not adequate to participants below age 65.

Reply 7:

Thank you for your valuable comment. The Geriatric Depression Scale (GDS) was developed as a self-rating screening tool to measure depressive symptoms in older adults. It was designed to identify depression in the elderly by distinguishing symptoms of depression and dementia. The

GDS has a simple format that accurately and efficiently assesses depressive symptoms in the elderly, aged from 65 to 85 years. The GDS can be applied to sample population of younger individuals; however, it may not be the best choice. We have inserted the pertinent sentence into the outcome measurements subsection as advised (See Page 11, line 269-272)

Changes in the text:

The GDS has a simple format that accurately and efficiently assesses depressive symptoms in the elderly, 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). (Page 11, line 269-272)

Comments 8:

(Page 9, Line 256)

Although the author considered funds, the study period, and recruitment opportunities for estimating the sample size, the evidence of sample size determination should be presented, such as, significance level, power and dropout rate.

Reply 8:

Thank you for your valuable comment. We have revised the sample size estimation subsection, as advised (See Page 13, line 306-313)

Changes in the text:

Therefore, a pilot study design was adopted considering the limited research funds, study period, and recruitment opportunities. The appropriate sample size for two- or three-arm pilot studies is >12 (34). In accordance with a previous study which demonstrated the effects of CHMs on MCI (35), we have established the number of groups as two, effect size as 1.252, two-sided alpha level as 0.05, and statistical power as 0.95. Based on these parameters, the required sample size calculated using G*Power is 36 (18 per group). Estimating a maximum dropout rate of 25%, we have determined that a total of 48 participants (24 in each group) will be required. (Page 13, line 306-313)

Comments 9:

(Figure 1)

The outcome measurements at 12 weeks and 24 weeks should be illustrated separately according to the two groups.

Reply 9:

Thank you for your valuable comment. We have revised Figure 1, as advised. (See Figure 1)

Changes in the text:

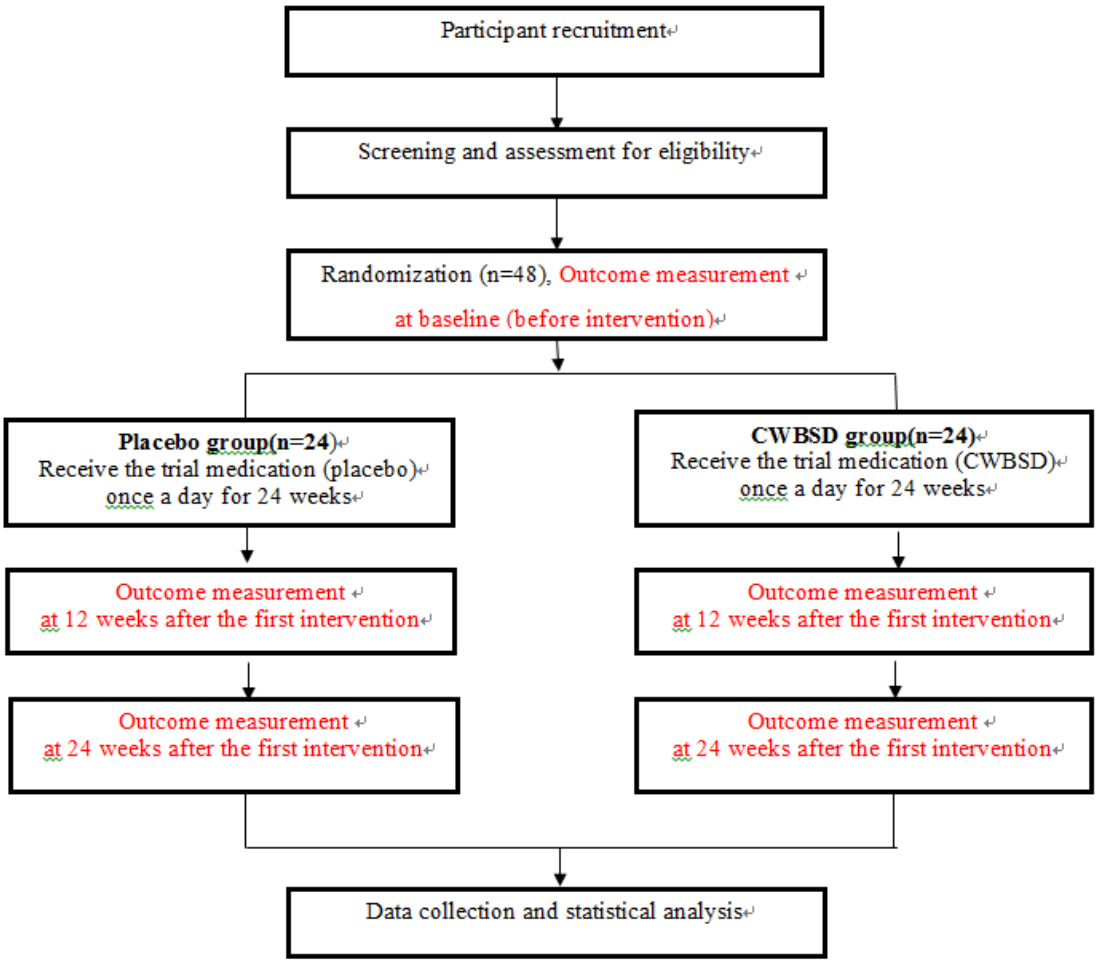

Figure 1. Study design flow chart

Comments 10:

(Page 19, Line 277)

The grammatical corrections are necessary.

Reply 10:

We appreciate your pertinent observations. Based on your observations, we have carefully rechecked the revised manuscript further for grammatical and spelling errors. We have had our manuscript re-edited by a professional English language editing service to ensure that the text is free from any spelling and grammatical errors. The edit has been done by editors at Editage, a division of Cactus Communications.

Reviewer B

The authors should also clarify the points listed below.

This study deals with the efficacy and safety of CWBSD for the treatment of MCI.

Introduction

Comments 11:

1. The authors should summarize the position of standard treatment and pharmacological treatments for MCI, citing international and national treatment guidelines.

Reply 11:

Thank you for your valuable comment. We have inserted the pertinent sentences in the introduction section as advised. (See Page 3-4, line 73-79)

Changes in the text:

Nine of the 13 guidance documents (four guidelines and nine consensus statements) cover the treatment and management of MCI, the recommendations for which are classified into four categories: intervention for risk reduction, pharmacologic interventions, non-pharmacologic interventions, and counseling. A total of three guidelines recommend no pharmacologic intervention. A total of seven guidance documents recommend non-pharmacological interventions including physical activity, cognitive, dietary, and nutritional interventions and acupuncture (12). (Page 3-4, line 73-79)

Comments 12:

2. The authors should describe the differences between the herbal remedy called Cheonwangbosimdan and other pharmacological treatments for MCI.

Reply 12:

Thank you for your valuable comment. We have inserted the pertinent sentences in the introduction section as advised. (See Page 4, line 81-84)

Changes in the text:

Conventional pharmaceutical treatments typically act on a single pharmacological target and do not address the multiple pathological components of MCI as a whole (19). However, CHMs including Cheonwangbosimdan (CWBSD) contain a variety of effective ingredients and exert several biological effects on multiple pathways and targets, thus improving cognition. (Page 4, line 81-84)

Comments 13:

Methods

3. Authors define dropout in the intervention and control groups.

I hope these comments will be helpful.

Reply 12:

Thank you for your valuable comment. We have revised the Dropout subsection as advised. (See Page 8-9, line 193-203).

Changes in the text:

Dropout and violation criteria

The dropout criteria will be as follows: 1) occurrence of a serious adverse event (SAE); 2)

reluctance to continue the trial; 3) incomplete data that could influence the trial; or 4) decision to terminate an individual's participation in the trial by the principal investigator (PI) or institutional review board (IRB). Participants who meet the dropout criteria will be excluded from the trial and will stop participating in this study..

The violation criteria will be as follows: 1) <80% compliance with the protocol procedures (less than 135 of 168 total doses); or 2) large errors in the protocol or significant deviations in implementation.

The participants who meet the dropout and violation criteria will be excluded from the per-protocol set (PPS) analysis. (Page 8-9, line 193-203)

Reviewer C

In this manuscript, the authors investigated cognitive improvement effects of Cheonwangbosimdan. It is meaningful work, however, there are some points to revised before publication for this journal.

Major point

Comments 14:

1. In this manuscript, the authors wrote the name of the Cheonwangbosimdan in Korean and Chinese pronunciation. For the Japanese researchers who use herbal medicine like to Chinese and Korean, the authors should write Japanese character together.

Reply 14:

Thank you for your valuable comment. We have inserted the pertinent Japanese pronunciation into the key words and the introduction section as advised. (See Page 3, line 56, Page 4, line 90-92).

Changes in the text:

Keywords: Mild cognitive impairment, cheonwangbosimdan, Tian Wang Bu Xin Dan, Tennohosintan, randomized controlled trial. (Page 3, line 56)

The herbal remedy called Cheonwangbosimdan (CWBSD) in Korea, Tian Wang Bu Xin Dan in China, and Tennohosintan in Japan is often used to treat insomnia, anxiety, and palpitation by providing energy and stabilizing patients' minds (21-23). (Page 4, line 90-92)

Comments 15:

2. In the method, the authors did not explain how they will prepare the pellet of Cheonwangbosimdan. The authors should describe in detail the method of production process of the Cheonwangbosimdan.

Reply 15:

Thank you for your valuable comment. We have inserted the pertinent sentence into the intervention subsection, as advised. (See Page 10, line 240-243).

Changes in the text:

The manufacturing 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 powders, excipients, and binders. Then, the mixture is converted into pellets, dried, coated, and packed. (Page 10, line 240-243)