A multi-center, randomized controlled trial by the Integrative Management in Japan for Epidemic Disease (IMJEDI study-RCT) on the use of Kampo medicine, kakkonto with shosaikotokakikyosekko, in mild-tomoderate COVID-19 patients for symptomatic relief and prevention of severe stage: a structured summary of a study protocol for a randomized controlled trial

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Trials

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A multi-center, randomized controlled trial by the Integrative Management in Japan for Epidemic Disease (IMJEDI study-RCT) on the use of Kampo medicine, kakkonto with shosaikotokakikyosekko, in mild-to-moderate COVID-19 patients for symptomatic relief and prevention of severe stage: a structured summary of a study protocol for a randomized controlled trial

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Abstract

Objectives: We aimed to test our hypothesis that additional administration of traditional Japanese (Kampo) medicine, kakkonto (kakkon-to: KT) and shosaikotokakikyosekko (sho-saiko-to-ka-kikyo-sekko: SSKKS), is more effective in relieving symptoms and preventing the onset of severe infection in mild-to-moderate COVID-19 patients compared to those treated only with conventional treatment.

Trial design: The study is designed as a multi-center, interventional, parallel-group, randomized (1:1 ratio), investigator-sponsored, two-arm study.

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Participants: Patients and inpatients will be recruited from 8 Japanese academic and non-academic hospitals. The inclusion and exclusion criteria are as follows:
Inclusion criteria:

1. Diagnosed as positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
2. Clinical stages of mild-to-moderate COVID-19
3. Symptomatic
4. ≥ 20 years of age
5. Male or female
6. Ability to communicate in Japanese
7. Outpatients and inpatients
8. Provided informed consent

Exclusion criteria:

1. Difficulty in providing informed consent due to dementia, psychosis, or psychiatric symptoms
2. Allergic to Kampo or Western medicines used in this study
3. Pregnant and lactating
4. Unable to follow up
5. Participating in another clinical trial or interventional study
6. Hypokalemic or taking oral furosemide or steroids
7. Determined unsuitable for this study by the physician

Intervention and comparator: Patients in the control group will receive conventional treatment with antipyretics, painkillers, or antitussives for symptoms that occurred after they contracted the SARS-CoV-2 infection.
Patients in the Kampo group will receive 2.5 g of KT (TJ-1@TSUMURA and Co.) and 2.5 g of SSKKS (TJ-109@TSUMURA and Co.) 3 times a day, orally, for 14 days in addition to the conventional treatment as mentioned above.

Main outcomes: The number of days till at least one of the symptoms (fever, cough, sputum, malaise, shortness of breath) improves in the first 14 days of treatment. To assess the cough, sputum, malaise, and shortness of breath, a numeric rating scale will be used to define improvement in terms of a 2-point decrease in the number of days from the start of treatment for at least 2 days. Fever will be defined as an improvement when the temperature is less than 37 °C.

Randomization: Patients are randomized (1:1 ratio) to each group using the minimization method, with balancing of the arms with severity of disease stage and patient age (< 65, 65 to < 75, or ≥ 75 years). Computer-generated random numbers will be used for the minimization method.

Blinding (masking): Open-label with no blinding

Numbers to be randomized (sample size): The main research hypothesis of this study is that the combination of Kampo medicine and conventional treatment will significantly improve the patients' symptoms (fever, fatigue, cough, sputum, and shortness of breath) during the first 14 days of treatment as compared with conventional treatment alone. Concerning the analysis of the primary endpoint, the duration of time before improvement of at least one of the common cold-like symptoms (fever, malaise, cough, sputum, and shortness of breath) will be estimated using the Kaplan-Meier method, and the survival curves will be compared between groups using the log-rank test. Assuming this method of analysis and based on previous studies reporting the efficacy of Kampo medicine for COVID-19 and H1N1 influenza patients, the median survival time in the Kampo medicine group is estimated as 3 days; this time will be 1.5 times longer in the control group. Assuming a one-sided significance level of 5%, a power of 70%, and an allocation ratio of 1:1, the required sample size is calculated as 126 cases. To compensate for a loss in follow-up, we plan to include 150 cases in both groups (Kampo group = 75, control group = 75).

Trial status: Protocol version 1.2 as of August 20, 2020
Recruitment start (expected): October 1, 2020
Recruitment finish (expected): October 31, 2023

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Trial registration: Japan Registry of Clinical Trials (jRCT) jRCTs021200020. Registered on August 25, 2020

Full protocol: The full protocol is attached as an additional file and is accessible from the *Trials* website (Additional file 1). In the interest of expediting the dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

Keywords: COVID-19, Randomized controlled trial, Protocol, Kampo medicines, Symptom relief, Prevention for severe stage

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-04746-9.

Additional file 1.

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Authors' contributions

All authors of the paper contributed to the design of the work and acquisition, analysis, and interpretation of the data. S.T., T.N., T.I., and R.A. were involved in the development of the intervention and design of the trial. S.T., T.N., and S.K. participated in drafting the work or revising it critically for important intellectual content. All authors have read and approved the final manuscript for publication.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This protocol was approved by the MHLW Certified Clinical Research Review Board, Tohoku University, Sendai, Miyagi, Japan, on August 4, 2020 (Certification No. CRB2180001). The authors certify that this trial has received ethical approval from the appropriate ethical committee as described above. Before inclusion in the study, conscious patients will be informed of the purpose and clinical procedures required by the protocol. The investigators in each hospital or clinic will explain the purpose, risks, and benefits associated with study participation. Also, patients will be informed of their right to withdraw from the study at any time without explanation and without losing the right to future medical care. Every patient is free to leave the study protocol at any stage of the study and can request to retire his consent and, consequently, ask for the elimination of all his data from the database.

Consent for publication

Not applicable.

Competing interests

S.T. and T.I. belong to the Department of Kampo and Integrative Medicine, Tohoku University Graduate School of Medicine, a joint research course with TSUMURA and Co., which is a paratheatrical company of Kampo medicine in Japan.

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