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Protocol

Clinical research on the clinical effectiveness and cost-effectiveness of Chuna manual therapy for temporomandibular disorder: A study protocol for a multicenter randomized controlled trial

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ABSTRACT

Introduction: Chuna manual therapy (CMT), one of the therapeutic modalities of Korean Medicine which is a kind of manual therapies, is well known among Korean Medicine doctors for the treatment of TMD but the evidence for the effect of CMT is insufficient. Therefore, this trial is designed to propose a protocol to investigate the efficacy and economic efficiency of CMT on TMD, compared to usual care (UC).

Methods: This trial is a prospective, assessor-blinded, two-arm parallel multicenter randomized controlled trial. Eighty patients with temporomandibular disorder, with numeric rating scale (NRS) above 4, will be randomly assigned to either the CMT or the UC group, with a 1:1 ratio. Participants will be recruited by five Korean Medicine hospitals. Participants will be treated eight times for 4 weeks, and will be assessed for pain, range of motion, depressive symptoms, and quality of life. Adverse events will also be reported. To evaluate the cost-effectiveness, medical consumption data (quality of life questionnaire) will be used to assess indices such as the Quality Adjusted Life Year.

Discussion: There were randomized controlled trials (RCTs) investigating the effect of CMT for TMD, however, evidence is evaluated as "Low". For this reason, this trial was designed as a high-quality RCT protocol.

Conclusion: We expect that this trial will contribute new knowledge on the effects of CMT for TMD, so that an economically efficient way of treatment could be developed and standardized, providing more populations with the benefits of an effective and economic treatment for TMD.

1. Introduction

The temporomandibular joint (TMJ) is a unique bilateral joint in the human body. It is the center axis of mandible movement, and constitutes the base of the cranial bones. It is required for the masticatory function, which is essential to survival [1]. Hyperactivity or overuse of this joint can lead to fatigue of the jaw muscles, and degeneration or dysfunction of the TMJ, which can affect the whole body system [2].

Temporomandibular disorder (TMD) has different causes. The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) [3], which is the gold standard for studying and treating TMD patients, consist of Axis 1 (muscular and articular problems) and Axis 2 (psychological problems). Axis 1 includes the three subgroups of myofascial pain, disc displacement, and joint problems, and Axis 2 is composed of the severity of TMD pain and the neuropsychological symptoms. This classification implies that psychological problems accompany the musculoskeletal ones.

The occurrence of TMD has been recently increasing, and large amounts of money are spent on its treatment. According to the cohort study of temporomandibular disorder (TMD) carried out by the OPPERA (Orofacial pain: Prospective Evaluation and Risk Assessment) project in 2013, the annual incidence rate of TMD in the United States is

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Table 1
Time point of each index.

Time point	Study period								
	Enrollment	Allocation	Active Treatment post-allocation				Follow-up		
Visit window	Week -1	Week 0 (Baseline)	Week 1 ± 3	Week 2 ± 3	Week 3 ± 3	Week 4 ± 3	Week 5 ± 3	Month 3 ± 7	Month 6 ± 7
Eligibility screening	○								
Written Informed consent	○								
Vital signs	○		○	○	○	○	○		
Sociodemographic characteristics, medical history (e.g. neck pain, medication history)	○								
RDC/TMD test & analysis	○								
Randomized allocation		○							
TMJ X-RAY			○						
Credibility and Expectancy			○						
Treatment in Chuna group (experimental group)			⟵ 2 times/week →						
Treatment in UC group (active control group)			⟵ 2 times/week →						
Symptoms and change in medicine			○	○	○	○	○	○	○
NRS of TMJ pain/ bothersomeness	○		⟵ every visit →				○	○	○
VAS of TMJ pain			○	○	○	○	○	○	○
K-BDI-2			○				○		○
JFLS			○				○		
TMJ Range of Motion (maximum mouth opening, mandibular excursive movement)	○		○	○	○	○	○		
PGIC							○	○	○
EQ-5D-5L			○				○	○	○
EQ-VAS			○				○	○	○
SF-12			○				○	○	○
Economic evaluation-medical consumption			○				○	○	○
Economic evaluation-time consumption				○					
Economic evaluation-cost of productivity impairment			○	○	○	○	○	○	○
Adverse events			⟵ every visit →				○	○	○

Abbreviations: RDC/TMDResearch diagnostic criteria for temporomandibular disorders; TMJTemporomandibular joint; UCUsual care; NRSNumeric rating scale; VASVisual analogue scale; K-BDI-2Korean version of Beck's depression index-2; JFLSJaw functional limitation scale; PGICPatient global impression of change; EQ-5D-5L5-level EuroQol-5 dimension; EQ-VASEuroQol-5 dimension visual analogue scale; SF-12Short form-12 health survey.

approximately 3.5%. In Korea, the National Health Insurance Service reported that the number of patients diagnosed with TMD increased by 40.5%, from 250,000 to 350,000, between 2010 and 2015, while medical expenses increased by 74.9%, from 17.3 billion won (about $15.5 million) in 2010 to 30.3 billion won (about $27.2 million). Outpatients account for most TMD cases, and the related medical expenses increased by 79.5% between 2010 and 2015.

Few clinical practice guidelines (CPGs) have been published on the treatment of TMD. "Diagnosis and treatment of TMD", by Gauer et al. [4] recommends patient education, self-management, cognitive behavioral therapy, medication, physical therapy, intraoral appliances, etc. Meanwhile, "Primary treatment of temporomandibular disorders: evidence-based CPGs, 2nd edition" [5], which uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, suggests using splint (Grade 2C) and physical therapy (Grade 2B), while intraoral appliances were not recommended (Grade 1D). CPGs for TMD in traditional Korean medicine [6] have also been published, and recommend the use of diverse therapeutic modalities of Korean Medicine (KM), including Chuna manual therapy (CMT).

Studies of TMD using KM have also appeared with regularity. Acupuncture, one of the classic KM tools, was conducted in the form of dry needling in a randomized controlled trial (RCT) reported by Gonzalez-Perez et al. [7], and showed better effectiveness for pain control, range of movement (ROM) improvement, and safety, than analgesics. In addition, Ferreira et al. [8] reported that the combination of splint therapy, ear acupuncture, and electrical stimulation improved the symptoms more than splint therapy alone, while Grillo et al. [9] reported that acupuncture around the pain area brought significant pain reduction and an improvement in the opening of the mouth. Beside these results, a few observational studies and RCTs showed significant improvements of TMD symptoms in the acupuncture group.

Studies about the use of manual therapy on the TMJ or the cervical spine also have been reported, both domestically and internationally. Calixtre et al. published in 2015 a systematic review [10] that analyzed 8 studies about manual therapy for TMD, and concluded that manual therapy on the upper cervical spine and myofascial release techniques around the neck improved pain, ROM, and tenderness in TMD. In particular, CMT is one of the therapeutic modalities of KM, in which a Korean Medicine doctor (KMD) treats structural and/or functional problems by stimulating the body structure of the patient using the hands or any part of the doctor's body, or additional tools such as Chuna tables [11]. CMT functionally addresses biomechanics, pathophysiology, and diagnostics, and uses therapeutic techniques to adjust the balance in the structure and function of the musculoskeletal system [12].

Research comparing the effects of a manual therapy group and a usual care group was published [13–15]. However, studies specifically examining the true "CMT" have not been conducted thus far. Clinical trials using CMT have been published in Korea [16,17], which however do not compare CMT to usual care [18]. CMT on TMD in Korea is well known among KMDs, but the evidence for the effect of CMT is insufficient. Therefore, this trial is designed to propose a protocol to investigate the efficacy and economic efficiency of CMT on TMD, compared to UC.

The purpose of this protocol is to propose a clinical design to determine the clinical effectiveness and cost-effectiveness of CMT for TMD, compared to usual care [18]. Participants will be treated eight times for 4 weeks, and will be assessed for pain, ROM, depressive

symptoms, and quality of life. We speculate that CMT will be more effective and have higher cost-effectiveness than UC. Adverse events will also be reported. If the sample size presumed in this study is not large enough to allow a definitive conclusion, the study will help determine the sample size needed in a prospective large-scale study.

2. Methods

This study protocol was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement [19] (see Additional file 1 for the SPIRIT checklist and Table 1 for the schedule of the whole procedure).

2.1. Study design and study setting

This trial is a prospective, assessor blinded, two-arm parallel multicenter RCT. Eighty patients with temporomandibular disorder, with numeric rating scale (NRS) above 4, will be randomly assigned to either the CMT or the UC group, with a 1:1 ratio. Participants will be recruited by five KM hospitals (Kyung Hee University Korean Medicine Hospital at Gangdong, Jaseng Hospital of Korean Medicine at Gangnam, Daejeon, Bucheon, and Haeundae). This study will be advertised through online news articles, posters in and around the hospitals, offline free newspapers, etc.

Within 3 days of screening, the participants will take part in 8 sessions of CMT or UC for 4 weeks. CMT will be conducted by KMDs. More than one method among thermotherapy, ultrasonic therapy, transcutaneous electrical nerve stimulation (TENS) [20], and interferential current therapy (ICT) will be selected for the UC group, according to the decision of the researcher at each hospital.

To evaluate the cost-effectiveness, medical consumption data (quality of life questionnaire) will be used to assess indices such as the Quality Adjusted Life Year (QALY). All the consumption data will be collected on the first visit of each week, through specially developed questionnaires. Furthermore, a follow-up questionnaire will be administered (face-to-face, by phone, or by distribution) up to 6 months after registration (Visit 12) to evaluate medical consumption, quality of life, etc.

This study protocol and the informed consent document were reviewed and approved by the Institutional Review Board of each participating hospital in August 2018. The study was registered on the Clinical Research Information Service (CRIS) website on 20 September 2018 (KCT0003192, https://cris.nih.go.kr/cris/search/search_result_st01.jsp?seq=12285). Only encrypted codes will be collected, without personal data.

2.2. Participants

2.2.1. Inclusion criteria

1) Unilateral or bilateral TMD
2) NRS for TMD pain (more severe side for bilateral TMD) of 4 or above
3) Continuous or intermittent TMJ pain lasting more than 3 months
4) Diagnosed as myofascial TMD, Axis I: Group 1 in RDC/TMD criteria
5) Aged 19–70 years at the signing of the participant agreement form
6) Agreement to participate in the clinical trial, and signing of the agreement form

2.2.2. Exclusion criteria

1) The symptoms originated from or were precipitated by a traumatic injury (i.e. traffic accident)
2) Patients with TMD but not included in Axis 1: Group I of the RDC/TMD criteria
3) Medical history of surgical operations related to TMJ
4) Other diseases that can affect the effectiveness and results of the treatment, such as rheumatoid arthritis, neoplastic disease, cerebrovascular accident, myocardial infarction, etc.
5) Current assumption of oral medications that can affect the results of the study, such as steroids, immunosuppressive drugs, psychiatric medications, etc.
6) Assumption of medications that can affect pain severity, such as non-steroidal anti-inflammatory drugs (NSAIDs), during the last week, or treated with CMT within the last 2 weeks, for any reason
7) Pregnant, planning to have babies or currently breastfeeding
8) Participated in other clinical trial within a month from the date of screening, or planning to take part in other trials during the period of this study
9) Other conditions investigators consider unfit to this trial

2.3. Randomization and allocation concealment

Participants, who intentionally signed a clinical trial agreement form, after being informed about the purpose and detailed procedure of the trial, are screened by the investigators for inclusion and exclusion criteria. A screening number is provided according to the order of signing, and demographic information is collected. The subjects are randomly allocated to each group (40 people per group) by the block randomization method by a statistics specialist with nQuery Advisor 7.0 (Statistical Solutions Ltd, Cork, Ireland) (or SAS 9.0 or SPSS 21.0) in the Kyung Hee University Korean Medicine Hospital at Gangdong (the block size will not be communicated to the participants). The results of random allocation will each be sealed in opaque envelopes before being sent to each study site and will be kept stored in double-locked cabinets. There will be no differences among the five hospitals regarding the randomization rule. Each hospital will be assigned 16 participants. Every participant will be assigned a randomized number by registration order, and this result will be communicated to each institution (central randomization).

2.4. Investigation on medical history and medications

Medical history and medications will be investigated through medical examination by interviews and inspection of the past medical history. Contents to be reported are the following:

- History of previous diseases (i.e. heart disease and gastrointestinal disease)
- History of any operations
- History of any other medications or treatments
- History of adverse events after Korean Medicine therapies (i.e. acupuncture, herbal medication, CMT, physical therapy, etc.)
- Current illness
- Assessment of the costs incurred before participating in the trial: the cost of treatment related to TMD will be considered from the onset of TMD to the present
- Evaluation of quality of life: quality of life will be assessed with the five-level version of the EuroQol five-dimensional questionnaire (EQ-5D-5 L) before beginning the trial

2.5. Blinding

Blinding of conductors and participants is not possible in this trial, and only assessor-blinding will be performed. Assessors do not take part in the treatment procedure, and a clinical research coordinator (CRC) or a resident who does not know the grouping information will assess the results of the procedure in a separate location. Participants will be supervised so that they do not inform the assessor of their treatment allocation before each assessment.

Table 2
Chuna manual therapy techniques that will be used in the current study.

CMT for TMJ	Sitting TMJ distraction with thumb technique
	Sitting lateral pterygoid pushing with index finger technique
	Sitting TMJ manipulation with thumb technique
CMT for cervical spine	Supine cervical spine distraction technique
	Supine cervical spine JS distraction manipulation technique
	Supine cervical spine manipulation technique

Abbreviations: CMT, Chuna manual therapy; TMJ, temporomandibular joint.

2.6. Interventions

2.6.1. Chuna manual therapy (CMT)

1) Standardization of CMT for treatment of TMD patients.
2) CMT will be standardized according to the content of this protocol to remove any bias due to the techniques used and the intensity of the performance.
3) Preparation for the procedure
4) The participant is sitting on a chair or lying on a table. A KMD washes hands with cleansing.
5) CMT procedure
6) CMT techniques: 6 techniques are selected as follows by referring to the textbook of Chuna manual medicine [11] and literature on the effect of manual therapy on the cervical spine for TMD patients (Table 2) [see supplementary file 1].
7) The intensity of the distraction technique (two of the techniques for cervical spine) will be set not to make participants feel uncomfortable, but to mobilize them as far as the limits of the passive range of motion.
8) After conducting all of the techniques, the participants will spend 10 min at rest, to observe any adverse events.
9) Frequency and duration of CMT
10) Frequency: a total of eight times over 4 weeks (two times a week)
11) Time duration of a performance: 20 min total (10 min for CMT, and 10 min for rest after treatment)

2.6.2. Usual care (UC) [18]

1) Physical therapies that were proven to alleviate TMD symptoms include thermotherapy, ultrasound therapy, TENS, ICT, etc. In this study, it will be limited to one of thermotherapy, ultrasound therapy, TENS or ICT for the UC group, and will be applied to the area around the neck or the TMJ. Reduction of pain, anti-inflammation, muscle activation, healing, and regeneration of tissue are the mechanisms reported thus far for these therapies [21].
2) Frequency and duration of UC
3) Frequency: a total of eight times over 4 weeks (two times a week)
4) Time duration of a performance: total 20 min (10 min for the treatment and 10 min for rest after treatment)

2.6.3. Co-interventions

Education on TMD will be conducted for the participants of both groups. It covers the causes, prevention, treatment, management, and self-stretching for TMD, using specially assembled materials [see supplementary file 2].

Medications, or visiting other medical services related to TMD and cervical spine are not permitted until the primary endpoint (Week 5) in either group. However, acetaminophen (i.e. Tylenol) will be available to all participants who need analgesics, and will be self-reported. The medical history during the follow-up period will be investigated on the last visit.

2.7. Outcomes

2.7.1. Primary outcomes

Visual Analogue Scale (VAS) for TMJ pain

VAS will be evaluated on the 1st, 3rd, 5th, and 7th treatment visits (week 1–4) and 5 weeks, 3 months, and 6 months after allocation. The average TMJ pain for the past week will be investigated. The primary endpoint is VAS at 5 weeks after allocation (a week after the last treatment). The far left end of a 100 mm scale line means “no pain” and the far right end means “the worst pain imaginable.” It is the most frequently used way to measure the pain severity. A participant puts a mark on the line, which approximates his/her own pain for the past week. If a participant complains of different pain levels on each TMJ, the more severe side will be recorded.

2.7.2. Secondary outcomes

2.7.2.1. Numeric Rating Scale (NRS) for TMJ pain and bothersomeness. This outcome will be checked at screening, at every treatment visit, and 5 weeks, 3 months, and 6 months after allocation. Participants will be asked to select one digit that shows the level of TMJ pain and bothersomeness for the past week (0 means no pain or bothersomeness, and 10 the most severe degree).

2.7.2.2. Range of Motion (ROM) of the TMJ. The ROM of the TMJ will be evaluated at screening, and at the 1st, 3rd, 5th, 7th treatment visits (week 1–4) and after 5 weeks. Active maximum mouth opening without pain, protrusion, and each lateral movement of the mandible will be measured using the Range of Motion Ruler (Therabite, Sweden). Participants will be asked to open the mouth as much as possible without any pain, to slightly open the mouth and protrude the mandible as much as possible and to slightly open the mouth and move the jaw as much as possible to each side (Fig. 1). The measuring process will be concretely conducted in accordance with the specifications for clinical examination provided by the international RDC/TMD consortium.

2.7.2.3. Beck’s Depression Inventory (BDI) [22]. This questionnaire will be conducted on the 1st treatment visit, before the treatment, 1 week after the last treatment, and at the 6-month follow-up. It is composed of 21 questions, and a value from 0 to 3 points is assigned to each answer. A higher score means a more severe depressive state. Clinical depressive disorder is diagnosed when the total score is 17 or above. In this case, the investigators will invite the participant to visit a psychological clinic.

2.7.2.4. Jaw Functional Limitation Scale (JFLS). Participants will be asked to complete this questionnaire on the 1st treatment visit, prior to the treatment, and a week after the last treatment. The functions of biting, moving, speaking, and emotional expression will be investigated through 20 items. Each item can be rated in the answer from 0 (no limitations) to 10 (maximum limitation).

Fig. 1. Assessment of range of motion. (A) active maximum mouth opening without pain, (B) protrusion, (C) lateral movement of the mandible to the right and (D) left.

2.7.2.5. Patient Global Impression of Change (PGIC). The PGIC questionnaire will be administered a week after the last treatment, and at the 3-month and 6-month follow-ups. Participants will subjectively evaluate the improvement of their health state with a 7-point Likert scale, ranging from 1 (very much improved) to 7 (very much worse).

2.7.2.6. Short Form-12 Health Survey (SF-12), version 2 [23]. SF-12 will be conducted on the 1st treatment visit, prior to the treatment, a week after the last treatment, and at the 3-month and 6-month follow-ups. It contains 12 items about health-related quality of life. A higher total score reflects a better quality of life.

2.7.2.7. 5-Level EuroQol-5 Dimension (EQ-5D-5 L) and EuroQol Visual Analogue Scale (EQ-VAS). EQ-5D-5 L and EQ-VAS will be conducted on the 1st treatment visit, just before the treatment, a week after the last treatment, and at the 3-month and 6-month follow-ups. The EQ-5D-5 L evaluates health state, and the total score is indirectly calculated through a specifically developed equation. It is composed of five items (mobility, self-care, usual activities, pain, and anxiety/depression). EQ-VAS uses a 100 mm line, which ranges from the worst health condition on the left end to the best health condition on the right end. Participants will be asked to mark the point corresponding to one's own health condition on that day.

2.8. Cost data investigation

2.8.1. Investigations on consumption profiles

Cost data include medical consumption, non-medical consumption and productivity loss cost of societal perspective. A questionnaire will be developed to evaluate consumption profiles, such as formal/informal medical consumption, non-medical consumption, and time consumption. While formal medical consumption refers to medical interventions and drugs, informal medical consumption refers to health food, medical instruments, etc. Non-medical consumption includes the cost of transportation, time consumption, and nursing. The Work Productivity and Activity Impairment questionnaire (WAPI) will be used for the cost of productivity impairment [24]. Medical consumption and non-medical consumption will be investigated with questionnaires which contains the cost data and the received treatment of participants and the cost data of Korean National Health Insurance will also be analyzed to calculate consumptions.

2.9. Credibility and expectancy questionnaire

The 9-point Likert scale for Credibility and Expectancy

This scale is used to assess the participants' expectancy of the trial. On the 1st treatment visit, before the treatment, they will be asked how much the symptom would be reduced by the CMT and UC (1 = not at all, 5 = somewhat, and 9 = very much).

2.10. Sample size

Since there are no studies comparing CMT and UC, we considered the effect size of the comparison on mean VAS differences as above medium (effect size = 0.7), based on clinical experience. G*Power (ver.3.1.7) (Heinrich-Heine-Universität Düsseldorf, Germany) was used to calculate the sample size, and showed that 68 participants are needed in total. However, analysis of covariance (ANCOVA) of the outcome with the baseline as covariate will be mostly used, and only 62 participants are required at a 0.3 level of baseline-outcome correlation [25]. Because drop-out rate is set to 30%, 80 participants are finally needed (40 in each group, and 16 in each of five hospitals).

2.11. Statistical analysis

Intention-to-treat (ITT) analysis will be used as the main method, which analyzes participants who get at least one treatment. The per-protocol (PP) analysis, which only includes individuals who completed the allocated treatment, will also be used. Last observation carried forward (LOCF) will be used for sensitivity analysis. Additional analysis will be performed for those who will have undergone five or more treatments out of eight treatments. Socio-demographic features and treatment expectancy will be assessed separately for each group. Continuous variables will be expressed as mean and standard deviation, or median and quartiles, and the comparison between groups will be conducted by Student's t-test. Categorical variables will be shown as frequency (%), and the chi squared test or Fisher's exact test will be used to compare them between groups.

The validation variables of the study are the differences between the baseline and each time point for continuous outcomes (VAS, NRS, MMO, K-BDI-2, JFLS, SF-12, EQ-5D-5 L, EQ-VAS) in each group. ANCOVA and repeated-measures analysis of variance (RM ANOVA) will be used. The area under the curve (AUC) will be computed at each time point, to compare the outcome at the primary endpoint (Week 5) and the whole period including follow-ups (6 months).

2.12. Economic evaluation

Economic evaluation will be implemented to compare the cost-effectiveness of CMT and UC. The primary economic endpoint will be an incremental cost-effectiveness ratio (ICER) of CMT compared with UC. ICER will be obtained by incremental cost between CMT and UC divided by incremental effectiveness between CMT and UC. Accordingly, additional cost will be calculated when 1 QALY is increased [26]. If predictions about subsequent periods are needed, cost and effectiveness after follow-up period will be extrapolated using regression models or secondary analysis such as decision modelling analysis. The treatment cost of this trial will be calculated by considering the number of treatments and their unit cost, derived from the health insurance cost and the agency cost. QOL inferred from the EQ-5D-5 L will be the primary measurement for the assessment of QALY, and the AUC method will be used [18]. If the total time horizon is more than 12 months, the cost unit will be standardized as the Korean currency (won), and a discount rate of 5% will be applied, based on the guidelines for economic assessment of the Health Insurance Review & Assessment Service. This analysis will be conducted from the societal perspective. Representative values (i.e. mean) of parameters will be used in the baseline analysis. Sensitivity analysis will be carried out in the form of probabilistic sensitivity analysis by using the distribution of all possible parameters and their representative values. In order to confirm the robustness of the analysis results, the probabilistic sensitivity analysis will be performed by setting the range of cost, effect and transition probability variable to 95% confidence interval. The utility weight and the transition probabilities will be analyzed with the triangular distribution and the cost data will be analyzed with the normal distribution for the distribution of the variable. Monte Carlo simulation will be performed 10,000 times and the mean and 95% confidence interval will be calculated. After conducting probabilistic sensitivity analysis, cost-effectiveness acceptability curve will be confirmed [27].

2.13. Adverse events

Adverse events will be assessed on every visit and investigation. Their seriousness and frequency will be investigated, and when a serious adverse event occurs, proper management will be conducted to keep the participant from incurring damage. Side effects of CMT are common but mostly temporary and mild, such as pain and discomfort localized in the treated area, fatigue, headache, etc. Serious adverse events such as cerebrovascular accident and spinal cord injury can

occur, especially with the rotational CMT technique applied on the cervical spine by pressuring the vertebral artery, but are rarely reported [28]. The CMT techniques used in this trial are adjusted to minimize adverse effects: For example, when conducting rotational CMT on the cervical spine, the rotation will be limited to 45° in one direction and counter-lateral flexion will be applied to manipulate the structure of the level [29]. Investigators will be instructed to check for any adverse event before and after the procedure. The causality between the process and possible side effects will be evaluated according to the World Health Organization Uppsala Monitoring Centre criteria (WHO-UMC) causality scale, comprising six categories. Subjective and objective severity of the symptoms will be assessed by the three-grade classification by Spilker et al [30].

2.14. Stopping rules

Participants will be eliminated when one of the following events occur: (a) the participant withdraws the agreement to participate, (b) the investigators detect any cause of ineligibility during the trial, (c) the participant receives any other treatment that can affect the result of this trial, or (d) the investigators detect any serious adverse event or other disease that can threaten the safety of the participant.

2.15. Data monitoring and safety monitoring

Safety review and comparison between the case report form (CRF) and evidence data will be conducted to ensure the safety of the participants and the completeness of the data.

Monitoring will be performed three times in total: at the starting point, during the trial, and after completion of the study. A monitoring manager in the Jaseng Spine and Joint Research Institute of the Jaseng Medical Foundation will be in charge of the process.

3. Discussion

This study is one of the large-scale national research projects aimed to the development of a set of Korean Medicine clinical practice guidelines, through the scientific validation of various Korean Medicine treatment methods, and to the standardization and scientific systematization of Korean Medicine. The project was undertaken under the supervision of the Ministry of Health & Welfare of Korea, and is planned to last 5 years starting in 2016. For the past two years, the researchers involved in this study have developed Korean Medicine clinical practice guidelines for TMD through systematic reviews, meta-analysis and expert consensus [6]. In a previous survey, not yet published, of the current clinical state of TMD, 73.12% of Korean Medicine practitioners were using CMT in the treatment of patients with TMD. Therefore, it is easy to conclude that the use of CMT for TMD is very common in Korean Medicine.

Three RCTs comparing CMT only and UC were identified. One study was conducted in Korea and two were conducted in China. In the study from Korea, acupuncture treatment and CMT were compared, and the distraction technique was used as CMT. The results were presented using the modified temporomandibular disorder index (mCMI). One of the two studies in China was a comparison between CMT (bombing method and rubbing method) and acupuncture, and another compared CMT (bombing method and rubbing method) with electroacupuncture.

In the Korean study of 31 subjects, there was no significant difference in the functional index between acupuncture treatment and CMT, the mean difference being -3.12 (95% confidence interval -10.06, 3.82; P = .38) [16]. In the two Chinese studies with 136 subjects, only the rate of improvement (treatment effect) analysis was conducted [31,32]. Meta-analysis of the two trials revealed no significant difference in the rate of recovery with a relative ratio of 1.04 (95% confidence interval 0.95, 1.14; P = .42).

Evaluation of the risk of bias in the three studies comparing CMT with acupuncture concluded that the method of random assignment was not specified, or that assignment concealment could not be confirmed. Therefore, the grade has been lowered by one unit due to the risk of bias in the evidence-based evaluation. Because the result variables used were different, the mCMI analyses were not lowered due to inconsistency or indirectness. Imprecision led to a lowering by one grade. In the meta-analysis of the rate of recovery, the I^2 statistic was 85%, and the chi-squared test resulted in a P-value of 0.010, leading to lowering by one grade. Therefore, both mCMI and the rate of recovery were evaluated as ‘’Low evidence”.

For these reasons, we designed a high-quality RCT protocol, with adequate trial design description, large-scale, accuracy of randomization and allocation process, blinding, and sufficient reporting of participant flow, estimated effect size of the intervention, and precision.

The CMT group will receive only CMT, without any other treatment, in order to improve the accuracy of the study, even though CMT and usual care are conducted together in the clinical practice. The control group will receive frequently used interventions, according to the analysis of Korea’s health insurance review & assessment system (HIRA) database. Compared to general CMT techniques on the spine, those on TMJ require more precise and detailed skills. Therefore, specialists from typical Korean Medicine hospitals for spinal disease in Korea will perform the procedure with their own hands, and all practitioners will be required to complete a training program for the standardization of the techniques. The reason for including the economic evaluation in this study is to bring CMT under Korea's health insurance system, through a cost-effectiveness analysis. This is also a social requirement consistent with the will of the Government of Korea, which aims to involve the general Korean population and all hospitals in evidence-based Korean Medicine.

4. Conclusion

The aim of this trial is to present a protocol to investigate the efficacy and economic evaluation of CMT on TMD, compared with UC. We expect that this trial will contribute new knowledge on the effects of CMT for TMD, so that an economically efficient way of treatment could be developed and standardized. This type of evidence can be used to provide more populations with the benefits of an effective and economic treatment for TMD.

Trial status

The present study started in October 2018 and is currently running.

Author’s contributions

IHH, YJL, MK, KWK, MYS and JHC developed the study design and study protocol. Particularly, IHH, YJL, MK and JHC made the outline of the setting and KWK did the analysis relating to cost-effectiveness. MYS is responsible for the statistics and regulatory aspects. JHC registered the protocol on the website. HK and WSC wrote the original draft and JHC and BCS reviewed and edited it.

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Conflict of interests

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eujim.2019.02.004.

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