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Study Protocol

Effects of a chattering teeth training oral appliance for working memory improvement in healthy volunteers: a cross-over randomized trial

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ABSTRACT

Background: Memory is an important part of the mental activity. Chattering teeth training practiced in Korean Medicine (known as *gochi* in Korean), which is a practice of making a sound by touching the upper and the lower teeth, has been accepted as a modality for the dental health. The purpose of this study is to confirm the effect of a specially designed intraoral appliance, the No-Sick Exerciser, on working memory improvement in healthy participants.

Methods: Thirty healthy participants aged between 16 and 30 years will be recruited and randomized into sequence A and B of 15 each, as in a cross-over design (sequence A: chattering teeth training oral appliance)-chewing the gum; sequence B: chewing the gum—chattering teeth training oral appliance with a washout period of one week. The primary outcome will be assessed by the digit span test and secondary outcomes by the symbol digit modality test and the word list recall, which will be conducted before and after each intervention, four times on each participant.

Discussion: This protocol proposes the rationale and method for the use of an intraoral appliance for working memory improvement. If the oral appliance demonstrates better feasibility for working memory improvement compared with chewing gum, a large scale study will be needed to investigate the effectiveness of the device on populations who require memory improvement.

1. Introduction

According to the Main Statistics of Health Insurance 2017 published by the National Health Insurance Service of Korea, the percentage of the elderly population (over 65 years of age) increased from 8.59% of 4,074,135 in 2006 to 13.36% of 6,806,213 in 2017.[1] Korea is already considered to be an aging society where the elderly population will continue to increase and the proportion of the young population will decline; it is predicted that Korea will become an ultra-aged society by 2025. As a result, how the youth population can evolve to propel future growth engine of the nation will be one of the important factors affecting national growth.

Among the various abilities of the young population enabling them to contribute to national growth of the country, learning ability is particularly important. Good learning ability helps to retain knowledge and implement tasks, which are important factors in citizens that enhance national growth in the long term. Learning ability can be measured through the evaluation of memory. Various clinical studies such as those using mindful meditation[2] and acupuncture[3] have been conducted to improve memory. Chewing gum, especially, is widely reported to have an effect on memory improvement by activating the hippocampal area.[4,5] A systematic review in 2017 analyzed 33 articles and concluded that chewing is helpful even in patients with dementia to improve cognitive function and memory.[6] However, use of medical intraoral device for the improvement of memory needs to be further investigated.

The chattering teeth (*gochi* method, 叩歯法), which is one of the preventive therapies in Korean Medicine,[7] is performed by making a sound by contacting the upper and lower teeth. This method has been improvised by applying intraoral coins or chopsticks and used to cure headache, epilepsy, dizziness, tinnitus, sore throat, odontalgia, dislocation of the temporomandibular joint (TMJ), and other conditions.[8] A study conducted in 2013 showed that Gochi stimulated the memory and cognitive regions of the brain, as visualized on functional magnetic resonance imaging (fMRI).[9]

In this study, a medical oral appliance that is specially designed to enable chewing by moving the TMJ bilaterally will be used. Although this was originally created to restore the normal

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function of the masticatory muscles, it is speculated that this modality can improve memory function, considering the literature regarding the association between chewing and memory improvement. We hypothesized that if there is a merit for memory improvement with chewing gum, using both side of temporomandibular joint (TMJ) would show better effect.

Therefore, we will compare the efficacy of the chattering teeth training oral appliance and gum for working memory improvement in healthy volunteers. A crossover design will be applied with 30 healthy participants to compare the effects of the oral appliance and gum.

2. Methods

2.1. Study design

This study will be performed as an assessor-blinded, cross-over, randomized controlled trial, at the Kyung Hee University Korean Medicine Hospital, to evaluate the feasibility of using the chattering teeth training oral appliance over gum for working memory improvement in healthy volunteers. This protocol was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement[10] (see Additional file 1 for the SPIRIT checklist). This trial protocol was approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital in October 2018 (KOMCIRB-2018-09-003). This protocol was registered on the Clinical Research Information Service (CRIS) on 26 Feb 2019 (KCT0003556, https://cris.nih.go.kr/cris/index.jsp).

2.2. Eligibility criteria

Participants will be screened by trained assistants through phone calls or visits. The following criteria will be applied to find eligible subjects.

2.2.1. Inclusion criteria

1) Healthy subjects aged between 16 and 30 years
2) Right-handedness[11]
3) ability to bite by moving the jaw joint
4) No pain during chewing
5) No severe memory impairment

2.2.2. Exclusion criteria

1) Prior use of dental appliances such as dentures, implants, and braces in the past three months
2) Oral inflammatory diseases, lacerations, wounds, and other similar oral conditions
3) Previous history of oral and maxillofacial surgery such as TMJ surgery
4) Change in any oral medications within the last one month
5) Inability to obtain agreement for participation through their legal representative or who cannot provide consent on their own
6) Inability to respond to questionnaires and tests
7) Any other factors because of which cases were considered inappropriate for inclusion in this research by researchers

2.3. Allocation and blinding

A 1:1 computerized allocation of subjects will be done to two sequences through block randomized allocation. This scheme will be used to allocate the sequence of analysis to determine whether the subject will take the oral appliance first or gum first in the cross-over design. Block size will be two, four, or six, and this information will not be revealed. This process will be conducted using the R. 3.2.5 for Windows (The R Foundation). Concealment will be achieved with the use of opaque envelopes. Investigators who assess the participants will hand out questionnaires and receive the dataset without any information on the sequence status. The statistician will receive data and send them back after analysis and will remain blinded to the grouping information during the whole process.

2.4. Procedures

The purpose and procedures of this study will be explained in detail to the subjects before their registration on the first visit. Informed consent will be obtained by their own will, and the screening number will be presented in order. Demographic information, physical examination, vital signs, medical history, and inclusion/exclusion criteria will be investigated. If participation in the trial is considered appropriate, the study subject identification code will be presented in order and recorded on the case report from (CRF).

This study will be conducted in two sequences. The sequence A will use the chattering teeth training oral appliance first on the second visit and then gum on the third visit, and sequence B will use gum first and then the oral appliance as in the cross-over design, with seven days of washout period between the oral appliance and gum. Outcome measurements will be measured immediately before and after each intervention. Every participant will undergo assessment for each outcome four times unless drop-out occurs. We will recommend the participants not to chew gum or jelly during the participation (Fig. 1).

2.5. Interventions

2.5.1. The chattering teeth training oral appliance

A participant will apply the oral appliance (*No-Sick Exerciser* by Hifeelworld, Inc., Korea) in the mouth and start chewing it softly while feeling the inbuilt springs a 100 times with the velocity of twice per one second. After that, the jaw joint will be relaxed without any force, and this relaxed position will be held for one minute. This masticatory exercise will be repeated 100 times and held again for one minute, followed by another 100 counts of the exercise (Total: 300 counts of the masticatory exercise and two minutes of relaxation). After use, the oral appliance will be removed and washed thoroughly in flowing water, dried, and stored in the case. All the procedures will be performed in the clinical trial room in the guidance of a researcher (Fig. 2).

2.5.2. Chewing the gum

The gum (Xylitol, 70 × 20 mm, 3.0 g; Lotte, Japan) to be used in this trial is easily available anywhere in Korea.

Participants in the gum group are not instructed for which side of the jaw they are using when chewing because the individual difference is one's habit. After chewing the gum 100 times with the velocity of twice per one second, the mandible will be relaxed for one minute without any movements. This procedure will be repeated until 300 times of chewing is completed, to simulate the method with the oral appliance. All the procedures will be performed in the clinical trial room in the guidance of a researcher.

2.6. Guidelines for the use of other drugs and investigations on chewing activity

Drugs that are considered to have no effect on the interpretation of the results of this study will be allowed under the investigator's judgement. All the information on drug intake in the last four weeks will be recorded in the CRF. Intake of muscle relaxants, analgesics, NSAIDs, or psychotropic medicines

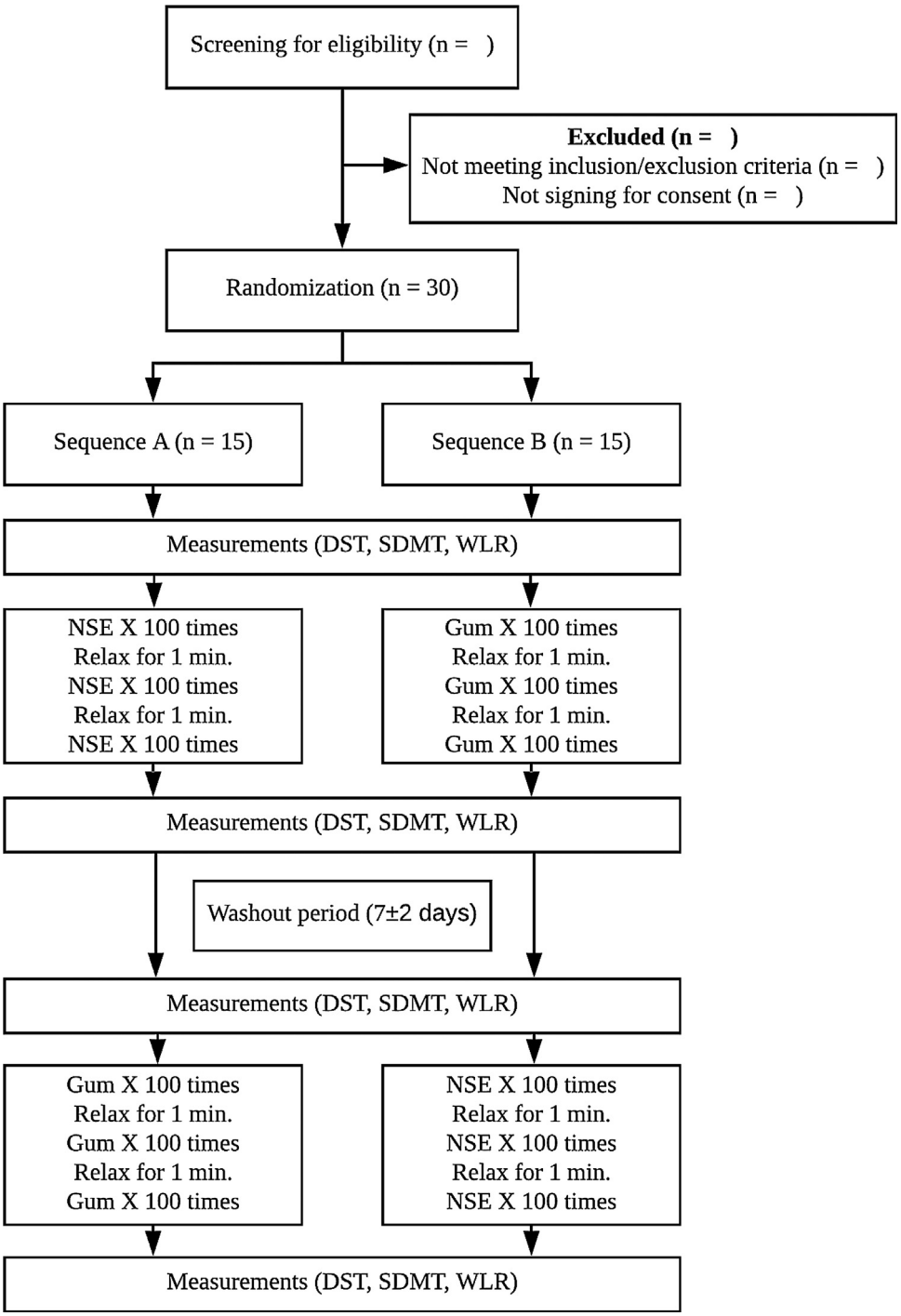

Fig. 1. Flow chart of the study.

will be recorded, and if these drugs are essential for the participants, they will be immediately withdrawn from the study. For the consideration of the individual differences on chewing activity, informations like meal intake amount, number of meals a day, average of eating time will be recorded on the CRF.

2.7. Outcome measurements

2.7.1. Primary outcome

2.7.1.1. Digit span test (DST). The DST is a neuropsychological test that measures the attention ability and working memory. It is simple and easy to perform, and hence, it has been used for the evaluation of memory impairment and cognitive function.[12]

DST is composed of digit span forward (DF) and digit span backward (DB). DF evaluates focusing ability and DB measures working memory. During the process, the subject should memorize the numbers that are spoken by the tester at intervals of one second. The numbers are composed of three to nine digits. Accuracy is the most important part of the test. The maximum number of numbers remembered correctly by the subject equals the score. If the patient repeats three incorrect answers consecutively, the test ends. Incorrect answers do not lead to deduction of the score earned by the subject.

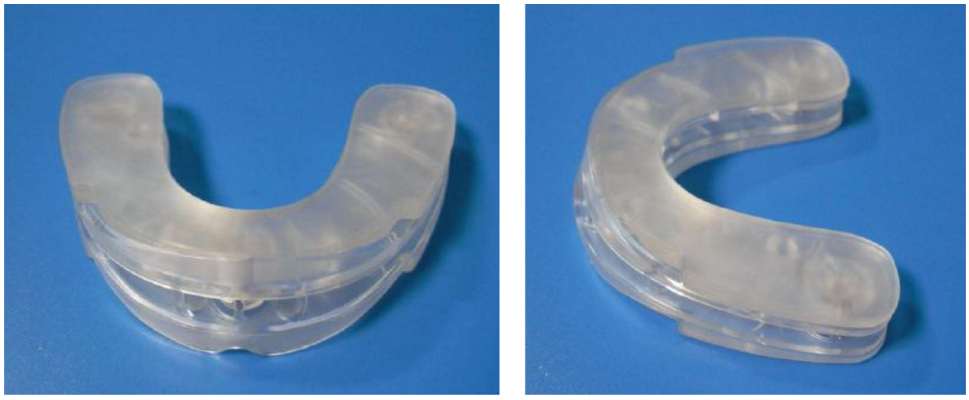

Fig. 2. Oral appliance (a) anterior view and (b) lateral view.

2.7.2. Secondary outcomes

2.7.2.1. Symbol digit modalities test (SDMT). The SDMT, first developed by Aaron Smith in 1973 and continuously updated, is an evaluation tool that can quantify the enforced cognitive function and concentration within a short time. Validity is assessed,[13] and a standardized score is presented by the developer. It is widely used in such studies as computer games and crossword puzzles for attention and cognitive function[14] and as chewing gum for learning ability.[5]

The evaluation method matches suggested numbers with the appropriate geometric models. A pair of symbols and a number between zero to nine are presented, and a number corresponding to the randomly displayed symbol is written. The implementation time is 90 s, and the total time for evaluation should not exceed five minutes. The question is composed of more than 75 items, and when the answer provided is over the number, it is regarded as a perfect score. The standardized score is calculated from the raw score in consideration of sex, age, education level, etc.

2.7.2.2. Word list recall (WLR). WLR is a free recall test using ten commonly used nouns. Ten words will be presented at intervals of two seconds; participants are instructed to read them aloud, and informed to recall as many words as possible for ninety seconds right after the presentation of words. This process will be repeated three times with the presenting order randomly mixed.

2.8. Sample size calculation

The purpose of this study is to investigate the efficacy and superiority of the oral appliance over gum, under the medical background that memory can be improved through chewing. This study is an exploratory, prospective, preliminary study, and the pilot study requires twelve or more participants.[15] Therefore, 30 participants will be recruited by the non-probability extraction method considering the number of eligible subjects, the minimum range of effectiveness evaluation, and the dropout rate of 60%. This is the most conservative estimated number to determine the difference between the two groups after correction by a mixed model in the cross-over design. Compliance will be defined as the ratio of the total number of required visits to the number of actual visits.

2.9. Statistics

SPSS for Windows Ver 18.0 (SPSS Inc., Chicago, IL, USA) will be used for statistical analysis. The study has a cross-over design, which will be used to analyze the difference between the two groups after correcting the crossing sequence and the patient number to a random variable by using a mixed model. The general characteristics, DST, SDMT, and WLR scores of the study subjects will be converted into percentages (%) and standardized scores, and continuous data are summarized as mean, standard deviation or median, quartile range, minimum value, and maximum value. Changes in the main measurements will be analyzed by the paired t-test when the values of the data follow a normal distribution. If not, the Wilcoxon rank sum test will be used as a nonparametric method. P-value of under 0.05 will be considered significant.

2.10. Recruitment and obtaining consent

In order to recruit the research subjects, advertisement posters will be posted on the bulletin board in the hospital and regularly distributed through mass media such as internet newspaper. If the registration process is delayed, the recruitment method can be expanded through subway advertisements, local advertisements, or local club advertisements. On registration after screening for the inclusion and exclusion criteria, the participants will visit the hospital, and instructions for obtaining consent will be provided by the tester. The investigator will ensure that the participants understand the contents well. The test will be conducted only on those who provide written consent by their own free will. As the subjects of this trial are categorized as minors, considered vulnerable by the Korean Good Clinical Practice (KGCP), consent of the legal representative will be obtained according to the civil law. Therefore, a legal representative (i.e. parent) will be required to accompany the participant for the confirmation and consent procedures and will be provided with a detailed explanation of the procedure of the trial and protection countermeasures.

2.11. Data management and safety monitoring

Every participant will be assessed with questionnaires (DST, SDMT, and WLR) at the baseline and after a week, immediately before and after each intervention. Scores of each outcome and dropout data will be typed in the excel sheet without presenting grouping information, and then sent to the statistician for analysis. This electronic file will be secured with username and password.

The NSE, licensed as a first-class medical device by the Korean Ministry of Food and Drug Safety, is not known to cause any side effects of high risk. However, fatigue and pain in the masticatory muscles can occur following intensive masticatory exercise, and nausea may develop in the course of adaptation. These mild adverse events usually disappear spontaneously. However, any discomfort will be required to be reported to the researcher to determine whether or not participation is to be continued.

All adverse events will be presented by severity and causality with NSE and gum. The occurrence rate and incidence rate of serious

adverse events, and dropout rate due to these adverse events will be analyzed with 95% confidence interval.

The chief investigator (WC) will provide training to investigators, participants, and legal representatives to report any adverse events and symptoms that may occur after applying interventions. It will be ensured that the clinical trial subjects receive appropriate medical treatment and follow up following any adverse events until symptoms disappear and the condition stabilizes. A report regarding the safety issue will be submitted.

Review and comparison for safety between raw data and the CRF will be performed to verify the participants' safety and the fulfillment of data. Data monitoring will be conducted at the beginning, in the middle of, and on completion of the study. A monitoring manager in Kyung Hee University Korean Medicine Hospital will manage the whole process.

3. Discussion

The purpose of this study is to verify the superiority of the chattering teeth training oral appliance (NSE) over gum for inducing memory improvement in healthy participants. Chewing gum for memory improvement has been studied, and it is suggested that mastication stimulates the hippocampus, resulting in this effect.[4] Although NSE is a first-class medical device invented originally for the improvement of masticatory function, it can also benefit memory function, considering the literature highlighting the effect of chewing gum on memory improvement. This oral appliance enables both TMJs to move at the same time with bilateral activation, regardless of the occlusal condition and individual habit. Hence, NSE will improve outcomes for memory. This study will provide a new approach for improving memory in learners in a noninvasive and safe manner.

Author contributions

WC made a hypotheses for this trial and HK, JB, and WC designed the method in detail. JB managed the statistical and ethical parts. HK wrote this manuscript and WC finally revised it to the complete version. All authors read and approved the final version of the manuscript.

Conflict of interest

This study is funded by Hifeelworld, Inc. for the oral appliances, research allowances, participants' compensation, etc. Hifeelworld, Inc. had not been involved in the study design; collection, management, analysis, and interpretation of data; nor writing of the paper.

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Ethical statement

This trial protocol was approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital in October 2018 (KOMCIRB-2018-09-003).

Data availability

The data of this study will be kindly provided when requested through the corresponding author's e-mail.

Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.imr.2019.09.001.

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