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Original Article

Effect of Bi-/Unilateral Masticatory Training on Memory and Concentration - Assessor-blind, Cross-over, Randomized Controlled Clinical Trial

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Objectives: This study aimed to explore the short-term effects of bilateral masticatory training using an intraoral device on memory and concentration, which is an advanced form of Gochi, compared to the unilateral form with gum.
Methods: Thirty young healthy participants (age, 16–30 years) were screened and randomly assigned to one of two sequences in a crossover design. The participants assigned to sequence A (n=15) performed bilateral mastication using an intraoral device with a total of 300 taps, followed by unilateral mastication using gum with the same number of repetitions and frequency, separated by a 7-day washout period. A reverse order was used for sequence B. The primary and secondary outcomes were the digit span test result and the symbol digit modality test and the word list recallresults, respectively, which were conducted before and after each intervention.
Results: Symbol digit modality test scores increased by 12.03±8.33 with bilateral mastication, which was significantly higher than that obtained with chewing gum (5.17 points;95% confidence interval: 0.99, 9.34; $p<0.05$). Changes in the digit span test and word list recall scores were not significantly different between the two groups. In the digit span test forward, symbol digit modality test, and word list recall test, bilateral mastication was not inferior to unilateral mastication in improving memory and concentration.
Conclusions: Bilateral masticatory exercises using an intraoral device are not inferior to unilateral mastication with gum for improving memory in healthy young individuals. Further research is needed to determine the efficacy of bilateral masticatory training on cognitive function.

Key Words : *Memory, Concentration, Traditional korean medicine, Bilateral mastication, Chewing exercise, Gochi*

Introduction

Working memory, which comprises both short-term memory and attentional control[1], is the cognitive process of holding and manipulating task-related information[2]. It is an essential part of cognitive function in humans and is involved in nearly all activities of everyday life. Similarly, concentration, which is the ability to focus attention on a particular subject without being distracted, is also necessary for daily life, and underlies the speed and capacity of recalling memories. Both working memory and concentration are major constituents of cognitive function, and human beings can learn new knowledge with these abilities[3].

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Masticatory activity has been shown to improve memory in an *in vivo* study that investigated the hippocampus of mice[4] and in review articles involving humans[5,6], as well as reinforce concentration[6]. The known mechanism of action for this improvement is that mastication activates the hippocampus indirectly through neuronal and humoral pathways[7] and changes the activity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a decrease in corticosterone levels. In addition, it blocks the activation of c-Fos, which is related to learning ability in the hippocampus[5]. These processes allow masticatory movement to influence working and spatial memory, as well as the storage and information recall.

The masticatory process involves the movement of both the jaws; however, people tend to chew mainly on one side[8]. Unilateral mastication has been demonstrated to be inferior to bilateral mastication in terms of muscular activation around the jaw and the range of movement of the temporomandibular joint[9]; it also results in worse masticatory performance[10]. To our knowledge, no study has compared bilateral mastication with unilateral mastication in relation to cognitive or masticatory function.

In traditional Korean medicine, there is a form of jaw tapping training called *Gochi*, which means ‘tapping teeth.’ It is a traditional Korean medicinal method of chattering teeth by repeatedly contacting the upper and lower teeth with the biting force of provoking tapping sounds. It has been used as preventive therapy to enhance cognitive function, and even overall human health, in traditional Korean medicine[11]. Recently, a study using functional magnetic resonance imaging (fMRI) proved that *Gochi* increased blood oxygen level-dependent signals in brain areas controlling memory and cognitive function[12]; another fMRI study showed that it activated similar brain areas just as clenching and chewing gum[13]. Although jaw tapping is a type of bilateral mastication, the absence of normal occlusion can reduce neural effects[14] and memory[15]. Thus, in this study, a specially designed intraoral device that used the concept of *Gochi* as a motif was utilized to allow efficient bilateral masticatory training regardless of occlusal conditions[16].

It can be speculated that simultaneous bilateral masticatory exercises may have a stronger effect than unilateral masticatory exercises and masticatory movements in improving brain function. We designed a crossover randomized trial to explore the feasibility by comparing bilateral masticatory training using an intraoral device with those of unilateral mastication training with gum chewing, which we used as an active control to improve cognition[17], memory, and concentration in healthy young volunteers.

Materials and Methods

The current study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT). A detailed description of the study protocol has been published elsewhere[18]. Participants were recruited through offline posters and online homepages. Thirty healthy participants were enrolled in the study after screening using the inclusion and exclusion criteria (Figure 1).

Only right-handed individuals were included because brain activation differs with handedness[19].

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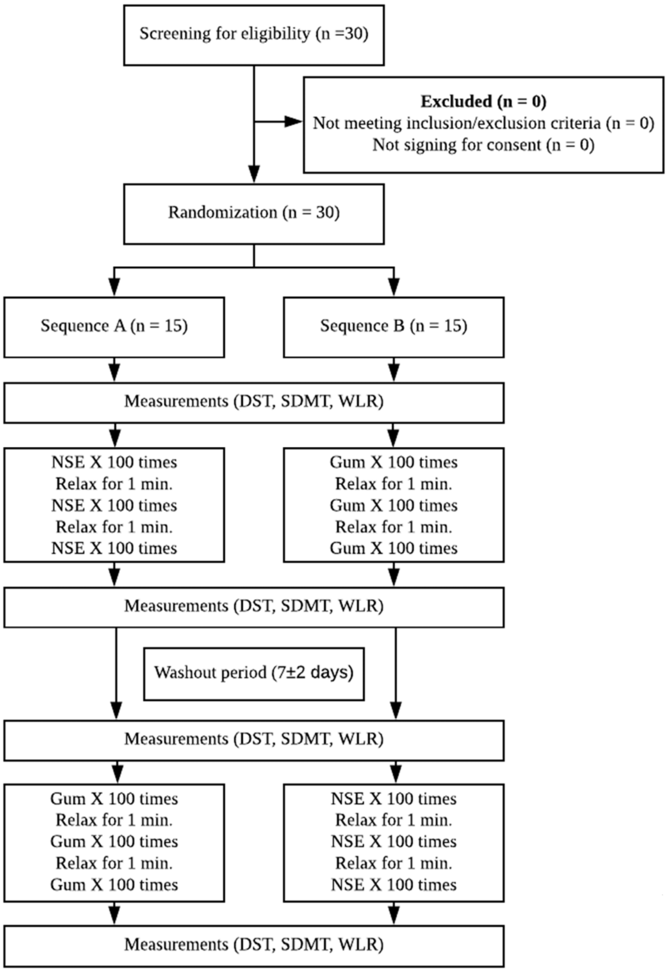

Fig. 1. Flowchart for the study.
DST, digit span test; SDMT, symbol digit modalities test; WLR, word list recall; NSE, No-sick Exerciser®.

The design was an assessor-blinded, crossover, randomized controlled trial. Half of the participants (n=15) were assigned to sequence *A*, and half to sequence *B*. Participants assigned to sequence *A* first underwent bilateral mastication training with the intraoral appliance, followed by a 1-week interval after which they underwent unilateral mastication training involving gum chewing. The participants assigned to sequence *B* received the training in the opposite order, beginning with gum chewing, followed by the use of the appliance. The interventions were performed between 3 and 5 p.m., with at least 2 h of fasting. All procedures were reviewed and approved by the institutional review board (IRB) of Kyung Hee University Korean Medicine Hospital (approval number: KOMCIRB-2018-09-003).

All participants provided written informed consent. Participants under 19 years of age were considered vulnerable, and their legal guardians signed informed consent according to the Korean Good Clinical Practice (KGCP). This study adhered to the principles of the World Medical Association Declaration of Helsinki.

1. Participants

The inclusion criteria were as follows. 1) Healthy population between 16 and 30 years of age, 2) Right-handed, 3) Capable of mastication by moving the temporomandibular joints, 4) No pain during mastication, and 5) No severe dysfunction in memory or concentration

The exclusion criteria were as follows. 1) Use of dentures, implants, or braces within the last 3 months, 2) Having oral conditions of inflammatory disease, lacerations, wounds, etc., 3) History of orofacial surgery, 4) Change in oral medication within the last 3 months, 5) Unable to provide consent for participation or obtain consent through a legal representative, 6) Unable to complete questionnaires or tests, and 7) Considered as inappropriate for the study by the investigators.

After screening, the participants were provided with a description of the study procedures and their legal rights and responsibilities during a one-on-one interview with a study investigator. The investigator verified that the participant understood the process and willingly signed a consent form. After obtaining consent, the investigator collected demographic information.

2. Sample size calculation, allocation, and blinding

This was an exploratory pilot study to compare bilateral mastication with unilateral mastication. A pilot study was required to have at least 12 participants[20]. This study recruited 30 participants (dropout rate, 60%). A block randomized allocation method was used to assign participants to sequence *A* or *B*, with block sizes of 2, 4, or 6, using R 3.2.5 for Windows (R Core Team, Vienna, Austria). The assignment information was transferred to an enclosed envelope and given to the evaluator and statistician.

3. Interventions

A specially manufactured device, the No-Sick Exerciser® (Hifeelworld, Inc., Seoul, Korea) (Figure 2), was used for simultaneous bilateral mastication exercises.

It has been approved as a first-class medical device by the Ministry of Food and Drug Safety of Korea and has been used in chewing training to restore muscular function around the jaw. The main body of the device was made of resin and there were three stainless steel elastic springs, all of which are known to be safe for use in humans. These springs enable the use of both sides of the jaw muscles simultaneously. The participants placed the device in the mouth between the upper and lower teeth and tapped it lightly up and down 100 times. Subsequently, they relaxed their jaw and rested for one minute without any movement or force of the jaw. They repeated this exercise for three rounds, with one-minute rest between rounds. A total of 300 taps were performed per session[21,22]. This process was conducted around noon, before lunch, to maintain the surrounding conditions in the same manner.

The participants on the trial of unilateral

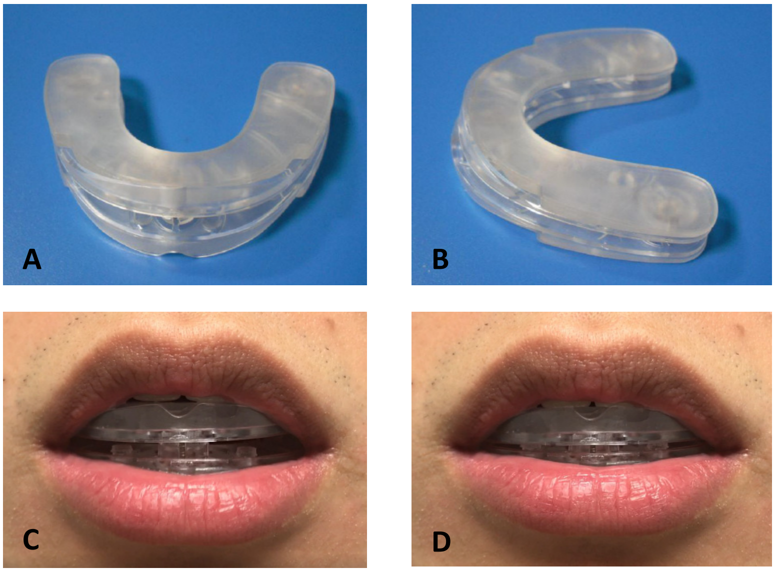

Fig. 2. The intraoral appliance: No-sick exerciser®.
(A) Anterior view. (B) Lateral view. (C) and (D) A person training with the intraoral device. Each trial of chewing starts from (C) without force to (D) with a biting force. (A) and (B) had been published in Integrative Medicine Research 8 (2019) 247-251.

mastication were instructed to chew a gum (Xylitol®, 70 × 20 mm, 3.0 g; Lotte, Japan) on one side of the mouth. Similar to the bilateral mastication sequence, the participants performed light chewing 100 times, followed by a minute of rest. The chew/rest sequence was repeated two more times for a total of 300 unilateral chews.

4. Outcome measurements

Participants in the current study completed three tests in regular order immediately before and after each intervention, as conducted in previous studies measuring the short-term effects of masticatory movement, with questionnaires given immediately after interventions[23,24]. Each participant completed the test four times. All tests were administered and scored according to standard instructions.

The digit span test (DST) was the primary outcome of this study. It is a neuropsychological test to evaluate memory and concentration and has been used to assess memory improvement in healthy young populations[25,26], as well as memory impairment in older adults and patients with cognitive symptoms[27]. It can be administered in two forms: DST forward, characterized by memorization in a forward order, and DST backward, characterized by memorizing in a backward order. DST forward measures concentration ability, while DST backward evaluates working memory. A tester tells the numbers at an interval of one second for three to nine digits at a time, and a testee memorizes the sequence. The length of the digits of the correct answer and the longest digit equals the test score.

The secondary outcomes are symbol digit modalities test (SDMT) and Wordlist recall (WLR).

SDMT is a common instrument used to assess cognitive function and concentration. It contains 75 questions, which are scored based on the standardized numbers assigned to the participant's sex, age, and educational background. It is used to assess the cognitive effects of computer games[28] and gum chewing[29].

WLR is a type of free recall test that uses 10 common words. The participants were instructed to read the 10 words aloud and to recall as many words as possible from the list. The task was performed three times, and the order of the words was randomized in each trial. This test evaluates working memory in various age groups[30].

5. Data management, safety monitoring, analysis

Data from the tasks were entered into Excel and given to the statistician without any information on the sequence of each participant. The data file was protected using a password. Monitoring was performed before, during, and after the study by the internal institutional monitoring staff.

All data analyses in this study were conducted using SPSS for Windows Version 18.0 (SPSS Inc., Chicago, IL, USA). This study used a crossover design, and a mixed model was used to correct crossover sequences and identify participants as random variables to analyze the differences between the two interventions. General characteristics and test scores were converted to percentages (%) and standardized z-scores. Continuous data are presented as means and standard deviations (SD), medians, interquartile ranges (IQR), as well as minimum and maximum values. Both paired sample t-tests and Wilcoxon rank-sum tests were used to compare the differences between the changes following the two interventions. Statistical significance was set at $P < 0.05$. Non-inferiority was verified by setting the tolerance to 10%.

Results

1. General demographic characteristics of the participants

A total of 30 people participated in this study, with no dropouts during the trial. The study included 13 male (43.3%) and 17 female (56.7%) participants (age range, 19-29 years; mean age, 25.7 years). Seven males and eight females were assigned to sequence *A*, and six males and nine females were assigned to sequence *B*. The mean ages of the participants were as follows: sequence *A*, 26.5 years; sequence *B*, 26.3 years.

2. Changes in DST score

The average score for the forward condition of the DST increased by 0.40 ± 1.22 after masticatory exercise with the intraoral device, whereas it decreased by 0.04 ± 1.16 after mastication with chewing gum. However, the difference between the changes in bilateral and unilateral mastication was not significant ($P > 0.05$) (Table 1). The average score for the backward condition of the DST increased by 0.33 ± 1.45 after bilateral mastication and by 0.60 ± 1.48 after unilateral mastication. The difference between these changes was not statistically significant ($p > 0.05$).

3. Changes in SDMT score

The SDMT score increased by 12.03 ± 8.33 after bilateral mastication and 6.87 ± 7.45 after unilateral mastication; the change was significantly higher in the bilateral mastication group than in the unilateral mastication group ($P < 0.05$) (Table 1).

4. Changes in WLR average score

The average increase in the total number of items recalled during the WLR was 0.69 ± 1.01 in the bilateral mastication group and 0.77 ± 0.75 in the unilateral mastication group, which was not significantly different ($P > 0.05$) (Table 1).

5. Results of non-inferiority of bilateral mastication with a medical device compared with unilateral mastication with gum

Bilateral mastication with the exercising device was not inferior to unilateral mastication with gum based on the test of non-inferiority during DST forward, SDMT, and WLR (Table 2) (Figure 3).

However, this was not proven during DST backward. The margin of the non-inferiority tolerance limit was set to 10%[31].

6. Adverse events after the intervention

Table 1. Changes in Digit Span Test, Symbol Digit Modalities Test, and Wordlist Recall Scores Before and After Bilateral and Unilateral Mastication

Variable		Bilateral mastication (n=30)				Unilateral mastication (n=30)				Difference			P-value (Paired t-test)	P-value (Wilcoxon test)
		Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	95% CI			
DST forward	Pre-mastication	6.27	1.14	7	1	6.57	1.07	7	0	-0.30	-0.83	0.23	0.2560	0.3151
	Post-mastication	6.67	0.55	7	1	6.53	0.78	7	1	0.13	-0.16	0.42	0.3545	0.3667
	Difference	0.40	1.22	0	0	-0.04	1.16	0	0	0.43	-0.12	0.99	0.1192	0.1494
DST backward	Pre-mastication	5.70	1.18	6	2	5.40	1.57	6	3	0.30	-0.30	0.90	0.3131	0.2984
	Post-mastication	6.03	1.25	7	2	6.00	1.23	6.5	2	0.03	-0.49	0.56	0.8973	0.9041
	Difference	0.33	1.45	0	1	0.60	1.48	0	2	-0.27	-1.01	0.48	0.4708	0.6521
SDMT	Pre-mastication	83.67	12.95	84.5	19	87.43	14.42	92.5	25	-3.77	-9.13	1.59	0.1614	0.1791
	Post-mastication	95.70	7.50	96.5	10	94.30	9.45	100.5	13	1.40	-1.27	4.07	0.2921	0.3091
	Difference	12.03	8.33	11.5	10	6.87	7.45	6	12	5.17	0.99	9.34	0.017*	0.0202*
WLR average	Pre-mastication	8.72	1.11	9.00	1.67	8.62	0.99	8.83	1.33	0.10	-0.46	0.66	0.7170	0.6013
	Post-mastication	9.41	0.76	9.67	1.00	9.39	0.77	9.67	1.00	0.02	-0.17	0.22	0.8157	0.6033
	Difference	0.69	1.01	0.50	1.33	0.77	0.75	0.67	1.00	-0.08	-0.54	0.39	0.7343	0.6648

DST, digit span test; SDMT, symbol digit modalities test; WLR, word list recall; SD, standard deviation; IQR, interquartile range; CI, confidence interval; *, $P < 0.05$.

Table 2. Non-inferiority Margin Scores for Each Outcome

Variable		Difference (bilateral - unilateral)			Total	Margin
		Mean	95% CI			
DST forward	Difference (post-pre)	0.43	-0.12	0.99	7	-0.7
DST backward	Difference (post-pre)	-0.27	-1.01	0.48	7	-0.7
SDMT	Difference (post-pre)	5.17	0.99	9.34	102	-10.2
WLR	Difference (post-pre)	-0.08	-0.54	0.39	10	-1.0

DST, digit span test; SDMT, symbol digit modality test; WLR, wordlist recall; CI, confidence interval.

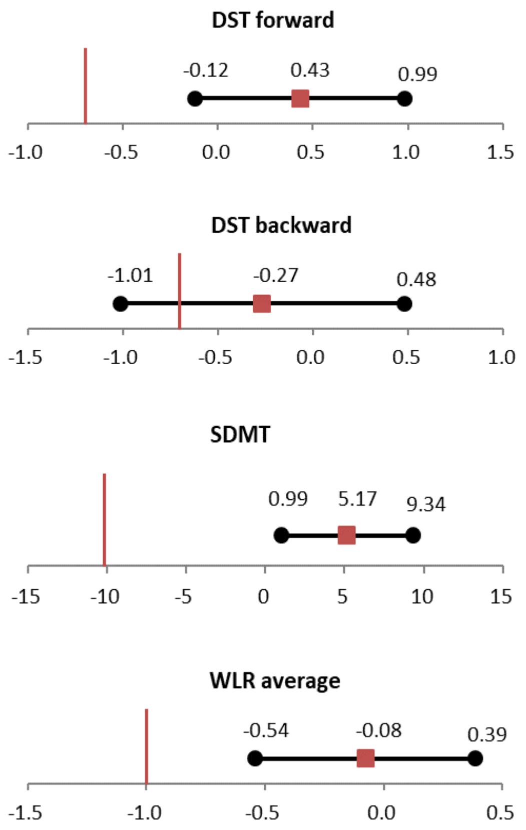

Fig. 3. Non-inferiority test of the DST, SDMT, and WLR.
DST, digit span test; SDMT, symbol digit modality test; WLR, word list recal

No adverse events were observed for the bilateral or unilateral interventions.

Discussion

Based on the hypothesis that bilateral mastication is more effective than unilateral mastication based on its effects on memory and concentration, mastication with a specially manufactured intraoral device and gum was compared to investigate the feasibility in this study.

The results of the current study shows that bilateral masticatory movement was not inferior to unilateral movement during the two tasks that assessed concentration (DST forward) and working memory (WLR). Additionally, on the secondary outcome, bilateral mastication was more effective than unilateral mastication in SDMT—a concentration test. This indicates that exercising with the device is not inferior to the widely accepted method of chewing gum and it improves the ability to focus within a shorter period than gum.

These results are important for several reasons. First, bilateral masticatory exercises using the device allows both jaw joints to be activated sufficiently at the same time, which may contribute to the activation of more areas of the brain by stimulating the masticatory muscles bilaterally[19,22]. Generally, people tend to masticate unilaterally[31], which causes unbalanced facilitation of soft tissues around the temporomandibular joints[32] and osseous morphology[33], resulting in less activation of the hippocampus and amygdala[34]. Second, bilateral masticatory training using the intraoral device is relatively safe for healthy volunteers because no adverse events were reported in this study. Therefore, bilateral mastication training using this device is likely to increase brain activity better than that with chewing gum. In addition, the springs inserted between the upper and lower bodies of the device facilitate the standardization and quantification of chewing exercises.

Formerly, other researchers have studied jaw tapping (*Gochi*) without any apparatus in the mouth to investigate its effect on cognitive function[12]. However, a training device was employed in this study to embody bilateral masticatory training by activating the muscles of both sides equally. Generally, individuals have individual intercuspal positions (ICPs) to obtain maximal occlusal contact[35], which causes an imbalance in muscular activation during mastication. The intraoral appliance, however, resolves the imbalance developed from the unique ICP and enables balanced masticatory movement with three springs between the upper and lower parts of the apparatus. In addition, the springs produce resistance during chewing movement, followed by increased activation of the surrounding muscles without any side effects.

The mechanism of improvement in memory and concentration from bilateral and unilateral mastication can be inferred based on previous research. In an animal study, mice with incomplete mastication due to dental problems had learning impairments and eventually underwent memory deficits. Loss of chewing movement affects CA1 and CA3−a sub-area of the hippocampus−and inhibits c-Fos expression[36]. This phenomenon impedes the synthesis of acetylcholine and accelerates the inflammatory response, resulting in the aging of the hippocampus. Masticatory movement increases cerebral blood flow[37], with simultaneous bilateral jaw movement possibly contributing to a bilateral increase in inflow, as investigated in an fMRI study[38]. Neuronal and humoral pathways are also considered to be activated during mastication, with the stimulation of both sides able to enhance this mechanism. In addition, when people use the other side of the body rather than the preferred side, new neuroanatomic connections are more likely to be generated[39].

A few limitations of this study must be addressed. First, the number of participants were insufficient to verify the superiority of the experimental group compared to the other groups. After power analysis, it was suggested that 50 or more participants would be required. This is an important point that future follow-up studies should address. Second, the time points for evaluation after the intervention were comparatively short. A study design for a long-term setup is necessary for a follow-up trial to investigate durational effects. The current exploratory pilot study focused on short-term effects, as suggested by a previous study in which masticatory movement was shown to activate the primary sensorimotor cortex immediately after the intervention[38]. Future long-term studies should be conducted based on the current study, with a short-term evaluation. Third, many preceding factors related to oral function, such as chewing habits and bruxism, were not considered before conducting the study. These factors need to be explored in future studies to understand the correlation between the factors and the results of the study. Fourth, the participants were limited to healthy young populations. As a pilot study, we tried to investigate if bilateral mastication affects memory and concentration of healthy participants. In the follow-up study, patients with mild cognitive impairment should be included. Fifth, the cross-over design may have caused recall bias for the outcomes because the measurements can be learned by participants. Sixth, two groups of participants could not have been blinded because using the intraoral device and chewing gum are impossible to be blinded. Lastly, the outcomes used in this study were limited to responses to a questionnaire for assessing task performance on cognitive tasks. Additional techniques, such as fMRI and near-infrared spectroscopy, must be used to identify the multidirectional analysis of the effects. Electromyography can also be used to compare bilateral muscular activation around the temporomandibular joint. Despite these limitations, this study is valuable in that it is the first exploratory study to demonstrate the effects of bilateral and unilateral masticatory training.

This pilot study investigated the effects of bilateral chewing training on young, healthy volunteers. The current study is only the beginning of an extensive investigation to verify traditional Korean medicine theory. A wide spectrum of participants, from healthy young people to aged populations or patients with cognitive impairment, which covers hyperfunctioning to hypo-functioning individuals, should be surveyed in the future with a more upgraded method with various measurement tools such as functional magnetic resonance imaging to assess the contribution of bilateral masticatory training with the device.

Conclusion

Bilateral masticatory exercise using an oral apparatus manufactured based on *Gochi*, the traditional Korean medicinal rehabilitative method, is not inferior to unilateral mastication using gum based on its effects on short-term memory in healthy young populations. In addition, it was beneficial for short-term concentration. The bilateral masticatory training conducted in this study was safe and demonstrated no adverse events. Limitations described above should be avoided in the future study. Additional clinical studies involving a broader category of participants, longer period of evaluation, and additional measurement techniques are required to prove the efficacy of bilateral masticatory training.

Data Availability

The data from this study will be distributed when requested from the corresponding author via e-mail.

Conflicts of Interest

This study was funded by Hifeelworld, Inc. However, the funder had no role in the study design, data collection and analysis, or preparation of the manuscript.

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