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Clinical trial for evaluating the effectiveness and safety of a new dental plaque removal device: Microscale mist unit

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Abstract

Objectives: The purpose of this study is to evaluate the effectiveness and safety of a microscale mist unit (MSM-UNIT), a newly developed dental plaque removal device that sprays high-speed fine water droplets, with regard to removal of dental plaque adhering to the oral mucosa (tongue, palate) and tooth surface.

Materials and Methods: Fifteen patients who had difficulty self-managing sufficient oral care were included in this study. Effectiveness was evaluated in at least five patients per tongue, palate mucosa, and tooth surface, and the safety evaluation was conducted at all three sites for all patients. Effectiveness was evaluated using the rate of degree of dental plaque removal, and safety was evaluated using a numerical rating scale (NRS) for pain and symptoms of inflammation. An operator who performs treatment and evaluator who evaluates effectiveness and safety were designated. In addition, as a third party, an image judgment committee judged the effectiveness.

Results: Although the evaluation for the tongue varied between the evaluator and the image judgment committee, after applying the MSM-UNIT, the rate for all degrees of plaque removal increased in all regions. In addition, low pain NRS and symptoms of inflammation were observed and within acceptable range.

Conclusion: The MSM-UNIT can be used effectively and safely for removing oral plaque not only from teeth but also from the oral mucosa.

Clinical Relevance: The MSM-UNIT may be used in whole oral care including for the removal of oral membranous substances in nursing and hospitalized patients.

Trial registration: This study was registered on the Japan Primary Registries Network (JPRN) of University Hospital Medical Information Network Center (UMIN-CTR). The registration number was JPRN-UMIN000035950 (date of first registration: 01/03/2019).

Introduction

Dental plaque causes not only dental caries and periodontal disease but also aspiration pneumonia, endocarditis, and fever [1, 2]. The removal of dental plaque has been reported to help prevent respiratory infections in older adults, who often require a long-term caregiver [3, 4, 5]. It has also been reported to prevent postoperative infection of hospitalized patients, contributing to reduced hospitalization periods [6, 7]. Therefore, dental plaque removal is important for both oral and general health. However, older adults who require long-term nursing care and hospitalized patients often do not have sufficient oral care, and a large amount of plaque is found to adhere to the tooth surface and oral mucosa. In particular, in bedridden older persons without oral intake who are receiving nursing care, oral membranous substances composed of inflammatory cells and bacteria have been frequently observed [8, 9, 10]. These substances attach firmly to the oral mucosa. Plaque can be removed from the tooth surface using a toothbrush or from the oral mucosa with a sponge brush. Because plaque removal with these devices is associated

with a risk of aspiration pneumonia, a special technique is required that is a burden for caregivers. New methods for removing oral plaque have been studied and shown to be effective for removing oral plaque, including a plasma jet [11], ultrasonic activated water [12, 13], and a water jet [14]. However, the application of these devices is limited to the teeth, and there have been no reports investigating the effect of these methods on the oral mucosa. Recently, air abrasion devices have also become available for plaque removal [15–20], and it has been recognized that proper use will not result in harmful effects on the oral mucosa [21]. However, the use of these devices is also limited to the areas around the tooth surface and gums and requires trained skills. Moreover, because they require extraoral suction, they are difficult to use at the bedside. No devices have obtained regulatory approval for removing dental plaque on the whole oral mucosa in Japan.

To overcome the problems of removing plaque film in these patients, we have developed a technology for plaque removal by injecting a small amount of water droplets of average diameter (≤40 μm) that are turned into mist at high pressure (few MPa) and high speed (≥ 100 m/sec), which we have termed the “Microscale Mist Unit” (MSM-UNIT; Fig. 1).

Using high-speed imaging, the plaque removal mechanism of the MSM-UNIT was verified, in which the droplets with a high kinetic state removed the artificial plaque by pushing it aside. No harmful effects occurred because of the extremely low mass of the droplets [22]. In addition, an in vitro study demonstrated that there were no harmful effects on simulated mucosa or tooth surfaces, and the technique had the same effectiveness for plaque removal as air abrasion devices [23]. Our clinical studies (registration number: JPRN-UMIN000026097, date of first registration: 16/02/2017 and registration number: JPRN-UMIN000031232, date of first registration:13/02/2018) using prototype devices confirmed the safety and effectiveness of plaque removal from the palatal mucosa and tooth surface. However, the in vitro study was not a complete nonclinical model, and prior clinical studies have been conducted on only a limited number of patients and conditions. To obtain regulatory approval, additional clinical studies are needed.

Therefore, the purpose of this study is to evaluate the clinical effectiveness and safety of plaque removal using the MSM-UNIT not only on teeth but also on the oral mucosa and to obtain data for regulatory approval.

Methods

Before starting this study, we obtained protocol consultations from the Pharmaceutical and Medical Device Agency (PMDA), a regulatory authority in Japan, and clinical trial notifications. In that consultation, the use of the device is simple, there is almost no influence of the differences in the usage method between medical institutions on the results of effectiveness and safety, and it was considered to not affect the evaluation. In addition, in Japan, there are no devices specified for removing oral plaque on the whole oral mucosa; the procedures used in conventional methods such as toothbrush, tongue scraper, and sponge brush are difficult to standardize because of operator dependence. As such, it is difficult to

set a control group, there is a high possibility that the control group will be biased, and before-and-after treatment comparisons within the same subject are preferable for evaluating the device's effectiveness and safety. Therefore, this study was designed as a single-arm, open-label, single-center, within-subject clinical trial in accordance with consultation of the PMDA.

The protocol of this study was approved by the Tohoku University Hospital Institutional Review Board (reference No. 183004) in accordance with the Declaration of Helsinki. This study was consistent with the Good Clinical Practice (GCP) guideline. In addition, This study was registered on the Japan Primary Registries Network (JPRN) of University Hospital Medical Information Network Center (UMIN-CTR). The registration number was JPRN-UMIN000035950 (date of first registration: 01/03/2019 https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000040945). Inclusion criteria were as follows: (1) patient age greater than 20 years; (2) patient signed/ a written consent form; (3) the case was evaluated for effectiveness on the tooth surface, with the presence of at least five remaining teeth in one jaw and at least 10 remaining teeth in both jaws, except for the third molar; (4) and the patient was judged to have significant plaque on the tongue, palatal mucosa, tooth surface, or at least two sites.

The exclusion criteria of patients were as follows: (1) the case was evaluated for efficacy on tooth the surface and for the presence of malocclusion; (2) extensive tooth restoration was required during the study period; (3) presence of at least 6-mm probing pocket depth and bleeding on probing periodontitis in more than half of the teeth; (4) presence of grade 3 Miller classification of tooth mobility; (5) presence of moderate hypersensitivity; (6) presence of malignant tumor, leukoplakia, lichen planus, oral candida, tongue pain, or other diseases judged by the dentist as affecting the evaluation; (7) presence of acute inflammation; (8) the patient was unable to stop taking analgesic drugs from 24 hours before the start of the evaluation; (9) participation in another clinical trial; (10) presence of a severe vomiting reflex; and (11) history of aspiration pneumonia.

Fifteen patients were included in this study. The effectiveness was evaluated in at least five patients per tongue, palate mucosa, and tooth surface, although two or more sites could be evaluated in one patient. The safety evaluation was conducted at all three sites for all patients. The number of patients was the minimum size needed for obtaining regulatory approval.

Treatment Protocol

Application of the MSM-UNIT

Spray conditions were set with a water flow rate of 10 mL/min and an air pressure of 0.2 MPa, respectively. The tip of the handpiece was positioned at least 6 mm above the target and moved for 60 seconds so that it did not spray a single site for more than 2 seconds.

To eliminate biases during the evaluation period as much as possible in this clinical trial, we designated an operator who performed treatment using the MSM-UNIT and an evaluator who evaluated effectiveness and safety. The operator and evaluator were different people and did not change their role during the

clinical trial period. Although the operator sprayed all parts of the tongue, palate, and tooth surface, only areas rated for a plaque adhesion degree of more than “high” were included for evaluation of effectiveness. Domains that were not evaluated for effectiveness were treated for safety evaluation. The degree of plaque adhesion was judged as “very high” (3), “high” (2), “low” (1), and “none” (0) with reference to the judgment sample (Fig. 2).

Figure 3 presents a chart of the treatment flow. The treatment was conducted in sequence of the tongue, palate, and tooth surface. The treatment was stopped at the point at which the degree of plaque adhesion was rated as “none” (0) or < 20% of O’Leary’s plaque control record (PCR) [24, 25] within 60 seconds. The treatment was performed up to three times until the degree of adhesion was rated as “none” (0) or < 20% of the PCR (the total treatment time was as long as 180 seconds). Safety evaluation domains were treated for 60 seconds. Palate and teeth were stained before treatment using Plaque Check Gel BR (GC). The safety assessment was conducted 1 day after (day 1) and 1 week after (day 7) the treatment.

Analysis

Analysis of effectiveness evaluation

The evaluators judged the scores by comparing sample photographs. In addition, a member of the image judgment committee evaluated whether the evaluator’s judgment was appropriate. Members of the committee had no conflict of interest in this trial.

Multiple primary endpoints were set in the study. Because a single endpoint could not provide an overall treatment effect, this trial was characterized by assessing treatment effects over multiple dimensions.

1. Plaque removal rate by O’Leary’s PCR (teeth)

We calculated the summary statistics of the PCR and the rate of changes before and after removal (number of instances, mean, 95% confidence interval for mean, standard deviation).

2. Rate for degree of plaque removal (palate and tongue)

We calculated the percentage of plaque adherence degree for “low” (1) or less (“low” [1] or “none” [0]) and 95% confidence interval of the percentage.

3. Plaque removal rate by binarization

We analyzed images of the teeth and palate that had “high” (2) or higher plaque adhesion at the time of eligibility confirmation. The validity of the cleaning rate was preanalyzed by the image judgment committee using Adobe Photoshop CC. Fixed teeth were excluded from the analysis because they are difficult to binarize. The region of interest (ROI) was set for natural teeth, which can be confirmed for front, left-side, and right-side views. The ROI area (pixel value), plaque adherence area (pixel value), and cleanup rate were set after calibration. Summary statistics of the removal rate and calibrated removal

rate for the plaque adherence area were calculated (number of instances, mean, 95% confidence interval for mean, standard deviation).

4. Plaque removal time (teeth, palate, and tongue)

Summary statistics were computed for the time taken to remove all plaque from the tongue and palate and PCRs less than 20% on tooth surface.

5. Subject satisfaction with MSM-UNIT treatment

To compare the MSM-UNIT with other treatment methods, we administered a questionnaire survey to the subjects regarding their satisfaction with both treatment and comfort, which they rated according to five grades (“strongly dissatisfied,” “somewhat dissatisfied,” “average,” “somewhat satisfied,” and “strongly” satisfied).

Safety assessment

The summary statistics of spontaneous pain of the teeth, gums, palate, and tongue of the numerical rating scale (NRS) were calculated. A frequency aggregation of the changes in the gingival index (GI) and inflammation symptoms was also performed. Adverse events were recorded with the device.

Results

This study was conducted from March 2019 to August 2019. Written informed consent was obtained from all 17 patients, and 15 patients were enrolled. An evaluation of effectiveness was performed for seven patients on the tooth surface (mean age 65.7 ± 7.9 years), six patients on the palate (mean age 72.0 ± 6.4 years), and 12 patients on the tongue (mean age 62.3 ± 12.1 years; see Table 1 and Fig. 4).

Table 1
Patient data

	Teeth	Palate	Tongue
Number of patients	6	5	12
Male (n)	3	0	6
Female (n)	3	5	6
Mean age (years)	65.7	72.0	62.3

Effectiveness

Figures 5 and 6 show examples of the application of the MSM-UNIT.

1. Plaque removal rate by O’Leary’s PCR

The mean PCR before treatment with the MSM-UNIT was 72.3% (48.45 − 96.15%), whereas after treatment it was 4.08% (− 3.07–11.14%). The mean removal rate of PCR was 68.22% (48.07 − 88.36%; Table 2).

Table 2
Plaque removal rate by PCR (%)

	Before treatment	After treatment	Amount of change
n	6	6	6
Mean (95% confidence interval)	72.30 (48.45–96.15)	4.08 (− 3.07 to 11.24)	68.22 (48.07–88.36)
Standard deviation	22.72	6.82	19.20

2. Rate of degree of plaque removal (palate and tongue)

The removal rate of the palate plaque with an adherence degree of “1 or less” (“none” [0] or “low” [1]) after treatment was 100.0% (47.8 − 100.0%) at any evaluation time. However, the rate for tongue plaque with an adherence degree of “1 or less” after treatment was 41.7% (15.2 − 72.3%). This changed to 25.0% at 1 day after treatment and 33.3% at 1 week after treatment (Tables 3 and 4).

Table 3
, Evaluation of the degree of palate plaque adherence

	None 0	Low 1	High 2	Very High 3	Low or none	95% confidence interval
Before treatment	0	0	4	1	0.0% (0/5)	0.0–52.2%
After treatment	3	2	0	0	100.0% (5/5)	47.8–100.0%

Table 4
Evaluation of the degree of tongue plaque adherence

	None 0	Low 1	High 2	Very High 3	Low or none	95% confidence interval
Before treatment	0	0	6	6	0.0% (0/12)	0.0–26.5%
After treatment	0	5	7	0	41.7% (5/12)	15.2–72.3%

The evaluation of the degree of plaque adhesion on the palate was consistent between both the evaluators and image evaluation committee. However, the committee evaluated the degree of tongue plaque adhesion to be higher than the evaluators did.

3. Plaque removal rate by binarization

The removal rate of binarization was 80.47% for the tooth surface and 96.3% for the palate (Table 5).

Table 5
Plaque removal rate by binarization (teeth and palate)

	Teeth	Palate
n	6	5
Mean (95% confidence interval)	80.47 (68.28–92.65)	96.38 (92.23–100.53)
Standard deviation	11.61	3.34

4. Plaque removal time (teeth, palate, and tongue)

The plaque removal times for the surface of the tooth, palate, and tongue were 163.3 ± 26.8 seconds, 58.2 ± 30.3 seconds, and 65.0 ± 51.2 seconds, respectively (Table 6).

Table 6
Plaque removal time (teeth, palate, and tongue)

	Teeth	Palate	Tongue
n	6	5	12
Mean ± standard deviation (seconds)	163.3 ± 26.8	58.2 ± 30.3	65.0 ± 51.2

5. Questionnaire survey for MSM-UNIT treatment

Of the patients, 80% reported on the survey that they were “satisfied” or “slightly satisfied.” In addition, 93.3% of patients provided a rating higher than “average.”

Safety evaluation

Four patients experienced spontaneous pain in the teeth and gingiva on day 0 (after the final injection), with a mean spontaneous pain NRS score of 0.3 ± 0.5 (maximum value: 1). Two patients experienced spontaneous pain on day 1, with a mean score of 0.1 ± 0.4 (maximum value: 1). In contrast, one patient had spontaneous pain in the palate on day 0, with a mean score of 0.1 ± 0.5 (maximum value: 2). One patient also had spontaneous pain in the tongue on day 0, with a mean score 0.1 ± 0.3 (maximum value: 1). The day after treatment, two patients experienced spontaneous pain in the tooth and gums, with a mean of 0.1 ± 0.4 (Table 7).

Table 7
Spontaneous pain as rated on the NRS

		Teeth/gum	Palate	Tongue
Before treatment	Mean ± standard deviation (n)	0.0 ± 0.0 (15)	0.0 ± 0.0 (15)	0.0 ± 0.0 (15)
	min, median, max	0, 0.0, 0	0, 0.0, 0	0, 0.0, 0
After treatment	Mean ± standard deviation (n)	0.3 ± 0.5 (15)	0.1 ± 0.5 (15)	0.0 ± 0.0 (15)
	min, median, max	0, 0.0, 1	0, 0.0, 2	0, 0.0, 0
Day 1	Mean ± standard deviation (n)	0.1 ± 0.4 (15)	0.0 ± 0.0 (15)	0.1 ± 0.3 (15)
	min, median, max	0, 0.0, 1	0, 0.0, 0	0, 0.0, 1
Day 7	Mean ± standard deviation (n)	0.0 ± 0.0 (15)	0.0 ± 0.0 (15)	0.0 ± 0.0 (15)
	min, median, max	0, 0.0, 0	0, 0.0, 0	0, 0.0, 0

An increase in GI score was observed in two patients on day 0 after treatment. In addition, two patients experienced an adverse event of palate bleeding on day 0 after treatment. There were no adverse events on days 1 or 7.

Discussion

In this clinical trial, the MSM-UNIT demonstrated sufficient effectiveness and safety for plaque removal, not only from the tooth surface but also the oral mucosa.

Because O'Leary's PCR is widely used in Japan, we investigated the effectiveness of the MSM-UNIT on the teeth in terms of plaque reduction rate. Kinoshita et al. reported that gingival health could be maintained when O'Leary's PCR was 20% or less, which is a guideline for oral hygiene evaluation [22]. In all subjects, we observed that the PCR was less than 20% within 3 minutes of using the MSM-UNIT. Our experimental results matched those of our previous clinical studies and nonclinical evaluations [23] and fully demonstrated the expected performance. With regard to the conventional method of cleaning teeth using a toothbrush, Conn et al. reported that O'Leary's PCR removal rate for a dental hygienist student was about 30% [26]. Furthermore, Yonenaga et al. showed that the removal rate of PCR after 3 minutes using a wet sheet was 10% and 8% using a sponge brush [27]. Nobre et al. showed that an electric toothbrush can remove 50.24% of plaque in older adults [28]. Therefore, because the removal rate of PCR by the MSM-UNIT was 68.22%, the MSM-UNIT can be considered to be more effective than conventional methods.

There have been many reports on the effectiveness of oral cleaning devices for plaque removal. However, the evaluation methods are literature specific, and there is no consensus in particular on dental plaque on the oral mucosa. There are currently no medical devices intended for plaque removal on the oral mucosa, such as the palate and tongue. Therefore, this study did not have a control group, and we used a new

evaluation method incorporating visual effectiveness. Removal of plaque from the oral mucosa is important for both patients in nursing homes and hospitalized patients. Yonezawa et al. reported that the use of a sponge brush for oral plaque removal on the oral mucosa decreased the amount of *Candida albicans* [29]. Yadav et al. showed that the number of bacteria on the oral mucosa was reduced by gargling chlorhexidine [30]. Tashiro et al. also reported that bacteria in the pharynx were reduced by wiping the oral mucous with a sponge brush soaked in chlorhexidine [31]. Furthermore, Nishiyama et al. showed that professional care for 20 minutes once per week, including mucosa and tongue cleaning, reduces the amount of mutans streptocci and *Candida* species [32]. In this study, the percentage of patients who had a degree of plaque adherence of “1 or less” (“none” [0] or “low” [1]) on the palate after treatment was 100.0% at any time during the evaluation, and the removal rate of binarization was 96.3% at the palate. The judgment of both the evaluator and the image evaluation committee were almost the same. Therefore, the evaluation method was reliable and suggested that the MSM-UNIT was useful and effective for removing plaque from the palate.

In contrast, the results of the effectiveness for the tongue did not match the expected performance. There was a discrepancy in the ratings between the evaluators and the image evaluation committee, in which the committee rated the degree of linguistic plaque adhesion higher than the evaluators did. In many cases, in order to avoid a vomiting reflex, the operator did not spray near the base of tongue. The evaluators evaluated only the area where the mist was sprayed, whereas the image evaluation committee evaluated the whole area of the tongue. This difference in evaluation area was considered to cause the discrepancy in results, indicating that the evaluation method needed to be specified in more detail. It is known that in conventional methods that apply tools for the mechanical removal of plaque, removing the tongue coating is associated not only with reduced inflammation but also reduction of bad breath [33, 34, 35]. Some studies have shown that chlorhexidine is useful for reducing bacteria on the oral mucosa [29, 36, 37]. In addition, a previous study reported that plaque removal from the tongue is effective for those on a ventilator and reduces the burden on caregivers [38]. Because the evaluation methods used for plaque removal from the tongue are also literature specific, it was judged visually in this study, similar to other studies. The evaluation method in this study was also considered to be more reliable, as it included not only the evaluator but also the image evaluation committee as a third party. The results from the sprayed areas on the tongue suggested that the method is effective for plaque removal. In their report, Berbe et al. also found that the total oral care time for nursing home residents was 37 minutes, in which cleaning alone took 7.4 minutes and oral care including the mucosa and tongue took 20 minutes [39]. Because the MSM-UNIT requires a shorter time to remove plaque, it is considered not only to be effective for patients at home but also for reducing the burden on operators.

Although five adverse events were observed, these were grade 1 events with no treatment required. The most frequent adverse event was gingivitis (13.3%). Because the area of gingivitis was limited, it was evaluated as “unrelated” to the MSM-UNIT. Occurrences of gingival pain (6.7%), tongue bleeding (6.7%), and oral bleeding (6.7%) were evaluated as “related” to the MSM-UNIT; however, these adverse events were transient and resulted in no clinical problems.

In addition, the results were considered to be within a sufficiently acceptable range compared with the adverse events of chlorhexidine, which includes allergies, soreness, irritation, mild desquamation, and mucosal ulceration/erosions [40]. Therefore, the risk of using the device was considered to be less than that associated with conventional oral care. Because there were no symptoms the next day or 1 week later, it is considered that the treatment with the MSM-UNIT could be safely performed on the palate and tongue once a week.

Conclusion

The results of this study showed that the MSM-UNIT device can be used to effectively and safely remove plaque on the tooth surface and oral mucosa (palate). With regard to the tongue, despite the discrepancy between the judgments of the evaluator and image judgment committee, the device was considered to be effective because of the overall reduction in plaque. Therefore, the MSM-UNIT can be used in whole oral care to effectively and safely remove plaque.

Ethics declarations

Declarations

Acknowledgments

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Conflict of interest

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Ethical approval

This study was approved by the Tohoku University Hospital Institutional Review Board (reference No. 183004) in accordance with the Declaration of Helsinki. This study was consistent with the Good Clinical

Practice (GCP) guideline. In addition, this study was registered on the Japan Primary Registries Network (JPRN) of University Hospital Medical Information Network Center (UMIN-CTR). The registration number was JPRN-UMIN000035950 (date of first registration: 01/03/2019).

Informed consent

Written informed consent was obtained from all patients for participation in this study and for publication of identifying information/images.

Availability of Data and Materials

The data that support the findings of this study are available from J. MORITA MFG. CORP and AMED but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of J. MORITA MFG. CORP and AMED.

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Figures

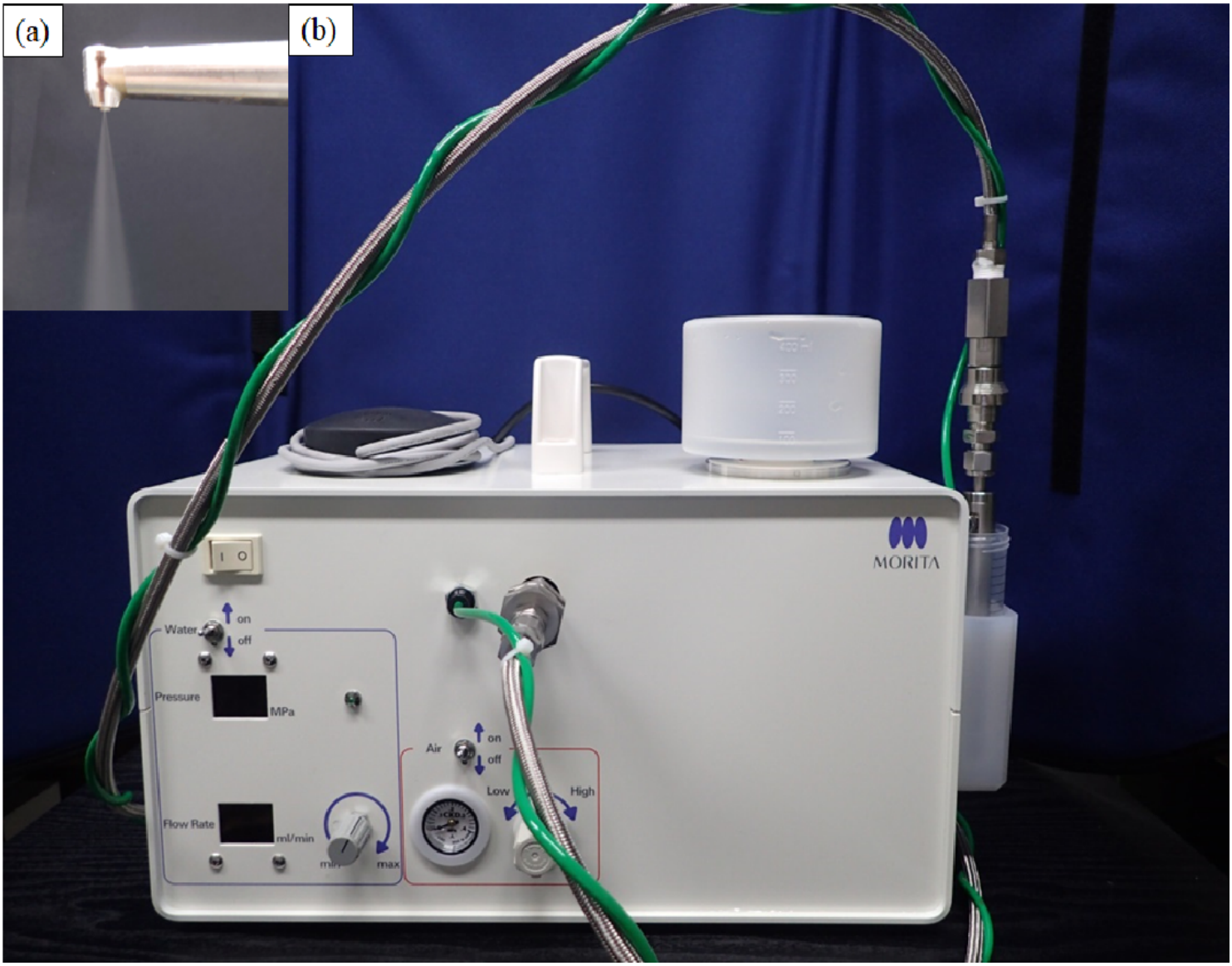

Figure 1

Photographic images of the MSM-UNIT spraying with a handpiece (a) and the main body.

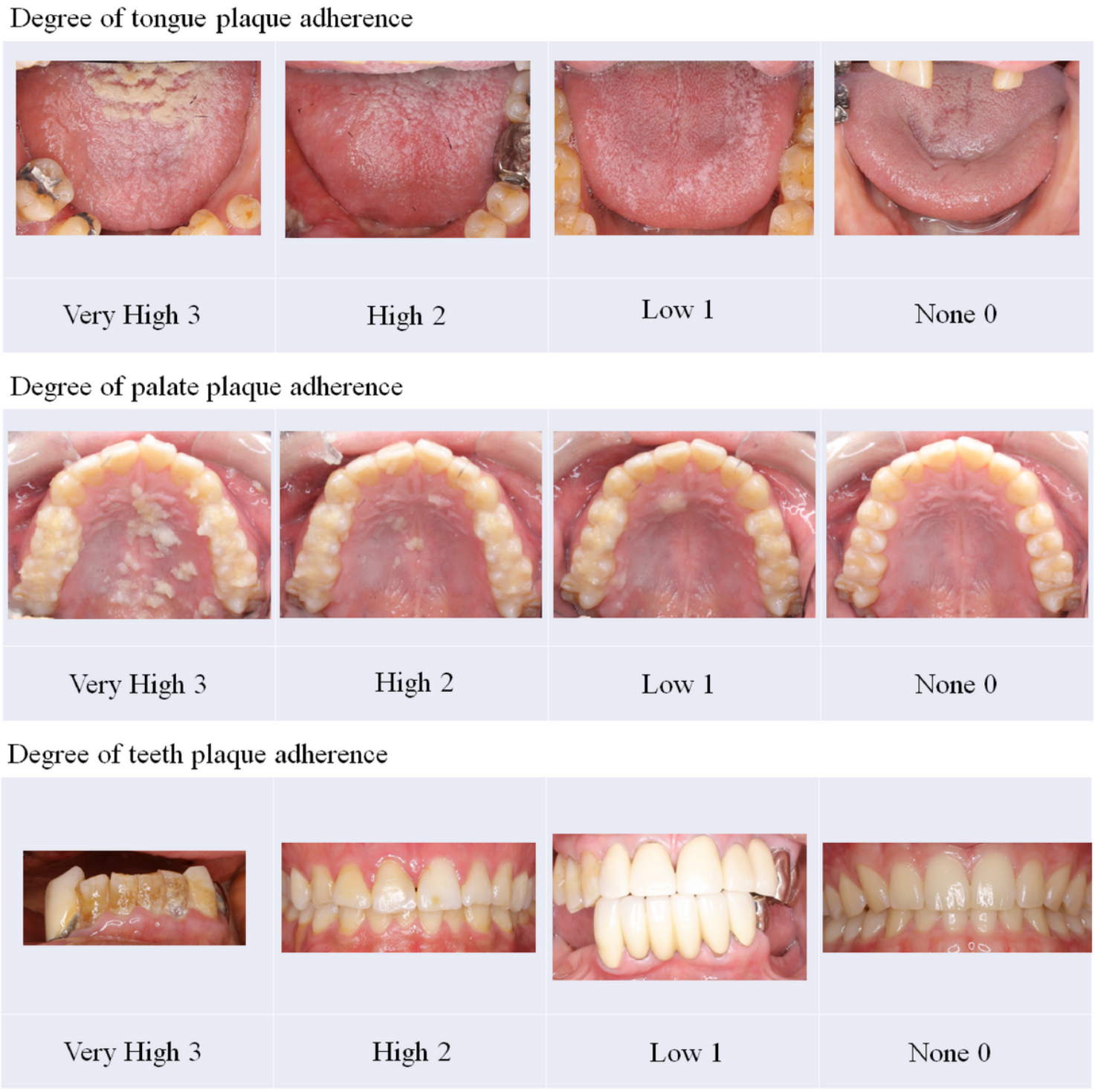

Figure 2

Judgment sample of the degree of plaque adhesion. Each area was evaluated as one of four grades: “very high” (3), “high” (2), “low” (1), and “none” (0).

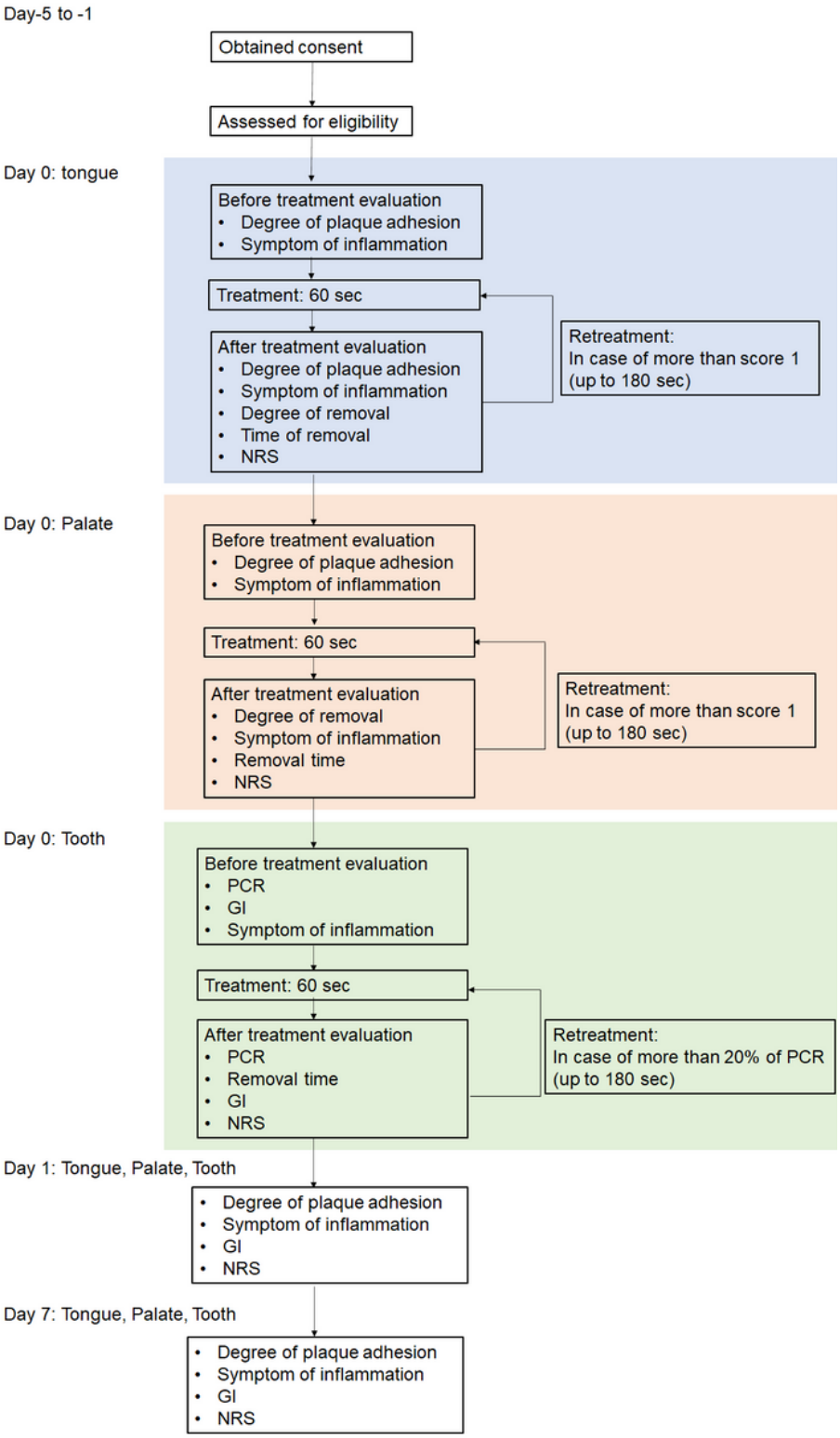

Figure 3

Chart of the treatment flow.

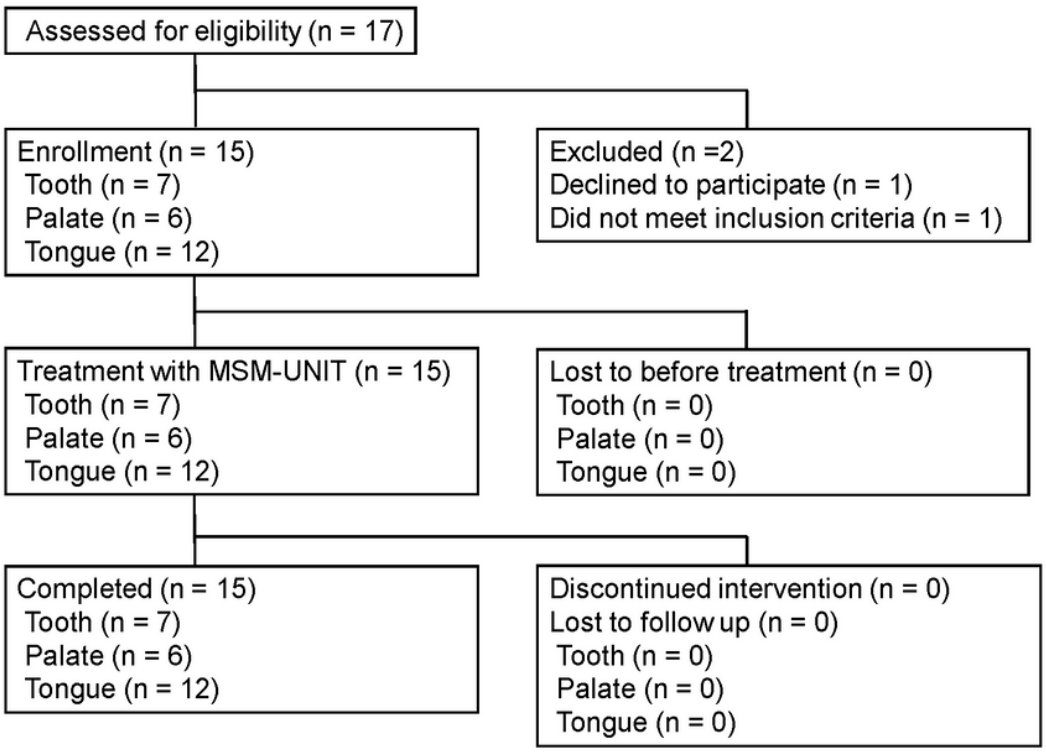

Figure 4

Flow chart of the study subjects.

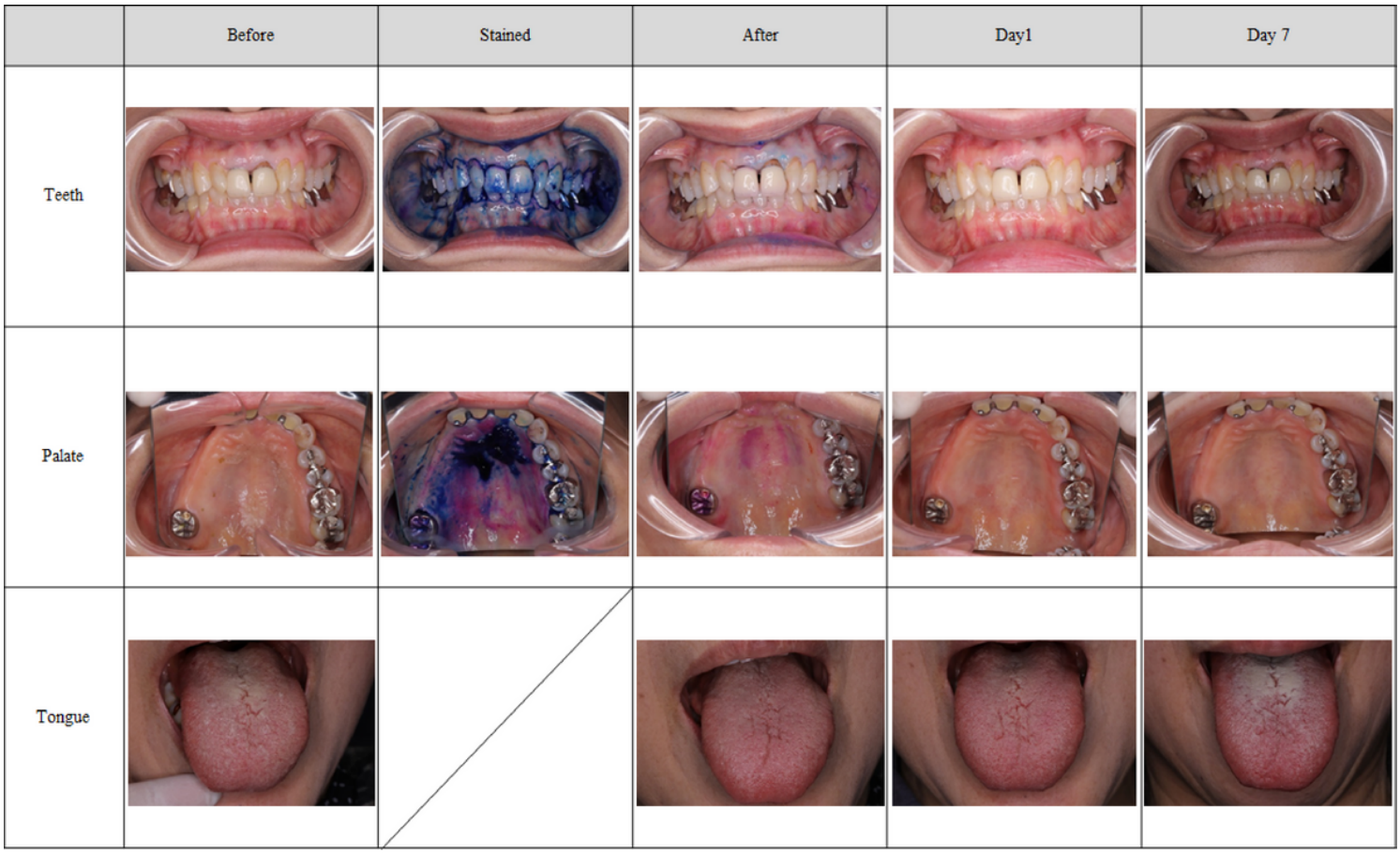

Figure 5

Teeth, palate, and tongue application results of the MSM-UNIT. Before treatment, stained, after treatment, day 1 and day 7 are shown.

Figure 6

Teeth and palate photographs before and after the binarization.