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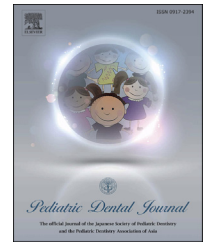

Research Paper

Effects of inhalation sedation with nitrous oxide on intraoral senses

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ABSTRACT

Objective: The dental treatment such as local anesthetic injections are a common source of anxiety and fear during dental procedures. One of the causes of these anxiety and fear are regarded as taste and tactile sensory input. The purpose of this study was to investigate the effects of inhalation sedation with nitrous oxide (IS–N_2O) on intraoral taste and tactile sensory input in human.

Materials and methods: We performed taste testing using electrogustometry and the filter paper disc test in the proglossis region, and precise tactile function testing using the Semmes-Weinstein monofilaments (SWM) test was performed on the mandibular incisor interdental gingival papilla of healthy male and female volunteers.

Results: On electrogustometry, the 50% IS-N_2O threshold was significantly higher than those of other conditions (vs. room air [RA], 100% O_2, Recovery, vs. 30% IS-N_2O). In the filter paper disc test, the 30%/50% IS-N_2O thresholds were significantly higher than those of other conditions (vs. RA, 100% O_2, Recovery) for all tastes. However, no significant difference in the recognition threshold was noted between 30% IS-N_2O and 50% IS-N_2O. In the SWM test, the 30%/50% IS-N_2O thresholds were significantly higher than those of other conditions (vs. RA, 100% O_2, Recovery), but the 50% IS-N_2O threshold was higher than the 30% IS-N_2O threshold.

Conclusion: IS-N_2O inhibit the input of taste and tactile sensations and may be an effective tool for patients undergoing dental procedures.

1. Introduction

Inhalation sedation using nitrous oxide (IS–N_2O) reduces a patient's psychological stress and fear and is utilized at many medical facilities. As IS-N_2O has an analgesic effect, it is used during painful procedures such as securing intravenous access in pediatric medicine [1]. In Japan, IS-N_2O is widely used at concentrations of 30% or below in clinical dentistry [2]. Because it is effective for reducing a patient's psychological

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burden, including anxiety, fear, and nervousness regarding dental treatment, while also inducing amnesia [3], IS-N_2O use is considered a psychosedation technique that can be effective for preventing the onset of dental fear. IS-N_2O is particularly useful in the fields of pediatric dentistry [4,5] and special care dentistry and is used in a wide range of settings, including for pain relief during restorative treatments performed on children [6], in combination with behavioral therapy for intellectually impaired patients [7], and to relieve stress in patients with cerebral palsy [8]. For children, IS-N_2O is a safe technique with no differences in adverse events by concentration [9].

IS-N_2O is also considered an effective behavioral adjustment method for patients with autistic spectrum disorder [10]. In fact, when individuals with abnormal sensory processing, such as autistic spectrum disorder patients, undergo dental treatment, they may reject the treatment as a result of various sensory inputs, such as visual, auditory, tactile, olfactory, or taste sensations [11]. Such sensory input is experienced as unpleasant sensations that enhance patients' anxiety and fear, thereby impeding their acceptance of dental treatment [12]. Our previous study demonstrated that such abnormal sensory processing correlates with strong dental fear [13]. Dental fear is a psychological response inducing aversion following a dental ill-defined stimulus such as intraoral tactile and taste sensations [14,15]. If IS-N_2O is used to modify such sensory input, this adjustment technique may be useful to reduce dental fear and increase the acceptance of dental care.

Very few reports are available regarding IS-N_2O effects on intraoral tactile and taste sensations, which are considered risk factors for the development of dental fear. Therefore, this study investigated the influence of IS-N_2O on intraoral tactile and taste sensory input thresholds in healthy volunteers using electrogustometry and filter paper disc tests for taste testing and using the Semmes-Weinstein monofilaments (SWM) test for tactile testing.

2. Materials and methods

2.1. *Subjects*

Subjects were informed of the study's outline, purpose, and methods both orally and in writing. Of the healthy male and female volunteers who provided consent, this study analyzed 51 subjects after excluding patients with contraindications to N_2O, including a closed cavity within the body (stenosis of the eustachian tube, pneumothorax, pneumocephalus, intestinal obstruction, recent pacemaker insertion, recent vitreoretinal surgery), patients in the first trimester of pregnancy, and patients with nasal obstruction. Smokers and individuals who regularly took medications that cause taste impairment as a side effect were also excluded [16–18].

2.2. *Study environment*

The study was conducted in an examination room with constant temperature (25 °C) and humidity (55%). The subjects fasted for 2 h before the experiments, assumed a horizontal dorsal position on a dental unit in the examination room, and were fitted with an arm cuff sphygmomanometer/pulse oximeter (Bedside Monitor, DS7000 System: Fukuda Denshi, Tokyo, Japan). N_2O inhalation was performed using an N_2O inhaler (Psychorich T-70®: SEKIMURA, Tokyo, Japan). N_2O inhalation concentrations were measured by a gas sampling tube fit to a nasal mask. Sealing of the nasal mask was confirmed based on capnogram waveforms to ensure a stable supply of N_2O. The total flow during measurement was set at 10 L/min, and the experiment was started after ensuring that the reservoir bag had sufficiently filled up.

2.3. *Study protocol*

During the experiment, noninvasive blood pressure (NBP), percutaneous arterial blood oxygen saturation (SpO_2), and the pulse rate (PR) were periodically measured in addition to using gas sampling to measure the respiratory rate (RR), inspired O_2 concentration, inspired N_2O concentration, and end-tidal CO_2 concentration. Taste testing was also performed by means of electrogustometry and the filter paper disc technique together with precise tactile function, and the thresholds for each were examined (Fig. 1). Measurements were repeated at following five time points: at 5 min of inhalation of room air (RA) and 100% O_2 inhalation (100% O_2) and at 10 min of 30%/50% N_2O inhalation (30/50% IS-N_2O) and 100% O_2 inhalation after IS-N_2O (Recovery). This protocol were referred to the preceding study that comfortable clinical onset of IS-N_2O needed 10 min at 30% nitrous oxide [19]. This study did not blind the participants. One examiner performed the assessments.

2.3.1. *Electrogustometry*

Electrogustometry was performed using a device (TR-06: RION, Tokyo, Japan) [20] and a reaction in the proglossis region. We chose this region because sensitivity is higher in this site than in the posterior lingual region and soft palate region. Using direct current, a probe (anode) with a 5-mm diameter was inserted into the site, and electric current was applied. The reference electrode was attached to the neck of the subject. After exposing the subject to an electric taste with electrical conduction of approximately 25–80 μA, stimulation was started at 0 μA and gradually increased to 80 μA. The stimulation time was 0.5–1.0 s, and the interval between stimulations was at least 3 s. If the subject felt some sort of taste or stimulation at the stimulated site, he or she pressed the response button in his or her hand, and the electrical current (μA) was recorded to evaluate changes in recognition thresholds. This test was repeated five times at intervals of several seconds, and the results were averaged after excluding the maximum and minimum values.

2.3.2. *Filter paper disc taste testing*

Taste testing with filter paper discs used to diagnose taste disorders was performed using quantitative taste-testing reagents (Taste Disc®: Sanwa Kagaku Kenkyusho, Aichi, Japan) [20]. Round filter paper discs with a diameter of 5 mm were soaked in liquids with five concentrations (sucrose (sweetness), table salt (saltiness), tartaric acid (sourness), and quinine (bitterness)). Subjects were instructed to poke their tongues out with their mouths closed, and a disc was placed on the tip of the tongue with tweezers. Testing was performed

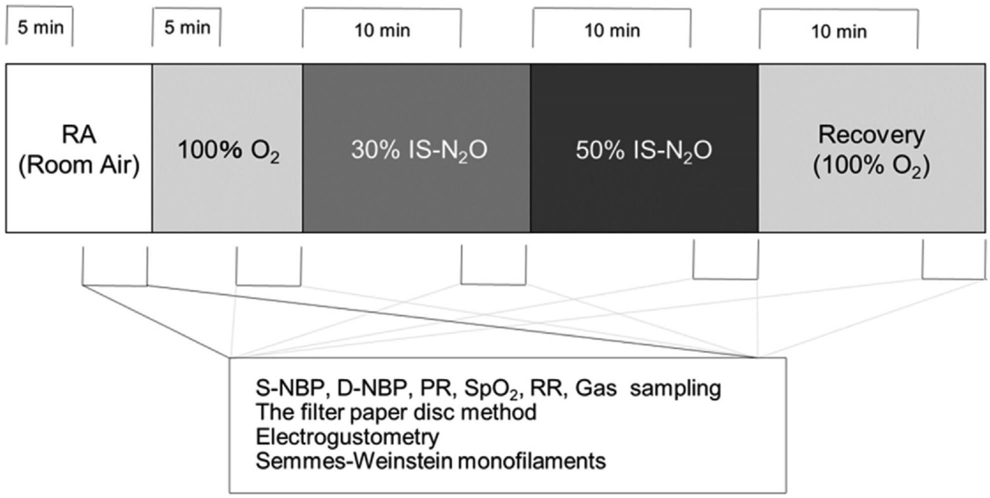

Fig. 1 – Experimental protocol. RA: room air; 100% O_2: 100% O_2 inhalation; 30% IS-N_2O: 30% N_2O inhalation; 50% IS-N_2O: 50% N_2O inhalation; Recovery: 100% O_2 inhalation after IS-N_2O; S-NBP: systolic noninvasive blood pressure; D-NBP: diastolic noninvasive blood pressure; PR: pulse rate; SpO_2: percutaneous arterial blood oxygen saturation; RR: respiratory rate.

starting at the lowest concentration and then gradually increasing concentrations. Subjects were instructed to report the lowest concentration at which they could correctly distinguish sweetness, saltiness, sourness, and bitterness (recognition threshold) using a taste instruction chart to maintain a fixed sedation degree. We removed the disc if the correct answer was not obtained within 10 s and switched to a higher concentration. This process was repeated in the order of sweetness, saltiness, sourness, and bitterness equally to determine the recognition thresholds.

2.3.3. *Tactile testing*

Precise tactile function testing was performed using the SWM test (SOT-DM20A: SAKAI Medical, Tokyo, Japan). The measurement site selected was the mandibular incisor interdental gingival papilla. The test was conducted according to the Enforcement guideline for the examination of exact sense of touch function [21]. The highest stimulation level of this study was set at 2.0 g. This test was repeated five times at intervals of several seconds, and the results were averaged after excluding the maximum and minimum values.

2.4. *Statistical analysis*

The NBP, PR, SpO_2, RR, inspired O_2 concentration, inspired N_2O concentration, and end-tidal CO_2 concentration are expressed as the means ± standard deviations (SDs). Recognition threshold data from electrogustometry and the filter paper disc method and the SWM test are expressed as the mean ± SDs. One-way analysis of variance was used to assess biological data and recognition threshold data from electrogustometry and the SWM test under each condition. Multiple comparisons using the Tukey test were performed only when the one-way analysis of variance results were meaningful. Bidirectional analysis with Friedman ranked variables using paired samples was used to assess the recognition threshold data from the filter paper disc method under each condition. Bonferroni correction was performed as the post hoc test. A P value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

3.1. *Subjects*

Fifty-one volunteers (28 males, 23 females) consented to participate in this study (Table 1). No adverse events related to IS-N_2O such as nausea and vomiting, headache, and dizziness were noted (data not shown). Moreover, no significant changes were observed in NBP, PR, SpO_2, and RR values. During the experiment period, the concentration of N_2O was maintained at an appropriate level (Table 2). The gender differences were not recognized in this study (data not shown).

3.2. *Taste testing*

3.2.1. *Electrogustometry*

Significant increases in recognition thresholds were observed with 50% IS-N_2O compared to RA, 100% O_2, and Recovery ($P < 0.01$). A significant increase in the recognition threshold was also noted with 50% IS-N_2O compared to 30% IS-N_2O ($P < 0.05$). Values returned to those observed for RA, 100% O_2, or Recovery following 10 min of 100% O_2 inhalation after IS-N_2O termination (Fig. 2). The gender differences were not recognized in this study (data not shown).

Table 1 – Descriptive data for the study.

Variables	n = 51 (Males: 28, Females: 23)
Age (year)	25.7 ± 3.5
Height (cm)	165.5 ± 8.6
Weight (kg)	59.5 ± 11.6

All values are the means ± SD.

Table 2 – The averages of the biological information and measured values under each condition.

	RA	100% O_2	30%IS-N_2O	50%IS-N_2O	Recovery
S-NBP (mmHg)	123 ± 13	124 ± 14	120 ± 19	121 ± 13	122 ± 23
D-NBP (mmHg)	71 ± 9	72 ± 9	70 ± 8	71 ± 8	73 ± 9
PR (beats/min)	70 ± 12	67 ± 11	65 ± 10	65 ± 10	64 ± 8
SpO_2 (%)	99 ± 1	100 ± 0	100 ± 0	100 ± 0	100 ± 0
RR (rate/min)	13 ± 2	13 ± 3	12 ± 3	12 ± 3	13 ± 2
Et CO_2 (mmHg)	41 ± 4	35 ± 4	34 ± 4	34 ± 4	33 ± 4
In O_2 (%)	21 ± 1	97 ± 2	68 ± 6	48 ± 4	98 ± 2
In N_2O (%)	0	0	30 ± 1	50 ± 2	0

All values are the means ± SD.
RA: room air.
100% O_2: 100% O_2 inhalation.
30% IS-N_2O: 30% N_2O inhalation.
50% IS-N_2O: 50% N_2O inhalation.
Recovery: 100% O_2 inhalation after IS-N_2O.
S-NBP: systolic noninvasive blood pressure.
D-NBP: diastolic noninvasive blood pressure.
PR: pulse rate.
SpO_2: percutaneous arterial blood oxygen saturation.
RR: respiratory rate.
Et CO_2: end-tidal CO_2.
In O_2: inspired O_2 concentration.
In N_2O: inspired N_2O concentration.

3.2.2. *Taste testing with the filter paper disc test*

For sweetness, saltiness, sourness, and bitterness, significant increases in recognition thresholds were noted with 30%/50% IS-N_2O compared to RA, 100% O_2, and Recovery ($P < 0.05$/$P < 0.01$). However, no significant difference in the recognition threshold was noted between 30% IS-N_2O and 50% IS-N_2O. Values returned to those observed with RA, 100% O_2, or Recovery following 10 min of 100% O_2 after IS-N_2O termination (Fig. 3). The gender differences were not recognized in this study (data not shown).

3.3. *Tactile testing*

Significant increases in recognition thresholds were observed with 30%/50% IS-N_2O compared to RA, 100% O_2, and Recovery ($P < 0.01$). A significant increase in the recognition threshold was also noted with 50% IS-N_2O compared to 30% IS-N_2O ($P < 0.01$). Values returned to those observed with RA, 100% O_2, or Recovery after IS-N_2O discontinuation (Fig. 4). The gender differences were not recognized in this study (data not shown).

4. Discussion

In this study, to evaluate the effects of IS-N_2O on intraoral sensations of taste and tactile perception, we performed taste testing using electrogustometry and the filter paper disc test in the proglossis region and precise tactile function testing using the SWM test was performed on the mandibular incisor interdental gingival papilla. The results revealed that recognition thresholds on electrogustometry, the filter paper disc test, and the SWM test significantly increased with inhalation of N_2O. Based upon these findings, IS-N_2O increases the threshold of intraoral sensations that may participate in the development of dental fear.

The sense of taste is managed by information from subsystems through unified taste buds, which is controlled by an intricate nerve network. Accordingly, as the influence of taste sensations in the central nervous system is speculated

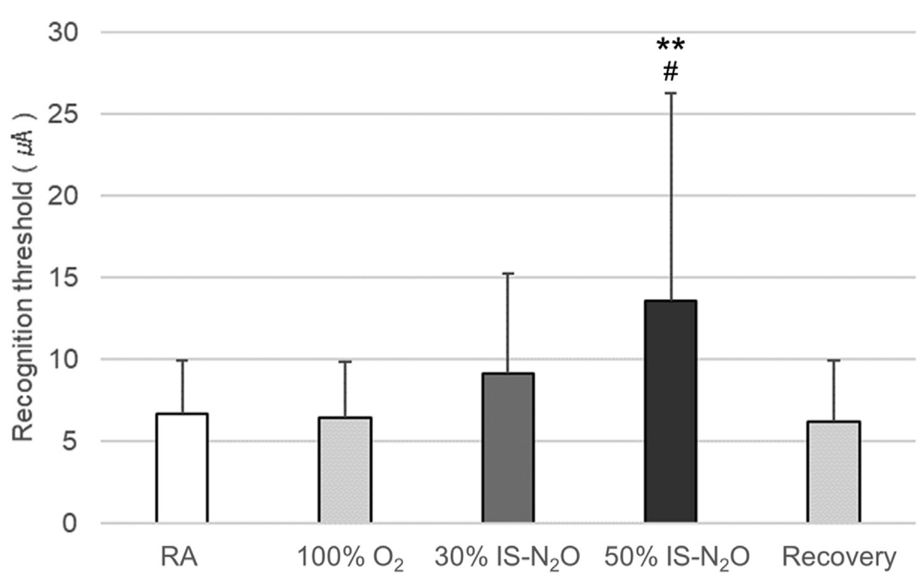

Fig. 2 – Electrogustometry thresholds with nitrous oxide. All values are the means ± SD. (n = 51); RA: room air; 100% O_2: 100% O_2 inhalation; 30% IS-N_2O: 30% N_2O inhalation; 50% IS-N_2O: 50% N_2O inhalation; Recovery: 100% O_2 inhalation after IS-N_2O; * vs. RA, 100% O_2, Recovery (<0.01); # vs. 30% IS-N_2O (# <0.05); No significant difference between RA and 100% O_2, Recovery periods.**

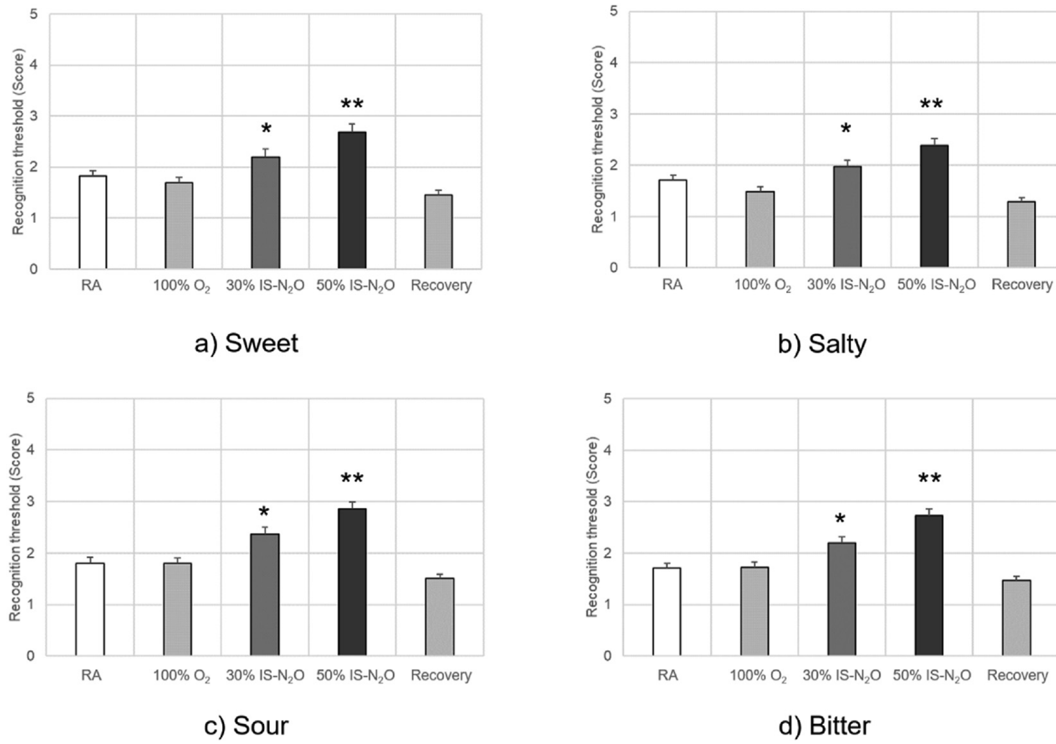

Fig. 3 – Thresholds of the filter paper disc method with nitrous oxide. All values are the means ± SD. (n = 51); RA: room air; 100% O_2: 100% O_2 inhalation; 30% IS-N_2O: 30% N_2O inhalation; 50% IS-N_2O: 50% N_2O inhalation; Recovery: 100% O_2 inhalation after IS-N_2O; * vs. RA, 100% O_2, Recovery (* <0.05, ** <0.01); No significant difference between RA and 100% O_2, Recovery periods.

to be large, taste sensations may also significantly impact a patient's psychological state. In fact, as dental drugs, intraoral bleeding, and taste during tooth extraction can contribute to dental fear [14,15], inhibiting such unpleasant tastes is effective in the field of dental care. In this study, electrogustometry revealed a significant increase in recognition thresholds with 50% IS-N_2O compared to 30% IS-N_2O. Electrogustometry can be used to quantitatively test regions

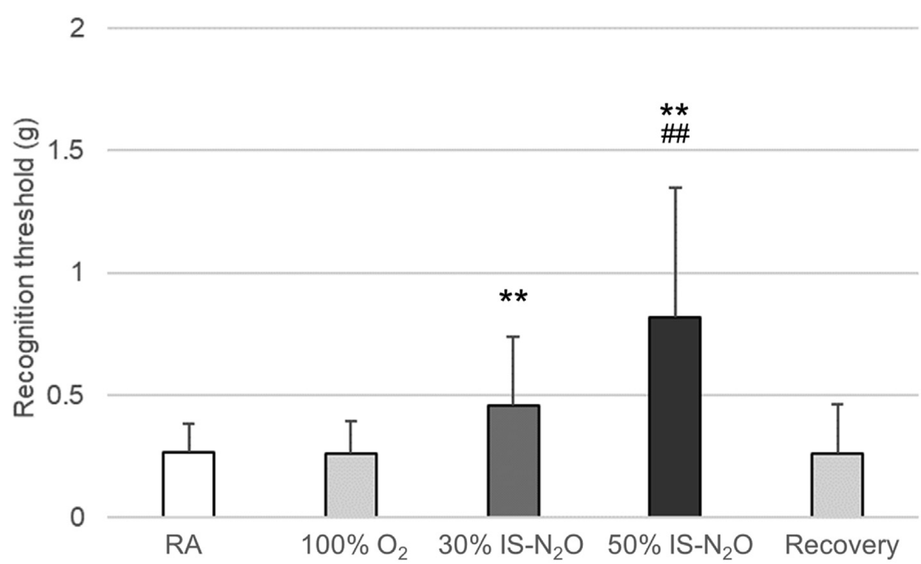

Fig. 4 – Tactile thresholds of the Semmes-Weinstein monofilaments tests with nitrous oxide. All values are the means ± SD. (n = 51); RA: room air; 100% O_2: 100% O_2 inhalation; 30% IS-N_2O: 30% N_2O inhalation; 50% IS-N_2O: 50% N_2O inhalation; Recovery: 100% O_2 inhalation after IS-N_2O; * vs. RA, 100% O_2, Recovery (<0.01); # vs. 30% IS-N_2O (## <0.01); No significant difference between RA and 100% O_2, Recovery periods.**

controlled by the intensity of stimulation and enables more accurate evaluations. However, some unclear points remain regarding electrogustometry mechanism. For example, a hypothesis involving ions produced due to the electrodialysis of saliva has been proposed [20]. On the other hand, the filter paper disc test revealed significant increases in the recognition thresholds of all tastes with both 30% IS-N_2O and 50% IS-N_2O. However, no meaningful difference was found between 30% IS-N_2O and 50% IS-N_2O. The filter paper disc test uses four of the five basic tastes (sweetness, saltiness, sourness, and bitterness) for additional testing of intraoral sensations of taste. This method can be used to identify which of the five basic tastes is impaired, rendering it a superior means of testing each region [22]. However, as only five concentrations were used for each taste liquid and the intervals between each concentration cannot be consistently set, this test lacks quantitative accuracy. Because comprehensively evaluating the degree of taste sensation based on thresholds for each taste is difficult, the sensitivity of this method is inferior to that of electrogustometry. However, we could not provide evidence for dose-dependent effects of IS-N_2O on taste input in this study, but we found that the threshold of 50% IS-N_2O was significantly higher than the threshold of 30% IS-N_2O on both electrogustometry and the SWM test. To our knowledge, IS-N_2O allowed the insertion of dental instruments into the oral cavity in a dose-dependent manner with the presence of an abnormal pharyngeal reflex [23]. Therefore, high concentrations of IS-N_2O may be better able to control unpleasant tastes during dental treatment.

The trigeminal nerve is the most important cranial nerve controlling the orofacial region and provides a large amount of information input to motor nerves, sensory nerves, and mixed nerves. Conditions such as trigeminal neuropathy, where a sensory abnormality arises when the function of this nerve is impaired for some reason, are well known. Such conditions are diagnosed with precise tactile function testing using the SWM test. We adopted this method of testing in the present study due to its good quantitative characteristics. As a result, the SWM test revealed significant increases in recognition thresholds with 50% IS-N_2O compared to 30% IS-N_2O. Thus, our results suggest that high concentrations of IS-N_2O may inhibit unpleasant tactile sensations such as instrument insertion and local anesthesia sensations, which can induce dental fear [14,15]. Sensory input is overseen by Aβ fibers, while pain input is overseen by Aδ and C fibers. Abnormal sensory input can cause abnormal pain, where tactile stimulation of a site that would not normally elicit pain is perceived as painful [24]. Thus, tactile and pain sensations appear to be closely related. Controlling tactile sensation might also be an analgesic approach to pain in dental patients. Many previous reports on the analgesic effects of IS-N_2O are available. IS-N_2O blocks *N*-methyl-D-aspartate (NMDA) receptors, causing the release of endogenous opioids and acting on nicotinic acetylcholine receptors to activate a downregulated system in the posterior horn of the spinal cord [25]. Analgesic effects might also be induced by activation of K-opioid receptors and a downregulated system in the spinal cord [26,27]. In an animal experiment, N_2O has also been demonstrated to be effective for long-term neuropathic pain caused by sciatic nerve injury in rats [28,29]. In clinical practice, one report indicated that IS-N_2O increased the pain threshold in the buccal area in humans [30], and another showed that the pressure pain threshold was increased in the jaw muscles [31]. Although there is the analgesic effect of dose-dependency in IS-N_2O, the local anesthesia is absolutely necessary for dental treatment [2]. The senses of tactile and pain are stimulated in the local anesthesia, and these may worsen dental fear [14,15]. Therefore, it may be effective to control the senses tactile and pain at dental treatment. As we did not investigate pain sensations in this study, further investigation will be necessary about the tactile sensation and the mutual relations of the pain in the future.

We were unable to eliminate the possibility of effects of sedation and amnesia induced by IS-N_2O on recognition thresholds of tactile and taste sensations in our study. IS-N_2O produces a sedative effect by inducing acetylcholine, gamma-aminobutyric acid, and NMDA receptors [25]. In a recent study, IS-N_2O caused a change in the brain network [32], and was reported to reduce the efficiency of information processing in an important frequency band for cognitive processes and to cause a sedative effect [33]. However, many points about these actions remain unclear. The possibility of sedative and amnestic effects of IS-N_2O on intraoral sensations must be considered.

In this study, no adverse events related to 50% IS-N_2O such as nausea and vomiting, headache, and dizziness were noted. Although the use of IS-N_2O may be limited by patient conditions and comorbidities, IS-N_2O is an established and safe tool for use in many departments such as obstetrics, emergency medicine, and psychiatry, which are using 50% IS-N_2O worldwide [34–36]. IS-N_2O can be administered as a 30–70% N_2O-oxygen mixture by a facial mask or nasal mask, and high concentrations of IS-N_2O (50–70%) have been shown to be safe with no significant difference in the rate of adverse events [37]. Because higher concentrations of IS-N_2O control the thresholds of intraoral sensations, 50% IS-N_2O should be selected.

This study was conducted based on healthy volunteers' self-reported sensations and the influence of taste and tactile sensations on dental fear was not investigated. The gender differences were not recognized in this study, but dental fear have been reported; women tend to be more fearful than men [38]. Thus, it will be very interesting to evaluate consideration that gender differences and presence of dental fear. The reason that performed a study only for healthy adult was to investigate the influence on pure intraoral sensations of IS-N_2O. As our previous study demonstrated that IS-N_2O is the most used for dental fear of children [39], clinical research to investigate the effects of IS-N_2O on taste and tactile sensations in children with or without dental fear is required in the future.

In conclusion, we found that IS-N_2O increases the recognition thresholds for intraoral taste and tactile sensations. Thus, IS-N_2O might be a useful method to counter dental fear during dental treatments due to increased thresholds for taste and tactile sensations, which are considered risk factors for the development of dental fear. These findings suggest that IS-N_2O can provide effective results in pediatric dentistry and special needs dentistry.

5. Conclusion

We concluded that IS-N_2O increases the recognition threshold for intraoral taste and tactile sensations. IS-N_2O appears to inhibit the input of taste and tactile sensations that can cause dental fear and may therefore be an effective tool for patients undergoing dental treatments.

Statement of ethics

This study was approved by the Institutional Review Board (IRB) of Kyushu Dental University (approval no. 18–67) and was conducted in accordance with the rules of the IRB.

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Declaration of competing interest

The authors have no conflicts of interest directly relevant to the content of this article.

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