Article

The use of equimolar mixtures of Nitrous Oxide and Oxygen in oral surgery - A retrospective study of patients in a Swiss university hospital setting

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Abstract

The purpose of the study was to evaluate the success of procedural conscious sedation, using inhaled equimolar nitrous oxide-oxygen (NOIS – EMONO), in patients undergoing routine dental and oral surgery procedures in a Swiss university hospital setting. The authors conducted a retrospective cohort study of patients that underwent NOIS-supported procedures between 2018 and 2022 at the oral surgery department of the University Hospital of Geneva (HUG), Switzerland. The primary outcome was the measurement of the procedure success and efficacy as defined by the European Society of Anesthesiology. Secondary objectives included the analysis of the types of treatments performed, their indications, patient behavior, and the patient - clinician satisfaction score. 55 patients were included in the study, 85% underwent surgical procedures, the remaining 15% underwent restorative and preventive procedures. The overall treatment success rate was 98.2%, and 97.9% for surgically treated patients. 62% of patients appeared relaxed, calm, and serene, while 16% expressed pain or fear during the procedure. Infiltrative administration of local anesthesia caused stress in 22% of patients, this was significantly lower in sub cohorts who received local topical anesthetics (0%) or a combination of systemic and local topical analgesics (7%). Patients (75%) and clinicians (91%) were satisfied with the procedure. Inhaled equimolar nitrous oxide-oxygen procedural sedation used during dental procedures and oral surgery results in high treatment success and satisfaction rates. The administration of additional topical anesthetics helps reduce the anxiety and stress related to infiltrative anesthesia. Further dedicated studies and prospective trials are needed to confirm these findings.

Keywords: Nitrous-oxide inhaled sedation 1; Oral surgery 2; Dental anxiety 3

1. Introduction

Dental-related anxiety is a common phenomenon that affects a significant portion of the population worldwide. It has been reported that up to 20% of adults experience some degree of dental anxiety or phobia [1]. Patients who experience this type of anxiety may avoid routine dental examinations, or treatment which can lead to undiagnosed dental problems and exacerbation of existing oral health issues [2], potentially resulting in altered dental function, poor oral hygiene, associated psychosocial impairment, or systemic health issues, all of which can significantly impact a patient's quality of life [2].

The mechanism behind this anxiety is complex and can be influenced by various factors, such as the type and invasiveness of the procedure, the patient's past experiences, and the clinical setting in which the treatment is provided. Research has shown that invasive surgical procedures, dental extractions, endodontic treatments, and dental injections are among the major anxiety-provoking stimuli for dentally anxious patients [3-5].

To address dental anxiety and facilitate the treatment of phobic patients, various pharmacological and non-pharmacological tools have been developed. Nitrous oxide-oxygen inhaled sedation (NOIS) represents one of the most

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effective and well-established pharmacological approaches to reduce anxiety and pain during dental treatment [6, 7]. NOIS involves the administration of an equimolar mixture of nitrous oxide and oxygen (EMONO), which has been shown to induce a state of analgesia, anxiolysis, and muscle relaxation by acting on type A γ-aminobutyric acid (GABAA) and, N-methyl-D-aspartate (NMDA) glutamate receptors [8]. The use of NOIS has been demonstrated to increase the pain threshold and reduce anxiety in patients undergoing dental procedures [9, 10].

The success of NOIS-supported dental procedures depends on various patient-related, treatment-related, and environmental factors [5, 10-13]. These factors include the interaction and management of the patient during treatment, as well the patient's medical history, the duration and type of procedure, the patient's level of cooperation, and the skills of the dental team [5, 10, 12, 13].

The aim of this retrospective cohort study was to describe and evaluate the success of inhaled equimolar nitrous oxide-oxygen procedural sedation in patients undergoing routine dental and oral surgery procedures over a three-and-a-half-year period in a Swiss university hospital setting.

2. Materials and Methods

2.1 Study Design

This retrospective study aimed to evaluate the success of nitrous oxide-oxygen procedural sedation (NOIS) using inhaled nitrous oxide/oxygen (N2O/O2) 50%-50% equimolar mixture (EMONO) for patients undergoing routine dental and surgical treatments in a Swiss university hospital setting. The study also aimed to analyze the dental procedures by indication and type, the patient's behavior, and the satisfaction of both the patient and clinician. Additionally, the study analyzed the frequency and type of additional local and systemic analgesics administered prior to infiltration anesthesia and their potential impact on the patient's behavior and typical adverse events. The evaluation was restricted to existing standard data records within the University Hospital's quality systems. No additional measurements, questionnaires, or scores were generated or used for this study. Treatments and reporting adhered to the Helsinki Declaration of ethical principles by the World Medical Association. This study was approved by the Institution's Ethical Review Board (IRB) (Commission Cantonale d'Ethique de la Recherche sur l'être humain, Geneva, Switzerland, (CCER)) under the appoval number 2020-00997.

2.2. Study Population

The studied population included all patients who underwent NOIS-supported dental procedures between September 2018 and May 2022 at the oral surgery department of the Geneva University Hospital, Switzerland. The inclusion criteria were patients diagnosed with a condition requiring dental or oral surgery interventions, who were classified as ASA class I or II and were unable to undergo such procedures with routine local anesthesia due to treatment-related anxiety, extremely low pain tolerance, intellectual/cognitive disability, or young age with uncooperative behavior. All patients or legal guardians gave their informed consent before treatment. Patients with a history of or currently presenting with intracranial hypertension, spontaneous or traumatic pneumothorax, emphysema, abdominal distension due to gas accumulation, intestinal obstruction, sinusitis, ear infection, post-surgical complications of the middle ear, recent sinus-treatments, maxillofacial trauma or fractures, first-trimester pregnancy, non-compliant patients, and those unable to wear masks were excluded from treatment. Patients were instructed to refrain from eating for at least 2 hours before the planned procedure.

2.3. Treatment Protocol

The treatment protocol followed the standard operating procedures of the University Hospital of Geneva. NOIS administration and treatments were restricted to assistants and clinicians specifically trained in this type of conscious sedation and who were certified in cardio-respiratory life-support and resuscitation. EMONO was administered via a nasal mask (Accutron™ PIP+™, Accutron, USA) at a flow rate of 12l/min or 6l/min for patients weighing less than 30 kg. Patients were instructed on how to operate the mask before treatment, and information on possible adverse events was reinforced immediately before treatment. The assistant performed mask administration in disabled patients or children. All patients were continuously monitored for vital signs, including heart rate, oxygen saturation, and any signs

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or expressions of pain throughout the procedure. Parents and accompanying persons were allowed to be present in the operating theatre. Treatment was started after an induction period of at least 3 min, and active verbal contact with the patient was maintained throughout the procedure.

2.4. Data Collection and Analysis

Data collection included demographic data such as age, gender, and pregnancy status, as well as data related to the evaluation of cognitive abilities, history of NOIS-supported treatments, patient history including relevant systemic conditions, allergies, medical risks, and contraindications related to dental treatments and the administration of EMONO. Recorded treatment-related aspects included the duration of the procedure, the use of self-administered systemic analgesics, the administration of topical anesthetics in addition to infiltration anesthesia, the patient's attitude before inhalation, the duration of the sedation, and the blood oxygen saturation during the procedure.

Treatment and NOIS administration were evaluated as successful and effective based on the European Society of Anesthesiology definition and were evaluated in conjunction with the patient's behavior and post-therapeutic evaluation [14].

The patients were further observed for their behavior and mental state during the NOIS-supported treatment, and the assistant rated the perceived qualitative tolerance to treatment by assigning one or several of the following attributes: calm and serene, stressed at the moment of local anesthesia administration, worried/panicking, visually expressing signs of pain or fear, a tendency to reject mask, a tendency to reject treatment. Finally, any obligation to interrupt the treatment was recorded, and any patient-reported adverse effects immediately after treatment and 10 min after cessation of the administration of EMONO were noted. Patient and clinician self-reported satisfaction was also recorded 10 min after treatment.

Data analysis and presentation were purely descriptive. Statistical comparisons of potential differences between patient sub-cohorts were not in the scope of the present study.

3. Results

3.1 Cohort characteristics

During the defined study period of 3.5 years, the records of 55 patients that underwent dental treatment under NOIS utilizing EMONO were analyzed for this study. These patients were between 3 and 60 years old, with an average age of 23.22 ± 14.4 years. Among the patient cohort, 56% were women, 91% of patients had no cognitive impairment, of the remaining 9%, one patient was autistic, two patients were affected by unspecified psychomotor retardation, one had Trisomy 21, and one was a 3-year-old pediatric patient. In total, there were 12 pediatric patients under the age of 12 years included in the study.

Out of the total patient cohort, 24% (N=13) had previously undergone NOIS-supported dental or medical treatments, while 70% (N=40) were being treated for the first time. Most patients were in good general health (98%, N=54) (ASA class I), with only one patient (2%) affected by exercise-induced asthma (ASA class II). None of the patients displayed any treatment-associated risk factors, as shown in (Table 1).

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Table 1. Patient-related descriptive characteristics. Age is reported as an average and standard deviation. All other parameters are reported as a percentage relative to the patient cohort.

Characteristic	Parameter	N	Mean ± SD / %
Age [years]	Age at Intervention	55	23.22 ± 14.4
Gender	Gender (%Men)	24	44%
	Gender (%Women)	31	56%
Cognitive capabilities	Normal cognitive capabilities	50	91%
	Altered cognitive capabilities	5	9%
Prior treatment exposure	None / first treatment	40	73%
	Prior exposure	13	24%
	Not assessed	2	4%
ASA physical status classification	ASA class I	54	98%
	ASA class II	1	2%
	ASA class ≥ III	0	0%
Treatment-associated risk factors	Present	0	0%
	Not present	55	100%

3.2 Indications

The success rate, evaluated by the ability to complete and successfully deliver the planned dental treatment, was 98.2%. One patient, who was scheduled for multiple third molar extractions, could not undergo treatment due to severe anxiety, despite the administration of EMONO. The success rate of patients treated surgically was 97.9%.

The absolute numbers and frequencies of treatments, stratified by type and indication, are reported in (Table 2).

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Table 2. Provided treatments per procedure type and indication. The reported percentage is based on the total patient cohort. †Number in brackets refers to the total number of extracted teeth.

Type	Indication	N	%
Surgical including flaps		**35**	**64%**
	Oral soft tissue biopsy	4	7%
	Surgical exposure of impacted tooth	4	7%
	Third Molar extraction, non-erupted, multiple†	18 (60)	33%
	Third Molar extraction, non-erupted, single	1	2%
	Tooth extraction, non-erupted, single	8	15%
Surgical without flaps		**12**	**22%**
	Dental extraction, multiple†	10 (21)	18%
	Dental extraction, single	2	4%
Other procedures		**8**	**15%**
	Dental hygiene procedure	3	5%
	Dental Impression taking	2	4%
	Endodontic treatment - multiple teeth	1	2%
	Endodontic treatment - single tooth	1	2%
	Orthodontic treatment	1	2%

Most dental procedures were classified as surgical (N=47, 85%). The most performed surgery involved the extraction of non-erupted third molars. A total of 60 single and multiple teeth were removed. Four patients underwent surgical exposure of impacted teeth (7%) and four had oral soft tissue biopsies accounting for 7% of procedures in total. Single and multiple extractions of a total of 21 erupted teeth represented the second most frequent surgical procedure (22%). Other nonsurgical procedures included dental hygiene procedures (5%), impressions (4%), endodontic treatments (4%), and orthodontic treatments (2%), which were overall less frequent (total patients N=8, 15%).

3.3 State prior to treatment and NOIS administration

Thirty-six patients (65%) reported feeling anxious prior to treatment and NOIS administration. 31 (56%) patients were calm and relaxed, while eight patients (15%) appeared to be uneasy and tense before treatment (Table 3). It is important to note that patient records could contain more than one attribute per patient.

Table 3. Clinician or assistant-judged patient state prior to treatment and NOIS administration. Reported percentage refers to the relative portion of patients in the total cohort. Note that patient records could contain more than one attribute per patient.

Patient state	N	%
Calm, relaxed	31	56%
Anxious	36	65%
Uneasy, tense	8	15%
Not reported	3	5%

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3.4 NOIS inhalation

The interventions in this study lasted an average of 44.55 ± 18.57 minutes, with a range of 10 to 90 minutes. Most of the interventions were almost entirely covered by EMONO inhalation, with an average of (42.54 ± 19.87) minutes and a range of 10 to 100 minutes. The patients' oxygen saturation levels were always within a normal range, with an average maximum of 99.23 ± 0.73% and an average minimum of (97.56 ± 1.12) %, and never fell below 94% (Table 4).

Table 4: NOIS administration-related characteristics, comprising the EMONO inhalation time, the duration of the total intervention and the minimum and maximum oxygen blood saturation values during treatment. Values are reported as averages and standard deviations, medians, interquartile ranges, and total ranges. Abbreviations: SD: standard deviation, IQR: Interquartile ranges.

Parameter	N	Mean ± SD	Median (IQR)	Range
Duration of the intervention [min]	55	44.55 ± 18.57	45 (30 - 60)	10 - 90
Inhalation time [min]	54	42.54 ± 19.87	45 (25 - 60)	10 - 100
Oxygen Saturation [max] [%]	53	99.23 ± 0.73	99 (99 - 100)	97 - 100
Oxygen Saturation [min] [%]	53	97.56 ± 1.12	98 (97 - 98)	94 - 99

3.5 Concomitant analgesics

The use of locally applied topical anesthetics or systemic self-administered anxiolytics or analgesics, in addition to local infiltration anesthesia, is reported in (Table 5).

Table 5: Administered topical anaesthetic or self-administered systemic analgesics/anxiolytics in addition to local infiltration anaesthesia, organized by type and active substance. Reported percentages refer to the relative portion of patients in the total cohort. Note that patient records could contain more than one attribute per patient.

Type	Active substance and dosage form	N	%
Topical anaesthetic	None	43	78%
	Xylocaine HCl Gel	9	16%
	Xylocaine HCl Spray	3	5%
Systemic analgesics/anxiolytics	None	50	91%
	Morphine	1	2%
	Lorazepam	3	5%
	Tramadol	1	2%
Combined topical and systemic	Combined	2	4%
	Only topical	12	22%
	Only systemic	5	9%
	No systemic or topical	36	65%

Local infiltration anesthesia was performed in all patients, except in one case (dental impression). Before local infiltration anesthesia, 12 patients (22%) were given local topical analgesics (Xylocain HCl), and five patients (9%) had taken

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Morphine derivatives, Lorazepam, or Tramadol. Most patients (65%, N=36) did not receive any additional analgesics. Only two patients (4%) received a combination of topical anesthetics and systemic analgesics in addition to EMONO.

3.6 Patient treatment state

The evaluation of the patient's physical state and level of cooperation for the total cohort and the sub cohorts as stratified by the use and administration of additional analgesics is reported in (Table 6).

Table 6: Clinician or assistant-judged patient state per total cohort and sub cohorts receiving no additional analgesics, topical anaesthetics, systemic analgesics, or a combination. Reported percentages refer to the relative portion of patients in the cohort or corresponding sub cohort. Note that patient records could contain more than one attribute.

Patient condition	**Total cohort (N=55)**		**Sub cohort topical anaesthetic (N=12)**		**Sub cohort Analgesics (local and/or systemic) (N=15)**		**Sub cohort without analgesics (N=36)**	
Category	N	%	N	%	N	%	N	%
Calm and serene	34	62%	9	90%	12	80%	22	55%
Stressed by local anaesthesia	12	22%	0	0%	1	7%	11	28%
Worried - panicked	2	4%	0	0%	0	0%	2	5%
Visual expression of pain or fear	9	16%	2	20%	4	27%	5	13%
Tendency to reject mask	1	2%	0	0%	0	0%	1	3%
Tendency to reject treatment	3	5%	0	0%	0	0%	3	8%

It shows that most patients in the cohorts appeared relaxed, calm and serene (62%, N=34). Stress by local anesthesia was the second most frequently recorded state (22% of total patients), and 16% of patients expressed pain or fear. Panicking or the tendency to reject the mask or treatment were rarely noted (4%, 2% and 5% of patients, respectively). Interestingly the relative proportion of patients that appeared to be stressed by the local anesthesia was distinctly lower in the sub cohorts receiving additional local topical anesthetics (0 out of 12 patients (0%)) or a combination of systemic analgesics and local topical anesthetics (1 out of 15 (7%)), compared to the sub cohort of patients that did not receive any extra analgesics (11 out of 36 patients (28%)).

3.7 Adverse effects

As reported in (Table 7), paresthesia in the hands and fingers was the most frequently patient-reported side effect (N=22, 40%). Seven patients (13%) further reported a feeling of euphoria, while all other side effects, including crying (5%), vertigo (2%), drowsiness (7%), agitation (7%), and hallucinations (4%) remained below a threshold of 10%. All side effects were reported to have completely vanished 10 min after ending EMONO inhalation.

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Table 7: Number and relative percentages of observed side effects. Reported individual side effects refer to the total patient cohort. Please note that a patient could have displayed more than one side effect.

Side effect	N	%
None	13	24%
Not reported	4	7%
Paraesthesia	22	40%
Crying	3	5%
Vertigo	1	2%
Drowsiness, sleepiness	4	7%
Agitation	4	7%
Sensation of inebriation	5	9%
Hallucination	2	4%
Euphoria	7	13%

3.8 Patient and clinician satisfaction

Patients (N=41, 75%) and clinicians (N=50, 91%) were overall satisfied with the procedure and none of the patients or clinicians expressed complete dissatisfaction (Table 8). 10 (18%) patients could not give their judgement and 2 (4%) were only partly satisfied. The clinicians were unsatisfied in one instance (2%). 4% of patients' and 7% of clinicians' evaluations were unreported.

Table 8: Patient and clinician-reported satisfaction after treatment. Reported percentages refer to the total patient cohort.

Category	Patient Satisfaction		Clinician Satisfaction	
	N	%	N	%
Not reported	2	4%	4	7%
Completely satisfied	41	75%	50	91%
Partly satisfied	2	4%	1	2%
Not satisfied	0	0%	0	0%
Not able to judge	10	18%	0	0%

4. Discussion

In this retrospective descriptive study conducted in a Swiss university hospital setting, the success of nitrous oxide-oxygen procedural sedation (NOIS) was evaluated during dental and surgical procedures using an inhaled nitrous oxide/oxygen (N2O/O2) 50%-50% equimolar mixture (EMONO). The study analyzed various aspects of the treatment, including patient-tolerability-related aspects, patient behavior, patient-clinician satisfaction, and the treatment type and indication.

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The findings of this study indicated a high success rate of 98.2% in the analyzed patient cohort, demonstrating the effectiveness of NOIS in dental treatments, which is consistent with previous research [7, 10, 11, 15]. The results are in line with a recent systematic review of randomized clinical trials conducted by Rossit et al. [7, 9, 10, 15], which reported an overall efficacy rate of 95% (CI: 88.8–98.9%) globally and 99.9% and 91.9% for adult and pediatric patients, respectively [7]. Although the study by Rossit et al. identified certain differences between adult and pediatric patients, our analysis did not indicate any significant differences between these two age-related groups.

This study focused on patients from the oral surgical unit of the HUG who were scheduled for NOIS-supported therapeutic or preventative dental interventions due to an over-proportional anxiety level and/or limited anxiety pain tolerance. Patient selection was not based on any specific criteria, and the patient cohort was representative of the corresponding patient pool at the university hospital.

The patients undergoing NOIS-supported dental treatments were relatively young, with a median age of 19 and interquartile ranges from 13.25 to 28.25 years and included both adult and pediatric patients. Recent clinical studies have shown the efficacy of NOIS in both mentally healthy and compromised patients [12, 15], both of which were included in this patient cohort.

A second indirect outcome of this study was related to the number of patients scheduled for NOIS-supported treatment over the study duration. Specifically, 55 patients underwent NOIS-supported dental treatment in 3.5 years, which corresponds to a relatively low estimated percentage of 0,3% of total dental patients undergoing this type of treatment, in our center.

Furthermore, approximately a quarter of the patients reported previous dental treatment experience under NOIS. The available research suggests that previous experience with NOIS may significantly improve patient satisfaction and collaboration during dental procedures compared to first time users, this must be taken into account for the adequate interpretation of the reported results [9, 16].

Regarding the treatment indications, most dental procedures delivered under NOIS in the routine setting can be classified as invasive and surgical (85%). Restorative procedures under NOIS represented a small proportion of delivered treatments.

The success rate of surgically treated patients was 97.9%. Invasive surgical procedures and dental extractions have been ranked as the most-anxiety provoking among dental patients [5]. In his publication, Berge demonstrated the efficacy of nitrous oxide as part of a large oral surgical patient cohort and has described its application as reliable, efficient and safe for use as part of oral surgical procedures in adult and pediatric patients [17]. Sandhu et al. have recently proven that inhalation of titrated nitrous oxide-oxygen with an N2O-concentration of up to 67% could reduce stress and stress-associated biomarkers such as cortisol during lengthy periodontal surgical procedures [18]. The efficacy of EMONO as part of surgical procedures was demonstrated and extensively documented as part of large multicenter trials comprising relevant surgically treated patient sub cohorts [10, 11].

An interesting potential finding of this study was related to the observation that the concomitant use of topical anesthetics helps to alleviate the stress and anxiety related to infiltration anesthesia injection. NOIS has been reported as having an analgesic and anxiolytic effect based on its capacity to trigger the release of endogenous opioid peptides, targeting both opioid and N-methyl-D-aspartate (NMDA) glutamate receptors and by inhibiting nitric oxide synthase, soluble guanylyl cyclase, and cyclic guanosine monophosphate-dependent protein kinase of the anxiolytic signaling pathways respectively [12, 19]. The corresponding effects greatly aide in the treatment of dentally anxious patients [19]. Anxiety related to anesthetic injection has been reported to represent one of the most important psychologic responses in dentally anxious patients [5, 20]. Jacobs et al. have shown that NOIS can significantly reduce injection-related pain during inferior alveolar nerve block anesthesia indicating that NOIS alone, i.e., without the administration of additional analgesics has proven effective in moderating these treatment-related fears [4]. Interestingly this study showed a distinct difference in the proportion of patients that presented signs of stress associated with the local infiltration anesthesia between patients that received additional topical anesthetic in the form of Xylocaine gel or spray in combination with NOIS and patients that did receive NOIS alone. Although a test for statistical significance was not in the scope of the descriptive research here, the observed differences and associated potential of concomitant topical anesthesia when

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applied in conjunction with NOIS to reduce injection-related stresses in dentally anxious patients appears to our knowledge as novel and may deserve future specifically dedicated studies to investigate this patient-relevant aspect.

Regarding the administration of systemic analgesics in conjunction with NOIS, the current evidence in the literature suggests potential effects of such combinations on pain and anxiety. However, this depends on the adopted combinations and dosages [8, 21]. To this extent, the relatively small patient cohort was considered inhomogeneous, which limited a clear interpretation of the results.

The results of this study and the total absence of serious adverse events also confirmed the well-documented high safety profile related to the use of EMONO-induced NOIS-supported dental treatment [10]. This study's most frequently observed side effects included paresthesia, euphoria, and the sensation of inebriation. These side effects represent commonly reported minor side effects related to NOIS and were completely resolved in all patients within 10 min after ending the administration [11, 22].

Finally, patient and clinician satisfaction with the treatments was overall high. In this regard, it must be considered that the evaluation of satisfaction and anxiety-related outcomes for the type of procedures and patient pools may not be associated with NOIS alone, but other factors such as the clinical setting and patient-experience-specific psychophysiological component beyond NOIS application, as well as the application of anxiety and pain management techniques provided by the dentist or assistant need to be taken into account for the adequate interpretation of such outcomes [3, 11, 13].

5. Conclusions

The findings of this retrospective descriptive study indicate that conscious sedation with an inhaled equimolar mixture of nitrous oxide and oxygen is a highly effective and satisfactory treatment option for anxious patients. The success rate was notable, particularly in surgical and invasive procedures, highlighting the benefits of this sedation technique in oral surgical practice. Further analysis showed that additional topical anesthetics may help alleviate the anxiety and stress related to infiltration anesthesia injections, and this possibility should be explored in future prospective trials.

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