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Conscious Inhalation Sedation with Nitrous Oxide and Oxygen in Children: A Retrospective Study

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Abstract: Dental anxiety is a common problem in younger children, especially those who have had traumatic or perceived traumatic dental treatments. Nitrous oxide (N_2O) and oxygen (O_2) have been recommended by the American Academy of Pediatric Dentistry as the optimal approach for uncooperative or anxious patients. The study aimed to evaluate the cooperation of children treated on deciduous teeth without local anesthesia and with rubber dam. A retrospective study was conducted from January 2019 to December 2020 in a private dental practice on children aged 4–10 years who had previously reported cases of dental anxiety during dental procedures or refused to undergo them. After an initial cognitive examination, the children underwent conservative treatment lasting a maximum of 30 min. Initially, 100% O_2 was administered, then N_2O dose was gradually increased to 35%. At the end of the treatment, 100% pure O_2 was administered for 5 min. Children's cooperation was assessed by Venham score before treatment (T0), at the end of induction (T1), and during the treatment (T2). A total of 371 children (age: 6.3 ± 1.7 years) were included in the study. Cooperation increased significantly from baseline at T1 ($p < 0.001$) and T2 ($p < 0.001$). Younger children (4–6 years) showed lower levels of cooperation at baseline ($p < 0.001$) but achieved optimal levels of cooperation at T1 ($p = 0.022$). Only 2.7% of children reported side effects. N_2O/O_2 proved to be an effective and safe method in achieving a good level of cooperation in younger children.

Keywords: nitrous oxide; dental anxiety; dental fear; children; Venham score

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1. Introduction

Dental anxiety is a common problem in pediatric dentistry and is a serious obstacle to the treatment of children's oral health. Estimates of dental fear and anxiety (DFA) in children and adolescents range from 5.2% to approximately 30% [1,2], with a higher incidence in children (7.4–93.8%) [3] and especially in those with dental caries, a history of dental pain, and previous dental treatment [4,5]. According to a recent systematic review, pooled dental anxiety in children and adolescents is estimated to be 23.9% (95% CI 20.4, 27.3) overall, with an increase to 36.5% (95% CI 23.8, 49.2) and 25.8% (95% CI 19.5, 32.1) in preschoolers and school-aged children, respectively [6]. The negative impact of dental anxiety on children's oral health-related quality of life (OHRQoL) and the higher prevalence of pain and infections in patients with higher levels of dental anxiety are well known [7–10]. According to a recent conceptual model assessing factors affecting children's OHRQoL, the relationship between dental anxiety and children's poor OHRQoL is bidirectional: just as dental anxiety leads to incorrect behaviors such as reducing dental visits and poor oral hygiene, poor OHRQoL may simultaneously cause or exacerbate dental anxiety [11]. In patients with poor OHRQoL, the invasiveness of dental procedures seems to act as a direct factor in triggering or exacerbating dental anxiety [6]. Nevertheless, recent studies have shown that dental anxiety in children is mainly related to subjective psychological factors rather than interventional factors [12] in which parental attitudes and perceptions toward dental treatment play a crucial role [13,14]. In 2012, Goettems et al., who studied 608 mother–child dyads, reported a significant association between maternal dental anxiety and the incidence of untreated dental caries in children [13]. Similar trends were also demonstrated by Goyal et al. (2019), who showed that the children whose mothers were "extremely anxious" (phobic) had the highest average number of decayed, missing, or filled teeth [14]. In younger children (24–36 months) with adolescent mothers, the presence of maternal anxiety disorders, such as agoraphobia and social phobia, was significantly associated with children's dental anxiety [15]. In children, early acquisition of dental anxiety is strongly related to negative experiences as well as to personality and certain beliefs regarding medical professionals [16]. However, the negative value attributed to the dental experience does not seem to be related to objective evaluations such as the invasiveness of the procedure or the number of dental procedures but rather to a subjective evaluation in which children and their parents view dental treatment as a negative experience [17]. Inadequate or perceived inadequate previous dental treatment leads to increasing dental anxiety [18], creating a vicious cycle in which OHRQoL is severely compromised.

Overall, children with behavioral disorders are twice as likely as children without behavioral disorders to have dental caries at age 5 [19], are less likely to have dental radiographs taken, are more likely to have restorative treatments performed without local anesthesia [20], and are more likely to have teeth extracted [21]. The treatment procedure is not only a tremendous source of stress for patients but also a time-consuming and stressful activity for dentists, who are often reluctant to provide dental care to anxiety patients because they do not know how to properly manage children's anxiety [22]. Although the etiology of dental anxiety disorders is multifactorial, negative and traumatic dental experiences have been shown to be one of the most common causes [23–26], making avoidance of negative experiences that may exacerbate a preexisting anxiety state essential for clinicians to ensure high levels of oral health in young patients.

In 2018, the American Academy of Pediatric Dentistry (AAPD) recommended the use of nitrous oxide (N_2O) and oxygen (O_2) as a safe, appropriate, and prudent approach for treating uncooperative children, children with dental anxiety during dental procedures, prolonged dental procedures, or uncomfortable procedures where the patient is not allowed to move [27,28]. The mechanism of action of nitrous oxide is characterized by a triple action: anesthetic, analgesic, and anxiolytic. The first, i.e., the anesthetic effect, is due to the non-competitive inhibition of NMDA in the central nervous system; the second, the analgesic effect, is due to the release of endogenous opioids that act on opioid receptors and achieve comparable results to morphine, while the third, i.e., the antianxiety effect, is due to the activation of GABA-A [29]. At concentrations less than 50%, N_2O is recommended to reduce anxiety and provide analgesia while maintaining a normal patient response to the dentist's instructions and allowing rapid recovery of mobility without loss of protective reflexes [28], with success rates ranging from 73 to 97% [30]. The success rate of nitrous oxide decreases slightly in patients younger than 5 years (91.8%) [31], which is due to the mixed breathing typical of younger children, which prevents complete inhalation of the nitrous oxide administered.

N_2O, a colorless and virtually odorless gas with a faint, sweet odor, is a potent analgesic/anxiolytic that depresses the central nervous system and induces euphoria but has little effect on the respiratory system [27]. Because N_2O has very low gas solubility in the blood, it rapidly reaches therapeutic levels in the blood, and conversely, blood levels decrease rapidly when N_2O is discontinued. In addition, compared with general anesthesia, N_2O has a low adverse event rate (0–0.3%) [32], rapid resolution of symptoms, lower cost [33], and is considered physiologically safe for the patient when administered with adequate O_2. The most common adverse effects, which are very transient, are nausea and vomiting, which are thought to be due to prolonged administration of nitrous oxide/oxygen, fluctuations in nitrous oxide levels, lack of titration, increased nitrous oxide concentrations, and a heavy meal prior to nitrous oxide administration [27]. Poor technique with high concentrations can also lead to an "excitement phase" in which the patient may feel uncomfortable, uncooperative, and delirious, which is similar to a transitional stage to general anesthesia.

Several studies conducted have shown that conscious sedation with N_2O elicits a positive behavioral response in children with dental anxiety [31,34–36]. In a recent cross-sectional study of 171 children (6–11 years) with moderate to severe dental anxiety and who required pulp treatment on one of their deciduous molars, Bangash et al. (2022) showed that a mixture of N_2O and O_2 played an important role in reducing dental anxiety in the short term ($p \leq 0.001$) [34]. Although, as previously described, dental anxiety is strongly related to demographic and psychosocial factors, children's cooperative behavior during treatment with nitrous oxide is not influenced by these factors, except for an authoritative parenting style, which may promote cooperative behavior [36].

The purpose of this retrospective study is to evaluate the efficacy and safety of the use of N_2O in a sample of very young pediatric patients (4–10 years) treated for dental procedures without local anesthesia as part of normal dental clinical practice and who had previously reported cases of dental anxiety during dental therapies or refused to perform them.

2. Materials and Methods

A retrospective study was conducted from January 2019 to December 2020. The study was conducted at one clinical center in conformity with the Good Clinical Practice Guidelines and according to Declaration of Helsinki ethical principles for medical research involving human subjects, as revised in Fortaleza (2013). Informed consent was obtained by all parents.

Children who needed conservative treatment of deciduous elements (carious lesions limited to enamel or superficial dentine which did not involve the pulp) for a maximum duration of 30 min and who had previously reported cases of dental anxiety during dental therapies or refused to perform them were included in the study. According to the AAPD guidelines, patients with chronic obstructive pulmonary diseases, ongoing infections of the upper respiratory tract, recent surgery or ongoing middle ear pathologies, disorders of the psychic sphere, treatments with bleomycin sulfate, methylene-tetrahydrofolate reductase deficiency, and vitamin B12 deficiency were excluded [27]. All patients were given the standard history/self-assessment questionnaire at the first visit according to the AAPD guidelines, and if there was any doubt about a possible exclusion condition, the pediatrician was consulted for information and clarifications. After parents received verbal and written explanations of the whole procedure and were informed about the benefits and the possible risks of the procedure and its alternatives, signed written consent to the dental treatment and authorization to process data were obtained for each child. At the end of the information interview, parents were asked not to give food in the 3 h before dental treatment.

The operating protocol was followed in accordance with the approach protocols applied by Galeotti et al. [35]. For each patient, two appointments were scheduled: first, cognitive visit, and second, session of pedodontics treatment. The parents accompanied the children and remained silent in the operating room during both the sessions. In the first session, the room, the dental unit, all the equipment, and the machinery were shown, telling the children that it was necessary to only breathe through the mask in the second session. All patients were examined, and the medical record was compiled, all the information was provided to the parents, and signatures were collected for the authorizations as per the law. At the second appointment, the patient, fasting for at least 3 h, underwent a conservative treatment on a deciduous element with the help of dispensing the N_2O/O_2 mixture through a disposable, scented nasal mask at a size suitable for the face. The protocol used for administering the combination of N_2O and O_2 complies with the requirements of the AAPD [27]. For the first 2 min, 100% O_2 was supplied; then, N_2O was titrated gradually by increasing 10% every 2 min up to 35%. After a 5 min induction period, pedodontics treatment began. The flow delivered was between 5 and 6 L per minute and was adjusted by monitoring the reservoir bag that had to pulsate cyclically with each breath without remaining hypo- or hyper-expanded. At the end of the treatment, 100% pure O_2 was delivered for 5 min. All patients were asked to breathe through their noses during treatment that lasted a maximum of 30 min while behavioral approach and guidance techniques were still applied. Composite fillings were performed on deciduous teeth with the help of a rubber dam.

Although the percentage of nitrous oxide administered did not exceed 50%, which is the maximum concentration recommended by the AAPD to avoid harmful effects of nitrous oxide [28], the maximum dose did not exceed 35%, which has been proved the typical N_2O dose to achieve ideal sedation in children [37]. To ensure high safety standards, patients were monitored every 10 min during the procedure using pulse oximetry, which allowed continuous control of heart rate and blood oxygen saturation. All clinical personnel were instructed to use the device for the delivery of N_2O and were certified for BLSD; the studies had oxygen cylinders with positive pressure delivery in case of emergency and an automatic defibrillator with pediatric plates. Constant visual and verbal contact was maintained throughout the treatments to ensure that the patients did not lose consciousness and to monitor their ability to understand and respond to verbal commands.

Success rates, i.e., completion of the scheduled treatment, and the degree of collaboration evaluated through the Venham scale measured before treatment beginning (T0), at the end of induction (T1), and during the treatment (T2), were defined. Venham scale is a six-point scale ranging from 0 (fully relaxed child) to 5 (completely disconnected and untreatable child) [38]. Side effects were monitored during treatment, for 1 hour after the end of treatment, and for a 48 h period. Respiratory disturbances (e.g., hyperventilation, hypoventilation, and hypoxia), digestive disturbances (e.g., nausea, vomiting), neurological disturbances (e.g., convulsions, epilepsy), behavioral disturbances (e.g., euphoria, agitation), and vagal disturbances (e.g., sweating, pallor) were registered.

Descriptive statistics are reported as mean and standard deviation for quantitative data and as frequencies and percentages for qualitative data. Comparisons pre/post were performed through Friedman test with subsequent Conover post hoc test, whereas comparisons between male and female patients between age ranges 4–6 years and 7–10 years were performed through Mann–Whitney U test. Comparison among groups for qualitative variables (Venham Score used as categorical data) were performed through the Fisher exact test. Non-normality distribution of quantitative variables was determined through the Shapiro–Wilk test. Significance was set at 0.02 after Bonferroni correction. Statistical analyses were performed using STATA17 (StataCorp., College Station, TX, USA).

3. Results

A total of 371 children (175 females and 196 males) with a mean age of 6.3 ± 1.7 years (range: 4–10) were enrolled and included in the study (Table 1). About 59% of the children were younger than 7 years old, while the remaining 41% were between 7 and 10 years old.

Table 1. Patient characteristics.

No. of Children	371
Gender, *n* (%)	
Female	175 (47.2%)
Male	196 (52.8%)
Age, years	
Mean (SD)	6.3 (1.7)
Min–Max	4–10
Age range, *n* (%)	
4–6 years	218 (58.8%)
7–10 years	153 (41.2%)

Legend: SD = standard deviation.

The Venham score decreased significantly from baseline (1.65 ± 1.53) to T1 (0.75 ± 1.35) ($p < 0.001$) and T2 (0.89 ± 1.45, $p < 0.001$) (Table 2). Statistically significant differences also emerged between T1 and T2 ($p < 0.001$). Improvement in Venham score was observed in both females and males, without any statistically significant difference between the two groups. On the contrary, starting from the baseline, the Venham score was higher in younger patients (1.94 ± 1.52) than in older ones (1.25 ± 1.46) ($p < 0.001$). The difference between the two age-range groups decreased at the end of induction (T1) and no statistically significant difference was observed. During the treatment (T2), younger patients reported higher Venham scores (1.10 ± 1.58) ($p < 0.001$).

Table 2. Venham score.

	Total	Male	Female	*p*-Value	4–6 Years	7–10 Years	*p*-Value
T0	1.65 (1.53)	1.59 (1.51)	1.72 (1.56)	0.437	1.94 (1.52)	1.25 (1.46)	<0.001
T1	0.75 (1.35)	0.70 (1.31)	0.81 (1.40)	0.498	0.91 (1.50)	0.52 (1.06)	0.022
T2	0.89 (1.45)	0.87 (1.42)	0.92 (1.47)	0.758	1.10 (1.58)	0.60 (1.18)	<0.001
p-value	<0.001	<0.001	<0.001		<0.001	<0.001	

Legend: T0, before treatment; T1, at the end of induction; T2, during the treatment. Values are reported as mean (SD).

Before induction (T0), 5.7% of children had a Venham score of 5 points, followed by 9.7% of children with a Venham score of 4 points. Approximately 12% of children showed unwillingness to treat (Venham score equal to 3), while 20.2% appeared tense. 22.1% of children showed some degree of anxiety but were capable of cooperation. Almost 30% of the total sample appeared relaxed and had a positive attitude toward the dentist. At the end of induction (T1), the number of children who protested to disrupt treatment (Venham score 4) or who were completely uncooperative (Venham score 5) decreased from 15.4% (T0) to 7%, and approximately 70% of children appeared relaxed, willing to cooperate, and had a good conversational attitude. During treatment (T2), 9.7% of children reported a Venham score of 4 or 5 points. The number of relaxed children decreased to 64.7%, while tense or unwilling behavior was observed in 8.1% and 6.7% of children, respectively. Complete results are reported in Table 3.

Table 3. Percentages of children.

Venham Score	T0	T1	T2
0 (Relaxed), *n* (%)	113 (30.5%)	258 (69.5%)	240 (64.7%)
1 (Uneasy), *n* (%)	82 (22.1%)	34 (9.2%)	40 (10.8%)
2 (Tense), *n* (%)	75 (20.2%)	30 (8.1%)	30 (8.1%)
3 (Reluctant), *n* (%)	44 (11.9%)	23 (6.2%)	25 (6.7%)
4 (Interference), *n* (%)	36 (9.7%)	14 (3.8%)	24 (6.5%)
5 (Out of contact), *n* (%)	21 (5.7%)	12 (3.2%)	12 (3.2%)

Legend: T0, before treatment; T1, at the end of induction; T2, during the treatment. Values are reported as frequencies (percentages).

Regarding the age range, children younger than 7 years had higher levels of uncooperativeness before induction: 7.3% and 11.0% of younger children had Venham scores of 5 and 4 points, respectively, compared with older children ($p < 0.000$). At the end of induction, 65.6% of younger children showed a higher level of cooperation (Venham score equal to 0) and 5.5% and 4.6% showed an uncooperative attitude, respectively ($p < 0.024$). During treatment, 75.2% of the older children maintained their high level of cooperation, while the younger children who were relaxed during the induction phase showed some level of discomfort (Venham score 1 or 2). The proportion of younger patients with a Venham score of 4 or more points increased again to 13.3%, whereas the proportion of older children with a Venham score of 4 or more points remained below 5%. No significant differences were found when comparing the Venham scores of male and female patients. All complete results are shown in Table 4.

Table 4. Venham score per age range and gender.

	Gender				Age Range		
	Venham Score	**Female**	**Male**	***p*-Value**	**4–6**	**7–10**	***p*-Value**
T0	0 (Relaxed)	50 (28.6%)	63 (32.1%)	0.922	45 (20.6%)	68 (44.4%)	<0.001
	1 (Uneasy)	39 (22.3%)	43 (21.9%)		50 (22.9%)	32 (20.9%)	
	2 (Tense)	37 (21.1%)	38 (19.4%)		53 (24.3%)	22 (14.4%)	
	3 (Reluctant)	20 (11.4%)	24 (12.2%)		30 (13.8%)	14 (9.2%)	
	4 (Interference)	17 (9.7%)	19 (9.7%)		24 (11.0%)	12 (7.8%)	
	5 (Out of contact)	12 (6.9%)	9 (4.6%)		16 (7.3%)	5 (3.3%)	
T1	0 (Relaxed)	119 (68.0%)	139 (70.9%)	0.978	143 (65.6%)	115 (75.2%)	0.024
	1 (Uneasy)	16 (9.1%)	18 (9.2%)		22 (10.1%)	12 (7.8%)	
	2 (Tense)	15 (8.6%)	15 (7.7%)		14 (6.4%)	16 (10.5%)	
	3 (Reluctant)	11 (6.3%)	12 (6.1%)		17 (7.8%)	6 (3.9%)	
	4 (Interference)	8 (4.6%)	6 (3.1%)		12 (5.5%)	2 (1.3%)	
	5 (Out of contact)	6 (3.4%)	6 (3.1%)		10 (4.6%)	2 (1.3%)	
T2	0 (Relaxed)	112 (64.0%)	128 (65.3%)	0.837	125 (57.3%)	115 (75.2%)	0.002
	1 (Uneasy)	20 (11.4%)	20 (10.2%)		31 (14.2%)	9 (5.9%)	
	2 (Tense)	12 (6.9%)	18 (9.2%)		18 (8.3%)	12 (7.8%)	
	3 (Reluctant)	12 (6.9%)	13 (6.6%)		15 (6.9%)	10 (6.5%)	
	4 (Interference)	14 (8.0%)	10 (5.1%)		18 (8.3%)	6 (3.9%)	
	5 (Out of contact)	5 (2.9%)	7 (3.6%)		11 (5.0%)	1 (0.7%)	

Legend: T0, before treatment; T1, at the end of induction; T2, during the treatment. Values are reported as frequencies (percentages).

During the treatment, none of the patients lost consciousness, and all maintained constant pharyngeal and laryngeal reflexes and visual and verbal contact with clinical staff. More than 97% of children reported no side effects after N_2O administration; only 2.7% reported transient and mild side effects (e.g., nausea or vomiting, asthma or cough, headache, hyperexcitability, or sleepiness). No statistically significant differences were observed in relation to gender and age range (Table 5).

Table 5. Side effects within 48 h after dental treatment.

	Total	**Male**	**Female**	***p*-Value**	**4–6 Years**	**7–10 Years**	***p*-Value**
No side effect	361 (97.3%)	190 (96.9%)	171 (97.7%)	0.664	212 (97.3%)	149 (97.4%)	0.680
Nausea or vomiting	3 (0.8%)	1 (0.5%)	2 (1.1%)		1 (0.5%)	2 (1.3%)	
Asthma or cough	1 (0.3%)	1 (0.5%)	0 (0.0%)		0 (0.0%)	1 (0.7%)	
Headache	3 (0.8%)	2 (1.0%)	1 (0.6%)		2 (0.9%)	1 (0.7%)	
Hyperexcitability	1 (0.3%)	0 (0.0%)	1 (0.6%)		1 (0.5%)	0 (0.0%)	
Sleepiness	2 (0.5%)	2 (1.0%)	0 (0.0%)		2 (0.9%)	0 (0.0%)	

Values are reported as frequencies (percentages).

A total of 335 patients completed the scheduled treatment (90.3%). Patients who did not complete treatment reported a Venham score of 4 or 5.

4. Discussion

Dealing with children who suffer from dental anxiety plays a crucial role in pediatric dentistry. Given the special conditions that characterize childhood, finding therapeutic approaches that increase the child's confidence in his or her own dentist and reduce feelings of insecurity about all dental procedures is an important first step toward appropriate management of the child's own healthcare. According to a recent study examining the potential reduction in the need for general anesthesia in 228 precooperative or anxious patients aged 3 to 12 years, nitrous oxide sedation combined with behavioral management techniques can play a critical role in invasive dental procedures and could be considered a reliable alternative to general anesthesia [39]. Therefore, the aim of this study was to investigate the efficacy of N_2O/O_2 sedation in a sample of children aged 4–10 years who required conservative treatment of deciduous teeth.

Throughout the observation period, a statistically and clinically significant improvement in Venham score from baseline was observed, with a strong relaxation and a strong reduction in anxiety and fear because of the analgesic and anxiolytic effects of N_2O sedation, which led to a reduction or elimination of pain, anxiety, and discomfort, although local anesthesia was not performed.

No difference was found between females and males, whereas there was a statistically significant difference between the two age groups for the Venham score. Notably, younger children had a higher Venham score from the beginning and maintained these higher scores throughout the dental procedure, although they responded optimally to procedural sedation with N_2O/O_2. These positive results were also confirmed by the analysis of the Venham score, not only in terms of mean and standard deviation but also as a categorical variable. Indeed, this second analysis showed that the cooperativeness of the younger children increased at the end of the induction phase: The percentage of fully cooperative patients increased from 20.6% to 65.6% and stabilized at 57.3% during treatment. In contrast, the older group had a higher percentage of relaxed children before treatment, which increased and was maintained throughout the dental procedure. The initial difference between younger and older children can be explained as further evidence of the different approach to dental treatment in children of different ages. Although there is no relationship between dental anxiety and fear in the current literature, our study has shown that younger patients approach dental treatments with higher dental anxiety levels: the children appeared tense but not to the point of disrupting the continuity of treatment. A psychometric study conducted in 1997 by Burnahm et al. on a sample of young American children showed that younger children are more likely to be anxious, especially when the anxiety is a reaction to unfamiliar situations such as those that may occur in a dental office [40]. Previous studies have reported that DFA is higher in younger children [9,10,41,42] and reduces with age [1,2], although the trend of decrease/increase in DFA appears not to be constant throughout childhood. According to Majstorovic and Veerkamp, a decrease in DFA was observed in children aged 4–11 years, which increased again after 11 years [43,44], whereas some longitudinal studies showed a different increase in prevalence (from 8.8% at age 5 years to 14.6% at age 9 years or a slight increase of about 3% points from 6 to 8 years) but without a specific trend given that many participants who were anxious at baseline were no longer anxious after 2 years [45]. After the initial anxiety, N_2O/O_2 therapy showed a positive effect in all patients, especially in the younger ones, reducing the difference between older and younger children in the Venham score. At the end of the treatment, younger children showed some degree of apprehension, although a good level of cooperation was maintained.

According to our results, the success rate, i.e., completion of dental treatment, was achieved in over 90% of patients, with a very low rate of side effects, which consisted mainly of nausea, vomiting, headache, and a single case of hyperexcitability. Nausea and vomiting occurred within a few minutes after interruption of dental treatment or after completion of dental treatment. In those cases where interruption of treatment was necessary because of the children's complete uncooperativeness, nausea and vomiting appear to be due mainly to symptoms of agitation that forced the dentist to interrupt treatment rather than to a side effect of nitrous oxide. Although the standard procedure of inhalation of 100% O_2 at the end of treatment was used in all children, nausea and vomiting would have occurred in children who required interruption for lack of adequate O_2 inhalation. Headache and hyperexcitability occurred within the first 12 h of treatment, and hyperexcitability was more symptomatic because the adverse effect coincided with sleep time.

Overall, the low side effect rate confirms the beneficial effect of N_2O/O_2 on children's relaxation during the dental procedure and the safe profile of this approach when the concentration does not exceed the recommended dose, which was also reduced to no more than 35% in our study. Galeotti et al. (2016) analyzed the efficacy and tolerability of N_2O/O_2 in a sample of 472 noncooperative pediatric patients (aged 4–17 years, but mainly in patients aged 4–6 years) who were unable to accept dental procedures because of dental anxiety and were treated with N_2O conscious sedation as an alternative to general anesthesia and showed a success rate (i.e., optimal sedation to complete dental procedures) in more than 86% of children with a very low rate of side effects (2.5%) [35]. According to Rossit et al., who analyzed the success rate of sedation with N_2O and O_2 in dentistry in a systematic review and meta-analysis that included 19 articles (8 RCTs and 11 crossover studies), with a total of 1098 pediatric patients and 195 adults, the success rate of N_2O/O_2 administration was 91.9% (95% CI: 82.5–98.1%) [46]. The higher success rate in our study may be explained by the combination of conscious sedation and the use of insulating rubber, a stress-reducing agent used in children during dental treatment that promotes nasal breathing and thus better inhalation of the total dose of N_2O administered. In a recent randomized, controlled trial conducted on a sample of 51 children (mean age 6.55 $\pm$ 1.81 years), 21 of whom were treated with conscious sedation (9 with rubber dam and 12 with cotton roll isolation), Vanhée et al. (2021) found that both Venham score and heart rate were lower in children treated with rubber dam and conscious sedation than in children treated with conscious sedation and cotton isolation only ($p < 0.05$) [47]. Similar results were also shown in a recent study that evaluated data from 112 medical records of children (mean age: 6.1 $\pm$ 1.8 years) who received restorative treatment under moderate sedation. After adjusting the regression model for sedation depth, sedation regimen, age, and sex, Current et al. (2022) reported better behavioral outcomes in patients treated with rubber dam compared with those treated with IsoVac, an innovative dental isolation treatment [48]. Placement of clamps without local or topical anesthesia, a procedure that has bothersome or even painful effects, is a potential barrier to appropriate treatment of children with dental anxiety. In our work, the behavioral approach and the first appointment for familiarization, during which the clinician explained the safe role of the rubber dam, helped to increase children's compliance during the first phase of dental treatment.

In the patients in whom treatment was discontinued, the lack of relaxation was not due to the lack of effect of N_2O/O_2 but to poor inhalation of nitrous oxide caused by a significant lack of cooperation on the part of the children. Unlike other forms of sedation such as midazolam, N_2O/O_2 is inhaled by the patient, and a certain degree of cooperation is required for proper inhalation: a child who is screaming or yelling either receives no N_2O/O_2 at all or a very low dose that prevents his or her relaxation.

This study has some limitations, mainly because of its retrospective study design and the lack of a control group. First, selection bias may have occurred because patients were selected without randomization. Second, DFA levels were not quantitatively determined in the children at baseline, so some degree of heterogeneity could not be excluded. Finally, nonpharmacological strategies were used in all patients before N_2O/O_2 sedation, but their effects on patient relaxation were not considered. Future prospective and randomized studies are needed to consider the exogenous and endogenous factors that may influence DFA and children's perception before and during dental treatment. Moreover, according to the recent study of Prud'homme and colleagues, who observed a certain level of children's attraction toward nitrous oxide in case of prolonged use [49], future studies should focus on this aspect and evaluate possible dependence effects with nitrous oxide prolonged use.

5. Conclusions

In conclusion, N_2O/O_2 is a reliable, safe, and not a time-consuming procedure for treating younger children with mild to moderate dental anxiety. The possibility of continuous communication between the child and the dentist during all procedures allows younger children to overcome their innate fear of the unknown so that they can approach dental treatments with great ease and adopt appropriate dental behaviors to reduce the risk of invasive dental treatments at a young age.

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References

1. Cianetti, S.; Lombardo, G.; Lupatelli, E.; Pagano, S.; Abraha, I.; Montedori, A.; Caruso, S.; Gatto, R.; De Giorgio, S.; Salvato, R. Dental fear/anxiety among children and adolescents. A systematic review. *Eur. J. Paediatr. Dent.* **2017**, *18*, 121–130. [CrossRef]
2. Shim, Y.S.; Kim, A.H.; Jeon, E.Y.; An, S.Y. Dental fear & anxiety and dental pain in children and adolescents: A systemic review. *J. Dent. Anesth. Pain Med.* **2015**, *15*, 53–61. [CrossRef]
3. Gao, S.; Lu, J.; Li, P.; Yu, D.; Zhao, W. Prevalence and risk factors of children's dental anxiety in China: A longitudinal study. *BMJ Open* **2021**, *11*, e043647. [CrossRef]
4. Torriani, D.D.; Ferro, R.L.; Bonow, M.L.; Santos, I.S.; Matijasevich, A.; Barros, A.J.; Demarco, F.F.; Peres, K.G. Dental caries is associated with dental fear in childhood: Findings from a birth cohort study. *Caries Res.* **2014**, *48*, 263–270. [CrossRef]
5. Versloot, J.; Veerkamp, J.S.; Hoogstraten, J.; Martens, L.C. Children's coping with pain during dental care. *Community Dent. Oral Epidemiol.* **2004**, *32*, 456–461. [CrossRef]
6. Grisolia, B.M.; Dos Santos, A.P.P.; Dhyppolito, I.M.; Buchanan, H.; Hill, K.; Oliveira, B.H. Prevalence of dental anxiety in children and adolescents globally: A systematic review with meta-analyses. *Int. J. Paediatr. Dent.* **2021**, *31*, 168–183. [CrossRef]
7. Celeste, R.K.; Eyjolfsdottir, H.S.; Lennartsson, C.; Fritzell, J. Socioeconomic Life Course Models and Oral Health: A Longitudinal Analysis. *J. Dent. Res.* **2020**, *99*, 257–263. [CrossRef]
8. Ramos-Jorge, J.; Marques, L.S.; Homem, M.A.; Paiva, S.M.; Ferreira, M.C.; Oliveira Ferreira, F.; Ramos-Jorge, M.L. Degree of dental anxiety in children with and without toothache: Prospective assessment. *Int. J. Paediatr. Dent.* **2013**, *23*, 125–130. [CrossRef]
9. Wogelius, P.; Poulsen, S. Associations between dental anxiety, dental treatment due to toothache, and missed dental appointments among six to eight-year-old Danish children: A cross-sectional study. *Acta Odontol. Scand.* **2005**, *63*, 179–182. [CrossRef]
10. Wogelius, P.; Poulsen, S.; Sørensen, H.T. Prevalence of dental anxiety and behavior management problems among six to eight years old Danish children. *Acta Odontol. Scand.* **2003**, *61*, 178–183. [CrossRef]
11. Buldur, B.; Guvendi, O.N. Conceptual modelling of the factors affecting oral health-related quality of life in children: A path analysis. *Int. J. Paediatr. Dent.* **2020**, *30*, 181–192. [CrossRef] [PubMed]
12. Vlad, R.; Pop, A.M.; Olah, P.; Monea, M. The Evaluation of Dental Anxiety in Primary School Children: A Cross-Sectional Study from Romania. *Children* **2020**, *7*, 158. [CrossRef] [PubMed]
13. Goettems, M.L.; Ardenghi, T.M.; Romano, A.R.; Demarco, F.F.; Torriani, D.D. Influence of maternal dental anxiety on the child's dental caries experience. *Caries Res.* **2012**, *46*, 3–8. [CrossRef] [PubMed]
14. Goyal, J.; Menon, I.; Singh, R.P.; Sharma, A.; Passi, D.; Bhagia, P. Association between maternal dental anxiety and its effect on the oral health status of their child: An institutional cross sectional study. *J. Family Med. Prim. Care* **2019**, *8*, 535–538. [CrossRef] [PubMed]
15. Costa, V.P.P.; Goettems, M.L.; Quevedo, L.; Armfield, J.; Pinheiro, R.T.; Demarco, F.F. Relation between anxiety disorders in adolescent mothers and dental fear in children. *Int. J. Paediatr. Dent.* **2022**, in press. [CrossRef]

16. Alasmari, A.A.; Aldossari, G.S.; Aldossary, M.S. Dental Anxiety in Children: A Review of the Contributing Factors. *J. Clin. Diagn. Res.* **2018**, *12*, SG01–SG03. [CrossRef]
17. Ten Berge, M.; Veerkamp, J.S.; Hoogstraten, J. The etiology of childhood dental fear: The role of dental and conditioning experiences. *J. Anxiety Disord.* **2002**, *16*, 321–329. [CrossRef]
18. Mendoza-Mendoza, A.; Perea, M.B.; Yanez-Vico, R.M.; Iglesias-Linares, A. Dental fear in children: The role of previous negative dental experiences. *Clin. Oral Investig.* **2015**, *19*, 745–751. [CrossRef]
19. Wigen, T.I.; Skaret, E.; Wang, N.J. Dental avoidance behaviour in parent and child as risk indicators for caries in 5-year-old children. *Int. J. Paediatr. Dent.* **2009**, *19*, 431–437. [CrossRef]
20. Klingberg, G.; Vannas Löfqvist, L.; Bjarnason, S.; Norén, J.G. Dental behavior management problems in Swedish children. *Community Dent. Oral Epidemiol.* **1994**, *22*, 201–205. [CrossRef]
21. Nuttall, N.M.; Gilbert, A.; Morris, J. Children's dental anxiety in the United Kingdom in 2003. *J. Dent.* **2008**, *36*, 857–860. [CrossRef] [PubMed]
22. Hill, K.B.; Hainsworth, J.M.; Burke, F.J.; Fairbrother, K.J. Evaluation of dentists' perceived needs regarding treatment of the anxious patient. *Br. Dent. J.* **2008**, *204*, E13. [CrossRef]
23. Beaton, L.; Freeman, R.; Humphris, G. Why are people afraid of the dentist? Observations and explanations. *Med. Princ.. Pract* **2014**, *23*, 295–301. [CrossRef] [PubMed]
24. Dahlander, A.; Soares, F.; Grindefjord, M.; Dahllof, G. Factors Associated with Dental Fear and Anxiety in Children Aged 7 to 9 Years. *Dent. J.* **2019**, *7*, 68. [CrossRef] [PubMed]
25. Freeman, R.E. Dental anxiety: A multifactorial aetiology. *Br. Dent. J.* **1985**, *159*, 406–408. [CrossRef] [PubMed]
26. Hussein, T.O.; Aksit-Bicak, D. Management of Post-Traumatic Dental Care Anxiety in Pediatric Dental Practice-A Clinical Study. *Children* **2022**, *9*, 1146. [CrossRef] [PubMed]
27. Use of Nitrous Oxide for Pediatric Dental Patients. *Pediatr. Dent.* **2021**, *39*, 273–277.
28. Association, A.D. Oral Health Topics: Nitrous Oxide: Dental Best Practices for Nitrous Oxide-Oxygen. Available online: https://www.ada.org/en/member-center/oral-health-topics/nitrous-oxide (accessed on 7 September 2022).
29. Knuf, K.; Maani, C.V. Nitrous Oxide. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
30. Subramaniam, P.; Girish Babu, K.L.; Lakhotia, D. Evaluation of nitrous oxide-oxygen and triclofos sodium as conscious sedative agents. *J. Indian Soc. Pedod. Prev. Dent.* **2017**, *35*, 156–161. [CrossRef]
31. Hennequin, M.; Collado, V.; Faulks, D.; Koscielny, S.; Onody, P.; Nicolas, E. A clinical trial of efficacy and safety of inhalation sedation with a 50% nitrous oxide/oxygen premix (Kalinox) in general practice. *Clin. Oral Investig.* **2012**, *16*, 633–642. [CrossRef]
32. Chi, S.I. Complications caused by nitrous oxide in dental sedation. *J. Dent. Anesth. Pain Med.* **2018**, *18*, 71–78. [CrossRef]
33. Yee, R.; Wong, D.; Chay, P.L.; Wong, V.Y.Y.; Chng, C.K.; Hosey, M.T. Nitrous oxide inhalation sedation in dentistry: An overview of its applications and safety profile. *Singapore Dent. J.* **2019**, *39*, 11–19. [CrossRef]
34. Bangash, M.; Mustafa, L.; Irshad, M.; Omer, Q.; Alam, M.K. Short Term Effects of Inhalation Sedation on Child Dental Fear and Anxiety. *Curr. Pediatr. Rev.* **2022**, in press. [CrossRef]
35. Galeotti, A.; Garret Bernardin, A.; D'Anto, V.; Ferrazzano, G.F.; Gentile, T.; Viarani, V.; Cassabgi, G.; Cantile, T. Inhalation Conscious Sedation with Nitrous Oxide and Oxygen as Alternative to General Anesthesia in Precooperative, Fearful, and Disabled Pediatric Dental Patients: A Large Survey on 688 Working Sessions. *Biomed. Res. Int.* **2016**, *2016*, 7289310. [CrossRef]
36. Moharrami, M.; Ali, S.; Dick, B.D.; Moeinvaziri, F.; Amin, M. The relationship between nitrous oxide sedation and psychosocial factors in the pediatric outpatient setting. *Paediatr. Anaesth.* **2022**, *32*, 548–555. [CrossRef] [PubMed]
37. Malamed, S.F.; Clark, M.S. Nitrous oxide-oxygen: A new look at a very old technique. *J. Calif. Dent. Assoc.* **2003**, *31*, 397–403. [PubMed]
38. Veerkamp, J.S.; Gruythuysen, R.J.; van Amerongen, W.E.; Hoogstraten, J. Dental treatment of fearful children using nitrous oxide. Part 3: Anxiety during sequential visits. *ASDC J. Dent. Child* **1993**, *60*, 175–182.
39. Mourad, M.S.; Splieth, C.H.; Al Masri, A.; Schmoeckel, J. Potential for nitrous oxide sedation in pedodontics practice to reduce the need for dental general anesthesia. *Quintessence Int.* **2022**, *53*, 598–606. [CrossRef]
40. Burnham, J.J.; Gullone, E. The Fear Survey Schedule for Children–II: A psychometric investigation with American data. *Behav. Res. Ther.* **1997**, *35*, 165–173. [CrossRef]
41. Dogan, M.C.; Seydaoglu, G.; Uguz, S.; Inanc, B.Y. The effect of age, gender and socio-economic factors on perceived dental anxiety determined by a modified scale in children. *Oral Health Prev. Dent.* **2006**, *4*, 235–241. [PubMed]
42. Klingberg, G.; Broberg, A.G. Dental fear/anxiety and dental behaviour management problems in children and adolescents: A review of prevalence and concomitant psychological factors. *Int. J. Paediatr. Dent.* **2007**, *17*, 391–406. [CrossRef]
43. Majstorovic, M.; Veerkamp, J.S. Developmental changes in dental anxiety in a normative population of Dutch children. *Eur. J. Paediatr. Dent.* **2005**, *6*, 30–34. [PubMed]
44. Majstorovic, M.; Skrinjaric, T.; Szirovicza, L.; Glavina, D.; Veerkamp, J.S. Dental anxiety in relation to emotional and behavioral problems in Croatian adolescents. *Coll. Antropol.* **2007**, *31*, 573–578. [PubMed]
45. Soares, F.C.; Lima, R.A.; de Barros, M.V.G.; Dahllöf, G.; Colares, V. Development of dental anxiety in schoolchildren: A 2-year prospective study. *Community Dent. Oral Epidemiol.* **2017**, *45*, 281–288. [CrossRef]
46. Rossit, M.; Gil-Manich, V.; Ribera-Uribe, J.M. Success rate of nitrous oxide-oxygen procedural sedation in dental patients: Systematic review and meta-analysis. *J. Dent. Anesth. Pain Med.* **2021**, *21*, 527–545. [CrossRef] [PubMed]

47. Vanhee, T.; Tassignon, C.; Porta, P.; Bottenberg, P.; Charles, T.; Vanden Abbeele, A. Behavior of Children during Dental Care with Rubber Dam Isolation: A Randomized Controlled Study. *Dent. J.* **2021**, *9*, 89. [CrossRef]
48. Current, J.L.; Unkel, J.H.; Berry, E.J.; Reinhartz, J.; Reinhartz, D. Comparing Behavior Outcomes with Rubber Dam or IsoVac Isolation in Patients Undergoing Moderate Sedation. *J. Dent. Child* **2022**, *89*, 83–87.
49. Prud'homme, T.; Allio, A.; Dajean-Trutaud, S.; Bulteau, S.; Rousselet, M.; Lopez-Cazaux, S.; Hyon, I.; Grall-Bronnec, M.; Victorri-Vigneau, C. Assessment of an Equimolar Mixture of Oxygen and Nitrous Oxide: Effects in Pediatric Dentistry. *Int. J. Clin. Pediatr. Dent.* **2019**, *12*, 429–436. [CrossRef]