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Original Article

Dentistry Section

Efficacy and Safety of Nitrous Oxide Inhalation Sedation in Paediatric Dental Patients: A Comparison of Different Concentrations

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ABSTRACT

Introduction: In order to effectively treat children, managing terrified and nervous paediatric dental patients is crucial. The choice of a specific behaviour control strategy is at the operator's discretion, but it may be influenced by parental approval. Clinically beneficial pharmacological therapies, such as Nitrous Oxide-oxygen Inhalation Sedation (NOIS), have been demonstrated. However, prolonged exposure to specific amounts of these therapies could pose health hazards for medical personnel.

Aim: To evaluate the clinical efficacy and safety of utilising N_2O inhalation sedation at a 70% concentration in a paediatric dental setting, compared to administering it at 50% and 60% concentrations.

Materials and Methods: A non randomised clinical trial was conducted in the Department of Paediatric and Preventive Dentistry at Saveetha Dental College, Chennai, India. The duration of the study was three months, from June 2022 to August 2022. A total of 42 young patients between the ages of 4 and 10 who required mandibular pulpectomy and crown were selected. During the study, the researchers recorded each patient's levels of sedation and cooperation at four specific time points while administering a fixed concentration of N_2O. The concentrations at these time points were 50% at the 10th minute, 60% at the 20th minute, 70% at the 30th minute, and 70% at the 40th minute. The study compared the primary outcomes of sedation and cooperation levels, along with the secondary outcome of adverse effects, between the different time intervals using the Kruskal-Wallis test followed by post-hoc tests for pair-wise comparison. The level of significance was set at $p<0.05$.

Results: The mean age of the children included in the present study was 7.4±1.324 years. At the end of 40 minutes at a 70% concentration, a deep sedation score of six was achieved by 7 (16.7%) of the patients, while none of the patients achieved this sedation level at concentrations of 50%, 60%, or 70% at the end of 30 minutes. The mean sedation score of patients at the end of 40 minutes at a 70% concentration (4.86±0.683) was higher than the sedation score of patients at the end of 30 minutes at a 70% concentration (4.36±0.656). Cooperation at a 70% concentration was better at the end of 40 minutes (5.83±0.377) than at the end of 30 minutes (5.40±0.497). At 50% and 60% concentrations, no adverse effects were observed.

Conclusion: Sedation at a 60% concentration was more effective than 50% in achieving satisfactory cooperation to complete dental treatment without any adverse effects. Additionally, at a 70% concentration, sedation and cooperation were higher, but adverse effects were noted, warranting caution when considering its use for extended periods.

Keywords: Cooperation, Nitrous oxide, Paediatric dentistry, Sedative agent

INTRODUCTION

The pioneering use of N_2O for painless dental and surgical procedures is attributed to Horace Wells, an American dentist, who is now revered as the Father of Anaesthesia. Since Wells' groundbreaking discovery in 1844, the practice of NOIS has undergone remarkable advancements, becoming a fundamental approach to pharmacological behaviour modification [1]. Initially, N_2O was used as a standalone gas technique for anaesthesia purposes. When used as the sole gas, it caused severe complications such as hypoxia, nausea, vomiting, mild agitation, and disorientation. However, the current standard of care necessitates its dilution with oxygen (O_2) to achieve precise titration levels [2]. NOIS is one of the well-accepted techniques by children and is used by more than 85% of paediatric dentists [3,4]. N_2O, when inhaled, is swiftly absorbed through the alveoli. Its onset of action occurs within 2 to 5 minutes. A noteworthy phenomenon associated with this type of sedation is the second-gas effect, wherein it diffuses more rapidly across alveolar basement membranes compared to other gases [5]. This rapid diffusion causes a concentration of remaining alveolar gases, accelerating the uptake of N_2O into the bloodstream and expediting the onset of anaesthesia. Conscious sedation with the N_2O-oxygen combination is an ideology that has opened new prospects for managing anxious, uncooperative children in almost all the allied fields of healthcare and has become liked by modern-day dentists [6]. N_2O sedation has proven to be highly effective, especially in paediatric dentistry, helping to manage the gag reflex and anxiety while promoting better cooperation among young patients [7]. Studies have also demonstrated that children treated with N_2O sedation experience lower postoperative anxiety levels compared to those treated under general anaesthesia [8-10]. As a result, N_2O sedation can be utilised repeatedly to alleviate anxiety in subsequent visits. The anaesthetic effect of NOIS is achieved through non competitive inhibition of N-Methyl-D-Aspartate (NMDA) in the central nervous system [11]. As for the analgesic effect, it involves the release of endogenous opioids that bind to opioid receptors, producing results comparable to morphine [12]. Lastly, the antianxiety effect arises from the activation of Gamma-Aminobutyric Acid type A (GABA-A) receptors [13]. These three actions collectively contribute to the comprehensive sedative and pain-relieving effects of N_2O [14]. Inhalation of this mixture of gas, after a particular induction period, is said to increase the cooperation level of children and decrease pain perception [15,16].

The N_2O can be administered at a 35-50% concentration prior to or during the administration of LA [4,17]. The concentration can be maintained at the same level during the entire procedure or may be slightly reduced [18]. Concentrations of N_2O below 50% are suggested to alleviate anxiety, offer analgesic effects, and ensure that patients can respond to the dentist's instructions normally [19]. Additionally, such concentrations allow for quick recovery of mobility without compromising protective reflexes [19]. In paediatric dentistry, N_2O is frequently used at a 50% concentration [20]. The degree of cooperation attained at this concentration might not be sufficient to complete the necessary treatment [7]. N_2O at concentrations higher than 50% has been used, but the long-term effects were inconclusive. There is evidence from a cohort study showing that 70% N_2O provides similar sedation as 50% with no adverse effects [21]. Another study proves that N_2O can be safely used for procedures that involve a short duration of time [20]. Numerous textbooks advocate for N_2O to be administered continuously throughout the procedure [22-24]. The benefit of N_2O-O_2 sedation is that the medication administrator can quickly alter the level of sedation and increase or decrease it in appropriate scenarios. Effectiveness and safety depend heavily on this control power [25].

In light of this, the published guidelines recommend that N_2O be used in ambient conditions and carefully monitored [26]. The intent of the present study was to evaluate the levels of sedation and compliance in patients receiving N_2O treatments at concentrations higher than 50%. The present study systematically explores varying concentrations (50%, 60%, and 70%) and durations (10, 20, 30, and 40 minutes) to provide a comprehensive analysis of their effects on sedation, cooperation, and adverse effects. The study highlights potential adverse effects associated with N_2O sedation, particularly at higher concentrations and longer durations.

MATERIALS AND METHODS

A non randomised clinical trial was conducted in the Department of Paediatric and Preventive Dentistry at Saveetha Dental College, Chennai, India. The duration of the study was three months, from June 2022 to August 2022. The study was done after obtaining approval from the Institutional Review Board (IHEC/SDC/PEDO-2102/22/648). Informed consent was obtained from the children who participated in the study.

Inclusion criteria: Children aged 4 to 10 years and belonging to ASA 1. Children exhibiting negative behaviour, scoring 2 on Frankl's behaviour rating scale [22]. Patients for whom basic behaviour guidance techniques have not been successful and those with vital or non vital mandibular primary molars without a sinus tract and absence of internal or external pathologic root resorption. Patients experiencing chronic dental pain during the night and the those with presence of adequate coronal tooth structure to receive a Stainless Steel (SS) crown were included in the study.

Exclusion criteria: Children lacking cooperative ability and with underlying systemic diseases or known allergies. Children with special healthcare needs and who have been administered analgesics six hours prior to the procedure. Children for whom adequate cooperation and sedation were achieved at 50% or 60% concentration to complete the treatment were excluded from the study.

Sample size calculation: The sample size was calculated from a previous study with 95% power using G power analysis, resulting in a total sample of 42 [23].

Study Procedure

Children aged 4 to 10 years who required mandibular pulpectomy but were healthy and reluctant to accept treatment (Frankl behaviour rating score 2) were selected. The primary outcomes, including sedation and cooperation levels, were noted at four time points using a fixed concentration of N_2O throughout the specified period. The concentrations at these time points were as follows: 50% at the end of the 10th minute, 60% at the end of the 20th minute, 70% at the end of the 30th minute, and 70% at the end of the 40th minute. The secondary outcomes measured were adverse effects. Before each study, an airway patency examination was conducted to ensure that the individual did not have an upper respiratory infection and could comfortably breathe through their nose.

The young patient was brought into the dental operatory and seated in the supine position on the chair. Prior to commencing the clinical operation, a comprehensive oral examination was performed, and intraoral periapical radiographs were taken of the teeth requiring pulpectomy. A pulse oximeter probe was attached to the index finger, allowing for continuous monitoring of physiological parameters such as Heart Rate (HR) and Haemoglobin (Hb) oxygen saturation. N_2O administration was carried out using the CONSED N_2O conscious sedation machine. The concentration was gradually increased by 10% through titration.

In all patients, sterile gauze was used to dry the injection site for local anaesthesia after 10 minutes of gas induction with a concentration of 50% N_2O and 50% O_2. Topical anaesthetic gel (progelB, septodont) was applied with a cotton-tip applicator for 45 seconds prior to local anaesthesia. To minimise discomfort, an inferior alveolar nerve and long buccal nerve block were performed using a 27-gauge needle and an aspirating syringe, administered at a slow flow rate (1-2 minutes). The level of anaesthesia was determined by assessing reactions to painful physical sensations, such as pinching. A mouth prop was inserted, and rubber dam isolation was achieved. Sedation and behaviour parameters were evaluated using the Ramsay Sedation Score (RSS) [27,28] and the Houpt behaviour rating scale [29], respectively. Adverse symptoms such as nausea, agitation, and sleepiness were recorded at the end of each phase. [Table/Fig-1,2] display the RSS and Houpt behaviour rating scale.

Score	Symptoms
1	Anxious, restless or both
2	Cooperative, oriented and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

[Table/Fig-1]: Ramsay sedation assessment scale.

Score	Symptoms
1	Aborted: No treatment rendered
2	Poor: Treatment interrupted; only partial treatment was completed
3	Fair: Treatment interrupted but was eventually completed
4	Good: Difficult but all treatment was completed
5	Very good: Some limited crying/movement
6	Excellent: No crying/movement

[Table/Fig-2]: Houpt behaviour rating scale.

To remove superficial caries, a high-speed handpiece was used with a no. 6 round bur from Mani, followed by complete deroofing of the pulp chamber using a no. 330 pear-shaped bur from Mani. The patency of the canals was assessed using a no.10 size K file (Mani). The Kedo S-Plus rotary file was used for canal preparation. After irrigation with physiological saline, the canals were dried with sterile absorbent paper points. Calcium hydroxide and iodoform paste (Metapex, Meta Biomed Co. Ltd., Korea) were gently pressed into the canal using cotton pellets for obturation. The access cavity was filled with glass ionomer cement (Shofu, Shofuinc. Japan), and the crown was rebuilt with stainless steel at the same appointment.

The gas concentration was increased to 60% at the end of 10 minutes and further raised to 70% at the end of 20 minutes. Children whose compliance and sedation could be maintained at 50% or 60% concentration throughout the therapy were not included in the trial to prevent unintended gas exposure. A trained observer who was not involved in the clinical procedures recorded each observation. Patient information, including age, gender, medical history, appointment number, type of intervention used, and the patient's level of sedation, were documented on a form during each session.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 23.0 was used for all statistical analyses. A significance level of 0.05 was set. Descriptive metrics such as Frequency (n), Percentage (%), mean, and Standard Deviation (SD) were employed for the primary overview. The study aimed to compare the primary outcomes of sedation and cooperation levels, as well as the secondary outcome of adverse effects, among different time intervals. The Kruskal-Wallis test was utilised for the comparison, followed by a post-hoc test for pair-wise comparisons.

RESULTS

The descriptive statistics for the age and gender of the participants in the study shown in [Table/Fig-3]. The mean age of the children included in the present study was 7.4±1.324 years. Among the participants, 22 (52.38%) were males, and 20 (47.62%) were females.

	Mean±SD
Age	**7.4±1.324**
Gender	**n (%)**
Male	22 (52.38)
Female	20 (47.62)

[Table/Fig-3]: Descriptive statistics.

At the end of 10 minutes (50% concentration), 15 (35.7%) children were anxious. Among the included children, 7 (16.7%) were unresponsive to stimuli and reached a deep sedation score of 6 at the end of 40 minutes (70% concentration). The mean sedation score of patients at the end of 40 minutes, with a concentration of 70%, was higher (4.86±0.683) compared to the sedation score at the end of 30 minutes, with a concentration of 70% (4.36±0.656) [Table/Fig-4b]. Cooperation improved at a concentration of 70%, with higher scores observed at the end of 40 minutes (5.83±0.377) compared to the end of 30 minutes (5.40±0.497) [Table/Fig-4b]. A significantly higher number of children displayed no adverse effects at concentrations of 50% {33 (78.6%)} and 60% {38 (90.5%)} [Table/Fig-4c]. The results revealed statistically significant differences ($p<0.001$) in sedation and cooperation levels when comparing different time intervals and concentrations (10 min 50% - 30 min 70%, 10 min 50% - 40 min 70%, 20 min 60% - 30 min 70%, 20 min 60% - 40 min 70%) ($p<0.001$) [Table/Fig-5a-c].

DISCUSSION

Incorporating N_2O into dental care helps create a more relaxed environment for receiving treatment, thus safeguarding the emotional well-being of young patients [22]. N_2O sedation is commonly used in both adult and paediatric patients for dental procedures. Previous research has shown that 89% of dentists utilise N_2O, but only 2% of them use concentrations higher than 50% [30]. The current study demonstrates that a higher percentage of sedated children exhibited tranquility at a concentration of 60% (30-71.4%) compared to 50% (27-64.3%). These findings align with a previous study by Kharouba J et al., which concluded that N_2O-oxygen administration at a concentration of 60% is effective for paediatric dental treatment when a 50% concentration is insufficient [7]. There appears to be an increased level of sedation at a concentration of 70%, with a score of 5 observed in 22 (52.4%) children, compared to a concentration of 60% with a score of 2 observed in 30 (71.4%) children. This finding was consistent with other studies that indicate

Score	10 minutes 50% concentration n (%)	20 minutes 60% concentration n (%)	30 minutes 70% concentration n (%)	40 minutes 70% concentration n (%)	p-value
1-Anxious, restless or both	15 (35.7)	0	0	0	<0.001
2-Cooperative, oriented and tranquil	27 (64.3)	30 (71.4)	0	0	
3-Responding to commands	0	12 (28.6)	4 (9.5)	0	
4-Brisk response to stimulus	0	0	19 (45.2)	13 (31)	
5-Sluggish response to stimulus	0	0	19 (45.2)	22 (52.4)	
6-No response to stimulus	0	0	0	7 (16.7)	
Sedation score (Mean±SD)	1.64±0.485	2.29±0.457	4.36±0.656	4.86±0.683	

[Table/Fig-4a]: Sedation scores by duration and concentration of Nitrous Oxide (N_2O) treatment.

Score	10 minutes 50% concentration n (%)	20 minutes 60% concentration n (%)	30 minutes 70% concentration n (%)	40 minutes 70% concentration n (%)	p-value
1- No treatment (aborted)	2 (4.8)	0	0	0	<0.001
2- Partial treatment (poor)	19 (45.2)	42 (100)	0	0	
3- Treatment interrupted but completed (fair)	21 (50)	0	0	0	
4- Difficult but all treatment completed (good)	0	0	0	0	
5 - Limited crying/movement (very good)	0	0	17 (40.5)	7 (16.7)	
6 - No crying/movement	0	0	25 (59.5)	35 (83.3)	
Cooperation score (Mean±SD)	2.45±0.593	2.95±1.103	5.40±0.497	5.83±0.377	

[Table/Fig-4b]: Mean Cooperation scores by duration and concentration of Nitrous Oxide (N_2O) treatment.

Score	10 minutes 50% concentration	20 minutes 60% concentration	30 minutes 70% concentration	40 minutes 70% concentration	p-value
0- No adverse effects	33 (78.6)	38 (90.5)	12 (28.6)	0	<0.001
1- Nausea	9 (21.4)	4 (9.5)	0	3 (7.1)	
2- Agitation	0	0	0	0	
3- Drowsiness	0	0	30 (71.4)	39 (92.9)	

[Table/Fig-4c]: Adverse effects correlated to Nitrous Oxide (N_2O) treatment.

Sedation level	z-value	p-value
10 min 50% - 20 min 60%	-2.265	0.141
10 min 50% - 30 min 70%	-8.520	<0.001
10 min 50% - 40 min 70%	-9.977	<0.001
20 min 60% - 30 min 70%	-6.255	<0.001
20 min 60% - 40 min 70%	-7.712	<0.001
30 min 60 % - 40 min 70%	-1.457	0.871

[Table/Fig-5a]: Pair-wise comparison of various sedation levels.

Cooperation level	z-value	p-value
10 min 50% - 20 min 60%	-0.993	1.000
10 min 50% - 30 min 70%	-7.960	<0.001
10 min 50% - 40 min 70%	-9.032	<0.001
20 min 60% - 30 min 70%	-6.967	<0.001
20 min 60% - 40 min 70%	-8.039	<0.001
30 min 60 % - 40 min 70%	-1.072	1<0.001

[Table/Fig-5b]: Pair-wise comparison of various cooperation levels.

Adverse effects	z-value	p-value
10 min 50% - 20 min 60%	0.617	1.000
10 min 50% - 30 min 70%	-6.388	<0.001
10 min 50% - 40 min 70%	-8.823	<0.001
20 min 60% - 30 min 70%	-5.771	<0.001
20 min 60% - 40 min 70%	-8.206	<0.001
30 min 60 % - 40 min 70%	-2.435	0.089

[Table/Fig-5c]: Pair-wise comparison of various adverse effects.

a shift in sedation depth from moderate to severe with an increased concentration of 70% [7,21].

A study by Zier JL et al., concluded that at a concentration of 50%, only minimal sedation is achieved [20]. The present study also revealed that a minimal sedation score of 1 or 2 was observed only at a concentration of 50%. A previous study has indicated that achieving a Ramsay sedation level of 3 and a Houpt cooperation score between 3 and 5 is considered satisfactory for completing dental treatments [31]. In the present study [Table/Fig-4a,b], 12 children achieved a Ramsay sedation level of 3, and none of the children had a Houpt cooperation score >3-5 at 20 minutes with a concentration of 60%. In the current investigation, a sedation level of 3 was achieved after 20 minutes in 12 (28.6%) cases with a concentration of 60%, and after 30 minutes, all children had a sedation score of 3 or higher.

The decision to administer N_2O beyond the previously established criteria of a Ramsay sedation level of 3 was based on individual patient needs and their demonstrated comfort levels during the procedure. While a Ramsay sedation level of 3 indicates responsiveness to commands, it does not guarantee complete relaxation or the absence of anxiety. If a child is still anxious (indicated by a sedation score of 1) but somewhat tranquil (indicated by a sedation score of 2), it may be beneficial to aim for a higher level of sedation to ensure the child's comfort and cooperation throughout the procedure.

Patients who achieved the desired sedation level and cooperation score with a concentration of 60% and displayed no signs of anxiety or fear did not require escalation to a higher concentration of 70%. These patients were not included in the study because they did not meet the criteria for requiring increased N_2O concentration to manage their anxiety. In [Table/Fig-4a,b], it was observed that at the 30-minute mark, all children had achieved a sedation score of 3 or higher. Additionally, 25 of these children had a behaviour score of 6, indicating calmness with no crying or movement. However, some patients, even though they had achieved the desired sedation level of 3 and the desired behaviour level of 6, expressed a preference to keep the mask supply in place. They continued to show signs of anxiety or fear when attempts were made to reduce the gas concentration, thus making it prudent to continue with the 70% concentration until the end of the 40 minute treatment. This also allowed for the assessment of adverse effects of prolonged gas exposure, which is important for the use of gas in longer procedures.

In essence, the decision to administer a 70% concentration was based on a patient-centred approach, prioritising their comfort, fearlessness, and overall experience during dental treatment. It was made in the best interest of each individual child's well-being and successful completion of the procedure. The suggested approach is to initiate with a 50% concentration of N_2O, and only when sufficient cooperation for psychological comfort is not achieved, consider escalating the concentration to 60% and subsequently to 70% [7]. An increased level of cooperativeness was observed at concentration levels higher than 50%.

The current study showed an increase in adverse effects at a 70% concentration, which contradicts a previous study by Babl FE et al., where no significant adverse effect was observed at a 70% concentration [21]. A review conducted by Galeotti A et al., confirmed that morbidity related to N_2O inhalation sedation is minor in children compared to general anaesthesia [16]. These unfavourable consequences were most likely caused by the lengthy duration of the treatment. The adverse effects, if present, were reported to last longer if the procedure exceeded 15 minutes [20]. When using N_2O, there is always the benefit that over-sedation or the onset of deep sedation can be swiftly and easily reversed by administering 100% O_2 or reducing the N_2O concentration [32]. The practitioner needs to be aware of these changes and prepared to address resulting situations by using appropriate equipment [7]. Previous literature indicates that only a portion of the gas released by the N_2O-O_2 delivery system is absorbed by the lungs. Several factors can contribute to this, such as gas leaks, mouth breathing, the child's respiratory condition, or dead space [32]. Therefore, when the gas concentration is set at 50%, only a limited portion is actually inhaled. If the concentration is increased to 70%, it is unlikely that the concentration of gas reaching the alveoli will exceed 30%-50% [32]. The effectiveness of the gas is also influenced by the child's psychological reassurance and overall condition. The acceleration of adverse effects at a 70% concentration might make N_2O-oxygen inhalation at 60% safer. In future research, enhancing the appeal of the nasal hood by introducing flavours or scents could potentially increase its acceptance among children with varying behavioural characteristics.

Limitation(s)

The present study was not conducted as a blinded controlled trial. The paedodontist was aware of the sedation type and dosage given. More aggressive procedures, such as extractions, were not performed; thus, the cooperation levels could have been more favourable due to this. No assessment regarding the usage of local anaesthesia was done. The anxiety levels of children could have also been assessed.

CONCLUSION(S)

The primary inference drawn from this investigation is that N_2O at a concentration of 60% proved superior in achieving satisfactory cooperation for dental procedures compared to 50%, aligning precisely with our study's primary objective. Prolonged utilisation of a 70% N_2O concentration led to an escalation of adverse effects, indicating the need for caution when considering its use for extended periods. While a Ramsay sedation level of 3 was traditionally considered satisfactory, the present study emphasised the importance of a patient-centred approach, with decisions on N_2O concentration based on individual comfort and cooperation. Adverse effects were more pronounced at a 70% concentration, likely exacerbated by the prolonged treatment duration, suggesting

that shorter procedures may be more suitable for this level of concentration. Future research may explore methods to enhance the appeal of the nasal hood to improve acceptance among children with varying behavioural characteristics.

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