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Original Article

Dentistry Section

Assessing the Brain Activity of Oral Sedation versus Nitrous Oxide Sedation in Paediatric Patients: A Randomised, Cross-over, Clinical Trial

NEHA RAVINDRA GHONGADE[1], NAMRATA GAONKAR[2]

ABSTRACT

Introduction: Managing Dental Fear and Anxiety (DFA) using pharmacological approaches including oral and Nitrous Oxide (N_2O) sedation techniques is a major challenge in paediatric dentistry. Although management of DFA using pharmacological approaches is considered safe, it is necessary to monitor vital indicators like Oxygen Saturation (SpO_2) and pulse rate levels to avoid unpredictable adverse events.

Aim: To compare and evaluate the differences in brain activity patterns, monitoring of pulse rate and SpO_2 levels during oral sedation and N_2O sedation in paediatric patients undergoing pulp therapy for primary mandibular molars.

Materials and Methods: The present randomised, cross-over, clinical trial study was conducted in the Department of Paediatrics and Preventive Dentistry, School of Dental Sciences, Krishna Vishwa Vidyapeeth, Deemed University, Karad, Maharashtra, India during the period of August 2023 to October 2025. A total of 14 (N=14) primary mandibular molars indicated for pulp therapy were included in the study. Midazolam oral sedation was administered to one primary molar at first visit (Group A) and N_2O inhalation was administered to another primary molar (Group B) in the same participant in the second visit in a cross over manner. Vital indicators, including SpO_2 and pulse rate were tracked at three different intervals (baseline, mid-treatment, after withdrawal of the drug). Clark's formula was applied for oral sedation and patient's flow rate was checked for N_2O sedation. Electroencephalogram (EEG) was used for interpretation. Statistical Package for Social Sciences (SPSS) statistical software (version 25; IBM, Armonk, NY, USA) was used to statistically analyse the data. Tukey's post-hoc and Chi-square test were used to compare mean and categorical variables.

Results: The mean pulse rate values obtained with oral sedation vs N_2O sedation at baseline, mid-treatment and post-treatment were 85.8±0.6; 85.7±0.5; 85.2±0.5(p=0.720) vs 85.8±0.6; 85.6±0.5; 85.3±0.5 (p=1.000; p=0.728; p=0.720), respectively. The mean SpO_2 levels with oral sedation vs N_2O sedation at baseline, mid-treatment and post-treatment were 97.7±0.02; 96.8±0.19; 97.07±0.17 vs 97.78±0.22; 97.2±0.19; 97.1±0.14, respectively (p=1.000; p<0.001; p=0.392). However, the intergroup differences were not statistically significant (mid-treatment vs post-treatment) (p=0.142 vs p=0.506) and the EEG displayed no notable deviations, indicating that there had been no appreciable changes in brain activity in both the groups.

Conclusion: According to the findings of the present study, both the groups resulted in acceptable, efficient and safe outcomes with no much difference in the brain activity levels.

Keywords: Electroencephalogram, Midazolam, Nitrous oxide inhalation, Oxygen saturation, Pulse rate

INTRODUCTION

The DFA associated with dental procedures, is both genetic and environmental driven condition that usually manifests in early infancy and is mostly associated with negative dental experiences [1]. Paediatric prevalence estimates range from 5 to 42%, with most reports falling around the 20% range. The percentage of adults who report having DFA ranges from 11 to 32% [2]. DFA ultimately results in child's recalcitrant behaviour making dental treatment more challenging for the Paediatric Dentist by applying routine Behavioural Management Techniques (BMT)/behaviour guiding approaches. To combat this issue, various pharmacological and non pharmacological options, ranging from basic techniques (distraction, voice control, tell-show-do, positive reinforcement, and parental presence or absence) to advanced tactics (sedation, protective stabilisation with active and passive restraint, and General Anaesthesia/GA) are deployed [3,4]. Compared to GA, conscious sedation is considered to be the cheaper and most convenient options. It can be administered to paediatric patients between 15 months and six years, orally, intramuscularly, intravenous, or intranasally. N_2O, midazolam, ketamine, dexmedetomidine, fentanyl, propofol, etomidate, chloral hydrate, pentobarbital, hydroxyzine, and sevoflurane are among the several substances used to induce conscious sedation [5]. Amongst all these, Midazolam is a benzodiazepine oral sedative which is highly lipophilic, water soluble, safe and non irritating effective medication with a half-life of 6-15 minutes and 1.5-2 hours, respectively, ideal for quick treatments. By significantly prolonging the effects of Gamma-Aminobutyric Acid (GABA), a stable sedative level is attained 30 minutes after taking midazolam orally, and its effects take longer to manifest and last longer [6]. N_2O is recommended as a first-line alternative, especially for children, and is regarded as a dependable and valuable dental sedation modality. Known as an anxiolytic agent, it is regarded as a widely accepted conscious sedation for its long-standing safety profile and track record of minimal complications post surgically [7].

Various evidence based comparative studies conducted by Hisham ARB et al., (2022), El Hay OA et al., (2015), Musani IE et al., (2015), Tavassoli-Hojjati S et al., (2014), Golpayegani MV et al., (2012), Somri M et al., (2012) and Manley MC et al., (2000) evaluated the different modes of administration (sublingual, intranasal, oral) and dosage (0.3 mg/kg -0.7mg/kg) of midazolam in paediatric patients [8-14]. Similarly, studies conducted by Musani IE et al., (2015), Shao Y et al., (2013), Piccialli F et al., (2015), Galeotti A et al., (2016), Ergüven SS et al., (2016), Kharouba J et al., (2020), Memè L et al., (2022), Mukundan D et al., (2023) and Bangash M et al., (2024) evaluated the efficiency of N_2O as a minimum sedative medication

when administered at different concentrations i.e., ≤ 50% and ≤ 50%, respectively [10,15-22]. Sivaramakrishnan G et al., (2017) a comparative study of N_2O with midazolam and showed that the combo approach resulted in consistent level of sedation for longer periods in dental procedures [23].

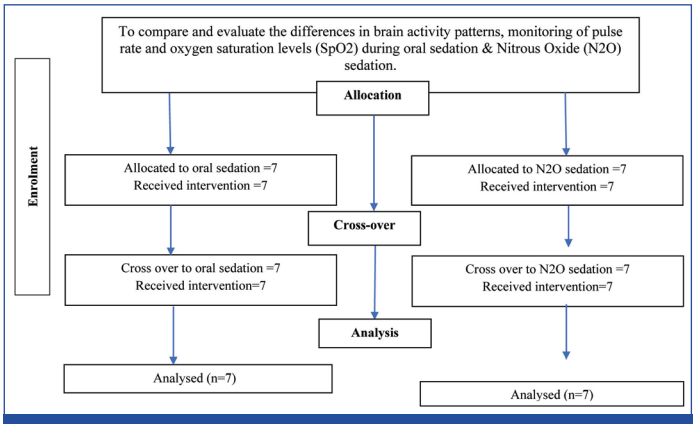
Advances in computational neuroscience and anaesthesia research over the last ten years have improved children's intraoperative EEG monitoring and expanded the use of EEG monitoring in clinical settings. Fong CY et al., (2014), de Heer IJ et al., (2019), Chan MT et al., (2020), Disma N et al., (2021) and Markus M et al., (2021) correlated EEG with anaesthetic effects and concluded that EEG monitoring should be considered as part of the vital organ monitors to guide anaesthetic management [24-28]. However, studies that compared the brain activity parameters along with vital indicators using different sedation techniques are scarce in the literature. Moreover, clinical and experimental trials measuring both the parameters concurrently are limited.

Based on this platitude, the present study aimed to compare and evaluate the differences in brain activity patterns, monitoring of pulse rate and SpO_2 levels during oral sedation and N_2O sedation in paediatric patients undergoing pulp therapy for primary mandibular molars. The primary objective was to compare and evaluate the differences in brain activity patterns, monitoring of pulse rate and SpO_2 levels during oral sedation and N_2O sedation. The secondary objectives were to individually compare and evaluate specific parameters by applying both the sedation procedures. The null hypothesis was set "there is no difference in brain activity patterns, pulse rate and SpO_2 levels in oral sedation and N_2O sedation methods".

MATERIALS AND METHODS

The present randomised, cross-over, clinical trial was conducted in the Department of Paediatrics and Preventive Dentistry, School of Dental Sciences, Krishna Vishwa Vidyapeeth, Deemed University, Karad, Maharashtra, India from August 2023 to October 2025. The study was initiated after due approval of Institutional Ethical Committee bearing the Protocol number 670/2022-2023. CTRI/2025/03/082298 was done (https://ctri.nic.in/Clinicaltrials/pubview2.php). The "World Medical Association Declaration of Helsinki (Carlson, Boyd, and Webb, 2004)" were duly followed in the conduct of this study. [Table/Fig-1] illustrates the Consolidated Standards of Reporting Trials (CONSORT) flow chart for the study design.

Sample size calculation: Sample size was calculated using a randomised, cross-over, clinical trial study conducted by Mozafar S et al., (2018) where the authors evaluated the safety and efficacy of N_2O/midazolam and N_2O/promethazine for dental treatment in eighteen (n=18) uncooperative children as parent article [29]. Using McNemar's test (α Type I error = 0.05, β Type II error = 0.2) and proportion discordance of 0.6, power analysis software (PASS II) calculated the sample size, resulting in a minimum of 12 samples of primary mandibular molar tooth. Hence, the total sample calculated and considered was fourteen samples of primary molar teeth (N=14).



[Table/Fig-1]: CONSORT flow chart.

Inclusion and Exclusion criteria: The inclusion criteria included patients belonging to the age group of 4-10 years, patients undergoing pulp therapy for two primary mandibular molars either in the same quadrant or opposing quadrant, American Society of Anaesthesiologists (ASA) I and II participants and uncooperative patients (Frankl's class II and III). The exclusion was participants with systemic conditions, physically handicapped patients and mentally retarded patients.

In the present study, a total of fourteen (N=14) primary mandibular molars indicated for pulp therapy were included in the study. Midazolam oral sedation was administered for one primary molar at first visit and N_2O inhalation was administered for another primary molar in the same participant in the second visit in a cross over manner. Group A samples of primary mandibular molars received midazolam oral sedation (n=7) while Group B samples received N_2O inhalation (n=7). This was followed by a two week wash out period where no treatment was administered. EEGs were taken at three different intervals i.e., at baseline, mid-treatment, and post-treatment. Throughout the process, pulse rate and SpO_2 levels were tracked and recorded using pulse oximeter.

Study Procedure

Preparation of patients for oral sedation procedure: Using Clark's method for drug dosage, the standard preparation of midazolam was prepared and administered orally at a dose of 0.5 mg/kg in the first visit [30]. Midazolam was combined with a sugar-free orange solution to reduce its unpleasant taste. After 20 to 30 minutes, the patient was closely monitored as per the protocol and the sedation level was determined and pulp therapy for one of the primary molar teeth was initiated. EEG was recorded at baseline (at the beginning of oral sedation), mid-treatment (midway through the course of treatment), and post-treatment (following drug withdrawal).

Preparation of patients for N_2O sedation: N_2O sedation was administered at the second visit. Each patient's N_2O concentration was determined by their flow rate which was 5-6 litres per minute (L/min) for 1-2 minutes. EEG was recorded at baseline (at the beginning of oral sedation), mid-treatment (midway through the course of treatment), and post-treatment (following drug withdrawal). The brain activity of the subjects was categorised as follows: Beta (13-30 Hz) denotes a cognizant state, alpha (8-13 Hz) denotes a relaxed, sleepy state and lastly gamma (30-100 Hz) signals two distinct senses simultaneously [31].

Vital recordings for both methods: Using a pulse oximeter, SpO_2 and pulse rate were recorded in addition to the EEG monitoring of the patient under oral and N_2O sedation.

STATISTICAL ANALYSIS

IBM SPSS statistical software (SPSS version 25; IBM, Armonk, NY, USA) was used for all statistical analyses. In descriptive analysis, all explanatory and outcome variables are expressed in terms of mean and standard deviation for continuous variables and frequency and proportions for categorical variables. Tukey's post-hoc test was used after repeated measures Analysis of Variance (ANOVA) to compare different parameters between and within groups at three distinct intervals between the two groups. At three distinct periods, the Chi-square test was used to assess how brain activity was distributed among the groups. A significance level (p-value) of $p<0.05$ was established.

RESULTS

In the present study, the mean age among all the participants was 6.2±1.5 years with 5 (71.4%) males and 2 (28.6%) females. The most common primary teeth requiring pulp therapy were mandibular

right first molar 7 (50%), mandibular right second molar 5 (35.7%), maxillary left first molar 1 (7.1%) and maxillary right first molar 1 (7.1%).

Comparison of pulse rate levels with oral vs N_2O sedation: At baseline, mid-treatment, and post-treatment, the mean pulse rate values obtained with oral sedation versus N_2O sedation were 85.8±0.6, 85.7±0.5, and 85.2±0.5 vs 85.8±0.6, 85.6±0.5, and 85.3±0.5, respectively. These values showed no significant deviation from the normal range, suggesting that the pulse rate was relatively constant in both groups with no statistically significant difference between the groups (p>0.05) [Table/Fig-2]. No notable alterations at any time were observed with N_2O sedation. Intragroup comparisons showed no significant difference in either of the groups (p>0.05) [Table/Fig-3].

Parameters	Interval	Oral sedation	Nitrous oxide (N_2O)	p-value
Pulse rate	Before treatment	85.857±0.614	85.857±0.614	1.000
	Mid-treatment	85.714±0.535	85.643±0.535	0.728
	Post-treatment	85.286±0.519	85.357±0.519	0.720
SpO_2 levels	Before treatment	97.786±0.227	97.786±0.227	1.000
	Mid-treatment	96.857±0.197	97.214±0.197	<0.001
	Post-treatment	97.071±0.171	97.143±0.171	0.395

[Table/Fig-2]: Comparison and observation of mean pulse rate and SpO_2 levels with oral vs N_2O sedation (baseline, mid-treatment, post-treatment).

Group	(I) Interval	(J) Interval	Mean Difference (I-J)	Std. Error	p-value
Oral sedation	Baseline	Mid-treatment	0.143	0.246	1.000
		Post-treatment	0.571	0.272	0.136
	Mid-treatment	Baseline	0.143	0.246	1.000
		Post-treatment	0.429	0.184	0.083
	Post-treatment	Baseline	0.571	0.272	0.136
		Mid-treatment	0.429	0.184	0.083
Nitrous Oxide (N_2O) Sedation	Baseline	Mid-treatment	0.214	0.246	1.000
		Post-treatment	0.500	0.272	0.232
	Mid-treatment	Baseline	-0.214	0.246	1.000
		Post-treatment	0.286	0.184	0.396
	Post-treatment	Baseline	-0.500	0.272	0.232
		Mid-treatment	-0.286	0.184	0.396

[Table/Fig-3]: Pairwise comparison of mean pulse rate using Tukey's post-hoc test.

Comparison of Oxygen Saturation (SpO_2) with oral vs N_2O sedation: The mean SpO_2 levels with oral sedation versus N_2O sedation at baseline, mid-treatment, and post-treatment were 97.7±0.02; 96.8±0.19; 97.07±0.17 vs 97.78±0.22; 97.2±0.19; and 97.1±0.14 respectively [Table/Fig-2]. During treatment, the SpO_2 levels was significantly more in the N_2O sedation group (p <0.001). Intragroup comparisons showed significant change from baseline in both the groups (p<0.05) [Table/Fig-4].

Comparison and observation of brain activity patterns with oral vs N_2O sedation: Oral sedation increased the number of patients

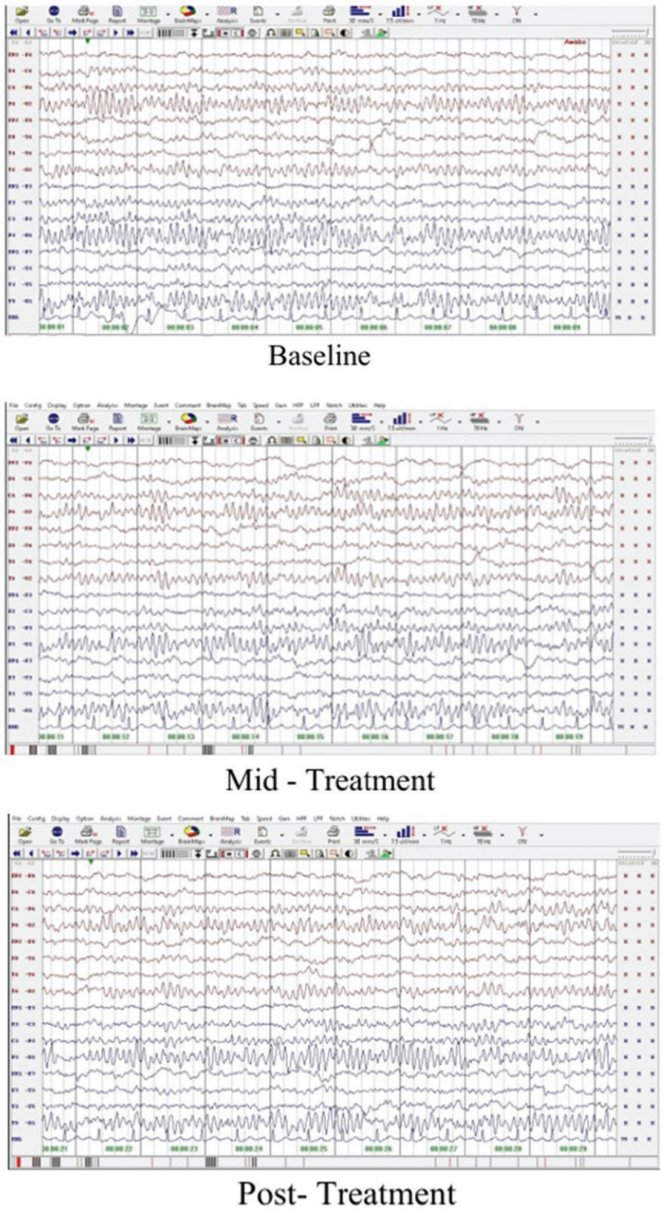
Group	(I) Interval	(J) Interval	Mean Difference (I-J)	Std. Error	p-value
Oral Sedation	Baseline	Mid-treatment	0.929*	0.199	<0.001
		Post-treatment	0.714*	0.246	0.022
	Mid-treatment	Baseline	-0.929*	0.199	<0.001
		Post-treatment	-0.214	0.218	1.000
	Post-treatment	Baseline	-0.714*	0.246	0.022
		Mid-treatment	0.214	0.218	1.000
Nitrous Oxide (N_2O)	Baseline	Mid-treatment	0.571*	0.199	0.024
		Post-treatment	0.643*	0.246	0.044
	Mid-treatment	Baseline	-0.571*	0.199	0.024
		Post-treatment	0.071	0.218	1.000
	Post-treatment	Baseline	-0.643*	0.246	0.044
		Mid-treatment	-0.071	0.218	1.000

[Table/Fig-4]: Pairwise comparison of mean SpO_2 levels using Tukey's post-hoc test.

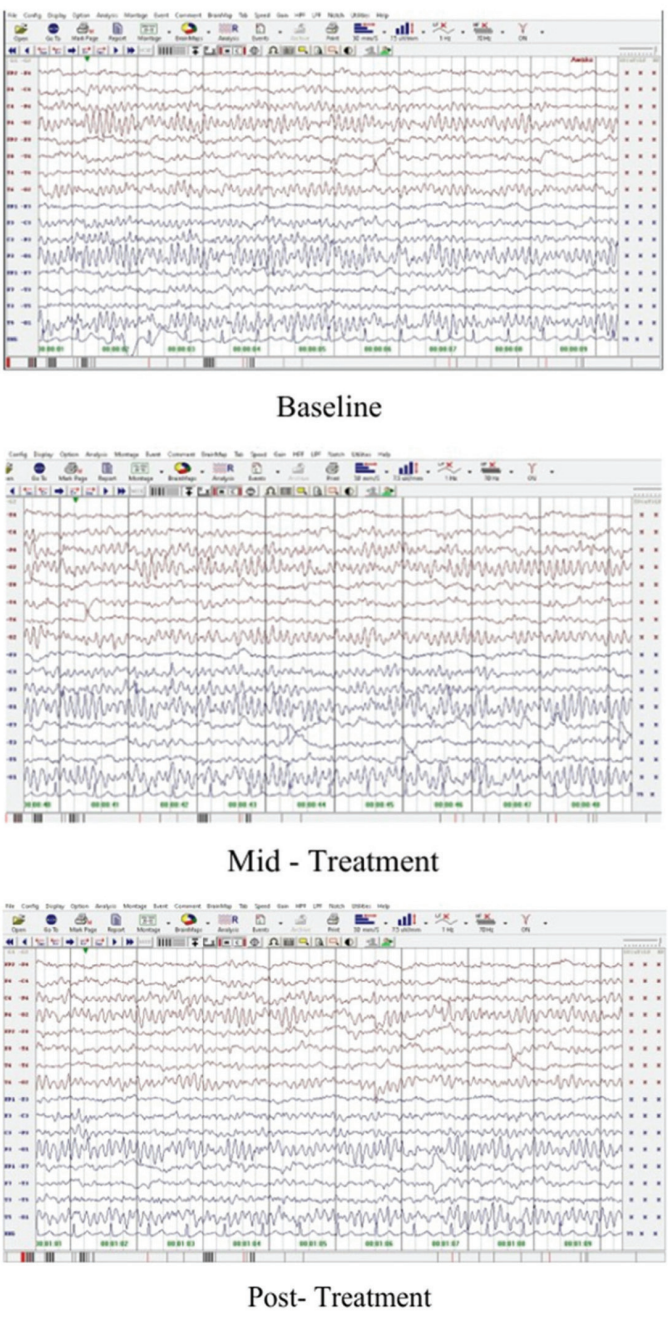
exhibiting alpha wave activity during treatment. Although the differences were not statistically significant (p=0.142, mid-treatment and p=0.506, post-treatment), trends indicate that oral sedation may encourage more relaxation during treatment. Both groups returned to diversified brain activity after treatment, primarily beta [Table/Fig-5,6a,b].

Brain activity Pattern	Oral sedation group			N_2O group			p-value
	Alpha	Beta	Gamma	Alpha	Beta	Gamma	
Baseline	0	14	0	0	14	0	NA
Mid-treatment	14	0	0	12	0	2	0.142
Post-treatment	5	7	2	3	10	1	0.506

[Table/Fig-5]: Comparison and observation of Brain activity patterns with oral vs N_2O sedation (baseline, mid-treatment, post-treatment).



[Table/Fig-6a]: EEG recordings with oral sedation during baseline, mid-treatment and post-treatment.



[Table/Fig-6b]: EEG recordings with N_2O during baseline, mid-treatment and post-treatment.

DISCUSSION

The present study investigated the effectiveness of oral sedation and N_2O sedation in terms of brain activity, pulse rate and SpO_2 levels in paediatric patients undergoing pulp therapy for two similar class of teeth in cross over manner. The comparison between two types of anaesthesia was done so as to assess achievable clinical outcomes and margin of safety with reduced risk of post complication effects with basic vital parameters such as pulse rate and SpO_2 levels. The brain activity level was assessed using EEG and the patterns were correlated with these parameters. Findings showed no difference between the groups for any of the parameters assessed, thus accepting the null hypothesis.

The reason to choose the similar type/class of teeth i.e., primary maxillary and mandibular molars was to minimise the biological variables, thereby strengthening the statistical power and limiting inter-tooth/inter-subject variability. Another reason for precise selection of mandibular molars over maxillary molars is due to the fact that mandibular molars are extremely difficult to anaesthetise as the dense buccal cortical bone reduces the reliability of typical infiltrations. Additionally, this arch offers a rigorous, extremely sensitive "stress test" to clearly distinguish real clinical efficacy and onset of various anaesthetic drugs. Hence, the present study samples were restricted to primary mandibular molar tooth advised for pulp treatment procedures [32].

In the present study, midazolam (dose of 0.5 mg/kg) was the preferred drug of choice for oral sedation. Previous studies conducted by Hisham ARB et al., (2022), El Hay OA et al., (2015), Musani IE et al., (2015), Tavassoli-Hojjati S et al., (2014), Golpayegani MV et al., (2012), Somri M et al., (2012) and Manley MC et al., (2000) reported positive outcomes with oral sedation with 0.5 mg/kg of midazolam indicating rapid absorption rate and faster onset when compared to other oral or intravenous sedatives [8-14]. These studies also reported that oral midazolam could avoid first-pass metabolism, ensuring sedation within minutes and enhanced behaviour in children with safety measures. In terms of dosage, these studies documented no discernible difference in the sedative effectiveness of 0.5, 0.75, and 1 mg/kg midazolam, however, minimal adverse effects was noted with 1 mg/kg midazolam. Hence, the present study administered 0.5 mg/kg midazolam concentration.

In the present study, N_2O concentration was administered depending on their flow rate i.e., 5-6 litres per minute (L/min) for 1-2 minutes. Study conducted by Musani IE et al., (2015), Shao Y et al., (2013), Piccialli F et al., (2015), Galeotti A et al., (2016), Ergüven SS et al., (2016), Kharouba J et al., (2020), Memè L et al., (2022), Mukundan D et al., (2023) and Bangash M et al., (2024) utilised various concentration of N_2O sedation at different time intervals and concluded that all the study participants were conscious and well aware of their surroundings and were able to follow oral instructions [10,15-22]. These authors reported that N_2O sedation could activate the opioid and Gamma-Aminobutyric Acid (GABA) receptor and provided safe anxiolytic/analgesic effect with significant impact on cognitive functions and is definitely a safe and effective anaesthetic technique. The present study adopted the similar concentrations of N_2O sedation and found significant results indicating beneficial effect of N_2O sedation on paediatric patients.

In the present study, vitals signs such as the pulse rate and O_2 saturation levels were further assessed to observe any notable changes in these parameters using pulse oximeter. The study results were in alignment with Sandhu G et al., (2017) who reported reduced stress levels during periodontal procedures and additionally found significant improvement in arterial blood O_2 saturation, respiratory rate, decrease in serum cortisol levels, Blood Pressure (BP), and pulse rate during periodontal surgery under Nitrous Oxide Induced Sedation (NOIS) [33]. Similar findings were found in a study conducted by Blumer S et al., (2018) wherein the mean pulse rate for children older than six years remained near baseline levels (90-91 bpm) during treatment, but for children younger than six years, it gradually increased from baseline levels of 95.06±15.01 bpm to 105.76±16.94 bpm after 75 minutes [34]. The mean pulse rate in the current study showed minimal deviation from the normal ranges at baseline, mid-treatment, and post-treatment. Furthermore, according to Blumer S et al., (2018), there were no variations in mean SpO_2 levels between males and females or between children under and over the age of six during the course of the treatment, with mean saturation levels remaining consistent at roughly 98% [34]. Similar outcomes were shown in the current investigation, where pO_2 dropped during mid-treatment but returned to normal post-treatment, falling within physiologically acceptable bounds. No participant in the current study experienced any adverse effects.

The present study findings were in contrary to Lee JM et al., (2020) where the EEG changes were most pronounced for alpha 1 and alpha 2 frequency bands and Foster BL et al., (2013) who inferred delta activity [35,36]. Lee JM et al., (2020) also reported significant change in 1/f dynamics indicating that changes in brain network

systems occur during N_2O administration [35]. Ryu JH et al., (2017) investigated changes in functional connectivity of the parietal-frontal network resulting from NOIS and inferred decreased theta, alpha, and beta frequency regions in the parietal-to-frontal direction. The findings were in accordance with the current investigations [37].

Limitation(s)

Smaller sample size could have resulted in bias in verifying if any changes in the brain activity when subjected to oral sedation using midazolam and N_2O sedation could have led to post-treatment complications. Interference from ambient light and motion artefacts are major disadvantages of pulse oximetry.

CONCLUSION(S)

In conclusion, N_2O sedation and oral sedation with midazolam are both safe and efficient methods of managing children's behaviour. The SpO_2 and pulse rate were both within the physiologically acceptable range and showed no deviation, indicating the safety profile of the sedative methods employed. An EEG is a useful tool that we used in the present study to document any changes in brain activity. To confirm if oral sedation with midazolam and N_2O sedation alters brain activity, more research with a bigger sample size is needed.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Paediatric and Preventive Dentistry, School of Dental Sciences, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, Maharashtra, India.
2. Associate Professor, Department of Paediatric and Preventive Dentistry, School of Dental Sciences, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Neha Ravindra Ghongade,
Postgraduate Student, Department of Paediatric and Preventive Dentistry, School of Dental Sciences, Karad-415539, Maharashtra, India.
E-mail: neha@gmail.com

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