RESEARCH ARTICLE

Comparison of the Sedative Effect of Inhaled Nitrous Oxide and Intranasal Midazolam in Behavior Management and Pain Perception of Pediatric Patients: A Split-mouth Randomized Controlled Clinical Trial

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Abstract

Background: Management of children has always been a challenging task in the dental office, as many children exhibit extreme fear, apprehension, and anxiety toward dental procedures. Pharmacological means of behavior management such as sedation are now at the forefront. Midazolam and nitrous oxide are the commonly employed pharmacological agents for sedation in pediatric dentistry. Though each route has its advantages and disadvantages, we compared the effect of atomized intranasal midazolam (dosage 0.3 mg/kg body weight) and nitrous oxide oxygen sedation in evaluating the behavior of child, pain experienced during local anesthesia administration, sedation level, and patient's acceptance.

Materials and methods: A total of 35 ($n = 35$) anxious pediatric patients aged 4–7 years with negative and definitely negative behavioral rating were randomized to receive intranasal midazolam and inhalational nitrous oxide through mask. The overall behavior, alertness, and cry were recorded using Houpt rating scale while pain and sedation were assessed by face, legs, activity, cry, and consolability (FLACC) and Ellis sedation scores, respectively.

Results: The children who received intranasal midazolam sedation were calm, had less adverse effects, and had better acceptance of the drug. Both the techniques of sedation were found to be equally effective in terms overall behavior rating.

Conclusion: Intranasal midazolam was found to be as effective as nitrous oxide sedation for controlling behavior and providing adequate sedation in pediatric dental patients. It can also be an effective alternative for anxious patients who are unable to maintain the nitrous oxide mask throughout the dental procedure.

Keywords: Anxiety, Dental fear, Intranasal midazolam, Nitrous oxide, Overall behavior, Pediatric dentistry, Sedation

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Introduction

Management of children has always been a challenging task in the dental office as many children exhibit extreme fear, apprehension, and anxiety toward dental procedures. The prevalence of dental fear and anxiety in pediatric population is around 5.7–19.5% with 9% of the children exhibiting behavior management problems.[1] Since parents are not comfortable with dentists using aversive conditioning on their children, as it leads to unnecessary emotional trauma,[2] pharmacological means of behavior management such as sedation and general anesthesia are now commonly used.[3] Sedation is a good alternative to general anesthesia for short procedures.[4] It involves the depression of conscious state induced by anesthetic agent, where the patient responds purposefully to verbal commands or tactile stimulation.[5] It can be achieved through different routes of drug administration. While oral, intravenous, intramuscular, and rectal routes show promising results, their drawbacks limitations such as low bioavailability and fear of needles limit their usage.[6,7]

Intranasal route of drug administration has a faster induction rate due to high vascularity and surface area of nasal mucosa[8,9] and requires minimal cooperation from the child.[10] Midazolam, ketamine, dexmedetomidine, and sufentanil are routinely administered through this route.[11,12] Midazolam, a short-acting benzodiazepine invented in 1983,[13] has a rapid onset of action and recovery with a wide safety margin.[14,15] Considering these properties and the advantages of intranasal route, the present study used atomized administration of intranasal midazolam.

Nitrous oxide–oxygen sedation is the standard sedative technique recommended by the Council of European Dentists. Nitrous oxide exerts its analgesic and anxiolytic properties by

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causing depression in the central nervous system.[16] It has a rapid induction and recovery. However, it is a technique sensitive procedure, as it depends on the patient's acceptance of the mask. Continuous administration of the agent is required throughout the procedure making the treatment difficult in fearful children.[17]

To overcome the drawbacks of nitrous oxide–oxygen sedation and to combine the advantages of intranasal midazolam, the present study compared the effect of atomized intranasal midazolam (dosage 0.3 mg/kg body weight) and nitrous oxide–oxygen sedation in evaluating the behavior of child, pain experienced during local anesthesia administration, sedation level, and patient's acceptance.

Materials and Methods

Study Design

This study was a randomized split mouth crossover clinical trial conducted in the Department of Pediatric and Preventive Dentistry, Saveetha Institute of Medical and Technical Sciences. The study design was reviewed and approved by the Institutional Review Board of the same institution (SRB/SDMDS16PED03). The risk and benefits of the study/treatment were explained to all the parents/guardians and a written informed consent was obtained. A total of 35 (n = 35) anxious pediatric patients aged 4–7 years with negative and definitely negative behavioral rating, belonging to American Society of Anesthesiologists (ASA) physical status I, whose treatment required bilateral pulp therapy (pulpotomy/pulpectomy) in lower two quadrants under inferior alveolar nerve block, were included in the study. Children with cognitive impairment, breathing difficulties, history of systemic illness, hypersensitivity to midazolam, and children on central nervous system (CNS) depressant drugs were excluded from the study.

Randomization

The participants were randomized using block randomization by a blinded observer to generate a block of 35 with either 1 or 2 treatment protocol for the first appointment (where 1 = intranasal midazolam group and 2 = nitrous oxide – oxygen group). The site of treatment was also randomized. In the second appointment, the other sedation technique was used for pulp therapy on the contralateral side.

Study Protocol

The behavior of the patients was assessed based on the Frankl's behavior rating scale.[18] Only those patients on whom basic behavior management failed were included. Preoperative instructions by the American Academy of Pediatric Dentistry (AAPD) guidelines were followed.[19]

The pain was evaluated using face, legs, activity, cry, and consolability (FLACC) score,[20] the level of sedation by Ellis sedation score,[21] behavior of the patient using Houpt behavior rating scale; [22] and adverse reactions such as vomiting, sneezing, coughing, hiccups, and prolonged/deep sedation caused by either of the drugs were recorded using a scale given by Shashikiran et al.[23] At the termination of the procedure, 100% oxygen was administered for 5 minutes. The patient was discharged when the recommended discharge criteria given by AAPD were met.[19] All the patients were followed till the next day with phone call to evaluate, if there were any posttreatment adverse reactions.

Intranasal Midazolam Administration

The patient was explained about the administration of the drug through euphemism. A dosage of midazolam 0.3 mg/kg (Mezolam® 5 mg/mL, Neon Laboratories Ltd.) was administered using mucosal atomizer (Wolf Tory Medical, Salt Lake City, Utah) attached to 2 mL syringe (Fig. 1 and 2). The patient's acceptance of drug was evaluated using a scale given by al-Rakaf et al. in 2001.[10] Inferior alveolar nerve block was then administered (2% lignocaine with 1:200,000 adrenaline) after signs of sedation such as being relaxed with slurring or slowing of speech was visible on the patient.

Nitrous Oxide–Oxygen Administration

Each child was demonstrated the placement of nasal mask using tell show do and euphemisms. The flow rate was determined by initial administration of 100% oxygen for 2–3 minutes. Then, a preadjusted mixture of nitrous oxide–oxygen was administered in the concentration of 30–70% using Matrx Porter Digital Relative analgesia machine (Fig. 3 and 4). The patient's acceptance of nasal mask was evaluated using a scale given by Wood in 2010.[24] Local anesthesia administration was initiated after the first signs of sedation.

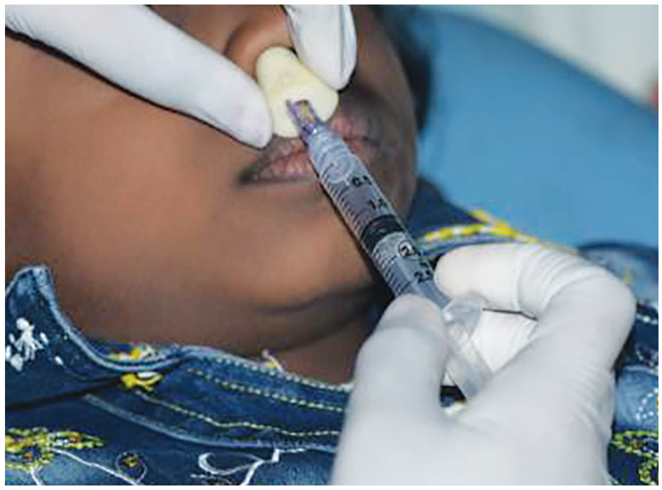

Fig. 1: Mezolam® 5 mg/mL (Neon Laboratories Ltd.) was administered using mucosal atomizer (Wolf Tory Medical, Salt Lake City, Utah) attached to 2 mL syringe

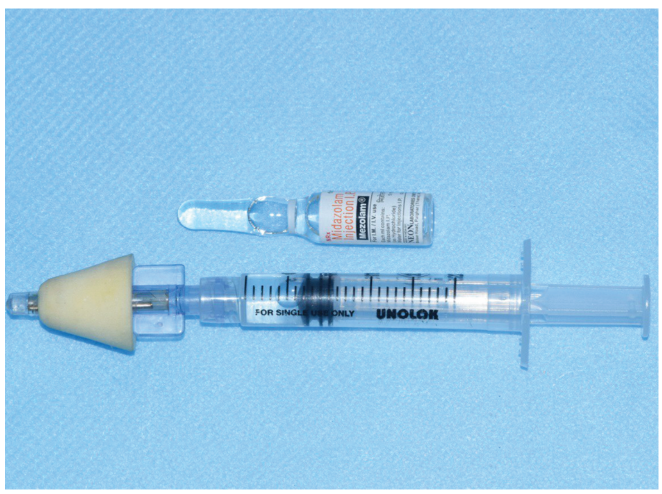

Fig. 2: Administration of intranasal midazolam

Fig. 3: Matrx Porter digital relative analgesia machine

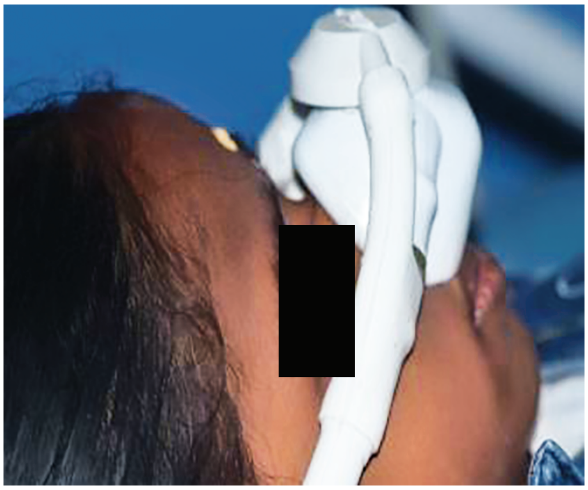

Fig. 4: Administration of inhalational nitrous oxide

The procedure was done in the out-patient department. Once the child was seated in the dental chair (Flowchart 1), monitors such as electrocardiogram (ECG), noninvasive blood pressure (NIBP), oxygen saturation (SpO_2), and end-tidal carbon dioxide ($ETCO_2$) were connected. Intravenous access was secured with a 22G cannula and necessary emergency equipment and drugs (including flumazenil, the definitive antidote for midazolam) were kept ready. As per protocol, sedation regimen was followed depending on randomization. The baseline values of heart rate, respiratory rate, systolic and diastolic blood pressure, SpO_2, and $ETCO_2$ were recorded and these parameters were monitored continuously by the anesthetist and the values at three time periods T1, T2, and T3 (T1 = baseline values, T2 = during local anesthesia administration, and T3 = at the termination of procedure) were taken for analysis. Study protocol is illustrated in (Flowchart 1).

Statistical Analysis

Analysis was done using SPSS software version 23 (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp. Released 2015). As the study is "split mouth design," to compare mean values between groups, paired t-test was applied. To compare FLACC scores between groups, Wilcoxon signed-rank test was applied. To compare proportions between groups, McNemar's Chi-square test was applied. $p < 0.05$ was considered to be statistically significant.

Results

A total of 35 participants were included in the study with a mean age of 5.66 ± 0.77 years.

There was no significant difference between the two sedation regimens with regard to overall behavior or crying—57.1% of the children showed excellent behavior under nitrous oxide sedation while 51.4% in midazolam group had excellent behavior.

Alertness during Treatment

Total cooperation with no limb movement, while 57% of the participants sedated using nitrous oxide had a score of 1. 20% of children who received midazolam sedation had a score of 3 (more uninvited limb movement; small degree of restlessness and anxiety; patient less cooperative; still able to perform all dental procedures).

94% of children who received midazolam sedation were relaxed and comfortable during the treatment. While 4% showed a mild discomfort during local anesthesia administration. The mean FLACC score was 1.57 ± 2.60 for nitrous oxide and 2.77 ± 3.70 for midazolam group, respectively. The FLACC score was significantly lower in nitrous oxide group as compared to midazolam group ($p = 0.049$).

In Table 1, the physiological parameter observation has been described and there was no significant difference in the physiologic parameters for both the groups except for the heart rate at T2 interval. It was 106.64 ± 12.68 bpm on nitrous oxide administration and 103.29 ± 12.69 bpm under midazolam at T2. The difference between the heart rates at T2 interval was statistically significant ($p = 0.049$) compared to T1 and T3.

Adverse Effects

There was a low incidence of vomiting (2.2%) with nitrous oxide sedation and none with midazolam ($p = 0.020$). Four participants had sneezing/coughing/hiccups during midazolam sedation and none with nitrous oxide ($p = 0.039$). No other adverse effect was reported with either of the sedation regimens.

Discussion

Behavior management is as an important aspect of pediatric dentistry to deliver optimal treatment for anxious children. Pharmacological behavior management strategies are always considered as an alternative when nonpharmacological behavior management strategies fail to reduce anxiety.[25] According to AAPD, sedation is aimed at providing safe and effective dental treatment.[26] Thus, in the present study, we compared the behavioral pattern of children with two methods of delivering sedation—intranasal midazolam and inhaled nitrous oxide–oxygen sedation.

This study followed a split mouth design, which allowed the patient to experience both the methods of sedation. It also permits less variation in the outcome after sedation. All the outcomes were assessed using objective methods of evaluation by a trained observer who was blinded to eliminate the risk of bias.

Fuks et al.[27] had stated that 0.2 mg/kg midazolam was similar in its effectiveness as 0.3 mg/kg of the drug. However, they had used midazolam in combination with 50% nitrous oxide. Since the present study has not used midazolam in combination with other agents, higher dosage of 0.3 mg/kg of midazolam was used.

Flowchart 1: Study protocol

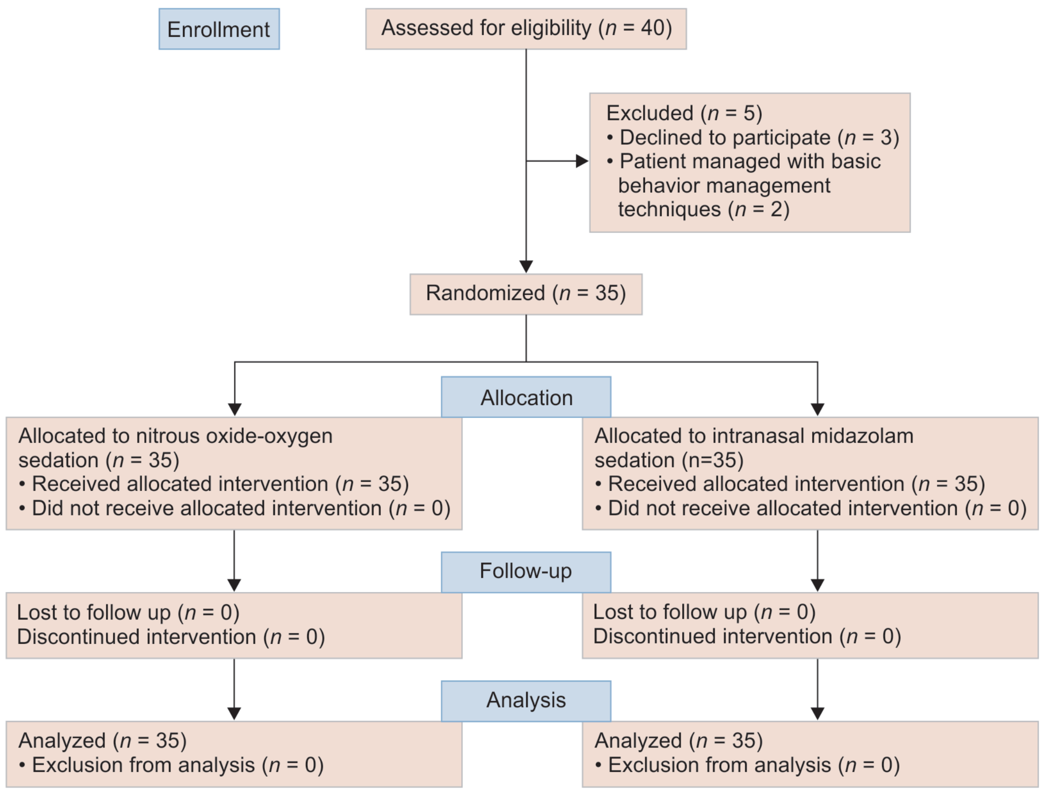

Table 1: Comparison of physiologic parameters between nitrous oxide sedation and intranasal midazolam sedation

Variables	*Group*	*N*	*Mean*	*Std deviation*	*t-value*	*p-value*
Oxygen saturation-T1	Nitrous oxide	35	99.71	1.126	0.269	0.790
	Midazolam	35	99.66	0.906		
Oxygen saturation-T2	Nitrous oxide	35	99.60	1.193	1.320	0.196
	Midazolam	35	99.23	1.285		
Oxygen saturation-T3	Nitrous oxide	35	99.63	1.003	0.734	0.468
	Midazolam	35	99.46	1.039		
Heart rate- T1	Nitrous oxide	35	102.77	11.951	0.084	0.934
	Midazolam	35	102.66	13.346		
Heart rate-T2	Nitrous oxide	35	106.54	12.682	2.031	0.049
	Midazolam	35	103.29	12.629		
Heart rate-T3	Nitrous oxide	35	103.69	11.749	0.049	0.961
	Midazolam	35	103.77	11.270		
Respiratory rate-T1	Nitrous oxide	35	22.57	2.266	0.085	0.932
	Midazolam	35	22.60	2.637		
Respiratory rate-T2	Nitrous oxide	35	23.00	2.722	0.000	1.0
	Midazolam	35	23.00	3.115		
Respiratory rate-T3	Nitrous oxide	35	23.03	2.256	0.821	0.417
	Midazolam	35	22.80	2.098		

Bahetwar et al.[11] had used 0.3 mg/kg of midazolam when not used in combination with other agents. Midazolam was administered through intranasal route through mucosal atomization. It produces a fine 30 µm particle spray providing 55% bioavailability of the drug.[28] The semipermeable soft plug in the mucosal atomizer cushions the naris and prevents any back-leak of the drug. This promotes rapid absorption of the drug into systemic circulation.[29] 30–70% of nitrous oxide was delivered as a premixed dose. A concentration of 30% was used since studies have demonstrated that 20–30% concentration provides adequate sedation without the risk of oversedation.[30] A premixed dose was given to standardize the dose of nitrous oxide for all the patients undergoing sedation.

Dental treatment was successfully completed in both the methods of sedation with limited movements, crying, and good overall behavior. We found no difference in the behavior of the child with intranasal midazolam and nitrous oxide–oxygen sedation. Intranasal midazolam was found to be as effective as nitrous oxide–oxygen sedation in controlling the behavior of the child during dental treatment. In previous studies, orally administered midazolam was used and was found to have a similar efficacy as nitrous oxide sedation.[31]

42% of the children in our study readily accepted the nasal mask without resistance since a proper tell show do technique was used prior to the mask placement. But, displeasure was associated with 91.4% of the children during the intranasal administration of the drug, which was due to the bitter taste of the drug. FLACC scores were found to be similar in both groups of sedation. However, Wilson et al. showed less children recalling local anesthesia administered with nitrous oxide sedation than oral midazolam sedation suggesting lower pain level with N_2O as compared to oral midazolam.[32]

Studies show that coughing and sneezing are the most common adverse effects of intranasal midazolam. This was due to the increased volume of the drug trickling through oropharynx.[33,34] Hence, in the present study, we used a higher concentration of intranasal midazolam (5 mg/mL) by mucosal atomization in order to prevent the adverse effects. The present study reported an incidence of sneezing in 11.4% of the patients for intranasal midazolam. The findings of our study were in resonance with the findings of Bahetwar et al.[11] who also reported minimal adverse effects with the use of highly concentrated intranasal midazolam.

Vomiting was reported in 2.2% of the patients receiving nitrous oxide sedation. However, it did not have effect on the overall treatment outcome and completion of the procedure. We believe that the low incidence of vomiting was due to strict preoperative fasting. Zier and Liu[35] also reported 2.2% incidence of vomiting which is in concurrence with the incidence reported in present study. The findings of our study re-emphasize the practice of alerting parents to the complications during the informed consent process to relieve anxiety and prepare them for postoperative care of the child.[36] We believe that the emesis might have been caused by the action of nitrous oxide on central opioid and dopaminergic receptors,[37] diffusion of nitrous oxide into the middle ear cavity,[38] and bowel distension. The adverse effects and acceptance could relate to the maturity level of the children and can influence their ability to cope with the feelings of sedation. This was observed by Wilson et al. in 2006 when they used a higher dose of midazolam in 10–16-years old and found this age could have influenced their behavior during sedation.

There was a statistically significant difference (103.29 ± 12.629 in midazolam versus 106.54 ± 12.682 in nitrous oxide) in the heart rates during local anesthesia administration for both the methods of sedation at the T2 interval ($p = 0.049$). However, we feel that the difference was not clinically significant.

The limitation of the present study is that the onset of sedation, recovery time, and the effect of other physiologic parameters were not evaluated. These factors would further provide better comparison for two different methods of sedation. The present study has only evaluated two most commonly used agents for sedation in anxious children. Comparison of multiple drug regimen used for sedation will aid in determining better method of sedation in pediatric dental patients.

Conclusion

Both nitrous oxide and intranasal midazolam were effective in controlling the anxiety with optimum level of sedation to complete the dental treatment. Intranasal midazolam was found to be as effective as nitrous oxide sedation for controlling behavior and providing adequate sedation in pediatric dental patients. It can also be an effective alternative for anxious patients who are unable to maintain the nitrous oxide mask throughout the dental procedure.

Clinical Significance

Intranasal midazolam is as effective as nitrous oxide sedation for controlling behavior and providing adequate sedation in pediatric dental patients. It can also be an effective alternative for anxious patients who are unable to maintain the nitrous oxide mask throughout the dental procedure.

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