RESEARCH ARTICLE

Intranasal Midazolam Premedication for Anxiolysis in Children Reluctant to Receive Nitrous Oxide Sedation via Nasal Hood: An *In Vivo* Randomized Control Trial

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Abstract

Aim and objective: The aim of the study was to compare administration of 0.1 mg/kg intranasal midazolam as premedication against a normal saline control in alleviating anxiety relating to and increasing acceptance of nasal hood by child patients receiving nitrous oxide sedation.

Materials and methods: After ethical clearance and informed consent, on the basis of odd and even numbers patients were allocated to group midazolam (group M) or group normal saline (group N), respectively. The physical parameters were recorded at the beginning and after the procedure; time required for the procedure was also recorded. The level of cooperation during acceptance of the nasal mask by the patient was evaluated using the four-point scale.

Result: Group M (midazolam premedication) was more effective in improving the acceptance of the nasal hood in children than the normal saline/traditional/conventional method of treating the teeth. The *p*-value is .002308.

Conclusion: In the present study the combination of midazolam and nitrous oxide proved to be an effective combination, resulting in good to excellent behavior in children who were Frankl's behavior rating definitely negative and negative.

Clinical significance: For successful sedation premedication with nitrous oxide, midazolam is an excellent premedication drug.

Keywords: Behavior management, Conscious sedation, Dental anxiety, Midazolam, Premedication.

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Introduction

Children and adolescent show diverse maturity, personality, temperament, and emotions, which lead to a variety in their vulnerability and coping ability in dental situations. Therefore, dentist needs a plethora of techniques to manage children.[1] For a long time now, behavior management is limited to an art rather than science.[2]

Fears in children can be acquired in two ways- by direct stimulation (objective fear) or based on feelings and attitudes suggested by parents, peers, siblings, etc. (subjective fear).[3] Also in children, generally, treatment is not one-to-one but a one-to-two relationship including the parents who are the intermediaries.[4] Thus parental attitudes also have an impact on child's behavior.

In this complex challenge of treating children a child's behavior can never become an alibi for sub-standard oral care.[2]

To proceed with such challenges, the most conservative behavioral approach should be attempted first. But since sometimes even passive restraint may fail, after weighing the associated risks and benefits, adjunctive form of treatment such as sedating the patient may be necessary.[5]

As many as 85% pediatric dentists have been reported to be using nitrous oxide-oxygen sedation which makes it quite frequently used agent. The gas, slightly sweet smell and is inert and colourless was discovered by Horace Wells in 1844.[6,7] Benzodiazepines (BZD) are used for their sedative, anxiolytic, amnesic, anticonvulsant, and muscle relaxant properties; are however associated with adverse effects.[7]

There are many other sedative drugs available, but midazolam a new generation benzodiazepine has enjoyed a lot of attention in the recent years as a good pediatric sedative agent. It has long been used as a premedication due to its sedative and anxiolytic properties.[8] It is an anxiolytic agent classified as short acting due to its short duration making it useful in simple procedures of dentistry.[9] Hence, sedation by inhalation nitrous oxide oxygen is used following midazolam premedication to prolong the effect of sedation.

Nasal administration of medication is emerging as a promising method of delivering medication directly to the blood stream.[10] There are few mechanisms that restrict the drug entry through the blood-brain barrier (BBB). In addition intranasal use circumvents the BBB by passage through cribriform plate and using para and trans cellular or active neural transport mechanism.[11,12]

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One common problem associated with inhalation sedation in children is fear of the nasal hood. Several efforts have been made to relieve this fear.[13] An acceptable means of countering this fear would be the use of an anxiolytic premedication.

The current research aimed to compare administration of 0.1 mg/kg intranasal midazolam as premedication against a normal saline control in alleviating anxiety relating to and increasing acceptance of Nasal Hood by child patients receiving nitrous oxide sedation.

Materials and Methods

The study was undertaken in the pediatric dental department of a dental hospital in a city of Western Maharashtra in India. The ethical clearance as warranted was obtained from the institutional ethical committee prior to the commencement of the study. The design was a double blind, split mouth cross over, with a wash out period of 1–2 weeks.

Thirty children between the ages 4–8 years requiring bilateral endodontic treatment with Frankl 's negative or definitely negative behavior were selected. A detailed case history of the pediatric patient was recorded prior to including them into the study; including the chief complaint, thorough health evaluation such as age-weight, medication/drug history, allergies if any, relevant diseases, physical and neurological impairments, etc., a previous history of complications during sedation or general anesthesia or unwarranted responses; after complete intraoral clinical examination. The physical status evaluation was done using ASA classification.[14]

A full verbal explanation of the procedure was provided to the parent/guardian of the child regarding the sedation, type of medication, its safety, and side effects. Information provided included objectives of the sedation, reason to select midazolam and nitrous oxide sedation, advantages and disadvantages of each technique, and changes after sedation in behavior were anticipated. A consent in writing was received from parents for the child participant in the study.

Preoperative instructions oral and in writing were provided to the parents including diet. They were asked to cancel appointment if the child got sick. On the day of the procedure, the child was examined by the anesthetist and heart rate, oxygen saturation, and BP were recorded at baseline.

Bases on odd and even numbers patients were allocated to group midazolam (group M) or group normal saline (group N) respectively. In group M on the first appointment, midazolam premedication was administered and on second appointment normal saline premedication was given; which was reversed in group N. On their first appointment, prior to administration of premedication by midazolam or saline, the level of anxiety of the patient were determined using a 5-point Modified Venham Picture Scale.[15] Physiologic parameters like, blood pressure, pulse, respiration rate & peripheral oxygen saturation (using a pulse oximeter) was recorded timely; from before medication, and at every 10 minutes interval up to post sedation. In order to prevent sedative drug identification, spray bottles received codes known only by the examiner. Intranasal midazolam (at a dose of 0.1 mg/kg) and normal saline was administered at respective appointments by the examiner. The time required for completion of the procedure from giving the premedication to the reversal of N_2O sedation by 100% oxygen was noted using a chronometer.

Patient's acceptability was assessed during drug administration by use of four codes. (HA Rakaf, LL Bello[16]) It was decided to postpone the appointment if a child expectorated whole or part of the drug (actually no such case occurred). The child was asked to wait with his/her parents and was kept under observation for 20 minutes (mean time of onset for intranasal midazolam 12.1 (8–18) minutes).[17] The patient was then moved for sedation and nasal hood introduced. 100% oxygen was delivered for 1–2 minutes with a flow rate of about 5–6 L/min, and nitrous oxide was introduced slowly by increasing the concentration at increments of 10–20% and gradually titrated upto 30–50% to patients needs.

A four point scale assessed the level of cooperation during nasal mask application.[15]

After initial onset of sedation, 2% Lidocaine was used as local anesthetic. Ellis score were employed to check the level of sedation[15]

Child's crying, movements during the treatment were recorded using 2nd and 3rd category of Houpt Behavior Rating Scale.[18]

Once required treatment was accomplished, at the end of dental procedure 100% oxygen was administered to the patient following treatment all patients were expected to stay in observatory for 20 to 90 minutes. The sensory perception levels (alertness) and overall behavior of the child was evaluated using the first and fourth category of Houpt Behavior Rating scale.[18] Adverse reaction like deep sedation, cough or sneeze, vomiting, or allergies that might occur during treatment.[2] The efficacy profile was checked from the score recorded from cooperation in mask acceptance, score of sedation, cry, movements and behavior on the whole of the patient. The child was discharged after assessing the vitals, response to verbal stimulation, state of wakefulness, and ability to walk unaided. After 24 hours the patient was recalled for follow-up.

Post-treatment questionnaire was given to parents to fill at home to grade their feelings about sedation and which of the two methods they preferred. The parents were expected to record adverse effects if any and cooperation with each type of sedation of their child and results were calculated with Chi-square test.

Results

The results of the acceptability of drug is seen in Table 1. Participants in group N consumed more time than the group M. Higher percentage of children were seen in the time frame of 31 minutes and more in group N and the group M timings were largely

Table 1: Acceptability of the drug in the two groups

	Group N		*Group M*	
Level of acceptability of drug	*Number*	*Percentage*	*Number*	*Percentage*
Good	30	100	30	100
Fair	00	00	00	00
Poor	00	00	00	00
Refused	00	00	00	00
Total	30	100	30	100

concentrated around the 30 minutes or less mark. This showed that statistically group M was more effective method than the normal saline/traditional/ conventional method of treating the teeth. The *p*-value is .002308. The result is significant at $p < .05$. In both the groups all the participants showed a good level of acceptability of the drug with no statistical difference in the observation among the two groups (Table 2). More participants in the group N exhibited lesser levels of co-operation (code 2)[15] as seen in Table 3. Very co-operative children were more ($n = 30$) in the group M compared to group N ($n = 22$), and this was found to be statistically significant. Higher percentage of children in the group M showed small amount of limb movement. Restlessness and anxiety was slightly more in the group N, but was not statistically significant (Table 4). In the group M, participants showed no movement at all during the treatment procedure; whereas in Group N, one patient showed continuous movements, and 13 patients showed controllable movement but the difference was insignificant. This could be because of a smaller sample size but nonetheless; there was better response to the group M method than the group N intervention. Higher proportion of participants treated with group M showed no crying at all compared to group N. The percentage of persistent and mild crying was more in the group N and this difference was found to be statistically significant ($\chi^2 = 10.76$, df = 4, $p = .0131$).

All the safety parameters recorded highly satisfactory performance with no adverse effects. There was also no statistically significant difference between the two groups. ($p = 1.000$) This shows that group M can be used in all cases without any complications to the patients under an ideal set up (as seen in higher percentage of participants were drowsy in the group M and comparatively more participants intervened with group N were alert. This difference was found to be statistically significant. Thus a better control and co-operation was observed in group M than group N and post-operative maintenance was required more in group M (Table 5). Shows that both the groups showed similar overall behavior, although patients with excellent overall behavior were more in group M compared to group N these differences were not found to be statistically significant ($\chi^2 = 2.89$, df = 4, $p = .5764$).

Discussion

The results of this randomized cross-over study prove that the use of midazolam premedication significantly improves the acceptance of nasal hood by reluctant children. It was observed that the patients were more relaxed with the use of midazolam premedication. The lesser limb movements and lesser crying by children in the midazolam premedication group attributed to a shorter and more efficient appointment.

It has been proposed that midazolam premedication can reduce not only the total working time but also reduces anxiety of the patients.

Nitrous oxide is clubbed with Inhalation anesthetic; it is weakest of all agents in inhalation with a lowest MAC of 105. The MAC is potency measurement of the anesthetic. N_2O is the sole inhalation agent with analgesic properties at sub anesthetic concentration; therefore there has been a renewed interest in the nitrous oxide and oxygen mixture during the past few years. N_2O does not undergo biotransformation in the body, therefore minimal side effects are observed. The concentration of N_2O required to produce sedation will vary among individuals.[9] This simple small molecule has excellent analgesia, anxiolysis and anesthesia effect of great clinical value. N_2O acts on central Nervous system and supraspinal GABA for its analgesic action - along with spinal GABA are also activated. Brain stem nonadrenergic neurons are disinhibited by N_2O induced endogenous opioid release and release of norepinephrine into the spine ceases pain signalling.[19] Numerous studies have shared the evidence of safety and efficacy of N_2O as anxiolytic in dentistry (Berger et al., 1972; Aspes, 1975; Anderson, 1980).[20,21]

Table 2: Distribution of the participants based upon the Ellis sedation score

	Group N		*Group M*	
Sedation score	*Number*	*Percentage*	*Number*	*Percentage*
Total cooperation	08	26.6	07	23.3
Small amount of limb Movement	13	43.4	18	60.0
More movement, slight anxiety and restlessness	09	30.0	05	16.7
Considerable restlessness	00	00	00	00
Severe limb movement, too un-cooperative	00	00	00	00
Total	30	100	30	100

$\chi^2 = 0.46$ df = 2, $p = 0.7945$

Table 3: Distribution of the participants based upon their crying ratings postintervention and during the treatment

	Group N		*Group M*	
Crying	*Number*	*Percentage*	*Number*	*Percentage*
Hyseterical crying	00	00	00	00
Persistent crying	03	10.0	00	00
Mild crying	16	53.3	07	23.3
No crying	11	36.7	23	76.7
Total	30	100	30	100

$\chi^2 = 10.76$, df = 4, $p = 0.0131$

Table 4: Distribution of the participants based upon the safety scale

Safety scale		*Number of observations*				
		Group N		*Group M*		
Parameters	*Grade*	*Number*	*Percentage*	*Number*	*Percentage*	*p–Valu e*
Vomiting score	0–unsatisfactor y (vomiting present)	0	0.00	0	0.00	1.000
	1–satisfactory (no vomiting)	30	100	30	100	
Allergic reaction	0–unsatisfactor y (allergic)	0	0.00	0	0.00	1.000
	1–satisfactory (no allergy)	30	100	30	100	
Sneezing/Coughing/H iccup	0–unsatisfactor y (present)	0	0.00	0	0.00	1.000
	1–satisfactory (not present)	30	100	30	100	
Respiratory depression	0–unsatisfactor y (too deep sedation)	0	0.00	0	0.00	1.000
	1–satisfactory (optimum sedation)	30	100	30	100	
Prolonged deep sedation	0–unsatisfactor y (present)	0	0.00	0	0.00	1.000
	1–satisfactory (not present)	30	100	30	100	

Table 5: Distribution of the participants based upon their overall behavior

	Group N		*Group M*	
Overall behavior	*Number*	*Percentage*	*Number*	*Percentage*
No treatment	00	00	00	00
Poor	01	03.3	00	00
Fair	00	00	00	00
Good	02	6.7	02	6.7
Very good	21	70.0	17	56.7
Excellent	06	20.0	11	36.6

$\chi^2 = 2.89$, df = 4, $p = 0.5764$.

High water solubility is the major advantage of midazolam when compared to diazepam.[22] The ihigh solubility helps packaging without dilutents and prevents venour irritation and or dysrhythmias (Greenblatt and Abernethy, 1985; Kanto and Allonen, 1983; Reves et al., 1985).[23–26] The drug has been used effectively for brief invasive procedures in children, such as during laceration repair (Walbergh et al., 1991)[27] or during bone marrow aspirations and lumbar punctures (Sievers et al., 1991).[28] It appears that midazolam may be effective for use in pediatric patients for mild pain, short duration and in minimal invasive procedures: Midazolam has been called "the ideal oral sedative" (Gallerado, Cornejoo et al., 1994, Kraft, Kramer et al., 1988.)[29] therefore will be good to combine ideal and standard sedatives to have benefits of both the sedatives. Administration through the nose is simple and painless, it maybe objected by some but less cooperation of a child patient is required compared to the oral route where the medicine needs to be swallowed by the patient (Hussain, 1989).[30] Some studies show the disadvantages of intranasal midazolam such as discomfort- burning sensation, variable absorption making dose determination difficult, and potential for damage to the nasal mucosa (Haas. et al., 1999).

Although administration through the nose is simple and painless. It maybe objected by some but less cooperation of a child patient is required compared to the oral route where the medicine needs to be swallowed by the patient, 8 out of 30 children did not allow intraoral examination (code 2)[15] whereas, in the group M children were more cooperative, and this was found to be statistically significant. A higher proportion of participants treated with group M showed no crying at all compared to group N. The percentage of persistent and mild crying was more in group N and this difference was found to be statistically significant.

Previously, Midazolam has been compared with other substances such as Ketamine and dexmedetomidine. A previous study has found midazolam to be as potent as Ketamine in sedation abilities but midazolam was a significantly better anxiolytic agent. Also, recovery is marginally faster with midazolam. These findings lead us to believe that the use of midazolam premedication is a safe and effective method of anxiolysis.

An important side-effect of midazolam is its respiratory depressive ability. Recently, a newly introduced alpha-2 agonist, dexmedetomidine has been studied as a sedative and analgesic which is said to be devoid of respiratory depressive effect which could make it useful as a premedication agent. However, there is a requirement to further substantiate these advantages of the drug in routine dental practice whereas Midazolam is a widely accepted anxiolytic.

Conclusion

It has been seen that at least 1 in 4 children delay dental treatment due to fear. This fear or anxiety can be overcome by PSA (Procedural Sedation and Analgesia) and reduce the need for general anesthesia.

The M-N_2O combination proved its effectiveness by resultant good to excellent behavior of kids, who were Frankl's behavior rating definitely negative and negative. The operator could carry out the procedure at all stipulated 60 appointments, the combination of the two agents proved to be 100% safe there were no adverse reactions reported in both the groups and the physiologic markers were within limits.

Clinical Significance

Premedication although an important part of general anesthesia, is seldom used in N_2O Sedation. The biggest hindrance to the success of N_2O sedation in children is anxiety. For successful sedation premedication with nitrous oxide, Midazolam is an excellent premedication drug.

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