

A Comparison of the Effectiveness of Oral Midazolam – N₂O Versus Oral Ketamine – N₂O in Pediatric Patients-An in-Vivo Study

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ABSTRACT

Introduction: Most children are casual and moderately agreeable in the dental treatment environment, however some of them show practices that upset the professional and make the protected conveyance of worthy treatment extremely troublesome. For such cases dental practitioner utilizes behavior management techniques. At the point when behavioral administration procedures come up short, some type of pharmacologic sedation or anesthesia may be an important and vital option. Dental sedation is a strategy in which the utilization of a medication or drugs produce(s) a condition of depression of the central sensory system empowering treatment to be completed during which verbal contact with the patient is kept up all through the time of sedation.

Aim: This study was designed to evaluate and compare the effectiveness of oral midazolam and oral ketamine in combination with N₂O-O₂ in children undergoing dental treatment.

Materials and Methods: This study involved a sample of 30 pediatric dental patients (age range is 3-9 years), whose selection criteria included ASA I & II health status, cooperative but apprehensive behavior and a need for multiple dental

extractions. The patients were assigned to receive oral midazolam on their first visit and on the follow up visit they received oral ketamine. Nitrous oxide (30%) was used during each sedation visit. Physiological parameters like Respiratory Rate (RR), pulse rate, and oxygen saturation were evaluated for each procedure, followed by the use of modified Bender Visual Motor Gestalt Test to evaluate psychomotor effects. Data were analyzed using Independent sample student t –test.

Results: Analysis of the data showed statistically no significant difference ($p > 0.05$) on comparison of effectiveness of oral midazolam-N₂O with oral ketamine-N₂O when pulse rate, oxygen saturation and respiratory rate were taken into consideration. Psychomotor performance was found to be marginally better with oral midazolam-N₂O compared to oral ketamine-N₂O.

Conclusion: Both the drugs were effective in reducing the patient anxiety while undergoing dental extractions. Though the t-test results were not statistically significant with respect to physiological parameters. Oral midazolam-N₂O showed marginally better results compared to oral ketamine-N₂O with respect to psychomotor effects.

Keywords: Anxious pediatric patients, Conscious sedation, Dental procedures, Premedication

INTRODUCTION

Delivering dental care to young pediatric dental patients can be very challenging [1]. Children who are present at the dental clinic for minor surgical procedures pose a problem for the dentist. Behavioral management alone is unfortunately not sufficient for these children, who can be more compassionately managed with sedation or general anesthesia. Conscious sedation is widely used in dentistry to help anxious patients undergo dental treatment with minimal stress [2]. Immature children, fearful and anxious children, medically and physically disabled children are commonly indicated for conscious sedation technique (AAPD 2006) [3]. Among various routes oral route is the commonly used route. The perfect premedication in children ought to be adequate, fast, and reliable in onset, have negligible symptoms, quick end, and an atraumatic course of administration [4]. The premedications utilized for this study were oral midazolam and ketamine 0.5mg/kg and 5mg/kg respectively.

These drugs such as midazolam and ketamine were not available for oral administration in India hence the syrup was made by adding variety of additives which can be taken orally. Conscious sedation with combination methods increases the adequacy and wellbeing, so N₂O-O₂ can be joined with other routes and agents. Midazolam is an imidazobenzodiazepine that can be given in the dose of 0.5-0.75mg/kg orally. Midazolam meets all the criteria of

a premedication drug, i.e., it has fast onset of activity, absence of significant side effects, no impedance with key signs furthermore more powerful in directing patient conduct, making it a good premedication drug [5,6]. Ketamine is a very much recorded anesthetic and analgesic with a wide margin of safety and keeps up defensive reflexes [7]. However there may be a varied reaction and response in the patients after the administration of a combination of drugs.

AIM

The aim of the study was to evaluate and compare the effectiveness of oral Midazolam – N₂O and oral Ketamine – N₂O by considering various psychological parameters of the child.

MATERIALS AND METHODS



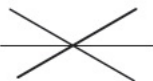
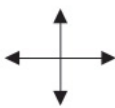
Thirty cooperative but apprehensive children in the age group of 3-9 years with in the normal range of weight categorized under American Society of Anesthesiology I and II, with multiple primary carious teeth indicated for extraction were selected from the outpatient Department of Pedodontics, St. Joseph Dental College, Eluru. As this study was designed to compare the effectiveness of two drugs in combination with N₂O-O₂, patients received oral midazolam 0.5mg/kg with N₂O-O₂ inhalation in the first appointment and oral ketamine 5mg/kg with N₂O-O₂ inhalation

in the follow up appointment. One to two weeks was minimum time interval between two appointments as primary healing of the extraction socket takes a period of minimum two weeks and the patient is advised not to take any hard diet on that side, and this time interval is sufficient for sedation procedure to be carried out on the contra lateral side. Ethical approval for this study was obtained from the local ethical committee. Full verbal and written explanation of the procedure was provided to parents regarding the sedation, type of medication, its safety and side effects. A written consent was obtained from the parent for participation of the child in the study.

Each patient's medical and dental history was recorded, followed by a detailed clinical and radiographic examination. Their behavior

Category	Frankel Behavioral Rating Scale
Rating 1	Definitely negative: Child refuse treatment, cries forcefully, fearfully, or display any overt evidence of extreme negativism.
Rating 2	Negative: Reluctant to accept treatment and some evidence of negative attitude (not profound).
Rating 3	Positive: The child accepts treatment but may be cautious. The child is willing to comply with the dentist, but may have some reservations.
Rating 4	Definitely positive: This child has a good rapport with the dentist and is interested in the dental treatment.

[Table/Fig-1]: Frankel Behavioral Rating Scale (1962).

<p>Triangle</p> <ol style="list-style-type: none"> Three clearly defined sides One corner higher than others 	
<p>Open Square and Circle</p> <ol style="list-style-type: none"> No more than slight separation of forms No major distortions or circle or open square Circle and two cornered square fairly equal size Bisector of circle passing through corner of square must project into square 	
<p>Three Lines Cross</p> <ol style="list-style-type: none"> Three continuous, intersecting lines Intersection fairly accurate One horizontal and two diagonals 	
<p>Directional Arrows</p> <ol style="list-style-type: none"> Absence of reversed or "floating" tips Sharp points on tips No indication of directional confusion Fairly equal length of "legs" 	

[Table/Fig-2]: Drawings of Bender Visual Motor Gestalt test.

category was assessed by Frankl's Behavior Rating Scale [Table/Fig-1] [8].

Palatable syrup was made by adding sorbitol 45 g, sucrose 15 g, saccharine 0.2 g, sodium benzoate 0.15 g, citrus extract 2 g, and distilled water to convey it to 100 ml [9]. A 10 ml of diluent was titrated to 10 ml of IV drug to achieve a final dose of 0.5mg of Midazolam per ml and 90 ml of diluent is titrated to 10 ml of IV drug to achieve a final dose of 5mg of ketamine per ml for oral use. And N₂O-O₂ (Quantiflex MDM Relative Analgesia Machine, Matrix medical Inc., Orchard Park, New York, USA.) sedation unit was used for the procedure.

Initially baseline pulse rate, oxygen saturation, respiratory rate and patient's weight were recorded. The child was shown drawings (Bender Visual Motor Gestalt Test [Table/Fig-2]) and asked to draw the same before the onset of sedation. The scheduled drug oral midazolam in the form of syrup was administered to the patient and the onset of sedation was monitored using Houpt's Sedation Rating scale [10]. The subjective signs were noted by observing their muscle coordination, look, eye movement, sleep, speech

at a regular interval of five minutes after the administration of the drug [11]. After 30 minutes, the picture drawing was (According to Bender Visual Motor Gestalt Test) repeated again. The objective signs and symptoms were noted.

First, 100% oxygen was delivered for 2 to 3 minutes at an appropriate flow rate. Once the flow rate was achieved, the nitrous oxide was gradually introduced by slowly increasing the concentration at increments of 10% in oxygen to a final dose of 30% in oxygen. Then the objective signs and symptoms were again recorded. According to the site, local anesthesia (2% lidocaine with epinephrine 1:100,000) was given, not exceeding the maximum recommended dosage (4.4mg/kg). Extraction procedure was carried out after five minutes of local anesthetic administration. Hundred percent oxygen was given for three minutes before removal of the nasal mask. As this study was designed to compare the effectiveness of oral midazolam and oral ketamine, the same protocol at first visit was followed but oral ketamine in addition with nitrous oxide and oxygen was used instead of oral midazolam in addition with nitrous oxide and oxygen. All hemodynamic parameters were monitored during the entire course of treatment after sedation and at the end of dental treatment. Before discharge, hemodynamic parameters were recorded and the patient was asked to draw the diagrams as per Bender Test.

STATISTICAL ANALYSIS

All data were tabulated and statistically analyzed using Independent sample t-test to test for its statistical significance.

RESULTS

A total of 30 cooperative but anxious children (3-9 years) were included in the study. On their first visit all patients received 0.5mg/kg oral midazolam with N₂O-O₂ (Midazolam group) and next visit they received 5mg/kg of oral ketamine with N₂O-O₂ (Ketamine group) to compare the effectiveness of two drugs. The data were analyzed using t-test and chi-square test.

Variable	Group	Mean	SD	t-value	p-value
Base line	Oral midazolam-N ₂ O	92.3333	9.93889	0.616	0.540 (NS)
	Oral Ketamine-N ₂ O	90.7000	10.59326		
Average value throughout the procedure	Oral midazolam-N ₂ O	100.2000	11.07155	-0.413	0.681 (NS)
	Oral Ketamine-N ₂ O	101.5333	13.81087		
Before discharge/ After sedation	Oral midazolam-N ₂ O	96.3167	9.24800	0.078	0.938 (NS)
	Oral Ketamine-N ₂ O	96.1167	10.66713		

[Table/Fig-3]: Comparison of pulse rate between two groups (beats per minute). NS- Not significant. Data were analyzed by using t- test.

Variable	Group	Mean	SD	t-value	p-value
Base line	Oral midazolam-N ₂ O	99.0667	1.20153	0.654	0.516 (NS)
	Oral Ketamine-N ₂ O	98.8667	1.16658		
Average value throughout the procedure	Oral midazolam-N ₂ O	99.1000	0.84486	-1.027	0.309 (NS)
	Oral Ketamine-N ₂ O	99.3000	0.65126		
Before discharge/ After sedation	Oral midazolam-N ₂ O	99.0833	0.74375	0.000	1.000 (NS)
	Oral Ketamine-N ₂ O	99.0833	0.70812		

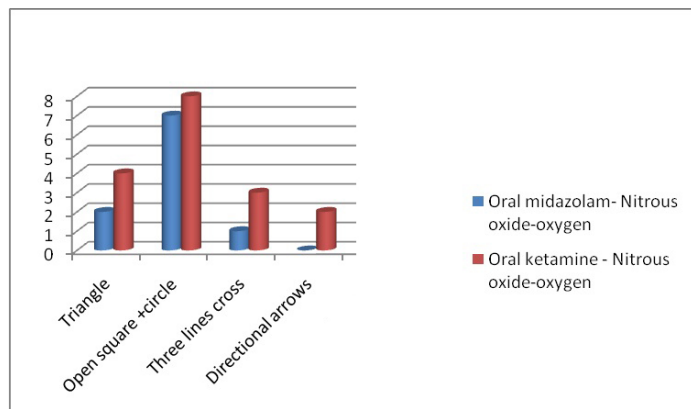
[Table/Fig-4]: Comparison of oxygen saturation between two groups (%). NS- Not significant. Data were analyzed by using t- test.

The pulse rate (beats per minute) and the oxygen saturation (%) scores for both midazolam and ketamine groups immediately after sedation are given in [Table/Fig-3,4] respectively. Both the figures show no significant difference between the midazolam group and ketamine group. The plot of average respiratory rate (in breathes per minute) after sedation for both midazolam and ketamine groups is given in [Table/Fig-5]. The figure shows no significant difference between the two groups.

The results of psychomotor test are given in [Table/Fig-6]. Objective signs were noted and tabulated in [Table/Fig-7]. The subjective symptoms are given in [Table/Fig-8]. The results of psychological effects are tabulated and given in [Table/Fig-9]. Comparative data of sensations in the fingers between the two groups is presented in [Table/Fig-10].

Variable	Group	Mean	SD	t-value	p-value
Base line	Oral midazolam-N ₂ O	21.0333	2.93003	-0.633	0.529 (NS)
	Oral Ketamine-N ₂ O	21.5333	3.18112		
Average value throughout the procedure	Oral midazolam-N ₂ O	23.4667	3.31905	-1.799	0.077 (NS)
	Oral Ketamine-N ₂ O	24.9000	2.83269		
Before discharge/ After sedation	Oral midazolam-N ₂ O	22.2667	2.46259	-1.586	0.118 (NS)
	Oral Ketamine-N ₂ O	23.2333	2.25424		

[Table/Fig-5]: Comparison of respiratory rate between two groups (breaths per minute).
NS- Not significant.
Data were analyzed by using t- test.



[Table/Fig-6]: Comparative data of psychomotor effects between the two groups.

	OBJECTIVE SIGNS		Chi-square value	p-value
	Oral midazolam-N ₂ O	Oral ketamine-N ₂ O		
	After	After	0.149	0.997 (NS)
Eyes open	24	26		
Smile	16	14		
Speaking	27	22		
Laughing	23	25		
Hands open	29	28		
Legs limp	23	22		
Abducted feet	7	6		

[Table/Fig-7]: Comparative data of objective signs between the two groups.
NS- Not significant.
Data were analyzed by using Chi-square test.

There was no statistical difference between the two groups with respect to objective signs (p=0.997), subjective symptoms (p=0.879), psychological effect (p=0.919) and sensation in the finger (p=0.826).

	Oral midazolam-N ₂ O	Oral ketamine-N ₂ O	Chi-square	p-value
Feel good	14	11	1.781	0.879 (NS)
Feel Bad	1	3		
Feel sleepy	6	7		
Feel ok	4	4		
Feel Different	5	5		
Sensation in lip	6	4		

[Table/Fig-8]: Comparison of subjective symptoms between the two groups.
NS- Not significant.
Data were analyzed by using Chi-square test.

HEAD	Oral midazolam-N ₂ O	Oral ketamine-N ₂ O	Chi-square	p-value
Tingly	8	7	0.169	0.919 (NS)
Light	9	6		
Ok	13	11		
Heavy	0	6		

[Table/Fig-9]: Comparative data of psychological effects of the two groups.
NS- Not significant.
Data were analyzed by using Chi-square test.

FINGERS	Oral midazolam-N ₂ O	Oral ketamine-N ₂ O	Chi-square	p-value
Tingly	23	21	0.382	0.826 (NS)
Warm	2	3		
Cold	0	0		
Light	5	6		

[Table/Fig-10]: Comparative data of sensations in the fingers between the two groups.
NS- Not significant.
Data were analyzed by using Chi-square test.

DISCUSSION

The pediatric dentist uses a wide variety of techniques to alleviate fears of children and improve their cooperation while getting dental treatment done. But still in some children safe, fast and non-traumatic dental treatment is needed and thus pharmacological management in the form of sedation is recommended. Sedation is commonly indicated for fearful and physical or mentally handicapped children [3]. Among different methods of medication administration, oral premedication was decided for this study as this is more suitable, most safe and easiest method of medication administration. Advantages of oral drug administration are that they are more acceptable, safe, have minimal side effects, minimal equipment and no specialized training [3,12].

Midazolam is administered in the oral measurements of 0.5-0.75 mg/kg and 3-10 mg/kg of ketamine administered orally, has a high margin of safety as the defensive reflexes are normally kept up [13]. Oral midazolam at the dose of 0.5mg/kg has shown to produce good anxiolysis when used as premedication [2]. And reported rare side effects associated with oral midazolam usage for behavior management [14]. Oral ketamine at 5mg/kg provides safe, successful, high-quality sedation for young children undergoing dental extractions under local anesthesia [15]. Hence in the present study 0.5mg/kg of oral midazolam and 5mg/kg oral ketamine dosage was administered to compare their efficacy in dental treatment of children.

In India there is no availability of midazolam and ketamine to administer orally. Hence intravenous preparation has been used orally. However, it has an extremely bitter taste. Hence, intravenous preparations of the above drugs were modified to make them palatable when taken orally by adding a variety of additives. The drugs were administered 45 minutes before the treatment to ensure adequate level of sedation [10].

Theoretically, under most circumstances, the addition of nitrous oxide to a combination of sedative agents results in the reduced

need for higher doses of the other agents, attaining the same sedation end point because of the potential effect of nitrous oxide. According to Friash M, levels of 30% and above N₂O provide an adequate level of sedation without the risk of over sedation [16].

Children in the age group of 3-9yrs were selected so as to have the capability to draw at least one figure on the psychomotor evaluation component [17]. The general health of ASA I and II patients is reasonably good and there is minimal likelihood that the physiologic stresses of the dental procedure, or local anesthetics and sedative will precipitate a significant medical complication [18]. Psychomotor impairment is an imperative marker of drug impact and recovery from a drug. Psychomotor effects were evaluated with a modified Bender Visual Motor Gestalt Test [10].

The parameters like pulse, respiratory rate, oxygen saturation (SaO₂), level of sedation were recorded just before the administration of sedative and the same were monitored once the sedative has been administered and at the end of the procedure. One study reported that in some children there was increase in blood pressure, pulse and respiratory rate over time, where as in others there was an initial increase in vital signs followed by a decrease [19]. According to another study heart rate and respiratory rate were marginally higher in children who were administered 5mg/kg of oral ketamine contrasted with 0.5mg/kg of oral midazolam [20]. In the present study, respiratory rate was increased after ketamine sedation than midazolam and pulse rate marginally increased after midazolam sedation than with ketamine. However comparing midazolam and ketamine with respect to pulse and respiratory rates, there was statistically no significant difference between the two drugs.

In the present study by comparing oral midazolam- N₂O-O₂ and oral ketamine - N₂O-O₂ with respect to oxygen saturation there was statistically no significant difference between the two drugs. Houpt M et al., had evaluated the psychomotor effects of the drugs - used in combination with N₂O sedation, and his study reported that N₂O have no significant effect on psychomotor performance [10]. In the present study psychomotor effects were evaluated by using Bender Visual Motor Gestalt Test. The children were made to draw diagrams (triangles, open square/circle, three lines cross, and directional arrows) pre and post sedation. On comparison of the psychomotor effects between the two groups oral midazolam - N₂O group performed marginally better than oral ketamine -N₂O. Oral midazolam at a dose of 0.5 mg/kg produces minimal side effects and successful premedication and on the other hand, 5mg/kg oral ketamine provides high margin of safety as the protective reflexes are usually maintained [13,21].

LIMITATION

Limitations of this study were in steady with other comparative studies. A few students were involved in the treatment and assessment and they were not prepared particularly for institutionalization of patient evaluation. Besides, the procedure

was supervised by experienced faculty member and data were collected according to AAPD guidelines. Further studies need to be conducted in the light of present situation, to arrive at a definite conclusion.

CONCLUSION

Oral midazolam – N₂O and oral ketamine N₂O as sedative regimens were found to be safe and effective and their use greatly reduced the patient anxiety during the therapeutic procedure. Overall the findings in the present study suggested that no significant difference was observed pertaining to pulse rate, oxygen saturation, respiratory rate, psychological effects, objective signs and subjective symptoms. However, psychomotor effect of the midazolam group appeared marginally better than ketamine group.

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