A COMPARATIVE STUDY BETWEEN ORAL MIDAZOLAM AND NITROUS OXIDE-OXYGEN FOR DENTAL EXTRACTIONS IN PAEDIATRIC PATIENTS

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ABSTRACT

BACKGROUND

Fear of pain is a major deterrent to delivery of dental care in paediatric patients. Local anaesthesia delivery is one of the most frightening and painful procedure associated with highest degree of disruptive behaviour, hence the need for conscious sedation. Oral Midazolam is a popular dental sedative due to rapid absorption and clinical action with amnestic properties. Inhalation is second commonly used route for conscious sedation. Nitrous oxide is the only available inhalation agent that meets the conscious sedation criteria.

Hence, this study focuses on comparing the sedation efficacy of oral Midazolam and nitrous oxide for dental extractions in children.

MATERIALS AND METHODS

In this randomised controlled trial study, patients aged 5 - 12 years indicated for bilateral or contralateral dental extractions were studied. After routine pre-anaesthetic workup, patients were induced with either-
Group M: Oral Midazolam (0.5 mg/kg)
Group N: Nitrous oxide + oxygen (50: 50)
Baseline parameters, relevant intraoperative details, ease of procedure, level of sedation, acceptability by patient, anxiety level and recovery from sedation compared between both groups.

RESULTS

Baseline parameters like Heart Rate, Blood Pressure, SpO_2 and Respiratory Rate were comparable in both groups. However, there was significant difference in onset time of sedation and recovery between two groups.

CONCLUSION

Oral Midazolam due to its more effectiveness, acceptability, amnestic property and long duration of action is the preferred drug of choice for conscious sedation for dental extractions. However, nitrous oxide-oxygen can be considered as an alternate to oral Midazolam due to its anxiolytic effect, early onset and recovery time.

KEY WORDS

Paediatric, Conscious Sedation, Midazolam, Nitrous Oxide-Oxygen, Tooth Extraction.

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BACKGROUND

Fear of pain is the major deterrent to the delivery of dental care today. Patients who are not in pain fear the visit to the dental office, because they believe that at some time during dental treatment they will be hurt. Fear of pain produces a heightened anxiety in these patients, a factor that may lead to the avoidance of dental care until they are truly in pain.(1)

Local anaesthesia delivery is one of the most frightening and painful procedures during dental treatment. It is therefore associated with the highest degree of disruptive behaviour when compared to other dental procedures. Young age and high level of anxiety are both correlated with low level of pain threshold.

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Provision of successful dental treatment on anxious and fearful children is largely dependent upon successfully gaining their cooperation. Technical skills are of a little value unless the child cooperates. Use of sedation can be very helpful in allaying apprehension and minimising an uncooperative child's attempt to resist treatment.

Conscious sedation can be defined as a minimally depressed level of consciousness that retains the patient's ability to independently and continuously maintain an airway and respond appropriately to physical stimulation and verbal command and that is produced by a pharmacologic and non-pharmacologic method or combination thereof.(1)

Goals of paediatric sedation are to make the child cooperative and comfortable, decrease anxiety for the patient, decrease pain apprehension, excessive fatigue for the dentist and the staff and to minimise the need for hospitalisation and related problems.

Sedation drugs are administrated through various routes such as oral, rectal, inhalational, intranasal, intramuscular, subcutaneous and intravenous. All these routes have certain advantages and disadvantages.

The oral route is the oldest of all routes of drug administration and is the most economical method of drug administration. From the patient's point of view, the main advantage of the oral route is the avoidance of an injection with its inherent risks and psychological effects. It is the most universally accepted and easiest route of drug administration. Most practitioners prefer use of this easiest route for drug administration with high safety, minimal complication and which is mostly accepted with ease by children. In addition, parents prefer the less invasive method of drug administration with the lowest cost.[2] Therefore, oral sedation is probably the most widespread form of conscious sedation in dentistry.

Benzodiazepines represent the most popular class of drugs available today for management of dental fear and anxiety via oral route of drug administration. Orally, administered midazolam is a very popular dental sedative, because absorption and onset of clinical action are more rapid than those of other benzodiazepines. Absorption of midazolam is better with oral route than intramuscular administration. Peak action after oral midazolam administration occurs within 30 minutes.[1]

Inhalation is the second most commonly used route for conscious sedation.[3] Nitrous oxide is the only available inhalational agent that meets the conscious sedation requirement. The inhalational route has certain unique advantages. Its onset of action is rapid and the effect can be maintained for as long as administration lasts. The depth of sedation can be titrated and adjusted because the drug is eliminated through the airway. Instead of a peak effect, a plateau can be reached within a few minutes and recovery from the state of sedation occurs within minutes of ceasing administration. Inhalational drugs have to be administered through the nasal passages with a special nasal mask, thus permitting access to the oral cavity by the operator.

Because the oral route is preferred by most of the children, while inhalation route has certain benefits. This study focuses on comparing the sedative efficacy of oral midazolam and nitrous oxide for dental extraction in children.

MATERIALS AND METHODS

In this randomised controlled trial study, forty patients scheduled for tooth extraction under conscious sedation were taken. The sample size was taken for convenience for the study. Approval from Institutional Ethical Committee was taken. The purpose of the study was explained and an informed valid consent was taken from the parent or the legal guardian in the language they can understand. Forty patients after considering inclusion and exclusion criteria were included in the study. Anaesthetist and paediatrician assessed fitness of child.

Those included in the study are[4,5]

1. 5 to 12 years old children.
2. ASA physical status I and II.
3. Anxious patients.
4. Two or more carious teeth with poor prognosis (bilateral or contralateral).

Those not included are-

- Those who needed pulp therapy or extractions.
- Patients who had recently used medications such as erythromycin or anticonvulsants that may interfere with the pharmacokinetics of midazolam.[2]
- Children with any condition that predisposes them to airway obstruction or difficulties (such as adenoid hyperplasia, nasal septum problems, enlarged turbinates or nasal polyp).

Preoperative Preparations and Examination

After meeting the requirements of inclusion criteria, patients were prepared for sedation. Patients were appointed for sedation and NPO guidelines were given to patient one day prior. Simple randomisation was done with chit selection method. Two operating teams of qualified paediatric dentists performed the procedure. Anaesthesiologist administered and monitored the sedation procedure and was present throughout procedure till discharge of the patient. Observer recorded the data at different intervals. The same operating team worked on each of the 40 patients. During the first visit patient's anxiety was recorded on the visual analogue scale for anxiety.[6] NPO status was confirmed by questioning parent or guardian. Weight of patient was measured on digital weighing scale. All the baseline vital parameters were recorded on record sheet with patient's details.

Anaesthesia Technique

Group M (Midazolam Group)

Patient was briefed about the procedure. Dose of oral midazolam was calculated according to the weight of patient (0.5 mg/kg). Calculated dose was administered to patient and time of administration was recorded. Patient was kept in calm and ambient room for observation. All the required armamentarium for extraction under conscious sedation was arranged. A qualified anaesthetist was always present during the procedure till the discharge of patient. After attending and after obtaining an adequate level of sedation, the child was transferred to dental chair with the sedation unit. Multipara monitor was attached through which the vital parameters (Heart rate, blood pressure and peripheral oxygen saturation) were recorded. Respiratory rate was measured by manual method. Ramsay Sedation Scale readings were recorded once the patient was adequately sedated.

Vital parameters like blood pressure, heart rate, peripheral oxygen saturation and respiratory rate were recorded at six different time intervals. They were at baseline, at maximum sedation, at injection of local anaesthetic, at tooth extraction, on entering recovery room and at discharge. Continuous visual monitoring of the patient's respiratory rate and level of consciousness were assessed during the whole procedure. Lignocaine 2% with 1:80,000 adrenaline was then administered using standard anaesthesia technique. After administering local anaesthesia, the tooth was extracted. Pressure gauge pack was held at extraction site until haemorrhage from extraction site was controlled. Patient was shifted to recovery room. Post-operative instructions were given to patient and the parents. Patient was discharged according to standard discharge criteria. A post-operative questionnaire having questions regarding amnesia effect and preferred form of sedation was asked to be filled by patient. Also, a post-operative

questionnaire having questions regarding adverse events was asked to be filled by parent or guardian.

Group N (Nitrous Oxide Oxygen Group)

Patient was briefed about the procedure. All the required armamentarium for extraction under conscious sedation was arranged. Nitrous oxide-oxygen sedation unit with breathing circuit was kept ready alongside dental chair. Appropriate nasal hood was selected and tried on the patient. Multipara monitor was attached through which the vital parameters (Heart rate, blood pressure and peripheral oxygen saturation) were recorded. Respiratory rate was measured by manual method. 100% oxygen was administered with flow rate of four to six litres per minute for the first one to two minutes. Appropriate flow rate of oxygen for individual patient was then adjusted after observation of reservoir bag. Flow of nitrous oxide was started and dose was titrated at increment of 10% interval. Maximum of 50% nitrous oxide and 50% oxygen (1: 1) mixture of gas was given until adequate level of sedation was achieved. Ramsay sedation scale readings were recorded once the patient was adequately sedated. Vital parameters like blood pressure, heart rate, peripheral oxygen saturation and respiratory rate were recorded at 6 different time intervals as depicted above.

Continuous visual monitoring of the patient's respiratory rate and level of consciousness were assessed during the whole procedure. Lignocaine 2% with 1:80,000 adrenaline was then administered using standard anaesthesia technique. After administering local anaesthesia, the tooth was extracted. Flow of nitrous oxide was discontinued after extraction. 100% oxygen was supplied to patient for next three to five minutes to prevent diffusion hypoxia. Pressure gauze pack was held at extraction site until haemorrhage from extraction site was controlled. Flow of oxygen was stopped and nasal hood was removed. Patient was shifted to recovery room and was kept under observation. Postoperative instructions was given to patient and parent. Patient was discharged according to standard discharge criteria. A post-operative questionnaire having questions regarding amnesic effect and preferred form of sedation was asked to be filled by patient. Also post-operative questionnaire having questions regarding adverse events was asked to be filled by patient or guardian.

At the second visit the child was subjected to the other sedative agent, that is if nitrous oxide and oxygen was administered at first visit, then at the second visit midazolam was administered and vice versa.

Statistical Analysis

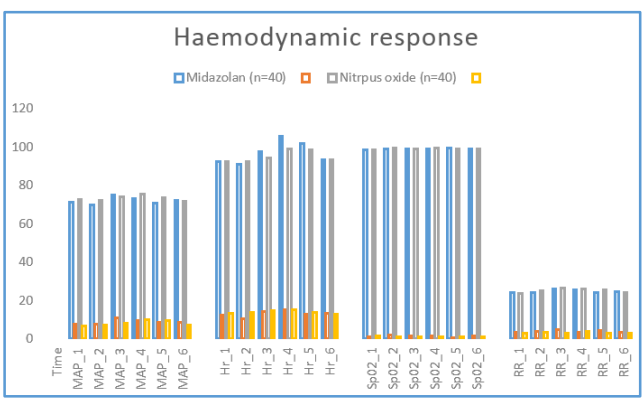
Descriptive statistics for continuous variables such as age and weight were presented as mean and standard deviation, while the inferential statistics for hypothesis testing were performed with the unpaired "t" test. Categorical data were compared using the Chi-square test.

RESULTS

Baseline variables and physiological response which include vital parameters of patient like blood pressure, heart rate, peripheral oxygen saturation (SpO2) and respiratory rate were comparable in both the groups (Table 1, Graph 1).

	Midazolam (n= 40)		Nitrous Oxide (n= 40)	
Time	**Mean**	**SD**	**Mean**	**SD**
MAP_1	71.3	7.38	72.53	6.4
MAP_2	69.53	7.8	71.9	7.28
MAP_3	75	10.89	74.13	8.02
MAP_4	72.95	9.48	75.28	9.98
MAP_5	70.73	8.47	73.63	9.54
MAP_6	72.08	8.64	71.6	7
Hr_1	92.23	12.23	92.3	13.4
Hr_2	90.7	10.17	92.08	13.78
Hr_3	97.28	14.04	94	14.66
Hr_4	105.43	15.09	98.68	15.24
Hr_5	101.55	12.95	98.4	13.61
Hr_6	93.35	13.3	93.35	12.79
Sp02_1	98.58	0.84	98.53	1.26
Sp02_2	98.85	1.69	99.28	0.88
Sp02_3	98.73	1.55	98.98	0.92
Sp02_4	98.75	1.66	99.15	0.95
Sp02_5	99.18	0.68	99	0.93
Sp02_6	98.95	1.36	98.85	0.95
RR_1	24.23	3.21	23.6	2.87
RR_2	23.85	3.75	24.75	3.41
RR_3	25.7	4.52	26.25	3.04
RR_4	25.5	3.5	25.75	3.63
RR_5	24.2	4.05	25.6	3.01
RR_6	24.33	3.53	24	2.81

Table 1. Haemodynamic Response

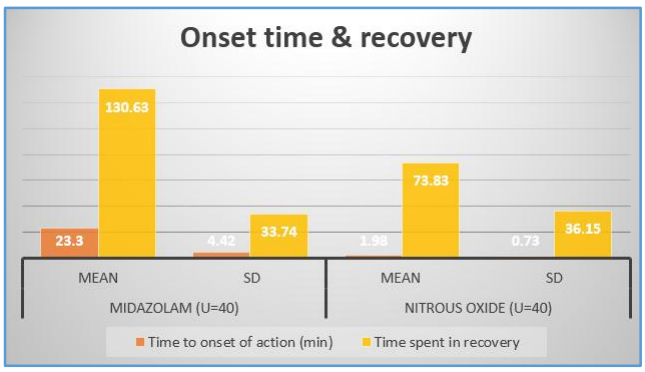


Graph 1

However, there was significant difference in onset of time of sedation and recovery from sedation in both the groups (P-value was less than 0.001) according to paired 't' test. The onset time of sedation for Group N is faster (Avg. is 1.98 mins) as compared to onset time of sedation for Group M (Avg. 130 mins) (Table 2, Graph 2). The recovery time from sedation for Group N is faster (Avg. 73 mins) as compared to recovery time from sedation for M Group (Avg. 130 mins) (Table 2, Graph 2).

	Midazolam (n=40)		Nitrous Oxide (n=40)	
	Mean	SD	Mean	SD
Time to onset of action (mins)	23.3	4.42	1.98	0.73
Time spent in recovery	130.63	33.74	73.83	36.15

Table 2



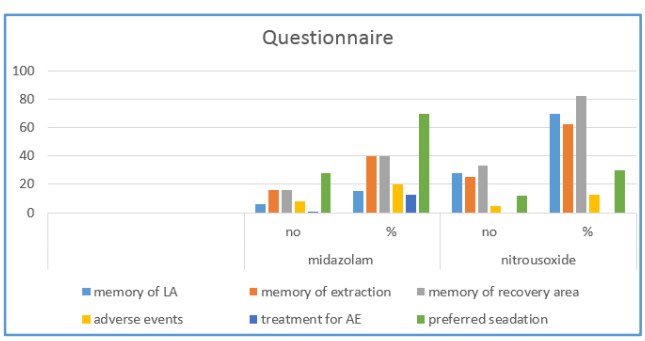
Graph 2

There is a significant difference in the amnesic response like memory of local anaesthesia injection and memory of recovery area between the two groups (P-value was less than 0.001) accordingly likelihood of ratio test (Table 3, Graph 3). But there is no significant difference in memory of extraction of teeth, adverse event after sedation and attention to get treated in both the groups according to likelihood ratio test (Table 3, Graph 3). In Group M 15% of children were able to remember delivery of local anaesthesia injection, but in Group N 70% of children were able to remember delivery of local anaesthesia injection. Likely, in Group M 40% children were able to remember being kept in recovery area, but in Group N 82.5% of children were able to remember of being kept in a recovery area (Table 3, Graph 3).

In Group M, 40% of kids were able to remember extraction of tooth as compared to 62.50% in Group N. In Group M, 20% of kids suffered from adverse event as compared to 12.50% in Group N and in Group M 12.50% kids required attention to get treated for as compared to no kids in Group N (Table 3, Graph 3). There is a statistically significant difference (p= 0.017) for preferred form of sedation in future by children between Group M (70% of children) and Group N (30% of children) according to likelihood ratio test (Table 3, Graph 3).

Questionnaire				
	Midazolam		Nitrous Oxide	
	No.	%	No.	%
Memory of LA	6	15	28	70
Memory of extraction	16	40	25	62.5
Memory of recovery area	16	40	33	82.5
Adverse events	8	20	5	12.5
Treatment for AE	1	12.5	0	0
Preferred sedation	28	70	12	30

Table 3



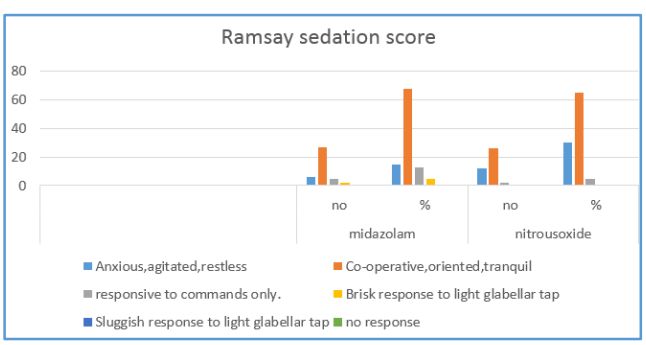
Graph 3

The sedation score of different patients according to Ramsay Sedation Score were (Table 4, Graph 4)

1. Patients with score 1 (anxious and educated and restless or both) was 15% (6 patients) in oral midazolam group as compared to 30% (12 patients) in nitrous oxide-oxygen group.
2. Patient with score 2 (cooperative, oriented and tranquil) was 67.50% (27 patients) in oral midazolam group as compared to 65% (26 patients) in nitrous oxide-oxygen group.
3. Patients with score 3 (responded to commands only) was 12.50% (5 patients) as compared to 5% (2 patients) in nitrous oxide oxygen group.
4. Four patients with score 4 (Brisk response to light glabellar tap on auditory stimulus) was 5% (2 patients) in oral midazolam group as compared to no patients in nitrous oxide-oxygen group.
5. No patient was there with score 5 (Sluggish response to light glabellar tab on loud auditory stimulus) in both the groups.
6. No patient was there with score 6 (No response) in both the groups.

Ramsay Sedation Score	Midazolam		Nitrous Oxide	
	No.	%	No.	%
Anxious, agitated, restless	6	15	12	30
Co-operative, oriented, tranquil	27	67.5	26	65
Responsive to commands only	5	12.5	2	5
Brisk response to light glabellar tap	2	5	0	0
Sluggish response to light glabellar tap	0	0	0	0
No response	0	0	0	0

Table 4



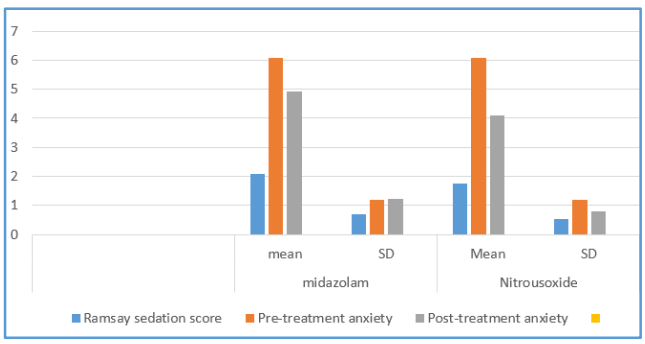
Graph 4

There was a statistically significant difference (p= 0.032) in the mean value of Ramsay sedation scale among the oral midazolam group and nitrous oxide oxygen group (Table 5, Graph 5).

Anxiety was recorded according to Visual Analogue Scale (VAS) once before any sedation appointment (at time of sample selection visit) and after each sedation visit. In oral midazolam group, mean score of preoperative anxiety was 6.09 which is reduced to 4.93 post-operatively. In nitrous oxide-oxygen group mean score of preoperative anxiety was 6.09, which is reduced to 4.10 post-operatively. There was statistically significant difference between group midazolam and group nitrous oxide-oxygen in post-operative anxiety reduction after sedation appointment (p= 0.001) (Table 5, Graph 5).

Mean Scores for Sedation and Anxiety				
	Midazolam		Nitrous Oxide	
	Mean	SD	Mean	SD
Ramsay sedation score	2.08	0.69	1.75	0.54
Pre-treatment anxiety	6.09	1.18	6.09	1.18
Post-treatment anxiety	4.93	1.21	4.1	0.79

Table 5



Graph 5

DISCUSSION

The purpose of our study was to compare oral midazolam and nitrous oxide-oxygen as a sedative agent for dental extraction. Two groups were comparable with respect to baseline variables and physiological responses which include vital parameters of patients like blood pressure, heart rate, peripheral oxygen saturation and respiratory rate. Most of the changes in heart rate, blood pressure, oxygen saturation and respiratory rate in the present study were within safe limits compared with normal physiological changes in children. In the present study, changes in heart rate was minimal in both regimens. There is no statistically significant difference in systolic blood pressure and diastolic blood pressure in midazolam and nitrous oxide-oxygen group during whole dental procedure. Some studies have reported that oral midazolam (0.5 mg/kg) does not significantly affect the physiologic parameters.[7] Fraone et al 1999 reported that oral midazolam 0.5 mg/kg did not significantly affect the physiologic parameters like heart rate, oxygen saturation, systolic and diastolic blood pressure of young children. Midazolam by itself has the least depressive effect on the respiratory system. In present study, changes in respiratory rate were within acceptable limits as no case showed respiratory depression.

The onset of time of sedation for oral midazolam group and nitrous oxide-oxygen group were from 13 to 32 minutes (mean 23. 30 minutes) and from 1 to 4 minutes (mean 1.98 minutes) respectively ($p < 0.0001$) (Table 2). Previous studies have reported sedation onset time ranged from 15 to 40 minutes for oral midazolam. McMillan et al in 1992 in their dose related studies reported that time taken to reach maximum sedation when using midazolam 0.5 mg/kg was 15 to 30 minutes.[8,9] The recovery time from sedation for Group M was ranged from 64 to 206 minutes (mean of 130.63 minutes), whereas the recovery time for Group N was ranged from 32 to 197 minutes (mean 73. 83 minutes) ($p < 0. 0001$). That means the time spent in recovery area was greater for Group M as compared to Group N. This is due to longer half-life (two hours) of oral midazolam, while nitrous oxide oxygen does not get metabolise in body at all. So the patients sedated with oral midazolam required longer duration of time for post-operative observation. This might act as disadvantage over nitrous oxide-oxygen group. The result of present study are in accordance with previous studies.[9,10,11]

Amnesia after sedation is considered a positive side effect of sedative agents, especially in uncooperative patients as any unpleasant memory of the dental procedures is lost. The result of the present study indicates a strong amnesic effect of oral midazolam on most of the children. The result of the present study are in agreement with previous studies, which reported amnesia in 50 to 80% of children after medical or dental procedures under oral midazolam sedation.[12]

Wilson et al 2002 evaluated the safety and effectiveness of oral midazolam alone and nitrous oxide alone for dental treatment of children 10 to 16 years old. They found that the median range of arterial oxygen saturation levels for patients in the midazolam and nitrous oxide group ware 95% (90% to 100%) and 98% (93% to 100%) respectively. However, a study by Litman et al 1997, while using a combination of midazolam 0.5 mg/kg and N2O (60%) for minor oral surgery in young children (one to three years) reported mild respiratory depression in some children. Again, the result could be attributed to the combination of high N2O concentration and very young age of the children. No incidence of nausea and vomiting occurs in the present study, which is in agreement with previous evidence that midazolam reduces the incidence of postoperative nausea and vomiting in children.[13]

70% of children preferred oral midazolam sedation as their future choice of sedation if required, indicating acceptability of oral midazolam over nitrous oxide oxygen (30%). The difference was found to be statistically significant. The difference was due to adequate level of sedation, relaxation and amnesic effect of midazolam.

Level of sedation according to Ramsay sedation scale was most suitable for treatment in oral midazolam group as compared to nitrous oxide-oxygen group. This difference was statistically significant ($p= 0.032$). Two children in oral midazolam group were responsive to light glabellar tap or loud auditory stimulus indicating that the deeper level of conscious sedation was achieved, but not deep sedation. Nitrous oxide-oxygen group showed higher number of children as compared to midazolam becoming anxious and agitated. Also, in present study we have delivered 50% nitrous oxide to 50% oxygen (Entonox) mixture, which can be increased to maximum 70: 30 ratio to reduce agitation and increase depth of conscious sedation. Interestingly, no child progresses to deep sedation in this study, while the incidence of deep sedation has been reported by previous studies.[14]

In the present study, preoperative anxiety was recorded when patient was first seen by dentist at the time of sample selection. While post-operative anxiety was measured after each sedation visit, that is after oral midazolam sedation and after nitrous oxide-oxygen sedation. This was done to reduce the bias as if the child undergoes oral midazolam sedation at first visit. There was a definite reduction of anxiety at the time of second visit as midazolam has strong amnesic effect. In the present study, nitrous oxide-oxygen group showed good anxiolysis following sedation procedure as compared to oral midazolam. The difference was statistically significant ($p= 0.001$). Emmanouil DE et al 2007 concluded that anxiolytic effect of N2O resembles that of benzodiazepines and may be initiated at selected subunits of the gamma

aminobutyric acid type A GABA-A receptor. The provision of oral midazolam for dental treatment of anxious children was found to be as effective as using N2O-O2 in many papers.[9]

So to summarise, oral midazolam showed adequate and appropriate level of conscious sedation. Also it has a strong amnesic effect, which is highly beneficial for anxious children. It is a highly preferred form of future sedation technique in children. Oral midazolam may be more appropriate for some individuals depending on their treatment requirement, level of anxiety and compliance with the treatment. Sedating young children requires a high level of knowledge and skill with the particular technique chosen and it is imperative that any clinician undertaking such treatment is fully competent to do so. The taste of the oral midazolam solution can often be a barrier and may result in the child rejecting the medication. The time to the maximum level of sedation, although greater for oral midazolam than nitrous oxide was still clinically acceptable and compares well with previous studies.[15,16]

CONCLUSION

1. Oral midazolam is more effective than nitrous oxide-oxygen as a conscious sedative agent for dental extraction in children aged 5 - 12 years.
2. Oral midazolam is more acceptable by children aged 5 - 12 years for dental extractions when compared to nitrous oxide-oxygen sedation.
3. Anxiolytic efficacy of nitrous oxide-oxygen is greater than that of oral midazolam children aged 5 - 12 years.
4. Oral midazolam produces anteretrograde amnesia in children aged 5 - 12 years.
5. Time of onset and recovery time is more for oral midazolam as compared to nitrous oxide-oxygen in children aged 5 - 12 years.

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