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Dentistry Section

Comparison of Nitrous Oxide-Oxygen as Inhalation Agent, Midazolam, Ketamine alone and in Combination as Oral Sedative Agents for In-office Paediatric Patients- A Randomised Control Trial

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ABSTRACT

Introduction: In-office pharmacological sedation techniques are best applied to manage an extremely fearful preschooler, especially during primary dentition or a child's early mixed dentition period. These should be used when non pharmacological behavioural management techniques fail either due to lack of communication or in children with special care needs.

Aim: To compare the efficacy of oral administrations of midazolam, ketamine, combination of midazolam-ketamine (M+K) and nitrous oxide-oxygen (N_2O) inhalational sedation in achieving favorable behavioural outcome compared by using the Houpt scale in the treatment of anxious and uncooperative paediatric patients.

Materials and Methods: A randomised clinical trial was conducted in the Department of Paediatric and Preventive Dentistry, SGT University, Haryana, India between September 2018 to December 2019. The study included 100 anxious children (Venham's picture scale) aged three to five years, who required procedures under local anaesthesia administration were divided into four groups using envelop method. Each group was given either oral midazolam (M) (0.3 mg/kg) or oral ketamine (K) (3 mg/kg) or oral combination of midazolam+ketamine (M+K) (0.3 mg/kg and 2 mg/kg) or inhalational nitrous oxide-oxygen (N_2O). The behaviour response of the child was recorded using the Houpt scale. The oxygen saturation level and heart rate of each patient were also recorded before, after, and during the procedure. Adverse drug reactions post-treatment was also recorded. Analysis of Variance (ANOVA), Chi-square test and Mann-Whitney U test was used for statistical analysis.

Results: The study comprised of 100 anxious children (mean age was 4.1±0.5 years) requiring administration of local anaesthesia with intent to complete in-office treatment. Statistically, a significant difference was found among behaviour outcomes of four groups (p-value=0.047). Acceptable behaviour was seen best in K+M group (88%), followed by oral ketamine (K) (68%), N_2O (59%), and oral midazolam (M) (52%). Adverse reactions were most commonly seen in the oral ketamine group.

Conclusion: Oral M+K combination group is significantly better than oral ketamine (K), oral midazolam (M) or N_2O inhalation sedation to achieve the required behaviour for dental treatment in three to five years old patients.

Keywords: Benzodiazepine, Conscious sedation, Inhalational sedation, Pharmacological behavioural management

INTRODUCTION

Paediatric patients have dental anxiety, with a reported range of prevalence between 5-24% in various studies [1-3]. Initially, non pharmacological behavioural management techniques were being used to achieve treatment goals. Management of fearful, anxious and specially-abled children many times need mild to moderate sedation in the dental office [4]. Midazolam and ketamine are the most commonly used sedative agents to modify undesirable behaviour to complete short term in-office procedures under moderate sedationas compared to other oral sedatives [5,6].

Midazolam is an imidazobenzodiazepine having a half-life of one two hours and rapid onset of action with a safe dose ranging from 0.2-0.5 mg/kg [7]. It works as mild analgesic resulting from the central suppression of pain [8]. Ketamine is fast acting sedative with wide margin of safety being a non narcotic, non barbiturate drug. This produces a unique combination of sedation, amnesia, and analgesia making this agent a choice for moderate sedation. Co-administration of these two drugs reduces the required dose of each by around 50%, managing the incidence and severity of side-effects related to both sedative agents [9,10]. The carefully titrated oral route has been proven to be an acceptable and familiar mode of drug administration [4,5], comparable to the famous inhalational conscious sedation technique, which uses nitrous oxide-oxygen with oxygen. It is a colorless gas having faint, sweet smell. It acts by Central Nervous System (CNS) depression initiates euphoria, analgesia along with minor effect on the respiratory system [11]. However, the best sedative outcome results due to superior efficacy as well as least side effects. To compare the efficacy of oral administrations of midazolam, ketamine, and combination of midazolam-ketamine with nitrous oxide-oxygen-(N_2O) inhalational sedation in achieving favorable behavioural outcome compared by using the Houpt scale in the treatment of anxious and uncooperative pediatric patients.

MATERIALS AND METHODS

This randomised clinical trial was carried out in the Department of Paediatric and Preventive Dentistry, SGT University, Haryana, India between September 2018 to December 2019, comprising 100 anxious children between the age group of three-five years. The approval from the university ethical committee was taken before starting the study letter No.: SGTU/Exam./SCY_17-18/10621.

Sample size calculation: The sample size of the present study was calculated on basis of a pilot study done on 20 children. A sample included a total of 100 patients was deemed sufficient (Statistical power of 0.80 and a significance level of 0.05).

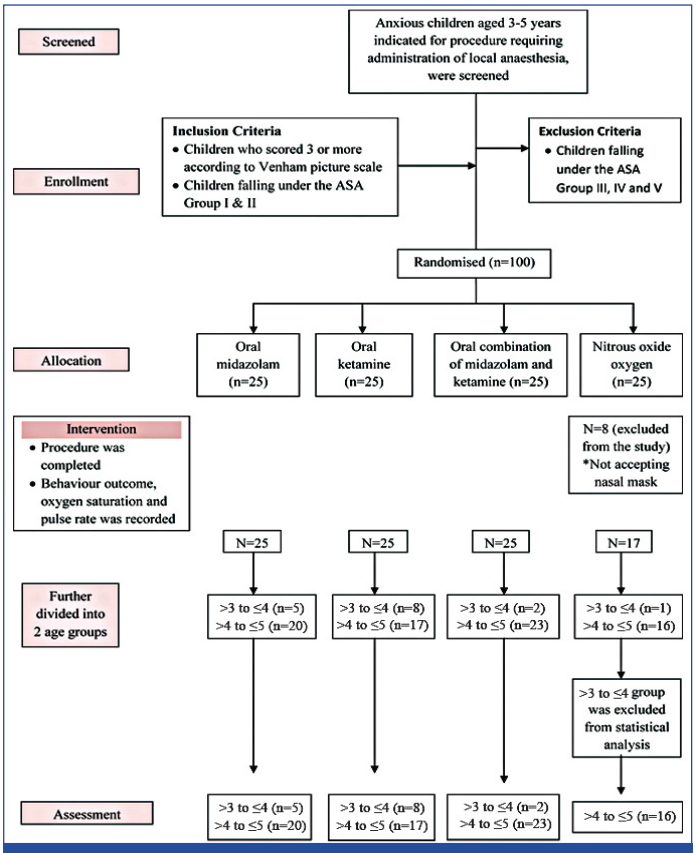
Sedation techniques used in the present study are routine pharmacological behaviour management procedures in paediatric dentistry. Written consent from parents of all patients was taken. Hundred children were equally divided into four groups (N=25) and were administered with either oral midazolam or oral ketamine or oral combination of midazolam+ketamine or inhalational N_2O. Also, the subjects were divided into two groups based on age (based on communicative stages i.e., stage 3-4 and 4-5) for statistical purpose.

Inclusion criteria: Children who were anxious between the age group of three-five years, who have scored three or more according to Venham picture scale [12], who required procedures with local anaesthesia administration, falling under the group I and II of the American Society of Anesthesiologists (ASA) physical status classification [13] and whose parents provided with consent were included in study.

Exclusion criteria: Children falling under the ASA Group III, IV and V were excluded from the study.

Randomisation was done using 100 sealed envelopes divided equally among four agents to be used in the given study. The moderate sedation agent was picked by the parents/guardian after shuffling the envelopes. The appointment was given to children with recommended pre-sedation set of instructions along with to report empty stomach. This included nil per oral prior to three hours of appointment including liquids.

The selected children were divided equally into four groups according to the drug for sedation. Children requiring oral administration of the drugs, oral midazolam (0.3 mg/kg) (group M), oral Ketamine (3 mg/kg) (group K), and a combination of oral midazolam-ketamine (0.3 mg/kg and 2 mg/kg) (group K+M) were given 30 minutes prior to the procedure. Although, the literature states that the safest dose of midazolam ranges from 0.2-0.5 mg/kg [6] and for ketamine, it's 3-10 mg/kg [4], but for the safety concern of paediatric patients authors used the minimal dose in this study, whereas, in the case of inhalational route administration of nitrous oxide-oxygen (group N_2O) was initiated at the time of procedure [Table/Fig-1].



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

Syrup was prepared from the intravenous vials of midazolam and ketamine. According to the weight of the child, sedative drug was mixed with a flavored drink (Frooti™-Parle Agro India Pvt Ltd.,) and was given to the patient in order to mask the bitter taste of medicines.

The behaviour response of the child was recorded using the Houpt scale [Table/Fig-2] [14] after administration of local anaesthesia. This classification was grouped for statistical evaluation into two scales for better understanding:

(i) Non acceptable behaviour -Aborted (no treatment rendered), poor and fair behaviour.

(ii) Acceptable behaviour- Good, very good, and excellent behaviour was considered.

Score	Houpt behaviour rating scale
Sleep	
1	Fully awake, alert
2	Drowsy, disoriented
3	Asleep
Movements	
1	Violent movement that interrupts treatment
2	Continuous movement that makes treatment difficult
3	Controllable movement that does not interfere with treatment
4	No movement
Crying	
1	Hysterical crying that interrupts treatment
2	Continuous, persistent crying that makes treatment difficult
3	Intermittent, mild crying that does not interfere with treatment
4	No crying
Overall behaviour	
1	Aborted- no treatment rendered
2	Poor- treatment interrupted, only partial treatment completed
3	Fair- treatment interrupted but eventually all completed
4	Good- difficult, but all treatment performed
5	Very good- some limited crying or movement, e.g. during anaesthesia or mouth prop insertion
6	Excellent- no crying or movement

[Table/Fig-2]: Houpt behaviour rating scale [14].

Authors further categorised the assessment of the intensity of behavioural response of sleep, movement, and crying as:

(i) Favorable (sleep score 1 and 2, movement score 3 and 4, crying score 3 and 4) and

(ii) Non-favorable (sleep score 3, movement score 1 and 2, crying score 1 and 2)

This method increases the possibility to detect minor changes in a child's behaviour between the age groups of three to five years. The oxygen saturation level and heart rate of each patient was recorded before drug administration, during the procedure (at the time of local anaesthesia administration), and after the procedure using a pulse oximeter.

Any adverse drug reactions were recorded. The patient was discharged only after the normal oxygen saturation level and heart rate were achieved. Post sedation instructions were given to the patient regarding eating and drinking to begin by giving clear liquid such as clear juices, water, gelatin, popsicles, if your child does not vomit after 30 minutes, you may continue with solid foods. Single operator carried out the study and behaviour assessment to prevent bias.

STATISTICAL ANALYSIS

Statistical analysis was done using software from IBM Corporation, Statistical Package for the Social Sciences (SPSS) Inc., Chicago, IL,

USA version 17.0 software package. The groups were compared using ANOVA, Chi-square test, and Mann-Whitney U test.

RESULTS

The study comprised of 100 anxious children (mean age: 4.1±0.5 years) requiring administration of local anaesthesia with intent to complete in-office treatment.

The difference between the male and female in the sample was not significant (p-value=0.376) [Table/Fig-3]. Eight (32%) children from the nitrous oxide-oxygen sedation group were excluded because they didn't accept the nasal mask and the sedative agent couldn't be initiated. These children were treated under general anaesthesia.

Group	>3 to ≤4 (years)		>4 to ≤5 (years)		Total
	Male	Female	Male	Female	
Ketamine (K)	4	4	11	6	25
Midazolam (M)	2	3	10	10	25
K+M	1	1	16	7	25
Nitrous oxide-oxygen sedation	7	1	9	8	25

[Table/Fig-3]: Age and gender wise distribution of sample size.

Evaluation of the overall behaviour was carried out through Houpt behaviour rating scale [Table/Fig-4]. Acceptable behaviour was seen best in the K+M group (88%) followed by ketamine (68%), nitrous oxide-oxygen (59%) and midazolam (52%). Statistically, a significant difference was found among behaviour outcomes of four groups using Chi-square test (p-value=0.047).

Group (n)	Aborted	Poor	Fair	Non acceptable behaviour	Good	Very good	Excellent	Acceptable behaviour
Ketamine (K) (25)	1 (4%)	2 (8%)	5 (20%)	8 (32%)	9 (36%)	5 (20%)	3 (12%)	17 (68%)
Midazolam (M) (25)	2 (8%)	2 (8%)	8 (32%)	12 (44%)	7 (28%)	5 (20%)	1 (4%)	13 (52%)
K+M (25)	0	0	3 (12%)	3 (12%)	8 (32%)	7 (28%)	7 (28%)	22 (88%)
Nitrous oxide-oxygen sedation (17)#	0	0	7 (41.1%)	7 (41.1%)	2 (11.6%)	2 (11.6%)	6 (35.2%)	10 (59%)

[Table/Fig-4]: Behaviour response evaluation in all the four groups after administration of local anaesthesia.
*p-value among behaviour outcome of 4 groups (p-value 0.047); ***Chi-square test; #Eight children from the nitrous oxide-oxygen sedation group were excluded because they didn't accept the nasal mask and the sedative agent couldn't be initiated

Intergroup comparison was done using the Mann-Whitney U test, a significant difference was seen only when combination (M+K) group was compared to other groups, no other intergroup comparison showed significant difference [Table/Fig-5].

Group comparison	p-value
Midazolam vs ketamine	0.271
Midazolam vs combination (M+K)	0.002**
Midazolam vs Nitrous oxide	0.585
Ketamine vs Combination (M+K)	0.035*
Ketamine vs Nitrous oxide-oxygen	0.198
Combination (M+K) vs Nitrous oxide-oxygen	0.01*

[Table/Fig-5]: Comparison amongst all four groups.
Mann-Whitney U test; *p-value= statistically significant, **highly significant

Nitrous oxide-oxygen group was removed from the >3 to ≤4 (years) age group as there was only one patient left in that group [Table/Fig-6]. For both age groups sleep scale with no loss of communication and movement along with no crying was the most favourable score observed in the K+M group in this group. Whereas, for age group >4 to ≤5 (years); the sleep scale was most favourable in nitrous oxide-oxygen analgesia group.

No statistically significant difference was found in oxygen saturation and heart rate amongst all four groups before the procedure, during the procedure, and after the procedure [Table/Fig-7].

Adverse reactions were most commonly seen in ketamine with 20% patients followed by N_2O with 11.7% patients, midazolam with 8% patients, and no patient was seen having any adverse reactions in combination (M+K) group (p-value-0.034) [Table/Fig-8].

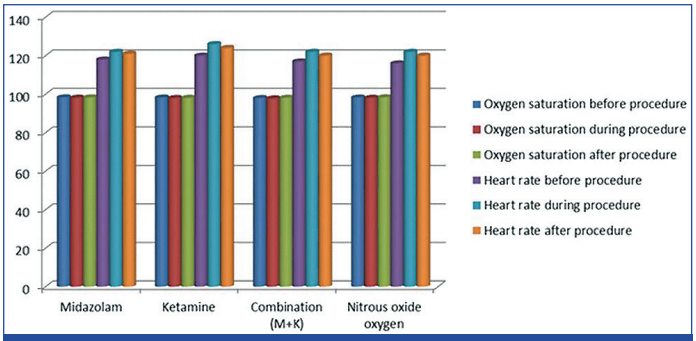
DISCUSSION

According to this study oral combination of midazolam-ketamine was most favourable than all other three groups. This result was per the study of Moreira TA et al., found that oral combination of midazolam and ketamine offered significantly better behaviour guidance than midazolam alone. Adding ketamine to midazolam may have enhanced the quality of sedation by adding analgesic effect without suppressing the upper airway reflex [15]. Menon A et al., in their study used the Houpt scale to assess behaviour and concluded that oral ketamine is a better sedative agent than oral midazolam or even oral midazolam-oral ketamine combination in three to six year anxious paediatric dental patients but their results were statistically insignificant [16].

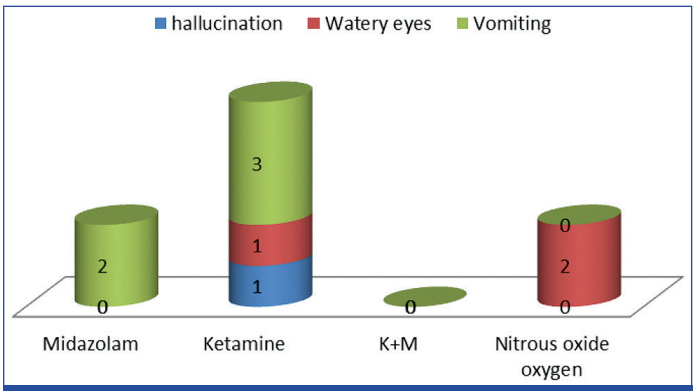
Lokken P et al., compared midazolam and combination midazolam with ketamine administered through rectal route. They found that children, who were sedated with combination showed lesser anxiety, were friendly and had lesser side-effects as compared to the one sedated with midazolam alone. Favorable effects must have been effects of ketamine which adds analgesia and counteracts the depressive effect of midazolam on vital functions. In addition, midazolam may have counteracted the psychic side effects of ketamine [17]. The authors concluded that when midazolam was added to ketamine the side-effects were greatly reduced and the result and was also significant. Similarly in a study conducted by Sado-Filho J et al., where they compared intranasal and oral combination of midazolam and ketamine with oral midazolam and found that combination group showed better behavioural outcome as compare to midazolam alone [18]. A study conducted by Pandey RK et al., comparing ketamine, midazolam, and their combination intranasally, found that Intranasal (IN) ketamine gave best results amongst (IN) midazolam (0.3 mg/kg) or the (IN) combination of ketamine and midazolam. The reason may be the large variance

Group (n)	Sleep				Movement				Crying			
	>3 to ≤4 (years)	p-value	>4 to ≤5 (years	p-value	>3 to ≤4 (years)	p-value	>4 to ≤5 (years)	p-value	>3 to ≤4 (years)	p-value	>4 to ≤5 (years)	p-value
Ketamine (K) (25)	7/8	0.023*	14/17	0.016*	3/8	0.026*	11/17	0.019*	4/8	0.037*	11/17	0.026*
Midazolam (N) (25)	4/5	0.039*	14/20	0.024*	1/5	0.046*	7/20	0.033*	2/5	0.049*	9/20	0.03*
K+M (25)	2/2	0.017*	19/23	0.008*	2/2	0.008*	17/23	0.011*	2/2	0.023*	15/23	0.017*
Nitrous oxide sedation (16)			16/16	0.007*			8/16	0.028*			10/16	0.029*

[Table/Fig-6]: Age wise favourable response for sleep, movement and crying.
ANOVA test; *p-value- significant difference between favourable and unfavourable outcome; The ratio signifies number of students showing favourable outcome among student present in each age group



[Table/Fig-7]: Graphical representation of oxygen saturation and heart rate before, during and after procedure.



[Table/Fig-8]: Adverse reactions following administration of drug in all the four groups.

in the dose of ketamine [19]. Ketamine was a better conscious sedative agent than midazolam in our study. Menon A et al. also found that an oral dose of ketamine (3 mg/kg) acted as better sedative agent than oral midazolam (0.5 mg/kg) [16]. Similar to our results Rai K et al., found Intravenous (i.v) ketamine superior to i.v midazolam as a sedative agent in uncooperative three-six-year-old children undergoing dental procedures. Though midazolam showed the extended duration of action but could not induce desirable behaviour to complete the treatment [20]. Moreover, Surendar MN et al., also found intranasal ketamine to be a better anxiolytic and sedative than intranasal midazolam, though vomiting was seen in one patient who was given ketamine [21]. Foley J reported that nitrous oxide-oxygen sedation was less accepted by younger patients than to older age group children [22]. The same results were found in our study where the patients in age group of less than four years showed significantly less acceptance for nasal mask and treatment could not be completed.

Nitrous oxide-oxygen was less effective than the K+M combination group in our study. While Ilasrinivasan JV and Shyamachalam PM compared N_2O inhalation sedation oral midazolam–ketamine combination for the treatment of anxious children aged between three-ten years for dental treatment and found no statistically significant differences between the groups [23]. In the present study, authors have assessed all sedative agents for the favourable and unfavourable outcome to find the best sedative agent with a favourable outcome.

In a study conducted by Wilson KE et al., the blood pressure, heart rate, and arterial oxygen saturation in both groups (oral midazolam and nitrous oxide-oxygen) were similar and within acceptable clinical limits. [24]. Whereas in a study conducted by Vasakova J et al. after administration of midazolam, arterial blood pressure and blood oxygen saturation decreased and heart rate increased, with values staying within the limits of physiological range [25].

Darlong V et al. concluded in their study that the combination of oral ketamine and oral midazolam has the least side effects than either midazolam or ketamine alone [26]. Moreover, Lokken P et al. compared midazolam (0.3 mg/kg) and midazolam with ketamine (1 mg/kg) as a rectal route. They found that side effects were more in the case of midazolam alone as compared to that of combination [17]. A study conducted by Ilasrinivasan JV and Shyamachalam PM oral combination of the midazolam-ketamine group reported 6.7% hallucinations during the sedation procedure, and 20% overslept [23]. In the present study, adverse reactions were most seen in ketamine followed by nitrous oxide-oxygen, midazolam, and no patient was seen having any adverse reaction in the combination (M+K) group.

In a study conducted by Galeotti A et al., the most frequent symptoms associated with nitrous oxide-oxygen oxygen sedation were nausea and vomiting [27]. However, in this study no such adverse effects were noticed on the administration of nitrous oxide-oxygen except for watery eyes. A summary of all the studies has been presented in [Table/Fig-9] [15-19,21,23,26].

Author	Route	Sedative agents	Place	Outcome
Moreira TA et al., (2013) [15]	Oral	Midazolam (0.5 mg/kg)+ketamine (3 mg/kg) Midazolam (1 mg/kg)	Brazil	Combination better than midazolam alone
Menon A et al., (2016) [16]	Oral	Midazolam 0.5 mg/kg Ketamine (3 mg/kg) Midazolam (0.3 mg/kg)+Ketamine (3 mg/kg)	Gurugram, Haryana	Oral ketamine is a better sedative agent than oral midazolam or even oral midazolam-oral Ketamine combination
Lokken P et al., (1994) [17]	Rectal	Midazolam (0.3 mg/kg) Midazolam (0.3 mg/kg)+Ketamine (1 mg/kg)	Norway	Combination of midazolam and ketamine better than midazolam alone.
Sado-Filho J et al., (2019) [18]	Intranasal and oral	(IN) Midazolam (0.2 mg/kg)+Ketamine (4 mg/kg) (O) Midazolam (0.5 mg/kg)+Ketamine (4 mg/kg) (O) Midazolam (1 mg/kg)	Brazil	Combination group showed better behavioural outcome as compare to midazolam alone.
Pandey RK et al., (2011) [19]	Intranasal	Midazolam (0.3 mg/kg) Ketamine (6 mg/kg) Midazolam (0.2 mg/kg)+Ketamine (4 mg/kg)	Lucknow, India	Oral ketamine gave better results than oral midazolam or even oral midazolam-oral Ketamine combination
Surendar MN et al., (2014) [21]	Intranasal	Midazolam (0.2 mg/kg) Ketamine (5 mg/kg) Dexmedetomidine 1 µg/kg Dexmedetomidine 1.5 µg/kg	Lucknow, India	ketamine to be a better anxiolytic and sedative than midazolam
Ilasrinivasan JV and Shyamachalam PM (2018) [23]	Inhalation Oral	Nitrous oxide-oxygen Midazolam (0.25 mg/kg)+Ketamine (3 mg/kg)	Bengaluru, Karnataka, India	Oral combination of midazolam and ketamine gives better result than nitrous oxide-oxygen
Darlong V et al., (2004) [26]	Oral	Midazolam (0.5 mg/kg) Ketamine (6 mg/kg) Midazolam (0.25 mg/kg)+Ketamine (3 mg/kg)	New Delhi, India	Combination of midazolam and ketamine better than midazolam and ketamine alone
Present study	Oral	Oral midazolam (0.3 mg/kg) Oral ketamine (K) (3 mg/kg) or Oral combination of midazolam+ketamine (M+K) (0.3 mg/kg and 2 mg/kg) or Inhalational Nitrous Oxide-Oxygen (N_2O).	Haryana, India	Oral ketamine and midazolam is a significantly effective alternative to oral ketamine or midazolam alone or nitrous oxide inhalation sedation.

[Table/Fig-9]: Comparison of related studies [15-19,21,23,26].

Limitation(s)

Although, the use of moderate sedation shows significant changes in the behaviour outcome but there were few limitations of the study like eight (32%) children from the nitrous oxide-oxygen sedation group were excluded because they didn't accept the nasal mask and the sedative agent couldn't be initiated. Ketamine, midazolam, and nitrous oxide-oxygen show side effects like vomiting, hallucination, and watery eyes. More studies are required for the search for a predictable, safe and efficacious sedative agent.

CONCLUSION(S)

Oral (midazolam+ketamine (M+K) regimen may be a significantly effective alternative to oral ketamine or midazolam alone or nitrous oxide-oxygen inhalation sedation in preschool children (three to five-year-old). This strategy may enable the paediatric dentist to tailor a sedation regimen friendly to both patients and parents, as K+M group showed no adverse effect. Ketamine acts as an analgesic to the combination K+M and decreases the depressive effect of midazolam on vital functions. Further the combination of local anesthesia with N_2O sedation provides an effective analgesia where parents preferred their child not being put to sleep and has less recovery time than K/M regimen.

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