RESEARCH ARTICLE

Evaluation of Efficacy of Oral Ketamine and Midazolam Combination Drug in Different Doses in Different Groups Used for Moderate Sedation in Pediatric Dentistry Randomized-comparative Trial

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Abstract

Background: Dental phobia and apprehension in children lead to difficulty with behavior management. During dental procedure if a child had a bad experience, he will develop greater apprehension, which makes further treatment difficult.

Aim and objective: The aim and objective of the present study is to assess and compare the sedation and wake-up behavior status of oral combinations of three different doses of ketamine and midazolam drugs in three different groups mixed in 1 mL of honey.

Methodology: This study was a randomized, clinical study that included patients ranging from 3 to 9 years of age with American Society of Anesthesiologists–I status with carious teeth, were randomly allocated among three groups where group (A) received 0.2 mg/kg of oral midazolam and 5 mg/kg oral ketamine combination drugs, group (B) received 0.3 mg/kg of oral midazolam with 3 mg/kg of oral ketamine combination drugs and group (C) received 0.4 mg/kg of oral midazolam with 2 mg/kg of oral ketamine combination drugs mixed in 1 mL of honey.

Child patient's who fulfilled the inclusion criteria, heart rate, blood pressure, and oxygen saturation was recorded from starting of the treatment until discharged from the monitoring room. Ease of treatment completion was evaluated according to the Houpt scale, patients' behavior, sedation, and wake-up behavior status were evaluated with modified observer assessment of alertness and sedation scale (MOAAS).

Results: In the study, various doses of ketamine-midazolam combination drugs in three different groups resulted in a clement increase in heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) during the procedure but variations among the groups were not significant. As per MOAAS, the sedation success rate in group B (83.3%) was more than group A (66.6%) and group C (66.6%).

All the three groups equally showed the same i.e., (91.6%), behavior score during treatment. Ease of treatment completion was excellent in group B (83.3%) followed by group A and group C [i.e.], (66.7%). Whereas, wake-up behavior score as per MOAAS scale was found to be calm and cooperative in group B (91.7%) followed by group C (88.9%) and group A (83.3%).

Conclusion: In the present study oral ketamine-midazolam combination drugs can be used without harm and effectively as moderate sedation in an uncooperative pediatric patient.

Keywords: Ketamine-midazolam, Moderate sedation, Pediatric dentistry.

International Journal of Clinical Pediatric Dentistry (2021): 10.5005/jp-journals-10005-2096

Introduction

Induction of anesthesia in a pediatric age-group is a challenging job. Fear of alien environment, separation anxiety, and fear for injections and needles can result in an agitated and crying patient which can add to the difficulty in inducing anesthesia. It becomes a skill full specialty as fear of operation theatre and injection can produce traumatic experiences in the tender minds of young children.[1]

Seventy percent of children before anesthesia showed a lot of stress and anxiety.[2] Preoperative anxiety can have negative physiological and psychological effects on a child.[3] It is considered that in most cases the forbidding and defiant children should be managed with non-pharmacological techniques such as tell-show-do, positive reinforcement, and modeling. Most of the time treating an apprehensive child is onerous and in some cases even unachievable by these practices. Therefore, in order to reinforce children's cooperative behaviors and quality dental treatment, pharmacological methods have been used.[4]

The primary aim of drug-induced sedation in pediatric dentistry is to alter the patient's behavior to an extent that permits to manipulate behavior management techniques.[4] Key features of ideal premedication are ease of administration, quick onset and smooth recovery and minimal side effects.[5]

So, the oral route for moderate sedation is preferable as it can be easily administered and accepted by children without much

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How to cite this article: Thakur S, Verma K, Singhal P, *et al.* Evaluation of Efficacy of Oral Ketamine and Midazolam Combination Drug in Different Doses in Different Groups Used for Moderate Sedation in Pediatric Dentistry Randomized-comparative Trial. Int J Clin Pediatr Dent 2021;14(S-2):S151–S156.

Source of support: Nil

Conflict of interest: None

hesitation. Easy acceptance, fast onset, and shorter duration with lesser side effects are desirable qualities in good premedication.[6]

Ketamine and midazolam are commonly used by oral, nasal, and rectal routes. Oral and rectal application of ketamine and midazolam are widely used in child age groups.[7] Both the drugs result in a slow onset time of 15–30 minutes and produce a calm child for anesthesia.[8] Warner, et al. have described that a combined effect of ketamine and midazolam provide superior premedication as compared to midazolam alone.[9]

Midazolam is a benzodiazepine derivative and depending on pH, when pH <4, drugs form highly water-soluble salts or become lipid-soluble when pH >4. Midazolam has many favorable effects such as the fast onset of action, good cardiovascular stability,[10] anxiolysis, and transient loss of memory. Although, undesirable postoperative behavior changes, paradoxical reactions, and hiccups have also been observed.[11,12]

Ketamine is a phencyclidine derivative and it acts by blocking n-methyl d-aspartate receptors hence, it induces dissociative sedation associated with an analgesic effect. The association of ketamine with benzodiazepines might attenuate ketamine's psychotomimetic effects.[13] In general pediatrics studies, it has been noted that premedication regimens that consist of both ketamine and midazolam resulted in better pediatric behavior outcome.[13,14]

However, a lot of research has been conducted on various doses of different premedication drugs used in sedation methods in pediatric dentistry, but still, a "golden" combination of drugs has yet to be discovered.[15]

Materials and Methods

The present study consisted of patient ranges 3–9 years of age, in the need of dental treatment showing negative behavior according to Frankl's behavior rating scale in their first visit, while attending the Department of Pediatric and Preventive Dentistry. Before conducting the present study ethical approval was prevailed from the Institute's Ethical Committee. Written consent was taken from parents/guardians accompanying the child patient after describing them the motive, methodology involved and associated benefits and risks, in a language well understood by them.

ASA Physical Status 1, children with 3–9 years of age, inclusion criteria was early childhood caries and negative behavior according to Frankl's rating scale with no mental or physical deficiency. In the present study child patients with heart, liver, endocrine, or metabolic dysfunction, high risk for airway obstruction, such as sleep apnea, obesity, stridor, snoring, maxillofacial deformities, gastro-esophageal disorder; history of previous allergy to drugs used for sedation; anemia (hemoglobin <10 g/dL); gastrointestinal disorders which affect the absorption of oral drugs; and failure of previous moderate sedation were excluded from the study.

Study Design

A total of 42 children were eligible for the present study but due to upper respiratory tract infection on the day of treatment 6 patients were excluded. Randomization of 36 children was done and divided into one of the three groups. Group A received 0.2 mg/kg of oral midazolam and 5 mg/kg oral ketamine combination drug mixed in 1 mL of honey. Group B received 0.3 mg/kg of oral midazolam with 3 mg/kg of oral ketamine combination drug mixed in 1 mL of honey. Group C received 0.4 mg/kg of oral midazolam with 2 mg/kg of oral ketamine combination drug mixed in 1 mL of honey. To make the present study unbiased, each drug was from the same brand midazolam hydrochloride (Mezolam 1 mg/mL, Neon Laboratories, Mumbai, India), and ketamine hydrochloride (Aneket 50 mg/mL, Neon Laboratories, Thane, India).

Randomization

Randomization among patients was done by the envelope draw method among three groups. Each group was assigned with different color codes and placed within the envelope to eliminate any bias. After that, the person accompanying the child patient chooses the envelope and gave it to the assistant, who opened it and knew which patient is allotted to which group. All drugs included in the study were prepared by a researcher, who was not engaged in the monitoring or administration of anesthesia for the patients. Evaluators and attending pediatric dentists who take part in the study were blinded to the drug given.

Methodology

The preanesthetic assessment was done a day prior to the dental procedure, by an anesthetist and all the dental procedures were carried out in the minor operation theater (OT) of the hospital. Patients were asked to fast 6 hours for solids diet and 2 hours for clear fluids as per GA guidelines[16] on the day of treatment.

Before starting the procedure, baseline body weight (BW), heart rate, blood pressure, oxygen saturation level (SpO_2), sedation, and behavior score were documented independently by two blinded evaluators. After documenting the baseline data, an oral combination of midazolam and ketamine was mixed with 1 mL of honey and was administered to the patient by the assistant under the supervision of an anesthetist. The patient was kept in a calm and darkroom until the start of sedation. The patient was observed every 15–20 minutes by the same two evaluators for recording the heart rate, SpO_2, and blood pressure, using a sphygmomanometer (Perfect, Gupta Sons India, Ambala, India) and pulse oximeter (Secure, GPC Medical Ltd., New Delhi, India) from the start of procedure until discharged from monitoring room. Similarly, behavior score and sedation level were also observed after every 15–20 minutes by the evaluators using a 6-point sedation scale and 4-point behavior scale which was modified from observer assessment of alertness and sedation (MOAA/S) scale (Table 1).[17]

Similarly, the MOAA/S scale was used by the evaluators for wake-up behavior score (Table 1).[17] Each dental procedure was completed between 25 and 45 minutes.

After the procedure was completed, patients were returned to the monitoring room until fully awake. After a final assessment by an anesthetist for overall attainment of the normal state, the patient was discharged from the monitoring room. The discharging procedure was performed by the anesthetist. Patients were discharged only after gaining full consciousness, able to walk properly without support.

Data Analysis

In the present study data analysis was done by Chi-square test, One-way Anova test, Wilcoxon signed-rank test, and Mann–Whitney U test, using SPSS software (IBM Corp 2013; version 22.0; Armonk, NY). Data is considered to be statistically significant as $p < 0.05$.

Table 1: (HOUPT) and (MOASS Scale).

	Sedation scores (MOAAS scale)	
1	Does not respond to mild prodding or shaking	
2	Responds only on mild prodding or shaking	
3	Responds only after name is called loudly or repeatedly	
4	Lethargic response to name spoken in normal tone	
5	Appear asleep but respond readily to name spoken in normal tone	
6	Appear alert and awake respond readily to name spoken in normal tone	
	Behavior scores (MOAAS scale)	
1	Calm and cooperative	
2	Anxious but reassurable	
3	Anxious and not reassurable	
4	Crying, or resisting	
	Ease of treatment completion (HOUPT scale)	
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
6	Excellent	No crying or movement
	Wake-up behavior scores (MOAAS scale)	
1	Calm and cooperative	
2	Not calm but could be easily calmed	
3	Not easily calmed, moderately agitated or restless	
4	Combative, excited, disoriented	

Results

The parameters like age, sex, and weight distribution among the three groups were statistically insignificant. In this study male and female children were 55.55% and 44.44%, respectively, similarly mean age and weight were (5.5 ± 1.30) and (15.20 ± 2.60). Midazolam and ketamine combination drugs were well accepted by all the patients. The mean ± standard deviation value of heart rate, SBP, DBP, and SpO_2 were assessed during three treatment stages of sedation (Table 2). Behavior score during four treatment stages (Table 3). Sedation score during four treatment stages (Table 4). The results showed no significant differences in behavior and sedation score. Ease of treatment completion was excellent in group B (83.3%) followed by 66.7% in group A and group C, very good in 8.3%, 0.0%, and 16.7% in group A, group B, and group C, respectively (Fig. 1). Wake-up behavior was calm and cooperative for the majority of subjects of group B and group C followed by group A (Fig. 2).

Discussion

In the present study, determination of behavior and sedation score was done by observer-based MOAAS scale which has been considered the most reliable documented sedation scale.[17] Previous studies have been reported that the outcome of analgesic property of ketamine and anxiolytic effect of midazolam resulted in better behavior score as compared to the use of these drugs alone.[13,18] In all the three groups' hemodynamic parameters, like SBP and DBP, heart rate, and SpO_2, remained relatively unchangeable during the treatment procedure. SpO_2 among three groups at all treatment stages was above 93%, which was quite similar to SpO_2 before the procedure.

Our results showed that group B sedation success rate was more than group A and C. Patients in group B (83.3%) were successfully sedated with midazolam-ketamine combination. In present study success rate in group B (Midazolam 0.3 mg/kg and Ketamine 3 mg/kg) is greater than Darlong et al.[19] 79.3%, Malhotra et al.[20] 75% Jaikaria et al.[21] 72.8%, Darlong et al.[22] 70.8%, Funk et al.[13] 70%, Soleimanpour et al.[23] 62.5%, Majidinejad et al.[24] 45.5% and Roelofse et al.[25] 40% whereas it is lesser in comparison to Ghai et al.[14] 97.96%, Barkan et al.[26] 94%, and Norambuena et al.[27] 93.3%. The differences in sedation success rate may be due to different scales used for interpretation, different combinations of drug dosages, and also different criteria were taken for success. In the present study sedation score <4, whereas in many previous studies sedation scores <3 were considered as successful criteria.

Among all the groups 91.6% patients accomplished improved behavior during the treatment procedures. These results were similar to previous studies where satisfactory anxiolysis was achieved with ketamine-midazolam combination drugs i.e., 90% Funk et al.[13] 88% Roelofse et al.[25] 85% Warner et al.[9] and Malhotra et al. 83.3%.[20] Whereas 73.46% improved behavior score was seen in a study by Ghai et al.[14] Whereas Jaikaria et al.[21] 27.3% of patients were calm and cooperative and 63.6% patients were anxious but reassurable while 9.1% patients were anxious and not reassurable during treatment, which shows that 90.9% of patients achieved better behavior score during treatment as the doses of combination drugs used in the previous study were less than that used by the present study.

In the present study ease of treatment completion was excellent in group B (83.3%) followed by 66.7% in group A and group C, very good in 8.3%, 0.0%, and 16.7% in group A, group B, and group C, respectively and the previous study was done by Jaikaria et al.[21] ease of completion was excellent in 27.33%, very good in 36.4% patients, good score in 27.3% of patients, fair in 18.2% patients and poor in 9.1% of patients and study by Malhotra et al.[20] ease of completion was excellent in 33.33%.

Wake-up behavior as scored by the MOAAS scale was found to be calm and cooperative in 83.3%, 91.7%, and 88.9% in three groups, respectively. According to Jaikaria[21] wake-up behavior as scored by MOAAS scale was found to be calm and cooperative in 72.7% children and study by Malhotra et al. 91.7%.[20] So findings of this study were in group B accordance with Malhotra and greater than Jaikaria et al. In the current study postoperative complications were found in 19.44% of patients given midazolam-ketamine combination drugs. However, these didn't adversely affect the delivery of dental treatment. One patient complained of postoperative hallucinations.

Almost all of the patients showed reduced activity and lethargy for the next 24 hours postdischarge. These results are in accordance with other studies by Warner et al.[9] Lin et al.[28] Ghajari et al.[29] Baygin et al.[30] Moriera et al.[31] who reported less postoperative complications in patients sedated with ketamine-midazolam combination drug. It appears from the previous studies that the ketamine and midazolam combination drug allowing easy treatment completion and can serve as an alternative moderate sedation drug used in pediatric dentistry.

Table 2: Oxygen saturation, heart rate, blood pressure

Oxygen saturation					
Groups	*Group A (n = 12)*	*Group B (n = 12)*	*Group C (n = 12)*	*Total (n = 36)*	*p value*
At baseline	94.3 ± 2.2	96.0 ± 1.3	95.1 ± 2.8	95.1 ± 2.2	0.16
Start of treatment	96.2 ± 3.0	94.4 ± 1.1	94.5 ± 2.8	94.0 ± 2.5	0.37
During treatment	94.0 ± 2.0	93.8 ± 1.3	94.5 ± 2.7	94.1 ± 2.0	0.68
End of treatment	94.4 ± 1.1	94.9 ± 1.4	93.9 ± 2.4	94.4 ± 1.7	0.39
Heart rate					
Groups	*Group A (n = 12)*	*Group B (n = 12)*	*Group C (n = 12)*	*Total (n = 36)*	*ANOVA*
At baseline	111.4 ± 7.9	104.2 ± 8.3	106.2 ± 11.1	107.3 ± 9.5	$p > 0.16$
Start of treatment	120.2 ± 10.5	113.4 ± 11.4	114.6 ± 10.6	116.1 ± 10.9	$p > 0.27$
During treatment	120.1 ± 8.6	111.6 ± 9.3	112.5 ± 8.2	114.8 ± 9.3	$p > 0.05$
End of treatment	114.6 ± 3.3	108.3 ± 6.7	109.8 ± 9.0	110.9 ± 7.1	$p > 0.07$
Systolic blood pressure					
Groups	*Group A n = 12*	*Group B n = 12*	*Group C n = 12*	*Total n = 36*	*ANOVA*
At baseline	96.0 ± 9.3	95.8 ± 4.9	92.5 ± 8.5	94.7 ± 7.8	$p > 0.47$
Start of treatment	101.0 ± 11.4	101.8 ± 7.4	96.8 ± 7.8	99.8 ± 9.1	$p > 0.36$
During treatment	103.0 ± 11.6	101.0 ± 6.0	97.3 ± 7.8	99.8 ± 9.1	$p > 0.29$
End of treatment	102.0 ± 10.3	98.5 ± 6.4	94.0 ± 6.4	98.1 ± 8.4	$p > 0.06$
Diastolic blood pressure					
Groups	*Group A n = 12*	*Group B n = 12*	*Group C n = 12*	*Total n = 36*	*ANOVA*
At baseline	65.3 ± 5.4	64.5 ± 3.2	63.0 ± 4.0	64.2 ± 4.3	$p > 0.41$
Start of treatment	69.1 ± 5.7	68.6 ± 4.7	66.1 ± 3.7	68.0 ± 4.8	$p > 0.27$
During treatment	69.6 ± 5.9	67.3 ± 4.3	65.6 ± 4.7	67.5 ± 5.2	$p > 0.16$
End of treatment	68.8 ± 5.0	65.3 ± 4.6	64.3 ± 4.4	66.1 ± 4.9	$p > 0.06$

Table 3: Behavior score during four treatment stages

Groups	*Treatment stages*	*Score 1 Calm and cooperative (%)*	*Score 2 Anxious but reassurable (%)*	*Score 3 Anxious but not reassurable*	*Score 4 Crying and resisting*	*p value*
Group A 0.2 mg/kg of oral midazolam and 5 mg/kg oral ketamine	Baseline	8	3	0	1	0.62
	Start of treatment	10	0	1	1	0.90
	During treatment	10	1	1	0	1.00
	End of treatment	9	2	1	0	0.86
Group B 0.3 mg/kg of oral midazolam with 3 mg/kg of oral ketamine	Baseline	7	5	0	0	0.62
	Start of treatment	11	0	1	0	0.90
	During treatment	10	1	1	0	1.00
	End of treatment	9	1	1	0	0.86
Group C 0.4 mg/kg of oral midazolam with 2 mg/kg of oral ketamine mixed in 1 mL of honey	Baseline	8	4	0	0	0.62
	Start of treatment	10	0	1	1	0.90
	During treatment	10	1	1	0	1.00
	End of treatment	10	1	1	0	0.86

Table 4: Sedation score during four treatment stages

Groups	*Group A (n = 12)*	*Group B (n = 12)*	*Group C (n = 12)*	*Asymp Sig*
At baseline	6.0 ± 0.0	6.0 ± 0.0	6.0 ± 0.0	$p > 1.00$
Start of treatment	4.2 ± 1.0	4.2 ± 0.9	4.5 ± 0.5	$p > 0.93$
During treatment	3.9 ± 1.0	4.0 ± 0.9	4.3 ± 0.7	$p > 0.56$
End of treatment	4.1 ± 1.1	4.8 ± 1.1	4.9 ± 0.9	$p > 0.18$

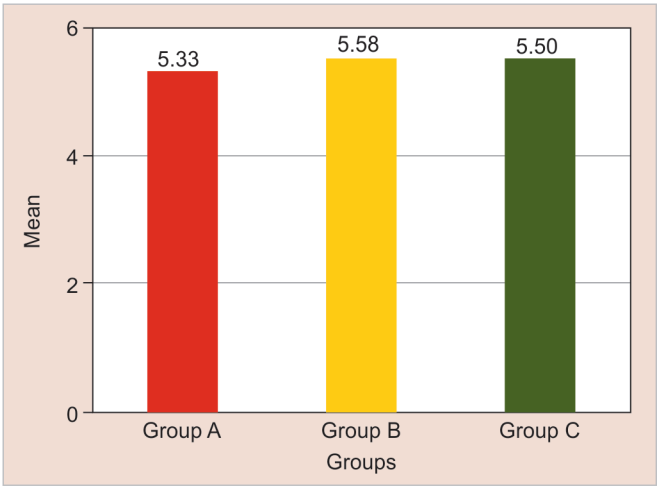

Fig. 1: Ease of treatment completion score

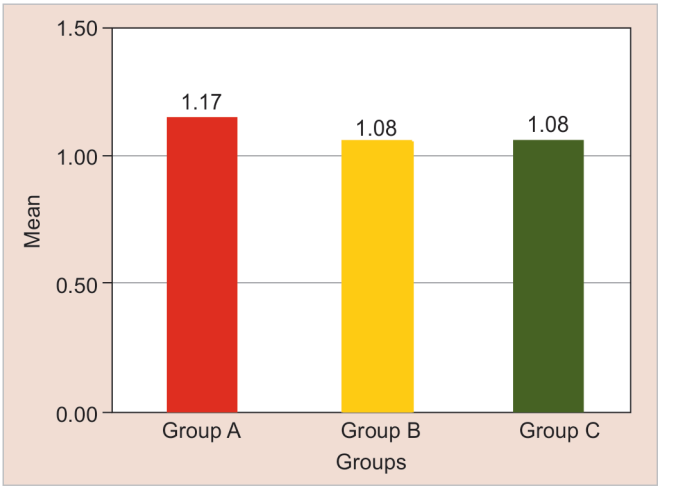

Fig. 2: Wake-up behavior score

In the present study, patients in the three groups were comparable with respect to age, gender, and weight. Hemodynamic parameters such as systolic and diastolic blood pressure, heart rate, and oxygen saturation remained unchangeable during the course of treatment among all three groups.

Usages of combination drugs in the present study, all three groups produced anxiolysis without loss of respiration or provide normal airway tone.

There was no statistically significant difference in sedation level produced by three different doses of ketamine-midazolam in group A, group B, and group C. Patients in group B were successfully (83.3%) sedated followed by group A (66.6%) and group C (66.6%). This may be attributed to the higher dose of ketamine (3 mg/kg) and midazolam (0.3 mg/kg) used in this study that produced additional sedation, as compared to ketamine (5 mg/kg) and midazolam (0.2 mg/kg) in group A and ketamine (2 mg/kg) and midazolam (0.4 mg/kg) in group C.

In the present study, the behavior score although was statistically not significant. behavior score during treatment 83.3% patients were calm and cooperative in all the three groups and similarly, 8.3% patients were anxious but reassurable in groups A, B, and C.

Ease of treatment completion was improved with midazolam-ketamine combination group B (83.3%) as a comparison to group A (66.7%) and group C (66.7%).

One patient complained of postoperative vomiting with the midazolam-ketamine combination. These differences in postoperative experiences of patients may be due to adverse effects like nausea, vomiting, slurred speech, blurred vision, double vision, and hallucinations associated with ketamine. The findings of this study do not challenge the universal popularity of oral midazolam-ketamine combination as an effective and safe sedative agent in the pediatric population.

In our investigation made no attempt to access the respiratory rate, recovery time, and analgesia potential of the drugs. There are currently no published studies to show the comparison of oral ketamine-midazolam combination, as moderate sedation agents in managing the behavior of uncooperative pediatric patients in a dental situation.

Our study has a few limitations. Firstly, greater sample size may be helpful to further determine the suitability of these drugs in the pediatric population. Secondly, children in our study were not subdivided into specific age groups as older children may exhibit more and easier acceptability of the drugs. Thirdly, we did not measure serum concentrations of administered combination drugs and further studies are required to clarify their efficacy and safety. Fourthly, serum cortisol, nor-epinephrine, cytokine (interleukin 6, tumor necrosis factor-alpha) levels, and blood glucose levels were not measured in our study. Further investigations are justified to access ketamine-midazolam combination, as pediatric moderate sedative agents.

Conclusion

Within the limits of the present study, it was concluded that: on the basis of overall success rates of the drugs used for sedation following order of performance can be inferred -

Success rate of sedation: midazolam-ketamine (group B) > midazolam-ketamine (group A) = midazolam-ketamine (group C).

Satisfactory behavior: midazolam-ketamine (group A) = midazolam-ketamine (group B) = midazolam-ketamine (group C).

Ease of treatment completion: midazolam-ketamine (group B) > midazolam-ketamine (group A) = midazolam-ketamine (group C).

To draw the definitive conclusion all three Different doses of the oral combinations of midazolam-ketamine can be used safely and effectively as sedative agents in uncooperative pediatric patients undergoing dental procedures in mentioned drug regimes.

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