Comparative evaluation of dexmedetomidine and midazolam-ketamine combination as sedative agents in pediatric dentistry: A double-blinded randomized controlled trial

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Abstract

Background: Pharmacological methods have been used as an adjunct to enhance child cooperativeness and facilitate dental treatment. **Objective:** Purpose of this study was to evaluate and compare the effect of sedation by intranasal dexmedetomidine and oral combination drug midazolam–ketamine in a group of children with uncooperative behavior requiring dental treatment. **Materials and Methods:** This was a prospective, randomized, double-blind study that included patients 3–9 years old with American Society of Anesthesiologists-I status. About 36 children presenting early childhood caries were randomly assigned to one of three groups studied: Group MK received intranasal saline and oral midazolam (0.5 mg/kg) with ketamine (5 mg/kg) mixed in mango juice; Group DX received intranasal dexmedetomidine (1 μg/kg) and oral mango juice; and Group C received intranasal saline and oral mango juice. Patients' heart rate, blood pressure, and oxygen saturation were recorded before, during, and at the end of the procedure. Patients' behavior, sedation status, and wake up behavior were evaluated with modified observer assessment of alertness and sedation scale. Ease of treatment completion was evaluated according to Houpt scale. **Results:** Hemodynamic changes were statistically insignificant in Group MK and Group DX. About 75% patients in Group MK were successfully sedated as compared to 53.9% Group DX and none of the patients in Group C. Ease of treatment completion was better with Group MK as compared to Group DX and least with Group C. Around 50% patients in Group MK had postoperative complications. **Conclusion:** Oral midazolam–ketamine combination and intranasal dexmedetomidine evaluated in the present study can be used safely and effectively in uncooperative pediatric dental patients for producing conscious sedation.

Keywords: Dexmedetomidine, midazolam–ketamine, pediatric dentistry, sedation

Introduction

Pain, fear, anxiety, and anger are the main emotional components to be dealt by a pedodontist while treating a child.[1] It is generally agreed that most fearful and uncooperative children should be managed with behavioral (nonpharmacologic) management procedures such as tell-show-do, positive reinforcement, controlled expectations, modeling, and suggestion. Often managing anxious children is arduous, and in some cases even unattainable by these methods. Pharmacological methods have been used as an addendum to augment child cooperativeness and provide quality dental care.[2] The primary aim of pharmacological sedation in pedodontics is to transform the patient's behavior to a level that allows employing behavior management techniques.[2]

Oral administration is established as efficacious, economic, and convenient among all routes of conscious sedation (CS). Intranasal administration of the drugs is well tolerated by children, effective and fast acting as this site is highly vascularized and very permeable for drug administration, ensuring rapid absorption into systemic circulation.[3]

Midazolam is a 1, 4-benzodiazepine derivative with a unique chemical structure and depending on environmental pH, the drug can produce highly water-soluble salts (pH < 4)

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or exist in lipophilic diazepine ring-closed form (pH > 4). It has been attributed several beneficial effects such as good cardiovascular stability,[4] anxiolysis, amnesia, and rapid onset of sedation; however, adverse postoperative behavior changes, hiccups, and paradoxical reactions have also been observed.[5,6]

Ketamine is a phencyclidine derivative and provides dissociative sedation associated with an analgesic effect by blocking n-methyl d-aspartate receptors. The association of ketamine with benzodiazepines might attenuate ketamine's psychotomimetic effects.[7] In general pediatrics, studies have reported that premedication regimens that combined the anxiolytic effect of midazolam and the analgesic property of ketamine resulted in better pediatric behavior than the use of these drugs alone.[7,8]

Dexmedetomidine is a potent, highly selective α-2 adrenoceptor agonist. Activation of these receptors in the central nervous system leads to inhibition of sympathetic activity, which causes a reduction in blood pressure and heart rate, sedation, and anxiolysis.[9] It produces dose-dependent milder analgesia without respiratory depression[10] and sedation induced by dexmedetomidine is characterized by an easy and quick arousal resembling natural sleep. Dexmedetomidine has been extensively investigated in the pediatric population, and various studies support dexmedetomidine as an anesthetic and sedative adjunct in children.

Although much research has been conducted on different sedation methods in children, a "golden" combination of sedation drugs has yet to be discovered.[11]

The present randomized, double–blinded, controlled study was conducted to evaluate and compare oral midazolam–ketamine combination drug and intranasal dexmedetomidine for their sedative properties, safety profile, and ease of treatment completion.

Materials and Methods

The study consisted of patients in the age group 3–9 years, requiring dental treatment (extractions, pulpectomy, and restorations) exhibiting negative behavior according to Frankl's behavior rating scale in their first visit attending the outpatient Department of Paediatric and Preventive Dentistry, Himachal Pradesh Government Dental College and Hospital, Shimla. A prior ethical approval was obtained from the Institute's Ethical Committee. The parents/guardian accompanying the patients were explained in detail about the purpose, methodology involved, and the related risks and benefits, in a language well understood by them and written consent was taken.

American Society of Anesthesiologists Physical Status 1 children 3–9 years of age, with no mental or physical deficiency, presenting early childhood caries and negative behavior were included in the study. Exclusion criteria were known allergy to drugs used for sedation; patients with hepatic, cardiac, endocrine, or metabolic impairment, high potential risk for airway adverse events, such as obesity, snoring, stridor, sleep apnea, maxillofacial malformations, history of previous airway difficulty, gastroesophageal reflux, and acute reactive airway disease; Gastrointestinal disorders which could affect absorption of the oral drug; anemia (hemoglobin <10 g/dl) and failure of previous CS.

Study design
Enrollment in the study involved assessment of 42 children for eligibility. Out of which 6 patients were excluded due to upper respiratory tract infection on the day of treatment. About 36 children included in the study were randomly allocated to one of three groups. Group MK received 0.4 ml intranasal placebo (normal saline) followed at 30 min by oral administration of midazolam 0.5 mg/kg and 5 mg/kg ketamine mixed in 30 ml mango juice. Group DX received intranasal dexmedetomidine at 1 μg/kg. To make final volume 0.4 ml, normal saline was added, followed at 30 min by oral administration of 30 ml mango juice. Group C received intranasal drops of 0.4 ml saline followed at 30 min by oral administration of 30 ml mango juice. To maintain uniformity throughout the study, each drug was from one brand - dexmedetomidine Hydrochloride (Dexmedit 100 μg/ml, Neon Laboratories, Mumbai, India), midazolam hydrochloride (Mezolam 1 mg/ml, Neon Laboratories, Mumbai, India), and ketamine hydrochloride (Aneket 50 mg/ml, Neon Laboratories, Thane, India).

Randomization
The patients enrolled in the present study were randomly allocated to one of three groups by envelope draw method. Three different color codes were decided for each group and were printed and placed within envelope to eliminate any dissimilarity. Mother of the patient picked envelope and gave it to anesthetist, who opened it and knew that which patient is allocated to which group. All study drugs were prepared by an independent researcher, who was not involved in the observation or administration of anesthesia for the children. Evaluators and attending pedodontist were blinded to the study drug given.

Methodology
One day before the date of dental procedure, the preanesthetic evaluation was done by an experienced anesthetist and all the procedures were performed in minor operation theater (OT) of the institute. On the day of procedure, patient fasted for 6 h for solids and 4 hr for breat milk and 2 hrs for clear fluids per GA guidelines.[12] At the start of procedure, baseline body weight, heart rate, blood

pressure, oxygen saturation (SpO_2), behavior, and sedation score were recorded independently by two evaluators who were blinded to the study design. Intranasal drug/placebo was administered with needleless 1 ml syringe by the anesthetist. After 30 min, oral drug/placebo was mixed with mango juice and was given to patient to drink in a disposable cup. During drug administration and till the start of sedation patient was kept in a quiet and dark room adjacent to minor OT Monitoring was performed after every 15 min intervals from the start of drug administration to the discharge point for blood pressure, heart rate, and SpO_2 using sphygmomanometer and pulse oximeter (Oxee Check Romsons, Rennex Medicals, New Delhi, India) by the evaluators. Similarly, sedation level and behavior score were also assessed after every 15 min by the evaluators using modified observer assessment of alertness and sedation (MOAAS) scale [Table 1].[13] All the treatment steps were performed by a single experienced pediatric dentist, who was blinded to the study design and who gave the ease of treatment completion score using Houpt scale[14] [Table 1]. Patient was discharged after final evaluation by the anesthetist for their overall fitness to be able to leave with parents. Wake up behavior score was given by the evaluators using MOAAS scale [Table 1].

Data analysis

One-way anova test, Chi-square test, Mann–Whitney U-test, and Wilcoxon signed-rank test were used for the statistical analysis, using IBM SPSS Statistics software, version 19 (New York, NY, USA). Statistical significance was defined as $P < 0.05$.

Results

Children were similar in the three groups regarding sex, age, and weight with mean age (4.60 ± 1.99) and weight (15.62 ± 4.21). All the drugs were well accepted by all the subjects. The mean ± SD value of SpO_2, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) during three treatment stages sedation with three groups were summarized in Table 2. The analysis of variance revealed that there was no statistically significant difference in SpO_2, heart rate, and DBP between the groups but statistically significant difference exists in SBP measurement during treatment stage ($P = 0.018$) with marked increase of SBP in the control group.

MOASS was used to assess the behavior of the patient at the baseline, during treatment, and end of treatment [Table 3] and scores were compared by Chi-square test. Score 1 (calm and cooperative) and 2 (anxious but reassurable) was considered as successful anxiolysis. At baseline, 91.7% of children in Group MK, 69.3% children in Group DX, and 90.9% children in Group C were cooperative. The behavior at baseline was statistically insignificant ($P = 0.381$). During treatment, 83.3% of the children in Group MK, 61.6% of the children in

Table 1: Evaluation scale

Modified observer assessment of alertness and sedation scale
Sedation scores
1 Does not respond to mild prodding or shaking
2 Responds only 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, response readily to name spoken in normal tone
Behavior scores
1 Calm and cooperative
2 Anxious but reassurable
3 Anxious and not reassurable
4 Crying, or resisting
Wake-up behavior scores
1 Calm and cooperative
2 Not calm but could be easily calmed
3 Not easily calmed, moderately agitated or restles
4 Combative, excited, disoriented
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

Group DX, and 0% children in Group C achieved successful anxiolysis. The behavior during treatment was statistically significant ($P = 0.007$).

Wilcoxon's test showed that the effect of sedation is different when data were statistically compared from the baseline to the end of treatment in Groups MK and DX ($P < 0.05$) as well when baseline is compared to during treatment ($P < 0.05$) [Table 4]. Level of sedation during treatment is deeper with Group DX as compared to Group MK. No sedation is achieved in Group C. Ease of treatment completion was very good with Group MK, fair with Group DX, and poor with Group C [Figure 1]. Mann–Whitney test was used to compare ease of treatment completion in study groups, and it was better with Group MK than DX ($P = 0.040$).

Table 2: Comparing the physiological parameters during three treatment stages

	MK	DX	C	*P*
Heart rate (mean±SD)				
Baseline	101.83±18.82	99.62±20.82	90.91±9.85	0.301
During treatment	106.08±19.41	99.58±20.25	106.36±10.44	0.571
End of treatment	112.00±22.78	100.15±15.99	112.36±10.279	0.149
Oxygen saturation (mean±SD)				
Baseline	93.33±4.51	93.38±4.01	94.09±3.70	0.886
During treatment	92.25±4.93	95.23±3.32	94.45±3.32	0.166
End of treatment	94.75±1.71	95.00±4.12	94.55±2.33	0.932
Systolic blood pressure (mean±SD)				
Baseline	111.08±10.10	118.46±10.03	117.27±6.46	0.117
During treatment	113.33±11.61	113.85±11.38	126.55±12.77	0.018
End of treatment	118.17±15.75	117.23±12.04	124.55±12.136	0.374
Diastolic blood pressure (mean±SD)				
Baseline	72.50±6.88	75.23±7.93	71.64±3.66	0.375
During treatment	72.00±12.56	76.77±9.71	82.55±6.87	0.056
End of treatment	72.67±12.54	75.85±13.67	78.45±11.91	0.559

SD: Standard deviation

Table 3: Behavior scores in Group MK, DX and C at three measured times

Groups	Treatment stage	Score 1 Calm and cooperative (%)	Score 2 Anxious but reassurable (%)	Score 3 Anxious and not reassurable (%)	Score 4 Crying, or resisting (%)	*P*
MK	Baseline	5 (41.7)	6 (50)	1 (8.3)	0 (0)	0.381
	During treatment	4 (33.3)	6 (50)	0 (0)	2 (16.7)	0.007
	End of treatment	5 (41.7)	2 (16.7)	2 (16.7)	3 (25)	0.013
DX	Baseline	4 (30.8)	5 (38.5)	3 (23.1)	1 (7.7)	0.381
	During treatment	3 (23.1)	5 (38.5)	2 (15.4)	3 (23.1)	0.007
	End of treatment	2 (15.4)	7 ()	0 (0)	4 (30.8)	0.013
C	Baseline	2 (18.2)	8 (72.7)	0 (0)	1 (9.1)	0.381
	During treatment	0 (0)	0 (0)	4 (36.4)	7 (63.4)	0.007
	End of treatment	0 (0)	1 (9.1)	3 (27.3)	7 (63.4)	0.013
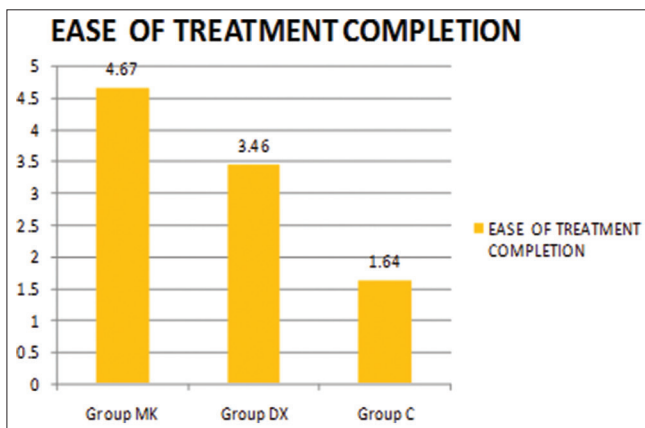
Figure 1: Ease of treatment completion is best achieved with midazolam–ketamine combination followed by dexmedetomidine and was poor in control group

Discussion

In this study, observer-based MOAAS scale was used for assessment of sedation and behavior, as it is one of the few sedation scales with documented reliability.[13] Although verbal analog scales which are easy to use, and commonly employed for pain assessment have questionable validity in assessing sedation.[15]

In the present study, midazolam–ketamine combination drug resulted in mild increase in heart rate and SBP during treatment but changes were not statistically significant. Reduction in SpO_2 was statistically insignificant and remained above 92%. These results are in accordance with previous studies by Warner *et al*.[16] and Roelofse *et al*.[17] who also reported reduced SpO_2 and increased SBP, DBP, and heart rate with the combination.

Table 4: Comparison of sedation level at three treatment stages within the group

						Percentiles		
Groups	**Treatment stage**	**n**	**Mean±SD**	**Minimum**	**Maximum**	**25th**	**50th (median)**	**75th**
				Descriptive statistics				
MK	Baseline	12	6.00±0.000	6	6	6.00	6.00	6.00
	During treatment	12	3.9167±0.79296	3.00	5.00	3.0000	4.0000	4.7500
	End of treatment	12	4.7500±0.62158	4.00	6.00	4.0000	5.0000	5.0000
DX	Baseline	13	6.00±0.000	6	6	6.00	6.00	6.00
	During treatment	13	3.4615±1.56074	1.00	5.00	2.0000	3.0000	5.0000
	End of treatment	13	3.6154±1.70970	1.00	6.00	2.0000	4.0000	5.0000
C	Baseline	11	6.00±0.000	6	6	6.00	6.00	6.00
	During treatment	11	6.0000±0.00000	6.00	6.00	6.0000	6.0000	6.0000
	End of treatment	11	5.9091±0.30151	5.00	6.00	6.0000	6.0000	6.0000

		Wilcoxon signed-ranks test		
Groups	**Statistical test**	**During treatment-baseline**	**End of treatment-baseline**	**End of treatment-during treatment**
MK	Z	−3.100[b]	−3.035[b]	−2.428[a]
	Asymp significant (two-tailed)	0.002	0.002	0.015
DX	Z	−3.225[b]	−2.956[b]	−0.351[a]
	Asymp significant (two-tailed)	0.001	0.003	0.726
C	Z	0.000[c]	−1.000[b]	−1.000[b]
	Asymp significant (two-tailed)	1.000	0.317	0.317

[a]Based on negative ranks; [b]Based on positive ranks; [c]The sum of negative ranks equals the sum of positive ranks. SD: Standard deviation

In our study, 75% patients were successfully sedated with midazolam–ketamine combination. The success rate of sedation in our study is more than Funk *et al*.[7] 70%, Soleimanpour *et al*.[18] 62.5% and 70.8%, Majidinejad *et al*.[19] 45.5%, and Roelofse *et al*.[17] 40%, whereas it is lesser in comparison to Barkan *et al*.[20] 94%, Darlong *et al*.[21] 79.3%, and Ghai *et al*.[8] 97.96%, These differences may be attributed to different scales used for evaluation, different drug dosages, and also different criteria taken for sedation success. In our study, score ≤4 was considered as successful sedation, whereas in many studies ≤3 was taken as criteria.

About 83.3% patients in Group MK achieved improved behavior during treatment. These results are in accordance with previous studies where sufficient anxiolysis achieved with midazolam–ketamine combination, i.e. 85% Warner *et al*.[16] and 90% Funk *et al*.[7] whereas our results were more than 73.46% Ghai *et al*.[8] as the doses used in their study was half of the dose used by us.

Wake up behavior as scored by MOAAS scale was found to be calm and cooperative in 91.7% children. Only one child became agitated and restless. Ketamine is known to cause postemergence delirium. In our study, due to less sample size, it was found in only one patient.

Postoperative nausea and vomiting were found in 50% of patients drugged with midazolam–ketamine combination.

However, these did not adversely affect the delivery of treatment. Postoperative hallucinations were observed in one patient. These results are in accordance with other studies by Fallahinejad Ghajari *et al*.,[22] Funk *et al*.,[7] Ghai *et al*.,[8] and Roelofse *et al*.[17] who reported postoperative complications in patients sedated with MK.

In the present study, dexmedetomidine was given by intranasal route because of better compliance and efficacy than oral route. It was administered in the dose of 1 μg/kg body weight, as according to Yuen *et al*.,[23,24] it has been found to be more effective as compared to 0.5 μg/kg body weight.[23] and equally effective as 1.5 μg/kg body weight.[24]

In the present study, dexmedetomidine exhibited relatively stable hemodynamic parameters. SpO_2 remained above 93% during entire procedure. SBP was decreased during the treatment, but changes were statistically insignificant. Heart rate and DBP in patients sedated with dexmedetomidine remained stable. These results are in accordance with studies by Akin *et al*.,[25] Yuen *et al*.,[24] and Schmidt *et al*.[26] Most of these studies reported greater decrease in heart rate 14–27%. This mild decrease in our study may be due to the different nature of procedures. In these studies, dexmedetomidine was tested as a premedication before induction of anesthesia, whereas in the present study, the environment of the dental treatment and continuous oral stimulation makes the child more alert.

In the present study, dexmedetomidine resulted in profound sedation with mean sedation score of 3.46 during the treatment and 3.62 at the end of treatment, as compared to baseline mean sedation score of 6. Sedation level was statistically significant when compared to the control group during treatment and end of the treatment. This result is similar to the study done by Ghali *et al.*[27] in which intranasal 1 µg/kg dexmedetomidine resulted in mean sedation score of 2.94 on the same MOAAS scale.

In our study, the overall success rate of dexmedetomidine was found to be 61.54% with median of 3 regarding ease of treatment completion. This parameter has not been studied previously in relation to intranasal dexmedetomidine in pediatric dental procedures. Wake up behavior was found to be calm and cooperative in 100% children. This is in accordance with previous studies by Yuen *et al.*[24] who found similar wakeup behavior.

None of the patients sedated with dexmedetomidine had any postoperative complications after the procedure. This result is also similar to other studies such as Surendar *et al.*,[1] Kundra *et al.*,[28] and Akin *et al.*,[25] whereas Gyanesh *et al.*[29] reported vomiting in two patients treated with intranasal dexmedetomidine.

There was statistically significant increase in heart rate ($P = 0.004$) and blood pressure ($P = 0.012$) in control group during treatment. This increase may be due to anxiety produced by dental setup and the procedure. There was statistically insignificant difference in sedation level produced by midazolam–ketamine combination and dexmedetomidine during treatment and at the end of treatment. However, more patients in Group MK (75%) were successfully sedated as compared to Group DX (53.9%) and none of the patients in Group C was sedated.

In the present study, combination of oral midazolam–ketamine (83.3%) resulted in better behavior than intranasal dexmedetomidine (61.6%) during the treatment, and both were better than control group (0%) though the results were statistically insignificant between midazolam–ketamine and dexmedetomidine ($P = 0.460$), the results were highly significant in relation to control group. Similar results were found in a study conducted by Daabiss and Hashish[30] who reported that patients receiving oral midazolam–ketamine combination (84%) were significantly more cooperative and calm as compared to patients receiving oral dexmedetomidine (51%).

No statistically significant differences were observed when MK combination was compared to intranasal dexmedetomidine in mentioned doses regarding stability of hemodynamic parameters, sedative efficacy, and anxiolysis potential. Both the drugs were found to be better than

placebo. Studies with greater sample size may be helpful to further determine the suitability of these drugs in pediatric population.

Our investigation made no attempt to access the respiratory rate, analgesia potential, and recovery time of the drugs. Literature does not show any published studies that have compared oral midazolam-ketamine combination and intranasal dexmedetomidine as sedative agents in managing the behavior of uncooperative pediatric patients in a dental situation.

Conclusion

Within the limits of present study, we conclude the following:
1. Hemodynamic parameters were stable with both oral midazolam–ketamine combination and intranasal dexmedetomidine
2. 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 > dexmedetomidine > placebo
   - Satisfactory behavior: Midazolam–ketamine > dexmedetomidine > placebo
   - Ease of treatment completion: Midazolam–ketamine > dexmedetomidine > placebo.

To draw the definitive conclusion both oral midazolam–ketamine combination and intranasal dexmedetomidine can be used safely and effectively as sedative agents in uncooperative pediatric patients undergoing dental procedures in mentioned drug regimes.

Conflicts of interest
There are no conflicts of interest.

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