A Comparison of Oral Midazolam-ketamine, Dexmedetomidine-fentanyl, and Dexmedetomidine-ketamine Combinations as Sedative Agents in Pediatric Dentistry: A Triple-Blinded Randomized Controlled Trial

Abstract

Introduction: It is common to encounter a patient who is anxious to the magnitude that precludes the possibility of provision of dental treatment. This study aims to evaluate and compare the sedative effect of oral combinations of midazolam-ketamine (MK), dexmedetomidine-fentanyl (DF), and dexmedetomidine-ketamine (DK) in a group of uncooperative children requiring dental treatment. **Methodology:** This was a prospective, randomized, triple-blind study where 36 children who were 3–9 year old with American Society of Anesthesiologists –I status and presenting early childhood caries were randomly assigned to: Group A – 0.3 mg/kg of M and 5 mg/kg K, Group B – 2 ug/kg of D with 3 ug/kg of F, and Group C – 2ug/kg of D with 5 mg/kg of K in 1 mL honey. Patients' blood pressure, heart rate, and oxygen saturation were recorded from the start of the procedure till discharge. Patients' behavior, sedation status, and wake-up behavior were evaluated with Modified Observer Assessment of Alertness and Sedation Scale and ease of treatment completion by Houpt scale. **Results:** Hemodynamic changes were statistically insignificant in all three groups. 72.8% of patients in Group A and 58.3% of patients in Group B were successfully sedated during treatment. Behavior improvement was seen in all three groups during treatment with statistically insignificant difference in behavior scores produced by Group C. Ease of treatment completion was moderately better with Group A. **Conclusion:** Oral DK has a comparable sedative property with oral MK combination. Oral DF promises to be a potential sedative agent for children due to its successful anxiolysis.

Keywords: *Dexmedetomidine-fentanyl, dexmedetomidine-ketamine, midazolam-ketamine, pediatric dentistry, sedation*

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Introduction

Uncooperative behavior in the pediatric dental settings is most typically attributed to behavioral manifestations of anxiety. Major consequences of such behavior may include a delay or termination of treatment before completion or a decline in the quality of care provided.[1] This highlights the need for various behavior management techniques which are mainly classified into nonpharmacological and pharmacological methods. Nonpharmacological methods usually alleviate the unwarranted fear and anxiety in most of the child patients. Managing anxious children is often grueling, and in some cases maybe even unattainable by these methods.[2] Pharmacological methods that produce moderate sedation aim toward promoting positive dental attitudes and improve the dental health of the pediatric patient.

Oral route is the most common and easily accepted technique of sedation in children[3] since it is simple and relatively inexpensive. However, some of its disadvantages include unpalatable taste of certain drugs[4] and limited oral absorption of some drugs due to physiochemical factors make a prediction of sedation depth and titration difficult.[5] It is however preferred in children since it is effective, economic, and painless as drugs are administered noninvasively.[6]

Midazolam is water-soluble 1,4-benzodiazepine derivative with rapid action and high lipophilicity. Its pharmacological actions include hypnosis, sedation, anxiolysis, anterograde amnesia, anticonvulsant, cardiovascular stability, and muscular relaxation.[7] It is also known to cause adverse effects such as postoperative behavioral changes, cognitive impairment, paradoxical reactions, and respiratory depression.[8,9]

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Ketamine is an N-methyl D-aspartate opponent that produces dissociative state and provides sedation, analgesia, and amnesia. It has an excellent safety profile and is highly effective, with preservation of spontaneous respirations and airway reflexes.[10] Postoperative nausea and vomiting are common; salivation is increased following the administration of the drug.[11]

Dexmedetomidine (DEX) is a potent, highly selective alpha-2 adrenoceptor agonist and causes induced sedation that is characterized by an easy and quick arousal from sedation resembling natural sleep. It is being regarded as a potentially successful sedative for pediatric dental procedure because of its additional stable respiratory profile, anxiolysis, analgesia, and antisalivatory properties.[12]

Fentanyl is a potent and highly selective opioid agonist that has a rapid onset and short duration of action, a lack of histamine release, and fewer cardiovascular effects than do other opioids.[13] Its most common side effect is respiratory depression, which is often dose related.[14]

Although much research has been conducted on different sedation methods in children, an ideal combination of sedation drugs has yet to be discovered.

The present randomized, triple-blinded, controlled study was conducted to evaluate and compare oral combination of midazolam-ketamine (MK), dexmedetomidine-fentanyl (DF), and dexmedetomidine-ketamine (DK) for their sedative properties, safety profile, and ease of treatment completion.

Materials and Methods

The study comprised fearful, anxious patients in the age group 3–9 years American Society of Anesthesiologists – I for whom basic behavior guidance has not been successful and could not cooperate due to a lack of psychological or emotional maturity, requiring dental treatment (extractions, pulpectomy, and restorations) exhibiting negative behavior according to Frankl's behavior rating scale. 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 obtained. Children 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 and failure of previous sedation.

Study design

Enrollment in the study involved assessment of 41 children for eligibility out of which 6 patients were excluded due to upper respiratory tract infection on the day of the study and 1 patient was excluded due to breach in fasting guidelines before the procedure. 34 children were included in the study who were randomly allocated to one of the three groups. Group MK received 0.3 mg/kg of oral midazolam with 5 mg/kg of oral ketamine mixed in 1 mL of honey. Group DF received 2 ug/kg of oral DEX with 3 ug/kg of oral fentanyl mixed in 1 mL of honey. Group DK received 2 ug/kg of oral DEX with 5 mg/kg of oral ketamine mixed in 1 mL of honey. To maintain uniformity throughout the study, each drug was from one brand – DEX hydrochloride (Dexem 100 μg/ml, Themis Medicare Limited, India), midazolam hydrochloride (Mezolam 1 mg/ml, Themis Medicare Limited, India), and ketamine hydrochloride (Ketamine 50 mg/ml, Themis Medicare Limited, India).

Randomization

The patients enrolled for the study were randomly allocated to one the 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. Parent/guardian of the patient picked one envelope and handed it over to the anesthetist, who opened it to see the group and allotted the patient to that group, respectively. All study drugs were prepared and administered by the anesthetist not involved in observation or treatment to the children. Observer 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 h for breast milk and 2 h for clear fluids per GA guidelines.[2]

At the start of the 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. After recording the baseline data, oral drug was mixed with 1 ml of honey and was given to the patient by the anesthetist. During drug administration and till the start of sedation, patient was kept in a quiet and dark room adjacent to the OT monitoring of the patient was performed every 15 min by the same two evaluators form the start of drug administration to the discharge point for heart rate, blood pressure, and SpO$_2$ using sphygmomanometer (Perfect, GuptaSons India, Ambala, India) and pulse oximeter (Scure, GPC Medical Ltd., New Delhi, India) by the evaluators. Likewise, sedation level and behavior score were also assessed every 15 min by the evaluators using

a 6-point sedation scale and 4-point behavior scale which was Modified from Observer Assessment of Alertness

Table 1: Evaluation scale

MOAA/S scale

Sedation scores

Does not respond to mild prodding or shaking

Responds only on mild prodding or shaking

Responds only after name is called loudly or repeatedly

Lethargic response to name spoken in normal tone

Appear asleep but respond readily to name spoken in normal tone

Appear alert and awake, response readily to name spoken in normal tone

Behavior scores

Calm and cooperative

Anxious but reassurable

Anxious and not reassurable

Crying or resisting

Wake-up behavior scores

Calm and cooperative

Not calm but could be easily calmed

Not easily calmed, moderately agitated, or restless

Combative, excited, disoriented

Ease of treatment completion (Houpt scale)

Treatment rating	Explanation
Aborted	No treatment rendered
Poor	Treatment interrupted, only partial treatment completed
Fair	Treatment interrupted but eventually all completed
Good	Difficult, but all treatment performed
Very good	Some limited crying or movement
Excellent	No crying or movement

MOAA/S: Modified observer assessment of alertness and sedation

and Sedation (MOAA/S) scale [Table 1].[15] 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 MOAA/S scale [Table 1]. The average time duration of all treatment procedures in all patients ranged between 20 and 40 min.

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, USA). Statistical significance was defined as $P < 0.05$.

Results

No statistical difference was found regarding sex, age, and weight distribution among the three groups with a mean age (4.59 ± 1.20) and weight (15.26 ± 2.41). All the drugs were well accepted by all the patients. The mean ± standard deviation value of SpO_2, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) during three treatment stages sedation [Table 2].

The analysis of variance revealed that there was no statistically significant difference in SpO2, heart rate, and SBP between the groups, but statistically significant difference exists in DBP measurement at baseline ($P = 0.033$) and at the start of treatment ($P = 0.008$) with slight decrease of DBP in DF 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. During treatment, 90.9% of

Table 2: Physiological parameters during four stages of treatment

	MK	DF	DK	*P*
Heart rate (mean±SD)				
Baseline	100±26.39	100±26.34	104.75±15.58	0.850
Start of treatment	106.55±18.94	115±27.28	109.33±21.84	0.681
During treatment	100.55±23.95	106.27±20.24	107.83±22.25	0.716
End of treatment	98.36±28.42	101.09±24.18	107.33±23.09	0.685
Oxygen saturation (mean±SD)				
Baseline	94.18±4.30	93.36±3.23	93.75±3.79	0.687
Start of treatment	93.91±4.50	94.27±3.19	93.67±2.60	0.146
During treatment	93.91±2.38	94.82±2.40	95.67±2.70	0.178
End of treatment	93.18±4.14	93.36±2.37	93.17±4.08	0.832
Systolic blood pressure (mean±SD)				
Baseline	110.9±18.14	117.2±24.53	103.5±14.47	0.248
Start of treatment	114.1±10.78	116.9±17.30	108.8±10.46	0.336
During treatment	113±15.26	112±12.71	105.3±13.99	0.365
End of treatment	106.9±6.89	107±10.13	105.3±10.20	0.881
Diastolic blood pressure (mean±SD)				
Baseline	72.1±9.52	80.7±17.60	66.6±7.78	0.033
Start of treatment	74.5±8.00	77±9.81	66.6±4.92	0.008
During treatment	74.9±8.21	76±11.45	71.2±9.07	0.471
End of treatment	71.6±6.12	68.7±8.11	67.3±4.45	0.272

Table 3: Behavior scores during four treatment stages

Groups	Treatment stage	Score 1 Calm and cooperative (%)	Score 2 Anxious but reassurable (%)	Score 3 Anxious but not reassurable (%)	Score 4 Crying and resisting	P
MK	Baseline	0	7 (63.6)	4 (36.4)	0	0.191
	Start of treatment	7 (63.6)	4 (36.4)	0	0	0.028
	During treatment	3 (27.3)	7 (63.6)	1 (9.1)	0	0.545
	End of treatment	10 (90.9)	1 (9.1)	0	0	0.811
DF	Baseline	0	10 (90.9)	1 (9.1)	0	0.191
	Start of treatment	3 (27.3)	4 (36.4)	0	0	0.028
	During treatment	5 (45.5)	6 (54.5)	0	0	0.545
	End of treatment	9 (81.8)	2 (18.2)	0	0	0.811
DK	Baseline	0	7 (58.3)	5 (41.7)	0	0.191
	Start of treatment	5 (41.7)	7 (58.3)	0	0	0.028
	During treatment	6 (50)	6 (50)	0	0	0.545
	End of treatment	10 (83.3)	2 (16.7)	0	0	0.811

MK: Midazolam-ketamine; DF: Dexmedetomidine-fentanyl; DK: Dexmedetomidine-ketamine

Table 4: Sedation scores at three stages of the treatment

Sedation scores during three treatment stages

Visit	Group	n	Mean	SD	Minimum	Maximum	Percentiles 25th	50th (median)	75th
Start of treatment	MK	11	4.18	1.079	3	6	3.00	4.00	5.00
	DF	11	4.91	0.701	4	6	4.00	5.00	5.00
	DK	12	4.00	0.739	3	5	3.25	4.00	4.75
During treatment	MK	11	4.36	0.674	3	5	4.00	4.00	5.00
	DF	11	6.00	1.136	3	6	4.00	6.00	6.00
	DK	12	4.33	0.651	3	5	4.00	4.00	5.00
End of treatment	MK	11	4.55	0.522	5	6	5.00	6.00	6.00
	DF	11	6.00	0.000	6	6	6.00	6.00	6.00
	DK	12	5.67	0.492	5	6	5.00	6.00	6.00

Wilcoxon signed ranks test

Group	During treatment - start of treatment	End of treatment - start of treatment	End of treatment - during treatment
MK			
Z	−0.439[b]	−2.401[b]	−2.919[b]
Asymptotic significance (two-tailed)	0.660	0.016	0.004
DF			
Z	−0.368[b]	−2.762[b]	−2.060[b]
Asymptotic significance (two-tailed)	0.713	0.006	0.039
DK			
Z	−1.414[b]	−2.836[b]	−2.724[b]
Asymptotic significance (two-tailed)	0.157	0.005	0.006

[b]Based on negative ranks. MK: Midazolam-ketamine; DF: Dexmedetomidine-fentanyl; DK: Dexmedetomidine-ketamine; SD: Standard deviation

children in Group MK and all children in Group DK and Group DF achieved successful anxiolysis and no statistical difference was found among the groups at any of the stages of treatment. There was a significant difference in sedation levels of patient at the end of treatment when compared with during the treatment with MK and DK and insignificant difference in Group DF [Table 4].

Treatment was successfully completed in all three groups with no statistical difference in ease of treatment between the groups at any stage of treatment [Figure 1].

Discussion

In this study, observer-based MOAA/S scale was used for the assessment of sedation and behavior, as it is one of the few sedation scales with documented reliability.[15] Verbal analog scales are easy to use and commonly employed for pain assessment, but they have questionable validity in assessing sedation.[16] 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
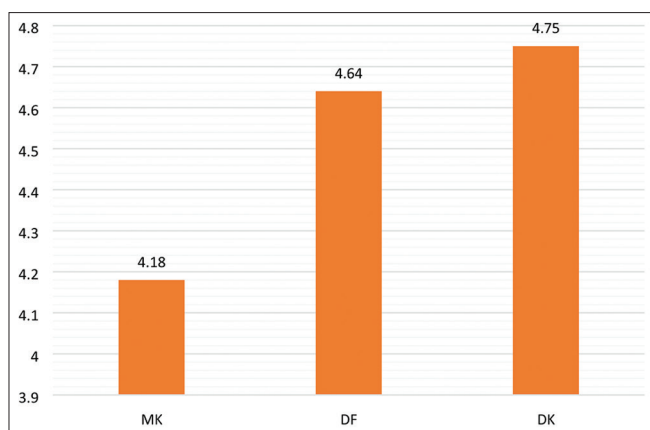
Figure 1: Ease of treatment completion was best seen with midazolam-ketamine group

drugs alone.[17,18] Hemodynamic parameters, namely heart rate, systolic and DBP, and SpO_2, remained relatively stable during the course of treatment in all the three groups. SpO_2 in all three groups at all treatment stages was above 93%.

More patients in MK group (72.8%) were successfully sedated as compared to DK group (58.3%) and DF group (36.4%).

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.[17,18] In our study, 72.8% of patients were successfully sedated with MK combination. This success rate is more than Funk *et al*.,[17] 70%; Soleimanpour *et al*.,[19] 62.5%; Darlong *et al*.,[20] 70.8%; Majidinejad *et al*.,[21] 45.5%; and Roelofse *et al*.,[22] 40% whereas it is lesser in comparison to Barkan *et al*.,[23] 94%; Norambuena *et al*.,[24] 93.3%; Darlong *et al*.,[20] 79.3%; Malhotra *et al*., 75%;[25] and Ghai *et al*.,[26] 97.96%. These differences in success rate of sedation may be attributed to different scales used for evaluation, different drug dosages, and also different criteria taken for success. In our study, score ≤4 was considered as successful sedation, whereas in many studies ≤3 was taken as criteria.

Our results showed 90.9% patients achieved improved behavior during treatment are in accordance with previous studies where sufficient anxiolysis was achieved with MK combination, that is, Warner *et al*., 85%;[27] Roelofse *et al*., 88%;[22] Malhotra *et al*., 83.3%;[25] and Funk *et al*., 90%[17] whereas 73.46% improved behavior was seen in a study by Ghai *et al*.[26] as the doses used in their study was lesser than that used by us.

Ease of treatment completion as per the scale used was excellent in 27.33% which was less than the study by Malhotra *et al*., 33.33%.[25] Findings in this study are in accordance with those of Roelofse *et al*.,[22] Warner *et al*.,[27] Lin and Durieux,[28] and Beebe *et al*.[29]

Wake-up behavior as scored by MOAA/S scale was found to be calm and cooperative in 72.7% children which was

less in comparison with study by Malhotra *et al*., 91.7%.[25]

Postoperative nausea and vomiting were found in 27.27% of patients in MK group. These results are in accordance with other studies by Fallahinejad Ghajari *et al*.,[30] Warner *et al*.,[27] Beebe *et al*.,[29] Baygin *et al*.,[31] and Moreira *et al*.[32] who reported minimal postoperative complications in patients sedated with this combination.

The opposing hemodynamic profiles of two, that is, negative hemodynamic effects of DEX[33,34] and positive cardiostimulatory effects of ketamine[35] may provide balanced hemodynamic parameters in sedated patients. In the present study, DK combination drug resulted in mild increase in heart rate and systolic and DBP during, but changes were not statistically significant. Whereas, SpO_2 also increased at the start and during treatment but always remained above 93%, this change was statistically insignificant too. In our study, 58.3% patients were successfully sedated with DK combination. This was slightly >42.1% found by Jia *et al*.[36] With DK group, all patients achieved improved behavior during treatment, whereas Jia *et al*.[36] showed 92.1% successful anxiolysis.

Wake-up behavior as scored by MOAA/S scale was found to be calm and cooperative in 75% children. Postoperative nausea and vomiting were found in 25% of patients drugged with DK combination in our study, which was >5% due to intranasal route of DEX used in the later study.[36]

Recent systematic reviews found that DEX could reduce opioid requirements and potentiate analgesia.[37-39] In the present study, DF combination resulted in mild increase in heart rate and SBP during treatment, but changes were not statistically significant, whereas DBP increased to statistically significant values during treatment. An increase in SpO_2 during treatment was seen, even though this change was found to be statistically insignificant.

In our study, 36.4% of patients were successfully sedated with DF combination. All patients achieved improved behavior during treatment.

Ease of treatment completion as per the scale used was excellent in 9.1% and very good in 27.3% patients. Wake-up behavior was found to be calm and cooperative in 81.8% children. Postoperative nausea and vomiting were found in 18.2% of patients drugged with DF combination.

Using the dosages and regimen described in this study, all three groups reliably produced anxiolysis without loss of respiratory drive or protective airway tone. There was statistically significant difference in sedation level produced by MK group during treatment followed by DK group and DF group, respectively. Although statistically insignificant, combination of DK group and DF group resulted in better behavior than MK group during the treatment. This may have been resulted due to better anxiolysis properties of DEX when compared with midazolam.[40]

There was an improvement in behavior score in all three groups during treatment. There was statistically insignificant difference in behavior scores produced by Group C and Group B resulted in better behavior than Group A during the treatment.

Treatment was also successfully completed in all three groups. Ease of treatment completion, however, was moderately better with Group A as compared to Group B and Group C.

Conclusion

This study concluded that oral combination all three oral combinations of MK, DF, and DK produced comparable sedation and behavior among pediatric dental patients. Oral combination of DK has a comparable sedative property with oral MK combination can serve as an alternative in pediatric sedation. Combination of oral DF also promises to be a potential sedative agent for children with regard to its successful anxiolysis during treatment procedures.

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Conflicts of interest

There are no conflicts of interest.

References

1. Forehand R, Long N. Strong-willed children: A challenge to parents and pediatric dentists. Pediatr Dent 1999;21:463-8.
2. American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: Application to healthy patients undergoing elective procedures: An updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. anesthesiology 2011;114:495-511.
3. Raadal M, Lundeberg S, Haukali G. Pain, pain control and sedation. In: Koch G, Poulsen S, editors. Pediatric Dentistry, A Clinical Approach. 2nd ed. Singapore: Blackwell; 2009. p. 54.
4. McDonald RE, Avery DR, Dean JA, Jones JE. Local anesthesia and pain control for the child and adolescent. In: Dean JA, Avery DR, McDonald RE, editors. McDonald and Avery's Dentistry for the Child and Adolescent. 9th ed. Reed Elsevier India Pvt., Ltd.; 2011. p. 307.
5. American Academy on Pediatrics, American Academy on Pediatric Dentistry. Guideline for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatr Dent 2008;30:143-59.
6. Cagiran E, Eyigor C, Sipahi A, Koca H, Balcioglu T, Uyar M, et al. Comparison of oral midazolam and midazolam-ketamine as sedative agents in paediatric dentistry. Eur J Paediatr Dent 2010;11:19-22.
7. Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S, et al. Premedication in the United States: A status report. Anesth Analg 1997;84:427-32.
8. Bergendahl H, Lönnqvist PA, Eksborg S. Clonidine: An alternative to benzodiazepines for premedication in children. Curr Opin Anaesthesiol 2005;18:608-13.
9. Bergendahl H, Lönnqvist PA, Eksborg S. Clonidine in paediatric anaesthesia: Review of the literature and comparison with benzodiazepines for premedication. Acta Anaesthesiol Scand 2006;50:135-43.
10. Green SM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation in children. Ann Emerg Med 2004;44:460-71.
11. Nagdeve NG, Yaddanapudi S, Pandav SS. The effect of different doses of ketamine on intraocular pressure in anesthetized children. J Pediatr Ophthalmol Strabismus 2006;43:219-23.
12. Ogawa S, Seino H, Ito H, Yamazaki S, Ganzberg S, Kawaai H, et al. Intravenous sedation with low-dose dexmedetomidine: Its potential for use in dentistry. Anesth Prog 2008;55:82-8.
13. Friedrichsdorf SJ, Kang TI. The management of pain in children with life-limiting illnesses. Pediatr Clin North Am 2007;54:645-72, x.
14. Grape S, Schug SA, Lauer S, Schug BS. Formulations of fentanyl for the management of pain. Drugs 2010;70:57-72.
15. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the observer's assessment of alertness/Sedation scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990;10:244-51.
16. Némethy M, Paroli L, Williams-Russo PG, Blanck TJ. Assessing sedation with regional anesthesia: Inter-rater agreement on a modified Wilson sedation scale. Anesth Analg 2002;94:723-8.
17. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: Double-blind randomized study of a combination of midazolam and ketamine vs. midazolam or ketamine alone. Br J Anaesth 2000;84:335-40.
18. Astuto M, Disma N, Crimi E. Two doses of oral ketamine, given with midazolam, for premedication in children. Minerva Anestesiol 2002;68:593-8.
19. Soleimanpour H, Mahmoodpoor A, Eftekhari Milani F, Shahsavari Nia K, Mehdizadeh Esfanjani R, Safari S, et al. Effectiveness of oral ketamine, midazolam, and atropine cocktail versus oral diphenhydramine for pediatric sedation in the emergency department. Iran Red Crescent Med J 2014;16:e21366.
20. Darlong V, Shende D, Subramanyam MS, Sunder R, Naik A. Oral ketamine or midazolam or low dose combination for premedication in children. Anaesth Intensive Care 2004;32:246-9.
21. Majidinejad S, Taherian K, Esmailian M, Khazaei M, Samaie V. Oral midazolam-ketamine versus midazolam alone for procedural sedation of children undergoing computed tomography; a randomized clinical trial. Emerg (Tehran) 2015;3:64-9.
22. Roelofse JA, Joubert JJ, Roelofse PG. A double-blind randomized comparison of midazolam alone and midazolam combined with ketamine for sedation of pediatric dental patients. J Oral Maxillofac Surg 1996;54:838-44.
23. Barkan S, Breitbart R, Brenner-Zada G, Feldon M, Assa A, Toledano M, et al. A double-blind, randomised, placebo-controlled trial of oral midazolam plus oral ketamine for sedation of children during laceration repair. Emerg Med J 2014;31:649-53.
24. Norambuena C, Yañez J, Flores V, Puentes P, Carrasco P, Villena R, et al. Oral ketamine and midazolam for pediatric burn patients: A prospective, randomized, double-blind study. J Pediatr Surg 2013;48:629-34.
25. Malhotra PU, Thakur S, Singhal P, Chauhan D, Jayam C, Sood R, et al. Comparative evaluation of dexmedetomidine and midazolam-ketamine combination as sedative agents in pediatric dentistry: A double-blinded randomized controlled trial. Contemp Clin Dent 2016;7:186-92.
26. Ghai B, Grandhe RP, Kumar A, Chari P. Comparative evaluation of midazolam and ketamine with midazolam alone as oral

premedication. Paediatr Anaesth 2005;15:554-9.

27. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric oral premedicant. Paediatr Anaesth 1995;5:293-5.

28. Lin C, Durieux ME. Ketamine and kids: An update. Paediatr Anaesth 2005;15:91-7.

29. Beebe DS, Belani KG, Chang PN, Hesse PS, Schuh JS, Liao JC, *et al.* Effectiveness of preoperative sedation with rectal midazolam, ketamine, or their combination in young children. Anesth Analg 1992;75:880-4.

30. Fallahinejad Ghajari M, Ansari G, Soleymani AA, Shayeghi S, Fotuhi Ardakani F. Comparison of oral and intranasal midazolam/Ketamine sedation in 3-6-year-old uncooperative dental patients. J Dent Res Dent Clin Dent Prospects 2015;9:61-5.

31. Baygin O, Bodur H, Isik B. Effectiveness of premedication agents administered prior to nitrous oxide/oxygen. Eur J Anaesthesiol 2010;27:341-6.

32. Moreira TA, Costa PS, Costa LR, Jesus-França CM, Antunes DE, Gomes HS, *et al.* Combined oral midazolam-ketamine better than midazolam alone for sedation of young children: A randomized controlled trial. Int J Paediatr Dent 2013;23:207-15.

33. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology 1992;77:1134-42.

34. Ingersoll-Weng E, Manecke GR Jr., Thistlethwaite PA. Dexmedetomidine and cardiac arrest. Anesthesiology 2004;100:738-9.

35. Aroni F, Iacovidou N, Dontas I, Pourzitaki C, Xanthos T. Pharmacological aspects and potential new clinical applications of ketamine: Reevaluation of an old drug. J Clin Pharmacol 2009;49:957-64.

36. Jia JE, Chen JY, Hu X, Li WX. A randomised study of intranasal dexmedetomidine and oral ketamine for premedication in children. Anaesthesia 2013;68:944-9.

37. Peng K, Wu S, Liu H, Ji F. Dexmedetomidine as an anesthetic adjuvant for intracranial procedures: Meta-analysis of randomized controlled trials. J Clin Neurosci 2014;21:1951-8.

38. Schnabel A, Meyer-Frießem CH, Reichl SU, Zahn PK, Pogatzki-Zahn EM. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. Pain 2013; 154:1140-9.

39. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic $\alpha 2$ agonists on postoperative morphine consumption and pain intensity: Systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2012;116:1312-22.

40. Daabiss MA, Hashish M. Dexmedetomidine versus ketamine combined with midazolam; a comparison of anxiolytic and sedative premedication in children. BJMP 2011;4:441-7.