

Comparison of ketamine-propofol and ketamine-dexmedetomidine combinations in children for sedation during tooth extraction

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Abstract

Objective: To evaluate the efficiency of ketamine-propofol and ketamine-dexmedetomidine drugs in children for sedation during tooth extraction.

Methods: The randomised, prospective study was conducted at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Erciyes University, Kayseri, Turkey, from September to November 2013, and comprised children who were due to undergo tooth extraction. Non-invasive blood pressures (systolic and diastolic), peripheral oxygen saturation, heart and respiratory rates and Ramsay Sedation Scores were assessed at baseline, after applying the drugs and then every 5 minutes thereafter. Further, the ketamine-propofol group received 1mg kg⁻¹ of ketamine and propofol, and the ketamine-dexmedetomidine group received 1mg kg⁻¹ of ketamine + 0.5 µg kg⁻¹ of dexmedetomidine.

Results: Of the 60 participants, there were 30 (50%) in each group. No statistically significant differences were found in terms of heart rate, non-invasive blood pressures at any time and the number of drug repetitions ($p > 0.05$). Nausea-vomiting was statistically higher in the ketamine-dexmedetomidine group ($p < 0.05$).

Conclusion: Ketamine-propofol might be a better option due to lower vomiting and nausea episodes and higher surgeon satisfaction levels.

Keywords: Dexmedetomidine, Ketamine, Propofol, Tooth extraction. (JPMA 67: 693; 2017)

Introduction

In recent years, an increasing number of uncooperative children are treated for dental problems under anaesthesia. For many years, nitrous oxide/oxygen inhalation and benzodiazepine anaesthesia have been used as sedation methods in dental clinics because they provide analgesia and anxiolysis with rapid onset and recovery time.^{1,2} However, there is a weak evidence regarding their efficiency. Therefore, further well-planned clinical studies are recommended to research other probable sedation methods.³ Tooth extraction is a dental procedure that is sometimes difficult to perform in some patients such as children because of fear and anxiety. Further, bad experiences in childhood in the dental office may lead to dental phobia in the future.⁴ Thus, developing a better anaesthetic method for uncooperative children with dental fear is important and may improve patient satisfaction. For this purpose, intranasal midazolam-sufentanil and ketamine-midazolam combinations, oral midazolam, chloral hydrate, ketamine, and propofol are used in paediatric dental treatment.^{2,3,5,6} Undoubtedly, each agent has different benefits from the others.

Dexmedetomidine, acts via α_2 adrenoreceptors and also provides analgesia, sedation and anxiolysis. It produces rapid and stable sedation with minimal respiratory effect.⁷ In procedural sedation, at the beginning 0.2-1 µg/kg/h through continuous infusion and then after, where necessary, a loading dose of 0.5-1 µg/kg is recommended. In children, dexmedetomidine is currently used in many studies in intra-operative sedation, post-operative analgesia, prevention delirium, and shivering with different dose regimens.⁸ In various invasive procedures of children, ketamine and propofol have been popular anaesthetic agents to use, either alone or in combination.⁹ However, there is limited data on the use of such combination therapy for children undergoing tooth extraction which is generally a short procedure. So short-acting anaesthetic agents may be useful for this procedure. In a study, it has been reported that ketamine-dexmedetomidine (KD) combination led to lower recovery time than ketamine-propofol (KP) combination in paediatric cardiac catheterisation.¹⁰ We hypothesized that KD combination may lead to lower recovery time than KP combination in children in tooth extraction as well.

The current study was planned to evaluate the efficiency of KP and KD drugs in tooth extraction in children for deep sedation. Recovery time was the primary endpoint, and haemodynamic changes, post-operative adverse

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effects, surgeon satisfaction, and anxiety score were the secondary endpoints of the research.

Patients and Methods

The randomised, prospective study was conducted at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Erciyes University, Kayseri, Turkey, from September to November 2013, and comprised children who were due to undergo tooth extraction. After obtaining approval from the institutional ethics committee, and written informed consent from the subjects' parents, children aged 2-8 years and classified as American Society of Anaesthesiologists (ASA) I-II were enrolled. All participants had severe anxiety due to dental procedures, and none of them could be treated under local anaesthesia in dental clinics. The Frankl Behaviour Rating Scale, which is known as one of the most dependable scales in dentistry for behaviour rating, was used to determine dental anxiety.¹¹ Patients who declined consent, and had severe organ dysfunction (breathing, cardiac, renal or bleeding disorders) allergy to the anaesthetic agents, epilepsy and extended restorative dental treatment were excluded. Only patients who were undergoing tooth extraction were included. After a minimum fasting period of 6 hours, the patients were taken in the operating room and were randomly divided into two equal groups.

For vascular access of the children, a local anaesthetic cream was applied, and they were pre-medicated by 0.1 mg/kg of intravenous (IV) midazolam. Patients were monitored with standard non-invasive method. During the procedure, using a nasal mask, supplemental oxygen (2 L/min) was administered. Non-invasive blood pressures (systolic and diastolic), peripheral oxygen saturation, the heart and respiratory rate, and Ramsay Sedation Scores (RSS)¹² were recorded at baseline, after applying the drugs (after the induction), and then every 5 minutes thereafter. The drug solutions were prepared as follows: 2ml of ketamine (Ketalar, Eczacibasi, Luleburgaz, Turkey) (50mg ml⁻¹) was diluted to 10-ml with 8ml of saline in an injector for both groups. Similarly for the KD group, 0.5ml dexmedetomidine (Precedex; Hospira, Rocky Mount, North Carolina, United States) (50 µg) was mixed with 9.5ml saline. Before applying the bolus suitable dose of dexmedetomidine (1µg kg⁻¹) to the patient, it was diluted with saline in another 5ml injector again.

For the induction of anaesthesia, Group KP received 1mg kg⁻¹ of ketamine+ propofol (Propofol 1% Fresenius, Fresenius Kabi Deutschland, Bad Homburg, Germany), and Group KD received 1mg kg⁻¹ of ketamine + 0.5 µg kg⁻¹ of dexmedetomidine. Dexmedetomidine was applied

slowly during a period of 60-90 seconds¹³ intravenously for the induction of anaesthesia. When discomfort was observed in the patients or RSS was lower than 4, Group KP received a half dose of propofol (0.5mg kg⁻¹) and group KD received dexmedetomidine (0.25µg kg⁻¹) intravenously. Discomfort was determined as moving, crying, or a 20% increase in heart rate (HR) or systolic blood pressure (SBP) compared with the baseline. Articaine solution (Ultracain D-S, Sanofi-Aventis, Lüleburgaz, Istanbul) was applied (a total of 2-4 ml), for each tooth to be extracted. After the induction, and every 5 minutes during the procedure, SBP, diastolic blood pressure (DBP), HR, respiratory rate (RR), RSS, and peripheral capillary oxygen saturation (SPO₂) values were recorded. The number of extracted teeth, pre-operative and post-operative anxiety scores, post-operative pain scores, Steward Recovery Score,¹⁴ duration of the procedure, surgeon satisfaction (bad/middle/good), additional drug needed, and adverse events were also recorded. A four-point scale¹⁵ was used to determine pre-operatively and post-operatively anxiety. Post-operative pain scores were evaluated with The Modified Objective Pain Scale (OPS).¹⁶

Adverse effects such as hypotension or hypertension, nausea and vomiting, arrhythmia, bradycardia, hypoxia, respiratory depression, were also assessed during and 2 hours after the process. Respiratory depression defined such as: respiratory rate <8 breaths/minute or an apnea lasting >15 seconds. A 20% decrease or increase in baseline values was sustained as hypotension or hypertension, respectively.

A previous study¹³ was used to determine the sample size. Power analysis showed that the number of children required to find a mean difference of 8.9 minutes in recovery time with a standard deviation of 9.6 and 10.5, an α of 0.05, and a β of 0.1 was 27. However, we added more children in case of their families may have decided to abandon the study.

The normality of the parametric data was analysed by the Shapiro-Wilk test. Student's t-test was used for comparison between groups for data with a normal distribution, and the Mann-Whitney U test was performed for comparison between groups for data that did not show a normal distribution. The inter-group comparison of repeated measurements was evaluated by one-way repeated measures analysis of variance (ANOVA). Categorical variables were evaluated with the exact method of the chi-square test. All tests were two-sided, and p-value of <0.05 was considered significant. All statistical analyses were performed using the R software

package (version 3.1.1) and MedCalc software (version 10.1.6© 1993-2009).

Results

Of the 60 participants, there were 30(50%) in each KP and KD group. There were no statistically significant differences regarding the demographic data and number of extracted teeth between the groups. The mean age was 5.37 ± 1.4 years in the KP group and 5.30 ± 1.7 in the KD group ($p=0.305$). The mean duration of the procedure and recovery time were 7.8 ± 3.8 and 15.4 ± 7.2 minutes in the KP group and 7.5 ± 3 and 18.6 ± 11.3 in the KD group ($p=0.764$ and 0.194). No statistically significant differences were observed in terms of blood pressures (SBP or DBP) and HR, at any time ($p>0.05$). Also, no statistically significant differences were found between the groups in terms of RR and SPO2 values or in RSS ($p>0.05$) (Table-1).

In addition, no statistically significant differences were observed in the groups regarding the pre-operative and post-operative anxiety scores or post-operative pain scores in the first and second hours ($p>0.05$) (Table-2).

Table-1: The demographic data, number of extracted teeth, duration of the procedure time, surgeon satisfaction and recovery time of the groups.

	Group 1 (KP) (n=30)	Group 2 (KD) (n=30)	P values
Age (year)	5.37 ± 1.4	5.30 ± 1.7	0.305
Weight (F/M)	13/17	12/18	1.00
Height (kg)	19.7 ± 4.5	20.9 ± 7.1	0.416
Duration of the procedure (min)	7.8 ± 3.8	7.5 ± 3	0.764
Recovery time (min)	15.4 ± 7.2	18.6 ± 11.3	0.194
Surgeon satisfaction (bad/middle/good)	0/4/26	8/8/14	$< 0.001^*$
The number of extracted tooth 1/2/3	8/6/7	5/11/16	0.336

Values are expressed as n, mean \pm SD. * P-values <0.05 were considered significant.

KP: Ketamine-propofol

KD: Ketamine-dexmedetomidine.

Table-2: Pre-operative or post-operative anxiety scores, and pain scores of the groups.

	Group 1 (KP) (n=30)	Group 2 (KD) (n=30)	P values
Preoperatively Anxiety Score			
Calm/could be reassured/could not be reassured/crying and resisting	23 / 4 / 3/0	22/ 5/ 3/0	0.936
Postoperatively Anxiety Score			
Calm/could be reassured/could not be reassured/crying and resisting	24 / 2 / 4/0	21/ 4 / 5/ 0	0.613
Pain Score in PACU			
(1 / 2 / 3)	29 / 1 / 0	30 / 0 / 0	1.00
Pain Score at 1st hour			
(1 / 2 / 3)	27 / 3 / 0	27 / 3 / 0	1.00

Values are expressed as n. *P-values <0.05 were considered significant.

KP: Ketamine-propofol.

KD: Ketamine-dexmedetomidine.

PACU: Post-anaesthesia care unit.

Table-3: The number of drug repetitions of the groups.

Additional drug The number of drug repetitions	Group 1 (KP) (n=30)	Group 2 (KD) (n=30)	P values
0 / 1 / 2 / 3	14 / 12 / 3 / 1	21 / 7 / 1 / 1	0.294

Values are expressed as n. P-values <0.05 were considered significant.

KP: Ketamine-propofol

KD: Ketamine-dexmedetomidine.

In the KP group, 12(40%) patients needed additional propofol and dexmedetomidine compared to 5(13.3%) in the KD group. No statistically significant differences were found in terms of the number of drug repetitions ($p=0.294$) (Table-3).

The percentage of surgeon satisfaction was 26(86.6%) patients in the KP group and 14(46.7%) patients in the KD group ($p<0.001$). Arrhythmia and bradycardia were not seen in any patients. Hypoxia (SPO2 <90) was observed in 2(6.6%) patients in the KP group ($p>0.05$). Nausea-vomiting was observed in 6(20%) patients of the dexmedetomidine group compared to 1(3.3%) patient in the other group ($p=0.026$).

Discussion

In the current study, a comparison between the two drugs combination showed that, both KP and KD provided effective deep sedation and analgesia in tooth extraction for uncooperative anxious children. However, surgeon satisfaction level was better with KP combination, and it caused less nausea and vomiting.

Several sedation regimens for tooth extraction are discussed in the literature on this topic.^{3,5} Ketamine and propofol became good anaesthetic methods for the several procedural sedation over the years. Haemodynamic stability, preservation of the airway, and

because of ketamine lead to dissociation alone, the ketamine-propofol combination preferred regimens nearly for procedural settings.⁹ Tosun et al.¹⁷ researched the efficacy of KD and KP combinations in paediatric cardiac catheterisation and found any differences in terms of SPO₂, RR and SBP during the procedure. They determined that patients in the KD group required more supplemental doses of ketamine than other group, so concluded that a KD combination was insufficient for sedation and analgesia. In our study, we observed that the additional drug repetitions needed were statistically similar in both groups, so the drug combinations had no superiority to each other on this topic. This may be due to shorter operation time of tooth extraction procedure.

Koruk et al.¹⁰ reported that KD combination led to lower recovery time than KP combination in paediatric cardiac catheterisation. Similarly, in our previous study¹³ we observed a lower recovery time in the KD group than the KP group in paediatric burn dressing changes. On the other hand, Tosun et al.¹⁷ concluded that KD combination led to a longer recovery time in paediatric cardiac catheterisation. In the current study, the sedation scores (evaluated using RSS) were similar in both groups. The recovery time was longer in the KD group in clinical evaluation, but the difference was not statistically significant. The similar recovery time of the groups may be due to the type or duration of the procedure, or patient population.

Although dexmedetomidine is recommended to be administered by infusion, in some studies it has been administered as a bolus dose.^{13,18} Goyal et al.¹⁸ used a KD combination for upper gastrointestinal endoscopy in children. They gave 1µg/kg of dexmedetomidine and 2mg/kg of ketamine intravenously as a bolus over 5 minutes. When required, they applied an additional 0.5-1 mg/kg of ketamine to the patients. Kim et al.¹⁹ managed uncooperative children behaviours successfully under dexmedetomidine sedation because of its minimal respiratory impairment, by administering 1µg/kg/h by continuous infusion over 10 minutes. Potts et al.²⁰ researched the different bolus doses of dexmedetomidine (1-4µg/kg) and suggested 0.5µg/kg bolus dosing followed by continuous infusion. In the present study, we preferred 0.5µg/kg bolus dosing during a period of 60-90 seconds, because the duration of the procedure was shorter and a loading dose regimen provided us more practical method. Thus, we researched if a KD combination may be an alternative to KP, which is usually used as intermittent bolus dosing in short procedures.

The anaesthetic drugs are generally related with undesirable side effects. Ketamine provides strong

analgesia, amnesia and sympathomimetic effects as well, and increases salivation, whereas dexmedetomidine has mild analgesic and anti-sialagogue effect. Because of opposing effects of this drug, a dexmedetomidine-ketamine combination has been favoured in invasive procedures for paediatric patients in recent years. When used together, they may compensate for the effects of each other.²¹ Airway events may occurred frequently with propofol than ketamine. Ketamine may lead to hypertension and tachycardia, whereas propofol may cause hypotension. Also, ketamine triggers vomiting and nausea, but vomiting is infrequent with propofol. Therefore, using a propofol and ketamine combination may provide stability by limiting these effects. So, KP has been favoured in painful procedures as well.⁹ Potts et al.²⁰ suggested 0.5µg/kg of a small bolus dosing to minimise dexmedetomidine's effects on mean blood pressure. Furthermore, they determined a biphasic effect of dexmedetomidine that is associated with a transient increase and then decrease in blood pressure on mean blood pressure. Hypotension and bradycardia are the common haemodynamic side effects of dexmedetomidine,⁸ but we did not encounter such side effects in either group. This could be a result of slow intravenous infusion application of the drugs. On the other hand, the sympathomimetic effect of ketamine may be compensated by dexmedetomidine. Also, both drugs cause minimal respiratory events and may increase vomiting.^{8,9} In this study, no respiratory effect, bradycardia, or arrhythmia was observed in the both groups, probably because of being more alert because the process was performed in oral cavity.

Goyal et al.¹⁸ observed vomiting episodes in 4 patients with a ketodex combination for upper gastrointestinal endoscopy. Similarly, we showed evidence of nausea and vomiting episodes in the KD group but none in the other. This may be due to the antiemetic effect of propofol. Surgeon satisfaction is important to determine the operation success. In our previous study, we observed similar surgeon satisfaction in the KP and KD groups in paediatric burn dressing changes.¹³ But in this current study, which was performed in tooth extraction, the surgeon satisfaction was better in the KP group than the KD group whereas the sedation scores, pre-operative and post-operative anxiety scores were similar. This could be due to the different types of procedures, or may be the different surgeons.

Conclusion

Although KP and KD combinations both provided effective deep sedation in tooth extraction for uncooperative children with severe anxiety, KP

combination ensured better surgeon satisfaction levels, and caused less nausea and vomiting. Therefore, KP may be a better option in tooth extraction in children.

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