Original Article

Comparison between dexmedetomidine and esketamine in pediatric dentistry surgery

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Background: Dexmedetomidine (D) and esketamine (K) are used for the sedation of pediatric dental surgery. This study was designed to compare the effect of intranasal D and K in producing moderate sedation for uncooperative pediatric dental patients.

Methods: This prospective single-center cohort study was conducted at the Maternal and Child Health Hospital of Hubei Province after approval of the Medical Ethics Committee. One hundred and fifty American Society of Anesthesiologists (ASA) grade I and II patients aged 3–10 years who were uncooperative and could not be managed by conventional behavior management techniques were included in this study. Patients were classified into four groups. Group K was administered with esketamine (0.5 mg/kg), and group D was given D1 (1 μg/kg), D2 (1.5 μg/kg), or D3 (2.0 μg/kg) intranasally. The outcome measurements included the sedation level, changes in vital signs, sedation onset and recovery times, analgesia, behavior, and overall success.

Results: The sedation onset time was significantly shorter for K and D3 compared with D1 and D2. The recovery time was fastest in group D1. The overall success rate was highest in group D3, followed by the D2, D1, and K groups; however, the difference between them was not significant. The intra-and postoperative pain scores in the D3 and K groups were significantly lower than those in the D1 group.

Conclusions: Intranasal D and K are effective in producing moderate sedation for uncooperative pediatric dental patients.

Keywords: Dexmedetomidine (D); esketamine (K); moderate sedation; pediatric dentistry

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Introduction

Pain, fear, anxiety, and anger are the major emotions children experience during treatment by a pedodontist (1). It is commonly believed that most children who are afraid or uncooperative should be managed with behavioral management procedures, including tell-show-do, positive reinforcement, modeling, and suggestion. Although children can be managed through these techniques, some are still unable to tolerate dental treatment comfortably. In these cases, management with pharmacological strategies is helpful.

Various drugs have been used for premedication to reduce anxiety and promote the smooth separation of children from their parents. The ideal sedative agent for children should be readily acceptable and have a prompt onset with minimal side effects (2). Dexmedetomidine (D) is a potent, highly selective α-2 adrenoceptor agonist and can inhibit sympathetic activity by activating receptors in the central nervous system, causing a reduction in blood pressure and heart rate, sedation, and anxiolysis (3). It

provides a dose-dependent mild analgesia without respiratory depression (4), and dexmedetomidine-induced sedation is characterized by an easy and quick arousal similar to natural sleep. Various studies have investigated the effect of D in pediatric populations, and their results support its use as an anesthetic and sedative adjunct in children. Esketamine (K), a phencyclidine derivative, is also widely used in pediatric patients because of its sedative, anesthetic, immobilization, and amnesic effects (5). With K protective airway reflexes remain relatively preserved. Adverse respiratory events such as laryngospasm are rare, at a reported of 0.4–0.7% (6). Moreover, K does not adhere to the typical dose-response sedation continuum; once the dissociative sate has been established, an increased dose will not increase the risk of impaired airway function and respiratory control (7).

The objective of this study was to evaluate and compare the efficacy of various doses of D and also to compare them with K as a premedication prior to general anesthesia (GA) in pediatric dental patients.

Methods

Study population

This prospective single-center cohort study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (8). The filled STROBE reporting checklist is available at https://dx.doi.org/10.21037/tp-21-435).

The study was conducted at the Maternal and Child Health Hospital of Hubei Province, China. Consecutive patients aged between 3 and 10 years who were fearful or anxious, and for whom basic behavior management techniques had been unsuccessful in rendering dental treatment [score 1 or 2 in the behavior/response to treatment rating scale (9,10)] and hence were indicated for treatment under GA, were considered for inclusion as follows: all children needed to be healthy without any physical, mental, or systemic disability, have no contraindications for the drugs used in the study, or history of previous dental treatment under sedation or anesthesia. Only children whose parents or guardians fully understood the related risks and benefits of this study and gave written consent were included. Patients were excluded if they had a known allergy to sedative drugs or a potentially high risk of adverse airway events. The study was approved by the Institutional Ethical Committee of the Maternal and Child Health Hospital of Hubei Province in China (No. 2021IECLW027). Written informed consent was taken from all the patients' guardians for publication of this study and any accompanying images. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Study design

According to their individual physician's choice, patients were divided into four groups: D1 (dexmedetomidine, 1 μg/kg), D2 (dexmedetomidine, 1.5 μg/kg), D3 (dexmedetomidine, 2.0 μg/kg), or K (0.5 mg/kg). All drug solutions were prepared as parenteral solutions in a total volume of 2 mL by adding normal saline, based on the dosages calculated from the children's weight and the level of sedation. Both sides of the nasal cavity were carefully cleaned before the drug administration to avoid outflow of the drug solution.

Data collection

According to the GA guidelines, patients were fasted from solid foods for 6 hours, breast milk for 4 hours, and clear liquids for 2 hours on the day of the procedure (11). The clinical status of all patients was reassessed on the day of surgery by the attending anesthesiologist. Their vital signs, oxygen, and oxygen saturation (SpO_2) levels were measured and recorded on the sedation chart. A volume of 0.2 mL of the drug solution was slowly administered by drops to both nostrils of the patients using a 1-mL syringe (without needle) (*Figure 1*). The children stayed supine or semi-recumbent for 5 minutes after the drug administration. The time of drug administration and sedation onset time were recorded. A multifunctional monitor was used to record patients' vital signs at 5-minute intervals, including heart rate, blood pressure (SBP, DBP), SpO_2, respiratory rate, and the bispectral index (BIS). The dental treatment was discontinued if the children exhibited uncooperative behavior at any time during a given session. Any adverse events were recorded during the procedure and the recovery period. The time of sedation onset, depth of sedation, behavior/response during dental treatment, vital signs, SpO_2 levels, adverse effects, recovery time, and the overall success of the sedation were assessed during the treatment period. In addition, the sedation level and behavior score were evaluated every 5 minutes, using the 5-point Modified Observer's Assessment of Alertness and Sedation (MOAAS) scale (10).

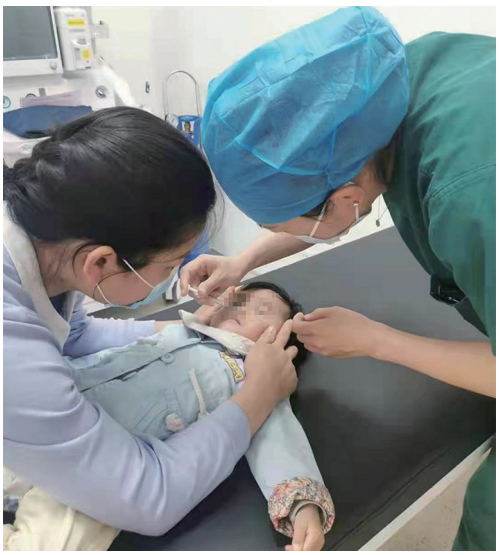

Figure 1 The anesthesia procedure. This image is published with consent from patients' parents.

Statistical analysis

The characteristics of patients in all four groups were compared. Continuous variables are presented as the mean ± standard deviation (SD) and were compared using one-way analysis of variance (ANOVA). Tukey's honestly significant difference (HSD) post hoc test was used to analyze the significance of the mean between-group differences. Categorical variables are expressed as percentages and were calculated using the Pearson χ^2 test or Fisher exact test. All analyses were performed using SPSS 19.0 for Windows (Chicago, IL, USA). A 2-tailed P value <0.05 was considered statistically significant.

Results

As shown in *Table 1*, the mean age of patients in the D1, D2, D3, and K groups was 8.14±1.83, 8.66±1.71, 8.95±1.62, and 8.02±1.83 years, respectively. ANOVA revealed that the mean age between the four groups was not significantly different (P=0.0833). Other demographic data (weight, gender, and behavior level) were also comparable between the groups.

As shown in *Table 2*, nine parameters during sedation were compared among the four groups. The ANOVA analysis showed no significant difference in the SpO_2 level, respiratory rate, and DBP between any of the groups (P>0.05). However, there were significant between-group differences in pulse rate, SBP, recovery time, onset time, intraoperative analgesia, and postoperative analgesia (P<0.05). The Tukey's HSD test showed that the pulse rate between D1 and K, D2 and K, and D3 and K groups were significantly different (P<0.01), but the difference between the D1, D2, and D3 groups was not significant (D1 *vs.* D2: P=0.779, D2 *vs.* D3: P=0.998, D1 *vs.* D3: P=0.705). The SBP level in the K group was significantly higher than in groups D1, D2, and D3 (P<0.05); however, the difference between D1 and D2, D2 and D3, and D1 and D3 groups was not significant (P>0.05). The sedation onset time in the K group was significantly shorter than that in the D1, D2, and D3 groups (P<0.05), and the sedation onset time was significantly longer in the D1 and D2 groups than in the D3 group (P<0.05).

The intra- and postoperative analgesic effects in the four groups were statistically different (P<0.05). The intraoperative pain score in the D3 and K groups was significantly lower than that in the D1 group (P<0.05); the postoperative pain score in the D1 group was significantly higher than that in the K group (P=0.029).

As shown in *Table 3*, the D3 group achieved an "adequate" depth of sedation and "satisfactory" completion of treatment in the highest number of sessions (79.41% and 82.35%, respectively), followed by the D2, K, and D1 groups. However, this difference was not significant (P>0.05, *Table 3*). The overall success rate was highest in the D2 (75.61%) and D3 groups (73.53%), followed by the D1 group (56.76%) and the K group (55.26%) (*Table 3*). However, the χ^2 test showed that the success rate among the four groups was not significantly different (P>0.05).

Discussion

In the present study, we performed a cohort study to compare the efficacy of D and K on the sedation of pediatric dental patients. D is a highly selective α-2 adrenoceptor agonist, which can inhibit sympathetic activity by activating the receptors in central nervous system (12-14). It has been extensively studies in dental surgery. K induces a state of dissociative sedation, which provides strong analgesia, sedation, immobilization, and amnesia while retaining spontaneous respiration and cardiopulmonary stability (3). Our study showed that sedation onset time, recovery time, pulse rate, and systolic blood pressure were significantly different between the D and K groups. The intra- and postoperative pain scores were significantly lower in the K group than in the D groups. Patients in the D3 group

Table 1 Patient characteristics of the four groups

Characteristics	D1 (N=37)	D2 (N=41)	D3 (N=34)	K (N=38)	P value
Age (y)	8.14±1.83	8.66±1.71	8.95±1.62	8.02±1.83	0.0833
Weight (kg)	17.56±4.41	18.05±5.18	17.88±4.65	17.54±4.93	0.9343
Gender					0.319
Male	19	20	17	20	
Female	18	21	17	18	
Behavior level					
4	25	28	22	25	0.985
5	12	13	12	13	

D, dexmedetomidine; K, esketamine.

Table 2 Primary outcomes among the four groups

Variables	D1 (N=37)	D2 (N=41)	D3 (N=34)	K (N=38)	P value
SpO_2 (%)	99.12±0.45	99.07±0.51	98.89±0.32	99.00±0.42	0.1373
PR (min)	103.44±6.15	104.65±5.44	104.88±5.63	112.43±5.31	<0.001
RR (min)	22.07±0.67	22.18±0.61	21.93±0.63	22.12±0.60	0.3726
DBP (mmHg)	74.15±1.45	74.21±1.71	73.88±1.21	74.12±1.41	0.7907
SBP (mmHg)	110.51±4.43	113.52±4.95	112.42±5.13	117.45±5.44	<0.001
Onset time	19.45±2.41	19.32±2.36	17.56±2.14	12.45±2.27	<0.001
Recovery time (min)	58.45±4.66	61.45±5.71	63.14±4.58	60.25±4.21	<0.001
Intra-operative analgesia (score)	3.75±0.41	3.51±0.58	3.38±0.65	3.41±0.54	0.0197
Post-operative analgesia (score)	1.39±0.42	1.27±0.74	1.18±0.50	1.01±0.61	0.0420

SpO_2, O_2 saturation; PR, pulse rate; RR, respiratory rate; DBP, diastolic blood pressure; SBP, systolic blood pressure; D, dexmedetomidine; K, esketamine.

Table 3 Measured outcomes among the four groups

Variables	D1 (N=37), n (%)	D2 (N=41), n (%)	D3 (N=34), n (%)	K (N=38), n (%)	P value
Sedation level					0.423
Adequate	24 (64.86)	32 (78.05)	27 (79.41)	26 (68.42)	
Inadequate	13 (35.14)	9 (21.95)	7 (20.59)	12 (31.58)	
Behavior scores					0.170
Satisfactory	23 (62.16)	31 (75.61)	28 (82.35)	24 (63.16)	
Unsatisfactory	14 (37.84)	10 (24.39)	6 (17.65)	14 (36.84)	
Overall success					0.124
Successful	21 (56.76)	31 (75.61)	25 (73.53)	21 (55.26)	
Unsuccessful	16 (43.24)	10 (24.39)	9 (26.47)	17 (44.74)	

D, dexmedetomidine; K, esketamine.

achieved an "adequate" depth of sedation and "satisfactory" completion of treatment in the highest number of sessions, and patients in the D2 group had a higher overall success rate than those in the other groups. However, these differences were not significant.

For uncooperative pediatric patients undergoing dental surgery, a good route of drug administration is crucial, and different routes have their advantages and disadvantages. Some require additional premedication drugs before the nasal mask is fitted to deliver the gases by inhalation. Intravenous (IV) and intramuscular (IM) routes can increase anxiety because of the syringe (15), whereas intranasal delivery can result in burning and sneezing (16), and the rectal route is invasive and can lead to awkwardness (17). In this study, we used the intranasal route because it has the advantages of being simple, non-invasive, universally acceptable, and familiar to this pediatric age group (7).

Time of sedation onset and recovery

In the present study, we found that the time of sedation onset and recovery was significantly different among the D and K groups. Patients in the K group had a significantly faster onset and recovery time than those in the D groups. Our results are consistent with those from a triple-blind, randomized study by von Elm *et al.* (8), who used oral D with a range of 3–5 μg/kg in 112 children. They found that the mean onset time in the three D groups was significantly longer than in the ketamine group (P<0.001) (8). Similarly, in another randomized, triple-blind comparative study (1), the authors found that the mean sedation onset time after intranasal D1 (1 μg/kg) and D2 (1.5 μg/kg) was longer than that of ketamine (18.24±2.00, 18.10±2.00, and 11.57±2.18, respectively). Other studies also reported similar results, but the onset time of D among these studies varied. This variation might be attributed to the differences in study design, sample size, child population, drug administration route, and drug dosage. An interesting finding of the present study was that onset time in the D1 and D2 groups was longer than that in the D3 group. This might be because a low D dosage has a lag time before reaching the required peak plasma concentration level (9).

Recovery time in our study was fastest in the D1 group, followed by the K group. The recovery time in the D2 and D3 groups was a little longer than in the D1 group. Our results were consistent with those of the previous studies, which reported a ketamine recovery time of less than 2 hours when administered at a dosage of 8–10 mg/kg (1,18-20).

Analgesic effect

In this study, we found that children in the D3 and K groups achieved better intra- and postoperative pain scores than those in the D1 and D2 groups. Our results were similar to the findings of previous studies (1). These studies suggested that oral ketamine produced a significant analgesic effect during the intra- and postoperative periods, and the fear of pain or needles while administering local anesthesia was significantly reduced. In the present study, D3 and K produced a better intra-operative analgesic effect than D1, and K produced a better postoperative analgesic effect than D1. Previous studies have reported that D results in a favorable analgesic effect in healthy volunteers when administered by IV injection (21). In addition, another study suggested that intranasal D produced good postoperative pain relief in patients who underwent unilateral third molar surgery with local anesthesia (4). Thus, intranasal D can be used as an analog-sedative in patients undergoing dental surgery.

In this study, the D dosage ranged from 1–2 μg/kg, and the sedative effect on pain scores improved with the increase in dosage. Our results align with findings from previous studies, which used an intranasal D dose ranging from 0.5–2 μg/kg (1). Rooney *et al.* (1) compared the effect of two different doses of intranasal D in children during dental procedures. They found that the intra-and postoperative analgesia pain scores were better in the D2 group (1.5 μg/kg) than in the D1 group (1.0 μg/kg) (1). However, the difference between the two groups was not significant. von Elm *et al.* (8) reported the analgesic effect of three dosages of oral D among uncooperative pediatric dental patients. Their results demonstrated that the intra- and postoperative analgesic effect of the three dosages of D and ketamine was statistically different (P≤0.001), and the pain score was significantly lower in the D3 (5 μg/kg) and ketamine (8 mg/kg) groups than in the D1 (3 μg/kg) and D2 (4 μg/kg) groups (22). The mean analgesia score was lowest in the ketamine group, followed by the D3, D2, and D1 groups. However, the analgesia scores between groups D1 and D2 and between D3 and the ketamine group were not significant (P>0.05) (23).

The vital signs

In this study, the SpO_2 and pulse rate were continuously monitored, and respiratory rate, SBP, and DBP were recorded at 5-minute intervals. Our results showed that

the average SpO_2 levels were more than 98% and remained stable in all four groups. Our results were consistent with the findings of previous studies (24). However, one study reported that the SpO_2 level was less than 93% (25). Cortiñas *et al.* (5) compared the efficacy of D during electroencephalographic analysis in 18 children where oral D (range, 2.9–4.4 μg/kg) was administered before the placement of an IV injection. The SpO_2 level in these children was 81.8% (range, 72.6–92.1%); however, no clinical intervention was required (5). Kamel *et al.* (22) found that pulse rate and SBP decreased with an increased dosage of D. However, we did not observe this phenomenon in our study. Other studies (26) have also reported similar effects; however, they all stated that no additional interventions were required for these patients.

Satisfaction

In this study, more than 65% of patients achieved an adequate sedation level, and more than 62% of patients expressed a high level of satisfaction. The highest rate of "adequate" depth of sedation or "satisfactory" completion of treatment was observed in the D3 patient group, followed by those in the D2, K, and D1 groups. However, there was no significant difference among the four groups. Our results are consistent with previous studies (1), which found that a higher dosage of D produced a better sedation depth and a higher satisfaction rate.

In conclusion, both D and K are efficacious for moderate sedation in uncooperative pediatric dental patients. Overall, D with three different doses (1, 1.5, and 2.0 μg/kg) showed similar effects in several of the assessed parameters. However, D3 seemed to produce the best outcomes and was comparable to K in terms of sedation level, analgesia, treatment completion, and overall success rate. In addition, there appears to be a correlation between the overall success rate and D dose. Considering the limited sample size, future larger-scale studies are required to explore the appropriate and safe dose of D for moderate sedation of uncooperative pediatric dental patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tp-21-435

Data Sharing Statement: Available at https://dx.doi.org/10.21037/tp-21-435

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tp-21-435). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Ethical Committee of the Maternal and Child Health Hospital of Hubei Province in China (No. 2021IECLW027). Written informed consent was obtained from all the patients' guardians for publication of this study and any accompanying images. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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