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CLINICAL RESEARCH

Propofol-ketamine versus dexmedetomidine-ketamine for sedation during upper gastrointestinal endoscopy in pediatric patients: a randomized clinical trial

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KEYWORDS
Dexmedetomidine;
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Abstract
Background and objectives: Day-case pediatric sedation is challenging. Dexmedetomidine is a sedative analgesic that does not induce respiratory depression. We compared dexmedetomidine to propofol when it was added to ketamine for sedation during pediatric endoscopy, regarding recovery time and hemodynamic changes.
Methods: We enrolled 120 patients (2—7 years in age) and randomly assigned them into two groups. Each patient received intravenous (IV) ketamine at a dose of 1 $mg.kg^{-1}$ in addition to either propofol (1 $mg.kg^{-1}$) or dexmedetomidine (0.5 $\mu g.kg^{-1}$). The recovery time was compared. Hemodynamics, oxygen saturation, need for additional doses, postoperative complications and endoscopist satisfaction were monitored.
Results: There was no significant difference in hemodynamics between the groups. The Propofol-Ketamine (P-K) group showed significantly shorter recovery times than the Dexmedetomidine-Ketamine (D-K) group (21.25 and 29.75 minutes, respectively, $p < 0.001$). The P-K group showed more oxygen desaturation. Eleven and 6 patients experienced $SpO_2 <$ 92% in groups P-K and D-K, respectively. A significant difference was noted regarding the need for additional doses; 10% of patients in the D-K group needed one extra dose, and 5% needed two extra doses, compared to 25% and 20% in the P-K group, respectively ($p = 0.001$). The P-K group showed less post-procedure nausea and vomiting. No statistically significant difference between both groups regarding endoscopist satisfaction.

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Conclusions: The P-K combination was associated with a shorter recovery time in pediatric upper gastrointestinal endoscopy, while the D-K combination showed less need for additional doses.
Registration number: Clinical trials.gov (NCT02863861).
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PALAVRAS-CHAVE
Dexmedetomidina;
Propofol;
Sedação;
Endoscopia;
Pediatria

Propofol-cetamina *versus* dexmedetomidina-cetamina para sedação durante endoscopia digestiva alta em pacientes pediátricos: estudo clínico randomizado

Resumo
Justificativa e objetivos: A sedação ambulatorial pediátrica é um desafio. A dexmedetomidina é um analgésico sedativo que não induz à depressão respiratória. Comparamos a dexmedetomidina ao propofol quando associados à cetamina para sedação durante endoscopia pediátrica, quanto ao tempo de recuperação e às alterações hemodinâmicas.
Métodos: Foram recrutados 120 pacientes (2—7 anos de idade) que foram aleatoriamente alocados em dois grupos. Cada paciente recebeu cetamina intravenosa (IV) na dose de 1 mg.kg^{-1}, além de propofol (1 mg.kg^{-1}) ou dexmedetomidina (0,5 μg.kg^{-1}). Comparamos o tempo de recuperação. A hemodinâmica, saturação de oxigênio, necessidade de doses adicionais, complicações pós-operatórias e satisfação do endoscopista foram monitoradas.
Resultados: Não houve diferença significante entre os grupos no que diz respeito à hemodinâmica. O grupo Propofol-Cetamina (P-C) apresentou tempos de recuperação significantemente mais curtos do que o grupo Dexmedetomidina-Cetamina (D-C) (21,25 e 29,75 minutos, respectivamente, $p <$ 0,001). Observou-se frequência maior de dessaturação de oxigênio no grupo P-C. Onze e 6 pacientes apresentaram SpO_2 < 92% nos grupos P-C e D-C, respectivamente. Uma diferença significante foi observada em relação à necessidade de doses adicionais; 10% dos pacientes no grupo D-C precisaram de uma dose extra e 5% precisaram de duas doses extras, em comparação com 25% e 20% no grupo P-C, respectivamente (p = 0,001). O grupo P-C apresentou menos náuseas e vômitos após o procedimento. Não houve diferença estatisticamente significante entre os dois grupos em relação à satisfação do endoscopista.
Conclusões: A combinação P-C foi associada a tempo mais curto de recuperação na endoscopia digestiva alta pediátrica, enquanto a combinação D-C mostrou menor necessidade de doses adicionais.
Número de registro: Clinical trials.gov (NCT02863861).
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Introduction

Sedation of children for day-case procedures is often challenging, as these procedures require patient immobility for variable durations. A perfect sedative regimen must provide rapid and reliable onset of sedation, maintain patent airway, ensure adequate spontaneous ventilation, maintain cardiovascular stability, and promote a smooth and predictable emergence.[1]

Combinations of propofol, benzodiazepines and opioids are frequently used for sedation. Opioids are usually added in painful procedures because benzodiazepines and propofol do not have any analgesic effect. However, opioid administration can lead to excessive sedation and some side effects.[2]

Propofol (non-opioid, non-barbiturate, short-acting anesthetic agent) is popular in ambulatory anesthesia because of its rapid induction and recovery times. However, its side effects, particularly cardiopulmonary depression, apnea and hypoventilation, have attracted attention to the search for alternatives.[3]

Ketamine can be an alternative to opioids because it provides good analgesia even at low doses, sparing the respiratory and cardiovascular adverse effects of opioids.[2] Unfortunately, its side effects (increased salivation, nausea, nightmares, delirium, and excitation) do not make it favorable as a single agent.

The past few years have carried increased interest in dexmedetomidine (a selective alpha-2 receptor agonist) in both anesthesia and intensive care. This alpha-2 receptor agonist has been used as the drug of choice for sedation in pediatric patients because of its lack of respiratory depressive effects, adequate sedative and analgesic action, and favorable antiarrhythmic effects.[1]

The primary outcome of this study was to compare the recovery time when using propofol-ketamine combination

compared to dexmedetomidine-ketamine combination in sedating pediatric patients undergoing upper gastrointestinal endoscopy.

Secondary outcomes included hemodynamic complications, oxygen saturation, postoperative complications, and endoscopist satisfaction.

Methods

After acquiring local medical ethics committee approval (FMASU R12/2016) and informed written consent from the parent or guardian, we enrolled 120 patients in this prospective, randomized study. The patients were of ASA (American Society of Anesthesiologists) physical status I—II, aged 2—7 years and scheduled for elective diagnostic upper gastrointestinal endoscopy. The procedure was performed as a day-case procedure in the pediatric endoscopy unit in a pediatric hospital. The study was carried out in the period between September 2016 and December 2016 and registered with Clinical trials.gov (ref: NCT02863861).

Exclusion criteria included significant cardiovascular disease, hypertension, glaucoma, increased intracranial tension, psychosis, neurological disease, vomiting, known allergy to any of the study drugs, and parent or guardian refusal.

All included patients were instructed to fast for at least 8 hours (clear fluid was allowed up to 2 hours before the procedure with a maximum volume of 50 mL), had a secured venous access, and received 10 $mL.kg^{-1}.h^{-1}$ of lactated Ringer's solution. Patients were premedicated with intravenous metoclopramide (0.1 $mg.Kg^{-1}$), and 2—3 puffs of lidocaine spray (10%, 10 mg/puff) were applied to the posterior pharynx to diminish the gag reflex during endoscopy.

After applying standard monitors (non-invasive blood pressure, 5-lead ECG and pulse oximetry), patients were randomly and evenly assigned to one of two groups (60 patients each) using a computer-generated list: group P-K (propofol-ketamine group) and group D-K (dexmedetomidine-ketamine group).

Randomization was performed using a computerized random number generator (Random Allocation Software; Version 1.0, May 2004). The allocation sequence was generated by a statistician who did not participate in the study except for the randomization and statistical analysis; as the patients' OR list was sent to him, he then performed the computer-generated random allocation, which was concealed in sequentially numbered, opaque, sealed envelopes, each with a patient's name on it, to be opened just before the procedure.

Group P-K: Patients in this group received intravenous ketamine at a dose of 1 $mg.kg^{-1}$ in addition to intravenous propofol (1 $mg.kg^{-1}$) for induction with added doses of intravenous propofol (1 $mg.kg^{-1}$) when needed.

Group D-K: Patients in this group received intravenous ketamine at a dose of 1 $mg.kg^{-1}$ in addition to intravenous dexmedetomidine (0.5 $\mu g.kg^{-1}$) for induction with additional doses of intravenous dexmedetomidine (0.5 $\mu g.kg^{-1}$) when required.

All patients were allowed to breath spontaneously 3 $L.min^{-1}$ oxygen supplementations through a nasal catheter. The same endoscopist performed all procedures with the patients in the left lateral position.

The sedation protocol was planned to maintain a Ramsay sedation score (RSS) of $\geq$ 5 (1, Anxious and agitated; 2, Cooperative, tranquil, oriented; 3, Responds only to verbal commands; 4, Asleep with brisk response to light stimulation; 5, Asleep without response to light stimulation; 6, Non-responsive).[4] The RSS was assessed every 5 minutes until the end of the procedure. If the sedation score was not achieved before the start of endoscopy or fell below 5 at any moment during the procedure, additional bolus of the study drug was given. The need for additional doses was recorded as well as the total dose given.

Hemodynamic variables including Heart Rate (HR), Mean Arterial Pressure (MAP), Respiratory Rate (RR) and Oxygen Saturation (SpO_2) were recorded: at the baseline (before the administration of study drugs), after the induction of sedation, and every 5 minutes until the end of the procedure.

The incidence of significant hypotension (defined as: systolic arterial pressure $\leq$ 70 mmHg plus twice the age in years or MAP < 43 mmHg and associated with clinical signs of altered peripheral perfusion; cold, pale, clammy, and mottled skin, associated with an increase in capillary refill time > 2 seconds);[5] and significant bradycardia (defined as: HR < 60 $beats.min^{-1}$) or respiratory depression (oxygen saturation less than 92%) was recorded.

In cases of significant hypotension, the patient was treated initially with an intravenous (IV) fluid bolus of 10 $mL.kg^{-1}$ normal saline, and if the condition persisted, the patient was given 0.1—0.3 $mg.kg^{-1}$ IV ephedrine, which was repeated every 3—5 minutes until the blood pressure was normalized. Significant bradycardia was treated, when needed, with IV atropine 0.02 $mg.kg^{-1}$.

If oxygen saturation dropped below 92%, the rate of nasal oxygen was increased to a rate of 5—6 $L.min^{-1}$, and if desaturation persisted, the patient was ventilated manually with 100% oxygen via a pediatric anesthesia circuit (Mapleson F [Jackson-Rees modification of Ayre's T-piece]).

Criteria for abortion of the endoscopy was included; persistent significant hypotension/ bradycardia/desaturation not responding to all emergency measures mentioned and hence patient would need resuscitation, the endoscopist's evaluation to the procedure as being impossible despite additional top up doses as planned. This would have necessitated aborting the procedure and/or changing the anesthesia plan. In such case the patient was excluded from the study and replaced by another.

After completion of the procedure, patients were transferred to the Post-Anesthesia Care Unit (PACU), and the modified Aldrete score was assessed every 5 minutes. Patients were discharged from the PACU when they reached a modified Aldrete score $\geq$ 9 (Table 1).[6] Recovery time, defined as the time from the end of the procedure until achieving a modified Aldrete score $\geq$ 9, was recorded. The incidence of complications such as shivering, nausea, vomiting, apnea, and desaturation was recorded.

Post-procedure agitation was recorded using a 4-point scale (1: calm, 2: not calm, but easily calmed, 3: moderately agitated or restless, 4: combative, excited or disoriented).[7] Grades 1 and 2 were considered favorable, while grade 3 and 4 indicated agitation.

Table 1 Modified Aldrete score.[6]

Activity	
Able to move 4 extremities voluntarily or on command	2
Able to move 2 extremities voluntarily or on command	1
Unable to move extremities voluntarily or on command	0
Respiration	
Able to breathe deeply and cough freely	2
Dyspnea or limited breathing	1
Apneic	0
Circulation	
Blood pressure ± 20% of the pre-anesthetic level	2
Blood pressure ± 20% to 49% of the pre-anesthetic level	1
Blood pressure ± 50% of the pre-anesthetic level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	0
O_2 saturation	
Able to maintain O_2 saturation > 92% on room air	2
Needs O_2 inhalation to maintain O_2 saturation > 90%	1
O_2 saturation < 90% even with O_2 supplementation	0
Total score	10

Endoscopist satisfaction was obtained at the end of the procedure by his evaluation of the easiness of the procedure using a three-point scale (1: easy, 2: adequate, and 3: impossible).[8]

Data were collected by an anesthetist (intraoperatively) and recovery nurse (in the PACU) not participating in the study.

Statistical analysis

The data collected were analyzed with statistical program SPSS (version 22.0 Chicago, Illinois, USA). Numerical data are presented as the mean (standard deviation) or median (range) while categorical data are presented as the number of cases (percentage). Between-group comparisons of numerical variables were performed by the independent sample *t*-test, or Mann-Whitney test as appropriate, while those of categorical variables were performed by the Chi-square test. For all tests, a *p* (probability) value < 0.05 was considered statistically significant.

Calculation of the sample size was determined based on the recovery time as the primary outcome of this study, with an α error of 0.05, and power of the study of 0.8 and β of 0.2 with a time difference of 10 minutes.[9–11]

Results

Of the 132 patients assessed for eligibility, we enrolled 120 pediatric patients (54 males and 66 females) in this randomized prospective study. The participants' ages ranged from two to seven years; in addition, they exhibited ASA physical status I—II, and were scheduled for elective diagnostic upper gastrointestinal endoscopy (Fig. 1). No significant difference was found between the two groups regarding sex, ASA physical status, age, weight, and time of procedure (Table 2).

Regarding hemodynamic and RR changes, there was no significant difference in the HR, MAP, and RR between the two groups during the procedure. Although the HR and MAP tended to decrease in both groups after induction, this finding proved to be statistically insignificant (Fig. 2).

Although no significant difference was noticed between the two groups regarding oxygen saturation at the baseline, after induction, after 5 minutes, or at the end of the procedure, patients in the P-K group experienced lower mean oxygen saturation than the D-K group, however, this was found to be statistically non-significant. Eleven patients (18.33%) in the P-K group experienced desaturation ($SpO_2 \leq$ 92%) compared to 6 patients (10%) in the D-K group (p = 0.418). Of the 11 patients who experienced desaturation, 6 in the P-K group responded to increased oxygen flow, while 5 required manual ventilation. In the D-K group, 3 of 6 patients responded to increased flow through the nasal cannula, and the other 3 required manual ventilation with a pediatric anesthesia circuit. Manual ventilation necessitated discontinuation of the procedure and removal of the endoscope (in both groups) until the patient was stabilized.

During the procedure time (lasting 5.6 ± 1.9 min in the P-K group and 5.7 ± 2.2 min in the D-K group), a statistically significant difference was noted regarding the need for additional doses of study drugs to achieve an RSS of ≥ 5 (p = 0.001); 15 (25%) patients in the P-K group needed one extra dose, and 12 (20%) patients needed two extra doses. In the D-K group, 6 (10%) patients needed one extra dose, and 3 (5%) patients needed two extra doses. No patient in any group required more than two extra doses.

The total dose of propofol used in group P-K was 1,788 mg (average, 1.98 $mg.kg^{-1}$ per patient), whereas the total dose of dexmedetomidine used in group D-K was 531 μg (average, 0.59 $\mu g.kg^{-1}$ per patient), with more additional doses needed in the P-K group.

The recovery time was significantly shorter in the P-K group than in the D-K group (p < 0.001). The average recovery time was 21.25 minutes (range of 15—40 min) in the P-K group and 29.75 minutes (range of 20—45 min) in the D-K group.

Regarding post-procedure complications, 2 patients in the P-K group experienced nausea and vomiting compared to 4 patients in the D-K group, which was not statistically significant (p = 0.679). None of the patients in either group showed agitation (score ranging between 1 and 2 in both groups).

No statistically significant difference was found between the groups in terms of endoscopist satisfaction (p = 0.232); the procedure was easily performed in 39 (65%) and 45 (75%) patients in groups P-K and D-K, respectively, and adequately performed in the remaining percentage. Fortunately, no case was impossible to perform.

Discussion

In this study, we compared P-K combination with a D-K combination in sedating pediatric patients during upper gastrointestinal endoscopy. Although the current practice is to give a loading dose of dexmedetomidine slowly over 10 minutes, to avoid its hemodynamic adverse effects, it is sometimes not feasible, especially in high turnover

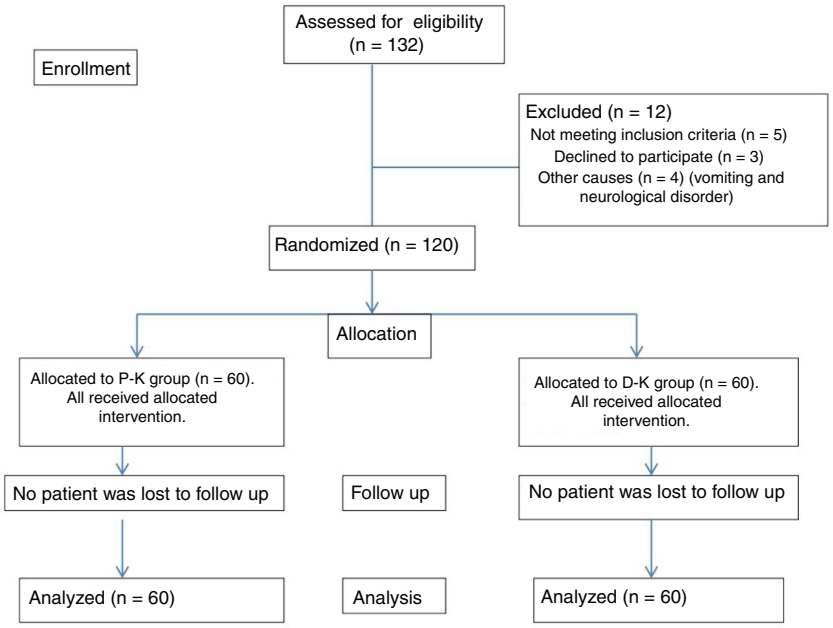

Figure 1 Consort flow diagram.

Table 2 Patient characteristics and procedural data.

	Group D-K (n = 60)	Group P-K (n = 60)	*p*-value
Sex, Male/Female, n (%)	30 (50%) / 30 (50%)	24 (40%) / 36 (60%)	0.505
ASA, I/II, n (%)	48 (80%) / 12 (20%)	42 (70%) / 18 (30%)	0.465
Age, years [mean ± SD (min–max)]	3.5 ± 1.6 (2–7)	4.25 ± 1.7 (2–7)	0.171
Weight, kg [mean ± SD (min–max)]	15 ± 4 (11–26)	17.3 ± 5.6 (10–32)	0.164
Time of procedure, minutes [mean ± SD (min–max)]	5.7 ± 2.2 (3–12)	5.6 ± 1.9 (3–10)	0.879

n, number; ASA, American Society of Anesthesiologists; SD, Standard Deviation; min, minimum; max, maximum; kg, kilogram.

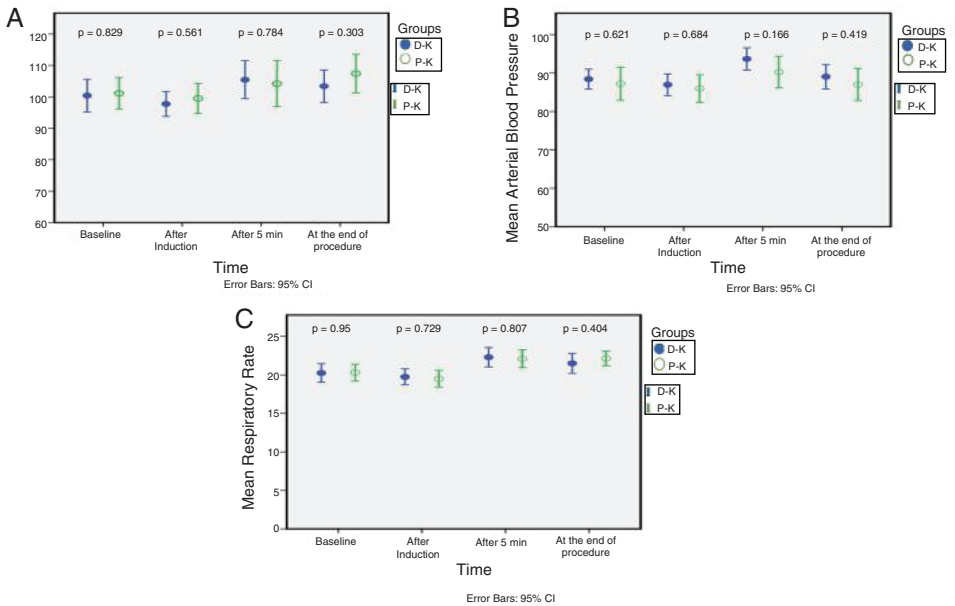

Figure 2 Hemodynamic and RR changes over time during the procedure in the 2 study groups. A, mean HR changes; B, MAP changes; C, mean RR changes.

pediatric anesthesia. A rapid bolus of dexmedetomidine (0.25−0.5 $\mu g.kg^{-1}$) was shown to be clinically tolerated without hemodynamic compromise.[12]

We added ketamine to dexmedetomidine so that the sympathetic activation associated with ketamine could minimize the biphasic hemodynamic changes associated with dexmedetomidine administration.[10] Propofol was combined with ketamine to antagonize its nauseating effect, in addition to the beneficial synergistic sedative effects of combining the two drugs.

The primary outcome of this study was to compare the recovery time between the two groups, which may affect the rapid turnover in pediatric day cases. We found a statistically significant difference in the recovery time, being shorter in the P-K group than in the D-K group by about 8.5 minutes per case, which accounted for about 85 minutes in average of 10 cases/day. This affected the number of cases performed per day, and also affected the number of caregivers in the PACU.

This longer recovery time reported with dexmedetomidine compared to propofol may be attributed to the difference in the pharmacokinetic profile between the two drugs. The elimination half-life of dexmedetomidine in healthy volunteers is about 2.1−3.1 hours, however, in propofol it is about 40 minutes, whether after a bolus dose or short-term infusion for less than 8 hours.

Canpolat and colleagues[10] compared Ketamine associated to Propofol (KP) or Dexmedetomidine (KD) in 60 pediatric patients undergoing burn dressing. A longer recovery time was observed in the KD group (36.6 ± 10.6 min) than in the KP group (27.7 ± 9.7 min). Although dexmedetomidine was found to be associated with longer recovery times,[8,11,13,14] few studies showed contradictory results.[15,16] Krouk and co-workers compared dexmedetomidine-ketamine to midazolam-ketamine in pediatric patients undergoing extracorporeal shock wave lithotripsy. They found shorter recovery time and more hemodynamic stability in the dexmedetomidine group.[16]

In our study, we found the incidence of oxygen desaturation was higher in the P-K group than in the D-K group. Although statistically non-significant, this may give dexmedetomidine some advantage regarding respiratory safety and airway protection, especially in patients susceptible to respiratory adverse events. The P-K group, on the other hand, showed a lower incidence of post-procedure nausea and vomiting.

The incidence of respiratory adverse events makes up a considerable percentage (5.5%) of the complications of sedation in children.[17] This percentage increases to 65.7% of reported complications associated with pediatric Esophago-Gastro-Duodenoscopy (EGD). Young age, higher ASA, female sex, and IV sedation have been identified as the main risk factors.[18]

Some studies have reported that dexmedetomidine does not affect RR, SpO_2, or End-Tidal Carbon Dioxide ($ETCO_2$).[19] However, respiratory complications have been reported with large and rapid initial loading doses.[20] Propofol, on the other hand, may decrease ventilation, inhibit pharyngeal and laryngeal reflexes, and cause temporary apnea.[21] However, these are not constant outcomes.[22]

Mogahed and Salama compared Ketamine-Dexmedetomidine (KD) to ketamine-propofol (KP) in sedating children undergoing upper gastrointestinal endoscopy.[23] They found no significant difference between both groups in SpO_2. The older age group in their study (2−12 years) compared to ours (2−7 years), with respiratory adverse events being more frequent in younger age group. Also, in their study, they used higher doses of ketamine in both groups (34.6 ± 2.9 mg in group KD and 29.2 ± 1.9 mg in group KP), being added in the top-up doses, unlike our study as we used ketamine in induction dose only. The higher dose of ketamine may account for the lower incidence of respiratory depression in their study.

Although we found no statistically significant difference between the groups in term of endoscopist satisfaction, the procedure was more easily performed in the D-K group with fewer additional doses needed. Differing from our results, endoscopist satisfaction was recorded to be significantly higher in patients receiving dexmedetomidine due to the decreased incidence of movement and gag reflex during non-invasive procedures.[24]

When dexmedetomidine was compared to propofol in the sedation of children undergoing magnetic resonance imaging,[25] both drugs prevented undesired movement in most of the children. Propofol provided more rapid rates of induction, recovery, and discharge but dexmedetomidine better preserved the MAP and RR and did not cause any desaturation.

There are conflicting results regarding dexmedetomidine hemodynamic effects.[26,27] Hypotension and bradycardia have been reported, particularly with large bolus doses, in patients suffering from cardiac problems and in patients given an initial dose in less than 10 minutes.[20] Hypotension and bradycardia have also been reported when propofol infusion is used as a single agent to achieve satisfactory sedation.[17,22]

In our study, although arterial blood pressure and HR decreased after dexmedetomidine and propofol injection, the decrease was found to be statistically insignificant. These decreases could have been minimized because of the addition of ketamine, the use of different dose regimens, and differences in the nature of the procedures.

This study has several limitations including: absence of $ETCO_2$ recordings, which we did not include because of its arguable accuracy with nasal cannula,[28] not measuring the total intervention time as the favorable faster induction and recovery characteristics of propofol may be compromised by the higher incidence of respiratory adverse events that may necessitate removal of the endoscope for manual ventilation.

Additionally, measuring the total financial cost in both groups might have added an advantage to one of the groups. We (the investigators) were not blinded to the drug used (propofol and dexmedetomidine having different colors), which may have created some bias. To mend this, all the people who collected the data were blinded to the study, so was the endoscopist.

In conclusion, the P-K combination was associated with a significantly shorter recovery time in pediatric patients undergoing upper gastrointestinal endoscopy and is thus suitable for short diagnostic procedures. The D-K combination, on the other hand, showed less need for additional doses, which makes it a better choice for longer procedures.

Conflicts of interest

The authors declare no conflicts of interest.

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