

A Comparison of Ketamine-Dexmedetomidine versus Ketamine-Propofol for Sedation in Children during Upper Gastrointestinal Endoscopy

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Received date: November 05, 2017; Accepted date: November 27, 2017; Published date: November 30, 2017

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Abstract

Background: Upper gastrointestinal endoscopy in pediatric patients have increased and become more frequent. Selection of a sedative with hemodynamic stability, rapid onset, short action and few side effects is essential.

Material and methods: 60 ASA/II patients between the age of 2-12 yrs of both sexes undergoing upper gastrointestinal endoscopy randomly allocated into two groups, 30 patients each, all patients received ketamine 1 mg/kg intravenous, then group KD received dexmedetomidine 1 µg/kg bolus dose slowly IV and patients in Group KP received propofol 1 mg/kg as initial doses then top-up doses of 2-4 ml of the prepared solutions were given till RSS of ≥ 5 . Hemodynamic parameters, total ketamine dose, time to RSS ≥ 5 and PADSS of 9-10, side effects and Parents' and Endoscopists' satisfaction were recorded.

Results: HR was significantly lower in group KD at T1, T2 and T3, no significant difference as regard MAP, RR, SpO₂ and time to achieve RSS and PADSS ($p > 0.05$), significantly higher total ketamine dose in group KD than group KP ($P = 0.001$), Parents' and Endoscopists' satisfaction was significantly higher in group KD than KP ($p < 0.05$).

Conclusion: Ketamine-dexmedetomidine for sedation in children during upper gastrointestinal endoscopy is an effective, reliable and safe alternative to ketamine-propofol without hemodynamic or respiratory drawbacks with comparable onset and recovery time.

Keywords: Ketamine; Dexmedetomidine; Propofol; Sedation; Children; Endoscopy

Introduction

Many challenges are encountered in the patients scheduled for upper gastrointestinal endoscopy as dehydration, electrolyte disorders, shock, sepsis, respiratory disorders and renal or hepatic dysfunctions. Hence, careful examination and full investigations are important [1]. Guidelines for pharmacological intervention were issued by the American Academy of Pediatric Committee on drugs to classify it into 3 categories: Conscious sedation, deep sedation and general anesthesia [2]. Because it is difficult to adjust the level of sedation especially in designated areas outside the operating rooms [3] and deep sedation is required in the pediatric age group to allow successful procedures [4], sedatives should be prescribed cautiously and as per body weight and titrated according to their therapeutic effects [5,6]. Children usually required high doses of these medications [7]. Many sedatives and anesthetics are used for pediatric sedation, however, the most frequently used are ketamine [8,9], midazolam, propofol [10,11] and dexmedetomidine [12,13].

Ketamine, a phencyclidine derivative, is N-methyl-d-aspartate receptors antagonist and also acts at opioid and sigma receptors. It produces dissociative sedation with rapid onset and short duration [14]. However, side effects such as laryngospasm, nausea [15,16], delirium, nightmares, and excitation [17] make its combination with other drugs such as propofol safe and reliable [18]. Propofol combination with other sedatives produces a synergistic action and

allows the use of fewer doses and fewer side effects [19-21]. Emergence reactions and vomiting caused by ketamine are opposed by the hypnotic and antiemetic properties of propofol while ketamine provides analgesia and combat the hypotension during propofol sedation [22]. Dexmedetomidine, an ultra-selective α_2 agonist, has anxiolytic, analgesic, amnesic and sedative properties with no risk of respiratory depression [23]. It can effectively reduce the hemodynamic and psychomimetic actions of ketamine [24]. Dexmedetomidine has a sympatholytic effect which causes reduction of heart rate and blood pressure [25] that can be countered by the sympathomimetic effect of ketamine [26]. The present study was designed to compare the effectiveness and safety of ketamine-dexmedetomidine versus ketamine-propofol combinations for procedural sedation in pediatric patients undergoing upper gastrointestinal endoscopy.

Materials and Methods

This randomized prospective controlled study was carried out after approval of hospital ethics committee and obtaining an informed written consent from parents or patients guardians on 60 ASA I or II patients of both sexes between the age of 2 and 12 yrs scheduled for diagnostic upper gastrointestinal endoscopy procedures.

Patients with upper respiratory tract infections, psychosis, increased intracranial tension, neurologic diseases, an abnormal anatomy of the jaw and face, glaucoma, hypertension, porphyria or history of hypersensitivity to any of the study drugs were excluded from the study. Also, patients whose parents refused to sign the consent to participate in the study were excluded. With the help of pediatric

endoscopist and endoscopy nurse, the procedure was performed in the endoscopy unit then after the finish, follow up was done in the recovery room by another qualified nurse.

During the pre-procedure evaluation visit, 6 h fasting was recommended for all the patients. A 22 or 20 G intravenous cannula was inserted after local anesthetic application in the nondominant hand and a triple way connection was connected for simultaneous administration of the study medications and IV fluids (NaCl 0.45% at a rate of 4 ml/kg/h). All patients were premeditated by IV midazolam 0.05 mg/kg, IV glycopyrrolate 0.01 mg/kg and topical pharyngeal anesthesia 10 min before shifting the patients to the endoscopy unit. All patients were continuously monitored for mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), and arterial O₂ saturation (SpO₂) during the procedure and recovery and baseline measurements were recorded before injection of the medication (T0). Patients were allocated randomly by computer-generated number assignment in sealed envelopes into one of two groups, group KD (n=30) received ketamine-dexmedetomidine and group KP (n=30) received ketamine-propofol. All patients received ketamine 1 mg/kg intravenous.

Patients in group KD received dexmedetomidine 1 µg/kg bolus dose slowly IV over 10 min and patients in Group KP received propofol 1 mg/kg as initial doses. Two 20 ml syringes were prepared; One for a mixture of dexmedetomidine-ketamine at concentration of 0.05 µg/ml dexmedetomidine and 1 mg/ml ketamine and the other syringe prepared for the mixture of propofol-ketamine with a concentration of 1 mg/ml propofol and 1 mg/ml ketamine (the mixture was 1:1 of propofol: ketamine). Sedation level was assessed by checking patients' response to verbal and tactile stimulation after two min of the initial dose using Ramsy Sedation Scale (RSS) ranging from 1-6; 1=anxious, agitated or restless, 2=co-operative, oriented, and tranquil, 3=responds to commands only, 4=brisk response to light glabellar tap or loud auditory stimulus, 5=sluggish response to light glabellar tap or loud auditory stimulus and 6=no response. Our target is RSS ≥ 5 and if the target was not achieved, top-up doses of 2-4 ml of the prepared solutions were given till achievement of RSS ≥ 5 and time to RSS of ≥ 5 was recorded.

All patients received oxygen supplementation via nasal cannula (2L/min) then turned to left lateral position and the endoscopist was asked to initiate the procedure. Patients then reassessed for sedation level at two min interval till the end of the procedure and top-up doses were administered if RSS<5. By the end, patients shifted to recovery and parents were allowed to accompany their children there.

Recovery time which is calculated from the end of the procedure till achieving modified Post Anesthetic Discharge Scoring System (PADSS) [27] of 9-10 was documented. HR, RR, SPO₂ and MAP were recorded after the loading dose (T1), 5 min later (T2), by end of procedure (T3), at 5 and 10 min during recovery (T4 and T5 respectively) and at discharge from recovery (EOR). The total dose of ketamine, incidence of nausea, vomiting, apnea or desaturation was documented. Endoscopists' and parents' satisfaction by the level of sedation achieved during the procedure and the children behavior during recovery respectively were assessed by asking them to rate their satisfaction by using a four points scale (1=Excellent, 2=Good, 3=Fair, and 4=Poor). A score of 1 and 2 were considered as satisfied and a score of 3 and 4 as unsatisfied.

Statistical analysis

The sample size of 30 patients in each group was calculated for 90% power, 95% confidence interval and 5% alpha error using statistical software version 17.0. Mean ± standard deviation (SD) was used to express Quantitative data while frequency and percentages were used to express the qualitative data. When comparing between two means, Independent-samples t-test of significance was used and Chi-square (X²) test of significance was used for comparing proportions and frequencies between the two groups. Statistical Program for Social Science SPSS version 20.0 IBM, Armonk, NY, United States of America was used to analyze the data. A value of P<0.05 was considered statistically significant.

Results

When comparing the two groups, there was no significant difference as regard Patients' age, gender, and weight (Table 1 and Figure 1).

In our study, There was no significant difference in duration of the procedure and the time to achieve RSS of more than or equal 5 (Table 2). Recovery time in group KP was shorter than in group KD but was not statistically significant (p=0.138) (Table 2). HR was significantly lower in group KD in comparison to group KP at T1, T2, and T3 but after that, it became comparable between both groups till the end of recovery and no pharmacological intervention required (Figure 2).

As regard MAP, although it was lower in group KD than in group KP at all recording times but didn't reach statistical significance or require pharmacological intervention (Figure 3), There was no significant difference between the two groups in terms of SpO₂ and RR (Figures 4 and 5). Total ketamine dose was significantly higher in group KD when compared to Group KP (P=0.001) (Table 2).

In group KP, 3 patients showed apnea and 2 patients developed desaturation, however, no patients in group KD (Table 3). 6 patients (20%) in group KD exhibited nausea and vomiting in comparison to 5 patients (16.7%) in group KP (p=0.64). There was significantly higher endoscopists' and Parents' satisfaction in group KD as compared to group KP (Table 4).

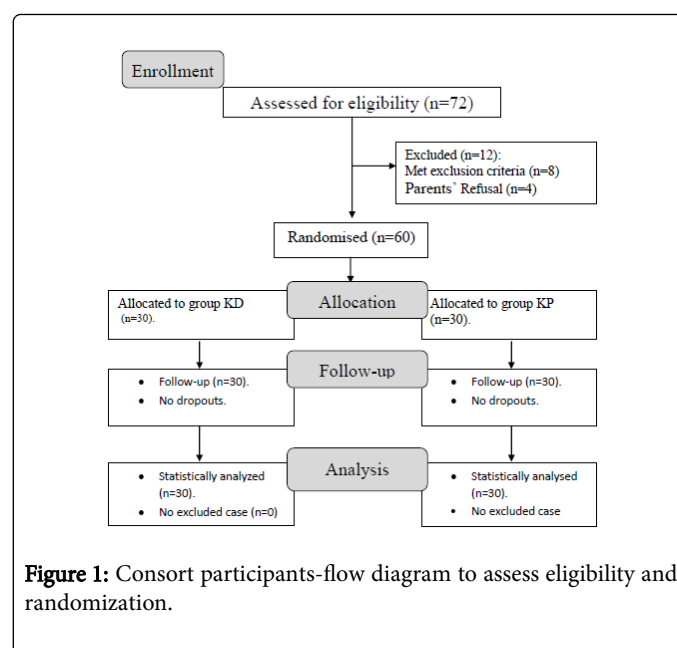


Figure 1: Consort participants-flow diagram to assess eligibility and randomization.

		Group KD (n=30)	Group KP (n=30)	p. value
Age (years)	Mean ± SD	9.1 ± 1.6	8.5 ± 1.4	0.128
Gender	Male (%)	18 (60%)	20 (66.7%)	0.592
	Female (%)	12 (40%)	10 (33.3%)	
Weight (kg)	Mean ± SD	23.6 ± 6.5	22.9 ± 5.9	0.664

Table 1: Demographic data.

Variable	Group KD (n=30)	Group KP (n=30)	p. value
Duration of procedure (min)	8.9 ± 1.8	9.1 ± 1.6	0.651
Time to RSS ≥ 5	4.6 ± 1.1	5.1 ± 1.2	0.098
Total ketamine dose (mg)	34.6 ± 2.9	29.2 ± 1.9	0.001*
Time to PADSS scores ≥ 9 (min)	17.2 ± 4.8	15.5 ± 3.9	0.138

Table 2: Duration of procedure, Total ketamine dose and time to achieve RSS ≥ 5 and PADSS scores ≥ 9.

Variable	Group KD (n=30)	Group KP (n=30)	p. value
Nausea and vomiting	6 (20%)	5 (16.7%)	0.739
Apnea (RR ≤ 8)	0 (0%)	3 (10%)	0.076
Desaturation (SpO ₂ ≤ 92%)	0 (0%)	2 (6.7%)	0.150

Table 3: Complications during the procedure and recovery.

Variable	Group KD (n=30)	Group KP (n=30)	p. value
Endoscopists' satisfaction	29 (96.7%)	24 (80%)	0.044*
Parents' satisfaction	28 (93.3%)	22 (73.3%)	0.038*

Table 4: Parents' and endoscopists' satisfactions score.

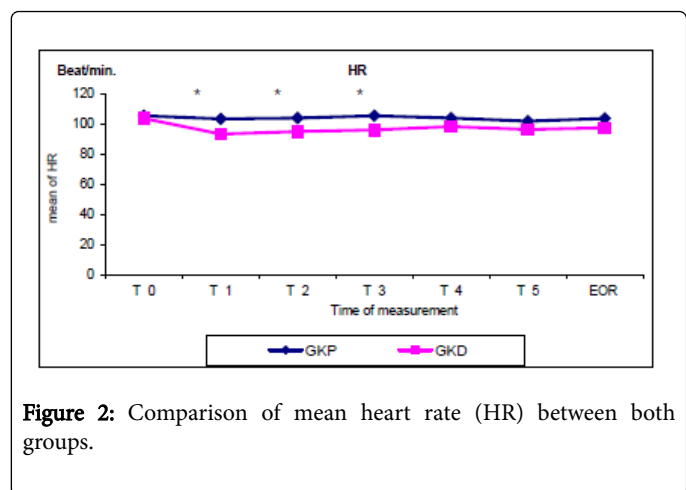


Figure 2: Comparison of mean heart rate (HR) between both groups.

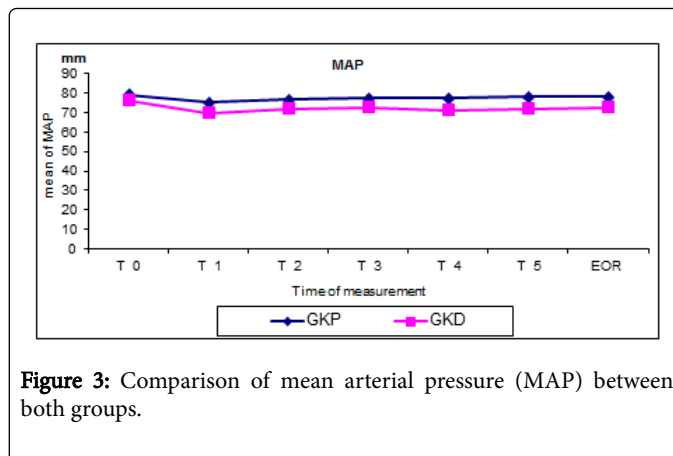


Figure 3: Comparison of mean arterial pressure (MAP) between both groups.

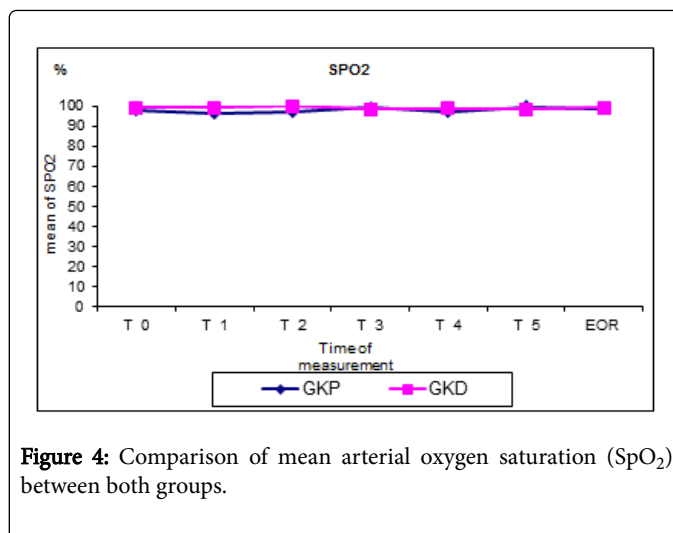


Figure 4: Comparison of mean arterial oxygen saturation (SpO₂) between both groups.

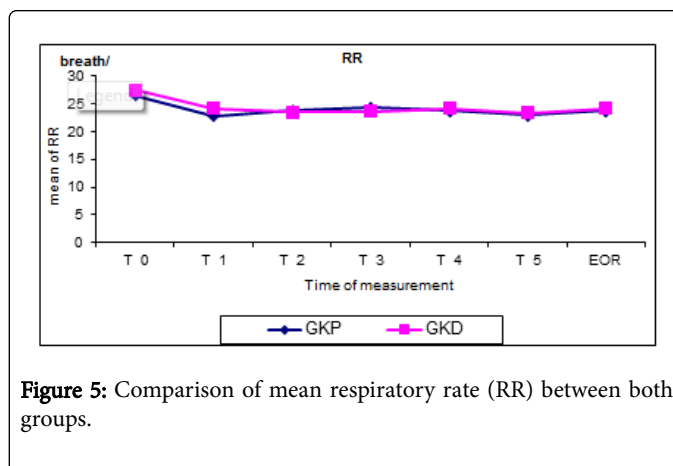


Figure 5: Comparison of mean respiratory rate (RR) between both groups.

Discussion

Upper gastrointestinal endoscopy procedures in pediatric patients for diagnostic and therapeutic purposes have increased and become more frequent [3]. Choosing a sedative should be on the basis of its onset time, associated adverse effects and time to restore cognitive function after stopping it [28]. In our study, we compared two pharmaceutical combinations (ketamine-propofol and ketamine

dexmedetomidine) for sedation in 60 children during upper gastrointestinal endoscopy. Ketamine was described as safe, effective and simple and was firstly hoped to be used as a sole anesthetic medication causing loss of consciousness, amnesia, and analgesia. However, its use rapidly decreased because of its associated psychological effects and the presence of other alternative anesthetic agents [29]. Combination of ketamine with either propofol or dexmedetomidine allows usage of lower doses adds synergism and decreases side effects.

The effects of ketamine-propofol and ketamine-dexmedetomidine combinations have been evaluated in some studies for sedation in adult and pediatric patients however to our knowledge; no other study evaluated the effects of those combinations for sedation in pediatric upper gastrointestinal endoscopy.

In our study, We observed no statistically significant difference between the two groups as regarding MAP, RR or SpO₂, however, HR was significantly lower in group KD in comparison to group KP at T1, T2 and T3 ($p < 0.05$) but after that HR became comparable between both groups ($p > 0.05$). Total ketamine dose was significantly less in group KP (29.2 ± 1.9 mg) when compared to group KD (34.6 ± 2.9 mg). Recovery time in group KP (15.5 ± 3.9 min) was shorter than that in group KD (17.2 ± 4.8 min) but not reach statistical significance ($p = 0.138$). 6 patients (20%) in group KD exhibited nausea and vomiting in comparison to 5 patients (16.7%) in group KP ($P = 0.739$). We found statistically significant higher Parents' and endoscopists' satisfaction in group KD than in group KP.

In the study of Joshi et al., they also compared same drug combinations (ketamine-propofol versus ketamine-dexmedetomidine) but in pediatric patients undergoing cardiac catheterization laboratory procedures, they found a statistically significant lower heart rate in group DK in comparison to group PK during the first 25 min but after that there was no significant difference between the two groups. Also, they found no significant difference between both groups as regards mean arterial pressure, SpO₂ and respiratory rate. However, they reported a statistically significant delay in recovery in group DK (40.88 ± 8.19 min) when compared to group PK (22.28 ± 3.63 min). This may be due to higher ketamine doses used on group KD (2.02 mg/kg/h) than in group PK (1.25 mg/kg/h) [30].

In a similar study by Tosun et al., they also evaluated the effects of ketamine-dexmedetomidine versus ketamine-propofol combinations in children undergoing cardiac catheterization on sedation level, hemodynamic parameters, and recovery time. They found that heart rate was significantly lower in Group 1 than Group 2 after induction and during the whole procedure. In our study, heart rate was significantly less in group KD till T3 but later, no significant difference between the two groups. They reported a decrease in diastolic, systolic and mean blood pressure after induction but there was no significant difference between the two groups as regards mean blood pressure during the procedure [31].

Also, Ali et al. compared ketamine-dexmedetomidine and ketamine-propofol as anesthetic agents in children undergoing cardiac catheterization. There was a similar clinical outcome in both groups although blood pressure was significantly different. There was no significant difference in terms of heart rate, respiratory rate, SpO₂ and recovery patterns and this was consistent with the finding of our study.

However, they suggested that recovery time, as assessed by modified Steward Score was significantly shorter in group P (39 ± 12.32 min) than in group D (48 ± 15.15 min). They also reported less required

ketamine doses in group D (22.76 ± 11.87 mg) when compared to group P (25.10 ± 20.73 mg) but this wasn't significant [29].

Takzare et al. studied 130 patients to compare the effect of propofol-ketamine (PK) and propofol-fentanyl (PF) on pediatric sedation during upper gastrointestinal endoscopy. They reported that the two combinations were good but more hemodynamic stability in group PK than group PF and so they recommend PK combination especially in patients with hemodynamic instability as in hypovolemic or dehydrated patients. However, as regarding the associated side effects, they found a significantly higher prevalence of nausea and vomiting in group PK (53.8%) in comparison to group PF (32.3%) ($p = 0.013$). This can be explained by the higher incidence of vomiting in gastrointestinal procedures than in others [3]. Respiratory complications during recovery as bronchospasm, cough, stridor, and Laryngospasm were significantly higher in group PK (9%) in comparison to group PF (2%) ($p = 0.024$). They also reported shorter recovery time in group PF in comparison to group PK [32].

In the study done by Hassan H.I.E.I, who studied 50 patients of both sexes to compare dexmedetomidine (Group D) versus ketofol (Group KP) for sedation in patients undergoing endoscopic retrograde cholangiopancreatography, reported a significant decrease of HR and MAP in group D in comparison to group KP after the loading dose and continue for thirty min. They found less time required to achieve RSS of 4 in group D (12.4 ± 1.1 min) when compared to group KP (13.2 ± 0.5 min) ($P = 0.44$). They also suggested that recovery time as assessed by Modified Aldrete's Scoring system was shorter in group D (11.4 ± 0.5 min) than in group KP (12.5 ± 1.8 min) although non-significant ($P = 0.23$). They also reported a higher incidence of PONV in group KP (16%) as compared to group D (8%) ($P > 0.05$), however, endoscopists' and patients' satisfaction score was higher in group KP than in group D [33].

In study by Mogahd et al., who studied 70 post CABG patients on mechanical ventilation for sedation comparing combinations of Propofol-Ketamine versus Dexmedetomidine-ketamine, there were no significant differences between the two groups as regarding MAP and HR. Also, they reported a significant decrease in total fentanyl requirements and shorter duration of mechanical ventilation in KD group [34]. The combination of ketamine-dexmedetomidine provided effective sedation reflected by better endoscopists' and parents' satisfaction than ketamine-propofol, however, the limitation of this study was the high costs required for group KD in comparison to group KP.

Conclusion

In this study, it was found that combination of ketamine-dexmedetomidine for sedation in children undergoing upper gastrointestinal endoscopy is an effective, reliable and safe alternative to ketamine-propofol without hemodynamic or respiratory drawbacks with comparable onset and recovery time.

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