A Study to Evaluate KM/Propofol versus KM Alone for Procedural Sedation in Children

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ABSTRACT

Background: The co-administration of ketamine and propofol (CoKP) is thought to maximize the beneficial profile of each medication, while minimizing the respective adverse effects of each medication.

Objective: Our objective was to compare adverse events between ketamine monotherapy (KM) and CoKP for procedural sedation and analgesia (PSA) in a pediatric emergency department (ED).

Methods: This was a prospective, randomized, single-blinded, controlled trial of KM vs. CoKP in patients between 3 and 21 years of age. The attending physician administered either ketamine 1 mg/kg i.v. or ketamine 0.5 mg/kg and propofol 0.5 mg/kg i.v. The physician could administer up to three additional doses of ketamine (0.5 mg/kg/dose) or ketamine/propofol (0.25 mg/kg/dose of each). Adverse events (e.g., respiratory events, cardiovascular events, unpleasant emergence reactions) were recorded. Secondary outcomes included efficacy, recovery time, and satisfaction scores.

Results: Thirty-two patients were randomized to KM and 29 patients were randomized to CoKP. There was no difference in adverse events or type of adverse event, except nausea was more common in the KM group. Efficacy of PSA was higher in the KM group (99%) compared to the CoKP group (90%). Median recovery time was the same.

Conclusions: We found no significant differences in adverse events between the KM and CoKP groups. While CoKP is a reasonable choice for pediatric PSA, our study did not demonstrate an advantage of this combination over KM.

Keywords: Ketamine, Propofol, Procedural Sedation.

INTRODUCTION

Pediatric procedural sedation and analgesia (PSA) is a frequent incidence in the emergency department (ED) setting. The aims of procedural sedation and analgesia contain adequate sedation, analgesia, and amnesia to permit for successful procedural completion, whereas diminishing adverse events and ensuring stable cardiopulmonary function. For years, ketamine monotherapy (KM) has been the primary pharmacologic agent utilized for reasonable to deep pediatric PSA. Numerous studies support the utilization of KM for sedation, amnesia, and analgesia on children experiencing painful processes in the emergency department setting [1,2]. Ketamine can correspondingly be managed intramuscularly if intravenous access is not obtainable. Ketamine monotherapy (KM) has been validated as safe and effective, even though unwanted side effects, such as emergence phenomenon, laryngospasm, and vomiting, are well documented [1,2]. Propofol is a sedative-hypnotic agent extensively utilized for procedural sedation. The benefits of propofol comprise rapid onset, quick and predictable recovery time, and antiemetic effects. Disadvantages comprise bradycardia, dose-dependent hypotension, pain with injection, and respiratory depression. Furthermore, propofol does not provide analgesia.

Ketamine and propofol managed together have been used effectively in a variability of settings, comprising cardiovascular, dermatologic, and interventional radiological procedures in children [3-7]. The co-administration of ketamine and propofol (CoKP) is expected to maximize the beneficial profile of each medication, while diminishing their respective adverse effects. When used in combination, reduced doses of each medication are managed, making a more stable hemodynamic and respiratory profile. This combination may reduce recovery time and frequency of emergence reactions, vomiting, and the pain of propofol injection [8]. Our objective was to compare adverse events between KM and CoKP for PSA in a pediatric emergency department.

Propofol is a sedative-hypnotic agent extensively utilized for procedural sedation. The benefits of propofol contain rapid onset, rapid and predictable recovery time, and antiemetic effects.

Disadvantages contain dose-dependent hypotension, pain with injection, respiratory depression, and bradycardia. In addition, propofol does not provide analgesia.

Ketamine and propofol managed together have been utilized successfully in a variety of settings, containing dermatologic, cardiovascular, and interventional radiological procedures in children [3-9].

The co-administration of ketamine and propofol (CoKP) is thought to maximize the beneficial profile of each medication, while minimizing their respective adverse effects. When used in combination, reduced doses of each medication are administered, producing a more stable hemodynamic and respiratory profile. This combination might decrease recovery time and incidence of emergence reactions, vomiting, and the pain of propofol injection. The purpose of this study was to compare adverse events between KM and CoKP for PSA in a pediatric ED.

METHODS

We performed a randomized, single-blinded, controlled trial of KM vs. CoKP in a convenience sample of pediatric patients receiving PSA for a fracture or dislocation decrease in an urban tertiary care children's hospital ED. Study subjects were recruited from patients between 4 and 21 years of age who had an American Society of Anesthesiologists physical status classification of I/IE or II/IIE [10]. After the parent(s)/guardian(s) consented to PSA, they were approached to participate in the study. Enrollment was limited to times when both an ED pharmacist and research associate were present. Exclusion criteria included hypertension (blood pressure > 95th percentile for age); increased intracranial pressure or central nervous system mass lesion; porphyria; glaucoma or acute globe injury; previous allergic reaction to ketamine; previous allergic reaction to propofol or its components, including egg lecithin, soybean oil, glycerol, and disodium edentate; disorders of lipid metabolism, including primary hyperlipoproteinemia, diabetic hyperlipemia, or pancreatitis; mitochondrial myopathies or disorders of electron transport; and pregnancy. After patient enrollment, patients were randomized to either the KM or CoKP group in a ratio of 1:1. The randomization table was computer-generated at the beginning of the study by the ED pharmacy and was maintained in the ED pharmacy. Staff members did not have access to the ED pharmacy, ensuring allocation concealment. The ED nurses drew up the ketamine with 0.5 mg/kg in two syringes and 0.25 mg/kg in 6 syringes, and gave to the attending physician in a bag with 2 normal saline flushes and brown opaque covers over the syringes. The ED pharmacist prepared the study medication for patients randomized to the CoKP group, drawing up propofol with 0.5 mg/kg in one syringe and 0.25 mg/kg in three syringes. For all patients, notwithstanding of study arm allocated to preserve blinding, the ED pharmacist and presence physician conferred after the nurse gave the attending physician the ketamine doses. For patients enrolled in the CoKP group, half of the ketamine syringes were switched with propofol syringes at this time, ensuring the same numbers of syringes were used irrespective of the studied group to maintain blinding. The brown opaque sleeves were used to maintain blinding of providers performing the procedure, nurses, research associates (RAs), and families.

The attending physician (pediatric emergency medicine board-certified/eligible), who was not blinded to the study drug due to safety concerns, administered either ketamine 1 mg/kg i.v. divided among 2 syringes (maximum single dose 100 mg) or ketamine 0.5 mg/kg and propofol 1.0 mg/kg propofol i.v. in separate syringes, changed early in the study to 0.5 mg/kg to better align with the literature. The medication in each syringe was administered over 30 s. After each syringe, the line was flushed with normal saline. The attending physician could administer up to a maximum of three additional doses of ketamine (0.5 mg/kg/dose) or ketamine/propofol (0.25 mg/kg/dose of ketamine and 0.5 mg/kg/dose propofol, changed to 0.25 mg/kg propofol early in the study) at their discretion to attain an appropriate level of sedation. For each ketamine/propofol dose in the CoKP group, the ketamine was administered first.

If further sedation and analgesia were required to complete the reduction, additional medication was administered at the discretion of the attending physician. Due to the milky nature of the propofol, a towel was used as a physical barrier over the syringe and tubing was used to maintain blinding of the provider performing the procedure, the nurse, and the RA recording adverse events during medication administration and families. Patients were monitored following guidelines recommended by the American Academy of Pediatrics Committee on Drugs, counting continuous measurements of vital signs, end-tidal CO2, and pulse oximetry at baseline, during and post-procedure [11]. Airway management equipment was available at the bedside.

Demographic and clinical variables, including age, gender, weight, procedure performed, and other medications given, were recorded onto a

standardized data collection sheet by RAs. Furthermore, the number of 0.5 mg/kg unit doses of sedation medications was calculated.

The minimal number of sedation medication doses managed would be two, as all patients received either two ketamine 0.5 mg/kg or ketamine 0.5 mg/kg and propofol 0.5 mg/kg. Efficacy of PSA, defined as no unpleasant recall of the procedure, no sedation-related adverse event resulting in abandonment of procedure, no permanent complication, no unplanned admission or observation, and patient did not actively resist or need physical restraint for completion of the procedure, was recorded on the Standardized Adverse Event Reporting Form [12].

The occurrence of all five criteria was essential to meet the definition of efficacy. Efficacy was determined by RA who received standardized training before the study and annual training on the study protocol through the period of the study. Oxygen was not provided except the patient experienced desaturation. Recovery time was recorded from time of management of KM or CoKP until discharge criteria were met. Discharge criteria were documented by trained RAs using the Vancouver Sedation Recovery Scale (VSRS), with discharge requiring a score ≥18.

Patients' pain levels were determined using the Faces Scale for drug management and pain experienced during the process [13,14]. Satisfaction scores on a scale from 1 to 10 (1 = unsatisfied, 10 = extremely satisfied) were collected from the providers performing the procedure, attending physicians administering the sedation, nurses monitoring the patient during the procedure, and parents. Data were analyzed as intention to treat. Per-protocol analysis was also performed. Continuous variables were reported as median with interquartile range (IQR), given their non-normal distribution, and comparisons were analyzed with the Wilcoxon rank-sum test. Categorical variables were reported as percentages, with comparisons as $\chi 2$ or Fisher's exact test for small cell sizes. Based on prior literature, we estimated an 11.5% difference in adverse events between KM and CoKP [15,16].

P value of ≤ 0.05 was considered statistically significant. These analyses were performed using SAS, version 9.3 (SAS Institute Inc, Cary, NC).

The study was done according to the ethical board of King Abdulaziz university.

RESULTS

Between December 2014 and December 2016, 62 patients were randomized to either KM or CoKP, with 32 and 30 assigned, respectively.

Moreover, 4 patients randomized to the CoKP group received KM instead as a result of the attending physician's discomfort with the study drug or change in availability of staffing. One patient randomized to receive KM received ketamine intramuscularly due to difficulties with intravenous access. Consequently, for the intention-to-treat analysis, 32 patients were analyzed in the KM group and 29 patients were analyzed in the CoKP. There was no difference in gender, age, race, ethnicity, weight, procedure performed, or narcotic administration within a half hour of the start of sedation between the two groups (Table 1).

Table 1. Patient demographics and clinical characteristics

Characteristic	KM (n = 32)	%	CoKP (n = 29)	%
Male sex	24	75	19	66
Age, y, median (IQR)	8,3	6	9,6	5
Weight, kg, median (IQR)	29	25	33	32
Procedure performed				
Fracture reduction	31	97	28	96,5
Dislocation reduction	1	3	1	3,5
Narcotic within half hour of start of sedation	1	3	1	3,5

CoKP = co-administration of ketamine and propofol; IQR = interquartile range; KM = ketamine monotherapy. Values are (%) unless otherwise noted.

There was no differences in total adverse events or type of adverse event among the two study groups, except for nausea. Even though nausea was more common in the KM group, there was no differences in vomiting/retching between the two groups. Oxygen desaturation was the most common type of respiratory event and responded appropriately to supplemental oxygen administration, except in 1 patient with apnea.

One patients with apnea required stimulation and bag valve mask ventilation, although the patient in the KM group did not have oxygen desaturation with the apnea (Table 2). There were no episodes of laryngospasm or clinically apparent pulmonary aspiration. The only cardiovascular event was an episode of hypotension in a 6-year-old in the KM group that responded to a normal saline bolus and was believed to be related to intravascular volume depletion with a prolonged nil per OS status (21 h).

Table 2. Patients with adverse events

Variable	KM, n (%) (n = 32)	CoKP, n (%) (n = 29)	p-Value
Patients with at least one adverse event	11 (34)	11 (38)	0.71
Respiratory events	3 (9)	4 (14)	0.21
Oxygen desaturation	3 (9)	4 (14)	0.13
Apnea	0	1 (3.5)	0.92
Cardiovascular events	1 (1)	0	1.0
Nausea	7 (22)	2 (7)	0.03
Vomiting/retching	7 (22)	6 (21)	0.76
Unpleasant recovery reaction	1 (3)	1 (3.5)	1.00

Total number of 0.5 mg/kg unit doses of sedation medications received was higher in the CoKP group than the KM group. Note that the first 3 patients who received CoKP received higher initial (1.0 mg/kg) and subsequent dosages (0.5 mg/kg) of propofol. There was no difference in the percentage of patients who experienced pain with injection between the groups, but more patients in the CoKP group were noted to have pain with the procedure. Median recovery time and median VSRS scores at discharge were the same for both groups. Efficacy of PSA was higher in the KM group compared to the CoKP group (Table 3).

Table 3. Sedation characteristics

Characteristic	KM (n = 32)	CoKP (n = 29)	p – Value
Total ketamine dose, mg/kg, median (IQR)	1.0 (0.5)	1.0 (0.5)	0.05
Total propofol dose, mg/kg, median (IQR)	NA	1.0 (0.5)	NA
Total no. of 0.5-mg/kg unit doses of sedation, median (IQR)	2 (1.0)	4 (2.0)	<0.0001
Pain with injection, n (%)	1 (3)	1 (3,5)	1.00
Pain with the procedure, n (%)	17 (53)	22 (75)	<0.0001
Recovery time, median (IQR)	42 (25)	41 (24)	0.78
VSRS at discharge, median (IQR)	18 (2)	18 (3)	0.79
Efficacy, n (%)	31 (97)	26 (90)	0.005

DISCUSSION

We found no significant differences in rates of adverse events between the KM and the CoKP groups. There were likewise no differences amid the types of adverse events seen in the two studied groups, apart from nausea, regardless of their very different side effect profiles. Serious adverse events were infrequent in both groups, suggesting that both sedation regimens are possible safe to manage to children, as has been verified previously [15-18]. Advocates of a ketamine and propofol mixture for pediatric sedation cite its reduction in hemodynamic uncertainty, medication management anxiety, respiratory adverse events, recovery time, and vomiting. In the present study, we did not see any of those benefits. Our rates of medication management anxiety, respiratory events, and vomiting were the same. Our only patient with hypotension was in the KM group, possibly subsequent from hypovolemia secondary to a prolonged fast. Shah *et al.* [18] found a statistically significant, although not likely clinically relevant, reduction of 3 min in total sedation time with a ketamine/propofol combination compared to ketamine. We found neither a statistical nor clinical difference in our time to recovery between the two studied groups. The addition of propofol to ketamine did not advance the quality of the sedation and it seemed worse in some regards. Efficacy was higher with KM compared to CoKP. Furthermore, more patients in the CoKP group were distinguished to have pain with their process, proposing that the patients were not as well sedated for the process compared to patients in the KM group. Our outcomes differed from prior studies, which presented CoKP to be highly efficacious and trending toward more dependable sedation depth [16-18]. Pediatric patients have a larger volume of distribution and regularly need higher doses of medication for efficiency. Furthermore, ketamine has a longer onset of action compared to propofol and, when managing propofol straightaway after ketamine, the consequence might be insufficient sedation, reliant on the length of the process. The lower efficacy and increased pain with the process can propose that the dose of propofol given in the present study was too low, even though other studies were successful with these doses [16-18].

Our contrary event rates were higher than stated in prior similar studies [16,17]. We believe this might be allied to having a dedicated, trained research associate documenting any opposing events throughout the PSA. Contrary effects are documented more regularly when observed by an independent observer rather than stated by providers caring for the patient at the bedside [19]. Vomiting was the most mutual contrary event, arising 21% of the time in both groups, and was not affected by less nausea in the CoKP group. This percentage is higher than Shah *et al.* [17] who stated

that 12% in the ketamine group and 2% in the ketamine/propofol group. We did contain retching in our definition of vomiting, which might clarify some of the difference. Vomiting is not dependably documented in all studies of ketamine and propofol. Oxygen desaturation likewise arisen more regularly in the present study than in some prior studies, but was alike to other studies [15-18]. Our study was performed at altitude, which can be responsible for some of this increased rate of oxygen desaturation.

Our convenience sample could have resulted in selection bias, as we only enrolled patients during the hours when both an ED pharmacist and research associate were available. Furthermore, several randomized patients were either withdrawn or received the other arm, primarily affecting the number of patients in the CoKP arm. Similarly, there were a large number of patients and families who the attending would not approach for consent. We did not collect information on why the attending would not consent certain patients, and this may have resulted in selection bias as well.

CONCLUSIONS

We found no significant differences in adverse events between the KM and CoKP groups. Serious adverse events were infrequent in both groups. Whereas a mixture of ketamine and propofol is a rational select for pediatric PSA, the present study did not determine an advantage of this combination over KM.

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