The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–9, 2017

0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2017.03.024

Original Contributions

ADVERSE EVENTS DURING A RANDOMIZED TRIAL OF KETAMINE VERSUS CO-ADMINISTRATION OF KETAMINE AND PROPOFOL FOR PROCEDURAL SEDATION IN A PEDIATRIC EMERGENCY DEPARTMENT

Keith Weisz, MD,* Lalit Bajaj, MD, MPH,* Sara J. Deakyne, MPH,† Lina Brou, MPH,* Alison Brent, MD,* Joseph Wathen, MD,* and Genie E. Roosevelt, MD, MPH‡

*Section of Emergency Medicine, Department of Pediatrics, Children's Hospital Colorado, Aurora, Colorado, †Department of Research Informatics, Children's Hospital Colorado, Aurora, Colorado, and ‡Department of Emergency Medicine, Denver Health Hospital, Denver, Colorado

Reprint Address: Keith Weisz, MD, Section of Emergency Medicine, Department of Pediatrics, Children's Hospital Colorado, 13123 East 16th Avenue, Aurora, CO 80045

☐ **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: Ninety-six patients were randomized to KM and 87 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. Satisfaction scores by providers, including nurses, were higher for KM, although parents were equally satisfied with both sedation regimens. 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—adverse events; ketamine; propofol; sedation; pediatric ED**

INTRODUCTION

Pediatric procedural sedation and analgesia (PSA) is a frequent occurrence in the emergency department (ED) setting. The goals of PSA include adequate sedation, analgesia, and amnesia to allow for successful procedural completion, while minimizing adverse events and ensuring stable cardiopulmonary function. For decades, ketamine monotherapy (KM) has been the primary

Presented at the Pediatric Academic Societies, Section on Emergency Medicine, San Diego, CA, April 29, 2015.

This project was supported by the National Institutes of Health/National Center for Advancing Translation Sciences Colorado Clinical and Translational Science Award grant number UL1 TR001082. Contents are the authors' sole responsibility and do not necessarily represent official National Institutes of Health views.

RECEIVED: 16 December 2016; FINAL SUBMISSION RECEIVED: 20 January 2017;
ACCEPTED: 11 March 2017

pharmacologic agent used for moderate to deep pediatric PSA. Numerous studies support the use of KM for sedation, amnesia, and analgesia on children undergoing painful procedures in the ED setting (1,2). Ketamine can also be administered intramuscularly if intravenous access is not available. Ketamine monotherapy (KM) has been validated as safe and effective, although undesirable side effects, such as emergence phenomenon, laryngospasm, and vomiting, are well documented (1,2).

Propofol is a sedative-hypnotic agent widely used for procedural sedation. The advantages of propofol include rapid onset, quick and predictable recovery time, and antiemetic effects. Disadvantages include dose-dependent hypotension, bradycardia, respiratory depression, and pain with injection. In addition, propofol does not provide analgesia.

Ketamine and propofol administered together have been utilized successfully in a variety of settings, including 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 may reduce recovery time and frequency of emergence reactions, vomiting, and the pain of propofol injection (6). Our objective was to compare adverse events between KM and CoKP for PSA in a pediatric ED.

METHODS

Study Design

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 reduction in an urban tertiary care children's hospital ED. The study was approved by the Colorado Multiple Institutional Review Board. Written informed consent was obtained from the parent or guardian of all patients enrolled in the study; written assent was obtained from all patients 7 years of age and older.

Study Setting and Population

Study subjects were recruited from patients between 3 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); glaucoma or acute globe injury; increased intracranial pressure or central nervous system mass lesion; porphyria; previous allergic reaction to ketamine; previous allergic reaction to propofol or its components, including soybean oil, glycerol, egg lecithin, and disodium edentate; disorders of lipid metabolism, including primary hyperlipoproteinemia, diabetic hyperlipemia, or pancreatitis; mitochondrial myopathies or disorders of electron transport; and pregnancy.

Study Protocol

After patient enrollment, patients were randomized to either the KM or CoKP group in a ratio of 1:1 (Figure 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 six 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, regardless of study arm assigned to maintain blinding, the ED pharmacist and attending 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 regardless of study 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