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The outcome of Ketamine and Propofol for Procedural Sedation and Analgesia (PSA) in Pediatric Patients in the Emergency Department: A Cross-Sectional Study

Bushra Qaiser Qureshi, Emad Uddin Siddiqui, Sayyeda Ghazala Kazi

ABSTRACT

Objectives: We aim to evaluate the outcomes of Ketamine and Propofol for PSA in pediatric Pakistani Emergency Department (ED) patients. Our primary objective is to observe sedation duration and recovery time. Secondary objective is to assess the need for repeat doses and potential complications associated with the use of these drugs.

Study Design & Setting: Descriptive cross-sectional study. Urban tertiary care hospital: Aga Khan University Hospital (AKUH) ED, Pakistan.

Methodology: 179 eligible patients requiring painful procedures in the emergency, under 16 years, selected through non-probability consecutive sampling, after consent from caregiver/children, were included. PSA was performed by certified PALS and PSA personnel, with single IV Ketamine dose (0.5 mg/kg) and Propofol (1 mg/kg, followed by 0.5-1 mg/kg as needed). [15] Oxygen saturation and vital signs were continuously monitored during and after the procedure until full consciousness was regained and patients were observed for potential complications.

RESULTS: 179 patients underwent PSA with Ketamine and Propofol combination; (57.0%) male and (43.0%) female, with a mean age of 3.91 years (± 2.80). Majority of patients were 1-5 years old (80.4%), 6-10 years (15.6%), and 11- 16 years (3.9%). Of these, (82.1%) required laceration repair. Some reversible complications were observed, including tachypnea in (28.5%) of cases, hypotension (22.3%), tachycardia (21.8%), bradycardia (2.2%) and hypoxia in (1.1%).

CONCLUSION: In our study, PSA using Ketamine and Propofol combination in the ED, by non- anesthesiologists, was found to be safe and linked to a low rate of reversible complications.

Key Words: Anxiety, Ketamine, Pain, Procedural Complications, Propofol.

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INTRODUCTION:

To provide comfort to infants and children undergoing diagnostic or therapeutic procedures in the ED, it's crucial to achieve sedation with adequate analgesia. This requires an agent with rapid induction, smooth recovery, and the ability to maintain adequate cardiovascular and respiratory functions, amnesia, anxiety and motor control throughout the procedure.[1] The goal of sedation is patient safety, minimize pain and psychological trauma, control anxiety and behavior, and movement throughout the procedure.[2]

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While there are limited medications available, a combination of pharmaceutical agents at different doses can be used to achieve the desired sedation level, maintaining airway reflexes and patency.[3, 4] this approach not only achieves controlled sedation but also reduces healthcare resource utilization by decreasing operating room patient load, anesthesia personnel, patient waiting time, hospital and ED stay, recovery time, and overall health care costs.

Procedural sedation and analgesia (PSA) involve administering sedation and analgesia to facilitate therapeutic or diagnostic procedure in the Pediatric ED (PED). Propofol combined with Ketamine has become standard practice for procedural sedation in a conscious patient in ED.[5-7]

A local retrospective study and several international studies that explored the safety, success rate, and side effects of combined use of Propofol and Ketamine during PSA by non-anesthesiologists in pediatric patients, yielded largely consistent findings. [8] However, these studies were out of the emergency room, but were controlled trials, though the results remained consistent.

Ketamine is a dissociative agent known for its strong amnesia and analgesic properties, maintains muscle tone, airway

reflexes, and respiration. However, some children may experience vivid dreams, nausea, or vomiting. In contrast, Propofol has a rapid onset of action, a short half-life, and quick recovery. Propofol has good antiemetic, and amnestic properties but may cause dose-dependent hypotension and respiratory depression. [9] Combining these drugs is theorized to preserve sedation potency while minimizing their respective adverse effects, potentially balancing out each other's side effects.

Procedures like lumbar puncture, laceration repair, foreign body removal, chest tube insertion, fracture/dislocation reduction, electrical cardioversion, abscess drainage, imaging studies like computed tomography (CT) scan or magnetic resonance imaging (MRI), endoscopy, etc. are painful and distressing for children. PSA is used to alleviate pain and stress in both children and parents. Hence, PSA is recommended in most developed EDs.

Few studies have addressed the success rate and side effects of Propofol and Ketamine combined for PSA by non-anesthesiologists in pediatric patients. Some institutions and physicians remain cautious due to known complications and parental concerns. Different dose regimens have been employed across studies, with no universally superior dose regimen identified.

Combining low-dose ketamine with carefully administered small doses of Propofol for effective PSA minimizes complications related to drug and dosage. This approach helps to achieve a balance between the two drugs and reduces the need for escalating or subsequent doses.[10]

Our study aims to evaluate the outcome of combining Ketamine and Propofol for pediatric PSA during diagnostic and therapeutic procedures in the emergency department of Aga Khan University Hospital, a tertiary care teaching hospital, in Pakistan. Our focus is on our unique population, which has distinct anatomical and genetic characteristics, making it challenging to apply results from other population. This study aims to evaluate the effect of PSA on sedation duration, recovery time as primary outcomes. The secondary objective is to assess the need for repeat doses and complications incurred. Additionally, the study seeks to reduce healthcare resource utilization, lower operating room patient load, anesthesia personnel requirements, reduce patient waiting time and healthcare cost at the study center.

METHODOLOGY:

This was a prospective cross-sectional hospital-based study. Nonprobability consecutive sampling was done of all subjects aged below 16 years presenting to the ED of an urban tertiary care hospital from January 1st, 2018 to December 31st, 2019, who required procedural sedation and analgesia, after approval from the Ethical Review Committee of The Aga Khan University Hospital; Reference number 2018-0529-1001. The study center currently practiced PSA with Ketamine and Propofol or Ketamine and Midazolam across the hospital and especially in the ED during PSA in children. Patients who were allergic to Ketamine, Propofol, egg, and soy or had a history of low blood pressure or hemodynamic instability were excluded from the study. Patients with a Mallampatti score of class =2, Modified Alderate score =6, or American Society of Anesthesiologist classification score of =3 were excluded from the study. Inclusion criteria include all children who need to go through painful procedures in the PED and caregiver/children agree to consent for PSA and don't fall under the exclusion criteria. Sample size calculated using Raosoft software with 3.2% margin of error and 95% confidence interval and sample size of 179 was calculated. Response distribution of Hypoxia was 5%. [7]

Informed consent from parents was taken as per the hospital policy, both for sedation and the procedure being undertaken. The PSA was taken care of by an ED physician who was credentialed for PSA and advanced airway care, while the procedure required was dealt with by another physician from ED or from another subspecialty. All cases had at least 4-6 hours of fasting.

We used ketamine 0.5 mg/kg IV as a single dose, repeat ketamine dose was used among children who during procedure perceived pain as per the visual analog pain scale among younger children and tachycardia or irritability in older children. Propofol with an initial dose of 1 mg/kg followed by 0.5-1 mg/kg as and when required.[15] Subsequent doses of Propofol were given as per physician advice when necessary in cases when tachycardia was observed and/or observed bodily movement/awakening child. Oxygen via face mask and crash cart was available at all times during the procedure. Continuous monitoring for oxygen saturation and vitals was carried out throughout the procedure and post-procedure till the patient gained full consciousness.

A predesigned and institutional approved official form was used by ED personnel for the data collection to record demographic characteristics of patient information related to the procedure, which included time out, procedure start and end time, doses administered, total sedation time (from initial sedation injection to spontaneous eye-opening), recovery time (time passed from end of the procedure to awakening), vital signs (Respiratory rate, Heart rate, Blood Pressure, Oxygen Saturation, and Temperature) and any complications associated with PSA (like bradycardia, hypoxia, apnea, hypotension, seizure, arrhythmia, laryngospasm, stridor, rash, vomiting or aspiration, etc.) and interventions undertaken. The primary outcome was to observe the duration of sedation, recovery time, and length of hospital stay, while the secondary outcome was to assess the need for repeat dose and complication. The Faces pain scale was used to record pain scale among children below 5 years of age while a numerical pain scale from 0 to 10 (where 0 as No pain and 10 severe intensity pain) was used in children who can understand and communicate their pain intensity. However, pain assessment was recorded pre and post-procedure (during

recovery). [8] The patient was discharged only when able to maintain good airway, was fully awake, presence of swallowing reflex, with ability to swallow clear liquids, and achieving the pre-sedation level of responsiveness.

Statistical Analysis: Data was entered and analyzed using IBM statistical package for social sciences (SPSS) software version 22. Frequency and percent were calculated for qualitative variables like gender and complications. Mean and standard deviation was calculated for age, sedation, and recovery time. Effect modifiers like age, gender, sedation, and recovery time were addressed through stratification. The post-stratification chi-square test was applied by taking p = 0.05 as significant.

RESULTS:

We enrolled 179 children who required PSA in the ED for various procedures. Among them, 102 (57.0%) were males, 77 (43.0%) females, with a mean age of 3.91±2.80 years. The majority of cases 147 (82.1%) involved laceration repair on the face, with forehead lacerations (66%) being the most common (49), followed by eyebrow lacerations (27). (Table 1)

Table 1: Procedures Undergone PSA

DIAGNOSIS	FREQUENCY	PERCENT
Forehead laceration	49	27.4
Eyebrow laceration	27	15.1
Eyelid laceration	10	5.6
Femur dislocation	2	1.1
Chin laceration	20	11.2
Radius fracture	4	2.2
Head trauma	2	1.1
Ear laceration	2	1.1
Cheek laceration	5	2.8
Nail bed laceration	4	2.2
Supracondylar fracture	2	1.1
Nose laceration	4	2.2
Lip laceration	13	7.3
Heel laceration	2	1.1
Back laceration	2	1.1
Facial laceration	2	1.1
Lateral canthus laceration	1	.6
Pleural effusion	2	1.1
Forearm laceration	1	.6
Left leg staples	1	.6
Finger laceration	6	3.4
Meningoencephalitis	2	1.1
Lumbosacral wound	2	1.1
Forearm fracture	6	3.4
Glass cut injury	2	1.1
Crush injury	2	1.1
Meningitis	4	2.2
Total	179	100.0

Total ED stay averaged 38 ± 15.5 minutes, ranging from 15 to 104 minutes. Sedation time averaged 16.63 ± 9.44 minutes, with a minimum of 04 minutes and maximum of 70 minutes. When examining sedation time further, we found that 100 (56%) children were sedated for < 15 minutes, and 72 (40%) were sedated for 16-30 minutes. (Table 2). Recovery time from PSA averaged 21.45 ± 11.81 minutes, varying from 10 to 87 minutes, before safe discharge. Further analysis showed that 43% of cases recovered in <15 minutes, 50% in 16-30 minutes, while 4% took 31-45 minutes, and 3.4% recovered after 45 minutes. (Table 2). All cases received a combination of Propofol and Ketamine, with ketamine given as a single dose in 170 (95%) cases, only 09 required (= 2) repeat dose. Regarding repeat doses of Propofol, 71 (40%) children received up to 3, 4, 5, or more doses, while 108 (60%) children responded well to a single dose. Notably, all 09 cases that required a repeat dose of ketamine also needed >3 doses of Propofol (Table 3). When examining gender distribution and the number of repeat doses of PSA drugs (Ketamine and Propofol), the majority of children underwent PSA with < 2 doses. (Figure 1). Reversible complications following PSA in this study included: bradycardia in 04 (2.2%), hypoxia in 02 (1.1%) cases. Tachypnea and tachycardia were noted among 51 (28.5%) and 39 (22%) children respectively. Fluid responsive hypotension was identified in 41 (23%) children. Vomiting was not recorded in any case. Secretion and gurgling associated with hypoxia were managed with position change, and deep suction was not required. No episode of apnea, seizure, laryngospasm, stridor, or rashes were observed in any patient during PSA.

Children under 5 years of age had a higher likelihood of experiencing complications following PSA. Among the 179 cases, 85% of those with hypotension were aged less than 5 years. Of which 28 were males and 13 females. 64% of tachycardic patients were under 5 years of age. Chi- square

Table 2: Sedation and Recovery Time in PSA

Time in minutes	Sedation Time	Recovery Time
<15	100 (56%)	77 (43%)
16 – 30	72 (40%)	89 (50%)
30 - 45	05 (2.8%)	07 (04%)
> 45	02 (01%)	06 (3.4%)

Table 3: Age and (Ketamine/Propofol) Repeat Doses Correlation

Age in years	Propofol repeat doses			Ketamine repeat doses	
	<2	3-4	>5	<2	>2
< 5	91	33	20	139	05
6 -10	15	07	06	25	03
11 -16	02	01	04	06	01
Total	108	41	30	170	09

Figure 1: Gender relation with PSA, sedative drug and Doses

Propofol | Ketamine

<2(Tota: 108)	58(Male)	50(Female)
3-4(Total: 41)	26(Male)	15(Female)
>5(Total: 30)	18(Male)	12(Female)

value= 24.351, P-value = 0.001. All cases of hypoxia and bradycardia were in children under 5 years of age. None of the patients vomited, and there was no need for either basic or advanced ventilatory support.

DISCUSSION:

The Ketamine and Propofol combination, though studied in a small single-center sample, has shown promising results when used by PED physicians. While the study's limited size prevents it from detecting significant differences, it demonstrates positive outcomes such as improved sedation, reduced hypotension, and increased patient comfort and safety. [10]

PSA is crucial in caring for children, reducing anxiety, and ensuring pain-free medical procedures. The demand for safe, painless diagnostic and therapeutic procedures is increasing. Children in ED are more anxious and frightened of pain during these procedures. [10, 14] Effective pain management and anesthesia in ED are pivotal for providing quality care, alleviating anxiety, and ensuring good sedation and analgesia.

Different medications and combinations are used for PSA. Ketamine is used effectively as an anesthetic and analgesic during PSA, but can lead to complications like delayed recovery, vivid dreams, increased salivation, nausea, and vomiting. Propofol, while safe due to its favorable pharmacokinetics, can cause hypotension and respiratory depression and lacks intrinsic analgesic properties. Combining low-dose ketamine with carefully measured small doses of Propofol for PSA helps minimize drug and dose-related complications, balance the effects of each other, potentially reducing the need for additional doses. [2, 10, 15] Heterogeneity in Ketamine and Propofol dosing has been observed in the literature, and optimal combination dose is debatable. Ketamine dose range from 0.5–1.5 mg/kg, while Propofol doses follow a similar pattern, often as small boluses. Some studies also use a single dose of ketamine before inducing unconsciousness with small doses/infusion of Propofol. [19]

The current study was conducted to determine the outcome of Ketamine and Propofol for PSA in pediatric Pakistani patients in the emergency department of Aga Khan University Hospital.

In this study, we observed minimal complications in patients who received PSA with Ketamine and Propofol, using lower individual drug doses compared to other studies using Ketofol as a single drug combination.[11] Likewise, similar studies, such as Jurair H, et al. and Grunwell JR, et al. have reported lower adverse effects with Ketamine and Propofol combination, in only 0.60% of children.[8,16] Oxygen desaturation in 3.86%, cough 1.46%, apnea 1.57%, etc.[16] On the contrary, Khutia SK, et al. reported higher complication rates: hypotension in 14.58%, apnea 4.16%, emergence reaction 10.42%, nausea and vomiting 10.42%.[17]

Similar to a study conducted in a low-resource setting by Bengono BR et al., our study demonstrated comparable sedation times. Bengono reported a mean sedation time of 17 minutes, while our study indicated a mean sedation time of 16 minutes. [25]

A meta-analysis by Foo. TY et al. found that Ketamine and Propofol didn't significantly improve clinician satisfaction and led to increased respiratory adverse events like airway obstruction, apnea, desaturation, and respiratory depression. However, they may reduce the incidence of hypotension, unlike our findings, and didn't result in bradycardia. Additionally, no significant gastrointestinal adverse events like nausea and vomiting were observed.[20]

This study aligns with Alletag et al.'s analysis of Ketamine and Propofol for PSA.[1] Combining low-dose Ketamine and Propofol lowers complication risks during sedation and recovery, in line with our findings.[16] Similarly, Andolfatto. G et al.'s study on intravenous (IV) Ketofol (mixed 1:1 ketamine-propofol) and A. Chiaretti et al's research comparing Propofol alone and in combination with Ketamine support our results, highlighting a lower risk and complication incidence with the combination, even without a control group. [13]

Kannikeswaran compared the need for re-dosing, sedation efficacy, duration, and adverse events between 3 commonly administered doses of parenteral ketamine in the ED in children aged 3 to 18 years. [18] Another study found that 1mg/kg of IV ketamine led to sedation-related dissatisfaction and painful recollections.[18] In our study, where Ketamine and Propofol were combined, some patients experienced short-lived hypotension, tachypnea, and tachycardia, but sedation-related dissatisfaction was not observed in any case.

In a meta-analysis by Foo. TY et al., comparing Ketamine and Propofol with Propofol alone in ED patients, with six RCTs, they found a higher frequency of adverse respiratory events when the combination (Ketamine and Propofol) compared to isolated Propofol. [20] In our unpublished comparative analysis of Ketamine/Propofol vs Ketamine alone, preliminary results indicate that Ketamine/Propofol is safer than Ketamine alone.

Males predominated among patients who undergoing PSA, similar to finings in studies by Jurair H, et al. and Grunwell JR, et al.[8,16] The younger age group had a significantly higher representation.[8] Possibly influenced by regional factors and healthcare availability. Combining Ketamine and Propofol reduced major desaturations, especially in children under 5 year, mirroring our findings. Using low-dose Ketamine and

Propofol for PSA offers benefits such as effective sedation, good analgesia and amnesia, hemodynamic stability, and minimizing distressing adverse effects like hallucinations.[13]

CONCLUSION:

In our study, PSA using Ketamine and Propofol combination in the ED, by non-anesthesiologists, was found to be safe and linked to a low rate of reversible complications. No episode of apnea, seizure, laryngospasm, stridor, or rashes were observed in any patient during PSA. However, its efficacy and associated complications need to further be investigated by a larger sample size, case-control, or randomized trial.

Authors Contribution:
Bushra Qaiser Qureshi: Did the literature search, formulated the study design and concept, questionnaire, data collection, and analysis with interpretation and drafting.
Emad Uddin Siddiqui: Data collection and drafting. All authors read and approved the final manuscript
Sayyeda Ghazala Kazi: Authors read and approved the final manuscript

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