The adverse effects of Ketamine on Procedural Sedation and Analgesia (PSA) in the Emergency Department

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Abstract

Background: Procedural sedation and analgesia (PSA) in the emergency department (ED) is mainly used for wound irrigation, reduction of fractures, and wound closure. Ketamine is one of the most commonly used drugs for PSA in the ED. The study was conducted in the ED of a large tertiary care hospital in southern India to evaluate the adverse effects of Ketamine on PSA.

Materials and Methods: This is a prospective observational study performed in the ED for 6 months (October 2019-March 2020) in 151 patients who required Ketamine for PSA. Titrated doses of Ketamine was administered in all patients; hemodynamic variables and adverse events were recorded at timed intervals. Results: During the study period, a total of 151 patients in the ED required PSA. The mean age of the study cohort was 37 ± 15 years, and males accounted for 83%. All individuals obtained adequate sedation and pain relief. It was found that the incidence of adverse reactions to Ketamine was higher in young people (18- to 40-year-old), which was 63%. The most common adverse reaction in the study population was 39 cases of hypertension (44.8%), followed by vomiting in 25 cases (28.7%) and delusion in 6 cases (4%). There was no significant adverse effect in any patients which necessitated admission.

Conclusion: Ketamine is a drug with good analgesic, sedative properties and has been shown to have a good safety profile with minimal adverse events for use as PSA in ED. Side effects were most common in the younger adult age group and hypertension was the most common side effect.

Keywords: Analgesia, dissociative anaesthesia, emergency department, Ketamine, procedural sedation

Introduction

The ideal drug for procedural sedation in the emergency department (ED) needs to have a fast onset, good analgesic effect and minimal side effects. Procedural sedation and analgesia (PSA) in the ED is a common practice to relieve anxiety, discomfort and pain of patients during invasive diagnosis and treatment. PSA is designed to suppress the level of consciousness while maintaining a firm response to verbal commands. This state is called moderate sedation. Emergency room, daycare unit and intensive care unit (ICU) are the most common settings managed by PSA. Procedures commonly done in the Emergency room under Ketamine are orthopedic manipulations, incision and drainage of abscess, wound debridement, direct current cardioversion etc.

Ketamine was discovered in 1970, and since then is used as a potent analgesic and dissociative anaesthetic agent. Ketamine is popular because of its unique ability to produce rapid sedation, effective analgesia, forgetfulness and its secondary beneficial properties. The latter include bronchodilation and maintenance of airway reflexes and sympathetic tone. Because of these unique characteristics and versatility, it is becoming more and more used in the ED.
Materials and Methods

Study Setting: The study was conducted in the ED of Christian Medical College, Vellore. The ED is a 49-bedded department that tends to attend around 300 trauma and non-trauma patients a day.

Study Design: This was a prospective observational study conducted over 6 months from October 2019 to March 2020 on patients requiring PSA in ED.

Inclusion Criteria: Trauma patients more than 16 years of age, requiring wound wash, suturing of a wound, screw fixation, closed reduction with ASA (American Society of Anesthesiologists) grade 1 or 2.

Exclusion Criteria: Pregnant patients or a history of psychiatric illness or patients who were unwilling to consent for the study were excluded from the study.

Variables: Patients undergoing procedures after sedation with Ketamine such as wound wash and debridement, reduction of the fracture, wound suturing, joint relocations were enrolled for the study. The dose, route of administration and the indications were noted in a standard proforma. The initial dose of Ketamine administered intravenously (IV) ranged from 0.8 mg/kg to 1 mg/kg. The further doses of Ketamine were titrated according to patient’s response and were separately documented. Patient’s vitals such as blood pressure, heart rate, respiratory rate, oxygen saturation, baseline ECG to look for any arrhythmias, end-tidal CO\(_2\), duration of fasting before the procedure and ASA grading were recorded. Any side effects such as nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, confusion, hallucinations, seizure, hypertension/hypotension, loss of appetite, nystagmus, apnea, respiratory depression, anaphylaxis, laryngospasm, injection site pain and arrhythmias were also noted.

Selection bias: Consecutive patients who had undergone PSA in ED during the study period were recruited to avoid selection bias.

Recall bias: The information regarding the PSA using Ketamine was obtained by directly questioning the ED physician within 24 h of the procedure to minimize the risk of recall bias.

Statistical Methods and quantitative variables: Quantitative variables were reported using Mean ± SD for normally distributed variables. Qualitative variables were reported using frequency and percentage. Data analysis was done by using the Statistical Package for the Social Sciences 21.0 version.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was reviewed and accepted by Institutional review board/Ethics committee, and the corresponding protocol/approval number is IRB Min. 12294 dated October 8, 2019. We also certify that we have not plagiarized the contents in this submission and have done a plagiarism check.

Results: Our study was conducted for 6 months (October 2019 to March 2020), during which 40,519 patients visited our ED for treatment. Among these patients, 2376 were trauma patients, of which 151 required PSA and were recruited into our study. [Figure 1].

Baseline Characteristics: The mean age group of the study population was 37 ± 15 SD years, with a majority being men i.e., 83%. The majority of patients (75/151: 50%) came to the ED in the early evening hours. Co-morbidities, patient segregation priority levels, and reporting time to ED are shown in Table 1.

Adverse effect: Among the total study population, 57.6%(87/151) had developed some adverse reaction to the drug. The most common adverse effect was hypertension, seen in 44.8%(39/87) of the patients with a mean increase of 116 mmHg from baseline at 30 minutes. Among those in the study population, 28.7% (25/151) had developed vomiting, 9.2% (8/87) had nausea and 6.9% (6/87) had emergence delirium. Details of the adverse reactions are given in Table 2. No patients developed any anaphylactoid reactions such as skin reactions, hives, itching, flushed or pale skin, low blood pressure, constriction of airway bronchioles, swollen tongue or throat. After administration of IV Ketamine for PSA, the hemodynamic variables such as pulse rate, systolic blood pressure and SpO\(_2\) were recorded at 15 minutes,
**Table 1: Baseline characteristics**

| Variables                        | Frequency n=151 (%) |
|----------------------------------|---------------------|
| **Demography**                   |                     |
| Age, mean (SD) years             | 37±15               |
| Age 18-40 years                  | 96 (64)             |
| 41-60 years                      | 43 (28)             |
| 61-80 years                      | 12 (8)              |
| **Gender distribution**          |                     |
| Male                             | 126 (83)            |
| Female                           | 25 (17)             |
| **Triage priority level**        |                     |
| Priority 1                       | 74 (49)             |
| Priority 2                       | 74 (49)             |
| Priority 3                       | 3 (2)               |
| **Time of presentation to ED**   |                     |
| 8 am-4 pm                        | 58 (39)             |
| 4 pm-12 am                       | 65 (43)             |
| 12 am-8 am                       | 28 (18)             |
| **Comorbidities**                |                     |
| Diabetes                         | 10 (7)              |
| Hypertension                     | 9 (6)               |
| Smoking                          | 10 (6)              |
| Alcohol                          | 13 (8)              |
| Others*                          | 7 (4)               |

Others* = Ischemic heart disease, Bronchial Asthma, Chronic obstructive pulmonary disease

**Table 2: Adverse effects of Ketamine**

| Variables            | Frequency n=87 (%) |
|----------------------|---------------------|
| Hypertension         | 39 (44.8)           |
| Vomiting             | 25 (28.7)           |
| Nausea               | 8 (9.2)             |
| Emergence Delirium   | 6 (6.9%)            |
| Desaturation         | 4 (4.6)             |
| Others*              | 5 (4.6)             |

Others* = Confusion, Disorientation

**ED disposition:** Amongst the study population, patients were admitted to the ward/ICU and most of them had to undergo major surgery. The rest were treated conservatively in the ward. Patients who were not admitted were either stably discharged (44/151: 29%) or left against medical advice (2/151: 1.5%) after primary care. Neither trauma nor PSA-related mortality were reported in this study group.

**Discussion**

Ketamine is considered as a promising drug for many clinical applications especially in prehospital care and emergency room, as it satisfies many requirements of ideal opioid alternatives, including strong analgesia, proper hemodynamic profile, less respiratory depression and minimal adverse effects. Ketamine exhibits dissociative sedation and analgesic properties as it is an N-methyl-D-aspartate receptor antagonist. Past studies have shown the effectiveness and safety of sub dissociated doses of Ketamine in emergency room, so it is one of the most commonly used drugs for PSA. Using Ketamine as an analgesic in the pre-hospital setting – especially in case of trauma patients have been reported beneficial. Procedures such as wound debridement/washing, closed reduction etc., in trauma patients require adequate sedation to prevent severe pain, agitation and anxiety. McGlone et al. and Ellis et al. reported a total of 590 Ketamine administrations, together with noting a high level of sedation efficacy, strong degrees of parental and staff satisfaction, and an adverse effect profile readily manageable by trained ED physicians. However, the use of 30th minute and 60th minute or until there was complete recovery of the patients in terms of regaining consciousness. The variations of these vital signs have been detailed in Table 3.
Ketamine can also lead to serious respiratory, cardiovascular and neuropsychiatric adverse events. This study was conducted to look for adverse effects related to the use of Ketamine in adult ED for PSA purposes.

Our study population included mainly young adults with a male preponderance which was consistent with a study done by Newton et al.[9] The mean dose of Ketamine used in our study was 0.8 mg/kg–1 mg/kg as against 0.7 mg/kg (range 0.5–1.0 mg/kg) in the study done by Newton et al. The mean initial heart rate and systolic blood pressure for our study population was 105.6 beats/minute and 112.4 mmHg respectively which was slightly higher when compared to the study of Newton et al. We found that the most common adverse effect among our study subjects was hypertension and vomiting which were consistent with other studies. Respiratory depression is one of the common side effects as reported in earlier literature.[13,14] Amongst the total study population (4/87; 4.6%) patient desaturated, however, responded well to supplemental oxygen. None of the study subjects required mechanical ventilation for the same. A study done by Andolfatto G et al. showed emergence delirium as their prime adverse effect, whereas we had only 6.9% (6/87) patients with emergence agitation, amongst whom two responded to verbal counselling while the rest required short-acting benzodiazepine.[15] Ramsay sedation score of more than 4 was attained in 58.9% (89/151) of patients at 15 minutes after administering IV Ketamine and rest required a second bolus dose of 0.45 mg/kg. In our study, we didn’t have any sedation failure, requiring the use of other sedative drugs to achieve sedation target as compared to the study done by Andolfatto G et al.[15] We had no patients with laryngospasm, as seen in multiple other studies. This could be explained by the fact that our study population included only adult age group patients, whereas laryngospasm is mostly common among the paediatric age group. Since our population included only trauma patients requiring PSA, conventional sedatives such as Midazolam were not co-administered to avoid unwanted hypotension. None of the patients included in the study population had any dreaded complications and they underwent uneventful procedures. There were no mortalities amongst the study population.

Limitation: We included only ASA 1 and ASA 2 patients; hence the safety of the drug cannot be extrapolated for the higher ASA classes. Our study included only adults, so the effects cannot be applied to the paediatric age group.

Conclusion: Ketamine is a drug with good analgesic, sedative properties and has been shown to have a good safety profile with minimal adverse events for PSA in ED. Most common side effects were hypertension followed by vomiting and nausea, seen in the young-adult age group. There was no event of laryngospasm or airway compromise.

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Conflicts of interest
There are no conflicts of interest.

References
1. Riddell J, Tran A, Bengiamin R, Hendey GW, Armenian P. Ketamine as a first-line treatment for severely agitated emergency department patients. Am J Emerg Med 2017;35:1000-4.
2. Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. Anesth Essays Res 2014;8:283-90.
3. Newton A, Fitton L. Intravenous Ketamine for adult procedural sedation in the emergency department: A prospective cohort study. Emerg Med J 2008;25:498-501.
4. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department Ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011;57:449-61.
5. Persson J. Wherefore Ketamine? Curr Opin Anaesthesiol 2010;23:455–60.
6. Treston G, Bell A, Cardwell R, Fincher G, Chand D, Cashion G. What is the nature of the emergence phenomenon when using intravenous or intramuscular Ketamine for paediatric procedural sedation? Emerg Med Australas 2009;21:315-22.
7. Aroke EN, Crawford SL, Dungar JR. Pharmacogenetics of Ketamine-induced emergence phenomena: A pilot study. Nurs Res 2017;66:105-14.
8. Lemoel F, Contenti J, Giolito D, Boiffier M, Rapp J, Istrìa J, et al. Adverse events with Ketamine versus ketofol for procedural sedation on adults: A double-blind, randomized controlled trial. Acad Emerg Med 2017;24:1441-9.
9. Mo H, Campbell MJ, Fertel BS, Lam SW, Wells EJ, Casserly E, et al. Ketamine safety and use in the emergency department for pain and agitation/delirium: A health system experience. West J Emerg Med 2020;21:272-81.
10. Baekgaard JS, Eskesen TG, Sillesen M, Rasmussen LS, Steinmetz J. Ketamine as a rapid sequence induction agent in the trauma population: A systematic review. Anesth Analg 2019;128:504–10.
11. Nichols KA, Pacullo CA. Subdissociative Ketamine use in the emergency department. Adv Emerg Nurs J 2019;41:15-22.
12. Ellis DY, Husain HM, Saetta JP, Walker T. Procedural sedation for paediatric patients: A prospective audit of Ketamine use in the emergency department. Emerg Med J 2004;21:286–9.
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13. Kopsky DJ, Keppel Hesselink JM, Bhaskar A, Hariton G, Romanenko V, Casale R. Analgesic effects of topical Ketamine. Minerva Anestesiol 2015;81:440-9.

14. Bellolio MF, Gilani WI, Barrionuevo P, Murad MH, Erwin PJ, Anderson JR, et al. Incidence of adverse events in adults undergoing procedural sedation in the emergency department: A systematic review and meta-analysis. Acad Emerg Med Off J Soc Acad Emerg Med 2016;23:119–34.

15. Andolfatto G, Willman E. A prospective case series of single-syringe ketamine–propofol (Ketofol) for emergency department procedural sedation and analgesia in adults. Acad Emerg Med 2011;18:237–45.