Original Article

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.[1,2] 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.[1-3] 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.[2-4]

Ketamine was discovered in 1970, and since then is used as a potent analgesic and dissociative anaesthetic agent.[2] 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.[2,5] Because of these unique characteristics and versatility, it is becoming more and more

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popular among ED physicians and anaesthesiologists working in ED or ICU setups all over the world. Newer uses include low-dose analgesia, adjuvant treatment of local anaesthesia and nerve block, and application in reactive airway diseases.[5] Despite the potential advantages of this drug, it has not yet been universally recognized due to its reportedly troublesome "emerging" phenomenon, excessive salivation, it's scope for abuse and the introduction of other sedatives and analgesics[6,7] The main purpose of this study is to evaluate the adverse effects of Ketamine on PSA in an ED setup. This study is an addition to the already available literature, however, first in an Indian ED setup.

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.

Interviewer bias: To minimize the interviewer bias, a standard proforma was prepared to document with regard to the procedure performed, drugs used, vital signs of the patient before and after the drug administration and adverse effects if any.

Sample size calculation: Based on the reference literature, "Adverse events with Ketamine versus ketofol for procedural sedation on adults: A double-blind randomized controlled trial (2017) done by lemon *et al.*", found the percentage of Ketamine related adverse reaction (nausea or vomiting) to be 18%.[8] With 6% precision and a 95% confidence interval, the required number of the study sample was around 160 subjects.

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,

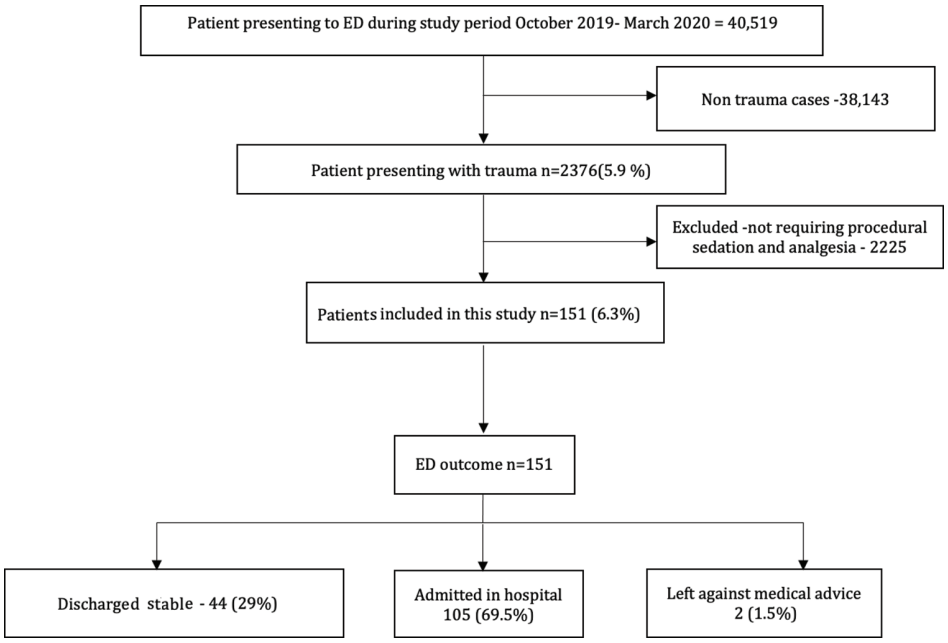

Figure 1: STROBE diagram

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, Drowsiness

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.

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.[9] 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.[8,9] 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.[10-12] However, the use of

Table 3: Hemodynamic variable in different time interval

Variables	0 min Frequency (%)	15 min Frequency (%)	30 min Frequency (%)	60 min Frequency (%)
Tachycardia (Heart rate ≥100 b/minute)	54 (35)	63 (41)	52 (34)	44 (29)
SpO_2 (<94%)	11 (7)	7 (4)	4 (2)	2 (1)
Respiratory rate (>24 per minute)	80 (52)	46 (30)	36 (23)	34 (22)
Systolic Blood Pressure (<90 mmHg)	20 (13)	17 (11)	15 (9)	14 (9)

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*.[3] 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 administrating 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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Nil.

Conflicts of interest

There are no conflicts of interest.

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