Procedural sedation in the emergency department: a randomized trial of ketamine versus etomidate

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Abstract

Introduction: Pain management, especially pain related to medical procedures, is a major concern for emergency physicians. While several drugs have proven effective, no single agent is considered ideal. This study aimed to compare the efficacy of Etomidate and Ketamine in preventing procedure-related pain in the emergency department (ED).

Methods: We conducted a prospective, randomized, single-center study over six months. The study included patients over 18 years old who required a painful medical procedure in the ED. Patients were randomly assigned to receive either a bolus of 0.1 mg/kg Etomidate or 0.5 mg/kg Ketamine. The primary outcome was a hybrid criterion: absence of awakening during the procedure and rapid recovery within 10 minutes.

Results: A total of 55 patients were enrolled, 25 in the Etomidate group and 30 in the Ketamine group. Four 15 patients experienced awakening during the procedure: three in the Etomidate group and one in the Ketamine group (p=0.3). The mean recovery time was 13.01 ± 3.7 minutes in both groups (p=0.26). Side effects occurred in 63.6% of patients (p=0.79). Complete recall of the painful procedure was reported in seven patients, six of whom were in the Etomidate group (p=0.03).

Conclusion: Ketamine does not appear to provide a significant advantage over Etomidate for procedural sedation in the ED. However, awakenings during the procedure were more frequent with Etomidate.

Key words: Pain, Sedation, Analgesia, Etomidate, Ketamine

INTRODUCTION

Pain management during medical procedures is a major concern for healthcare professionals, particularly in emergency settings. Procedural sedation is widely used by emergency physicians, achieving success rates of up to 98% (1). This approach involves administering sedative or dissociative agents, with or without analgesics (2). A thorough understanding of pharmacology is essential, as the selection of sedative and analgesic agents must be tailored to each clinical situation (3). Over the years, international guidelines for procedural sedation have been developed and updated. Commonly used medications include propofol, ketamine, fentanyl, midazolam, etomidate, and benzodiazepines (4,5). However, no single drug or combination fully meets all procedural requirements, explaining the lack of consensus on the optimal choice. Ideally, the perfect sedative agent would provide analgesic, hypnotic, anxiolytic, amnesic, and muscle-relaxant effects while being easily reversible, free of hemodynamic or respiratory complications, and offering both rapid onset and short duration of action (6). Since no such ideal drug exists, clinicians must carefully weigh the benefits and risks of each option based on the patient and the procedure (7,8). This study aimed to compare the efficacy and adverse event profiles of etomidate and ketamine in preventing procedure-induced pain in the ED.

METHODS

The study was conducted in the ED of a university hospital center in Tunis, receiving approximately 75,000 patients per year. This was a prospective, open-label, randomized, single-center, per-protocol clinical study conducted over a period of 6 months, from July 1st to December 31st, 2019. We included patients aged 18 years and over for whom a deemed painful, diagnostic, or therapeutic "medical act" was indicated by the attending emergency physician. We did not include pregnant or breastfeeding women, patients in shock or with a Glasgow coma score (GCS) <15, a respiratory rate <12 cycles/min, hepatic cirrhosis, a history of epilepsy, acute coronary syndrome, or allergy to morphine, ketamine, midazolam, or etomidate. We excluded patients for whom there was a protocol violation and those who were transferred to another department within 60 minutes after the start of the protocol.

Study procedure: For any patient presenting to the ED and meeting the inclusion criteria, the study interest was explained, and consent was documented. Once included, they were admitted to the Intensive Monitoring Unit, where vital signs monitoring was set up. Patients were randomized by random dice rolls to receive either a direct intravenous (DIV) bolus of 0.1mg/kg for the Etomidate group, or a single bolus of 0.5mg/kg based on weight for the Ketamine group. We administered a dose of 25 mg IVD for weights under 70 kg, 30 mg for weights between 70 and 90 kg, and 50 mg for weights of 100 kg or more. During ketamine administration, we encouraged pleasant dreams, and a bolus of 2 mg of midazolam was added when uncontrollable agitation was observed. Morphine hydrochloride, at a dose of 0.05 mg/kg, was used during sedation in both groups whenever the patient expressed verbal or facial pain during the procedure.

An antidote administration protocol (Naloxone and Flumazenil) was established. Patients were

kept under surveillance and monitoring with the collection of various vital parameters: respiratory rate, SpO2, heart rate, blood pressure, level of consciousness (according to the Alertness Scale) at 5, 10, 20 minutes, and until patient awakening at 60 minutes with recovery to a normal state of consciousness.

We defined Sedation Time (ST) as the time interval between the injection of the Etomidate or Ketamine bolus at T0 and the achievement of effective sedation, defined by an alertness scale score <2. Recovery Time (RT) was defined as the time interval between the initial Ketamine or Etomidate bolus injection at T0 and the recovery of a strictly normal state of consciousness (alertness scale score = 12). Effective Sedation Duration (RT – ST) was defined as the time interval between achieving effective sedation and recovering a strictly normal state of consciousness. The primary outcome criterion was the absence of awakening during the procedure (alertness scale less than 2 throughout the procedure) and a rapid recovery within 10 minutes of the end of the procedure to a good state of consciousness. The secondary outcome criteria were the occurrence of adverse effects, amnesia of the painful episode, defined by a vague or absent memory of the procedure, apprehension of potential future sedation, and the occurrence of dreams during the procedure.

Statistical tests and computer equipment: Data were entered and analyzed using SPSS version 22 software. Percentages were calculated for qualitative variables, and means with standard deviations for quantitative variables. Comparison of means was performed using the Student's T-test for independent series. To compare percentages on independent series, we used Pearson's chi-squared test, and in case of non-validity of this test, Fisher's exact bilateral test. In all statistical tests, the significance level was set at 0.05. At the end of the univariate study, we conducted a multivariate analysis using logistic regression to calculate an adjusted OR with a 95% confidence interval (CI) for each factor directly related to the event.

Ethical Considerations: We declare no conflict of interest. Written consent was obtained from each patient. The two molecules we used are internationally recommended for procedural sedation. Information was processed anonymously, and we respected medical confidentiality for all patients.

RESULTS

During the study period, we collected 55 patients (Figure 1). The mean age of the population was 39 ± 15 years in the etomidate group and 34 ± 16 years in the ketamine group (p = 0.3).

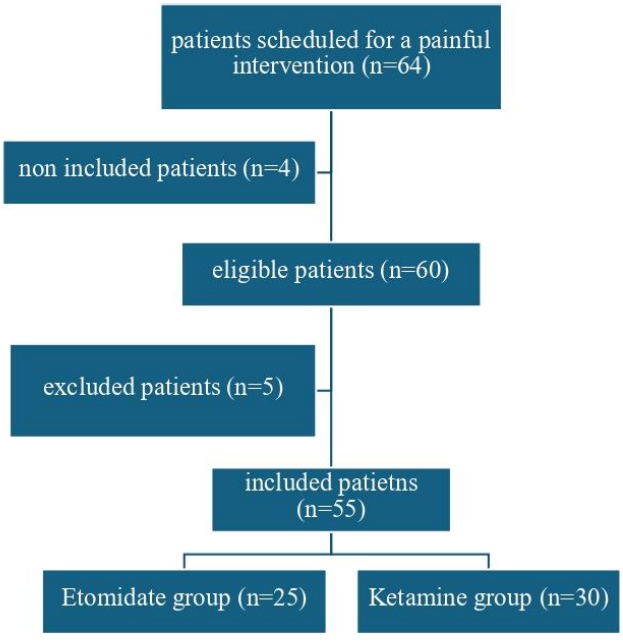

Figure 1: Flow chart of the study population

A male predominance was observed in both groups, with a sex ratio of 3.2 in the etomidate group and 2.3 in the ketamine group (p = 0.7).

Two patients (8%) in the etomidate group had received morphine within the six months preceding the procedure, compared to one patient (3%) in the ketamine group (p = 0.58).

The medical procedures requiring procedural sedation are summarized in Table 1.

Table 1. Type of procedure performed in both groups

Procedure; n (%)	Etomidate group n=25	Ketamine group n=30	p
Reduction of a dislocation	5 (20)	11 (36.7)	0.08
Wound care	6 (24)	5 (16.7)	0.73
Chest tube (thoracic drain)	6 (24)	4 (13.3)	0.49
Incision and drainage of a cutaneous abscess	3 (12)	6 (20)	0.27
Central venous catheter	2 (8)	3 (10)	0.64
Lumbar puncture	3 (12)	1 (3.3)	0.3

The mean duration of procedures was 4.93 ± 1.55 minutes in the etomidate group and 5.6 ± 1.8 minutes in the ketamine group (p = 0.61). Forty-one patients achieved an alertness scale score of less than 2 within 5 minutes, including 19 patients in the etomidate group and 24 patients in the ketamine group (Table 2). Four patients awakened during the medical procedure: three in the etomidate group and one in the ketamine group (p = 0.3). A single bolus of morphine was administered to these four patients to allow completion of the procedure without pain.

No patient exhibited hemodynamic or respiratory instability during the procedures. There was no significant difference in mean arterial pressure or respiratory rate between the two groups (p = 0.3) (Figure 2).

Table 2. shows the timing related to procedural sedation in both groups.

	Etomidate group n=25	Ketamine group n=30	p
Duration of the procedure (min); mean ±SD)	5.2 ± 1.4	5.6 ± 1.8	0.3
Sedation time (min); mean ±SD)	4 ± 2	4 ± 1.8	0.8
Recovery time (min); mean ±SD)	12 ± 3	13.5 ± 4	0.2
Effective sedation duration (min); mean ±SD)	8,6± 3	10 ± 3	0.2
Awakening time (min); mean ±SD)	4 ± 2.7	4.3 ± 2.3	0.7

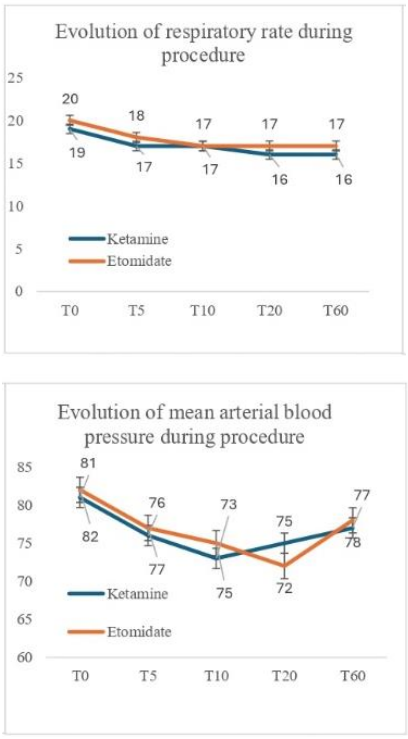

Figure 2: Variation in respiratory rate arterial pressure during the procedure in both groups

Occurrence of Adverse Events

Thirty-five patients (63.6%) experienced adverse events: 12 patients (48%) in the etomidate group and 23 patients (76%) in the ketamine group (Table 3).

Table 3: Adverse Events Reported in Each Group

Adverse effects; n (%)	Etomidate group N=25	Ketamine group N=30	p
Agitated awakening	5 (20)	10 (33.3)	0.2
Laryngospasm	1 (4)	2 (6.7)	0.8
Desaturation <90%	1 (4)	1 (3.3)	0.8
Apnea lasting 30 seconds	0	1 (3.3)	0.7
Nausea	1 (4)	8 (26.7)	0.03
Hallucinations	2 (8)	6 (20)	0.2
Cough	2 (8)	4 (13.3)	0.6
Myoclonus	4 (16)	1 (3.3)	0.1
Vomiting	2 (8)	3 (10)	0.7

Among the 10 patients in the ketamine group who experienced agitated awakening, six required a 2 mg bolus of midazolam to control the agitation.

Amnesia of the Painful Episode and Dreams During the Procedure:

Seven patients (12.7%) retained a complete memory of the painful procedure, including six in the etomidate group (p=0.03). During the procedure, 32 patients (58.1%) reported experiencing dreams (Table 4).

Multivariate Analysis

Our multivariate analysis showed that only amnesia of the painful episode was significantly higher in the etomidate group of patients, with an odds ratio (OR) of 0.1, 95% confidence interval [0.012; 0.980] (p = 0.04).

DISCUSSION

The results of our study revealed that etomidate and ketamine are two comparable agents in terms of efficacy for procedural sedation in emergency settings. Their rapid onset of action, ability to ensure quick recovery, hemodynamic and respiratory profiles make them preferred choices for clinicians.

Table 4: Dreams and Recall of the Procedure in Both Groups

	Etomidate group N=25	Ketamine group N=30	p
No memory; n(%)	17 (68)	19 (63.3)	0.03
Vague memory; n(%)	2 (8)	10 (33.3)	
Complete memory; n(%)	6 (24)	1 (3.3)	
Pleasant dream; n(%)	5 (20)	11 (36.7)	0,68
Unpleasant dream; n(%)	3 (12)	13 (43.3)	0.68

Our findings are consistent with those reported in the literature. The study by Salen et al. compared the efficacy of etomidate and ketamine in aligning dislocations and observed a similar success rate in both groups. Although two failures were reported in the etomidate group (n = 34), no failures occurred in the ketamine group (n = 46). These results suggest that both agents are comparable in terms of efficacy and management of immediate complications (9).

Ketamine, widely used in emergency medicine for procedural sedation, is recognized for its dissociative, analgesic, and anesthetic effects. It provides sedation, analgesia, and amnesia while preserving hemodynamic and respiratory stability (10). Thanks to its rapid onset and relatively short duration of action, it is particularly suitable for brief and painful procedures. In general, its effects last between 15 and 30 minutes (11).

When administered at low doses, ketamine induces analgesia and mild disorientation. Once

the dissociative threshold is reached, further increases in ketamine do not impact the level of sedation (12).

Etomidate, on the other hand, offers several advantages: a simple dosing regimen, rapid onset, short duration of action, rapid metabolism, and hemodynamic stability (13). Its action begins immediately and generally lasts between 5 and 15 minutes (14). However, etomidate does not possess analgesic properties and often requires co-administration of a short-acting opioid, which may increase the risk of respiratory depression (15).

In our study, the mean sedation time was 4 minutes in both groups ($p = 0.8$). These results are similar to those found in the literature. In the study conducted by Dişel et al. comparing the efficacy of etomidate versus ketamine for dislocations alignment, the sedation time was 4.3 minutes for the etomidate group and 2.2 minutes for the ketamine group ($p < 0.001$) (16).

Our study showed that both drugs can cause adverse effects, which is consistent with available data in the literature. Newton et al. observed that 21.7% of patients receiving ketamine-based procedural sedation experienced side effects, including emergence agitation (13%), vomiting (4%), myoclonus (4%), and hypersalivation (2%) (17). Nevertheless, etomidate may be responsible for myoclonus, adrenal suppression, nausea, and vomiting (18).

Furthermore, etomidate was sometimes associated with more pronounced awakening and a clearer memory of the procedure, a phenomenon we observed in 12.7% of patients who reported complete recall of the painful event. This difference between groups was statistically significant ($p = 0.03$), confirming the increased risk of procedural recall in patients who received etomidate.

A study by Ruth et al. found that among patients who received etomidate before a painful procedure, 69% had no memory of the event, 27% had partial recall, and 4% had complete recall ($p = 0.03$). These results are in line with our findings, although the proportion of complete recall in our population appears slightly higher (19).

Our study has several limitations. The main weakness is undoubtedly the small sample size. Additionally, at the time of the study, we did not have access to capnography, an essential tool for monitoring procedural sedation.

On the other hand, one of the strengths of the study lies in the originality of the work, which was conducted in an emergency setting and focused on addressing pain associated with medical procedures, a key mission for emergency physicians.

CONCLUSION

Etomidate and ketamine are effective agents for procedural sedation, with similar safety and efficacy profiles. However, the choice between these two medications should consider the specific clinical situation, particularly the duration of the procedure and the patient's post-procedural comfort. Although etomidate has a very rapid onset of action and is unlikely to cause severe hemodynamic or respiratory effects, the risk of

procedural recall remains an important factor, especially for painful procedures. Further research is needed to better understand the factors influencing procedural recall and to develop strategies aimed at minimizing this while maintaining effective and safe sedation.

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Conflicts of interest*: The authors declare no conflict of interest*

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