Intravenous Ketamine Is As Effective As Midazolam/ Fentanyl for Procedural Sedation and Analgesia in The Emergency Department

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SUMMARY

The study compared the effectiveness of ketamine and midazolam/fentanyl as procedural sedation and analgesia agents for reduction of fractures and dislocated joints. Forty-one adult patients were enrolled by convenience sampling. They were randomized to receive ketamine or midazolam/fentanyl. Depth of sedation, pain score, procedural outcome and memory of the procedure were documented. The ketamine group had deeper sedation, but there was no statistical difference in other variables between the two groups. Three patients in the midazolam/fentanyl group had oxygen desaturation. More adverse effects were associated with ketamine. Intravenous ketamine is as effective as midazolam/fentanyl for procedural sedation.

KEY WORDS:
Analgesia; Fentanyl; Ketamine; Midazolam; Pain; Procedural sedation

INTRODUCTION

Alleviation of pain and anxiety is an integral part of emergency procedures. Various guidelines have been recommended to guide the conduct of procedural sedation and analgesia (PSA) for painful procedures[1]. These are, however, not universally applicable because patients, procedures, practitioner expertise and working environments differ between centers[1].

Procedural sedation in the Emergency Department (ED) for reduction of fractures and dislocated joints require an agent that is safe, has a rapid onset of action, rapid recovery and minimal adverse effects. Multiple agents such as propofol, etomidate, barbiturates, benzodiazepines and opioids have been used for PSA. Other agents, such as methohexital, are not commonly utilized due to respiratory complications[2,3]. Several studies have reported that the combined use of opiates and benzodiazepines produces a synergistic response but, with significant risk of respiratory depression[4, 5].

The use of a single, safe and effective drug aids the ease of preparation and reduces administration error. The American College of Emergency Physician (ACEP) PSA clinical policy give propofol, midazolam/fentanyl and ketamine as a level 'B' recommendation and etomidate a level 'C' for PSA use in ED[2]. Ketamine has a longer recovery time as compared to propofol and etomidate, however it offers analgesic effect that outlasts its sedative effect[1].

Unlike other PSA agents, ketamine acts by disconnecting the limbic and thalamocortical systems. This leads to detachment between the central nervous system and external stimuli such as pain. The ensuing dissociative state preserves cardiopulmonary stability while allowing the performance of painful procedures with minimal risk of complications[6]. Emergence delirium phenomenon has been said to occur more frequently in adults than children, but there is limited evidence to support this assumption[7].

The purpose of this study is to compare the effectiveness of ketamine and midazolam/fentanyl as PSA agents in the ED of a university hospital.

MATERIALS AND METHODS

The study was conducted between March and November 2008 following the approval of the institutional ethics committee. Patients aged between 18 and 60 years who presented to the ED with fractures and dislocations requiring reductions were enrolled by convenience sampling. Patients with hemodynamic instability, alcohol influence, known or suggestive renal and liver disease, pregnant or lactating, ASA III and above, a previous history of allergy to opioids, benzodiazepines or ketamine and hypertensive (systolic blood pressure > 145 mmHg and diastolic blood pressure > 100mmHg) were excluded.

Patients were divided into two groups by block randomization. The patients were blinded from the sedative agents used but not the procedure. They either received midazolam/fentanyl or ketamine as PSA. Demographic data, procedure type, medication doses, administration time, procedure outcome and pain score (before and after the procedure) were recorded on a standardized data collection sheet. Medication was titrated accordingly to achieve desired clinical effects. A single dose of intravenous fentanyl was administered at a dose of 1 mcg/kg. This was followed by intravenous midazolam at a dose 0.05mg/kg titrated to the depth of sedation, every three minutes to a maximum dose of

This article was accepted: 7 August 2011
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7.5 mg. Intravenous ketamine was administered at a dose of 0.5 mg/kg and titrated every three minutes with a maximum dose of 2 mg/kg. Clinicians treating the patient were not blinded to the medication regimes to ensure safety. Depth of sedation was categorized according to the Modified Ramsay Sedation Score (MRSS) [8]. The target for optimal sedation before the reduction procedure began was MRSS ≥ 5. All patients received supplementary oxygen by facemask during the procedure. Blood pressure was serially recorded every three minutes during the first 15 minutes and every five minutes thereafter until completion of the procedure and the patient had regained full consciousness.

The primary outcomes of this study were pain score reduction, success of procedure, depth of sedation and memory of the procedure. Pain was documented using the 11-point Numerical Rating Scale (NRS) [9]. Significant pain control was defined as the difference of at least two points on the NRS before and after the procedure in an alert and conscious patient. The reduction of pain score was defined as percentage of difference between the pain score before and after the procedure. Procedures were considered successful if adequate reduction was achieved in the ED without further reductions required in the operating theatre. Secondary outcomes of this study were to document adverse effects during and following the PSA.

Data, represented as mean or proportions and differences in these values were calculated with 95% confidence intervals (95%CI). Variables were tested for normality (Kolmogrov-Smirnov test) before analysis. Demographic data are given as median or mean values with ranges. Comparisons of pain score reduction were made using the student t-test (p value < 0.05) and 2-sample test assuming unequal variances and a Mann-Whitney U (p value < 0.05) test for depth of sedation. Categorical data were analyzed using the chi square test (successfulness of reduction, memory of the procedure, p < 0.05). All analysis was performed using SPSS version 13.0 (SPSS, Inc., Chicago, IL).

RESULTS

Forty-one patients were enrolled during the nine month study period. Twenty-three patients received midazolam/fentanyl and 18 patients received ketamine. The baseline characteristics of the study group are presented in Table I. The primary outcomes of the study are displayed in Table II. The relationship between successful reductions, complete amnesia, and percentage of reduction in the pain score in the two groups is not statistically significant. Patients receiving ketamine had significantly deeper sedation compared to the midazolam/fentanyl group (p=0.021).

Adverse effects occurred in 14 patients (Table III). Oxygen desaturation of less than 90% was observed in three patients in the midazolam/fentanyl group. These patients required an increase in supplemental oxygen and stimulation to return to normal saturation levels. Significant adverse effects with ketamine sedation were dizziness (p= 0.001), nausea (p= 0.017) and emergence delirium (p=0.017). Five patients who received ketamine had more than one adverse effect. One patient in the ketamine group had asymptomatic ventricular ectopics which resolved spontaneously after 2 hours. One procedure following ketamine sedation was abandoned when the patient developed myoclonus with generalized muscle rigidity. The patient awoke with no recall of the event. The PSA was repeated with another sedative agent with a favourable outcome.

DISCUSSION

This study addresses specific issues on PSA in the emergency department. The hypothesis was PSA with a single drug (ketamine) is as effective as midazolam/fentanyl in facilitating and ensuring success for painful procedures in the ED. A recent prospective study of 92 adult patients, who received intravenous ketamine as PSA agent, demonstrated that adequate sedation and successful completion of procedure was achieved in 98.9% of patients6. This is comparable to our study results that documented greater than 90% success rate for the procedures performed though the differences between the two groups are not statistically significant.

Table I: Patient characteristics in PSA groups

	Midazolam/ Fentanyl (n=23)	Ketamine (n=18)
Median age	36 (18-81)	28(18-54)
Sex (%)		
Male	65%(15)	94%(17)
Female	35% (8)	6%(1)
Mean weight(kg) (± SD)	68 (±11.8)	69 (±13.0)
Mean Initial SBP(mmHg)	95.3 (±10.6)	91.5 (±8.29)
Mean Initial HR(bpm)	81.2 (±15.18)	76 (±13.0)
Procedure (Fracture & Joint reduction)		
Hand	0%	5.6%
Wrist and forearm	21.7%	38.9%
Elbow and arm	4.3%	0%
Shoulder	43.5%	44.4%
Hip	13.0%	0%
Knees	8.7%	5.6%
Ankle	0%	5.6%
Foot	8.7%	0%

SBP- Systolic Blood Pressure
HR- Heart rate

Table II: Primary outcomes in PSA groups

	Midazolam/Fentanyl n=23	Ketamine n=18	95%CI	P values
Pain score before (median)	7	7	-	-
Pain score after (median)	1	3	-	-
Percentage of pain score reduction (mean)	72.6	63.83	12.5-30	0.409
Successful procedure (%)	95.7	94.4	0.07-22.2	0.859
Depth of sedation (mean)	4.78	5.33	-	0.021
Complete amnesia (%)	82.6	100	0.37-0.7	0.06

The median pain score for both groups prior to PSA was seven (severe pain). Reduction in pain was noted in both groups after the procedure. The median pain score for the midazolam/fentanyl group was lower than the ketamine group. Despite the good reduction in pain score between the two groups, the percentage of pain score reduction was not statistically significant. It is uncertain if this reduction in pain is purely due to the analgesia or in combination with other factors such as the severity of injury treated, the interventional outcome or environmental factors that provided relaxation and comfort to the patient. A combination of these factors may have influenced the pain score reported in both groups. This study however, did not attempt to identify the PSA agents that provided analgesic effect outlasting the sedative effect.

Although the result is not statistically significant, three patients who received midazolam/fentanyl had oxygen desaturation to less than 90%. There was no episode of hypoxaemia documented in the ketamine group. However, several studies have reported hypoxaemia and respiratory depression when ketamine and midazolam are used in combination. A recent study of 260 children who received midazolam/fentanyl as PSA had 15% more respiratory complications than patients receiving ketamine/midazolam, despite midazolam dose titration[4]. A study that evaluated the effects of sedative doses of midazolam and an analgesic dose of fentanyl on 12 young healthy volunteers showed that a combination of midazolam/fentanyl caused hypoxaemia in 92% and apnoea in 50% of subjects[7]. These reports suggested that respiratory complications were due to the administration of fentanyl rather than midazolam. Therefore, intravenous ketamine appears to be as effective as, midazolam/fentanyl in providing optimal sedation while minimal the risk of airway compromise.

The emergence delirium documented in this study is a known adverse effect of ketamine. Benzodiazepines have been administered with ketamine as prophylaxis against potential agitation following PSA. However, paediatric patients effective sedation without significant emergence phenomena has been reported with intravenous ketamine alone[10, 11, 12]. It is still uncertain if these findings apply in adults. In a recent study, midazolam significantly reduced the incidence of emergence phenomenon after ketamine procedural sedation and analgesia in adults[13].

The frequency of vomiting (7%) and myoclonic movements (7%) in this study is similar and comparable to other published data[6]. The limited sample size may not be sufficient to detect all potential adverse events related to the use of these PSA agents. Furthermore, the medical officers and nurses were not blinded to the PSA drugs administered, which may produce bias in the recording of adverse effects and pain score documentation.

Ketamine is unique in its versatility of utilization, safety and storage. It is an alternative agent for PSA in the emergency department and in pre-hospital care. Newer PSA agents such as ketofol may have superseded ketamine as PSA agent in a controlled working environment but they may not be as versatile or applicable in environments such as mass casualty situation, disaster response, battlefield medicine and minimally equipped or understaffed emergency departments[14].

CONCLUSION

Intravenous ketamine is as effective as midazolam/fentanyl to facilitate the success of fractures and dislocated joint reductions in the emergency department. More adverse effects were associated with ketamine and adequate precautions, including close monitoring of vital signs and the presence of physician experienced in airway management are recommended during PSA.

ACKNOWLEDGEMENT

We would like to thank Prof. Colin Robertson, Professor of Emergency Medicine, University of Edinburgh, UK for reviewing this manuscript and Prof. Abu Hassan Shaari Mohd Nor, Faculty of Economics and Business, University Kebangsaan Malaysia for assisting in statistical analysis of the study.

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Declaration Of Originality

There is no conflict of interest or sources of financial support involved with this manuscript.