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Continuous Infusion Ketamine for Adjunctive Sedation in Medical Intensive Care Unit Patients: A Case Series

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Abstract

Ketamine has been rarely described for use in critically ill patients. We describe our institutional experience using continuous infusion ketamine for sedation. This was a retrospective chart review of patients admitted to the medical intensive care units (MICUs). An informatics query of patients who received continuous infusion ketamine between 1/1/2010 and 7/1/2012 was conducted. Mechanically ventilated patients in the MICU who received continuous infusion ketamine were included. Twelve patients met criteria. Mean age was 41; 60% were Caucasian and 60% were female. Six patients were admitted for pneumonia, three for asthma exacerbation. Median duration of ketamine therapy was 1.57 days. Median minimum and maximum rates were 0.24mg/kg/hr and 0.83mg/kg/hr. The maximum documented dose used was 2.8mg/kg/hr. The ketamine infusion was discontinued secondary to tachycardia or hypertension in two patients. No patient who received concomitant benzodiazepines experienced hemodynamic changes prompting ketamine cessation. Median maximum SBP, DBP, and HR while on ketamine were 154, 96 and 121, respectively. No further adverse events were identified. Five of the patients had decreases in concomitant sedative and analgesic doses while five had increases. Continuous infusion ketamine can safely be used for adjunctive sedation/analgesia in mechanically ventilated MICU patients. Larger trials are needed to further define optimal dosing and confirm safety.

Keywords: Ketamine; Sedation; Continuous infusion; Mechanical ventilation; Critically ill; Intensive care unit

Introduction

Despite advances in the care of critically ill patients, pain, agitation, and anxiety occur frequently in this population [1]. Untreated or undertreated pain and agitation/anxiety can result in several negative short- and long-term outcomes, including arterial vasoconstriction, impaired tissue perfusion, hypercatabolism, and post-traumatic stress disorder [2-4]. Alternatively, deep levels of sedation have consistently been linked to prolonged duration of mechanical ventilation (MV), intensive care unit (ICU) and hospital length of stay (LOS), and delirium [5-9]. Various strategies to decrease the occurrence of and manage these problems have been recommended in the 2013 American College of Critical Care Medicine Guidelines for Management of Pain, Agitation, and Delirium (PAD) [1]. Common drug therapies for pain and agitation include opioid and non-opioid analgesics, dexmedetomidine, propofol, and benzodiazepines. Ketamine has historically been used as an anesthetic induction agent and exhibits dose-dependent analgesia, sedation, and amnesia [10]. The 2013 PAD Guidelines mention the use of ketamine as a possible adjunct for non-neuropathic pain management. Due to a lack of supporting data, they do not provide recommendations for the appropriate use of ketamine for managing pain and agitation in the critically ill population [1]. In light of current critical drug shortages, the use of a sedative agent that displays analgesic properties in addition to a favorable hemodynamic and pharmacokinetic profile is worth assessing further. We present this case series to describe the use and hemodynamic effects of ketamine in medical intensive care unit (MICU) patients in our institution.

Methods and Materials

Data were collected in patients who were admitted to the medical intensive care units (MICUs) at Barnes-Jewish Hospital between January 2010 and July 2012 and received continuous infusion ketamine. All patients were retrospectively identified via an informatics query. There were no exclusion criteria for subjects in this study. Baseline demographics, process of care data and hemodynamic variables were collected from medical charts and assessed. Any adverse drug events documented in the medical record were also collected. Descriptive statistics were used to analyze the data collected. Data collection for this case series was approved by the Washington University School of Medicine Human Studies Committee.

Results

A total of 12 subjects were included in this case series. The majority of subjects were Caucasian females with a mean age of 41 years. The median APACHE II score calculated upon ICU admission was 18. The most common admitting diagnosis was healthcare-associated pneumonia (HCAP). Findings related to the ketamine infusion and hemodynamic variables may be found in (Table 1,2). The use of ketamine in the individual patients with their hemodynamic responses is described in (Table 3). Ketamine infusions were discontinued secondary to tachycardia or hypertension in two patients. One of these patients was receiving dexmedetomidine in addition to fentanyl; the other was receiving only concomitant propofol. No patient that received concurrent benzodiazepines experienced hemodynamic changes prompting ketamine cessation. No further adverse drug reactions were identified, including rash, although 83% of patients in the study received concurrent corticosteroids for their underlying illness. Additionally, no reports of hallucinations were recorded with the use of ketamine. (Table 4) summarizes the concomitant sedatives and analgesics patients received with ketamine. Ten patients were receiving fentanyl infusions prior to the initiation of ketamine while eleven received midazolam and one patient received propofol. Two patients were receiving propofol in combination with midazolam and two patients received dexmedetomidine with midazolam and one patient received dexmedetomidine alone. Twenty-four hours after ketamine initiation, there were no changes in sedative/analgesic doses in one patient and decreases in five patients. Two patients had an increase in midazolam dose and a decrease in propofol dose while one patient was discontinued on fentanyl and dexmedetomidine and started on propofol. Two patients receiving midazolam and one receiving propofol had dose increases in the 24 hours after ketamine.

Table 1: Baseline Demographics

Mean age (range)	41 years (22 - 75)
Male, n (%)	5 (42)
Caucasian, n (%)	7 (58)
Median weight, kg (range)	100 (47 - 133)
Median APACHE II Score (range)	18 (7-23)
Known PSA, n (%)	4 (33)
Admitting diagnosis	
HCAP, n (%)	4 (33)
Asthma, n (%)	3 (25)
CAP, n (%)	2 (17)
Other, n (%)	3 (25)
Mean duration of mechanical ventilation, hours (range)	22.22 (1.06-121.58)
Mean ICU length of stay, days (range)	16.92 (3.33-41.23)

**PSA: Polysubstance abuse, HCAP: healthcare associated pneumonia, CAP: community acquired pneumonia, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate

Table 2: Ketamine Infusion Variables

Infusion variables	
Median duration (range)	1.6 days (0.4 - 11.3)
Median inital rate, mg/kg/hr (range)	0.3 (0.2-0.9)
Median maximum rate, mg/kg/hr (range)	0.8 (0.3-2.8)
Median rate over first 24h, mg/kg/hr (range)	0.6 (0.2-1.4)
Hemodynamic variables during infusion	
Median maximum SBP (range)	154 (122-209)
Median maximum DBP (range)	96 (54-108)
Median maximum HR (range)	121 (77-157)

Table 3: Individual Patient Variables

Pt. no.	Age, Gender	Admitting diagnosis	Initial Dose (mg/kg/hr)	Max Dose (mg/kg/hr)	Length of infusion (days)	BP 1 hour before ketamine	BP 1 hour after ketamine	HR 1 hour before ketamine	HR 1 hour after ketamine
1	26 yo, F	CAP	0.2	0.3	4.8	145/82	134/78	92	86
2	45 yo, M	CAP	0.9	0.9	2	116/67	122/70	62	64
3	42 yo, M	Asthma	0.2	0.8	0.7	124/74	118/70	88	87
4	43 yo, F	Septic Shock	0.2	1.6	11.3	101/65	100/62	57	60
5	75 yo, M	HCAP	0.8	1.5	0.4	85/42	109/50	51	59
6	31 yo, M	Asthma	0.3	0.8	1.1	121/63	121/64	108	108
7	32 yo, F	HCAP	0.9	2.2	2.9	122/73	141/86	97	109
8	64 yo, M	HCAP	0.2	0.4	1.1	117/54	135/78	94	79
9	22 yo, F	Asthma	0.9	2.8	0.6	115/63	131/72	56	82
10	26 yo, F	Lung transplant rejection	0.2	1	2.3	102/55	94/51	82	74
11	33 yo, F	Sarcoidosis	0.3	0.5	0.7	122/80	93/63	120	131
12	55 yo, F	HCAP	0.5	0.5	2.5	99/40	148/63	83	85

Table 4: Concomitant Sedative and Analgesic Agents

Pt. no.	Fentanyl dose prior to ketamine (mcg/hr)	Median fentanyl dose 24 hr after ketamine (mcg/hr)	Midazolam dose prior to ketamine (mg/hr)	Median midazolam dose 24 hr after ketamine (mg/hr)	Propofol dose prior to ketamine (mcg/kg/min)	Median propofol dose 24 hr after ketamine (mcg/kg/min)	Dexmedetomidine dose prior to ketamine (mcg/kg/hr)	Median dexmedetomidine dose 24 hr after ketamine (mcg/kg/hr)
1	200	200	5	5	0	0	0.0	0.0
2	600	600	8	10	15	0	0.0	0.0
3	150	0	0	0	0	30	0.9	0.0
4	75	75	2	4	0	0	0.0	0.0
5	150	75	10	4	0	0	0.0	0.0
6	0	0	0	0	40	60	0.0	0.0
7	100	100	4	6	65	0	0.0	0.0
8	50	0	6	3	0	0	0.0	0.0
9	125	125	3	0	0	0	1.3	1.3
10	100	100	8	6	0	0	1.4	1.4
11	300	200	6	4	0	0	0.0	0.0
12	0	50	2	3	0	0	0.0	0.0

Discussion

Our findings suggest adjunctive ketamine may be used safely in MICU patients for sedation and analgesia. In general, the hemodynamic effects of continuous infusion ketamine were limited, as demonstrated by a lack of significant change in blood pressure and heart rate in the majority of patients. However, two of the twelve patients included in this study experienced hemodynamic effects resulting in ketamine discontinuation. This limits the generalizability of the safety of ketamine in this patient population and illustrates the need for a well-designed study to more definitively determine the effect of the drug on hemodynamics. Patients receiving concomitant benzodiazepines for sedation did not require discontinuation of ketamine. There was also no incidence of hallucinations reported. This may be due to our practice to initiate ketamine following established concurrent sedative therapy and to discontinue an hour prior to stopping the concurrent sedative.

Ketamine provides sedation and analgesia primarily through antagonizing N-methyl-D-aspartate (NMDA) receptors in the central nervous system [11]. In addition, it has analgesic activity with actions on mu and kappa opioid receptors. Compared to other agents, ketamine does not provide deep levels of sedation or cause hypotension upon administration. This makes the drug an attractive option to use in critically ill patients. It may be especially appealing for use in patients requiring high doses of sedative and/or analgesic drugs. Ketamine may also be beneficial in patients with airway disease such as COPD or asthma, due to its bronchodilator properties [11]. The potential for hypertension and tachycardia may be related to the effects of ketamine in promoting central sympathetic stimulation and inhibiting catecholamine uptake [11]. Neuroprotective, antidepressant and antinflammatory properties have also been suggested [12,13].

The optimal dose and duration of ketamine for adjunctive sedation and analgesia in critically ill patients is unknown. Several small studies and case reports have been published describing the use of ketamine in mechanically ventilated patients [11]. Many of these have been performed in pediatric patients or for refractory status asthmaticus. Ketamine used in combination with morphine at a dose of 0.06-0.12 mg/kg/hr for 48 hours has been shown to be effective in managing post-operative pain, lowering morphine consumption [14,15]. A case report of patient with respiratory failure secondary to acute lymphocytic leukemia describes the use of ketamine for adjunctive sedation (to midazolam) with an average dose of 1.18 mg/kg/hr for 4.27 days [16]. A prospective, randomized study was performed in twenty-five patients with severe head injury [17]. Twelve received ketamine with midazolam at an average infusion rate of 4.92 mg/kg/hr for the first four days of therapy. Comparison of sedation assessments was not performed in this study. Compared to adjunctive sufentanil, ketamine was associated with higher heart rates on the third and fourth days of infusion (94 beats/min vs. 78 beats/min, p=0.03). Another small study presented in abstract form describes the use of adjunctive ketamine with midazolam compared to fentanyl. The doses and duration were not specified, and ketamine was associated with higher blood pressures and lower incidence of airway resistance [18].

One of the potential advantages of adjunctive ketamine may be its impact on concomitant sedative and analgesic doses. Our data also demonstrate inconsistencies with regard to this effect. There appears to be a similar number of patients who required dose escalation and decreases of concurrent sedative infusion rates in the 24 hour period after ketamine was initiated. Therefore, it is difficult to make any conclusions regarding the effect of adjunctive ketamine on sedative/analgesic dose requirements based on our data. A well-designed prospective study is needed to determine this outcome.

Compared to previous studies and case reports, our findings are consistent in relation to the doses of ketamine and potential for adverse cardiovascular effects. Similar to the literature, there was no incidence of hallucinations or other neurologic adverse effects with the use of concomitant benzodiazepines. Although higher doses of ketamine were reported in brain-injured patients, this represents a population with significantly different problems compared to patients in the MICU. Based on the collective findings, it seems reasonable to conclude a low dose of ketamine infusion, approximately 0.2 to 1 mg/kg/hr, is safe for adjunctive sedation and analgesia in MICU patients up to 48 hours.

There are some limitations in applying the findings from this case series. Several factors may affect outcomes related to sedation and analgesia, making interpretation of the impact of ketamine difficult to ascertain since this report is completely retrospective. Secondly, there is a lack of a control group to compare the use of ketamine to the use of standard sedation practices. The effect of ketamine on hemodynamics is also difficult to interpret since we have reported single values one hour before and one hour after the infusion was started. As previously described, the data from our case series also do not provide meaningful conclusions on the effects of ketamine on doses of concomitant sedative and analgesic drugs. This may be an additional advantage of using adjunctive ketamine, however, it requires investigation in larger, well-designed studies. Finally, little is known about the long-term effects of continuous infusion ketamine in MICU patients. The majority of the patients in our study received infusions for 48 hours or less.

Despite these limitations, our data suggest that low-dose ketamine infusions may be safe as adjunctive therapy for sedation and analgesia in MICU patients. Future study should be directed towards the optimal dosing regimen and duration of adjunctive therapy in this patient population. Additionally, studies should be designed to better evaluate the effects of ketamine on sedation assessments in order to better elucidate its role in therapy.

Conclusions

Adjunctive low-dose ketamine may be safely used in MICU patients for sedation and analgesia. Further study is required to obtain the optimal dosing, duration, and place in therapy of ketamine for this indication.

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