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ORIGINAL ARTICLE

Comparison of intravenous ketamine and fentanyl sedation in duration of mechanical ventilation in intensive care unit

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ABSTRACT

Background and aims : To compare the duration of mechanical ventilation in patients receiving ketamine compared to fentanyl for sedation in mechanically ventilated patients in intensive care unit.

Methods: One hundred and six patients requiring mechanical ventilation were randomized to receive continuous intravenous infusion of either ketamine (1 mg/kg bolus followed by 0.4 to 0.8 mg/kg/h) or fentanyl (1mcg/kg bolus followed by 0.3-0.5 mcg/kg/min) with the dose titrated to achieve Richmond Agitation Sedation Scale (RASS) score of 0 to -1 and Behavioral Pain Scale (BPS) score of 3 to 7. The primary outcome was the duration of mechanical ventilation. Secondary outcomes were sedation score, analgesia score and need of vasopressors.

Results: The mean duration of ventilation was 2.5±0.6 days and 2.2±1.0 days (p=0.1) in patients receiving ketamine and fentanyl respectively. More patients required vasopressors: 27 (50.9%) vs 9 (17%) in patients receiving fentanyl compared to ketamine (p<0.05). There were no significant changes in hemodynamic variables after the initiation of the study drug in both the groups. Infusion was discontinued for adverse effects in seven (13%) patients in both the groups.

Conclusion: When compared with fentanyl, continuous ketamine infusion was tolerated similarly by critically ill adults, with similar duration of mechanical ventilation. Ketamine sedation was associated with decreased requirement for vasopressors.

Keywords: *analgesia, fentanyl, ketamine, mechanical ventilation, sedation.*

INTRODUCTION

Sedation depresses awareness of the environment and response to external stimulation.[1] Whereas anxiolysis is the reduction of emotional and physical responses to real or perceived danger the patient experiences in the ICU.[2,3] Analgesia refers to alleviation of pain which needs to be addressed in mechanically ventilated patients as inadequate analgesia can cause tachycardia, hypertension, increased myocardial oxygen consumption, and can induce myocardial ischemia.[4]

Critically ill, mechanically ventilated patients experience pain and anxiety. Inadequate analgesia and sedation might have detrimental physiological consequences, including an increase in sympathetic nervous activity and ventilator dyssynchrony.[5]

Fentanyl, when used for sedation and analgesia in mechanically ventilated patients has a prolong effect after repeated dosing or infusion. It is metabolized in liver and excreted by kidneys and may accumulate in patients with renal insufficiency,[6] causes dose dependent depression of ventilation, which is a major concern in a critically ill. It also inhibits bowel function and can cause constipation or ileus.[7]

Ketamine is recently being explored for sedation in ICU setting.[8] Ketamine has a positive inotropic action and induces vasoconstriction, which preserves hemodynamic stability, has bronchodilator activity and also has anti-inflammatory properties.[9] Ketamine clearance is not affected by kidney diseases.[10] It has analgesic effect and has opioid sparing effect when used as adjunct to opioid sedation in ICU.[6]

Since the current evidence regarding the effect of ketamine as an analgo-sedative in mechanical ventilation is lacking in literature, we aimed to assess if ketamine sedation decreased the duration of ventilation when compared with fentanyl in mechanically ventilated patients.

METHODS

A prospective, comparative study was conducted to evaluate and compare intravenous ketamine and fentanyl in duration of mechanical ventilation in intensive care unit. The study adhered to ethical principles outlined in the Declaration of Helsinki and approval from the institutional review committee was obtained for the study. Prior to enrollment, written consent was obtained from the first-degree relative of the patient.

The study was conducted in ICU of a tertiary care center. All patients aged 18 years and more requiring mechanical ventilation for greater than 24 hours in the ICU were included. Patients with pregnancy, head injury, hypertension (systolic blood pressure>180mmHg or diastolic blood pressure>100mmHg), tachycardia>150 bpm and seizures were excluded.

This study considered 95% confidence interval and 80% power. Sample size was estimated as 48 in each arm. Considering 10% dropouts the total sample size considered was 106.

After arrival in the ICU, eligibility was assessed in the patients who required intubation or were already intubated elsewhere. Each eligible consecutive patient was randomized on 1:1 basis in to two groups, group A and B. Randomization was done using computer generated random numbers that were concealed in a sealed envelope. Group A received infusion of ketamine and Group B received fentanyl infusion titrated to achieve a sedation goal of Richmond Agitation Sedation Scale (RASS) Score of -1 to 0 and Behavioral Pain Scale (BPS) score of 3 to 7.

Group A patients received intravenous ketamine 1 mg/kg bolus followed by initial infusion rate of 0.4 mg/kg/hr that was increased depending upon clinical need up to a maximum of 0.8 mg/kg/hr, titrated to the desired Richmond agitation sedation scale (RASS) and Behavior Pain Scale (BPS).

Group B patients received intravenous fentanyl as bolus of 1 mcg/kg followed by continuous infusion at 0.3 mcg/kg/hr that was titrated to achieve sedation goal (RASS score -1 to 0 and BPS 3 to 7). Infusion was increased up to a maximum of 0.5 mcg/kg/hr. Patients were considered under-sedated if desired level of sedation was not achieved with the study drugs. Intravenous midazolam 1 mg bolus was administered as rescue sedative. Patients were considered to be over-sedated when the RASS score was less than -1. The study drugs were stopped till RASS score reached 0.

The infusion of ketamine was terminated if there was evidence of new onset atrial fibrillation/flutter with rapid ventricular response, heart rate >150 bpm, supraventricular tachycardia, ventricular tachycardia and ventricular fibrillation.

The infusion of fentanyl was terminated if there was evidence of gastroparesis (gastric residual volume >500ml), hypotension (SBP<90mmHg or DBP<50mmHg) despite using two vasopressors, ventricular tachycardia, fibrillation, bradycardia (HR<50 bpm). Rest of the patient management followed the institutionalized ICU protocol.

Weaning and Extubation:

Patients underwent spontaneous breathing trials when they met the following screening criteria: PaO2/FiO2 ratio >200, positive end-expiratory pressure 5 cm of H2O, intact cough and airway reflexes, one minute frequency to tidal volume ratio of over 105 (RSBI) and not requiring vasopressors. Extubation was performed if there were no signs of major respiratory impairment with tidal volume>5ml/kg, respiratory rate 10 to 25/min, PaO2>70mmHg, PaCO2<55mmHg at FIO2<0.5. The patient was discharged from ICU if he/she was cooperative, with hemodynamic stability and normal ABG analysis (PaO2>60mmHg, PaCO2 of 35-45mmHg).

Outcome parameters included duration of ventilation, sedation score using RASS, analgesia score using BPS and use of vasopressors (Figure 1).

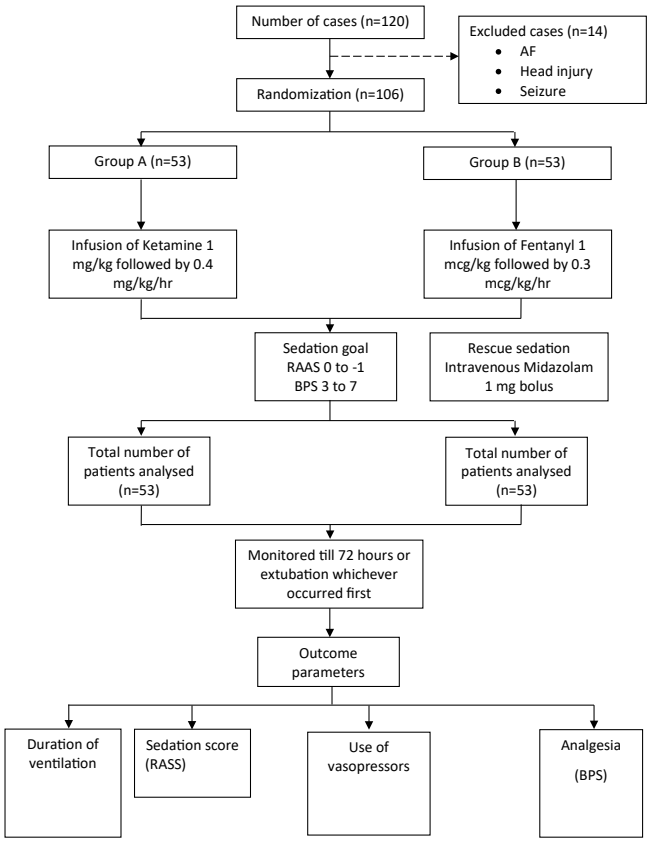

Figure 1. Study design.

Analgesia and sedation were recorded in the printed proforma by nursing personnel using RASS and BPS at six hourly intervals till three days, or extubation whichever occurred first. Mean arterial pressure (MAP) and heart rate (HR) were recorded every six hour. The dose requirement of study drugs was noted.

Statistical Analysis:

The data was entered into microsoft excel, and was analyzed for normality using Shapiro Wilk test. Categorical data were expressed as numbers (%), normally distributed continuous data as mean ± SD and ordinal data or not normally distributed data as median (IQR). The p value of <0.05 was accepted as significant. For intergroup comparison, normally distributed continuous variables were compared with Students t test. Not normally distributed continuous variables and ordinal data were compared with Mann Whitney U test. Categorical variables were compared with Pearson Chi Square or Fishers exact test as appropriate. For intragroup comparisons for repeated measures at different time points, repeated measurement ANOVA was used to compare normally distributed parameters assessed at different time points on the same patients. Ordinal data and not normally distributed data that were measured repeatedly were assessed with Friedman's test.

RESULTS

A total of 120 patients aged greater than 18 years who required mechanical ventilation for greater than 24 hours were assessed for eligibility. Fourteen patients could not be included because of varied reasons (five presented with head injury, four were in atrial fibrillation and five presented with seizures). There was no significant difference in the two groups in age, sex and distribution of diseases (Table 1).

Table 1. Baseline characteristics of the patients

Characteristics	Fentanyl group	Ketamine group
Age (years)	44.5±17.3 (20-78)	43.6±7.5 (20-77)
Sex	26/27 (M/F)	33/20 (M/F)
Mean dose	0.43±.07 (mcg/kg/hr)	0.6±.14 (mcg/kg/hr)
Diagnosis at admission		
Stroke	1 (1.9%)	0 (0%)
Abdominal surgery	16 (30.2%)	10 (18.9%)
COPD	3 (5.7%)	5 (9.4%)
Cardiothoracic surgery	2 (3.8%)	3 (5.7%)
Dengue	1 (1.9%)	1 (1.9%)
Head and neck surgery	1 (1.9%)	1 (1.9%)
Gynaecological surgery	1 (1.9%)	1 (1.9%)
Liver disease	3 (5.7%)	3 (5.7%)
Metabolic encephalopathy	2 (3.8%)	4 (7.5%)
Necrotising fasciitis	1 (1.9%)	0 (0%)
Neurotoxic envenomation	2 (3.8%)	2 (3.8%)
Organophosphate poisoning	3 (5.7%)	0 (0%)
Orthopedic surgery	0 (0%)	1 (1.9%)
Renal disease	2 (3.8%)	2 (3.8%)
Sepsis	14 (26.4%)	20 (37.7%)
Urosurgery	1 (1.9%)	0 (0%)

Duration of Ventilation:

The mean±SD duration of ventilation was 2.7±0.8 days in patients receiving ketamine and was 2.2±1.07 days in patients receiving fentanyl infusion. Student's t test revealed that duration of ventilation was comparable between the two groups (p=0.136) (Figure 2).

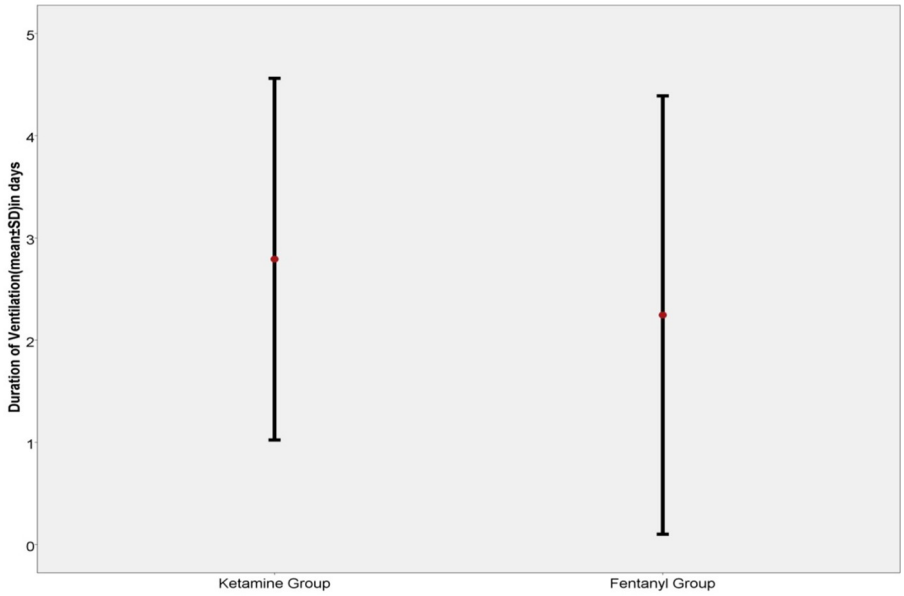

Figure 2. Mean duration of mechanical ventilation.

Richmond Agitation Sedation Scale (RAAS):

RASS scores were similar (p >0.05) at various time points in patients receiving infusion of ketamine, whereas RASS scores were significantly variable at different time points (p<0.05) in patients receiving infusion of fentanyl. Wilcoxon tests with Boneferroni correction was applied to follow up this finding, which revealed no significant variations in RASS scores in patients receiving fentanyl at various time points (Figure 3).

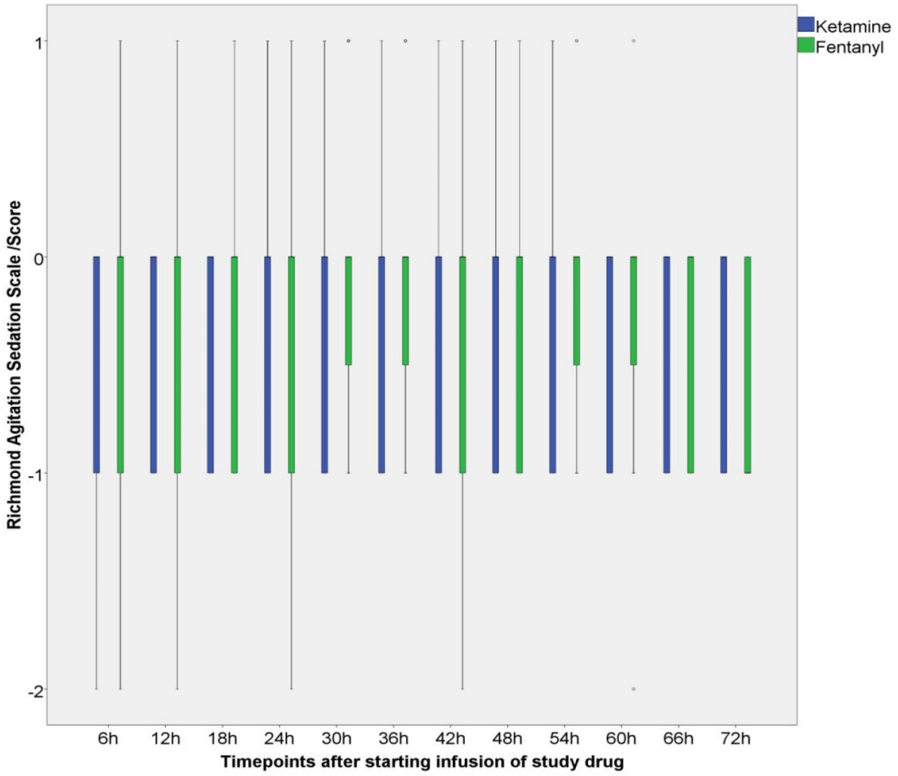

Figure 3. RASS score in two groups at various time points.

Behavioral Pain Scale (BPS) score:

Friedman's test was used for intragroup comparison of BPS score at various time point in each group. BPS score was reduced ($p<0.05$) significantly at various time intervals in the patients receiving ketamine as infusion compared to fentanyl infusion at different time groups (Figure 4).

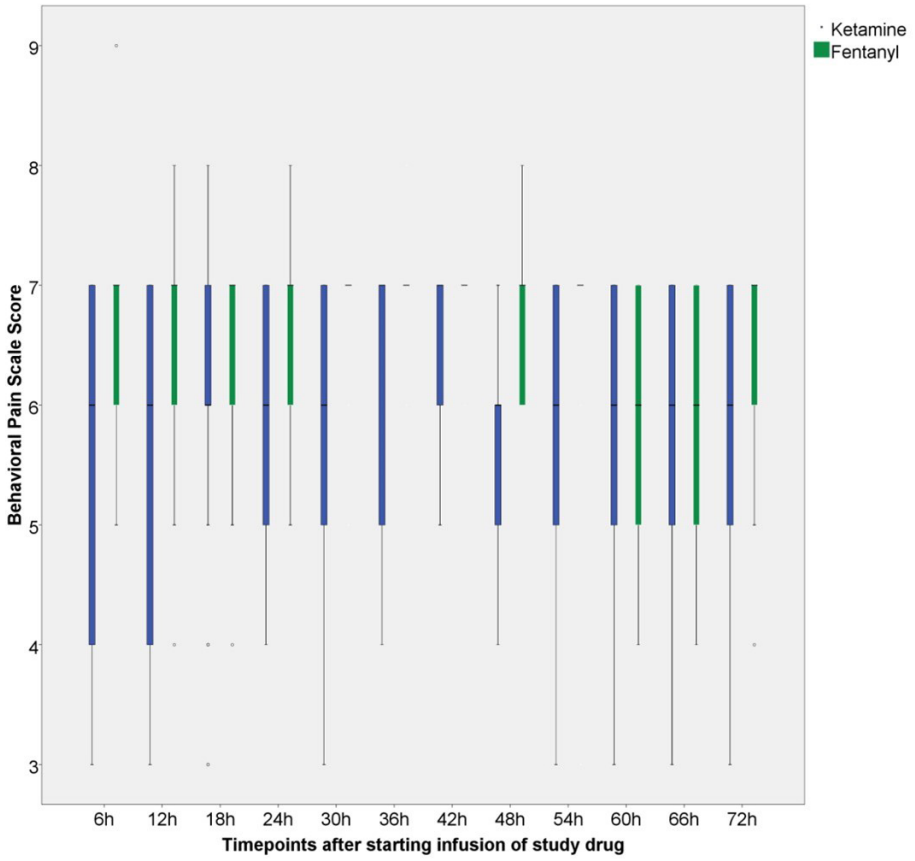

Figure 4. BPS score in two groups at various time points.

Use of Vasopressors:

Nine patients receiving ketamine infusion and 27 patients receiving fentanyl infusion were administered vasopressors. Pearson's Chi Square test revealed that the number of patients receiving vasopressors were significantly less in the patients receiving ketamine infusion compared to those receiving fentanyl infusion ($p < 0.05$) (Figure 5).

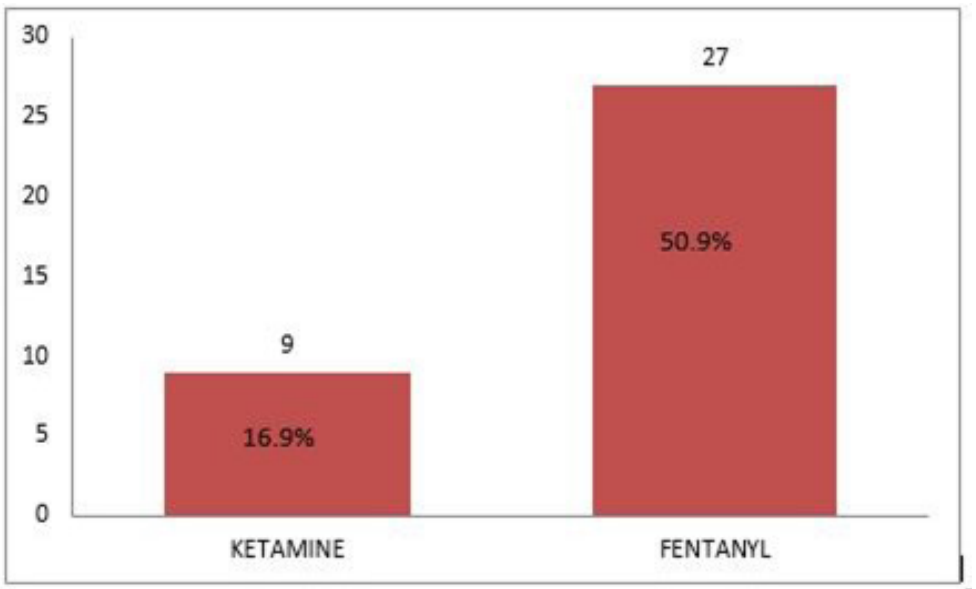

Figure 5. Vasopressor requirement in two groups.

DISCUSSION

In this single centered comparative study involving 106 mechanically ventilated patients, we compared the effects of ketamine and fentanyl with respect to duration of ventilation, sedation, analgesia, use of bronchodilators and use of vasopressors. We found that ketamine was similar to fentanyl when compared to duration of ventilation, but the use of rescue sedatives was found to be more in group receiving IV fentanyl infusion. The patients in group receiving ketamine and fentanyl infusion were sedated as per target sedation score (RASS 0 to 1) and were more comfortable during procedures (BPS 3 to 7). More patients receiving fentanyl infusion required vasopressors. Use of bronchodilators was similar in the both groups and ICU length of stay and duration of ventilation did not differ in between the groups receiving ketamine and fentanyl infusion.

In a study done by Rozendaal et al., the authors found that continuous infusion of remifentanil and propofol decreased the duration of ventilation in the patients who were mechanically ventilated. The mean duration was 2 days, which was similar to our study where the mean duration of ventilation was 2.2 days in patients receiving fentanyl infusion and 2.5 days in patients receiving intravenous infusion of ketamine.[11] Fraser et al compared the effect of benzodiazepines and non-benzodiazepine sedative in 1235 mechanically ventilated patients and concluded that use of non-benzodiazepines as sedative was associated with decrease in duration of ventilation by half.[12]

In this study majority of patients receiving infusion of intravenous ketamine and fentanyl were found to achieve defined sedation scale (RASS 0 to -1). There was no statistically significant difference observed regarding duration of ventilation in the both study groups. Similarly, in a study done by Umunna and colleagues also found efficacy of ketamine as a continuous agent in achieving appropriate sedation with motor activity assessment scale (MAAS) averaging 1.9. However, the scoring system in our study was different from one used by Umunna and colleagues. The sedative action of ketamine reflects its action on NMDA receptors.[13] Elamin et al. in their study of 66 mechanically ventilated patients who received ketamine as continuous infusion concluded that ketamine provided adequate sedation and analgesia (defined as Ramsay sedation score of four) and can be used for continuous infusion in ICU.[14]

We studied the analgesic effect of ketamine in mechanically ventilated patients using behavioral pain scale with targeted BPS score of 3 to 7. In our study only ten patients had their BPS scores more than 7. As mentioned in the study by Patanwala and colleagues, the patients receiving continuous infusion of ketamine had 1.5 times lesser requirement of opioids when compared to opioid only group in controlling pain.[15]

Nine out of 53 patients (16.9%) required vasopressors in our study when compared with control where 27 out of 53 (50.9%) patients required vasopressors. This decreased vasopressor requirement in ketamine group can be attributed to the sympathomimetic action of ketamine. The finding of our study was similar to the study done by Schmittner et al., in 24 patients with traumatic brain injury where the authors compared the effects ketamine and opioids and found that there was decrease in need for use of vasopressors by more than half in the patients receiving ketamine as infusion when compared with patients receiving opioids.[16]

Infusion was discontinued for possible adverse effects in seven (13%) patients receiving ketamine due to development of tachyarrhythmia's in six patients with one patient being over sedated (RASS score -1), whereas seven (13%) of patients receiving infusions of fentanyl had their infusion discontinued due to over sedation and feed intolerance. Six or 11% of patients had tachyarrhythmia in ketamine group. A similar rate was also seen in study done by Riker et al. with 10% patients in remifentanil and morphine reporting tachyarrhythmia's.[17] The study elucidates that ketamine can safely be used in mechanically ventilated patients with no added adverse effects when compared to fentanyl.

The study has several limitations. Firstly, it was a single centered study with small sample size and we did not stratify the patients (medical/surgical) equally in both groups. Secondly, the investigators were not blinded and lastly, we had a small sample size to draw conclusion on the duration of mechanical ventilation.

CONCLUSION

The result of this study suggests that continuous ketamine infusion for light sedation was similarly tolerated by critically ill adults, with similar duration of mechanical ventilation, and lesser need for vasopressors when compared with fentanyl.

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