Efficacy and safety of ketamine in mechanically ventilated intensive care unit patients: a scoping review

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In Australian and New Zealand, mechanically ventilated patients account for about 35% of all adult patients admitted to the intensive care unit (ICU).¹ In addition to treating the primary illness, international clinical practice guidelines emphasise five critical domains in the management of ventilated patients. These are pain assessment and management, sedation and agitation prevention, delirium assessment and treatment, rehabilitation and mobilisation, and minimising sleep disruption.^{2,3}

Ketamine has been recommended for use as an opioid sparing agent to treat pain and discomfort in mechanically ventilated ICU patients. However, such a recommendation is only conditional, because of very low quality of evidence.³ This narrative scoping review focuses on current knowledge of the use of ketamine, concluding with a focus on mechanically ventilated adult patients in the ICU.

Methods

We searched MEDLINE and EMBASE for relevant articles. Search terms included: ketamine, ketalar, sedation, analgo-sedation, analgo-sedation, analgesia, critical illness, critical care, intensive care, mechanical ventilation, ventilation, outcome and survival. Bibliographies of retrieved articles were examined for references of potential relevance.

Results

Ketamine was first synthesised almost 60 years ago and is similar in structure to the psychotropic agent phencyclidine.^{4,5} In a number of countries (eg, Australia and New Zealand),⁶ it is prepared as a racemic mixture of two enantiomers, with each having slightly different receptor affinities.⁷ Ketamine is a selective, non-competitive, N-methyl-D-aspartate (NMDA) receptor antagonist.⁸⁻¹⁰ NMDA receptors are one of the group of receptors for glutamate, the main excitatory neurotransmitter in the brain and spinal cord.¹¹ They are present at all levels in the central nervous system (CNS) and play crucial roles in many neurological functions, including pain, breathing, locomotion, learning, and memory formation.¹²

ABSTRACT

Objectives: Mechanically ventilated patients account for about one-third of all admissions to the intensive care unit (ICU). Ketamine has been conditionally recommended to aid with analgesia in such patients, with low quality of evidence available to support this recommendation. We aimed to perform a narrative scoping review of the current knowledge of the use of ketamine, with a specific focus on mechanically ventilated ICU patients.

Methods: We searched MEDLINE and EMBASE for relevant articles. Bibliographies of retrieved articles were examined for references of potential relevance. We included studies that described the use of ketamine for postoperative and emergency department management of pain and in the critically unwell, mechanically ventilated population.

Results: There are few randomised controlled trials evaluating ketamine's utility in the ICU. The evidence is predominantly retrospective and observational in nature and the results are heterogeneous. Available evidence is summarised in a descriptive manner, with a division made between high dose and low dose ketamine. Ketamine's pharmacology and use as an analgesic agent outside of the ICU is briefly discussed, followed by evidence for use in the ICU setting, with particular emphasis on analgesia, sedation and intubation. Finally, data on adverse effects including delirium, coma, haemodynamic adverse effects, raised intracranial pressure, hypersalivation and laryngospasm are presented.

Conclusions: Ketamine is used in mechanically ventilated ICU patients with several potentially positive clinical effects. However, it has a significant side effect profile, which may limit its use in these patients. The role of low dose ketamine infusion in mechanically ventilated ICU patients is not well studied and requires investigation in high quality, prospective randomised trials.

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Pharmacokinetics and pharmacodynamics

Following intravenous bolus administration, ketamine's rapid onset of action within 30 seconds for "dissociative anaesthesia" (see below) is due to its high lipid solubility and low protein binding, allowing it to cross the blood–brain barrier readily. Its elimination half-life is 3.1 hours in healthy volunteers¹³ and 5.0 hours in critically unwell patients.¹⁴ Ketamine is hepatically metabolised to norketamine and dehydronorketamine which are then renally excreted. Only norketamine has significant metabolic activity, with up to one-third the potency of ketamine.¹⁵ Norketamine has an elimination half-life of 5.3 hours,¹⁴ potentially prolonging the clinical effects following ketamine administration, especially in patients with renal failure. However, overall, the influence of kidney function on ketamine pharmacokinetics is believed to be low,¹⁶ and there are no dose adjustment data available for patients receiving continual renal replacement therapy. Expert opinion is to dose for a glomerular filtration rate of 10–50 mL/min/1.73m² in patients receiving continual renal replacement therapy.¹⁷

Although incompletely understood, ketamine has multiple effects throughout the CNS. It blocks certain reflexes in the spinal cord and inhibits excitatory neurotransmission in selected areas of the brain. It functionally appears to dissociate the thalamus (which relays sensory impulses from the periphery) from the limbic cortex (involved in awareness of sensation).¹⁸ Ketamine used in anaesthetic doses (1–4.5 mg/kg intravenous) leads to dissociative anaesthesia: the patient appears conscious (eyes open, able to swallow) with preserved respiratory function and pharyngeal and laryngeal reflexes, but is unaware, unable to process or respond to sensory input.^{19–21}

In addition, analgesia may also be mediated through serotonin and noradrenaline receptor activation and reuptake inhibition, as well as effects on δ , κ and μ opioid receptors.^{9,10,22–24} Unlike opioid medications, ketamine is thought to have little effect on gastrointestinal μ receptors, minimising the risk of constipation.^{25,26}

Another CNS effect of ketamine is NMDA receptor blockade of the dorsal horn cells of the spinal cord. These are thought to be important in the pain "wind up" phenomenon, leading to opioid desensitisation, and increased acute and chronic pain.^{15,27} Ketamine boluses of 0.15 mg/kg have been shown attenuate this process.²⁷ Estimates of the rates of chronic pain in the year after ICU admission are 14–77%,²⁸ and it is unknown what role ketamine may have in reducing this critical illness complication.

In addition, a meta-analysis of six studies with a total of 331 patients reviewed the evidence for the anti-inflammatory effects of ketamine, as evidenced by interleukin (IL)-6 levels, when given during surgery.²⁹ All were randomised

single-centre studies, two were single-blind and four were double-blind. Four studies included patients undergoing cardiac surgery and two included patients undergoing abdominal surgery. Most used ketamine as an adjunct to induction of anaesthesia or just before incision and the dose range was an intravenous bolus of 0.15–0.5 mg/kg. One study compared an S-ketamine anaesthesia of a bolus of 1–3 mg/kg followed by infusion of 2–4 mg/kg/h versus sufentanil infusion. Five of the studies reported that racemic or S-ketamine reduced the inflammatory response after surgery as measured by plasma/serum IL-6 concentrations. This response was most pronounced in the early (within 6 hours) postoperative period. It is possible that this anti-inflammatory effect of ketamine may provide some benefit to mechanically ventilated ICU patients.

Dose recommendations

Although the intravenous dose required for induction of anaesthesia has been reported to be 1–4.5 mg/kg,³⁰ a commonly recommended dose regime is 1.0 mg/kg followed by repeated boluses of 0.5–1.0 mg/kg if initial sedation is inadequate.³¹ A recommended dose for analgesia is an intravenous infusion of 0.27–0.75 mg/kg/h.³² Low dose ketamine when given as an intravenous bolus for acute postoperative pain has been defined as a subanaesthetic dose or < 1 mg/kg.^{6,33} Low dose ketamine, when given as an infusion, is less well defined. One review defined low dose infusion as ≤ 0.2 mg/kg/h.³³ Alternatively, subdissociative dosing of 0.1–0.4 mg/kg/h has also been described as low dose.³⁴

The recommended dose for ICU sedation is 1 mg/kg/h.³² Recommended doses for analgesia in mechanically ventilated patients are an intravenous bolus of 0.5 mg/kg followed by an infusion of 1–2 μ g/kg/min (0.06–0.12 mg/kg/h).³ For the purposes of this review, a low dose intravenous bolus of ketamine is considered < 1 mg/kg and low dose intravenous infusion may be a median dose of ≤ 0.3 mg/kg/h aligned with international studies^{35,36} of the use of ketamine as an adjunct for analgesia and sedation.

Analgesic effect in the non-ICU setting

It is prudent to briefly review the data available on ketamine as an adjunct to analgesia in the non-ICU setting, which may provide some guidance as to the possible effectiveness when ketamine is used in mechanically ventilated ICU patients.

Effect on postoperative pain

Brinck and colleagues³⁶ performed a Cochrane review of the use of ketamine for postoperative pain. The review included 130 randomised, double-blind, controlled trials of 8341 patients, of which 4588 received ketamine and 3753 were controls. A wide range of surgeries were included.

Ten studies used only S-ketamine and one study used only R-ketamine. The rest of the studies used racemic ketamine at predominantly bolus doses of 0.25–1 mg/kg and infusions of 2–5 µg/kg/min (0.12–0.3 mg/kg/h). Most studies had less than 50 patients in each arm. Ketamine infusion reduced morphine equivalents by 8 mg at 24 hours and by 13 mg at 48 hours with associated decreased pain scores. Pooled CNS adverse events included hallucinations, dizziness, confusion, drowsiness, sedation, nightmares, and visual disturbances. There was no statistical difference in pooled events when ketamine was compared with placebo (5.2% v 4.2%; risk ratio, 1.17; 95% CI, 0.95–1.43). The authors concluded that “perioperative intravenous ketamine probably reduces postoperative analgesic consumption and pain intensity. CNS adverse events were little different with ketamine or control”.

Pain management in the emergency department

A systematic review of low dose ketamine versus morphine for analgesia in the emergency department described three randomised double-blind studies examining 261 patients.³⁷ The doses of ketamine boluses were either 0.3 mg/kg (two studies) or 0.5 mg/kg (one study) compared with 0.1 mg/kg morphine for acute pain. Patients either had long bone fractures (one study) or abdominal/flank or musculoskeletal pain (two studies). The review found that ketamine was not inferior to morphine as an analgesic agent. One trial reported dysphoria (not defined) and hallucinations in 16.6% and 12.5% respectively in the ketamine group and none in the morphine group.³⁸

Frequency of use in the ICU setting for mechanically ventilated patients

There are many retrospective cohort studies or case series of mechanically ventilated ICU patients who have had routine administration of ketamine.^{24,35,39–44} In a survey of German ICUs in 2006, ketamine was used in undescribed doses in 15% of patients ventilated for more than 72 hours and in 26% of patients to assist with weaning from the ventilator.⁴⁵ In a multicentre international longitudinal observational study of 703 mechanically ventilated patients, 5.5% of patients received ketamine, again in undescribed doses.⁴⁶ In another multicentre, international trial of 3918 patients comparing dexmedetomidine with usual care for early sedation, ketamine was used in 6.8% and 5.8% respectively before randomisation, and was continued in between 2% and 5% of patients up to 14 days after randomisation.⁴⁷ However, it is unknown at what doses ketamine was prescribed or whether it was given as intermittent boluses or as infusion (personal communication with study authors). A pragmatic multicentre trial in Australia comparing morphine and fentanyl for analgesia and sedation for mechanically ventilated adult patients showed the use of ketamine was 9.1%.⁴⁸

The median doses were infusions of 9.7 mg/h in the fentanyl group and 8.5 mg/h in the morphine group. The median cumulative dose of fentanyl in the first 24 hours and the first 3 days for the fentanyl group compared with the morphine group were 70 mg versus 40 mg and 228 mg versus 188 mg respectively ($P = \text{not significant}$).

Evidence of effect in the ICU setting

Analgesia and sedation

Low dose. Guillou and colleagues⁴⁹ performed the only prospective randomised double-blind controlled trial of low dose ketamine for analgesia in mechanically ventilated patients. This was performed on 93 patients in a single centre in France. The trial included postoperative surgical patients (mainly hepatectomy and oesophagectomy with a combined incidence of 69%) who were planned to be ventilated in the surgical ICU. Patients were educated on pain scores and patient-controlled analgesia (PCA) before surgery. Forty-one patients were randomised to receive a bolus of 0.5 mg/kg and an infusion of 2 µg/kg/min (0.12 mg/kg/h) for 24 hours and then 1 µg/kg/min (0.06 mg/kg/h) in the following 24 hours. Fifty-two patients were randomised to receive placebo and both groups used a morphine PCA. Although the findings showed decreased mean morphine consumption at 48 hours with ketamine (80 mg $\pm$ 37 mg v 58 $\pm$ 35 mg; $P < 0.05$), it is not reported how long patients required mechanical ventilation during the postoperative period.

Buchheit et al³⁵ performed a retrospective study of 40 patients in two surgical ICUs examining the effect of ketamine infusion on morphine equivalents in mechanically ventilated surgical ICU patients. The patients had a median age of 59 years, 77.5% were male, and over 50% were either vascular or trauma patients. The median dose of ketamine prescribed was 5 µg/kg/min (0.3 mg/kg/h). There was a reduction in morphine equivalents at one hour pre-ketamine to 6 hours post-ketamine (from 6.7 mg/h to 5 mg/h; $P = 0.004$) in 40 patients.

High dose. Most other data are retrospective or descriptive in nature or case series.^{24,39–44} Three studies that described ketamine purely for sedation assessed 12,⁴⁰ 30³⁹ and 91⁴² patients and used median ketamine infusion doses of 0.6 mg/kg/h, 2 mg/kg/h and 0.41 mg/kg/h respectively. Several studies describe the use of ketamine infusion for analgesia and sedation or analgosedation.^{24,41,43,44} The median dose ranges were 7 µg/kg/min (0.42 mg/kg/h) to 0.94 mg/kg/h. Several literature reviews have failed to identify any large, high quality randomised trials of ketamine for analgesia and sedation in ICU mechanically ventilated patients.^{7,22,50–54}

The available low quality evidence suggests that the use of ketamine infusion in mechanically ventilated patients

may decrease opioid and sedative consumption,^{24,42,43} with improved times in target sedation range and pain score ranges.⁴²⁻⁴⁴

Use for intubation in ICU

Low dose. There are no studies examining low dose ketamine for induction of anaesthesia for intubation in the ICU. However, a recent retrospective study at two campuses of a tertiary medical ICU in 2673 critically ill patients compared etomidate, ketamine, and propofol for induction of anaesthesia for intubation.⁵⁵ The recorded doses of each of the agents are not described. The propofol group included 962 patients with an average age of 61 years and 58% were male. The ketamine group included 792 patients with an average age of 64 years and 59% were male. The etomidate group included 919 patients with an average age of 65 years and 58% were male. Almost half of the patients were admitted from the hospital ward, and most (about 20%) patients had a general (non-cardiac) surgical/medical or transplant diagnosis. Sixty per cent of patients were intubated for acute respiratory failure and 25% were intubated for altered conscious state. Compared with propofol, more patients in the ketamine group were intubated for respiratory failure (66% *v* 51%), and fewer patients were intubated for altered conscious state (20% *v* 26%). When compared with propofol, ketamine was associated with increased risk of cardiac arrest within 2 hours (3% *v* 1%), increased sustained cardiovascular collapse (defined as systolic blood pressure $\leq$ 65 mmHg once and/or $\leq$ 90 mmHg lasting 30 minutes despite fluid bolus between 30 and 120 minutes after intubation; 22% *v* 16%; $P < 0.017$), and an increased severe sustained hypoxia (9% *v* 5%; $P < 0.017$). There were no differences in duration of mechanical ventilation, ICU or hospital length of stay; however, ketamine was associated with increased ICU mortality (22% *v* 13%; $P = 0.015$) compared with propofol, even when adjusted for illness severity.

High dose. A multicentre single-blind trial of 469 adult patients in 12 emergency medical services (ambulance based) or emergency departments and 65 ICUs in France compared 2 mg/kg of ketamine versus 0.3 mg/kg of etomidate for intubation in critically unwell patients.⁵⁶ Patients in the ketamine group had a mean age of 59 years and 57% were male. Sixty-nine per cent of ketamine patients were intubated for coma, while 17% were intubated for respiratory failure. There was no difference in intubation conditions between the groups and no serious adverse events with either drug. Adrenal insufficiency was higher in the etomidate group.

Although ketamine leads to adequate intubation conditions when used as an induction agent in critically

unwell patients, there is some evidence that it has significant adverse effects compared with propofol and requires further investigation to determine its safety for this indication.

Adverse effects

Several adverse effects potentially limit ketamine's use in critically unwell patients. Patients can have emergence phenomena including hallucinations, agitation and delirium when it is used for deep sedation or as an anaesthetic for short procedures.⁵⁷ A review of 87 studies examining ketamine use for procedural sedation at doses greater than 1 mg/kg described emergence phenomenon in 10–20% of patients.⁵⁸ These effects can be decreased by co-administration of a γ -aminobutyric acid (GABA) receptor agonist (eg, midazolam)⁵⁹ or a central acting α agonist (eg, dexmedetomidine).⁶⁰ An early systematic review reported increased neuropsychiatric effects (hallucinations, psychiatric disturbances, unpleasant dreams, diplopia, blurred vision, nystagmus or dysphoria) when ketamine in analgesic doses was compared with placebo for postoperative pain.⁶¹ However, as described, a more recent Cochrane review described no difference in CNS effects compared with placebo.³⁶ The co-administration of other sedatives, such as propofol, may minimise these unwanted effects. Other side effects including tachycardia, hypertension, raised intracranial pressure (ICP) hypersalivation and laryngospasm have been described.

A review of the clinical data of these side effects in mechanically ventilated ICU patients will follow.

Delirium and coma

Low dose. Garber and colleagues⁴³ performed a two-centre retrospective study of mechanically ventilated adult patients in the United States assessing the impact of adjunctive continuous ketamine infusion for analgosedation. One-hundred and four patients who had mostly medical (41%) and surgical (19%) diagnoses were assessed. The median age was 41 years and 68% were male. The median infusion starting dose was 5.0 μ g/kg/min (0.3 mg/kg/h) for a median duration of 91 hours. The doses increased with longer duration to a maximum median dose of 7.0 μ g/kg/min (0.42 mg/kg/h) at 72 hours in 61 patients. Fifty-seven patients (54.8%) had adequate delirium screening, of which 44 (72%) were Confusion Assessment Method for the ICU (CAM-ICU) positive in the 24 hours before and 47 (82%) were CAM-ICU positive in the 24 hours after commencement of ketamine infusion.

Guillou et al⁴⁹ showed there was no difference in confusion or hallucinations in 93 postoperative surgical patients, with a mean 48-hour ketamine consumption of 367 ± 37 mg (7.6 mg/h).⁴⁹

Table 1. Studies describing central nervous system complications

Author and year	Setting	Study period	Study type	Patients	Primary outcome	Total number of patients	Description of patients	Dose of ketamine	Findings related to CNS complications
Umunna et al, 2015 ³⁹	Tertiary care suburban community Level 1 Trauma centre in the US	September 2011 to March 2012	Single-centre retrospective cohort study	Adult mechanically ventilated patients who received ketamine for sedation > 24 hours	To determine the incidence of adverse events of ketamine as a sedative agent	30	<ul style="list-style-type: none"> Age: 67 Sex, male: 53% Diagnosis: <ul style="list-style-type: none"> Sepsis, 27% Acute lung injury, 39% 	<ul style="list-style-type: none"> Dose: 2 (1.1–2.5) mg/kg/h Dose in patients with adverse events: 2.25 mg/kg/h (2–2.9 mg/kg/h) 	<ul style="list-style-type: none"> Two patients (6.7%) had agitation believed to be due to ketamine leading to infusion cessation
Pruszkowski et al, 2017 ²⁴	University-affiliated trauma centre in the US	January 2014 to July 2015	Single-centre retrospective cohort study	Adult mechanically ventilated trauma patients who received ketamine for sedation	To examine the effect of initiation of ketamine on sedative and analgesic use	36	<ul style="list-style-type: none"> Age: 44 ± 19.7 Sex, male: 81% Blunt trauma: 58% ISS: 21.3 ± 11.1 	<ul style="list-style-type: none"> First 24 h: 0.64 ± 0.39 mg/kg/h (N = 36) 24–48 h: 0.81 ± 0.56 mg/kg/h (N = 31) 48–72 h: 0.94 ± 0.62 mg/kg/h (N = 24) 	<ul style="list-style-type: none"> Use of antipsychotics: 42% in 72 h before ketamine, 53% in 72 h after ketamine Cumulative dose ziprasidone: 120 mg (25–200 mg) before ketamine (N = 9), 220 mg (42.5–240 mg) after ketamine (N = 12); P = 0.018 Cumulative dose haloperidol: 10 mg before ketamine (N = 2), 10 mg after ketamine (N = 2) Cumulative dose quetiapine: 925 mg (375–1875 mg) before ketamine (N = 6), 675 mg (406.25–1637.5 mg) after ketamine (N = 8); P = 0.223
Groetzing et al, 2018 ⁴²	University-affiliated tertiary medical centre in the US	January 2012 to April 2016	Single-centre retrospective cohort study	> 16 years old mechanically ventilated patients (for at least 24 h) and who received at least 6 h of ketamine infusion as adjunct sedation	To describe the ICU's experience of using ketamine for adjunct sedation	91	<ul style="list-style-type: none"> Age: 48 (35–58) Sex, male: 66% Type of ICU: <ul style="list-style-type: none"> Medical, 59% Transplant, 20% Trauma, 15% Other, 6% Diagnoses: <ul style="list-style-type: none"> Pulmonary, 32% Sepsis, 14% Trauma, 12% Toxicological, 10% Other, 32% 	<ul style="list-style-type: none"> Starting dose: 0.1 mg/kg/h Dose: 0.41 mg/kg/h (0.20–0.52 mg/kg/h) 	<ul style="list-style-type: none"> 3 patients had ketamine ceased due to CNS disturbance: <ul style="list-style-type: none"> 1 patient had dysphoria (not defined) at 0.12 mg/kg/h 1 patient had increased agitation at 0.33 mg/kg/h 1 patient had increased agitation at 0.23 mg/kg/h

(Continues)

Table 1. Studies describing central nervous system complications (continued)

Author and year	Setting	Study period	Study type	Patients	Primary outcome	Total number of patients	Description of patients	Dose of ketamine	Findings related to CNS complications
Shurtleff et al, 2020 ⁴⁴	Tertiary care centre in the US	November 2015 to April 2017	Single-centre retrospective cohort study	Adults who received at least 6 h of ketamine infusion matched with a similar number of patients who received propofol	Number of days alive without delirium or coma until hospital discharge or for up to 12 days	39 (K), 40 (N)	<ul style="list-style-type: none"> Age:† 59 (53–68) (K); 54 (43–67) (N) Sex, male: 54% (K); 38% (N) Medical: 56% (K); 83% (N) Surgical: 21% (K); 5% (N) Vasopressors:‡ 80% (K); 43% (N) Inotropes:§ 28% (K); 3% (N) 	<ul style="list-style-type: none"> Initial Dose:† 5 mg/kg/min (5–5 mg/kg/min) [0.3 mg/kg/h (0.3–0.3 mg/kg/h)] Dose:† 7 mg/kg/min (5–9 mg/kg/min) [0.42 mg/kg/h (0.3–0.54 mg/kg/h)] 	<ul style="list-style-type: none"> Days without delirium or coma:† 6 (2–9) (K); 4 (3–7) (N); $P = 0.35$ Delirium: 74% (K); 85% (N); $P = 0.27$ Coma: 41% (K); 15% (N); $P = 0.13$ ICU LOS (days):† 11 (7–24) (K); 8 (5–13) (N); $P = 0.02$ Hospital LOS (days):† 15 (11–28) (K); 12 (7–20) (N); $P = 0.03$

CNS = central nervous system; ISS = Injury Severity Score; ICU = intensive care unit; K = ketamine group; N = non-ketamine group; LOS = length of stay. Age is presented in years. * Mean only. † Median with interquartile range. ‡ Mean $\pm$ standard deviation. § $P = 0.001$.

High dose. There are four studies that examined the CNS complications when ketamine was used in high doses in mechanically ventilated ICU patients.^{24,39,42,44} These studies and the CNS findings are summarised in Table 1.

Overall, from the available evidence, it is unknown whether low or high dose ketamine infusion regimes are associated with increased risk of delirium or agitation in mechanically ventilated ICU patients compared with non-ketamine regimes.

Haemodynamic effects

The haemodynamic effects of ketamine have been reported in several studies and reviews. Ketamine is believed to have a direct action on serotonergic and noradrenergic receptors and prevent transmitter reuptake leading to increased catecholamine levels.^{22,62} The net effect is increased sympathomimetic activity and potential positive effects on blood pressure and pulse, but increased arrhythmias.

Somewhat paradoxically, hypotension has also been reported in anaesthetic doses and in the critically unwell. A proposed mechanism is patients who are critically unwell have high sympathomimetic activity before induction, allowing less substrate on which ketamine could act to maintain haemodynamic stability.⁶³ In addition, there is some in vitro evidence that ketamine is a negative inotrope when applied directly to cardiac muscle.⁶⁴ In some clinical conditions, for example when patients have maximum sympathomimetic activity or if ketamine is used in large doses,⁶⁵ the direct negative inotropic action of ketamine may overcome its sympathomimetic activity and produce pronounced cardiovascular depression.

Low dose. Garber et al⁴³ also described adverse events. Sixty-five patients (62.5%) experienced tachycardia and 17 (16.3%) had hypotension. It is not reported whether these changes were thought to be due to ketamine and whether it was necessary to cease the infusion. Seventy per cent of the 17 patients who were receiving vasopressors before ketamine had this therapy reduced or off at 24 hours following ketamine commencement.

A prospective observational study of the Helicopter Emergency Medical Service in Australia compared the effect of induction of anaesthesia with ketamine in patients with a low shock index or a high shock index as determined by division of pulse rate by systolic blood pressure (< 0.9 = low shock index).⁶³ The study included 112 patients,

Table 2. Studies which describe cardiovascular complications of ketamine

Author and year	Setting	Study period	Study type	Patients	Primary Outcome	Number of patients	Description of patients	Dose of ketamine	Findings related to CVS complications
Kolenda et al, 1996 ⁶⁶	Single-centre university-affiliated trauma hospital, Germany	Not described	Prospective randomised unblinded trial comparing ketamine with fentanyl for analgesedation	16–72 year-old patients with moderate or severe traumatic brain injury who had a predicted need for analgesedation for at least 3 days in the first 24 h	Not specifically defined. Aimed to test if ketamine was applicable to patients with head injury compared with standard analgesedation	12 (K); 12 (F)	<ul style="list-style-type: none"> Sex, male: 92% (K); 67% (F) Age: * 38 (18–72) (K); 29(16–59) (F) Severe traumatic brain injury: 50% (K); 58% (F) 	Dose: * 104 mg/kg/day (4.3 mg/kg/h)	<ul style="list-style-type: none"> MAP in ketamine group about 10 mmHg above fentanyl group — statistically significant days 3 and 7 ($P < 0.05$) Dopamine dose day 1: * 36 mg (0–252 mg) (K) v 184 mg (0–630 mg) (F) Mean HR, 20 beats per min higher in ketamine group — statistically significant days 2, 3 and 7 ($P < 0.005$)
Christ et al, 1997 ⁶⁷	Not well described. Presumed single centre university-affiliated ICU in Austria	Not described	Prospective randomised unblinded trial comparing fentanyl–midazolam v sufentanil–midazolam at randomisation	Mechanically ventilated catecholamine-dependent patients with heart failure (LVEF < 40% and need for catecholamines to achieve CI > 2.0 L/min/m ²)	Not specifically defined. Compared the cardiovascular effects and catecholamine requirements of ketamine v sufentanil	13 (K); 12 (S)	<ul style="list-style-type: none"> Sex, male: 69% (K); 83% (S) Age: * 61 ± 14 (K); 64 ± 11 (S) LVEF: * 27 ± 13% (K); 33 ± 7% (S) Coronary disease: 46% (K); 67% (S) 	Dose: * 2.5 ± 0.9 mg/kg/h	<ul style="list-style-type: none"> No changes in haemodynamics in sufentanil group Ketamine group associated with several changes over first 24 h: <ul style="list-style-type: none"> Decreased CI: * 2.9 ± 0.7 to 2.3 ± 0.6 L/min/m²; $P = 0.001$ Increased MAP: * 68 ± 11 to 77 ± 14 mmHg; $P = 0.01$ Increased MPAP: * 29 ± 8 to 33 ± 10 mmHg; $P = 0.04$ Increased PCWP: * 20 ± 7 to 24 ± 8 mmHg; $P = 0.03$ Non-significant decrease in HR and SVI
Bourgoin et al, 2003 ⁶⁸	Single centre university-affiliated trauma hospital in France	Not described	Prospective randomised double blind trial comparing ketamine v sufentanil (control) for analgesia and sedation	16–75 year-old patients with traumatic brain injury with post resuscitation GCS of 3–8 and who required mechanical ventilation and ICU monitoring	Not specifically defined. Compared the two drugs in combination with midazolam on ICP control and maintenance of CPP	12 (K); 13 (S)	<ul style="list-style-type: none"> Sex, male: 83% (K); 69% (S) Age: * 30 ± 11 (K); 27 ± 7 (S) Post Resuscitation GCS: * 6 (K); 5 (S) ISS: * 34 (K); 29 (S) 	<ul style="list-style-type: none"> Dose over first 4 days: * 82 ± 25 µg/kg/min (4.9 ± 1.5 mg/kg/h) 	<ul style="list-style-type: none"> HR day 3: * 94 ± 10 beats per min (K) v 78 ± 18 beats per min (S); $P = 0.03$ HR day 4: * 101 ± 12 beats per min (K) v 78 ± 18 beats per min (S); $P = 0.01$ Day 1 fluid administration: * 429 ± 405 mL (K) v 992 ± 703 mL (S); $P < 0.050$ Non-significant trend to less dopamine and noradrenaline use with ketamine days 1–4
Schmittner et al, 2007 ⁶⁹	Not well described. Presumed single centre university-affiliated neuro-surgical ICU in Germany	18-month period. Dates not described	Prospective randomised unblinded trial comparing S-ketamine and methohexitone v fentanyl and methohexitone titrated to BIS 30–50 or Ramsay Sedation score of 6	Adult patients suffering severe traumatic brain injury* or SAH (Hunt and Hess Scale > 2)	Not specifically defined. Aimed to investigate effect of S-ketamine v fentanyl on ICP, GIT function, and catecholamine consumption	12 (K); 12 (F)	<ul style="list-style-type: none"> Sex, male: 58% (K); 67% (F) Age: * 49 ± 17 (K); 51 ± 15 (F) Initial GCS: * 7.8 ± 4.6 (K); 9.4 ± 4.9 (F) 	<ul style="list-style-type: none"> Dose not reported but protocol was a bolus of 0.5 mg/kg followed by infusion titrated to BIS to maximum of 2 mg/kg/h 	<ul style="list-style-type: none"> Trend to decreased noradrenaline dose less with S-ketamine v fentanyl: * 3.6 ± 5.1 µg/kg/h v 12.8 ± 18.4 µg/kg/h; $P = NS$

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Table 2. Studies which describe cardiovascular complications of ketamine (*continued*)

Author and year	Setting	Study period	Study type	Patients	Primary Outcome	Number of patients	Description of patients	Dose of ketamine	Findings related to CVS complications
Sibley et al, 2011 ⁷⁰	HEMS setting in single city in Canada	December 2006 to December 2008	Prospective cohort study	All patients who received ketamine to facilitate intubation	Not specifically defined. Aimed to examine the use of ketamine to facilitate intubation in pre-hospital setting	71	<ul style="list-style-type: none"> Sex, male: 73% Age: 50 ± 23 Type of emergency: <ul style="list-style-type: none"> Medical: 59% Trauma: 41% GCS pre-ketamine: 10 (7–14) Head injury: 30% 	<ul style="list-style-type: none"> Dose IV bolus: 80 mg (60–100 mg) (≈ 1 mg/kg) 	<ul style="list-style-type: none"> MAP pre- and post-ketamine: 88.9 ± 25.0 mmHg to 91.7 ± 23 mmHg; <i>P</i> = NS HR pre- and post-ketamine: 108.8 ± 28.3 beats per min to 109.2 ± 26.9 beats per min; <i>P</i> = NS Hypotension (change ≥ 15% leading to MAP ≤ 65): 7% Hypertension (change ≥ 15% leading to MAP ≥ 120) 6% Bradycardia (HR change ≥ 20% to HR ≤ 60): 1% Tachycardia (HR change ≥ 20% leading to HR > 120): 3%
Whitman et al, 2015 ⁴⁰	Single centre university-affiliated medical ICU in the US	January 2010 to July 2012	Retrospective case series	Mechanically ventilated adult patients who received a ketamine infusion to aid with sedation	Not specifically defined. Provided a description of the use and haemodynamic effects of ketamine	12	<ul style="list-style-type: none"> Sex, male: 42% Age: 41 (22–75) APACHE II score: 18 (7–23) Admitting diagnosis: <ul style="list-style-type: none"> HCAP, 33% Asthma, 25% CAP, 17% 	<ul style="list-style-type: none"> Starting dose: 0.3 mg/kg/h (0.2–0.9 mg/kg/h) Maximum rate: 0.8 mg/kg/h (0.3–2.8 mg/kg/h) Rate over first 24 h: 0.6 mg/kg/h (0.2–1.4 mg/kg/h) 	<ul style="list-style-type: none"> Systolic BP 1 hour after commencement: <ul style="list-style-type: none"> Increased, 6 (50%) Decreased, 5 (42%) Unchanged, 1 (8%) HR changes 1 hour after commencement: <ul style="list-style-type: none"> Increased, 7 (58%) Decreased, 4 (33%) Unchanged, 1 (8%) 2 patients (17%) had ketamine infusion discontinued due to tachycardia or hypertension
Ununpa et al, 2015 ³⁹	Tertiary care suburban community Level 1 trauma centre in the US	September 2011 to March 2012	Single-centre retrospective cohort study	Adult mechanically ventilated patients who received ketamine for sedation greater than 24 h	To determine the incidence of adverse events of ketamine as a sedative agent	30	<ul style="list-style-type: none"> Age: 67 Sex, male: 53% Diagnosis: <ul style="list-style-type: none"> Sepsis, 27% Acute lung injury, 39% 	<ul style="list-style-type: none"> Dose: 2 mg/kg/h (1.1–2.5 mg/kg/h) Dose in patients with adverse events: 2.25 mg/kg/h (2–2.9 mg/kg/h) 	<ul style="list-style-type: none"> Two patients (6.7%) developed atrial fibrillation requiring cessation of ketamine although both had associated sepsis

APACHE = Acute Physiology and Chronic Health Evaluation; BIS = bispectral index; BP = blood pressure; CAP = community-acquired pneumonia; CI = cardiac index; CPP = cerebral perfusion pressure; CVS = cardiovascular; F = fentanyl group; GCS = Glasgow Coma Scale; GIT = gastrointestinal tract; HCAP = health care-associated pneumonia; HEMS = helicopter emergency medical services; HR = heart rate; ICP = intracranial pressure; ICU = intensive care unit; K = ketamine group; LVEF = left ventricular ejection fraction area; MAP = mean arterial blood pressure; MPAP = mean pulmonary artery pressure; NS = not significant; PCWP = pulmonary capillary wedge pressure; S = sufentanil group; SAH = subarachnoid haemorrhage; SVI = stroke volume index. Age is presented in years. * Median (minimum-maximum); † Severe traumatic brain injury = Glasgow Coma Scale 3–8; ‡ Median only; § Mean ± standard deviation. ¶ Median (interquartile range). ** Mean (range). †† Mean only.

Figure 1. Intracranial pressure (ICP) measurements in four ketamine trials

* $P < 0.05$ only on days 8 and 10. Kolenda et al⁶⁶ presented median ICPs after initiation of therapy. Bourgoin et al⁶⁸ presented mean ICPs after initiation of therapy — ICPs are not presented numerically, but values represented here are estimated from the figure in the article. Bourgoin et al⁷³ presented baseline ICPs (presented here) and stated no difference 15 minutes after the infusion commenced. Schmittner et al⁶⁹ presented mean ICPs after initiation of therapy.

who were mostly male (73%), young (median age, 36 years), and with more than one-half having a severe traumatic brain injury with threatened airway. The median ketamine dose was 0.5 mg/kg with a low shock index and 0.4 mg/kg with a high shock index. Overall, hypotension was observed in 9% of the entire sample but in 2% of the low shock index group and in 26% of patients in the high shock index group.

Buchheit et al³⁵ provided a secondary outcome analysis, which revealed the dose of phenylephrine equivalents decreased from 70 mg/h to 40 mg/h ($P = 0.19$) 6 hours after ketamine introduction.

High dose. There are seven studies that examine the haemodynamic effects of the use of high dose ketamine in mechanically ventilated ICU patients (Table 2).^{39,40,66-70}

From the available evidence, it is unclear whether the haemodynamic changes are detrimental or beneficial in the critically unwell. However, the apparent negative effects when ketamine is used in large doses or in patients with significant sympathetic activity are concerning. The doses of ketamine in the studies mentioned are greater than the 0.12 mg/kg/h recommended for analgesedation in guidelines,³ leading to difficulties extrapolating the available data to mechanically ventilated ICU patients when ketamine is used as low dose for analgesedation.

Raised intracranial pressure

Early observational studies suggested ketamine was associated with raised ICP in patients with space-occupying lesions^{71,72} and there were concerns with its use in traumatic and non-traumatic brain injury. However, to address these concerns, there have been several small randomised controlled trials of ketamine combined with midazolam versus narcotic combined with midazolam.^{66,68,69,73}

Low dose. There are no studies using low dose ketamine to study its effects on raised ICP.

High dose. There are four studies that examine the effect of ketamine infusion on ICPs.^{66,68,69,73} Kolenda et al,⁶⁶ Bourgoin et al⁶⁸ and Schmittner et al⁶⁹ are described in Table 2. The fourth study, also by Bourgoin and colleagues,⁷³ was a single-centre randomised controlled trial of 30 patients with severe traumatic brain injury which compared ketamine with sufentanil as target-controlled infusions for sedation. Both groups also received midazolam. Target plasma concentrations of ketamine and sufentanil were set and efficacy of sedation assessed. The patients had a mean age of 29 ± 11 years and 29 ± 12 years for ketamine and sufentanil respectively. Plasma concentrations were targeted and doses were not reported.

The reported ICPs of all studies are presented in Figure 1.

In addition, there have been a number of systematic

reviews of prospective and retrospective studies of ketamine use in traumatic and non-traumatic brain injury.^{54,74-76} Overall, there appears to be no significant effect on ICP, cerebral perfusion pressure, or long term neurological outcomes when ketamine is used with other sedatives in mechanically ventilated patients with intracranial injury.

Hypersalivation and laryngospasm

A prospective open label trial of 146 patients who had undifferentiated agitation in the pre-hospital environment compared a median dose of 5.2 mg/kg intramuscular ketamine versus 10 mg intramuscular haloperidol in the pre-hospital environment.⁷⁷ Hypersalivation occurred in 21/56 ketamine patients (30%) versus none in the haloperidol group, leading to intubation for this reason in four patients. Laryngospasm occurred in 3/55 patients (5%) in the ketamine group and none in the haloperidol group. Another prospective observational study examined the effectiveness of a median dose of 4.9 mg/kg intramuscular ketamine in 49 patients with pre-hospital profound agitation. Hypersalivation occurred in nine patients (18%), of which four received atropine therapy.⁷⁸ Pre-medication with glycopyrrolate or atropine has been shown to decrease this adverse effect.^{79,80} Umunna and colleagues³⁹ showed there was no increased hypersalivation when ketamine was used as an infusion at 2.0 mg/kg/h for analgesia and sedation.

It is unknown whether these potential side effects are clinically relevant when low dose ketamine is used for analgosedation in intubated, mechanically ventilated adult patients.

Conclusion

Ketamine is used in mechanically ventilated ICU patients and has several potentially positive clinical effects in this population, including analgesia, sedation and improved haemodynamics in some patients. However, it has a significant side effect profile, which may limit its potential benefits. The role of low dose ketamine infusion for analgesia and sedation in mechanically ventilated patients is currently unknown, despite being recommended in international guidelines, and requires investigation in suitably powered, prospective randomised trials.

Competing interests

All authors declare that they do not have any potential conflict of interest in relation to this manuscript.

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