The Effect of Ketamine on Intracranial and Cerebral Perfusion Pressure and Health Outcomes: A Systematic Review

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Study objective: We synthesize the available evidence on the effect of ketamine on intracranial and cerebral perfusion pressures, neurologic outcomes, ICU length of stay, and mortality.

Methods: We developed a systematic search strategy and applied it to 6 electronic reference databases. We completed a gray literature search and searched medical journals as well as the bibliographies of relevant articles. We included randomized and nonrandomized prospective studies that compared the effect of ketamine with another intravenous sedative in intubated patients and reported at least 1 outcome of interest. Two authors independently performed title, abstract, and full-text reviews, and abstracted data from all studies, using standardized forms. Data from randomized controlled trials and prospective studies were synthesized in a qualitative manner because the study designs, patient populations, reported outcomes, and follow-up periods were heterogeneous. We used the Jadad score and Cochrane Risk of Bias tool to assess study quality.

Results: We retrieved 4,896 titles, of which 10 studies met our inclusion criteria, reporting data on 953 patients. One study was deemed at low risk of bias in all quality assessment domains. All others were at high risk in at least 1 domain. Two of 8 studies reported small reductions in intracranial pressure within 10 minutes of ketamine administration, and 2 studies reported an increase. None of the studies reported significant differences in cerebral perfusion pressure, neurologic outcomes, ICU length of stay, or mortality.

Conclusion: According to the available literature, the use of ketamine in critically ill patients does not appear to adversely affect patient outcomes. [Ann Emerg Med. 2015;65:43-51.]

Please see page 44 for the Editor's Capsule Summary of this article.

A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2014.06.018

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INTRODUCTION

Background

Ketamine is a rapidly acting dissociative agent that can provide analgesia, sedation, and amnesia for rapid sequence intubation in critically ill patients.[1] It is associated with limited suppression of ventilatory drive and has stable hemodynamic properties,[2,3] yet North American emergency physicians have been reluctant to adopt its use when intubating critically ill patients with undifferentiated pathology. In a prospective registry of emergency department (ED) intubations including 22 hospitals, only 3% of ED intubations were performed with ketamine.[4]

Emergency physicians' reluctance to use ketamine is based on case reports and case control studies—published more than 40 years ago—suggesting that ketamine increases intracranial pressure.[5-8] These reports are based on observations of patients with preexisting intracranial pathology, most with space-occupying lesions or obstructive hydrocephalus causing cerebrospinal fluid outflow tract obstruction. In the absence of additional safety data, and with the licensing of etomidate, another rapidly acting intravenous sedative agent with a favorable hemodynamic profile, most emergency physicians opted to use etomidate for critically ill patients for whom traumatic or other neurologic injuries had not been ruled out.[4]

However, in the past decade, important safety concerns about etomidate have reemerged because induction doses of etomidate have been linked with transient adrenal dysfunction,[9,10] and intact adrenal function has been associated with improved mortality in critical illness.[11,12] As a result, the use of ketamine in the management of undifferentiated critically ill patients has resurged, and with it, the debate over its potentially deleterious effects on neurologic outcomes.[13-15]

Editor's Capsule Summary

What is already known on this topic

Historically, ketamine has been considered contraindicated in the setting of potential elevation of intracranial pressure.

What question this study addressed

Does ketamine raise intracranial pressure or worsen neurologic outcomes?

What this study adds to our knowledge

This systematic review of 10 trials including 953 adults either intubated or undergoing intubation found mixed effect on intracranial pressure (all changes mild) and no adverse effect on cerebral perfusion pressure or neurologic outcomes.

How this is relevant to clinical practice

The best available evidence suggests that ketamine is unlikely to meaningfully elevate intracranial pressure.

Importance

EDs see a high volume of undifferentiated critically ill patients who require imminent airway management before investigations to rule out neurologic injuries can be completed. Given the lack of alternative rapidly acting intravenous induction agents with favorable hemodynamic profiles, evidence to support the safety of ketamine for rapid sequence intubation in this group of patients would be reassuring.

Goals of This Investigation

Our main objective was to synthesize the available evidence on the effect of ketamine compared with other sedative agents on intracranial and cerebral perfusion pressures in a population of undifferentiated patients requiring intubation. Secondary objectives were to examine its effect on neurologic outcomes, ICU length of stay, and mortality.

MATERIALS AND METHODS

Study Design

This was a systematic review of the literature. This study did not involve the use of human subjects or medical records and did not require ethics approval.

Search Strategy

We developed a systematic search strategy in collaboration with a professional librarian (M.M.D.-W.). We developed search terms by identifying key words and mapping them to Medical Subject Headings (MeSH) terms. We reviewed the scope notes to identify alternate and previous indexing terms. For our MEDLINE search, we combined relevant MeSH terms and keywords for ketamine, cyclohexanes, intubation, anesthesia, emergency or critical care, and health outcomes. We applied filters for random controlled trials, controlled clinical trials, and observational studies. We excluded animal and non-English studies (Appendix E1 for MEDLINE search, available online at http://www.annemergmed.com). These terms were then translated into equivalent terms for other electronic reference databases. We searched MEDLINE and EMBASE from inception to November 2012 and updated the search in March 2014. We searched the Web of Science, CENTRAL, the Cochrane Database of Systematic Reviews, and the Central Register of Controlled Trials from inception to November 2013. We conducted a gray literature search using the search engine Google and searched the Web sites of the trial registries Current Controlled Trial, the National Research Register, and clinicaltrials.gov. We hand searched the following specialty medical journals in November 2013: *Annals of Emergency Medicine*, *Academic Emergency Medicine*, *Critical Care Medicine, Resuscitation*, *Intensive Care Medicine*, and *Anesthesiology*. Finally, we hand searched the bibliographies of all relevant retrieved articles to identify any additional studies.

Study Selection

We included studies that reported human data on the effect of intravenous ketamine used as an infusion or bolus dose in patients who had previously been intubated or who were being intubated at data collection. Acceptable study designs were randomized controlled trials and prospective controlled studies, including designs in which the patient served as his or her own control. Studies had to enroll patients older than 16 years, report on at least 1 outcome of interest, and include a comparison group treated with an intravenous drug that might be used for rapid sequence intubation in the ED. We excluded studies if they examined the effect of ketamine in nonintubated patients, if they lacked a comparison group, or if they were written in languages other than English.

Data Collection and Processing

Two study authors (L.C. and V.A.), independently and in duplicate, screened retrieved titles, abstracts, and full-text articles for inclusion. Titles and abstracts that were deemed potentially relevant by 1 or both authors were put forward for full-text review. If the study was deemed eligible after full-text review, the same authors extracted data independently and in duplicate, using standardized and piloted data extraction forms. Any disagreements were resolved by consensus or through discussion with a third investigator (C.M.H.). We extracted data on identifying information, study objectives, study design, inclusion and exclusion criteria, indication for intubation, study and control interventions, co-interventions, allocation concealment, method of randomization, blinding, potential confounders,

withdrawal from study, statistical analysis, patient baseline characteristics, and outcomes of interest. The data extractors were not blinded to authorship or journal.

Outcome Measures

The primary outcome measures for this study were intracranial cerebral perfusion pressures. Secondary outcome measures included neurologic outcomes, ICU length of stay, and mortality.

Validity Assessments

We evaluated randomized controlled trials for their risk of bias with the standardized Jadad score and the Cochrane Risk of Bias tool.[16] We used the latter to rate the likelihood of selection, performance, attrition, and detection bias for nonrandomized studies.[17] Two authors independently assigned Jadad scores for randomized controlled trials and rated the likelihood of biases in nonrandomized comparator studies (L.C. and V.A.). All disagreements were resolved by adjudication by a third reviewer (C.M.H.).

Primary Data Analysis

We decided a priori to limit any pooling of data to outcomes reported by studies of the same design, conducted in comparable patient populations, using the same measures and reported during the same follow-up period. After a formal comparative review of all quantitative outcomes after data extraction was complete, there were insufficient clinically homogenous data points to allow meaningful meta-analysis. Therefore, we synthesized the data in a qualitative manner.

RESULTS

Characteristics of Retrieved Studies

Our search identified 4,896 studies, of which 4,308 were excluded on title review and 396 on abstract review (Figure). We reviewed the full texts of 192 articles, of which 10 met inclusion criteria.[18-27] Five randomized trials reported data on 854 patients,[19-21,24,25] and 5 prospective controlled studies reported data on 99 patients.[18,22,23,26,27] Tables 1 and 2 characterize the individual studies. Three of 5 included randomized trials were

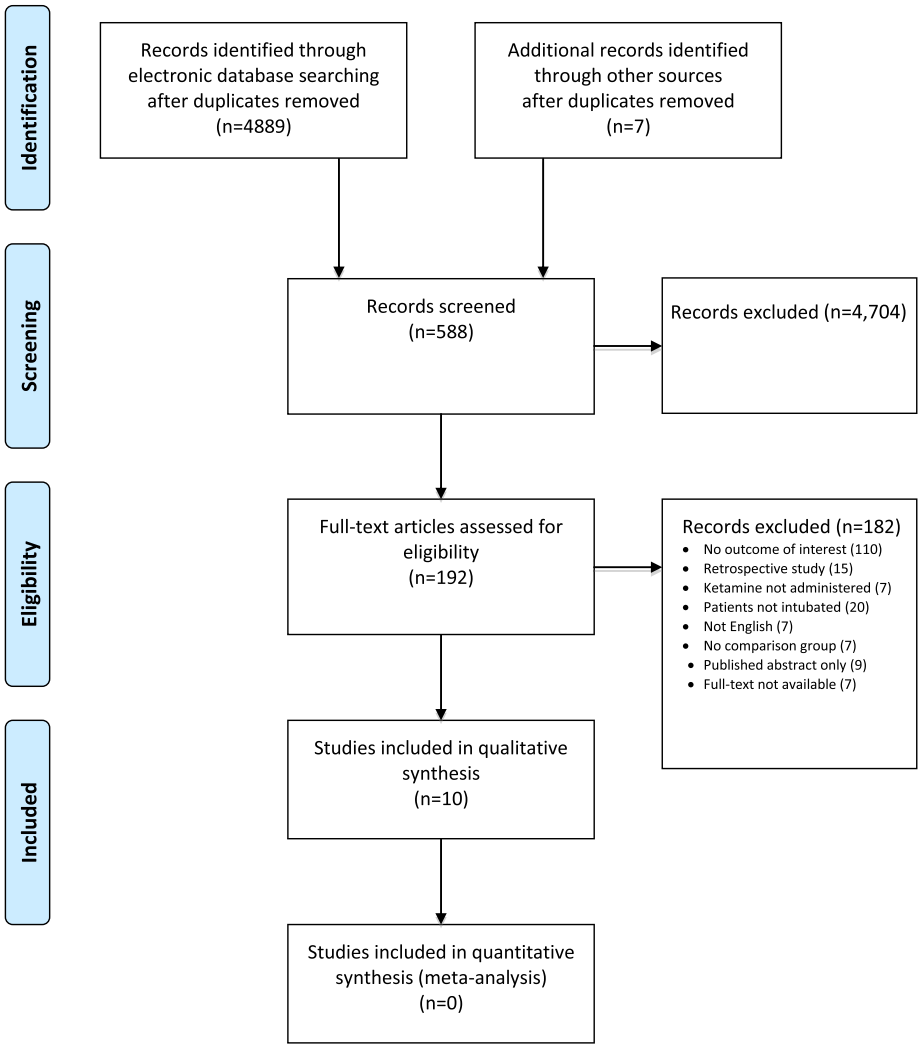

Figure. PRISMA flow diagram for selection of trials.

Table 1. Characteristics of included randomized controlled trials.

Study	Country	N	Setting	Patients	Intervention	Comparison	Cointerventions	Relevant Outcomes	Reported Results (Intervention vs Control)	Jadad Score
Bourgoin[20]	France	25	ICU	Severe TBI (GCS score <8), postcraniotomy	Titrated ketamine infusion for mean duration of 6.2 days	Titrated sufentanil infusion for mean duration of 5.3 days	Midazolam infusion, protocol-driven care for ICP	1. Mean daily ICP 2. Mean daily CPP 3. ICU LOS (SD) 4. Favorable GCS at 6 mo 5. ICU mortality	1. No difference 2. No difference 3. 21 days (SD 13 vs 18 days) (SD 13 days; *P*=NR) 4. 4/12 vs 6/13; *P*=NR 5. 4/12 vs 3/13; *P*=NR	5
Bourgoin[19]	France	30	ICU	Severe TBI (GCS score <8)	Ketamine infusion, rate doubled for 15 min	Sufentanil infusion, rate doubled for 15 min	Midazolam infusion, protocol-driven	1. Mean ICP during 15 min 2. Mean CPP during 15 min	1. No difference 2. No difference	3
Jabre[21]	France	655	EMS, ED, ICU	Critically ill, requiring RSI	Ketamine 2 mg/kg bolus	Etomidate 0.3 mg/kg bolus	Midazolam, fentanyl and sufentanil infusions	1. GCS (95% CI) 2. 28-day mortality (95% CI)	1. Δ: 0 (1 to −1), *P*=.95 2. Δ: −4% (−12 to 4), *P*=.36	3*
Nagels[25]	Belgium	120†	OR	Elective heart surgery	Intraoperative ketamine 2.5 mg/kg bolus and 125 μg/kg/min infusion	Intraoperative remifentanil infusion	Propofol infusion	1. 16 neuropsychometric tests 2. Median ICU LOS (interquartile range)	1. No differences in at 1 and 10 wk 2. 2.0 days (1.1) vs 2.0 days (1.3); *P*=.65	2*
Schmittner[24]	Germany	24	ICU	Severe TBI (GCS score <8), SAH (Hunt and Hess >II)	Ketamine 0.5 mg/kg bolus and infusion for 5 days	Fentanyl 3 μg/kg bolus and infusion for 5 days	Methohexitone bolus ad infusion; mannitol or HS	1. Mean daily ICP 2. Mean daily CPP 3. GCS score at ICU discharge	1. No difference 2. No difference 3. 2.0 vs 2.6: no significant difference	2

TBI, Traumatic brain injury; *ICP*, intracranial hemorrhage; *LOS*, length of stay; *NR*, not reported; *EMS*, emergency medical services; *RSI*, rapid sequence intubation; *SAH*, subarachnoid hemorrhage; *HS*, hypertonic saline solution; *CPP*, cerebral perfusion pressure.

*Patients and outcomes assessors were blinded to the group assignment, but not the treating physicians.

†There were 12 postrandomization exclusions: 3 deaths, 6 losses to follow-up, and 3 incomplete outcomes assessments because of postoperative complications.

Table 2. Characteristics of included controlled clinical studies.

Study	Country	N	Setting	Patients	Intervention	Comparison	Cointerventions	Relevant Outcomes	Reported Results (Intervention vs Control)	Risk of Bias
Albanese[18]	France	8	ICU	Severe TBI (GCS score <8)	Ketamine 1.5, 3, and 5 mg/kg boluses in 6-h intervals	Patient's baseline before boluses	Propofol infusion	1. Mean ICP at 2, 5, 20, and 30 min 2. Mean CPP at 2, 5, 20, and 30 min	1. Decrease 1–5 mm Hg at 2 min in all groups; increase 3–4 mm Hg at 30 min in 2 groups 2. No sustained difference	Selection: high risk Performance: high risk Attrition: low risk Detection: unclear
Belopavlovic[27]	Netherlands	15	OR	Requiring neurosurgery for tumor or hydrocephalus	Ketamine 1 mg/kg IV	Patient's baseline before bolus	Midazolam 0.15 mg/kg or diazepam 0.2 mg/kg, meperidine 50- to 100-mg bolus	1. Mean ICP before and after ketamine bolus and peak value after intubation 2. Mean CPP before and after ketamine bolus and peak value after intubation	1. Increase in mean ICP by 8 mm Hg in midazolam and 3 mm Hg in diazepam pretreated groups after ketamine administration 2. Decrease in mean CPP, but no summary measure reported	Selection: high risk Performance: high risk Attrition: unclear Detection: unclear
Caricato[26]	Italy	21	ICU	Severe TBI (GCS score <8)	Ketamine 100 μg/kg/min infusion for 10 min starting before ETS	Patient's baseline before infusion	Propofol 3–5 mg/kg/h and remifentanil 0.05–2 μg/kg/min infusions, ETS	1. Mean ICP after ketamine 2. Mean ICP after ketamine and ETS	1. No difference 2. No difference	Selection: high risk Performance: high risk. Attrition: low risk Detection: unclear
Kolenda[22]	Germany	35*	ICU	TBI (GCS score 3–15)	Ketamine 65 mg/kg/day	Fentanyl 65 μg/kg/day	Midazolam infusion 6.5 mg/kg/day, mannitol, glycerol, thiopental	1. Mean daily ICP (days 1–10) 2. Mean daily CPP (days 1–10)	1. ICP significantly higher on days 8 and 10 2. No difference	Selection: unclear Performance: high risk Attrition: high risk Detection: unclear
Mayberg[23]	United States	20	OR	Requiring craniotomy for tumor or SAH	Ketamine 1 mg/kg bolus	Patient's baseline before bolus	Thiopental 4–6 mg/kg, nitrous oxide and isoflurane	1. ICP 2. CPP	1. Decreased from 16 to 14–15 mm Hg for first 10 min, $P<.05$. 2. No difference	Selection: high risk Performance: high risk Attrition: low risk Detection: unclear

ETS, Endotracheal suctioning.
*There were 8 withdrawals after group assignment: 5 for persistently elevated ICP, 2 after cardiac arrests, and 1 because of organ failure.

conducted with patients with severe traumatic brain injury (Glasgow Coma Scale [GCS] score <8),[19,20,24] one with a population of undifferentiated critically ill patients including trauma patients,[21] and one with elective heart surgery patients.[25] Of the 5 prospective controlled studies, 3 were conducted with traumatic brain injury patients,[18,22,26] of which 2 were with patients with severe traumatic brain injury (GCS score <8)[18,26] and 1 was with patients with minor and severe brain injuries (GCS score 3 to 15).[22] Two studies enrolled patients undergoing neurosurgical interventions for either space-occupying lesions or obstructive hydrocephalus,[27] or for space-occupying lesions or nontraumatic subarachnoid hemorrhage.[23] Among the prospective controlled studies, 4 of 5 used the patients' own baseline data as controls.[18,23,26] All included studies used intravenous ketamine in bolus doses or as an infusion. Comparator agents included sufentanil, remifentanil, fentanyl, and etomidate.

Quality of Included Studies

There was a large degree of variability in the quality of the included randomized trials, with only 1 small trial being assigned a Jadad score of 5 (Table 1).[20] Two of 5 trials were thought to be at high risk of selection bias because the methods for random sequence generation and allocation concealment were inadequately described.[24,25] Three trials, among them the largest multicenter trial that we included, were assigned Jadad scores of 2[25] and 3[19,21] because they were not double blinded and therefore were at high risk of performance bias. In 2 of these trials, the patients and outcomes assessors were blinded, but not the care providers.[21,25] All trials were deemed to be at low risk of detection bias for the outcomes of intracranial and cerebral perfusion pressures, ICU length of stay, and mortality despite inadequate blinding because these measures are objective and easily quantifiable.[19-21,24,25] Three trials reported the results of neuropsychometric tests and GCS score as secondary outcomes.[20,21,25] These outcomes were deemed to be at high risk of detection bias in the nonblinded trials because of the subjective nature of interpreting the scales.[21,25] All trials were deemed to be at low risk of attrition and reporting bias. One trial analyzed the results of 16 neuropsychometric tests without adjusting for multiple tests and was deemed at high risk of multiple testing bias.[24]

All prospective controlled studies were deemed to be at unclear or high risk of selection bias because they did not report adequate methods to allocate patients to the intervention or control groups in an unpredictable or quasi-random manner.[18,22,23,26,27] The only prospective study that used 2 groups of patients for the intervention and control groups used their medical record numbers to assign them to treatment allocation.[22] All other studies used the patients' baseline data as controls, but did not ensure adequate methods to protect from the influence of temporal trends; for example, by randomizing to intervention or control phases.[18,23,26,27] One study on patients receiving ventilation systematically allocated those who coughed during endotracheal suctioning to the intervention group, introducing selection bias.[26] Because of lack of blinding, all studies were deemed at high risk of performance bias.[18,22,23,26,27] Attrition bias was low in all but 2 studies. One study was deemed at high risk of attrition bias because 9 of 30 patients were withdrawn from it because of adverse outcomes.[22] The other was at unclear risk of attrition bias because no patients were withdrawn from the study, but data points were missing without any explanation.[27] Prospective comparator studies were deemed to be at unclear risk of detection bias for the outcomes of intracranial and cerebral perfusion pressures. Although these measures are objective and easily quantifiable, the timing of their measurement was not always specified and the outcomes assessors were not blinded. All prospective comparator studies were deemed to be at low risk of reporting bias.

Main Results

Intracranial pressure and cerebral perfusion pressure. Three randomized trials[19,20,24] and 5 prospective controlled studies[18,22,23,26,27] examined the relationship between ketamine and comparator induction agents with respect to intracranial and cerebral perfusion pressures, and reported data on 168 patients. The study designs, patient populations, and timing of the measurements were too heterogeneous to allow pooling of results. Two double-blind, randomized, controlled trials compared the effect of prolonged ketamine and sufentanil infusions in the ICU in patients with severe traumatic brain injury postcraniotomy.[19,20] These studies found no differences in mean daily intracranial or cerebral perfusion pressures. Schmittner et al[24] compared the effect of ketamine and fentanyl in patients with severe traumatic brain injuries or aneurysmal subarachnoid hemorrhages and found no significant differences in mean daily intracranial or cerebral perfusion pressures. There were also no differences in the use of additional pharmacologic interventions for elevated intracranial pressure, including the use of vasopressors, neuromuscular-blocking agents, and additional sedative agents.

Albanese et al[18] conducted a prospective controlled study to determine the effect of 3 intravenous bolus doses of ketamine (1.5, 3, and 5 mg/kg) on intracranial and cerebral perfusion pressures in patients with severe traumatic brain injury, using the patients' baseline as controls. The authors measured intracranial and cerebral perfusion pressures at 4 points and noted small but statistically significant decreases in intracranial pressures (of 1, 4, and 5 mm Hg after the ketamine doses of 1.5, 3, and 5 mg/kg, respectively) measured 2 minutes after the ketamine administration. They noted statistically significant increases in intracranial pressure in 2 groups (of 3 and 4 mm Hg in the ketamine bolus groups of 1.5 mg/kg and 5 mg/kg, respectively) at 30 minutes. There were no differences in cerebral perfusion pressures. Mayberg et al[23] investigated the effect of a single bolus dose of ketamine in neurosurgical patients requiring craniotomy for either tumors or aneurysmal subarachnoid hemorrhage and used the patients' baselines as controls. They detected small but statistically significant decreases in intracranial pressures (of 1 to 2 mm Hg) during the first 10 minutes post–ketamine

administration, with no statistically significant difference in cerebral perfusion pressure. Caricato et al[26] reported no differences in intracranial pressures (11.7 [SD 7.3] in the ketamine phase versus 11.0 [SD 6.4] mm Hg at baseline) or cerebral perfusion pressures (values not reported) after starting an infusion of ketamine, whereas Kolenda et al[22] reported statistically significant increases in intracranial pressures (of 8 and 10 mm Hg) only after prolonged infusions of ketamine, on days 8 and 10 of treatment. One study, published in 1982,[27] reported a mean increase in intracranial pressure of 8 mm Hg (statistical significance not reported) for a mean duration of 6 minutes after bolus doses of ketamine were administered to elective neurosurgical patients with space-occupying lesions or obstructive hydrocephalus after pretreatment with midazolam. This was followed by an increase in intracranial pressure of 21 mm Hg with intubation and a return to baseline after administration of meperidine. This study found a smaller mean increase in intracranial pressure of 3 mm Hg for a mean duration of 3 minutes in patients pretreated with diazepam.

Neurologic outcomes. Four of the 5 included randomized trials reported data on neurologic outcomes reporting data on 824 patients.[20,21,24,25] Studies used different neurologic outcome scales and collected data at different points, precluding any pooling of data. None of the studies reported differences in GCS score at discharge from the ICU (2.0 in the ketamine group versus 2.6 in the fentanyl group)[24] or at 6 months ("favorable" GCS scores observed in 4 of 12 in the ketamine group and 6 of 13 in the sufentanil group).[20] Nagels et al[25] compared the effect of an intraoperative infusion of ketamine to remifentanil in patients undergoing elective open-heart surgery and found no differences between groups according to extensive neuropsychometric testing at 1 and 10 weeks postoperatively; 20% of the ketamine group patients, compared with 25% of the control patients, demonstrated deficits on 2 or more neuropsychometric tests 10 weeks after surgery (95% confidence interval [CI] –9% to 19%). Jabre et al[21] completed the largest randomized trial included in this review and compared an induction dose of ketamine with etomidate in a population of undifferentiated critically ill patients undergoing rapid sequence intubation in the out-of-hospital or ED setting. They found no difference in median GCS score between groups (difference 0; 95% CI –1 to 1; P=.95).

ICU length of stay. Two randomized studies reported ICU length of stay as a study outcome (n=145).[20,25] In one trial, patients with traumatic brain injury were exposed to prolonged ketamine or sufentanil infusions during their ICU stay.[20] In the other, patients undergoing elective open-heart surgery were exposed to intraoperative ketamine or remifentanil infusions.[25] Neither study found a difference in length of stay.

Mortality. Two randomized trials reported mortality data on 680 patients.[20,21] Jabre et al[21] found no difference in 28-day mortality in undifferentiated critically ill patients who were intubated with either ketamine or etomidate; in the etomidate group, 35% of patients died compared with 31% of ketamine patients (95% CI –4 to 12). Bourgoin et al[20] found no difference in ICU mortality in patients with severe traumatic brain injury who were sedated with ketamine compared with sufentanil infusions.

LIMITATIONS

There are several factors limiting our systematic review. Only few prospective comparator studies have been published comparing the effect of ketamine with that of other intravenous induction agents. We do not believe that selection or retrieval bias affected our results because we used an exhaustive search strategy constructed with the help of a professional librarian and updated our searches in March 2014 to ensure that no new data had been published since we began our review. The quality of reporting for most studies was modest. We were able to classify only 1 of the 9 reviewed studies as low risk for bias in all quality domains. None of the other studies reported optimal methods to randomize patients, conceal treatment allocation, or ensure blinding of study participants, treating personnel, and outcomes assessors. Only 1 randomized trial reported a sample size calculation,[21] and none for the study outcomes we were interested in. Therefore, our finding of no difference between ketamine and the comparator induction agents may be the result of lack of power of the individual studies to detect a difference. Accordingly, the results presented in our review should be interpreted with caution.

As with all systematic reviews, publication bias is a concern. However, we do not believe that this affected our study results. None of the reviewed studies found clinically relevant differences in the outcomes we studied, even if differences were statistically significant. In this field, any study reporting differences in outcomes would have been more likely to be published than the studies we found with negative results. Therefore, any publication bias would have strengthened the evidence in favor of a clinically significant difference between ketamine and the comparator agents. In addition, we were unable to include studies published in non-English languages. Finally, the majority of patients contributing data to this systematic review were enrolled in 1 large randomized controlled trial that was not double blinded.[21] Therefore, any bias inherent in the design or conduct of that study could have influenced the results of our systematic review.

DISCUSSION

This systematic review examined the effect of ketamine compared with other intravenous induction agents on intracranial and cerebral perfusion pressures, neurologic outcomes, ICU length of stay, and mortality. Although 2 studies reported small, clinically insignificant reductions in intracranial pressure shortly after ketamine administration and 2 studies reported increases in intracranial pressure, most reported no significant differences. We found no evidence of any sustained changes in intracranial pressure or cerebral perfusion pressure in any of the studies. We also found no evidence of an effect of ketamine on the other outcomes we examined.

The findings of our systematic review support the conclusions of previous narrative reviews and 1 systematic review of randomized trials that challenged the dogma that ketamine should not be used for rapid sequence induction in head-injured patients.[1,13-15] In 2005, Himmelseher et al[15] reviewed a body of literature on animal models suggesting that an important neuroprotective role for ketamine may exist because it antagonizes the *N*-methyl-D-aspartate receptor, thus protecting the brain from an injury cascade mediated through its unbalanced activation. The clinical significance of this cellular mechanism of action remains unknown. From the authors' review of human studies that were published before 2004, they concluded that ketamine may exert additional neuroprotective effects by preventing hemodynamic compromise, thus protecting the brain from secondary physiologic insults such as hypotension[28] and increasing cerebral blood flow without impairing cerebral autoregulation. In 2011, Roberts et al[1] published a systematic review of randomized controlled trials that compared the effect of different intravenous sedatives on intracranial and cerebral perfusion pressures, neurologic outcomes, mortality, and adverse effects in patients who received a diagnosis of severe traumatic brain injuries (GCS score <8). The authors found no convincing evidence that one sedative regimen was more efficacious or superior to another in this patient population. Since then, 1 large randomized controlled trial was published comparing the effects of ketamine and etomidate.[21] The review by Roberts et al[1] included only 2 small trials enrolling 55 patients who had been exposed to ketamine.[19,20] The outcomes of these patients were compared with those of patients treated with sufentanil, an agent not commonly used in the ED setting. Therefore, the results of the review by Roberts et al[1] should not be extrapolated to the ED setting.

In traumatic brain injury, contused brain is often surrounded by a penumbra of tissue that is at risk for secondary ischemic injury.[28] A previous narrative review on ketamine suggested that the increases in mean arterial pressure and possible increases in cerebral perfusion pressures that may be associated with ketamine may lead to increased cerebral blood flow to these vulnerable areas, thereby preventing secondary injury.[13] Our systematic review found no significant effect of ketamine on cerebral perfusion pressure.

The use of ketamine as an induction agent for rapid sequence intubation in undifferentiated critically ill patients in whom neurologic injury has not been ruled out remains an important point of debate for emergency physicians: Researchers have established a strong association between the degree and duration of hypotension and neurologic outcomes in patients with traumatic brain injury.[28] Therefore, clinicians generally avoid using induction agents that cause or may exacerbate preexisting hemodynamic instability such as the opioids, propofol, or benzodiazepines in this population. However, in light of the uncertainty over the clinical significance of the adrenal suppression associated with etomidate,[9] and the frequent complication of sepsis in patients with major trauma, the available evidence suggests that ketamine should be considered an alternative induction agent. This is particularly true for patients who present to the ED after having been "found down," in whom neither sepsis nor neurologic injuries have been ruled out.

The available data suggest that ketamine does not adversely affect intracranial or cerebral perfusion pressures, neurologic outcomes, or mortality compared with other intravenous induction agents commonly used to intubate adult patients in the ED. Our study is limited by the lack of large, well-designed, randomized, controlled trials addressing this topic. High-quality, adequately powered, randomized trials comparing induction agents with respect to patient-oriented outcomes are urgently needed to optimize treatment strategies for critically ill patients in the ED.

Supervising editor: Steven M. Green, MD

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Author contributions: VA, NGWR, and CMH conceived the study, designed the protocol, and obtained funding. LC, VA, MMD-W, NGWR, and CMH designed the search strategy, and MMD-W and MEW completed the searches. LC, VA, and MEW collected the data. LC, VA, and CMH assessed the quality of the individual studies. All authors contributed to interpreting the data. LC drafted the first article. All authors provided feedback. CMH takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist and provided the following details: This work was supported by a grant from the Canadian Association of Emergency Physicians. During the study period, Dr. Hohl was supported by a CIHR New Investigator Award (grant #261895).

Publication dates: Received for publication May 7, 2014. Revision received June 12, 2014. Accepted for publication June 16, 2014. Available online July 23, 2014.

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APPENDIX E1.

Search Strategy.

Database: Ovid MEDLINE 1946 to Present with Daily Update

Search Strategy:

1 Ketamine/(8437)
2 Cyclohexanes/(5290)
3 limit 2 to yr="1968 - 1972" (1258)
4 Anesthetics/(15193)
5 limit 4 to yr="1968" (308)
6 Analgesics/(32836)
7 limit 6 to yr="1966 - 1971" (2653)
8 Anesject.mp. (0)
9 Brevinaze.mp. (0)
10 calipsol.mp. (18)
11 Calypsol.mp. (36)
12 imalgene.mp. (1)
13 Ivanes.mp. (0)
14 Kanox.mp. (0)
15 kalipsol.mp. (27)
16 Keiran.mp. (0)
17 Ketacor.mp. (0)
18 Ketalar.mp. (201)
19 keta-hameln.mp. (0)
20 tekam.mp. (1)
21 Ketamax.mp. (0)
22 Ketamin-S.mp. (0)
23 ketamine.mp. (11963)
24 Ketanest.mp. (33)
25 ketased.mp. (1)
26 ketaset.mp. (15)
27 Ketashort.mp. (0)
28 Ketalin.mp. (0)
29 Ketava.mp. (0)
30 ketaved.mp. (0)
31 ketavet.mp. (1)
32 Ketazol.mp. (0)
33 Ketmin.mp. (0)
34 Ketalor.mp. (0)
35 ketoject.mp. (0)
36 ketolar.mp. (13)
37 Narkamon.mp. (3)
38 paard.mp. (131)
39 Soon-Soon.mp. (0)
40 Tekam.mp. (1)
41 Velonarcon.mp. (1)
42 vetalar.mp. (8)
43 ci-581.mp. (113)
44 ci581.mp. (2)
45 (cn 52,372 2 or cn 52372 2 or cn 523722 or cn52,372 2 or cn52372 2 or cn523722).mp. (0)
46 (cl 369 or cl369).mp. (1)
47 (1867-66-9 or 6740-88-1 or 81771-21-3).rn. (8437)
48 or/1,3,5,7-47 (16019)
49 Intubation, Intratracheal/(27412)
50 Intubation/(4372)
51 intubat$.mp. (57968)
52 (intra?tracheal adj5 intub$).mp. (27481)
53 anesthesia/(39810)
54 anesthesia, intravenous/(9834)
55 an?esthesia.mp. (207332)
56 anesthesia, general/(31549)
57 anesthetics/(15193)
58 an?esthetic$.mp. (98316)
59 (airway adj5 protection).mp. (505)
60 Laryngoscopy/(8531)
61 laryngoscop$.mp. (12321)
62 (sedative or sedate or sedation).mp. (31833)
63 "Hypnotics and Sedatives"/(20391)
64 Deep Sedation/(356)
65 single bolus dose.mp. (275)
66 induction.mp. (382111)
67 Conscious Sedation/(6096)
68 limit 67 to yr="1991 - 2007" (4357)
69 or/49-66,68 (696633)
70 48 and 69 (8863)
71 intensive care units/or burn units/or coronary care units/or recovery room/or respiratory care units/(37086)
72 Intensive Care/(13576)
73 Critical Care/(22920)
74 Emergencies/(32515)
75 emergenc$.mp. (229475)
76 Emergency Treatment/(7477)
77 air ambulances/(1691)
78 ambulance$.mp. (9332)
79 emergency service, hospital/or trauma centers/(42243)
80 Emergency medical services/(29093)
81 trauma.mp. (153458)
82 Critical Illness/(13818)
83 ((intensive or critical$ or serious$) adj5 (ill$ or care or sick)).mp. (141750)
84 ICU.mp. (22173)
85 or/71-84 (499835)
86 48 and 85 (983)
87 Mortality/(32043)
88 mortality.mp. (403260)
89 heart arrest/(20671)
90 "Length of Stay"/(50572)
91 Respiration, Artificial/(35323)
92 Ventilators, Mechanical/(7552)
93 ventilator$.mp. (41648)
94 Postoperative Care/(49292)
95 Intraoperative Care/(12761)
96 Perioperative Care/(6919)
97 treatment outcome/(523698)
98 clinical outcome.mp. (36424)

99 "outcome and process assessment (health care) "/or "outcome assessment (health care) "/or "process assessment (health care) "/(64228)
100 risk factors/(484344)
101 risk$.mp. (1312376)
102 Survival Analysis/(88499)
103 (adverse adj3 effect$).mp. (94457)
104 fatal outcome/(44892)
105 Adrenal Insufficiency/(4166)
106 (adrenocortical adj4 (suppression or function)).mp. (1994)
107 Blood Pressure/(224795)
108 blood pressure.mp. (325975)
109 exp hemodynamics/(537300)
110 hemodynamic$.mp. (169780)
111 hypotension/(16791)
112 hypotension.mp. (48630)
113 or/87-112 (2840200)
114 48 and 113 (4155)
115 ae.fs. [Adverse Effects] (1232618)
116 ct.fs. [Contraindications] (15727)
117 mo.fs. [Mortality] (367117)
118 de.fs. [Drug Effects] (2223083)
119 co.fs. [Complications] (1465219)
120 or/115-119 (4805528)
121 48 and 120 (8983)
122 cerebrospinal fluid pressure/(1316)
123 intracranial pressure/(12653)
124 Intracranial Hypotension/(741)
125 intracranial hypertension/or hydrocephalus/or dandy-walker syndrome/or hypertensive encephalopathy/or posterior leukoencephalopathy syndrome/(20718)
126 craniocerebral trauma/or exp brain injuries/or cerebrospinal fluid otorrhea/or cerebrospinal fluid rhinorrhea/or coma, post-head injury/or exp cranial nerve injuries/or exp head injuries, closed/or head injuries, penetrating/or exp intracranial hemorrhage, traumatic/or exp skull fractures/(88632)
127 (head adj3 injur$).tw. (18946)
128 ICP.tw. (10125)
129 cerebral perfusion pressure.tw. (2178)
130 CPP.tw. (5304)
131 Cerebrovascular Circulation/de [Drug Effects] (8645)
132 craniotomy/or decompressive craniectomy/(9002)
133 Blood Flow Velocity/(48200)
134 cerebral arteries/or anterior cerebral artery/or "circle of willis"/or middle cerebral artery/or posterior cerebral artery/or temporal arteries/(20516)
135 or/122-134 (209156)
136 48 and 135 (433)
137 trauma severity indices/or abbreviated injury scale/or glasgow coma scale/or glasgow outcome scale/or injury severity score/(20091)
138 48 and 137 (19)
139 or/70,86,114,121,136,138 (12930)
140 randomized controlled trial/(327565)
141 Random allocation/(74438)
142 Double blind method/(114836)
143 Single blind method/(16163)
144 clinical trial/or clinical trial, phase i/or clinical trial, phase ii/or clinical trial, phase iii/or clinical trial, phase iv/or controlled clinical trial/or multicenter study/(588750)
145 exp Clinical Trials as topic/(255499)
146 or/140-145 (910704)
147 (clinic$ adj trial$).tw. (168647)
148 Placebos/(30898)
149 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (112461)
150 placebo$.tw. (135838)
151 randomly allocated.tw. (13590)
152 (allocated adj2 random).tw. (670)
153 or/147-152 (346442)
154 or/146,153 (1013610)
155 Case report.tw. (166172)
156 Letter.pt. (747648)
157 Historical article.pt. (282825)
158 or/155-157 (1186293)
159 154 not 158 (986081)
160 Epidemiologic studies/(5367)
161 exp case control studies/(552690)
162 exp cohort studies/(1175046)
163 Case control.tw. (60038)
164 (cohort adj (study or studies)).tw. (60320)
165 Cohort analy$.tw. (2719)
166 (Follow up adj (study or studies)).tw. (32855)
167 (observational adj (study or studies)).tw. (30403)
168 Longitudinal.tw. (108698)
169 Retrospective.tw. (211400)
170 Cross sectional.tw. (121931)
171 Cross-sectional studies/(140309)
172 or/160-171 (1570693)
173 or/159,172 (2321546)
174 animal/not (animal/and human/) (3627467)
175 173 not 174 (2223535)
176 139 and 175 (1806)
177 limit 176 to yr="1968 -Current" (1780)
178 176 not 177 (26)
179 limit 177 to English language (1503)
180 177 not 179 (277)