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ORIGINAL ARTICLE

Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials

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Abstract
Background Ketamine is traditionally avoided in sedation management of patients with risk of intracranial hypertension. However, results from many clinical trials contradict this concern. We critically analyzed the published data of the effects of ketamine on intracranial pressure (ICP) and other cerebral hemodynamics to determine whether ketamine was safe for patients with hemodynamic instability and brain injuries.
Methods We systematically searched the online databases of PubMed, Medline, Embase, Current Controlled Trials, and Cochrane Central (last search performed on January 15, 2014). Trial characteristics and outcomes were independently extracted by two assessors (Xin Wang, Xibing Ding). For continuous data, mean differences (MD) were formulated. If the P value of the chi-square test was >0.10 or I^2 <50 %, a fixed-effects model was used; otherwise, the random effects model was adopted.
Results Five trials ($n = 198$) met the inclusion criteria. Using ICP levels within the first 24 h of ketamine administration as the main outcome, the use of ketamine leads to the same ICP levels as opioids [MD = 1.94; 95 % confidence interval (95 % CI), −2.35, 6.23; $P = 0.38$]. There were no significant differences in mean arterial pressure values between the two groups (MD = 0.99; 95 % CI, −2.24, 4.22; $P = 0.55$). Ketamine administration was also comparable with opioids in the maintenance of cerebral perfusion pressure (MD = −1.07; 95 % CI, −7.95, 5.8; $P = 0.76$).
Conclusions The results of this study suggest that ketamine does not increase ICP compared with opioids. Ketamine provides good maintenance of hemodynamic status. Clinical application of ketamine should not be discouraged on the basis of ICP-related concerns.

Keywords Ketamine · Opioids · Intracranial pressure · Hemodynamic instability · Brain injuries

Introduction

Patients with or at risk of neurological injury are associated with elevated intracranial pressure (ICP), which could lead to secondary cerebral injury and poor outcome [1]. Several medicines are used in the management of these patients. The function of each medication is to maintain sedation, reduce elevated ICP, prevent agitation, and facilitate manipulation of mechanical ventilation. These drugs include opioids, benzodiazepines, clonidine, propofol, etomidate, and ketamine [2–6]. Each can be used alone or combined with others to maintain stable hemodynamics [4–7].

Opioids have long been used to treat acute pain. They have also been used in sedation and anesthesia for patients with traumatic brain injury (TBI) or neurological disease to

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prevent secondary brain damage [7]. Opioids may reduce the use of other sedatives and provide an alternative option for analgesia and anxiolysis. Fentanyl, sufentanil, and remifentanil are commonly used intravenous opioids. These drugs have certain good pharmacokinetics properties such as fast action and short half-time. Metabolization to inactive metabolites reduces their accumulation in the kidneys. All opioids can cause side effects, one of the most common being hypotension [6, 8]. Reduction in cerebral blood flow (CBF) could decrease cerebral blood volume and ICP. Opioids generally cause minor decreases in CBF and ICP [7, 8]. However, previous studies on the effect of opioids on CBF and ICP are not consistent. For example, when opioids are administered as a bolus, there will be a risk of increased ICP although they are frequently applied in patients with TBI.

Ketamine is an *N*-methyl-D-aspartate receptor antagonist [9]. As a potent cerebral vasodilator, it has traditionally been excluded or used with caution in the management of patients with TBI or at risk of intracranial hypertension owing to increased ICP [10–14]. These concerns, however, originated from the small number of early cases, and these studies may be not well designed and may lack adequate controls. For example, light anesthesia was induced with ketamine without additional sedatives or anesthetic agents and spontaneous breathing was maintained. Elevated ICP was observed during a diagnostic pneumoventriculography [13, 14].

However, this early view has recently been challenged by a number of studies indicating that ketamine was safe in patients with elevated ICP and showed no significant increase in ICP. Even a marked decrease in ICP was observed [10, 12, 16–22, 24, 25]. Thus, we have analyzed those previous reports about randomized clinical trials (RCTs) in the perioperative and intensive care setting. We focused on the effects of ketamine on cerebral hemodynamics in comparison with opioids in patients with or without neurological injury using meta-analysis.

Methods

Search strategy

A systematical literature search was performed to identify studies that compared the effects of ketamine on cerebral hemodynamics in patients with or without neurological disease. We performed a computerized literature search of PubMed, Medline, Embase, Current Controlled Trials, and Cochrane Central from establishment through January 15, 2014. Briefly, the following medical subject headings (MeSH) were included: ketamine, opioids, intracranial pressure, and randomized controlled trials. Alternative spellings were considered when searching. The reference articles of the appropriate trials were then manually searched.

Inclusion criteria

RCTs conducted in humans of cerebral hemodynamics comparing ketamine with opioids were eligible, regardless of whether the subjects were head injured, ventilated, underwent surgery, or received additional medications. The study had to analyze the ICP levels after administration of ketamine or opioids. The dose, timing, and other details of anesthesia drugs were not limitations.

Selection of studies

After a primary screening of titles and abstracts using the defined search strategy, full-text papers of potentially relevant RCTs were retrieved and further evaluated for eligibility. Five RCTs were identified. Full articles were independently screened and cross-checked by two reviewers (Xin Wang, Xibing Ding). If selection decisions were disputed, a third reviewer (Quan Li) was consulted.

Data extraction

We summarized the following data in a data extraction form: first author name, publication details, details of patient population, study design, settings, interventions between ketamine and opioids group, ICP levels, mean arterial pressure (MAP) levels, and cerebral perfusion pressure (CPP) levels within 1 day after administration of ketamine or opioids. We defined the ICP levels within the first 24 h after administration of ketamine or opioids as the primary outcomes; MAP levels and CPP levels were defined as the secondary outcomes. The two reviewers (Xin Wang, XiBing Ding) who selected the appropriate studies also extracted the data and evaluated the risk of bias.

Assessing the risk of bias

To assess the risk of bias in the included studies, we used the Cochrane Risk of Bias tool [23]. The following items were evaluated by two reviewers (Xin Wang, XiBing Ding): (1) sequence generation (checking for possible selection bias); (2) allocation concealment (checking for possible selection bias); (3) blinding (checking for possible performance bias); (4) incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations); and (5) selective reporting bias. Any disagreement was resolved by an arbiter (Quan Li).

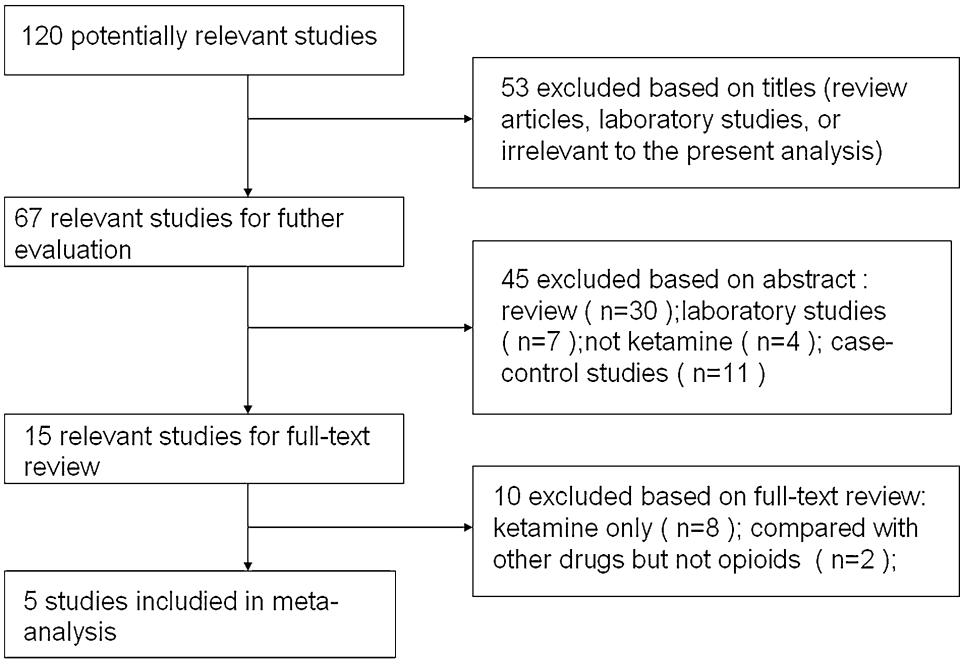

Fig. 1 Flow chart of the study selection procedure

Statistical analysis

Review Manager Software (Revman 5.0; Cochrane Collaboration, Oxford, United Kingdom) was used for statistical analysis. Heterogeneity among studies was evaluated using the chi-square test and I^2 statistic. If the P value of the chi-square test was >0.10 or I^2 <50 %, a fixed-effects model was used; otherwise, the random effects model was adopted. For the continuous data in the studies included in the meta-analysis (ICP, MAP, and CPP levels within the first 24 h of ketamine administration), we used mean difference (MD) and 95 % confidence interval (95 % CI). If the heterogeneity was >50 %, a sensitivity analysis was performed by sequentially removing each trial and reanalyzing the remaining data set. All tests of statistical significance were two sided.

Results

Search results

Initially, 120 records were identified through the PubMed, Medline, Embase, Current Controlled Trials, and Cochrane Central. Of these, 15 potentially eligible studies were retrieved for detailed evaluation. Only 5 were found to fulfill the inclusion criteria [15, 19, 20, 24, 25]. The remaining 10 articles [16–18, 26–32] were removed because the studies did not compare ketamine and opioids or the original data were not relevant to our study. Therefore, 5 RCTs with 198 patients were included in the meta-analysis. A detailed explanation of the full electronic strategy is shown in Fig. 1. Four RCTs in mechanically ventilated, head-injured patients who stayed in an ICU with or without increased ICP were included [19, 20, 24, 25]. In addition, 1 RCT in patients without cerebral compromise who were undergoing surgical intervention or procedure was included because the findings also indicated the cerebral hemodynamic effects of ketamine administration for fear of spuriously elevating ICP in the operative environment [15]. The characteristics of each included trial are described in Table 1.

Risk of bias of included studies

The risk of bias assessment of each study is described in Fig. 2. According to the Cochrane Risk of Bias tool, each trial had a low risk of bias. Each study was described as a randomized trial. Two studies used the allocation concealment method, and the other three studies were unclear. Four studies were blinded as to participants and personnel. Two studies were blinded in outcome accessors. Incomplete outcome data had a low risk of bias in all articles as well as in selection of reporting bias.

Sensitivity analysis

We performed a sensitivity analysis of ICP levels and CPP levels. Under this condition, with the exclusion of the study by Michalczyk et al. [15], we resolved the heterogeneity of ICP (MD = −0.34; 95 % CI, −2.64, 1.95; $I^2 = 40$ %; $P = 0.77$). Fixing the limits should not change the essence of the results; however, the exclusion of Kolenda et al. [25]

Table 1 Characteristics of randomized controlled studies

References	Journal	Patients	Age	Sample size	Dose	Ventilation
Michalczyk et al. [15]	Pediatric Critical Care Medicine	84	82 ± 49 months	35	Midazolam/ketamine 1 mg/kg, midazolam 0.1 mg/kg,	Spontaneous
				39	Ketamine 1 mg/kg	
				10	Propofol/fentanyl	
Schmittner et al. [24]	J Neurosurg Anesthesiol	24	25−77 years	12	Ketamine 0.5 mg/kg BW bolus, S(+), 3.6 ± 5.1 μg/kg BW/h cont. infusion	Controlled
				12	Fentanyl F:3 μg/kg BW bolus, 12.8 ± 18.4 μg/kg BW/h cont.infusion	Normoventilation
Bourgoin et al. [20]	Crit Care Med	30	18–75 years	15	Ketamine 95 μg/kg/min Ket cont. infusion, racemic	Controlled
				15	Sufentanil 0.007 μg/kg/min Suf cont. infusion	Normoventilation
Bourgoin et al. [19]	Crit Care Med	25	16−75 years	12	Ketamine 4.92 ± 1.5 mg/kg/h cont. infusion, racemic	
				13	Sufentanil 0.008 ± 0.002 μg/kg/min, cont. infusion	Hyperventilation
Kolenda et al. [25]	Acta Neurochirurgica	35	16–72 years	17	Ketamine 104 mg/kg/day Ket	Controlled or normo- or hyperventilation
				18	Fentanyl 100 μg/kg/day F	

Fig. 2 Methodological quality summary: review authors' judgments about each methodological quality item for each included study

resolved the heterogeneity of CPP levels. This change had no effect on the final results (MD = 1.59; 95 % CI, −2.81, 5.98; $I^2 = 13$ %; $P = 0.48$).

Clinical outcomes

Meta-analysis showed that ketamine led to the same ICP levels as did opioids, which was one of the common agents for sedation (mainly sufentanil and fentanyl) (MD = 1.94; 95 % CI, −2.35, 6.23; $I^2 = 85$ %; $P = 0.38$) (Fig. 3a). Data were derived from three articles for the analysis of MAP [19, 20, 25]. No statistical significance was found in MAP values between the groups (MD = 0.99; 95 % CI, −2.24, 4.22; $I^2 = 0$ %; $P = 0.55$) (Fig. 3b). Data from four articles were used for the analysis of CPP [19, 20, 24, 25]. Ketamine administration was comparable with opioids in the maintenance of CPP (MD = −1.07; 95 % CI, −7.95, 5.8; $I^2 = 83$ %; $P = 0.76$) (Fig. 3c).

Discussion

This meta-analysis substantiates the idea that there is no significant variation of ICP and MAP with or without ketamine administration. The use of ketamine causes the levels of ICP and MAP to be similar to those of opioids. In addition, our analysis suggests that ketamine and opioids result in a similar level of increase in CPP. Bourgoin et al. [19, 20] performed two prospective, randomized trials on ketamine for sedation in patients with TBI. No significant change was observed in ICP, MAP, or CPP during a long infusion or after a transient doubling of plasma drug concentration of ketamine or sufentanil. One trial compared sedation between ketamine/midazolam and sufentanil/

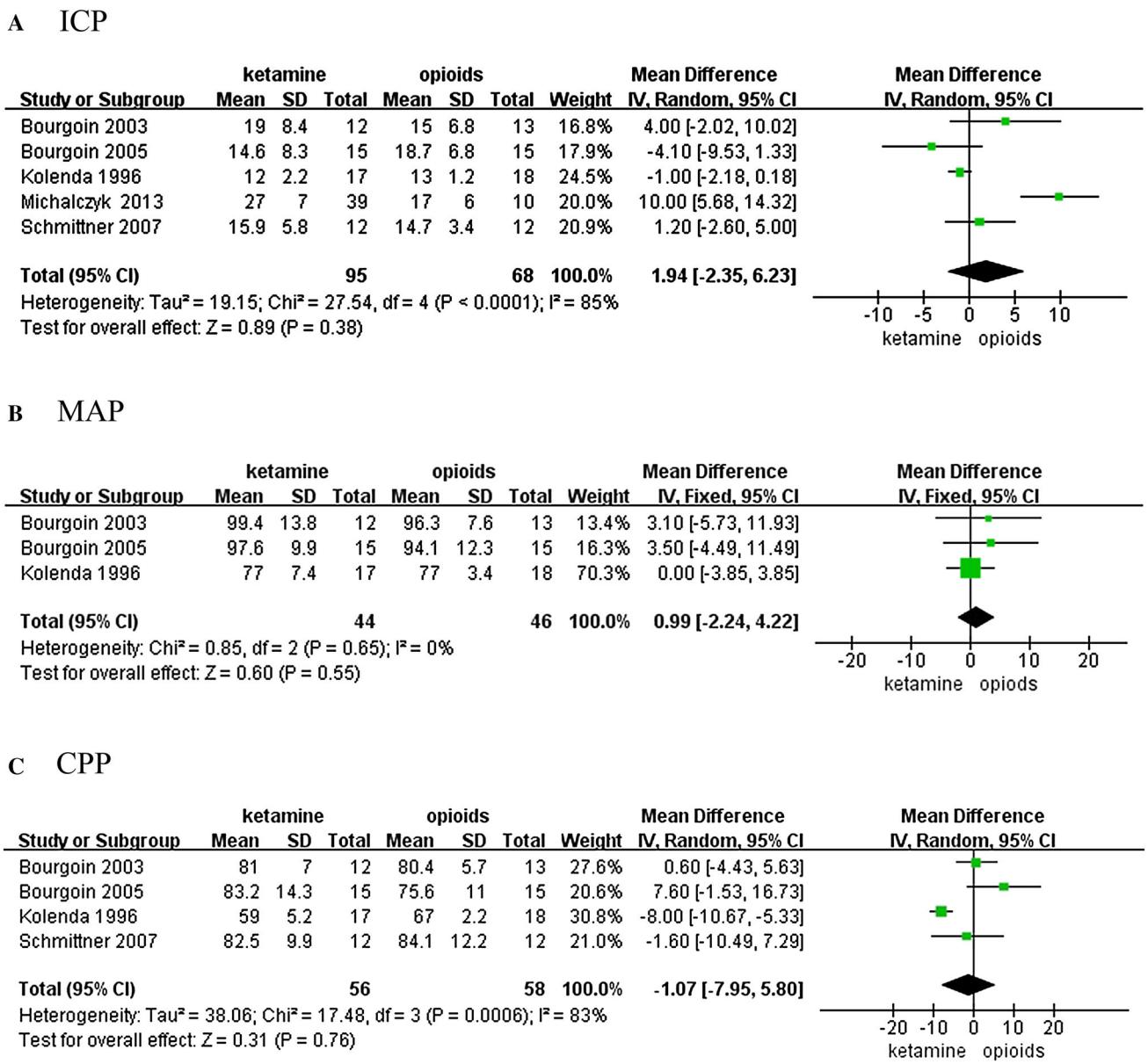

Fig. 3 Meta-analysis of intracranial pressure (ICP) levels (**a**), mean arterial pressure (MAP) levels (**b**), and cerebral perfusion pressure (CPP) levels (**c**) within the first 24 h of ketamine administration or opioids administration

midazolam in 25 patients with TBI under mechanical ventilation [19]. The results of this study showed that ketamine led to the same ICP levels as sufentanil. These results were consistent with their previous study [18] that showed the administration of ketamine (1.5, 3, and 5 mg/kg) significantly reduced ICP. There was no significant difference in CPP and jugular vein bulb oxygen saturation (SjO_2). The potential advantages of ketamine compared with opioids include maintenance of CPP and hemodynamics, tolerance of enteral nutrition, and no withdrawal symptoms [19]. Recently, a study by Caricato et al. [10] allocated 21 head-injured patients to sedation with ketamine when endotracheal suctioning was performed. This study indicated that the use of a racemic mixture of ketamine caused no significant variation in ICP, MAP, CPP, SjO_2, and blood flow velocity in the middle cerebral artery (mV MCA) in mechanically ventilated TBI patients during continuous analog-sedation. The study found that when ketamine was used as an adjuvant to other agents, ICP and other cerebral hemodynamics remained stable, and cough reflex after endotracheal suctioning was prevented. Bar-Joseph et al. also observed that the administration of ketamine reduced ICP in 88 % of patients during a potentially distressing intervention such as endotracheal

suctioning, respiratory physiotherapy, or bed linen change [16].

A number of studies refuted the longstanding issue that ketamine increases ICP [10, 12, 15–22, 24, 25]. It has also been argued that when compared with widely used sedative agents, ketamine may preserve CPP and does not decrease blood pressure. In fact, the evidence supporting concerns that ketamine increases ICP is rather limited [12–14, 21, 32–46]. Reasons for the conflicting results are not clear [10]. Ketamine varied in different brain regions according to the dose administered and the type of ketamine (racemic, *S*-, or *R*-enantiomers), but the effects of ketamine on cerebral metabolic rate (CMR) and CBF are equivocal. Recently, even neuroprotective effects of ketamine have been discussed. There are also conflicting data on whether ketamine induces epileptiform activity [7]. Ketamine is classified as an *N*-methyl-D-aspartate (NMDA) receptor antagonist [9, 37]. The blocking of NMDA receptors may limit seizure activity. It is believed to provide neuroprotection for patients with TBI by preventing the stimulation of the excitatory amino acid receptor and reduction in glutamate excitotoxicity [37, 38]. Thus, ketamine is considered as an induction agent in patients with hemodynamic instability and TBI.

To our knowledge, this is the first meta-analysis attempting to answer whether use of ketamine in patients with hemodynamic instability and TBI is acceptable, and we obtained promising results. Recent data suggest that the cerebral effects of ketamine were the result of the design of the experiments to a large extent [14, 39–42], such as with or without mechanically controlled ventilation [26, 42, 43] or concomitant medication [17, 44–47]. To address these issues, we employed subgroup analysis of these conditions and obtained similar results. We also performed sensitivity analysis, which did not change the final results either. Limited by the small number of patients, additional well-controlled, randomized trials are still needed to confirm our results.

There were several limitations in our meta-analysis. First, although our meta-analysis showed promising results on the cerebral effects of ketamine, it was based on relatively few patients. Second, the study of Michalczyk et al. [15] used a bolus dose of ketamine whereas the other four studies used infusions. The patients for this study were children although other studies were not. These differences may have a meaningful influence on the results. Third, the RCTs took place over 17 years, raising the question of how the nonexperimental aspects of the patients' care may have differed and influenced the outcomes. Finally, there is significant heterogeneity in the primary and secondary outcomes in our meta-analysis, which may be related to the differences in type, dose, and duration of ketamine, whether used in a ventilated patient, and whether combined with other sedation agents. Thus, the total number of clinical studies is insufficient to make conclusions.

In summary, compared with opioids, which is one of the commonly used agents for sedation, ketamine does not increase ICP, and maintains cerebral hemodynamics in patients with TBI or at risk of intracranial hypertension. Further clinical studies with large sample size and well-controlled conditions should be encouraged.

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