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REVIEW ARTICLE

Ketamine as adjunctive or monotherapy for post-intubation sedation in patients with trauma on mechanical ventilation: A rapid review

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ABSTRACT

Background: The effectiveness of ketamine as adjunctive or monotherapy for post-intubation sedation in adults with trauma on mechanical ventilation is unclear.

Methods: A rapid review of systematic reviews of randomized controlled trials, then randomized controlled trials or observational studies was conducted searching three electronic databases (PubMed, Embase, Cochrane Library) and one clinical trial registry on June 1, 2022. We used a prespecified protocol following Cochrane rapid review methods.

Results: We identified eight systematic reviews of randomized controlled trials and observational studies. Among the included reviews, only the most relevant, up to date, highest quality-assessed reviews and reviews that reported on critical outcomes were considered. Adjunctive ketamine showed a morphine sparing effect (MD −13.19 μmg kg^{-1} h^{-1}, 95 % CI −22.10 to −4.28, moderate certainty of evidence, 6 RCTs), but no to little effect on midazolam sparing effect (MD 0.75 μmg kg^{-1} h^{-1}, 95 % CI −1.11 to 2.61, low certainty of evidence, 6 RCTs) or duration of mechanical ventilation in days (MD −0.17 days, 95 % CI −3.03 to 2.69, moderate certainty of evidence, 3 RCTs).

Adjunctive ketamine therapy may reduce mortality (OR 0.88, 95 % CI 0.54 to 1.43, $P = 0.60$, very low certainty of evidence, 5 RCTs, $n = 3076$ patients) resulting in 30 fewer deaths per 1000, ranging from 132 fewer to 87 more, but the evidence is very uncertain. Ketamine results in little to no difference in length of ICU stay (MD 0.04 days, 95 % CI −0.12 to 0.20, high certainty of evidence, 5 RCTs $n = 390$ patients) or length of hospital stay (MD −0.53 days, 95 % CI −1.36 to 0.30, high certainty of evidence, 5 RCTs, $n = 277$ patients).

Monotherapy may have a positive effect on respiratory and haemodynamic outcomes, however the evidence is very uncertain.

Conclusion: Adjunctive ketamine for post-intubation analgosedation results in a moderate meaningful net benefit but there is uncertainty for benefit and harms as monotherapy.

African relevance

- Ketamine as adjunctive or monotherapy is an essential component of critical care, however its effectiveness for post-intubation sedation in adults with trauma on mechanical ventilation is unclear.
- Ketamine as adjunctive therapy for post-intubation analgosedation provides a meaningful net benefit, with little to no difference in length of ICU or hospital stay.
- Monotherapy may have a positive effect on respiratory outcomes and haemodynamic outcomes, however the evidence remains uncertain.

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- Our rapid review provides clear evidence supporting the use of adjunctive ketamine in trauma patients for post-intubation sedation on mechanical ventilation.

Background

Analgosedation is an essential component of critical care and reduces physiological stress, enables mechanical ventilation, and facilitates nursing care [1,2]. The approach to analgosedation and choice of drugs influence the outcomes in mechanically ventilated patients and have an effect on prognosis, length of mechanical ventilation and length of stay in intensive care units [3–5]. The optimal approach to analgosedation depends on the treatment requirements and existing medical conditions and should therefore be individualized for each patient [6–8]. The lack of an ideal analgesic and sedative, have however resulted in widespread variation in practice in emergency centres, intensive care units and in the prehospital setting [6,9,10].

Opioids are the backbone of analgosedation in critically ill patients and used in more than 80 % of mechanically ventilated patients [10]. Its use is however limited by the risk of hypotension and haemodynamic instability, as well as the risk of tolerance and withdrawal [11,12]. Benzodiazepines are commonly used for adjunctive sedation but poses a risk of delirium, cardiorespiratory depression and unintended over-sedation from drug accumulation [11,13]. Alternatives to benzodiazepines like propofol and dexmedetomidine are often preferred. Dexmedetomidine is expensive and not freely available in low-resource settings and even though it lowers the risk of delirium, duration of ventilation and ICU length of stay, it increases the risk of bradycardia and hypotension [14]. Propofol has a negative effect on cardiac output and systemic vascular resistance and poses a significant risk of hypotension, rendering it not suitable in patients who are haemodynamically compromised [11]. Data on a preferred analgesic or sedative for mechanically ventilated patients who are haemodynamically compromised is limited.

Ketamine's pharmacokinetic properties, reasonable side-effect profile, and favourable haemodynamic effects, make it an attractive alternative [15]. It is both an analgesic and sedative, has a quick onset and rapid recovery with limited bioaccumulation [11,16]. Its bronchodilatory and anti-inflammatory effects have shown benefit as a sedative hypnotic in patients with reactive airway disease [4,17]. Ketamine does not increase intra-cranial pressure and may improve cerebral perfusion pressure, rendering it a feasible option for analgosedation in mechanically ventilated patients with traumatic brain injury [18–20]. Evidence also suggests that ketamine has an opioid and sedative spring effect when used as an adjunct to standard analgosedation strategies [10,11,15–17]. Dose-dependent psychometric side effects, risk of increased blood pressure and tachycardia may be potentiated by high-dose infusions when used as monotherapy [11,17,21].

The South African National Standard Treatment Guidelines (STG) and Essential Medicines List (EML) lists morphine, midazolam, propofol and fentanyl as standard of care for analgosedation in mechanically ventilated patients, with ketamine listed only as an induction agent to facilitate intubation.

The South African National Essential Medicines List Committee (NEMLC) is a ministerially appointed, non-statutory advisory committee that is responsible for the development and maintenance of the National EML and the STGs [22]. An essential medicines list is defined by the World Health organisation as medicines that satisfies the priority health care needs of a population, and includes medicines that people should have access to at all times and in sufficient amounts [23]. The process of conducting rapid reviews for NEMLC has been previously described for COVID-19 therapeutic interventions [24]. The rapid review methodology has also been adopted for essential medicine list evidence reviews more generally in South Africa, supported by the SA Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Network [25]. Rapid reviews are a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining specific methods to produce evidence for stakeholders in a resource-efficient and timely manner [26]. The response to COVID-19 highlighted the need for timely evidence review to inform decision-making and advanced rapid review methods, specifically in response to urgent or emergency evidence requests from decision makers [24]. One rapid review method is to use a tiered approach whereby reviewers first consider high-quality, relevant, and up-to-date clinical practice guidelines, then systematic reviews, randomized controlled trials and other designs if the review question is still not answered [27]. To settle the uncertainty and inform the Adult Hospital Level STGs and EML for Emergency and Injuries, we conducted a rapid review to determine whether ketamine as adjunctive or monotherapy should be used for post-intubation sedation in adults with trauma on mechanical ventilation.

Methods

We used a prespecified protocol following the rapid review Cochrane methodology and South African National EML Health Technology Assessment guidelines for rapid systematic reviews as previously described [26,28]. In summary, rapid reviews is a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining specific methods to produce evidence for stakeholders in a resource-efficient and timely manner. These reviews balances rigor with speed, with the aim of reducing research waste and duplication of effort [28–31].

We included Randomized Controlled Trials (RCTs) and Systematic Reviews (SRs) of RCTs or observational studies considering ketamine as either adjunctive or monotherapy in intubated adults with trauma on mechanical ventilation. Prioritized patient important outcomes for monotherapy included sedation and analgesia, ventilator asynchrony, provider satisfaction, Richmond Agitation-Sedation Scale (RASS), physiological parameters, mortality, and hospital length of stay. For adjunctive therapy prioritized outcomes included reduction in opioid requirements, mortality, hospital length of stay, serious adverse events (SAEs), and adverse events (AEs). We systematically searched three databases (Ovid MEDLINE, Embase and the Cochrane Library) and one trial registry for ongoing studies (Pan African Clinical Trial Registry). The search strategy was developed and conducted by an experienced information specialist with no language or publication restrictions on 1st of June 2022 (Appendix 1: Search Strategy).

Screening of title and abstracts, full text screening, selection of studies and data extraction was conducted independently and in duplicate by two reviewers (IK and CH). Screening was done using the Covidence software. AMSTAR II [32] was used to appraise all the systematic reviews included by a single reviewer (VN) and checked by a second reviewer (IK). Any disagreements were resolved through discussion or in consultation with a third reviewer (MM). Where multiple eligible SRs were included, we reported evidence from the most relevant, recent, and highest-quality-assessed review or reviews that provided evidence across all *a priori* outcomes. Results from reviews that were eligible but not up-to-date, credible, or failed to report on critical outcomes were not prioritized, however results and direction of effects were cross-checked. If any eligible RCTs were not included by the SRs authors (e.g., published after the SR search date), these were included in the pooled synthesis if appropriate. RCTs identified by our searches that were already considered by the included systematic reviews were excluded to avoid double counting. We conducted a GRADE [33] assessment to establish the certainty of the evidence across each outcome, considering risk of bias, directness, consistency, precision, and other considerations such as publication bias to determine whether the confidence in the overall results was high, moderate, low or very low. Pooled effects across outcomes and certainty of evidence are reported in the Summary of Findings (SoFs) tables using GRADEPro software.

Results

The search produced 841 records and included 41 reports for full text screening and included eight systematic reviews in the final review (Fig. 1). AMSTAR II assessment of all eight reviews ranged from low quality to critically low quality (Appendix 4). Chan et al. (2022) was considered the most relevant, trustworthy, and up-to-date review and included GRADE certainty of evidence judgements. Outcomes of interest not reported in Chan et al. (2022) were reported from Manasco et al. (2020) and Wang et al. (2019) [4,6,11]. No additional trials were found outside of the included SRs.

Description of included studies

Appendix 2 has a detailed description of the included studies stratified by monotherapy and adjunctive therapy. See Appendix 3 for characteristics of excluded studies.

Adjunctive therapy studies

Chan et al. (2022) aimed to assess the impact of continuous ketamine infusion on opioid and sedative consumption in critically ill patients on mechanical ventilation as primary outcome [11]. The review included trials with ketamine as adjunctive therapy (with sedatives or opioids) compared to various standard treatment control combinations. Their secondary outcome was to assess the effect of ketamine on all-cause mortality, the duration of mechanical ventilation, duration of ICU and hospital stay and intracranial pressure elevation. They included 13 RCTs and 6 observational studies with a total of 2 258 participants. Risk of Bias (ROB) was assessed in all included studies using the Cochrane ROB 1.0 tool [34] or ROBINS-I for cohort studies [35]. GRADE was reassessed for all outcomes and certainty of overall evidence ranged from high to very low certainty across outcomes.

Manasco et al. (2020) assessed ketamine use in mechanically ventilated patients to determine its effect on sedative use and patient-oriented outcomes. Three RCTs and 12 cohort studies with a total of 892 patients were included in the review [4].

Wheeler *at al.,* 2020 assessed the efficacy and safety of non-opioid adjunctive analgesia for patience in the intensive care unit. They included 34 RCTs examining various analgesia with only 4 studies evaluating the effect of ketamine as an adjunctive therapy. This study does not mention the number of study participants included in the study [10].

Wang *et al.* (2019) conducted a network meta-analysis that determined the effect of sedative drugs on all-cause mortality, duration of mechanical ventilation, and ICU stay, risk of delirium and hypotension in mechanically ventilated ICU patients. Only one study (and comparison) directly considered Ketamine (with benzodiazepines) with a total of 25 patients [6].

Patanwala *et al.* (2017) compared the ketamine and non-ketamine analgesic and sedative effects in mechanically ventilated ICU patients. They included 6 RCTs, one cohort study and six case reports with a total of 256 patients in their review [16].

Cohen, *et al.* (2015) determined the effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes in mechanically ventilated ICU patients. They included five RCTs and five non-RCTs with a total of 953 patients in the review [20].

Zeiler *et al.* (2014) investigated the effect of Ketamine on intracranial pressure in ventilated patients with traumatic brain injury. They included four RCTs, two cohort studies and one case-report with a total of 166 patients [18].

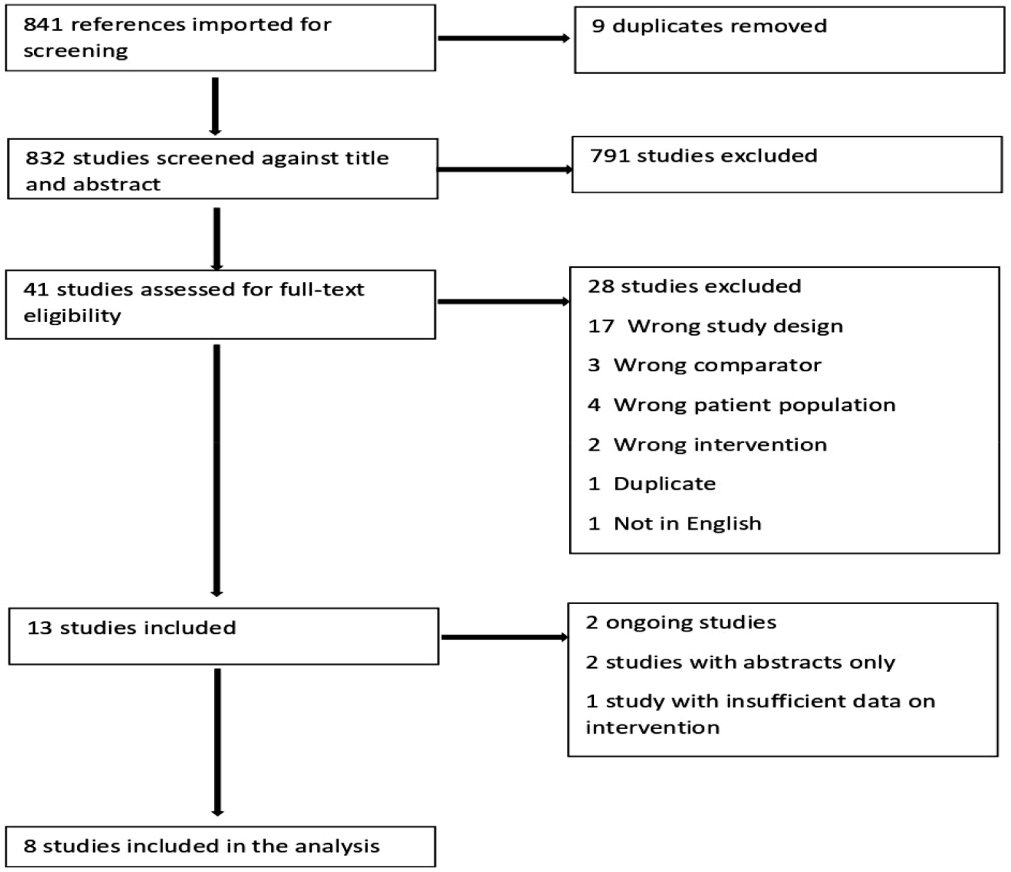

Fig. 1. PRISMA flow diagram of the search.

Monotherapy studies

Miller *et al.* (2011) assessed the pulmonary and haemodynamic effects of continuous ketamine infusion for sedation maintenance in patients on mechanical ventilation. They included four RCTs in which the comparator sedative agents were Fentanyl and Midazolam, 11 case series and five case reports with a total of 281 patients [17].

Internal validity of the systematic reviews and GRADE SoFs

AMSTAR II was used to evaluate the internal validity of the systematic reviews included in the study. In order to reduce the duplication of synthesis, we used the SR that was most recent, was of highest quality and most relevant to our PICO. Chan *et al.* (2022) and Manasco *et al.* (2020) included RCTs relevant to the PICO and any additional individual RCTs found in the review searches were excluded to avoid double counting [4,11]. Of all the studies included, Chan et al., (2022) and Manasco et al. (2020) had the highest AMSTAR II overall score (low quality review), however Chan was considered in the analysis as this review was the most recent, included the most recent trials, considered the most relevant and used GRADE in reporting its findings [4,11]. Outcomes were re-GRADED accounting for difference in contextual/clinical interpretation such as indirectness and imprecision (Summary of Findings Table 1).

Risk of bias of included trials in SR

Chan et al. (2022) reported high risk of bias across five of the 13 RCTs and high risk of bias across all 6 observational (cohort) included studies [11]. Overall, we consider the ROB to be low to unclear across included trials in Chan et al. (2022) [11] (Fig. 2).

Effect of interventions

Ketamine adjunctive therapy

Morphine consumption

Ketamine as adjunctive therapy probably reduces the consumption of morphine compared to non-ketamine analgesia therapy (fentanyl, midazolam, sufentanil, pregabalin) in mechanically ventilated patients (MD −13.19 μg kg^{-1} h^{-1}, 95 %CI −22.10 to −4.28, moderate certainty of evidence, 6 RCTS, $n = 494$ participants), which equates to ~1 mg/h less Morphine consumption for an average 70 kg adult, ranging from 1.5 mg/h less to 0.3 mg/h less (Chan *et al.* 2022) [11] (Fig. 3).

Midazolam consumption

Ketamine adjunctive therapy may have a trivial effect to no effect on the consumption of midazolam compared to non-ketamine analgesia (fentanyl, midazolam, sufentanil, pregabalin) in mechanically ventilated patients (MD 0.75 μg kg^{-1} h^{-1}, 95 % CI −1.11 to 2.61, low certainty of evidence, 6 RCTs, $n = 289$ patients), which equates to 0.05 mg/h more midazolam consumption for an average 70 kg adult, ranging from 0.078 less to 0.18 more (Chan *et al.* 2022) [11]. Manasco *et al.* (2020) similarly reported no significant effect of adjunct ketamine on the consumption of Midazolam (MD −0.3 mg/h, 95 % CI −0.95 to 0.35, 5 RCTs, $n = 234$ patients) [4] (Fig. 4).

Table 1
Ketamine adjunctive therapy compared to standard of care for trauma patients intubated on mechanical ventilation in ICU, EC or prehospital.

Patient or population: trauma patients intubated on mechanical ventilation in ICU, EC or prehospital.
Intervention: Ketamine adjunctive therapy
Comparison: standard of care

Outcomes	N⁰ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Ketamine adjunctive therapy
Mortality	307 (5 RCTs)	⨁◯◯◯ Very low[a,b]	**OR 0.88** (0.54 to 1.43)	382 per 1000	**30 fewer per 1000** (132 fewer to 87 more)
Length of ICU stay (days)	390 (5 RCTs)	⨁⨁⨁⨁ High[c]	-	The mean length of ICU stay (days) was **14** days	MD **0.04 days higher** (0.12 lower to 0.2 higher)
Length of hospital stay (days)	277 (5 RCTs)	⨁⨁⨁⨁ High	-	The mean length of hospital stay (days) was **20** days	MD **0.53 days lower** (1.36 lower to 0.3 higher)
Morphine consumption	494 (6 RCTs)	⨁⨁⨁◯ Moderate[d]	-	The mean morphine consumption ranged from **−140 to 37** ug/kg/h	MD **13.19 ug/kg/h lower** (22.1 lower to 4.28 lower)
Midazolam consumption	289 (6 RCTs)	⨁⨁◯◯ Low[e,f]	-		MD **0.75 higher** (1.11 lower to 2.61 higher)
Duration of mechanical ventilation (days)	(3 RCTs)	⨁⨁⨁◯ Moderate[f]	-		MD **0.17 fewer** (3.03 fewer to 2.69 more)

*__The risk in the intervention group__ (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95 % CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio.
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Explanations:
[a] Although 3/5 trials had at least one domain with high ROB, Perbet (2018) had overall low ROB and contributed to the majority of the pooled effect [36].
[b] Extremely serious imprecision: 95% CI of the absolute effect ranges from large benefits to moderate to large harms. Additionally, there is clinically meaningful inconsistency across included trials (varied direction of effects), undetected statistically ($I^2 = 0\%$), however likely due to small study effects contributing to imprecise trial effect estimates. Not downgraded for inconsistency as linked to imprecision.
[c] Anwar contributed 99% of the pooled estimate with overall low ROB [37].
[d] Serious inconsistency: Perbet 2018 contributing to significant heterogeneity [36].
[e] Serious risk of bias: High risk of bias in Dzierba (2016) and Bourgoin (2003) with Dzierba (2016) contributing to the majority of the pooled effect [38,39].
[f] Serious imprecision: The 95% CI around the absolute effect ranges from meaningful (important) benefit and harms.

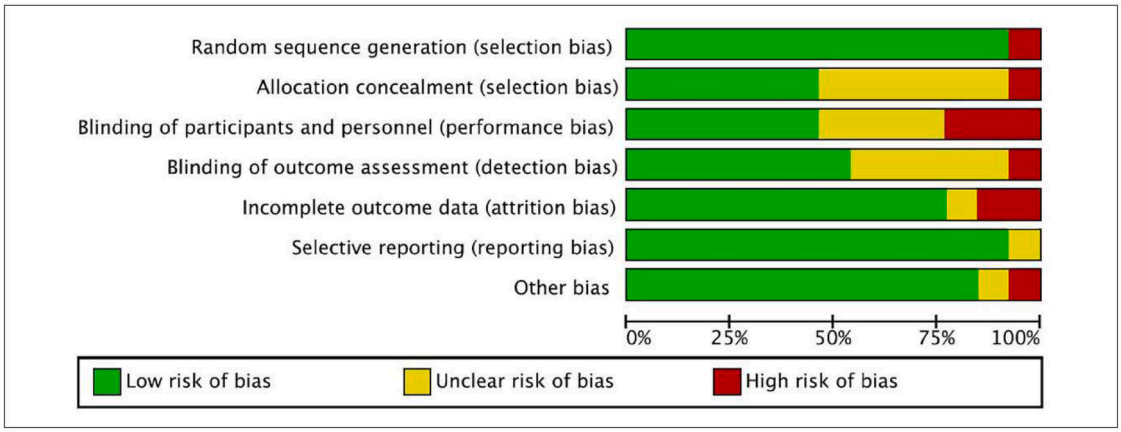

Fig. 2. Risk of Bias of included RCTs [11].

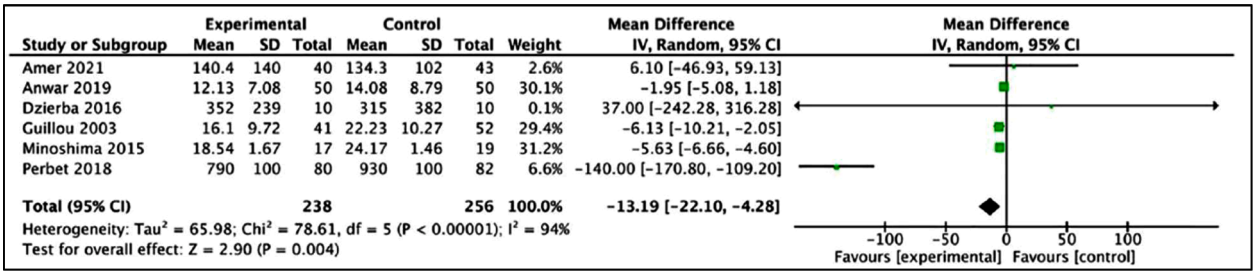

Fig. 3. Forest plot of comparison of mean morphine dose for ketamine vs non-ketamine regimen (Chan *et al.* 2022) [11].
Mean morphine equivalent dose (ME) (μg kg^{-1} h^{-1}).

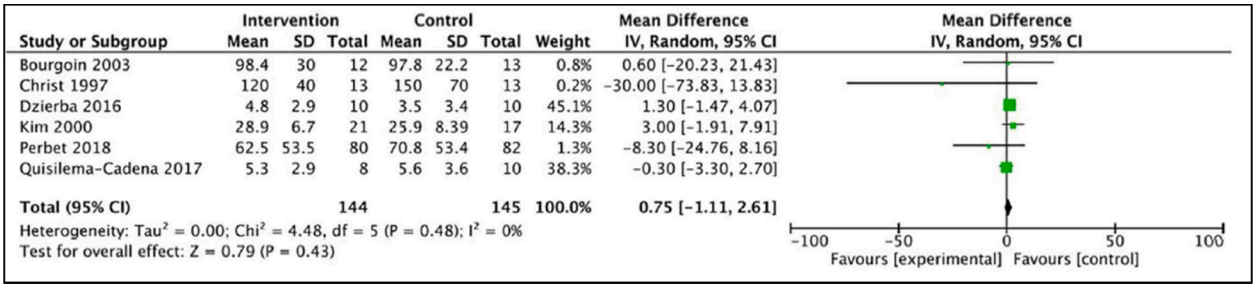

Fig. 4. Forest plot of comparison of mean midazolam dose for ketamine vs non-ketamine regimen (Chan *et al.* 2022) [11].
Mean midazolam dose (μg kg^{-1} h^{-1}).

Mechanical ventilation

Ketamine adjunctive therapy may have a trivial effect to no effect on the duration of mechanical ventilation (MD −0.17 days, 95 % CI −3.03 to 2.69, moderate certainty of evidence, 3 RCTs, n = 265 patients) compared to control (Chan et al. 2022) [11]. No significant difference in duration of mechanical ventilation was also reported by Manasco et al. (2020), (MD 0.4 days, 95 % CI −0.6 to 1.4, 3 non-randomized studies, n = 287) [4] (Fig. 5).

Mortality

Chan et al. (2022) found ketamine adjunctive therapy may reduce mortality (OR 0.88, 95 % CI 0.54 to 1.43, P = 0.60, very low certainty of

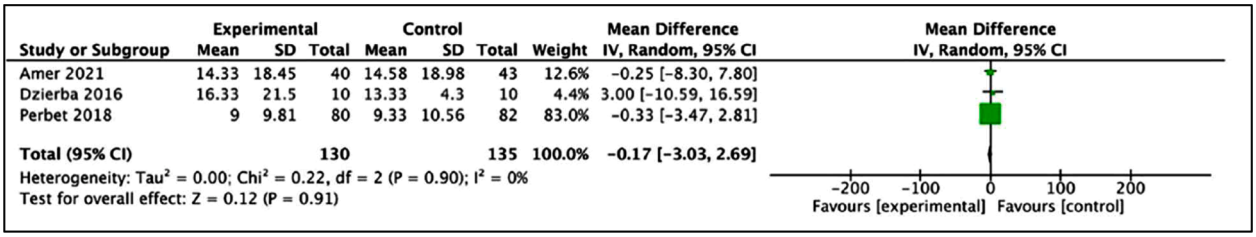

Fig. 5. Forest plot of comparison of mean duration of mechanical ventilation for ketamine vs non-ketamine analgesia (Chan et al. 2022) [11].

evidence, 5 RCTs, $n = 307$ patients) resulting in 30 fewer deaths per 1000, ranging from 132 fewer to 87 more, but the evidence is very uncertain [11]. Similar uncertain findings were also reported by Manasco et al. (2020) (OR 1.13, 95 % CI 0.70 to 1.81, $p = 0.61$, 1 RCT, 5 non-randomized studies $n = 385$ patients) [4] (Fig. 6).

Length of ICU stay

Chan et al. (2022) ketamine adjunctive therapy results trivial effect to no effect in length of ICU stay (days) (MD 0.04 days, 95 % CI −0.12 to 0.20, high certainty of evidence, 5 RCTs $n = 390$ patients) [11]. Manasco et al. (2020) reported longer stay in ICU with the use of adjunct ketamine, (MD 2.4 days, 95 % CI, 1.3 to 3.5, $p<0.001$, 2 RCTs, 2 non-RCTs, $n = 312$ patients) [4]. Likely inflated by inclusion of observational data (Fig. 7).

Length of hospital stay

Both Chan *et al.* (2022) (MD −0.53 days, 95 % CI −1.36 to 0.30, $P = 0.21$, high certainty of evidence, 5 RCTs, $n = 277$ patients) and Manasco et al. (2020) (MD 0.5 days, 95 % CI −5.95 to 6.95, $p = 0.88$, 3 non-randomized studies, $n = 173$ patients) reported no change in length of hospital stay with the use of ketamine or that ketamine adjunctive therapy results in little to no difference in length of hospital stay (days) [4,11] (Fig. 8).

Level of sedation (RASS)

In Manasco et al. (2020) qualitative analysis was done by one non-randomized study reporting no difference in proportion of time at RASS goal, while another non-randomized study reported greater time within target RASS [4].

Ventilator asynchrony, provider satisfaction and physiological parameters were not reported across included SRs.

Respiratory parameters

Narrative review of respiratory parameters was done. Two RCTs and four case reports (73 patients) reported no respiratory depression in ketamine group compared to control group. 1 RCT, 2 case series and two case reports (41 patients) reported an increase in chest wall dynamic compliance with the use of Ketamine. Three case reports and 7 case series (64 patients) reported an increase in partial oxygenation (PO_2) with continuous ketamine infusion while four case series and four case reports (46 patients) found a decrease in partial carbon dioxide (PCO_2) with Ketamine use.

Haemodynamic parameters

Narrative review of haemodynamic parameters was done. 2 case series (20 patients) found no changes in systolic blood pressure with continuous ketamine use while 1 case report found a decrease in systolic blood pressure with continuous ketamine infusion. 2 RCTs (29 patients) found an increase in mean arterial blood pressure with continuous ketamine use compared to the control group, while 2 case series and 1 case report (21 patients) found no change in mean arterial blood pressure with the use of continuous ketamine. 1 RCT (24 patients) reported decrease in vasopressor in ketamine group compared to control and another RCT (5 patients) reported decrease in shock with continuous ketamine use.

Discussion

This rapid review was conducted to determine whether ketamine as adjunctive or monotherapy should be used as analgosedation for mechanically ventilated adults with trauma. As adjunctive therapy, ketamine demonstrated a clinically meaningful morphine sparing effect and may reduce mortality, although the evidence for this effect remains very uncertain. Ketamine, compared to other agents shows little to no difference in ICU or hospital length of stay. There is insufficient evidence to recommend for or against ketamine as monotherapy. Following this review, the South African National Essential Medicines List Committee accepted ketamine for adjunctive analgosedation in adults with trauma and was integrated in the National Adult Hospital Level STGs and EML.

Ketamine as adjunctive analgosedation reduced morphine consumption by 13.19 μg/kg/h, which equates to around ~1 mg/h less than standard of care for a 70 kg adult. This effect was consistent across the individual trails that was included [11]. The potential benefits related to less morphine usage, including iatrogenic withdrawal, gastrointestinal dysmotility and tolerance were not described [16,40]. Ketamine has the potential to decrease vasopressor requirements compared to morphine-based regimens as a result of histamine-related vasodilation but haemodynamic outcomes were not described either [16]. Ketamine demonstrated no midazolam sparing effect. Chan et al. (2022) and Manasco et al. (2020) reported an uncertain mortality effect with adjunctive ketamine therapy (6 RCTs and 5 non-randomized studies), with low certainty of evidence, but no effect on ICU and hospital length of stay [4,11].

The dosage of ketamine as adjunct that was used in the included trials and SR varied between 2 and 5ug/kg/min (8.4–21 mg per hour in 70 kg adult) to initiate the infusion, followed by an up-titration to a desirable level of analgosedation between 5 and 25ug/kg/min (21–105 mg per hour in 70 kg adult) [4,11,16]. However, no upper limit or maximum dosage were described. Boluses of 0.5–1 mg/kg (35–70 mg in a 70 kg adult) to facilitate procedures or due to acute agitation has been described to rapidly increase serum concentration, similar to the dose recommended for procedural sedation and analgesia [16,41].

Information from this review assessing ketamine as monotherapy for analgosedation for mechanically ventilated adults were not sufficient to recommend for or against the use of ketamine. It is not feasible to extrapolate findings from the adjunctive therapy to the monotherapy limb for various reasons: (i) it can be expected that a higher dosage of

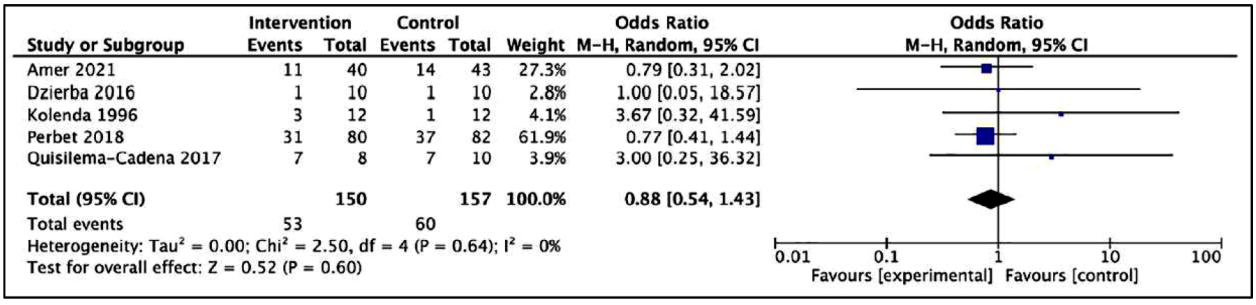

Fig. 6. Forest plot of ketamine adjunctive therapy effect on mortality (Chan et al. 2022) [11].
Length of ICU stay (days).

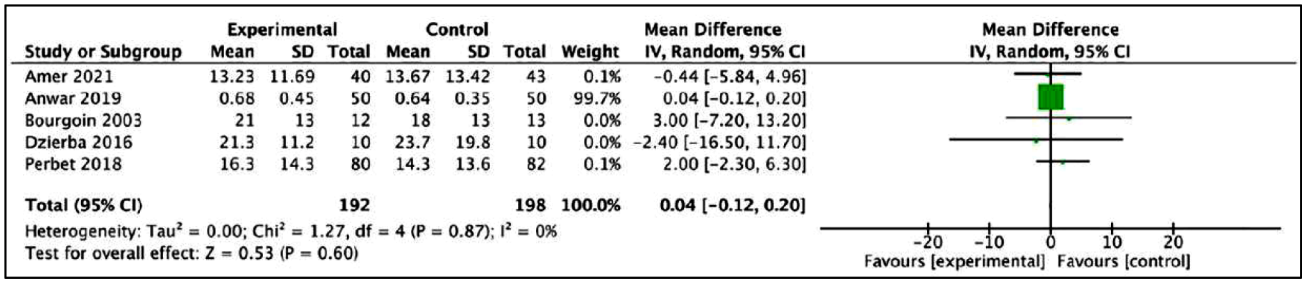

Fig. 7. Forest plot of ketamine adjunctive therapy effect on ICU length of stay (Chan et al. 2022) [11].
Length of hospital stay (days).

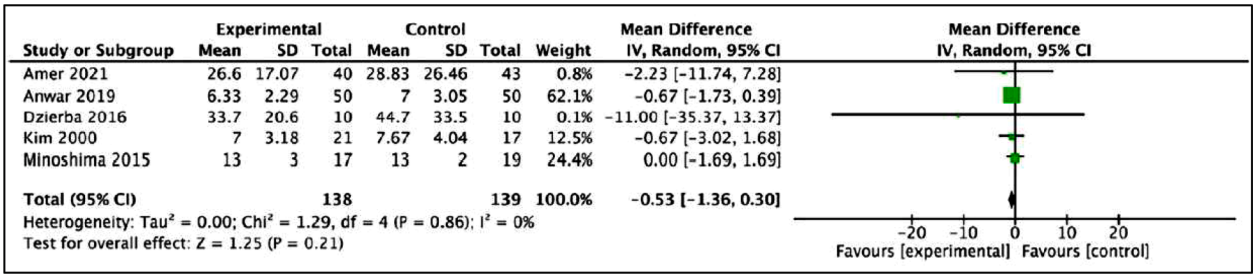

Fig. 8. Forest plot of ketamine adjunctive therapy effect on Hospital length of stay (Chan et al. 2022) [11].

ketamine is required to provide adequate analgosedation as monotherapy. Because of its dose-related side-effects, it can therefore be deduced that at as monotherapy, ketamine may cause more side-effects compared to adjunctive therapy [11,17,21]. The effect on patient-orientated outcomes and haemodynamic parameters would have to be assessed in future trials. (ii) the loss of synergistic effects may potentiate side-effects as higher doses may be required: the combination of ketamine with other drugs at lower doses has the advantages of having the desired effects with less harm, in comparison to administering ketamine as monotherapy at a larger dose [42–44].

Ketamine as adjunctive therapy did not cause significant side-effects. Trials included in this review demonstrated no effect on intracranial pressure or cerebral perfusion pressure [4,16,18,20]. The theory that ketamine is not suitable as induction or maintenance analgosedation in patients with traumatic brain injuries is ungrounded as it may actually improve cerebral perfusion pressure secondary to the favourable effects on systemic blood pressure [18–20]. Manasco *et al.* reported a greater time within the RASS target and a lower incidence of delirium was present across all studies in Chan *et al.* as compared to benzodiazepines [4,11].

At the time of this rapid review, no high-quality trials had been conducted to assess ketamine as monotherapy for analgosedation in ventilated patients. The favourable cardiovascular and respiratory effects need to be assessed against dose-related side-effects in future trials. Psychomimetic effects and other patient-orientated outcomes were sparsely reported on in included trials and reviews and should be included in forthcoming trials, instead of focusing on surrogate outcomes. Robust clinical outcome data is required, together with an in-depth assessment of side-effects. Results from ongoing studies need to be incorporated [45].

It is important to note several limitations in conducting rapid reviews compared to traditional reviews. Rapid reviews are tailored to address the urgent or emergency request from decision-makers especially where no alternative evidence synthesis options are available. Towards this, rapid reviews aim to streamline scope and timeliness across all steps of the review process but should not replace traditional systematic reviews when making healthcare or policy decisions. To date, it is unclear what the impact is on streamlining steps (e.g. screening and data extraction) within the rapid review process and any biases the process may introduce, further exploration is still required [28]. When making healthcare decisions, recommendations or EML decisions, systematic reviews play a pivotal and necessary role in the evidence ecosystem, however on their own are not sufficient as further judgements is still required beyond effectiveness including equity, cost-effectiveness, feasibility and acceptability implications when guideline panels consider a new action or intervention.

Conclusion

The evidence for use of adjunctive ketamine as post-intubation sedation in intubated adults with trauma on mechanical ventilation shows clinically meaningful morphine sparing effects, however the evidence is very uncertain whether ketamine may reduce mortality. Ketamine compared to other agents shows little to no difference in ICU or hospital length of stay. Overall, the introduction of adjunctive ketamine for post-sedation intubation may result in a moderate meaningful net benefit as a sedative-sparing agent. However, we are very uncertain whether monotherapy results in an overall positive effect on respiratory and haemodynamic outcomes.

Author's contribution

Authors contributed as follows to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: MM and CH contributed 30% each, IK and VN contributed 15% each and TL contributed 10%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Dissemination of results

The is review has informed the South African National Essential Medicine List Committee proceedings (including national standard treatment guidelines) and has been presented at various conferences. Results have been disseminated through national circulars and newsletters linked to the NDoH.

The results of this study has been disseminated in various conferences and is publicly available at the South African National Department of Health Knowledge Hub (https://knowledgehub.health.gov.za/).

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.afjem.2023.10.002.

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