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Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD011456.

DOI: 10.1002/14651858.CD011456.

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Ketamine and propofol in combination for adult procedural sedation and analgesia in the emergency department

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Editorial group: Cochrane Emergency and Critical Care Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2019.

Citation: Mah GT, Turgeon RD, Loh G, Tejani AM, Sweet DD. Ketamine and propofol in combination for adult procedural sedation and analgesia in the emergency department. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No.: CD011456. DOI: 10.1002/14651858.CD011456.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of the combination of ketamine and propofol compared with ketamine or propofol alone or any other sedation regimen for adult procedural sedation and analgesia in the emergency department.

BACKGROUND

Description of the condition

The emergency department is a specialized area of clinical practice in which patients often require interventional procedures; such procedures include laceration repair, foreign object removal, abscess incision and drainage, necrotic tissue debridement, orthopaedic manipulation, direct current cardioversion, central line insertion, or tube thoracostomy. It is however inhumane to perform such procedures without taking measures to minimize patient discomfort. Procedural sedation and analgesia (PSA) involves the use of sedatives with or without analgesics to facilitate patient tolerability during painful or unpleasant medical procedures (Godwin 2014). The American College of Emergency Physicians

recommend proactive treatment of anxiety and pain associated with such procedures as a standard of care (Godwin 2014). Depending on the medical procedure, the degree of sedation and analgesia required ranges from minimal to deep sedation (ASA 2002). For this reason, it is mandatory to monitor patient responsiveness, respiratory drive, oxygenation, and cardiovascular function in case corrective intervention is required (Godwin 2014).

Medications used in PSA should have predictable effects on sedation, analgesia, amnesia, and motor control. Additionally, drugs with rapid onset, steady maintenance, short recovery period, minimal recall, and tolerable drug-related adverse effects are desirable. Unfortunately, despite various anaesthetic agents available for use in clinical practice, no single drug has demonstrated superiority for all patient scenarios.

Description of the intervention

Ketamine exerts its effects predominantly through inhibition of N-methyl-D-aspartic acid (NMDA) receptors and thus dampens neuroexcitatory responses mediated by glutamate (Green 2011a; Guldner 2006; Haas 1992; Hirota 1996). This leads to an effective disconnect between the corticothalamic and limbic regions of the brain and produces a dissociative-type sedation described as a “trance-like cataleptic state of sensory isolation” (Green 2011a; Guldner 2006). Thus, sedation with ketamine is graded as whether or not the patient is dissociated, rather than using the usual sedation continuum (ASA 2002). In addition to dissociative sedation, ketamine also produces marked analgesia and amnesia (Green 2011a; Guldner 2006; Haas 1992). Standard intravenous adult bolus doses (e.g., 1 mg/kg) for dissociative sedation have an onset of 1 minute and a typical duration of effective dissociation of 5 to 10 minutes (Green 2011a). Potential adverse effects associated with ketamine include recovery agitation (e.g., nightmares, vivid hallucinations, physical combativeness), nystagmus, ataxia, laryngospasm, excessive salivation, and emesis (Green 2011a; Guldner 2006). Transient respiratory depression is associated with rapid administration of ketamine; however, prolonged respiratory depression beyond the period of initial drug administration is unusual (Green 2011a). In some cases, ketamine may even act as a respiratory stimulant (Guldner 2006; Haas 1992). Ketamine also increases the effect of catecholamines, which leads to increases in heart rate, cardiac output, and blood pressure (Green 2011a; Guldner 2006; Haas 1992).

Propofol is a sedative that causes global central nervous system depression primarily through enhancing gamma-aminobutyric acid (GABA) transmission (Kotani 2008; Miner 2007; Symington 2006; Vasileiou 2009). Although a strong sedative and amnesic agent, it does not have clinically important analgesic properties (Kotani 2008; Miner 2007; Symington 2006). Use of propofol is gaining popularity in emergency department settings as it is an ultra short-acting agent with predictable loss of consciousness and rapid emergence (Burton 2006; Miner 2007; Symington 2006). Standard intravenous adult bolus doses (e.g., 1 mg/kg) for emergency department PSA have an onset within 30 seconds and a duration of about 6 minutes (Miner 2007). Use of propofol is limited by dose-dependent respiratory depression, transient arterial hypotension, and venous irritation (Kotani 2008; Miner 2007). Propofol infusion syndrome (e.g., metabolic acidosis, cardiac instability, rhabdomyolysis, hyperlipidaemia, liver dysfunction) is not expected in patients receiving intermittent bolus doses of propofol for PSA (Kam 2007; Kotani 2008; Miner 2007; Short 2003). Emesis is rare with propofol (Miner 2007), and there are reports that propofol may act as an anti-emetic (Godwin 2014; Vasileiou 2009).

How the intervention might work

The combination of ketamine and propofol (also called “ketofol”) used for PSA was first reported in the early 1990s (Friedberg 1993; Guit 1991; Mayer 1990; Schüttler 1991). The clinical appeal of combination therapy for PSA is that targeted sedation is achieved using lower doses of each agent compared with using either alone. This should result in similar efficacy and decreased dose-related toxicities. Interestingly, ketamine and propofol produce physiologic effects that are complementary and should, in theory, offset each other’s dose-dependent adverse effects (Thomas 2011). For instance, as ketamine is associated with transient blood pressure elevation and respiratory stimulation, it should counteract dose-limiting side-effects of propofol, such as hypotension and respiratory depression. Similarly, the GABA-enhancing effects of propofol should attenuate the risk of recovery agitation associated with ketamine, and the anti-emetogenic potential of propofol may blunt nausea and vomiting associated with ketamine. Lastly, as ketamine has potent analgesic properties, addition of an opioid agent is unnecessary and therefore avoids the risk of additive respiratory depression and hypotension. The potential benefits of combination ketamine and propofol may translate into improved clinical conditions to complete the procedure, faster recovery times, and improved patient satisfaction.

Why it is important to do this review

The value of ketamine and propofol in combination for PSA is the subject of ongoing debate (Green 2011b). Although ketamine and propofol have theoretical synergistic efficacy and counterbalance each other’s deficits, it is uncertain whether or not the combination translates to improved patient outcomes. New clinical trial evidence has become available since the publication of previous reviews that have addressed this topic (Loh 2007; Slavik 2007; Thomas 2011). The purpose of this systematic review is to provide clinicians, patients, and researchers with an updated literature summary that evaluates the relative efficacy and safety of combination ketamine and propofol for adult PSA in the emergency department.

OBJECTIVES

To assess the efficacy and safety of the combination of ketamine and propofol compared with ketamine or propofol alone or any other sedation regimen for adult procedural sedation and analgesia in the emergency department.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all parallel randomized controlled trials (RCTs) and quasi-randomized controlled trials of the combination of ketamine and propofol compared with other sedation regimens for adult PSA in the emergency department. We will include studies irrespective of language and publication status.

We will exclude cross-over trials because of the acute, temporary, and non-repeating nature of circumstances requiring procedural sedation in the emergency department. We will also exclude cluster-randomized controlled trials as the relevant unit of analysis for procedural sedation and outcomes of interest in this review are the individual participants rather than emergency departments or institutions.

Types of participants

We will include studies of adults (i.e., individuals aged 18 years or older) who are undergoing any diagnostic or therapeutic procedure requiring PSA within the setting of the emergency department. Examples of procedures include, but are not restricted to, laceration repair, foreign object removal, abscess incision and drainage, necrotic tissue debridement, orthopaedic manipulation, direct current cardioversion, central line insertion, or tube thoracostomy. We will exclude studies evaluating the use of sedation specifically for diagnostic imaging as these are not considered painful procedures and thus represent a different patient population with different needs for PSA.

For studies that enrolled a mixed adult and paediatric population, we will request relevant baseline and outcome data from the corresponding author for the adult subset and include this in our review. If original study authors do not provide additional information for these mixed studies, we will include the studies in our review if individuals aged 18 years or older comprised greater than 50% of participants.

We will exclude trials of sedation employed in rapid sequence intubation, as most patients are sedated for prolonged durations after intubation.

Types of interventions

The intervention will be the combination of ketamine and propofol at any dose, route of administration (e.g., intramuscular or intravenous), formulation (e.g., administered concomitantly in a single syringe or separate syringes), or number of doses administered (e.g., single dose or repeated administration).

The comparator will be any other single or combination sedation regimen with or without analgesia. Examples of comparators include, but are not restricted to, ketamine alone, propofol alone, dexmedetomidine, etomidate, and midazolam with or without fentanyl or other opioids.

We will include studies that permitted administration of non-study cointerventions, such as analgesics or supplemental oxygen,

as long as the study protocol allows for equal opportunity of receiving these cointerventions between groups. We will exclude studies where participants received inhalational anaesthetics.

Types of outcome measures

Primary outcomes

1. Success of procedure (as defined by the study authors) without the additional use of a non-study agent.
2. Clinically significant haemodynamic compromise (defined as hypotension or cardiac arrhythmias requiring administration of intravenous fluids, medications, cardiopulmonary resuscitation with the intention of improving cardiovascular function, or a combination of these).
3. Clinically significant respiratory compromise (specific adverse events and their definitions as detailed in [Appendix 1](#)).

Secondary outcomes

1. Mortality.
2. Serious adverse event (SAE) rate (defined as any event from time of treatment group allocation to time when discharge criteria met that requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening, or results in death).
3. Sedation consistency (defined as whether or not sedation throughout the procedure was maintained at a depth consistent with the study's target level of sedation without need for additional non-study medication to complete the procedure).
4. Intraprocedure drug-related adverse event rates (from first dose of sedative to time of procedure completion) (specific adverse events and their definitions as detailed in [Appendix 1](#)).
5. Recovery period drug-related adverse event rates (from end of procedure to time when discharge criteria were met) (specific adverse events and their definitions as detailed in [Appendix 1](#)).
6. Induction time (defined as time from first dose of sedative to attainment of target sedation level).
7. Recovery time (defined as time from last dose of sedative to time when discharge criteria are met).
8. Practitioner satisfaction (as defined by study authors, e.g., using a 10-point visual analogue scale).
9. Participant satisfaction (as defined by study authors, e.g., using a 10-point visual analogue scale).

Search methods for identification of studies

Electronic searches

We will search the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Appendix 2);
- MEDLINE through Ovid SP (from 1946 onwards) (Appendix 3); and
- Embase through Ovid SP (from 1974 onwards) (Appendix 4).

We will employ search strategies adopted from the Cochrane Highly Sensitive Search Strategy (Lefebvre 2011). For each included article, we will also screen the reference list and search the citation through Web of Science™ to identify additional articles. We will not apply any language restrictions.

Searching other resources

Ongoing trials databases

We will search for completed or ongoing trials using the World Health Organization (WHO) International Clinical Trials Registry platform (www.who.int/ictrp/en/).

Conference proceedings

If available, we will review the titles and abstracts from scientific conferences of the following journals to identify all appropriate trials: *Academic Emergency Medicine*, *Anaesthesia*, *Anesthesiology*, *Annals of Emergency Medicine*, *BMJ* (formally *British Medical Journal*), *Canadian Journal of Emergency Medicine*, *Emergency Medicine Australasia*, *Emergency Medicine Journal*, *European Journal of Emergency Medicine*, *Journal of Emergency Medicine*, *The Lancet*, *New England Journal of Medicine*, and *Pharmacotherapy* (from 2008 onwards).

Unpublished literature

We will contact authors of included trials to inquire about any unpublished data and to check if they are aware of any other investigators who are involved in relevant trials or who have conducted relevant research in the past.

Data collection and analysis

Selection of studies

We will combine the results of the searches above and exclude duplicate records. Two review authors (GM and RT) not blinded to trial details will independently screen all titles and abstracts for eligibility. We will independently record the reason for trial exclusion. For all titles or abstracts deemed by either review author

to be relevant or potentially meeting the criteria, we will retrieve the full article for further evaluation. We (GM and RT) will assess these articles for eligibility. We will resolve disagreements between authors on trial selection initially by discussion. If we are unable to reach consensus, we will consult with a third author (AT), who will arbitrate on trial inclusion. If we require further information to make a decision about trial inclusion, RT will contact the corresponding author of the relevant trial. We will compile a list of all eligible trials (Appendix 5).

Data extraction and management

Two review authors (GM and RT) will independently extract and collect data on an electronic data extraction form, in addition to entering result data directly into Review Manager 5 (RevMan 5.3) for statistical analysis. A copy of the data extraction form is in Appendix 6. We will resolve any discrepancies in data extraction by discussion. If we are unable to reach a consensus, we will consult with a third author (AT). Where published data provide inadequate information for the review or we cannot extract relevant data, RT will contact the corresponding author of the relevant trial for additional data.

Assessment of risk of bias in included studies

We will perform 'Risk of bias' assessments using the "Risk of bias" tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a); a copy of the form we will use is in Appendix 6.

Briefly, two review authors (GM and RT) will independently assess each trial according to the quality domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any other potential threats to validity. If unclear, RT will contact the corresponding author of the relevant trial for clarification using the open-ended question method described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 8.3.4 (Higgins 2011a). We will consider a trial as having a low risk of bias if we assess all domains as adequate. We will consider a trial as having a high risk of bias if we assess one or more domains as inadequate or they remain unclear to us after contacting the study author. We will resolve disagreements between review authors on risk of bias initially by discussion. If we are unable to reach consensus, we will consult with a third author (AT), who will arbitrate.

Measures of treatment effect

We will present dichotomous data as relative risk (RR) with 95% confidence intervals (CI). We will calculate the number needed to treat to benefit (NNTB) or the number needed to treat for an additional harmful outcome (NNTH), as appropriate. For continuous data, when outcome variables are available in the same units

(e.g., 10-point visual analogue scale), we will summarize these using the mean difference (MD). In instances where trials measure the same underlying construct using different scales or units (e.g., visual analogue scales with different total scores), we will present the data using standardized mean difference (SMD).

Dealing with missing data

For dichotomous data, we will extract and analyse participant data according to the treatment group to which they were allocated, regardless of whether or not they received the intervention, according to intention-to-treat (ITT) principles. For studies where the number of randomized participants does not match the number of participants analysed and reported in each treatment group, RT will contact the corresponding author of these studies to obtain missing outcome data. If unsuccessful, we will report the percentage of participants lost to follow up and also present best- and worst-case scenarios for outcomes comparisons.

We will calculate missing standard deviations from the standard errors or confidence intervals, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 7.7.3 (Higgins 2011b). Where we cannot calculate standard deviations, we will impute these using the mean of the reported standard deviations from the other trials, as described in Section 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We will address the impact of missing data in the 'Discussion' section of the review.

Assessment of heterogeneity

We will assess statistical heterogeneity by visually inspecting the forest plot and calculating the I^2 statistic, as described in Section 9.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will consider any outcome comparison with an I^2 statistic of greater than 50% to be indicative of potential inappropriateness for meta-analysis, as well as need for sensitivity analyses to further examine heterogeneity.

Assessment of reporting biases

In order to minimize publication bias, we will employ a comprehensive search of both published and unpublished literature, as described above in [Search methods for identification of studies](#). We will assess for publication bias and small study effects by visual inspection of the funnel plot, as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). If the number of studies is less than 10 and therefore does not allow for visual inspection, we will draw no conclusions about the presence or absence of publication bias; we will describe this implicitly in our review.

In order to minimize outcome reporting bias, RT will contact the corresponding authors of included trials for data on clinically important outcomes, as listed earlier in this protocol ([Types](#)

[of outcome measures](#)), that are not reported in their published manuscripts.

Data synthesis

If the degree of clinical and statistical heterogeneity is not excessive as described earlier ([Assessment of heterogeneity](#)), we will meta-analyse study findings and generate summary estimates using [RevMan 5.3](#). We will perform a fixed-effect model meta-analysis for all comparisons where the I^2 statistic is less than or equal to 25%. In cases where the I^2 statistic exceeds 25% and we still deem the data as appropriate for meta-analysis based on visual inspection of the forest plot, we will use a random-effects model.

Subgroup analysis and investigation of heterogeneity

We do not plan to perform subgroup analyses.

We will investigate for clinical heterogeneity of the included studies according to different PICO (Participants, Interventions, Comparisons and Outcomes) components (e.g., experience level of clinician providing sedation, total doses administered in each group, coadministration of oxygen, method of measuring outcome) and will address these important differences in the 'Description of studies' and 'Discussion' sections of the review, as well as in sensitivity analyses if there is also sufficient statistical heterogeneity.

We will investigate for methodological heterogeneity using The Cochrane Collaboration's tool for assessing risk of bias and, if appropriate, perform sensitivity analyses based on methodological differences (Higgins 2011a).

Sensitivity analysis

If we identify sufficient trials to allow it, we will perform sensitivity analyses to analyse separately trials at high risk and low risk of bias, as determined using The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011a).

'Summary of findings' tables

We will use the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes in our review and construct a 'Summary of findings' (SoF) table using [RevMan 5.3](#). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodologic quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias.

We will report the following outcomes in the SoF table:

Primary outcomes

1. Success of procedure (as defined by the study authors) without the additional use of a non-study agent.
2. Clinically significant haemodynamic compromise (defined as hypotension or cardiac arrhythmias requiring administration of intravenous fluids, medications, cardiopulmonary resuscitation with the intention of improving cardiovascular function, or a combination of these).
3. Clinically significant respiratory compromise (specific adverse events and their definitions as detailed in [Appendix 1](#)).

Secondary outcomes

1. Mortality.
2. Serious adverse event (SAE) rate (defined as any event from time of treatment group allocation to time when discharge criteria met that requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital

malformation, results in persistent or significant disability or incapacity, is life-threatening, or results in death).

3. Practitioner satisfaction (as defined by study authors, e.g., using a 10-point visual analogue scale).

4. Participant satisfaction (as defined by study authors, e.g., using a 10-point visual analogue scale).

ACKNOWLEDGEMENTS

We would like to thank Karen Hovhannisyan, Cochrane Anaesthesia Review Group (CARG)'s Trials Search Co-ordinator, for his help with developing our database search strategy. We also thank Jane Cracknell, Managing Editor of CARG, for her guidance and assistance with the preparation of this review. We would like to thank Ronan O'Sullivan (content editor); Vibeke E Horstmann (statistical editor); Lim Beng Leong, Gary Andolfatto, and Bitu Mesgarpour (peer reviewers) for their help and editorial advice during the preparation of this protocol for the systematic review.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Definitions

Adapted from the Quebec Group for consensus-based recommendations for standardizing terminology and reporting of adverse events for emergency department procedural sedation and analgesia in children (Bhatt 2009).

Clinically significant respiratory compromise as evidenced by one or more of the following.

1. **Oxygen desaturation:** oxygen desaturation and one or more interventions are performed with the intention of improving oxygen saturation, such as vigorous tactile stimulation, airway repositioning (chin lift, jaw thrust, neck extension, midline repositioning), suctioning, supplemental or increased oxygen delivery, oral or nasal airway placement, application of positive pressure or ventilation with bag-valve mask, or tracheal intubation.

2. **Central apnoea:** cessation or pause of ventilatory effort, and one or more interventions are performed with the intention of stimulating or assisting ventilation, such as vigorous tactile stimulation, application of bag-valve mask with assisted ventilation, tracheal intubation, or administration of reversal agents (opioid or benzodiazepine antagonists).

3. **Partial upper airway obstruction:** incomplete obstruction to air exchange manifested by the presence of one or more of the following: stridor; snoring; chest wall and suprasternal retractions and rapid resolution with either airway repositioning, suctioning, oral or nasal airway placement, or application of positive pressure with bag-valve mask but without assisted ventilation.

4. **Complete upper airway obstruction:** ventilatory effort with no air exchange and one or more interventions are performed with the intention of relieving airway obstruction, such as airway repositioning, suctioning, oral or nasal airway placement, application of positive pressure with bag-valve mask with or without assisted ventilation, tracheal intubation, administration of additional sedation agents, or administration of neuromuscular-blocking agents. No air exchange is manifested by the absence of upper airway (e.g., stridor or snoring) and breath sounds on auscultation and the loss of CO₂ waveform when capnography is used).

5. **Laryngospasm:** partial or complete upper airway obstruction with oxygen desaturation caused by involuntary and sustained closure of the vocal cords and is not relieved by routine airway-repositioning manoeuvres, suctioning, or insertion of a nasal or oral airway. A characteristic stridulous noise can be heard with partial laryngospasm but will be absent in complete laryngospasm.

6. **Clinically apparent pulmonary aspiration:** suspicion or confirmation of oropharyngeal or gastric contents in the trachea during the sedation or physiologic recovery phase and the appearance of respiratory signs and symptoms that were not present before the sedation. The new signs and symptoms must present before the end of the emergency department recovery phase and include cough; crackles; rales; decreased breath sounds; tachypnoea; wheeze; rhonchi; respiratory distress; decrease in oxygen saturation from baseline and requiring supplemental oxygen; or chest radiograph findings of focal infiltrate, consolidation, or atelectasis.

Retching or vomiting

1. The motor reflex response characteristic of retching with or without the expulsion of gastric contents through the mouth or nose that occurs during sedation, emergency department recovery, or postdischarge phases of sedation.

Myoclonus

1. Involuntary, brief contraction of some muscle fibres, of a whole muscle, or of different muscles of one group, leading to movements of the corresponding body parts, usually not longer than 1/10 of a second and interferes with the procedure, requiring an intervention or administration of medications. Hiccupping is a form of myoclonus.

Muscle rigidity

1. Involuntary muscle stiffening in extension that can be associated with shaking and interferes with the procedure, requiring an intervention or administration of medications.

Generalized motor seizure

1. Temporary abnormal neural electrophysiologic phenomenon that manifests as involuntary contractions or series of contractions of the voluntary muscles. The contractions can be sustained (tonic) or repeated (tonic-clonic).

Unpleasant recovery reactions

1. Abnormal patient affect or behaviours during the emergency department recovery phase that requires additional treatment and a change or delay in patient discharge from the emergency department. The behaviours include one or more of the following: crying (inconsolable), agitation (restless continuous activity), delirium (state of severe confusion or physical combativeness), dysphoria (inappropriate mood of sadness), nightmares (unpleasant dreams), hallucinations (responds to sensory phenomena, such as seeing, hearing, or feeling, that are not physically present).

Permanent neurologic injury

1. A neurologic deficit that was not present before sedation and does not resolve.

Death

1. The irreversible cessation of cerebral function, spontaneous function of the respiratory system, and spontaneous function of the circulatory system.

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

1. ketamine.mp. or exp ketamine/
2. propofol.mp. or exp propofol/
3. 1 and 2
4. ketofol.mp.
5. 3 or 4

Appendix 3. MEDLINE (Ovid SP) search strategy

1. ketamine.mp. or exp ketamine/
2. propofol.mp. or exp propofol/
3. 1 and 2
4. ketofol.mp.
5. 3 or 4
6. ((randomized controlled trial.pt. or controlled clinical trial.pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) or (exp Controlled Clinical Trial/ or exp Clinical Trial/ or exp Clinical Trial, Phase III/ or exp Clinical Trial, Phase II/ or exp Clinical Trial, Phase I/ or exp Clinical Trials as Topic/ or exp Randomized Controlled Trial/ or exp Controlled Clinical Trial/ or exp Randomized Controlled Trials as Topic/ or exp Random Allocation/ or exp Double-Blind Method/)) not (animals.sh. not (humans.sh. and animals.sh.))
7. 5 and 6

Appendix 4. Embase (Ovid SP) search strategy

1. ketamine.mp. or exp ketamine/
2. propofol.mp. or exp propofol/
3. 1 and 2
4. ketofol.mp.
5. 3 or 4
6. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp. or (groups.ab. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) or (exp random sample/ or exp "randomized controlled trial (topic)"/ or exp "controlled clinical trial (topic)"/ or exp controlled clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "phase 4 clinical trial (topic)"/ or exp "phase 1 clinical trial (topic)"/ or exp "phase 2 clinical trial (topic)"/)) not (animals not (humans and animals)).sh.
7. 5 and 6

Appendix 5. Eligible studies

Trial number	Title	Author(s)	Year	Reference
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Appendix 6. Data collection form

I. General information

Date form completed (<i>dd/mm/yyyy</i>)	
Name/identification of person extracting data	
Report title (<i>title of paper/abstract/report</i>)	
Lead author	
Reference details	
Report identification	
Report author contact information	
Publication type (<i>e.g., full report, abstract, letter</i>)	

(Continued)

Study funding sources (including role of funders)	
Possible conflicts of interest (for study authors)	
Other publications of this study (e.g., duplicate publications, follow-up studies)	
Notes:	

2. Study eligibility

Study Characteristics	Eligibility criteria	Eligible?			Location in text (page & paragraph/figure/table)
		Yes	No	Unclear	
Type of study	Randomized controlled trial				
	Quasi-randomized trial				
Participants					
Types of intervention					
Types of outcome measures					
INCLUDE/ EXCLUDE					
Reason for exclusion (if applicable)					
Notes:					
DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW					

3. Population and setting

	Description <i>Include comparative information for each group (i.e., intervention and controls) if available</i>	Location in text <i>(page & paragraph/figure/table)</i>
Number of sites (single versus multicentre)		
Country/Countries		
Location in hospital		
Monitoring equipment used		
Inclusion criteria		
Exclusion criteria		
Method(s) of recruitment of participants		
Informed consent obtained	Yes ☐ No ☐ Unclear ☐	
Notes:		

4. Methods

	Descriptions as stated in report/paper	Location in text <i>(page & paragraph/figure/table)</i>
Objective of study		
Design <i>(e.g., parallel, cross-over)</i>		
Unit of allocation <i>(e.g., individuals, groups, wards)</i>		
Start date		
End date		
Total study duration		
Ethical approval obtained for study	Yes ☐ No ☐ Unclear ☐	

(Continued)

Notes:

5. 'Risk of bias' assessment

Domain	Risk of bias			Support for judgement	Location in text (page & paragraph/figure/table)
	Low risk	High risk	Unclear		
Random sequence generation (<i>selection bias</i>)					
Allocation concealment (<i>selection bias</i>)					
Blinding of participants and personnel (<i>performance bias</i>)					
Blinding of outcome assessment (<i>detection bias</i>)					
Incomplete outcome data (<i>attrition bias</i>)					
Selective outcome reporting (<i>reporting bias</i>)					
Other bias					
Notes:					

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group

	Description as stated in report/paper	Location in text (page & paragraph/figure/table)
Total number randomized		
Baseline imbalances		
Withdrawals and exclusions (if not provided below by outcome)		
Age		
Sex		
Other treatment received (in addition to study intervention)		
Subgroups reported		
Notes:		

7. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	Location in text (page & paragraph/figure/table)
Group name		
Number randomized to group		
Dosing regimen		
Duration of treatment period and follow up		
Delivery method (e.g., single versus sep- arate syringes)		
Providers		
Cointerventions		
Notes:		

8. Outcomes

Copy and paste table for each outcome

Outcome 1

	Description as stated in report	Location in text (page & paragraph/figure/table)
Outcome name		
Time points measured		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Unit of measurement (if relevant)		
Is outcome validated?	Yes ☐ No ☐ Unclear ☐	
Imputation of missing data (e.g., assumptions made for intention-to-treat (ITT) analysis)		
Assumed risk estimate (e.g., baseline or population risk noted in Background)		
Power		
Notes:		

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required

Dichotomous outcome

	Description as stated in report/paper	Location in text (page & paragraph/figure/table)
Comparison		
Outcome		
Subgroup		

(Continued)

Time point (specify whether from start or end of interven- tion)					
Results	Intervention		Comparison		
	Number of events	Number of partici- pants	Number of events	Number of participants	
Number of miss- ing participants and reasons					
Number of partici- pants moved from other group and reasons					
Any other re- sults reported					
Unit of analy- sis (e.g., indi- viduals, cluster/ groups, or wards)					
Sta- tistical methods used and ap- propriateness of these methods					
Reanalysis re- quired? (specify)	Yes ☐ No ☐ Unclear ☐				
Reanalysis pos- sible?	Yes ☐ No ☐ Unclear ☐				
Reanalysed re- sults (if applica- ble)					

(Continued)

Notes:									
Continuous outcome									
	Description as stated in report/paper						Location in text (page & paragraph/figure/table)		
Comparison									
Outcome									
Subgroup									
Time point (specify whether from start or end of intervention)									
Postintervention or change from base-line?									
Results	Intervention			Comparison					
	Mean	SD (or other variance)	Number of participants	Mean	SD (or other variance)	Number of participants			
Number of missing participants and reasons									
Number of participants moved from other group and reasons									
Any other results reported									
Unit of analysis (e.g., individuals, cluster/groups, or wards)									

(Continued)

Statistical methods used and appropriateness of these methods		
Reanalysis required? (<i>specify</i>)	Yes ☐ No ☐ Unclear ☐	
Reanalysis possible?	Yes ☐ No ☐ Unclear ☐	
Reanalysed results (if applicable)		
Notes:		

10. Applicability

Have important populations been excluded from the study? (<i>consider disadvantaged populations and possible differences in the intervention effect</i>)	Yes ☐ No ☐ Unclear ☐	
Is the intervention likely to be aimed at disadvantaged groups? (<i>e.g., lower socioeconomic groups</i>)	Yes ☐ No ☐ Unclear ☐	
Does the study directly address the review question? (<i>any issues of partial or indirect applicability</i>)	Yes ☐ No ☐ Unclear ☐	
Notes:		

11. Other information

	Description as stated in report/paper	Location in text (page & paragraph/figure/table)
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information (<i>from whom, what, and when</i>)		
Notes:		

WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Greg T Mah (GM), Ricky Turgeon (RT), Gabriel Loh (GL), Aaron M Tejani (AT), David D Sweet (DS)

Conceiving the review: GM

Designing the review: GM and RT

Co-ordinating the review: GM

Undertaking manual searches: GM and RT

Screening search results: GM and RT

Organizing retrieval of papers: GM

Screening retrieved papers against inclusion criteria: GM and RT

Appraising quality of papers: GM and RT

Abstracting data from papers: GM and RT

Writing to authors of papers for additional information: RT

Providing additional data about papers: GM and RT

Obtaining and screening data on unpublished studies: GM and RT

Data management for the review: GM

Entering data into Review Manager 5 ([RevMan 5.3](#)): GM and RT

Statistical analysis using Review Manager 5: GM, RT, and AT

Other statistical analysis not using Review Manager 5: GM, RT, and AT

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Interpretation of data: GM, RT, AT, GL, and DS

Statistical inferences: GM, RT, and AT

Writing the review: GM and RT

Securing funding for the review: not applicable

Performing previous work that was the foundation of the present study: GM

Guarantor for the review (one author): GM

Person responsible for reading and checking review before submission: GM

DECLARATIONS OF INTEREST

Greg T Mah: nothing to declare.

Ricky Turgeon: nothing to declare.

Gabriel Loh: nothing to declare.

Aaron M Tejani: I received four honorariums for doing presentations (“Dabigatran for atrial fibrillation”) for the Community and Rural Internal Medicine Society in Vancouver; the Research Education and Action for Community Health (REACH) clinic in Vancouver (no pharmaceutical industry funding was involved; they provided the money from membership fees from their members); Vancouver Island Health Authority (VIHA) Pharmacy for several talks on several different drugs (again, no pharmaceutical industry funding was involved); from the University of British Columbia (UBC) Faculty of Medicine, the Department of Family Practice, for teaching medical students (all money I received came from the Faculty of Medicine or Pharmacy and was University faculty money); and from Fraser Health Pharmacy Services (they received money from a government grant) for various drug-related topics but not drugs in this review. I received a grant from the Canadian Institutes of Health Research (CIHR) - the government-funded research grant organization - for educational activities and for a systematic review of daptomycin and several other knowledge translation grants. None of the relationships listed above will influence the output of this Cochrane review.

David D Sweet: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Karen Hovhannisyan, Denmark.
Trial Search Co-ordinator (Cochrane Anaesthesia Group)

External sources

- No sources of support supplied