










CRITICAL CARE

Pharmacological agents for procedural sedation and analgesia in the emergency department and intensive care unit: a systematic review and network meta-analysis of randomised trials

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Abstract

Background: We aimed to evaluate the comparative effectiveness and safety of various i.v. pharmacologic agents used for procedural sedation and analgesia (PSA) in the emergency department (ED) and ICU. We performed a systematic review and network meta-analysis to enable direct and indirect comparisons between available medications.

Methods: We searched Medline, EMBASE, Cochrane, and PubMed from inception to 2 March 2023 for RCTs comparing two or more procedural sedation and analgesia medications in all patients (adults and children >30 days of age) requiring emergent procedures in the ED or ICU. We focused on the outcomes of sedation recovery time, patient satisfaction, and adverse events (AEs). We performed frequentist random-effects model network meta-analysis and used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to rate certainty in estimates.

Results: We included 82 RCTs (8105 patients, 78 conducted in the ED and four in the ICU) of which 52 studies included adults, 23 included children, and seven included both. Compared with midazolam-opioids, recovery time was shorter with propofol (mean difference 16.3 min, 95% confidence interval [CI] 8.4–24.3 fewer minutes; high certainty), and patient satisfaction was better with ketamine-propofol (mean difference 1.5 points, 95% CI 0.3–2.6 points, high certainty). Regarding AEs, compared with midazolam-opioids, respiratory AEs were less frequent with ketamine (relative risk [RR] 0.55, 95% CI 0.32–0.96; high certainty), gastrointestinal AEs were more common with ketamine-midazolam (RR 3.08, 95%

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CI 1.15–8.27; high certainty), and neurological AEs were more common with ketamine-propofol (RR 3.68, 95% CI 1.08–12.53; high certainty).

Conclusion: When considering procedural sedation and analgesia in the ED and ICU, compared with midazolam-opioids, sedation recovery time is shorter with propofol, patient satisfaction is better with ketamine-propofol, and respiratory adverse events are less common with ketamine.

Keywords: analgesia; critical care; emergency; network meta-analysis; procedural sedation; systematic review

Editor's key points

- Despite many large RCTs comparing procedural sedation and analgesia medications, uncertainty persists regarding the optimal medication or combination of medications considering both safety and efficacy.
- In this systematic review with network meta-analysis, the authors highlight the importance of an individualised approach to procedural sedation and analgesia based upon patient and procedure characteristics.
- These findings provide a current, comprehensive summary of evidence to guide clinical practice for procedural sedation and analgesia. The specific regimes represented by smaller nodes in the analysis would benefit from more randomised clinical trial data.

Procedural sedation and analgesia (PSA) refers to the administration of medications with sedative, analgesic, or dissociative properties with the goal of suppressing a patient's consciousness to facilitate care or to perform procedures.¹ PSA is commonly performed in-hospital, particularly in the emergency department (ED) and ICU to facilitate procedures such as bronchoscopy, tracheostomy, emergent endoscopy,² orthopaedic manipulation, abscess incision and drainage, and electrical cardioversion.³ There are a variety of medications that can be selected for PSA with propofol, fentanyl, and midazolam being the most commonly used⁴; however, etomidate, ketamine, and dexmedetomidine have seen increased use of late.⁴

Despite the large number of RCTs comparing these medications, uncertainty persists regarding the optimal medication or combination of medications considering both safety and efficacy, as there have been numerous randomised trials since the last review on this subject was published.^{1,5,6} Also, previous systematic reviews and meta-analyses have been limited to head-to-head pairwise comparisons between two drug regimes.¹ The objective of this study was to perform a systematic review and network meta-analysis of patients (adult or paediatric >30 days of age) undergoing PSA for emergent procedures in the ED and ICU in an effort to compare the efficacy and safety of various i.v. PSA medications. From a safety perspective, we will focus on reporting adverse events (AEs). From an efficacy perspective, we will focus on patient satisfaction and sedation recovery time. All these outcomes were selected with patient importance in mind as per Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidance.⁷ We chose these outcomes as one of

the purposes of PSA is to ensure that patients have adequate analgesia and anaesthesia for their painful procedure; furthermore, sedation recovery time is a useful measure to ensure that we find which medications are most likely to save the healthcare resource of monitoring time in the department.

Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement extension for network meta-analysis ([Supplementary Appendix](#)).^{8,9} We registered the protocol with the Center for Open Science (<https://osf.io/vrkns/wiki/home/>). There was no external funding.

Data sources and strategy

We searched four databases (Medline, EMBASE, Cochrane, and PubMed) from inception to May 2021. The search was updated on 2 March 2023. The search strategy was developed by an expert health sciences librarian and peer-reviewed ([Supplementary Appendices 1 and 2](#)). To search for unpublished studies, we reviewed conference proceedings from the following organisations for 2020 and beyond: Society of Critical Care Medicine, American Thoracic Society, American College of Emergency Physicians, Canadian Association of Emergency Physicians, European Society of Intensive Care Medicine, and the American Academy of Pediatrics.

Study selection

Screening of titles and abstracts was performed independently and in duplicate by pairs of reviewers using Covidence software (Melbourne, Australia). The same pairs of reviewers assessed the eligibility of full texts of those citations deemed potentially eligible at title and abstract review, independently and in duplicate. We resolved disagreements at full text through discussion and consensus. We included published full text or conference abstracts of RCTs, without language restriction ([Supplementary Appendices 1 and 2](#)).

Inclusion criteria

We used the following eligibility criteria to include studies that: (i) enrolled adults or children (>30 days of age); (ii) compared at least two different i.v. PSA medication regimes—these may have included single or combined medications used for procedural sedation; (iii) examined sedation in patients for a specific procedure performed in the ED or ICU; (iv) evaluated at least one of the outcomes of interest.

Exclusion criteria

We excluded RCTs that used PSA in the following contexts: (i) noninvasive positive pressure ventilation (NIPPV); (ii) as part of a strategy that included general anaesthesia; (iii) for tracheal intubation; (iv) in combination with neuromuscular block; (v) restraining and controlling aggression or delirium; (vi) procedures exceeding a duration longer than 1 h, as procedures of this length are not frequently undertaken in the ED or ICU.

We included the following outcomes of interest: sedation recovery time (defined as time from procedure completion until return to baseline mental status, or as defined by study authors), patient satisfaction (defined as patient perception of procedure success based on any scale used by study authors), and AEs related to PSA medications (as defined by study authors). Studies that examined non-synthetic opioids, such as morphine, as part of PSA were analysed as separate notes in the analysis. Synthetic opioids, such as alfentanil, remifentanyl, and fentanyl, are highly lipid-soluble with a far more rapid onset of action than morphine¹⁰; therefore, combining these classes of opioids would introduce a high degree of clinical heterogeneity.

Data extraction and risk of bias assessment

Using a pre-designed data extraction form, two investigators extracted the following data: author names, study inclusion and exclusion criteria, number of patients enrolled and randomised, patient age and setting, procedure type and length categorisation, and outcomes data. Pairs of investigators independently collected all study data in duplicate and assessed risk of bias (RoB) of the included studies using the modified Cochrane RoB 2.0 tool.¹¹ Although the published protocol describes using the Cochrane RoB 1.0 tool to assess individual study RoB, we used the modified Cochrane RoB 2.0 tool. We believe this RoB tool is optimal as it eliminates the 'unclear' category found in the original RoB tool and instead rates RoB across domains as either low, probably low, probably high, or high.¹² The RoB examines the bias from the following domains: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results. We resolved disagreements in data extraction and RoB assessments through discussion.

Data synthesis and analysis

For continuous outcomes such as sedation recovery time, we calculated the mean difference (MD) and corresponding 95% confidence intervals (CIs); this includes the analysis of patient satisfaction as a continuous outcome. Specifically, for patient satisfaction as a continuous outcome, when studies used instruments that measured the same construct, we used linear transformation to convert measure to a 0–10 scale¹³ and used weighted MD for pooling study estimates. For dichotomous outcomes such as AEs, we calculated the relative risk (RR) and the corresponding 95% CIs including when patient satisfaction was reported as a dichotomous outcome. We assessed statistical heterogeneity between trials using visual inspection of the forest plots, the I^2 statistic and the χ^2 test. When only median was reported for a continuous outcome, we converted this to a mean using the Hozo method.¹⁴ Moreover, we used the methods by Weir to calculate standard deviation when not reported.¹⁵ No other imputation was performed and any

residual missing data were incorporated into RoB and GRADE certainty assessments. When the number of events was zero, we used the continuity correction as recommended by Sweeting and colleagues.¹⁶ We assessed the feasibility of performing network meta-analysis for each outcome by checking network connectivity, ensuring the availability of more trials than number of intervention nodes, and having at least 10 trials for each outcome network. When appropriate to perform network meta-analysis, we calculated direct effect estimates using the DerSimonian and Laird random-effects model, for all comparisons with two RCTs or more.¹⁷

We performed frequentist random-effects network meta-analysis using multivariate meta-analysis assuming a common heterogeneity parameter.^{18,19} We assessed the transitivity assumption by comparing the distribution of important characteristics of trial populations, interventions, and co-interventions, and the methodological characteristics of the studies across treatment comparisons. We identified issues of incoherence by comparing direct evidence with indirect evidence using the side-splitting method.²⁰ We also confirmed the coherence assumption in the entire network using the 'design-by-treatment' model.²¹ At the request of reviewers, we performed a *post hoc* sensitivity analysis without ICU studies.

After display of the rank probabilities using rankogram, we used the surface under the cumulative ranking (SUCRA) to aid in interpretation of relative effect of the interventions. All analyses were performed using the 'network' suite in Stata (version 17.0, StataCorp., College Station, TX, USA).²²

Assessment of certainty of evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence for each outcome.²³ First, we assessed certainty of evidence in direct estimates using the traditional GRADE framework incorporating RoB, consistency, directness, and publication bias. Next, we rated certainty of indirect estimates using the lowest certainty of the highest order loop while also considering issues related to intransitivity. We then rated the certainty in network estimates based on the higher certainty between the direct and indirect estimates, while also considering issues of incoherence and imprecision at the network estimate level.²³ We used a minimally contextualised approach to evaluate certainty in effect estimates²⁴ using the null as the threshold for all outcomes except sedation recovery time. For sedation recovery time, we used 5 min as the threshold for clinically important effect. The GRADE approach was used by two authors with extensive experience (SS and BR) to rate certainty of evidence. These ratings were discussed amongst the authorship group to ensure consensus. In keeping with GRADE methods, ratings have been provided along with transparent description and rationale to inform readers. We used GRADE narrative statements to communicate the findings from the network meta-analysis (e.g. 'probably', 'may', etc.).²⁵

Subgroup analyses

We performed subgroup analysis using a network meta-regression model for the following *a priori* defined subgroups: (i) adults (aged 18 yr or older) vs paediatrics (under 18 yr of age); (ii) short procedures (cardioversion, central line insertion, incision and drainage, foreign body removal) vs long procedures (orthopaedic procedures, bronchoscopy, endoscopy,

tracheostomy, lumbar puncture, chest tube insertion); (iii) patients admitted to the ICU vs those in the ED; (iv) high vs low RoB studies; and (v) PSA with opioids vs without opioids.

Results

Search results and study characteristics

We identified 15 341 citations (Fig. 1) in the search. Of these, 168 underwent full-text review and we included 82 RCTs with a total of 8105 patients. Characteristics of the included trials are in [Appendix 3, Supplementary material, Supplementary Table S1](#). Seventy-eight studies were performed in the ED ($n=7822$ patients)^{26–102} and four in the ICU ($n=283$ patients).^{103–106} Nineteen were determined to be at overall high or probably high RoB^{29,34,35,38,42,49,51–53,57,59,75,80,83,95,98,101,104,105} and 63 were found to be at low or probably low RoB^{26–28,30–33,36,37,39–41,43–48,50,54–56,58,60–74,76–79,81,82,84–94,96,97,99,100,102,103,106,107} ([Supplementary Appendix 3, Supplementary Table S2](#)). Fifty-two studies included adults only ($n=4850$ patients),^{26–28,30,32,33,36,38–40,47–50,52,54,57–60,65–75,77–80,82–84,87,89–95,98,99,102–105,107} 23 included paediatrics only ($n=2358$ patients),^{34,35,42–46,51,53,55,61–64,76,85,86,88,96,97,101,103,106} and seven included a mix of both populations ($n=897$ patients).^{29,31,37,41,56,81,100}

The most common comparators were midazolam-opioid ($n=1188$ patients), ketamine-propofol ($n=1497$ patients), propofol ($n=912$ patients), and ketamine alone ($n=894$ patients). The opioids included were fentanyl, remifentanyl, and alfentanil. The definitions of all AEs recorded from the 79 RCTs that reported them are provided in [Supplementary Appendix 3, \(Supplementary Table S3\)](#). The dosing regimens of the PSA

medications used in the included studies are provided in [Supplementary Appendix 3, \(Supplementary Table S4\)](#). The network maps for all the outcomes are in [Supplementary Appendix 5](#). The league tables and GRADE assessment of evidence are also provided in the online supplementary appendix.

Sedation recovery time

Compared with midazolam-opioid, sedation recovery time was shorter with propofol (MD 16.3 min less, 95% CI 8.4–24.3 min less; high certainty), and probably shorter with propofol-opioid (MD 13.6 min less, 95% CI 6.6–20.7 min less; moderate certainty), ketamine-propofol (MD 10.5 min less, 95% CI 3.4–17.6 min less; moderate certainty), etomidate-opioid (MD 14.8 min less, 95% CI 3.5–26.0 min less; moderate certainty), and opioids (MD 12.1 min less, 95% CI 25.4 min less to 1.3 min more; moderate certainty) ([Table 1; Supplementary Appendix 3, Supplementary Tables S5 and S13](#)). Compared with midazolam-opioid, sedation recovery time may be longer with the use of ketamine-midazolam (MD 8.3 min more, 95% CI 1.1–15.5 min more; low certainty) ([Table 1; Supplementary Appendix 3, Supplementary Tables S5 and S13](#)).

Compared with ketamine-propofol, recovery time may be shorter with propofol (MD 5.8 min less, 95% CI 12.01 min less to 0.4 min more; low certainty) ([Table 1; Supplementary Appendix 3, Supplementary Tables S5 and S14](#)). Compared with ketamine-propofol, there is probably no difference in sedation recovery time with the use of propofol-opioids (MD 3.1 min less, 95% CI 8.5 min less to 2.3 min more; moderate

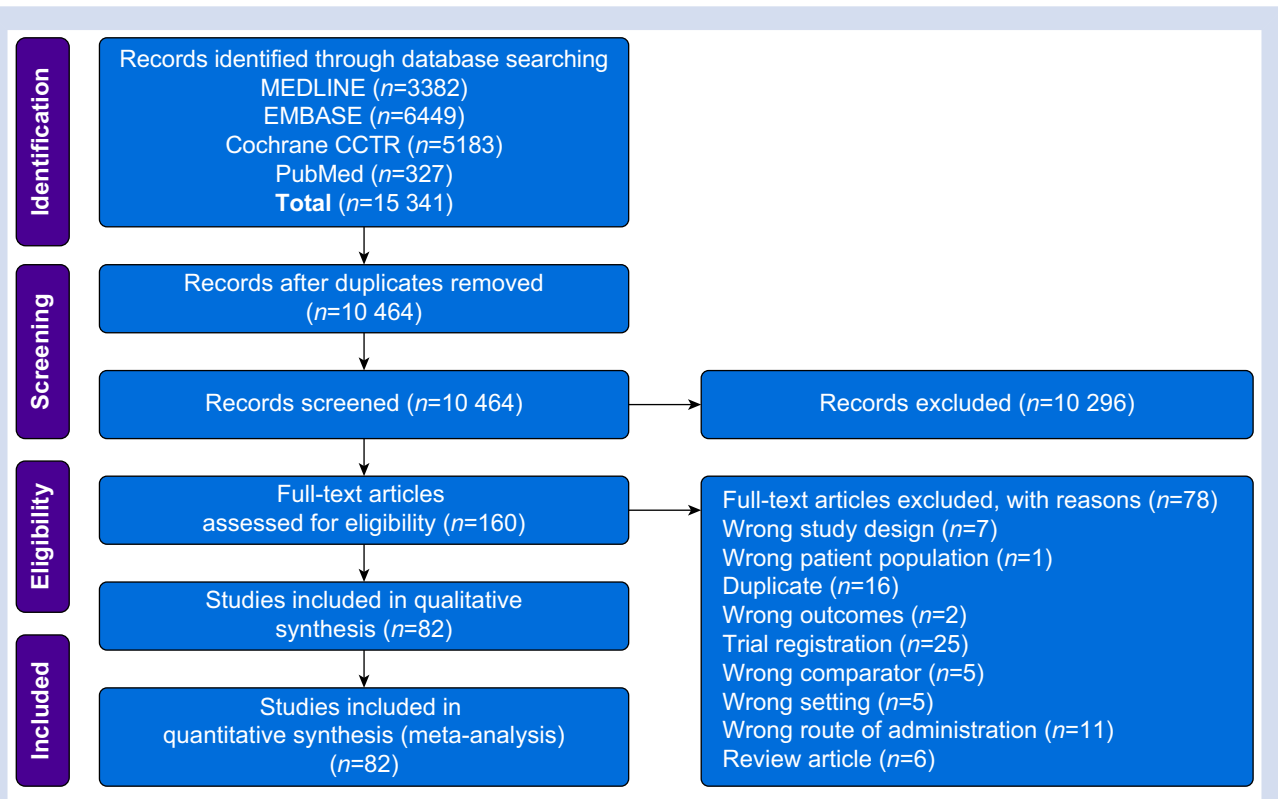


Fig 1. Study flowchart.

Table 1 Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for recovery time. CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference. *Imprecision only incorporated at network level, not at direct or indirect. †Lowered for imprecision. ‡Lowered for inconsistency. †Lowered two levels for very serious imprecisions.

Comparison	Direct estimate MD (95% CI)	Indirect estimate MD (95% CI)	Network estimate* MD (95% CI)	GRADE	Narrative summary
Midazolam-opioids vs propofol	21.7 (3.7–39.7)	14.7 (5.4–24.0)	16.3 (8.4–24.3)	High	Midazolam-opioids have a longer recovery time compared with propofol
Opioids vs midazolam-opioids	–5 (–25.2 to 15.2)	–18.6 (–37.3 to 0.2)	–12.1 (–25.4 to 1.3)	Moderate†	Opioids probably have a shorter recovery time compared with midazolam-opioids
Etomidate-opioids vs midazolam-opioids	–9.9 (–27.0 to 7.1)	–18.5 (–34.6 to –2.4)	–14.8 (–26.0 to –3.5)	Moderate†	Etomidate-opioids probably have a shorter recovery time compared with midazolam-opioids
Midazolam-ketamine vs midazolam-opioids	2.7 (–7.6 to 13.1)	14.3 (3.9–24.8)	8.3 (1.1–15.5)	Low†,‡	Midazolam-ketamine may have a longer recovery time compared with midazolam-opioids
Ketamine-propofol vs midazolam-opioids	–6.9 (–24.0 to 10.1)	–11.3 (–19.7 to –3.0)	–10.5 (–17.6 to –3.4)	Moderate†	Ketamine-propofol probably has a shorter recovery time compared with midazolam-opioids
Ketamine-propofol vs propofol	8.4 (–0.2 to 16.9)	2.1 (–7.8 to 12.0)	5.8 (–0.4 to 12.0)	Low†,§	Ketamine-propofol may have a longer recovery time compared with propofol
Ketamine-propofol vs propofol-opioids	0.5 (–6.4 to 7.4)	11.0 (0.6–21.5)	3.1 (–2.3 to 8.5)	Moderate†	Ketamine-propofol probably has no difference in recovery time compared with propofol-opioids
Ketamine-propofol vs ketamine	–3.6 (–13.7 to 6.5)	–5.0 (–15.3 to 5.2)	–3.6 (–9.8 to 2.7)	Low†,‡	Ketamine-propofol may have no difference in recovery time compared with ketamine
Ketamine vs propofol	10.1 (–7.4 to 27.6)	10.0 (1.3–18.7)	9.4 (2.2–16.5)	Moderate†	Ketamine probably has a longer recovery time compared with propofol
Ketamine vs propofol-opioids	1.2 (–15.5 to 17.9)	8.0 (–0.1 to 16.0)	6.8 (–0.5 to 13.8)	Moderate†	Ketamine probably has a longer recovery time compared with propofol-opioids
Ketamine vs etomidate-opioids	4.9 (–13.0 to 22.8)	10.9 (–4.9 to 26.7)	7.8 (–3.5 to 19.1)	Moderate†	Ketamine probably has a longer recovery time compared with etomidate-opioids
Ketamine vs ketamine-midazolam	–8.1 (–18.4 to 2.1)	–21.6 (–32.1 to –11.1)	–15.2 (–22.4 to –8.1)	High	Ketamine has a shorter recovery time compared with ketamine-midazolam
Etomidate vs ketamine	6.6 (–6.0 to 19.2)	–9.6 (–23.7 to 4.6)	–0.2 (–9.6 to 9.1)	Low†	Etomidate may have no difference in recovery time compared with ketamine

certainty) and may be no difference with the use of ketamine (MD 3.6 min more, 95% CI 2.7 min less to 9.8 min more; low certainty) (Table 1; Supplementary Appendix 3, Supplementary Tables S5 and S14).

Compared with ketamine, recovery time is probably shorter with propofol (MD 9.4 min less, 95% CI 2.2–16.5 min less; moderate certainty), propofol-opioids (MD 6.7 min less, 95% CI 13.8 min less to 0.5 min more; moderate certainty), and etomidate-opioids (MD 7.8 min less, 95% CI 19.1 min less to 3.5 min more; moderate certainty) (Table 1; Supplementary Appendix 3, Supplementary Tables S5 and S15). Compared with ketamine, there was a longer recovery time with the use of midazolam-ketamine (MD 15.2 min more, 95% CI 8.1–22.4 min more; high certainty) and may be no difference with etomidate (MD 0.2 min less, 95% CI 9.6 min less to 9.1 min more; low certainty) (Table 1; Supplementary Appendix 3, Supplementary Tables S5 and S15).

Patient satisfaction

Patient satisfaction was reported as a continuous outcome in 22 studies (involving 2126 patients) and measured as number of patients satisfied with sedation/analgesia in 24 studies (involving 2711 patients). With respect to the continuous scales, a wide variety were used, including but not limited to scales ranging from 1 to 5, 0 to 100, and 1 to 10 (Supplementary Appendix 3, Supplementary Table S6). Compared with midazolam-opioids, patient satisfaction was higher using ketamine-propofol (MD 1.5 points higher, 95% CI 0.3–2.6 points higher, high certainty), and may have been higher with dexmedetomidine (MD 1.0 points higher, 95% CI 0.4 points lower to 2.4 points higher; low certainty) and propofol-opioids (MD 1.0 points higher, 95% CI 0.2 points lower to 2.2 points higher; low certainty) (Supplementary Appendix 3, Supplementary Tables S7, S13 and S16). Compared with midazolam-opioids, etomidate-opioids may have no impact on patient satisfaction (MD 0.01 points higher, 95% CI 1.2 points lower to 1.2 points higher; low certainty) (Supplementary Appendix 3, Supplementary Tables S7, S13 and S16) while opioids may result in decreased patient satisfaction (MD 0.7 points lower, 95% CI 2.2 points lower to 0.8 points higher; low certainty) (Supplementary Appendix 3, Supplementary Tables S7, S13 and S16).

Compared with ketamine-propofol, patient satisfaction may be lower with the use of propofol-opioids (MD 0.5 points lower, 95% CI 1.7 points lower to 0.7 points higher; low certainty), and may have no impact on satisfaction with the use of ketamine (MD 0.03 points higher, 95% CI 1.5 points lower to 1.6 points higher; low certainty) or propofol (MD 0.01 points lower, 95% CI 1.1 points lower to 1.1 points higher; low certainty) (Supplementary Appendix 3, Supplementary Tables S7, S14 and S16). Compared with ketamine, patient satisfaction was probably lower with the use of etomidate-opioids (MD 1.5 points lower, 95% CI 3.6 points lower to 0.6 points higher; moderate certainty) (Supplementary Appendix 3, Supplementary Tables S7, S15 and S16). Compared with midazolam-opioids, there was probably no difference in patient satisfaction as a dichotomous outcome with the use of opioids (RR 1.01, 95% CI 0.86–1.19; moderate certainty) or ketamine-midazolam (RR 1.01, 95% CI 0.90–1.14; moderate certainty) (Supplementary Appendix 3, Supplementary Tables S8, S13 and S17).

Compared with ketamine-propofol, patient satisfaction as a dichotomous outcome was probably worse with the use of ketamine (RR 0.89, 95% CI 0.79–1.02; moderate certainty), and propofol-opioids (RR 0.93, 95% CI 0.83–1.05; moderate certainty), and may be worse with propofol (RR 0.94, 95% CI 0.82–1.07, low certainty) (Supplementary Appendix 3, Supplementary Tables S8, S14 and S17). Compared with ketamine, there was probably no difference in patient satisfaction as a dichotomous outcome with propofol (RR 1.05, 95% CI 0.92–1.20; moderate certainty), midazolam-ketamine (RR 1.07, 95% CI 0.94–1.23; moderate certainty), and propofol-opioids (RR 1.04, 95% CI 0.91–1.19; moderate certainty) (Supplementary Appendix 3, Supplementary Tables S8, S15 and S17).

Respiratory adverse events

Respiratory AEs were defined variably by the included studies and included the following: apnoea, laryngospasm, bag-valve mask ventilation, oxygen desaturation, intubation, aspiration, hypoxia (as defined by the authors) amongst others (Supplementary Appendix 3, Supplementary Table S3). The network diagram for this outcome is available in Figure 2. Compared to midazolam-opioids, there were fewer respiratory AEs with the use of ketamine (RR 0.55, 95% CI 0.32–0.96; high certainty), ketamine-midazolam (RR 0.57, 95% CI 0.37–0.86; high certainty), ketamine-propofol (RR 0.52, 95% CI 0.31–0.87; high certainty), and may be fewer with the use of propofol (RR 0.71, 95% CI 0.43–1.16; low certainty) (Table 2, Fig 3; Supplementary Appendix 3, Supplementary Tables S7 and S11). Compared with midazolam-opioids, there may be no effect on respiratory AEs with the use propofol-opioids (RR 1.05, 95% CI 0.61–1.81; low certainty), etomidate-opioids (RR 0.85, 95% CI 0.42–1.74; low certainty), midazolam (RR 0.49, 95% CI 0.14–1.67; low certainty), or dexmedetomidine-opioids (RR 0.84, 95% CI 0.15–4.83; low certainty) (Table 2, Fig 3; Supplementary Appendix 3, Supplementary Tables S9 and S13). Compared with midazolam-opioids, there may be more respiratory AEs with the use of opioids (RR 1.22, 95% CI 0.57–2.60; low certainty) (Table 2, Fig 3; Supplementary Appendix 3, Supplementary Tables S9 and S13).

Compared with ketamine-propofol, there were more respiratory AEs with the use of propofol-opioids (RR 2.03, 95% CI 1.32–3.13; high certainty) and probably more with propofol (RR 1.37, 95% CI 0.98–1.91; moderate certainty) (Table 2; Supplementary Appendix 3, Supplementary Tables S9 and S14). Compared with ketamine-propofol, there was probably no difference in respiratory AEs with the use of ketamine (RR 1.07, 95% CI 0.76–1.49; moderate certainty) (Table 2; Supplementary Appendix 3, Supplementary Tables S9 and S14).

Compared with ketamine, there were more respiratory AEs with the use of propofol-opioids (RR 1.90, 95% CI 1.15–3.15; high certainty), and may be more with etomidate (RR 1.43, 95% CI 0.73–2.79; low certainty) or propofol (RR 1.29, 95% CI 0.85–1.95; low certainty) (Table 2; Supplementary Appendix 3, Supplementary Tables S9 and S15). Compared with ketamine, there may be no difference in respiratory AEs with the use of midazolam-ketamine (RR 1.03, 95% CI 0.63–1.67; low certainty), and dexmedetomidine-ketamine (RR 0.91, 95% CI 0.46–1.80; low certainty). There was an uncertain effect on respiratory AEs with midazolam (RR 0.89, 95% CI 0.26–2.98;

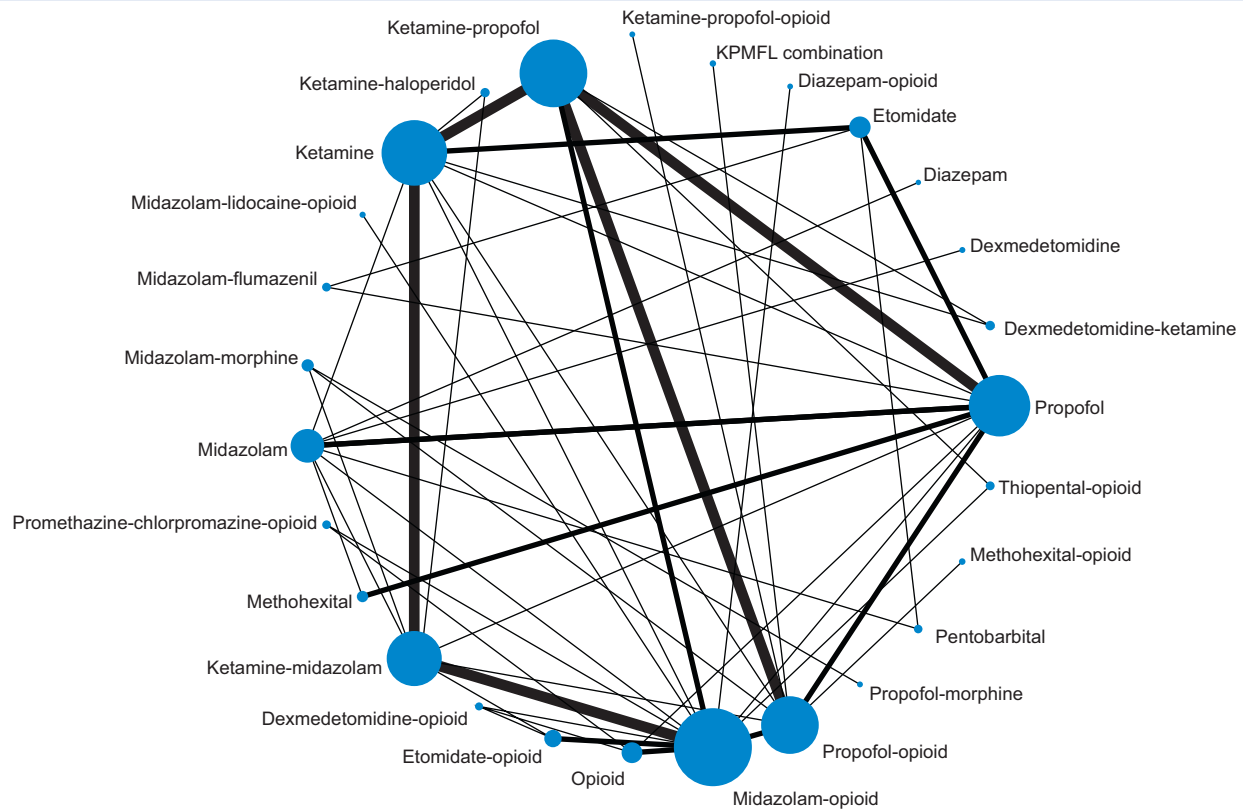


Fig 2. Network map for respiratory adverse events for x-node analysis. The size of the node corresponds to the number of patients randomised to that intervention. The thickness of the line and the associated numbers correspond to the number of studies comparing the two linked interventions. KPMFL, ketamine-propofol-midazolam-flumazenil-lidocaine.

very low certainty) (Table 2; Supplementary Appendix 3, Supplementary Tables S9 and S15).

Cardiac adverse events

Cardiac AEs were defined differently amongst the included trials but most of them included hypotension and bradycardia, whereas others also included dysrhythmias and the use of an inotrope or vasoactive agent (Supplementary Appendix 3, Supplementary Table S3). Compared with midazolam-opioids, there may be fewer cardiac AEs with the use of ketamine-propofol (RR 0.38, 95% CI 0.10–1.44; low certainty) and an uncertain effect on cardiac AEs with the use of ketamine-midazolam (RR 0.83, 95% CI 0.25–2.81; very low certainty) (Table 3; Supplementary Appendix 3, Supplementary Tables S10 and S13). Compared with midazolam-opioids, there was an uncertain effect on cardiac AEs with the use of opioids (RR 2.67, 95% CI 0.22–32.19; very low certainty), propofol (RR 1.89, 95% CI 0.44–8.04; very low certainty), propofol-opioids (RR 1.44, 95% CI 0.39–5.30; very low certainty) and dexmedetomidine-opioids (RR 4.02, 95% CI 0.37–43.87; very low certainty) (Table 3; Supplementary Appendix 3, Supplementary Tables S10 and S13).

Compared with ketamine-propofol, there were more cardiac AEs with the use of propofol-opioids (RR 3.80, 95% CI 2.02–7.16; high certainty) and propofol (RR 4.99, 95% CI 1.91–13.02; high certainty), and probably more cardiac AEs

with ketamine (RR 2.56, 95% CI 0.72–9.08; moderate certainty) (Table 3; Supplementary Appendix 3, Supplementary Tables S10 and S14). Compared with ketamine, there was an uncertain effect on cardiac AEs with the use of propofol (RR 1.95, 95% CI 0.44–8.67; very low certainty), propofol-opioids (RR 1.48, 95% CI 0.39–5.48; very low certainty), midazolam-ketamine (RR 0.82, 95% CI 0.14–4.81; very low certainty) or dexmedetomidine-ketamine (RR 0.92, 95% CI 0.16–5.48; very low certainty) (Table 3; Supplementary Appendix 3, Supplementary Tables S10 and S15).

Gastrointestinal adverse events

Almost all the included studies defined gastrointestinal (GI) AEs as nausea, vomiting, or both (Supplementary Appendix 3, Supplementary Table S3). Compared with midazolam-opioids, there were more GI AEs with ketamine-midazolam (RR 3.08, 95% CI 1.15–8.27; high certainty), and there may be more with ketamine-propofol (RR 1.97, 95% CI 0.58–6.66; low certainty) (Supplementary Appendix 3, Supplementary Tables S11, S13, and S18). Compared with midazolam-opioids, there were probably fewer GI AEs with the use of dexmedetomidine-opioids (RR 0.07, 95% CI 0.00–0.97; moderate certainty) and an uncertain effect with the use of opioids (RR 0.32, 95% CI 0.04–2.30; very low certainty), etomidate-opioids (RR 1.35, 95% CI 0.44–4.15; very low certainty) and propofol (RR 1.99, 95% CI 0.30–13.21; very low

Table 2 Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for respiratory adverse events. CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk. *Imprecision only incorporated at network level, not at direct or indirect. †Lowered for imprecision. ‡Lowered two levels for very serious imprecisions. †Lowered three levels for very serious imprecisions. §Lowered for incoherence.

Comparison	Direct estimate RR (95% CI)	Indirect estimate RR (95% CI)	Network estimate* RR (95% CI)	GRADE	Narrative summary
Ketamine-propofol vs midazolam-opioids	0.22 (0.04–1.15)	0.56 (0.32–0.99)	0.52 (0.31–0.87)	High	Ketamine-propofol has fewer respiratory adverse events compared with midazolam-opioids
Ketamine vs midazolam-opioids	0.08 (0.01–0.7)	0.54 (0.3–0.97)	0.55 (0.32–0.96)	High	Ketamine has fewer respiratory adverse events compared with midazolam-opioids
Midazolam-ketamine vs midazolam-opioids	0.55 (0.32–0.93)	0.53 (0.23–1.26)	0.57 (0.37–0.86)	High	Midazolam-ketamine has fewer respiratory adverse events compared with midazolam-opioids
Opioid-dexmedetomidine vs midazolam-opioids	1 (0.02–52.41)	0.84 (0.12–6.14)	0.84 (0.15–4.83)	Low [†]	Opioid-dexmedetomidine may have no effect on respiratory adverse events compared with midazolam-opioids
Opioids vs midazolam-opioids	0.88 (0.22–3.61)	1.5 (0.58–3.91)	1.22 (0.57–2.60)	Low [†]	Opioids may have more respiratory adverse events compared with midazolam-opioids
Midazolam-opioids vs propofol	0.69 (0.22–2.13)	1.71 (0.95–3.06)	1.41 (0.86–2.32)	Low [†]	Midazolam-opioids may have more respiratory adverse events compared with propofol
Midazolam-opioids vs propofol-opioids	0.81 (0.22–2.9)	0.85 (0.44–1.63)	0.95 (0.55–1.64)	Low [†]	Midazolam-opioids may have no effect on respiratory adverse events compared with propofol-opioids
Midazolam vs midazolam-opioids	0.09 (0.01–0.89)	0.7 (0.19–2.59)	0.49 (0.14–1.67)	Low [†]	Midazolam may have no effect on respiratory adverse events compared midazolam-opioids
Ketamine-propofol vs propofol	0.83 (0.53–1.29)	0.54 (0.29–0.99)	0.73 (0.52–1.02)	Moderate [†]	Ketamine-propofol probably has fewer respiratory adverse events compared with propofol
Ketamine-propofol vs ketamine	1.03 (0.6–1.77)	1.18 (0.59–2.34)	0.94 (0.67–1.31)	Moderate [†]	Ketamine-propofol probably has no difference in respiratory adverse events compared with ketamine
Ketamine-propofol vs propofol-opioids	0.32 (0.16–0.65)	0.53 (0.29–0.98)	0.49 (0.32–0.76)	High	Ketamine-propofol has fewer respiratory adverse events compared with propofol-opioids
Dexmedetomidine-ketamine vs ketamine-propofol	0.71 (0.15–3.39)	1.06 (0.47–2.43)	0.97 (0.49–1.93)	Moderate [†]	Dexmedetomidine-ketamine probably has no effect on respiratory adverse events when compared with ketamine-propofol
Etomidate vs ketamine	4.84 (1.8–12.99)	0.84 (0.45–1.58)	1.43 (0.73–2.79)	Low ^{†,§}	Etomidate may have more respiratory adverse events compared with ketamine
Ketamine vs propofol	1.6 (0.89–2.87)	0.53 (0.33–0.85)	0.78 (0.51–1.18)	Low ^{†,§}	Ketamine may have fewer respiratory adverse events compared with propofol
Ketamine vs midazolam	0.96 (0.02–49.82)	0.97 (0.26–3.58)	1.13 (0.34–3.79)	Very Low [†]	Ketamine has uncertain effect on respiratory adverse events compared with midazolam
Ketamine vs midazolam-ketamine	0.72 (0.37–1.42)	1.1 (0.5–2.44)	0.97 (0.60–1.58)	Low [†]	Ketamine may have no difference in respiratory adverse events compared with midazolam-ketamine
Ketamine vs midazolam-opioids	0.08 (0.01–0.7)	0.54 (0.3–0.97)	0.55 (0.32–0.96)	High	Ketamine has fewer respiratory adverse events compared with midazolam-opioids
Dexmedetomidine-ketamine vs ketamine	1.28 (0.25–6.42)	0.85 (0.38–1.88)	0.91 (0.46–1.80)	Low [†]	Dexmedetomidine-ketamine may have no effect on respiratory adverse events when compared with ketamine
Ketamine vs propofol-opioids	0.43 (0.25–0.75)	2.37 (0.60–9.40)	0.53 (0.32–0.87)	High	Ketamine has fewer respiratory adverse events compared with propofol-opioid

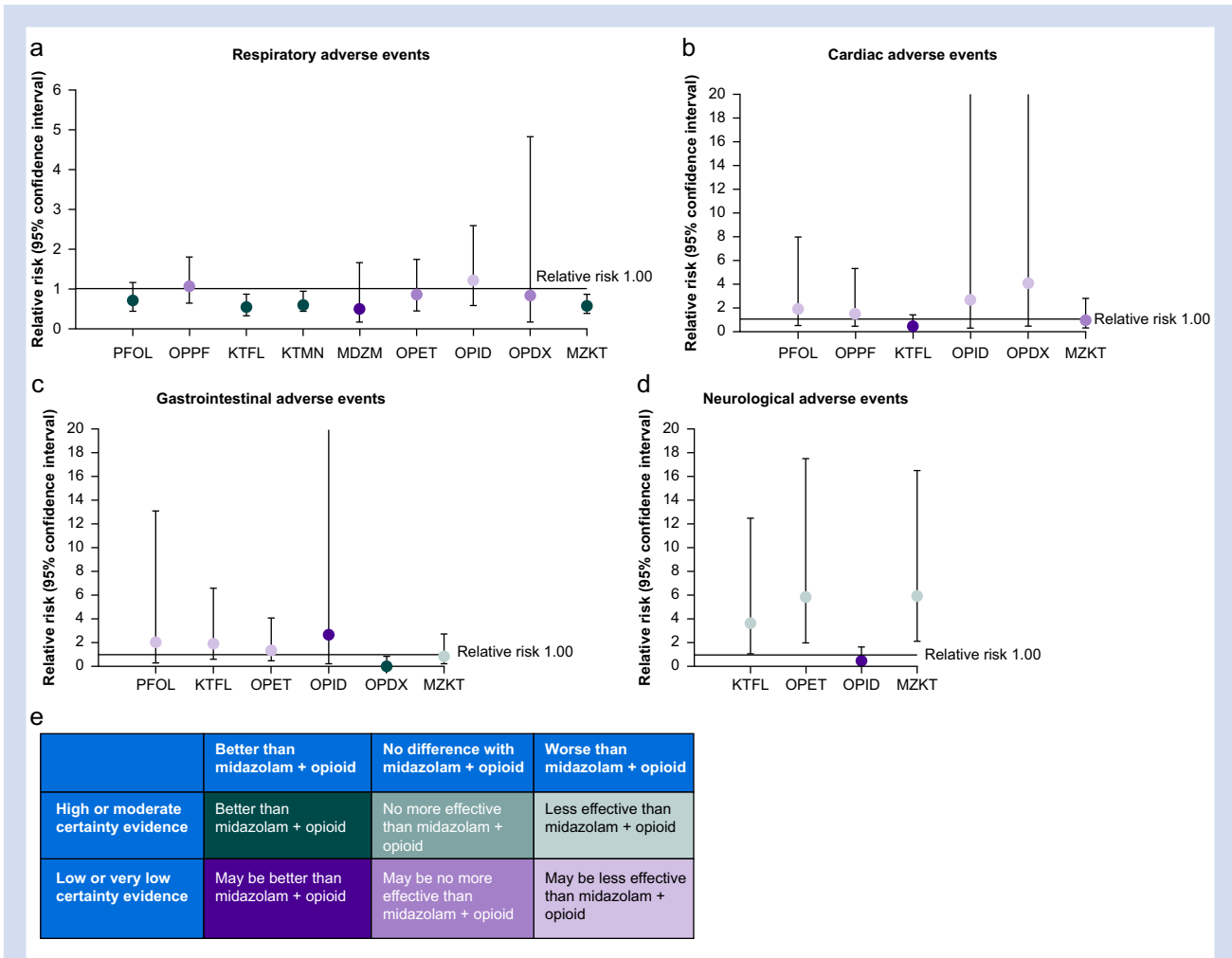


Fig 3. Network meta-analysis results based on Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) certainty of evidence and treatment effectiveness for the comparisons of active treatments vs midazolam-opioid for the outcome of adverse events. (a) respiratory adverse events; (b) cardiac adverse events; (c) gastrointestinal adverse events; (d) neurological adverse events; (E) GRADE certainty of evidence table and figure legend. KTFL, ketamine-propofol; KTMN, ketamine; MDZM, midazolam; MZKT, midazolam-ketamine; OPDX, opioid-dexmedetomidine; OPET, opioid-etomidate; OPID, opioid; OPPF, opioid-propofol; PFOL, propofol.

certainty) (Supplementary Appendix 3, Supplementary Tables S11, S13 and S18).

Compared with ketamine-propofol, there were probably more GI AEs with ketamine (RR 2.08, 95% CI 1.05–4.11; moderate certainty) and may be fewer with propofol-opioids (RR 0.66, 95% CI 0.32–1.37; low certainty) (Supplementary Appendix 3, Supplementary Tables S11, S14 and S18). Compared with ketamine-propofol, propofol has an uncertain effect on GI AEs (RR 1.01, 95% CI 0.17–5.86; very low certainty) (Supplementary Appendix 3, Supplementary Tables S11, S14 and S18). Compared with ketamine, there were fewer GI AEs with the use of propofol-opioids (RR 0.32, 95% CI 0.13–0.74; high certainty) (Supplementary Appendix 3, Supplementary Tables S11, S15 and S18). Compared with ketamine, there may be no effect on GI AEs with the use of midazolam-ketamine (RR 0.75, 95% CI 0.35–1.59; low certainty) and an uncertain effect with propofol (RR 0.49, 95% CI 0.08–2.85; very low certainty) (Supplementary Appendix 3, Supplementary Tables S11, S15 and S18).

Neurological adverse events

There was a lot of variation in how the included studies defined neurological AEs; briefly, the included recovery agitation, fasciculations, hallucinations, myoclonus, and vertigo (Supplementary Appendix 3, Supplementary Table S3). Compared with midazolam-opioids, there were more neurological AEs with the use of ketamine-propofol (RR 3.68, 95% CI 1.08–12.53; high certainty), etomidate-opioids (RR 5.88, 95% CI 1.96–17.62; high certainty), and ketamine-midazolam (RR 5.97, 95% CI 2.15–16.62; high certainty) (Supplementary Appendix 3, Supplementary Tables S12, S13 and S18). Compared with midazolam-opioids, there was an uncertain effect on neurological AEs with the use of opioids (RR 0.34, 95% CI 0.07–1.72; very low certainty) (Supplementary Appendix 3, Supplementary Tables S12, S13 and S19).

Compared with ketamine-propofol, there were more neurological AEs with ketamine (RR 2.38, 95% CI 1.33–4.23; high certainty) (Supplementary Appendix 3, Supplementary

Table 3 Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for cardiac adverse events. AE, adverse events; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk. *Imprecision only incorporated at network level, not at direct or indirect. †Lowered for imprecision. ‡Lowered two levels for very serious imprecisions. †Lowered three levels for very serious imprecisions.

Comparison	Direct estimate RR (95% CI)	Indirect estimate RR (95% CI)	Network estimate* RR (95% CI)	GRADE	Narrative summary
Ketamine-propofol vs midazolam-opioids	0.333 (0.014–7.88)	0.387 (0.088–1.694)	0.38 (0.10–1.43)	Low [‡]	Ketamine-propofol may have fewer cardiac AEs compared with midazolam-opioids
Midazolam-ketamine vs midazolam-opioids	0.967 (0.236–3.964)	0.552 (0.051–5.909)	0.80 (0.24–2.69)	Very low [†]	Midazolam-ketamine may have no effect on cardiac AEs compared with midazolam-opioids
Opioid-dexmedetomidine vs midazolam-opioids	7.001 (0.373–131.382)	1.334 (0.021–83.063)	4.02 (0.37–43.87)	Very low [†]	Opioid-dexmedetomidine has an uncertain effect on cardiac AEs compared with midazolam-opioids
Midazolam-opioids vs propofol	3.77 (0.158–90.033)	0.305 (0.06–1.555)	0.53 (0.12–2.25)	Very low [†]	Midazolam-opioids has an uncertain effect on cardiac AEs compared with propofol
Midazolam-opioids vs propofol-opioids	0.441 (0.06–3.249)	1.142 (0.202–6.473)	0.69 (0.19–2.55)	Very low [†]	Midazolam-opioids has an uncertain effect on cardiac AEs compared with propofol-opioids
Ketamine-propofol vs propofol	0.155 (0.05–0.483)	0.345 (0.056–2.117)	0.20 (0.08–0.52)	High	Ketamine-propofol has fewer cardiac AEs compared with propofol
Ketamine-propofol vs ketamine	0.167 (0.02–1.412)	0.305 (0.016–5.766)	0.39 (0.11–1.38)	Moderate [†]	Ketamine-propofol probably has fewer cardiac AEs compared with ketamine
Ketamine-propofol vs propofol-opioids	0.32 (0.159–0.643)	0.119 (0.017–0.83)	0.26 (0.14–0.50)	High	Ketamine-propofol has fewer cardiac AEs compared with propofol-opioids
Dexmedetomidine-ketamine vs ketamine-propofol	2.00 (0.19–20.93)	4.03 (0.04–425.10)	2.37 (0.34–16.34)	Very low [†]	Dexmedetomidine-ketamine has an uncertain effect on cardiac AEs when compared with ketamine-propofol
Ketamine vs propofol	1.063 (0.022–52.527)	0.912 (0.111–7.486)	0.51 (0.12–2.29)	Very low [†]	Ketamine has an uncertain effect on cardiac AEs when compared with propofol
Ketamine vs midazolam-ketamine	0.969 (0.02–48.05)	2.986 (0.272–32.82)	1.21 (0.21–7.07)	Very low [†]	Ketamine has an uncertain effect on cardiac AEs when compared with midazolam-ketamine
Ketamine vs propofol-opioids	0.16 (0.01–2.46)	1.00 (0.23–4.46)	0.67 (0.18–2.59)	Very low [†]	Ketamine has an uncertain effect on cardiac AEs when compared with propofol-opioids

Tables S12, S14 and S19) and may be no difference in neurological AEs with the use of propofol-opioids (RR 1.00, 95% CI 0.35–2.80; low certainty) or propofol (RR 0.79, 95% CI 0.38–1.63; low certainty) (Supplementary Appendix 3, Supplementary Tables S12, S14 and S19). Compared with ketamine, there were fewer neurological AEs with the use of propofol (RR 0.33, 95% CI 0.15–0.71; high certainty), and probably fewer with propofol-opioids (RR 0.42, 95% CI 0.15–1.15; moderate certainty) and dexmedetomidine-ketamine (RR 0.37, 95% CI 0.12–1.17; moderate certainty). Compared with ketamine, there may be no difference in neurological AEs with the use of midazolam-ketamine (RR 0.68, 95% CI 0.32–1.45; low certainty) (Supplementary Appendix 3, Supplementary Tables S12, S15 and S19).

Additional analyses

We explored the impact of age (adults vs paediatrics), duration of procedure (long vs short), and RoB on network estimates using network meta-regression but found no evidence of important subgroup effect in relative effects across outcomes of interest (Supplementary Appendix 4, Supplementary Tables S20–S56). We did not have sufficient studies or granularity in data to perform subgroup analysis for the comparison of ICU vs ED admission. Our *post hoc* sensitivity analysis without ICU studies did not show a difference in conclusions for any of the outcomes of interest (Supplementary Appendix). Ranking probabilities and SUCRA values are provided in Supplementary Appendix 3.

Discussion

This systematic review and network meta-analysis highlights the strengths and weaknesses of various PSA medications and combinations. Specifically, this analysis demonstrates that compared with midazolam-opioids for PSA in the ED and ICU, ketamine has fewer respiratory AEs. Furthermore, compared with ketamine-propofol, propofol-opioids have more respiratory and cardiac AEs, and may have fewer GI AEs. However, recovery time is shorter with propofol, and patient satisfaction is greater with ketamine-propofol. Moreover, compared with ketamine, propofol-opioids have fewer GI AEs and probably fewer neurological AEs but have more respiratory AEs.

Patient and procedure characteristics often dictate the choice of PSA medications used by healthcare providers. Based on this analysis, ketamine and combination ketamine-propofol may be the best choice for patients who have a tenuous airway status (i.e. those with lung pathology). In contrast, healthcare providers may want to avoid propofol, propofol-opioids, and opioid-midazolam in these patients given their association with more respiratory AEs. Healthcare providers providing PSA for patients undergoing procedures such as emergent endoscopies may want to use combination midazolam-opioids, as the analysis found that this regimen had the fewest GI AEs. Conversely, ketamine should perhaps be avoided in this clinical circumstance given it is associated with the most GI AEs. In circumstances where healthcare providers want the benefit from ketamine's respiratory protective features, but want to avoid its GI AEs, using propofol in combination with ketamine may be advisable as this results in fewer GI AEs.

Critically ill patients made up a smaller number of patients included in this analysis. Amongst their complex clinical factors, many of them are often hypotensive as a result of shock of various aetiologies. In these instances, healthcare providers

may wish to avoid propofol and propofol-opioids, as they were associated with the most cardiac AEs. A plausible alternative in these circumstances would be using either midazolam-opioid or ketamine-propofol as they were associated with the fewest cardiac AEs. Although both opioids and benzodiazepines can cause hypotension, the use of a combination has been shown to require lower doses of each individual drug, perhaps abrogating negative sequelae.¹⁰⁸

In clinical circumstances where patients with an altered mental status need PSA, healthcare providers may wish to avoid ketamine and etomidate given they were associated with the most neurological AEs. This is likely a result of the post-emergence phenomenon that is associated with ketamine use; it is characterised by euphoria, vivid dreams, illusions, and hallucinations.¹⁰⁹ However, etomidate is associated with myoclonic jerks which can explain the increase in noted neurological AEs.¹¹⁰

The time it takes for a patient to recover from PSA is important from a resource utilisation perspective, as these patients must be monitored closely until they fully recover. This time includes monitoring by the registered nurse, the respiratory therapist, and the most responsible physician. This is particularly noteworthy when sedating for short procedures such as electrical cardioversions. In these instances, healthcare providers may wish to avoid using ketamine and combination midazolam-ketamine, as they were associated with longest recovery time. Conversely, opioids, propofol, propofol-opioids, and opioid-etomidate were associated with the shortest recovery time. From a satisfaction perspective, patients prefer ketamine-propofol followed by propofol-opioids. Opioids, propofol, and ketamine alone were associated with the lowest patient satisfaction. Although the absolute differences in patient satisfaction were small, there is a consistent signal that combination drugs may be associated with higher patient satisfaction, perhaps by optimising benefit while minimising potential adverse effects associated with higher doses.

We did not identify any relative subgroup effect when comparing children vs adults (Supplementary Appendix 4). Of the 23 studies that focused on a paediatric population alone, 21 examined ketamine alone or in combination with another drug. Ketamine has a good safety profile,¹¹¹ and with many of the studies in children including it as one of their arms, it may partly explain why no differences were found between the adult and paediatric populations. We could not perform a subgroup analysis comparing studies done in the ICU vs those conducted in the ED because of a lack of data. There were four studies that examined PSA in critically ill patients with two in a paediatric population. One of the paediatric studies examined sedation for the insertion of central venous catheters¹⁰³ whereas the other examined sedation for procedures such as a lumbar puncture and bone marrow aspiration.¹⁰⁶ Of the adult ICU studies, one examined the sedation of burn patients for the purpose of dressing changes¹⁰⁴ and the other assessed sedating post-coronary artery bypass graft patients for synchronised cardioversion for atrial fibrillation.¹⁰⁵

Strengths of this review include a pre-registered protocol, a comprehensive literature search including unpublished sources, duplicate and independent screening and data abstraction, network meta-analysis allowing for inclusion of both direct and indirect evidence, and GRADE assessment of certainty of evidence. These findings represent the most current, comprehensive summary of evidence to guide clinical practice

for PSA. Moreover, inclusion of studies in children allows for a more robust and generalisable understanding of the various PSA medications used.

Limitations

First, there were only four ICU studies included and therefore conclusions regarding critically ill patients are less certain. Second, because many of the findings had low or very low certainty of evidence because of imprecision and wide CIs, further RCTs are needed to improve certainty of findings. Specifically, PSA regimens that are represented by smaller nodes in the analysis (i.e. etomidate-opioids, dexmedetomidine-opioids, dexmedetomidine alone) would benefit from more RCT data. Third, many of the included studies used different definitions for AEs which introduced some heterogeneity into the findings. These limitations were considered when using the GRADE approach assessing the certainty of evidence. Fourth, given the clinical heterogeneity between studies, indirect comparisons may have a degree of intransitivity, although we did not lower for this GRADE domain.

Conclusions

Overall, these data illustrate that there is no perfect pharmacological agent for procedural sedation and analgesia. Compared with midazolam-opioids for procedural sedation and analgesia in the acute care setting, ketamine was associated with fewer respiratory adverse events, sedation recovery time is shortest with propofol, and patient satisfaction is highest using a combination of ketamine-propofol. Compared with ketamine-propofol, propofol-opioids may be associated with higher rates of respiratory and cardiac adverse events, and probably fewer gastrointestinal adverse events. As such, our data highlights the importance of an individualised approach based upon patient and procedure characteristics.

Authors' contributions

Designed the study: SS, BR
 Collected the data: JK, FR, BF, MH, AG, SS
 Analysed and interpreted the data: SS, BR, BS
 Contributed to the writing of the manuscript: SS, BR, BS, SMF, LM, ME, RS, MD, MB, LB, JP, AP, GM, PP, MW

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Declaration of interest

SS holds a McMaster University Department of Medicine Internal Career Research Award.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2023.11.050>.

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