KETAMINE SEDATION IN THE INTENSIVE CARE UNIT: A SURVEY, SYSTEMATIC REVIEW, NETWORK META-ANALYSIS, AND PILOT STUDY PROTOCOL

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TITLE: Ketamine sedation in the intensive care unit: A survey, systematic review, network meta-analysis, and pilot study protocol

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ABSTRACT

This thesis consists of two studies presented as two separate manuscripts (one has been published in a peer-reviewed journal and the other is in the process of being submitted to a peer-reviewed journal) and a protocol for a pilot randomized controlled trial. The overarching aim of this thesis was to explore the evidence examining the use of ketamine as a sedative for critically ill mechanically ventilated patients in the Intensive Care Unit (ICU).

We conducted a national survey to understand the beliefs and practices of Canadian ICU physicians regarding the use of ketamine as a continuous intravenous sedative in critically ill patients and to gauge interest in participating in a randomized controlled trial (RCT). We surveyed 400 physician members of the Canadian Critical Care Society and found that most respondents rarely use ketamine as a continuous infusion for sedation or analgesia in the ICU. We found that there were a number of clinical circumstances that would make physicians more likely to use ketamine such as asthma exacerbation and established tolerance to opioids. Conversely, physicians were concerned about the potential side effects of ketamine, particularly psychotropic effects including delirium. Overall, the majority of physicians surveyed agreed that there is a need for a clinical trial to evaluate the effectiveness and safety of ketamine as a sedative infusion in the ICU. The results of this survey informed the second manuscript which is a systematic review examining the use of procedural sedation medications in acutely ill patients.

Prospective data examining ketamine as a continuous sedative in critically ill patients is sparse and insufficient for pooled analysis. Therefore, we focused on an indirect source of evidence, the role of ketamine as a procedural sedation drug. In order to summarize this data, we performed a systematic review and network meta-analysis (NMA) comparing all peri-procedural sedative drugs in acutely ill patients. The NMA provides the ability to include indirect data into the pooled point estimates. We performed a search of multiple databases and found 82 RCTs (8,105 patients) that met eligibility criteria, 78 conducted in the Emergency Department and 4 in the ICU. Compared to alternative medications, we found that ketamine was associated with the fewest respiratory adverse events based on high certainty evidence. Furthermore, we found that combining ketamine with propofol resulted in the highest patient satisfaction (high certainty) and the fewest cardiac adverse events (low certainty).

The final component of this thesis is a pilot RCT protocol examining the feasibility of a larger RCT assessing the efficacy and safety of an adjunctive ketamine continuous infusion in mechanically ventilated ICU patients. We plan to submit this protocol for peer-reviewed funding as a first step to address this clinically important question.

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DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is submitted in fulfillment of the requirements for the Master of Science program in Health Research Methodology.

The work takes the form of a sandwich thesis, consisting of two separate, but related manuscripts and a related pilot study protocol which will be submitted for peer-reviewed funding.

Sameer Sharif is the first author of both manuscripts and the principal investigator of the pilot grant submission. Sameer Sharif and Bram Rochwerg developed the protocol for the systematic review and network meta-analysis. Sameer was involved with title and abstract review, case report form generation, data abstraction, analysis and GRADE application. Behnam Sadeghirad, our statistician, ran the network meta-analysis for the multiple outcomes of interest. Sameer wrote the first draft of each manuscript prior to group revisions.

Sameer developed the pilot study protocol under the mentorship of his committee, and in particular his supervisor, Dr. Bram Rochwerg. Sameer was financially supported by the Department of Medicine Early Career Award at McMaster University, Hamilton, Ontario.

INTRODUCTION

Sedation is frequently used in critically ill patients

Sedation is administered to critically ill patients in the intensive care unit (ICU) to treat discomfort, anxiety, agitation, and to help facilitate care (e.g. optimize mechanical ventilation). Often, sedatives are coupled with analgesics (e.g. opioids) to provide adequate pain relief [1].
In a North American cohort study evaluating ICU occupancy, the number of beds filled with mechanically ventilated patients ranged from 20.7% to 38.9% [2]. Mechanically ventilated patients often require sedation with 85% of ICU patients given intravenous sedatives to help attenuate anxiety, pain and agitation associated with mechanical ventilation [3, 4].

Choice of sedative infusions are limited with important limitations

Various sedative drugs administered via continuous infusion are used in the ICU but the most common include propofol, midazolam, and dexmedetomidine [5]. Although they are all effective sedatives, there are downsides to each. First, most of these sedatives do not have adequate analgesic properties [5]. Second, propofol can lead to bradycardia, hypotension, hypertriglyceridemia, pancreatitis, and propofol-infusion syndrome [6]. Third, midazolam is associated with prolonged sedation [6] which can lead to a high risk of delirium [6], prolonged duration of mechanical ventilation, and ventilator-associated pneumonia [7]. Fourth, dexmedetomidine can cause bradycardia, hypotension, and nausea [6].

The lack of meaningful analgesic properties in most of these medications is troublesome as recent studies examining an analgesia-first, no-sedation approach found that patients who had their pain addressed received less sedation, and this was associated with more days without mechanical ventilation and shorter ICU and hospital stays [8, 9]. As such, an ideal sedative to alleviate anxiety and agitation would also have analgesic properties to diminish pain.

Ketamine as a sedative in the ICU

Ketamine is a general anesthetic with sedative and analgesic properties [10]. It is commonly used by emergency physicians and anesthesiologists for procedural sedation which often lasts minutes; furthermore, its use is endorsed by a number of emergency department policies [11] due to its advantageous safety profile [12]. Specifically, ketamine preserves cardiac output, maintains airway reflexes, and causes bronchodilation [10]. Given this and its analgesic properties, it may be an ideal alternative sedative option [10].

At present, most patients in the ICU receive opioids for analgesia [13]. New opioid use in the ICU is not without risk as 20% of mechanically ventilated patients received a new opioid prescription on hospital discharge [14]. Furthermore, ongoing opioid use may result in tolerance, dependence, and opioid withdrawal [15]. Not only could ketamine be a safer option than opioids, but it may also decrease opioid use in the ICU [16, 17]. The most common side effect associated with ketamine is a transient dysphoric emergence phenomenon that occurs in 10-20% of patients

undergoing procedural sedation [18] while significant cardiorespiratory events are rare [18]. Primary or adjunctive ketamine use could represent an important alternative to achieve adequate sedation and reduce opioid use in the ICU [16].

There is limited data on ketamine use as a longer-term continuous sedative in the ICU

Ketamine use as a continuous sedative in the ICU is not common and has not been well studied [19]. In a survey of ICUs in Germany, ketamine infusions were used in 15% of critically ill patients [20]. Moreover, in the SPICE-III trial that examined the early use of dexmedetomidine versus usual care as a sedative in centres across Australia and New Zealand, ketamine was used in approximately 6% of patients prior to randomization [21].

A randomized controlled trial (RCT) examined the use of ketamine in a surgical ICU in France enrolling patients following hepatectomy or esophagectomy who were also using patient-controlled analgesia [22]. Investigators enrolled 93 patients from a single center and randomized them to receive 0.5mg/kg of ketamine intravenous bolus followed by an infusion of 1ug/kg/minute (0.06 mg/kg/hour) for the next 24 hours or placebo. They found that ketamine decreased the mean morphine consumption at 48 hours [22]. This trial informed the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU guidelines (PAD-IS) to make a conditional recommendation for ketamine in post-surgical ICU patients to help reduce opioid consumption [23].

Another single-center, parallel-group, open label feasibility RCT examining the use of adjunctive ketamine for sedation in critically ill mechanically ventilated patients enrolled 85 recently intubated adults [24]. They excluded patients with a history of dementia or psychiatric disorders or those who were comatose on admission due to hepatic encephalopathy. Patients were randomized to adjunctive ketamine 1-2 mcg/kg/min (0.06 to 0.12 mg/kg/hour) for 48 hours or placebo. This pilot RCT demonstrated feasibility with a consent rate of 89% and protocol adherence of 76%. They also reported that the median ventilator-free days in the control and ketamine arm was 19. Moreover, they found that more patients attained their goal sedation at 24 and 48 hours with the use of ketamine. There were no serious adverse events reported.

Ketamine use in the ICU is increasing

In the United States, use of ketamine as a continuous infusion for sedation in the ICU increased during the coronavirus disease 2019 (COVID-19) pandemic despite physicians reporting discomfort with its use as the main barrier to wider adoption [25]. Some of the proposed reasons for increased ketamine use were high sedation needs of COVID-19 patients, and shortages of more commonly used sedatives [26]. An American led survey identified three themes as reasons for physician discomfort with ketamine use: (i) lack of supporting evidence; (ii) lack of personal experience; and (iii) desire for more education and protocols [25].

Indirect evidence from the Emergency Department

The evidence examining ketamine as a sedative agent predominantly comes from procedural sedation studies performed in the Emergency Department. These studies have established ketamine as the most commonly used sedative agent in children requiring procedural sedation in the ED [12]. Studies examining adverse effects found that ketamine was associated with a higher incidence of vomiting, agitation, and laryngospasm; of note, these adverse effects were tempered when ketamine was used in combination with propofol [27]. Importantly, serious adverse events with ketamine use were rare [27].

Summary

Given there is limited RCT data examining the efficacy and safety of ketamine as a continuous sedative in the ICU, indirect evidence from procedural sedation studies may be helpful in evaluating efficacy and safety. Despite lack of direct data, ketamine is being used more frequently in the ICU. Even though ketamine has a good safety profile in the Emergency Department, uncertainty regarding its safety and efficacy when used as a continuous sedative in the ICU persists. As such, RCT data examining the efficacy and safety of ketamine as a continuous sedative in the ICU is needed.

Manuscript #1 – Ketamine Sedation in the ICU: A Survey of Canadian Intensivists

Objective Manuscript #1: Understand the beliefs and practices of Canadian intensivists regarding their use of ketamine as a sedative in critically ill patients and to gauge their interest in a RCT examining its use in the ICU.

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Ketamine Sedation in the ICU: A Survey of Canadian Intensivists

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Tweet: The majority of Canadian Intensivists rarely use ketamine as a sedative infusion in the ICU; over 70% of Intensivists agree there is a need for a trial investigating the safety and efficacy of ketamine as a sedative infusion for critically ill patients in the ICU

ABSTRACT:

Purpose: To understand the beliefs and practices of Canadian intensivists regarding their use of ketamine as a sedative in critically ill patients and to gauge their interest in a randomized controlled trial (RCT) examining its use intensive care unit (ICU).

Methods: We designed and validated an electronic self-administered survey examining the use of ketamine as a sedative infusion for ICU patients. We surveyed 400 physician members of the Canadian Critical Care Society (CCCS) via email between February and April 2022 and sent 3 reminders at two-week intervals. The survey was re-distributed in January 2023 to improve the response rate.

Results: We received 87 (22%) completed questionnaires. Most respondents reported they rarely use ketamine as a continuous infusion for sedation or analgesia in the ICU (52, 57.8%). Physicians reported the following conditions would make them more likely to use ketamine: asthma exacerbation (73, 82.0%); tolerance to opioids (68, 77.3%); status epilepticus (44, 50.0%); and severe acute respiratory distress syndrome (33, 37.5%). Concern for side-effects that limited respondents' use of ketamine include adverse psychotropic effects (61, 69.3%) and delirium (47, 53.4%). The majority of respondents agreed there is need for a RCT to evaluate ketamine as a sedative infusion in the ICU (62, 71.3%).

Conclusion: This survey of Canadian Intensivists illustrates that use of ketamine as a continuous infusion for sedation is limited, at least partly driven by concerns of adverse psychotropic effects. Canadian physicians endorse the need for a trial investigating the safety and efficacy of ketamine as a sedative for critically ill patients.

INTRODUCTION

Sedation is administered to critically ill patients in the intensive care unit (ICU) to treat discomfort, anxiety, and agitation, and to help facilitate care (e.g. optimize mechanical ventilation). The recognition and management of pain, oversedation, and delirium are crucial as they are associated with increased morbidity and mortality in ICU patients.[6] Pain, in particular, is essential to identify and manage as it is prevalent in the majority of ICU patients at various points during their clinical course.[28] Consequences of untreated pain include delirium, agitation with higher energy expenditure, post-traumatic stress disorder, anxiety, and depression.[6] Furthermore, pain is the most common memory patients have of their ICU stay.[28]

The most commonly used drugs for sedation in the ICU include propofol, midazolam, and dexmedetomidine; however, most of these drugs lack analgesic effects.[5] Ketamine is a general anaesthetic with sedative and analgesic properties and is frequently used for procedural sedation by anesthesiologists and emergency physicians, but has not been well studied in the ICU. In addition to its analgo-sedative properties, ketamine has favourable physiological properties as it preserves cardiac output, maintains airway reflexes, and causes bronchodilation; this makes it an attractive substitute to opioids.[10] Alternatives to opioid based analgesia have become increasingly relevant as the COVID-19 pandemic resulted in significant drug shortages worldwide.[16] Furthermore, some literature has found that opioid use has been associated with delirium in a dose-dependent fashion.[29] Prolonged use of opioids may precipitate tolerance, dependence, hyperalgesia, and iatrogenic opioid withdrawal.[15] In a study of opioid-naïve patients, 20% of invasively mechanically ventilated patients received a prescription for opioids

after hospital discharge and 2.6% met criteria for persistent use.[14] This is particularly problematic with an aging population being hospitalized more frequently,[30] and being at a higher risk of developing opioid-related side-effects.[31] Adjunctive ketamine may decrease opioid use in the ICU.[16]

At present, it is unclear how often ketamine is used in Canadian ICUs, and the perspectives of Canadian intensivists regarding the role of ketamine for critically ill patients are not known. It is important to explore ketamine use in Canadian ICUs to better understand barriers and facilitators to expanded clinical use, and acceptability of clinical trials.

The objective of this survey is to understand the beliefs and practices of Canadian intensivists regarding their use of sedatives in the ICU and to gauge their support for a RCT examining the use of ketamine in this setting. The results of this survey will inform a research program examining the role of ketamine in mechanically ventilated ICU patients.

METHODS

Ethics

The Hamilton Integrated Research Ethics Board approved the study (Project# 13586). We de-identified survey responses using the LimeSurvey software (Hamburg, Germany).[32]

Instrument Development

We designed a survey instrument adhering to formal development and testing methods.[33] We generated an exhaustive list of items based on informal literature review and email correspondence among co-investigators representing Canadian Intensivists and pharmacists. We performed item reduction to ensure parsimonious, functional, and internally consistent items

were included.[34] This was conducted by assessing for duplication and prioritizing questions based on relevance with co-investigators. The self-administered instrument (Electronic Supplemental Material) consisted of 15 items that focused on 4 domains: respondent and ICU characteristics, current personal sedation practices, views about the risk of current sedatives used in the ICU, and interest in participating in a future trial. Responses were yes/no, "select all that apply," Likert scales, and optional free text entry.

Instrument Testing

We conducted a sensibility assessment and pilot testing of the survey. We invited 7 colleagues (5 Intensivists and 2 pharmacists; including 4 methodologists) with clinical and methodologic expertise to evaluate the comprehensiveness, clarity, and text of the instrument. This feedback helped refine the questions and assess content validity. Furthermore, six members of the Canadian Critical Care Trials Group (CCCTG) pilot tested the instrument to ensure functionality and ease of completion.

Instrument Administration

Following approval from the Canadian Critical Care Society (CCCS), we sent the survey to all Critical Care physician members of the CCCS (n=400). On February 2022, we sent an e-mail with a link to the web-based survey on LimeSurvey (Hamburg, Germany) which included instructions for completing the survey. We raffled three gift cards as incentives for survey completion. We distributed three standardized reminders every 2 weeks. The link to the survey was closed two weeks after the final reminder email in April 2022 (a total response window of 10 weeks). We

distributed the survey once more for a 2-week period on January 10th, 2023 due to a low response rate on initial distribution.

Statistical Analysis

We used descriptive statistics for reporting. Data are presented as mean [standard deviation (SD)]. Absolute counts and proportions are presented as appropriate. The American Association for Public Opinion Research defined a completed questionnaire as at least 80% of complete responses [35]; however, for the purposes of this survey manuscript, a 'complete questionnaire,' is one with 100% complete responses. At the request of reviewers, we analyzed the frequency of the use of ketamine as an infusion by medical specialty.

RESULTS

Of the 400 potential respondents, we received 101 responses from 63 centers across Canada. Of those, 14 partially completed the survey and these partially completed surveys were excluded from analysis, leaving 87 (22% completed questionnaires) in the final analysis. Upon initial distribution of the survey, we had a completed questionnaire rate of 16.2%. The answers to the survey questions in 2023 were remarkably similar compared to those of the initial distribution in 2022 suggesting there was no big temporal impact on ketamine usage or views and preferences related to ketamine during this short interval between distributions. Close to half of the respondents were in practice for more than 10 years (47.1%) (Table 1). The highest proportion of respondents had a background of Internal Medicine (43, 49.4%), followed by Anesthesia (16, 18.4%), Emergency Medicine (9, 10.3%), and General Surgery (6, 6.9%) (Table 1). Three-quarters of the survey respondents work at an academic center (63, 72.4%), and a smaller

proportion work at an academic community center (17, 19.5%) or a non-academic community center (7, 8.0%).

Survey respondents reported propofol as the most common first-line sedative infusion in the ICU (82, 91.1%), followed by midazolam (5, 5.6%), dexmedetomidine (2, 2.2%), and ketamine (1, 1.1%) (Figure 1). With respect to the second sedative infusion of choice if the first was not available, survey respondents reported using midazolam (52, 57.8%), followed by dexmedetomidine (18, 20.0%), opioids only (5, 5.6%), propofol (8, 8.9%), and ketamine (6, 6.7%) (Figure 1). When asked about adjunctive sedative medications when the first-choice infusion was not adequate to attain the goal sedation depth, respondents reported using midazolam (32, 35.6%), ketamine (22, 24.4%), dexmedetomidine (21, 23.3%), and opioids (9, 10.0%). Importantly, the aforementioned questions focused only on sedative agents and outlined that appropriate analgesia had already been achieved.

In terms of patient populations, most survey respondents reported that they rarely use ketamine as a continuous infusion for sedation/analgesia in the ICU for general medical mechanically ventilated patients (52, 57.8%) (Figure 2) while a smaller proportion said they sometimes use ketamine in this circumstance (26, 28.9%). When comparing ketamine use amongst different medical specialties, we did not find any meaningful differences between the specialties of Anesthesia, Emergency Medicine, General Surgery, or Internal Medicine (Figure 3). Survey respondents reported that the following clinical circumstances would make them more likely to use ketamine as an adjunctive infusion: (i) pain refractory to opioids (78, 86.7%); (ii) asthma exacerbation (73, 82.0%); (iii) known tolerance to opioids (68, 77.3%); (iv) to minimize the side-effects of other sedatives (54, 60.7%); (v) status epilepticus (44, 50.0%); (vi) deep

sedation for acute respiratory distress syndrome (33, 37.5%); (vii) non-invasive positive pressure ventilation (22, 25.0%) (Figure 4).

With respect to side-effects that would limit their wider use of ketamine, respondents reported the following: (i) possible psychotropic effects (61, 69.3%); (ii) delirium (47, 53.4%); (iii) tachycardia (20, 22.7%); (iv) increased secretions (15, 17.0%); (v) arrhythmias (13, 14.8%); and (vi) hypertension (10, 11.4%) (Table 2).

Most survey respondents reported it was more important to study the use of ketamine as an adjunctive sedative infusion (64, 73.6%) rather than a primary sedative infusion (12, 13.8%). Overall, 71.3% of respondents responded that they would be willing to enrol their patients in a randomized controlled trial to examine the efficacy and safety of ketamine as an adjunctive sedative in the ICU.

DISCUSSION

In this national survey, 1.1% of Intensivists reported using ketamine as a primary sedative infusion, and 24.4% as an adjunctive sedative infusion when the first-choice sedative was insufficient to maintain the goal depth of sedation. Importantly, 71.3% of respondents expressed their interest in participating in a trial examining the efficacy and safety of ketamine as a sedative in the ICU.

Ketamine has been the most commonly used agent for painful ED procedures in children for over 20 years.[36] Studies done in adult EDs also demonstrates the safety and efficacy of ketamine for dissociative transient sedation to facilitate care for procedures such as cardioversion, and reduction of fractures.[18, 37-39] A 2018 survey of 10,737 paramedics in the United States found that two-thirds of them had administered ketamine for acute sedation or

pain and 94% were comfortable with its use.[40] This comfort with ketamine use amongst emergency providers is also reflected in Canadian prehospital practice, as well as in medical directives for its use by paramedics which exist in several provinces.[41] Despite this, our survey findings indicate that ketamine use as an infusion in the ICU is fairly consistent amongst different medical specialties.

This survey demonstrated clear interest among respondents in participating in a RCT to further investigate the role of ketamine in critically ill patients. This may, in part, be due to the potential benefits of ketamine in other settings. In the ED, procedural sedation with ketamine has rare associated adverse events while preserving pharyngeal reflexes and stimulating cardiovascular tone thereby avoiding hemodynamic sequalae.[18] Furthermore, for perioperative analgesia, ketamine has been found to significantly reduce opioid consumption.[42] In mechanically ventilated patients, use of adjunctive ketamine infusions has been associated with decreased vasopressor requirements compared to propofol and fentanyl.[43] In addition to a more optimal side effect profile, another reason for the interest in ketamine in the ICU may be due to the increased comfort of physicians given it has been used more often since the COVID-19 pandemic due to drug shortages and standardization of intubation protocols.[25, 44] With reports of drug shortages worldwide due to manufacturing issues and supply being outstripped by demand, it is incredibly important to establish the efficacy and safety of multiple sedative options, including, but not limited, to ketamine.[45]

Despite its potential benefits, more than half of our survey respondents were concerned about possible psychotropic effects and delirium as a side effect of ketamine. Given that the duration of ICU delirium may be associated with mortality up to 1 year after ICU admission,[46]

it is important to determine the safety profile of ketamine as it is being used with increasing frequency in ICUs since the COVID-19 pandemic.[26, 47] From a physiological perspective, ketamine is a rapid-acting antidepressant drug.[48] However, ketamine is also a psychoactive drug with known hallucinogenic properties[49] that could theoretically contribute to agitation and delirium, especially in vulnerable patients (i.e. alcohol use disorder, substance use disorders).[50] At present, the evidence evaluating the association of delirium with ketamine is conflicting and inconclusive.

In ED patients undergoing procedural sedation, ketamine is associated with adverse emergence phenomena in 10-20%, including recovery agitation and delirium.[18] In the peri-operative setting, physicians sometimes use benzodiazepines to attenuate the emergence phenomenon associated with ketamine.[51] Whether ketamine infusions in the ICU would result in patients requiring benzodiazepines to curb emergence phenomena is unclear. In a multicenter retrospective study of ketamine use in the ICU, it was not associated with an increased risk for delirium.[52] Furthermore, in a RCT of 162 patients, an adjunctive ketamine infusion (0.20 mg/kg/hour) was associated with a decreased duration of delirium compared to placebo.[53] Whether related to side effects or other considerations, the findings of this survey are consistent with other data reporting that Intensivists express a lack of comfort with ketamine use and rarely use it.[25] All of the sedatives used in the ICU are associated with potential adverse effects. Propofol can cause bradycardia, hypotension, propofol infusion syndrome, hypertriglyceridemia, and pancreatitis.[6] Midazolam is associated with a higher risk of delirium and prolonged sedation,[6] and dexmedetomidine can cause hypotension, bradycardia, and nausea.[6]

Although ketamine also has side-effects, the reported data associates it with fewer complications.[18]

This reported discomfort with ketamine use in the ICU setting is relatively pervasive. Guidelines for managing mechanically ventilated patients continually acknowledge the lack of high-quality evidence on which to base recommendations for use of this drug to facilitate sedation and analgesia.[23, 54] In fact, there are no specific recommendations for ketamine use as an infusion in the ICU apart from a conditional recommendation for its use in post-surgical patients to help reduce opioid consumption.[23] Commonly employed justification for this lack of guidance includes the heterogeneity of the eligibility criteria of published studies and the fact that published studies have not focused on patient important outcomes.

Strengths of this study include the novel question, rigorous survey development with interprofessional input, the diverse medical specialty background and broad geographic representation of respondents. To our knowledge, this is the first survey evaluating ketamine practice and beliefs amongst Canadian Intensivists. Furthermore, we employed a comprehensive approach to the development of this survey using rigorous methods, exhaustive item generation, item reduction, and piloting. The limitations of this study include the low response rate, limited number of pediatric practitioners, and possible response bias, including the over-representation of academic Intensivists. Of note, although 72% of respondents practiced in academic ICU, this is only slightly higher than a 2019 Canadian Medical Association poll which reported that 59% of all Intensivists in Canada work at an academic teaching hospital. [55] Another limitation this study was the re-distribution of the survey to garner more responses 8 months after the initial invitation. Of note, the responses acquired after the initial survey distribution were similar to the

original responses indicating that practice and perceptions around sedatives did not change over that 8-month span. Reasons for the low survey response rate are likely multifactorial and likely, in part, due to increased burnout amongst Intensivists (63.8% in a survey).[56] Furthermore, there is emerging evidence on survey fatigue during the COVID-19 pandemic with post-pandemic survey response rates significantly reduced in comparison to pre-pandemic levels.[57] In the future, we could perhaps increase our survey response rate by using means other than email to disseminate the survey.

CONCLUSION

This survey of Canadian Intensivists illustrates that current use of ketamine as a continuous infusion is limited and is likely driven by concerns of adverse psychotropic effects or delirium. Canadian physicians agree with the need for a trial investigating the safety and efficacy of ketamine as a sedative in ICU.

CONTRIBUTORS:

BR, SS designed the study and analyzed the results. BR, SS drafted the initial manuscript. LM, LB, SG, DC, GM, MD, and RS all equally contributed in editing the contents of the manuscript.

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None.

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Table 1. Characteristics of physician survey respondents

Years in Critical Care practice, n (%)	
0-4 years	30 (34.5%)
5-10 years	16 (18.4%)
11-15 years	11 (12.6%)
More than 15 years	30 (34.5%)
Primary Specialty	
Internal Medicine	43 (49.4%)
Anesthesia	16 (18.4%)
Emergency Medicine	9 (10.3%)
General Surgery	6 (6.9%)
Respirology	4 (4.6%)
Pediatrics	3 (3.4%)
Cardiology	1 (1.2%)
Neurology	1 (1.2%)
Number of beds in the ICUs of respondents, n (%)	
0-9 beds	7 (8.0%)
10-15 beds	10 (11.5%)
16-30 beds	27 (31.0%)
31-50 beds	27 (21.0%)
More than 50 beds	16 (18.4%)
ICU patients cared for by respondents, n (%)*	
Medical	84 (96.6%)
Surgical	84 (96.6%)
Cardiac Surgery	20 (23.0%)
Trauma	48 (55.2%)
Burns	31 (35.6%)
Neurological	54 (62.1%)
Pediatrics	4 (4.6%)
Other	6 (6.9%)

This table shows the practice profiles of 101 physician survey respondents (not all answered all questions)
**Categories are not mutually exclusive. ICU, Intensive Care Unit*

Table 2. Reported reasons for not using ketamine (n, %)

Possible Psychotropic Effects	61 (69.3%)
Delirium	47 (53.4%)
Tachycardia	20 (22.7%)
Increased Secretions	15 (17.0%)
Arrhythmias	13 (14.8%)
No side-effects limit my wider use	13 (14.8%)
Hypertension	10 (11.4%)
Laryngospasm	6 (6.8%)
Other	9 (10.2%)

Other: Cost; lack of experience with; nausea/vomiting; dysphoria

Figure 1. First and second choice sedatives of survey respondents for ICU patients.

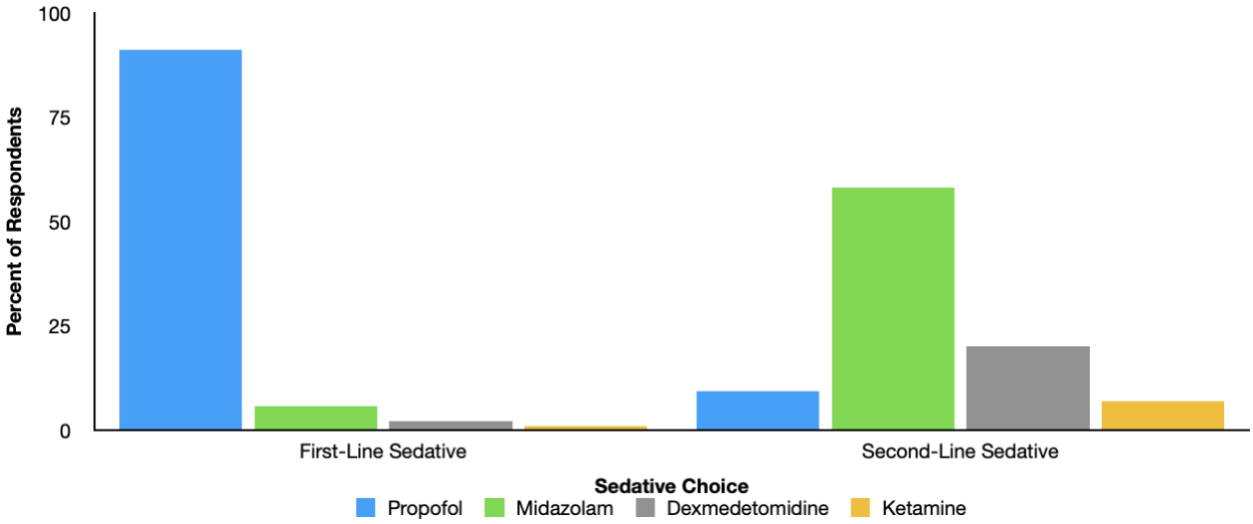


Figure 2. Frequency with which survey respondents use ketamine as a continuous infusion for sedation/analgesia in the ICU.

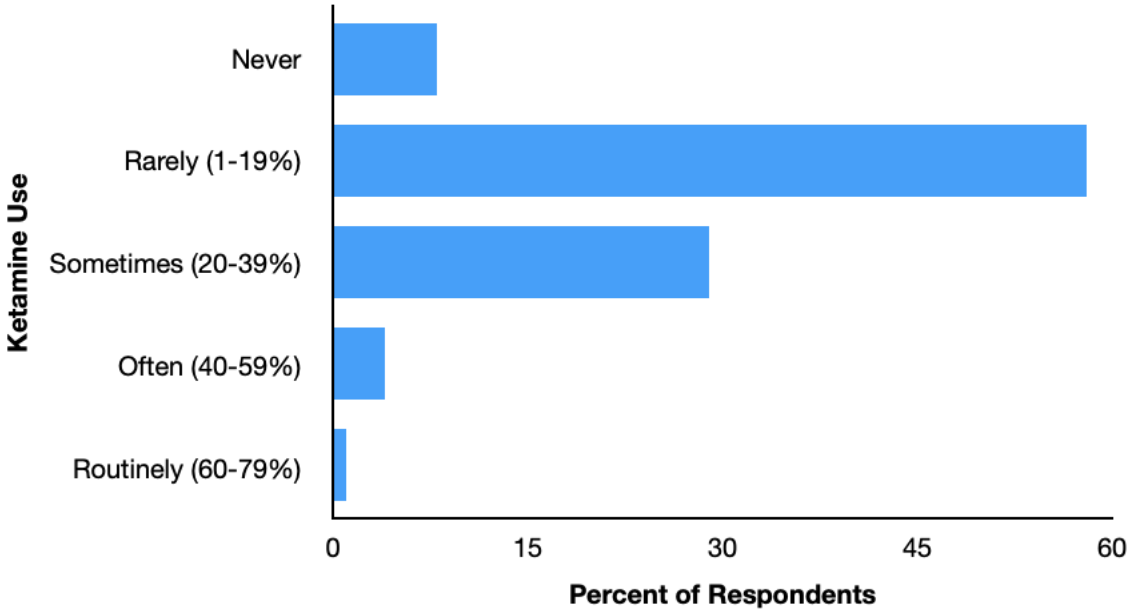
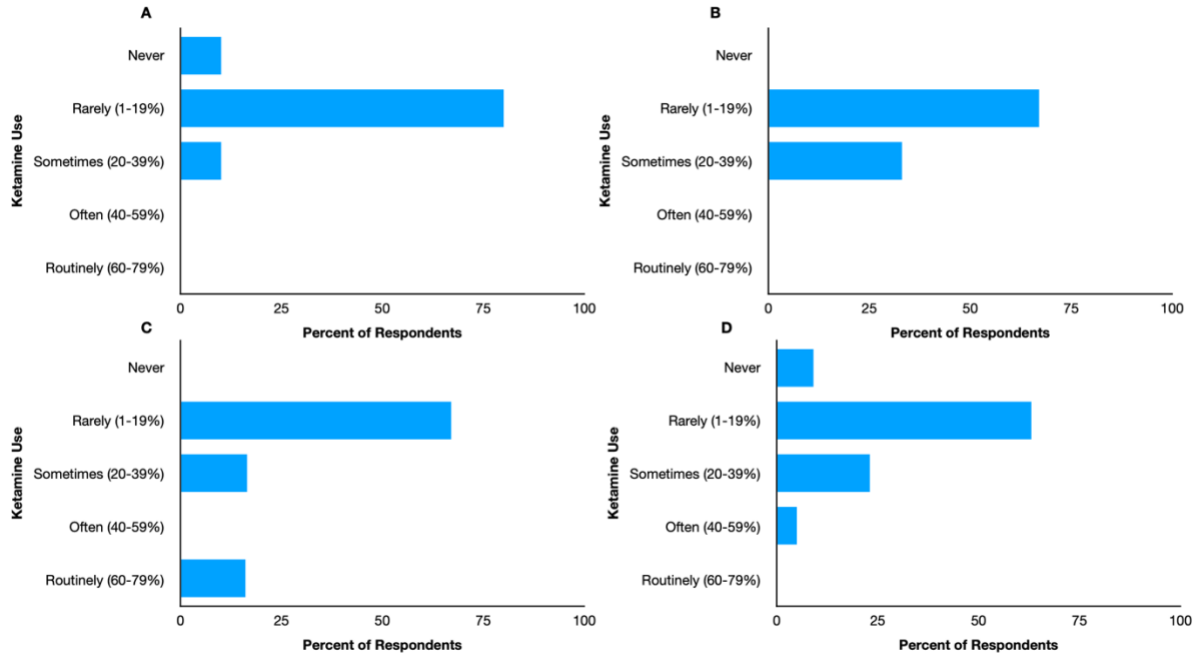
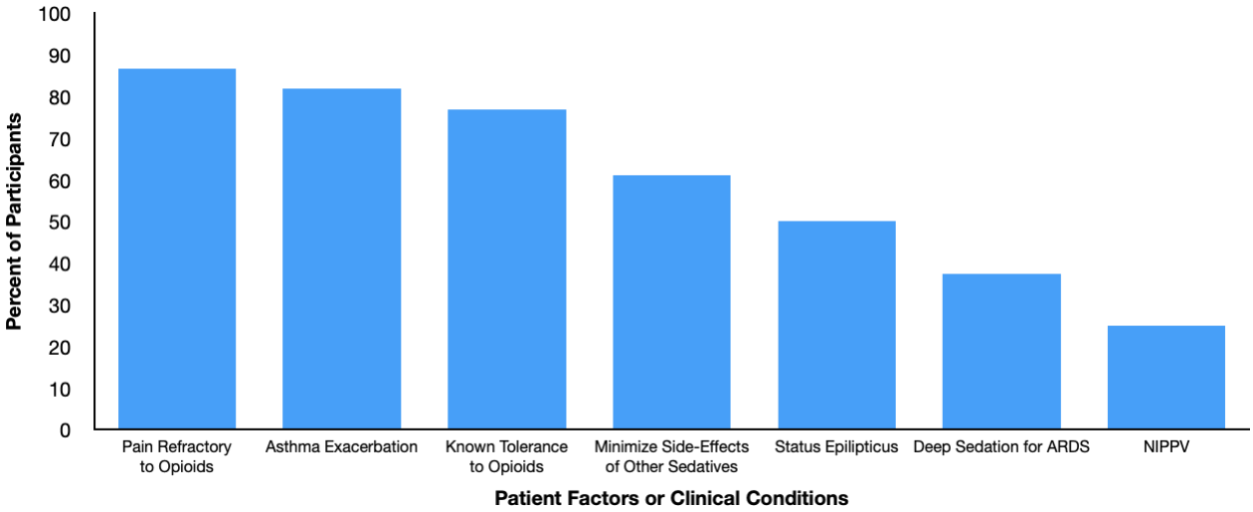


Figure 3. Frequency with which survey respondents from different medical specialties use ketamine as a continuous infusion for sedation/analgesia in the ICU.



Abbreviations: A, Anesthesia; B, Emergency Medicine; C, General Surgery; D, Internal Medicine

Figure 4. Factors or conditions that would make respondents more likely to use ketamine as a first line continuous sedative/analgesic infusion or as an adjunct.



Abbreviations: ARDS, acute respiratory distress syndrome; NIPPV, non-invasive positive pressure ventilation

Manuscript #2 – Procedural Sedation and Analgesia in the Emergency Department and Intensive Care Unit: a Systematic Review and Network Meta-Analysis

Objective Manuscript #2: To compare the efficacy and safety of various intravenous procedural sedation and analgesia medications for emergent procedure sin the ED and ICU

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TITLE PAGE

Procedural sedation and analgesia in the emergency department and intensive care unit: a systematic review and network meta-analysis

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ABSTRACT:

Background: We aim to evaluate the comparative effectiveness and safety of various intravenous pharmacologic agents used for procedural sedation and analgesia (PSA) in the Emergency Department (ED) and Intensive Care Unit (ICU). Drawing from a large body of evidence, 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 March 2, 2023 for randomized controlled trials (RCTs) comparing two or more PSA 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 GRADE approach to rate certainty in estimates.

Results: We included 82 RCTs (8,105 patients, 78 conducted in the ED and 4 in the ICU) of which 52 studies included adults, 23 included children, and 7 included both. Compared to midazolam-opioids, recovery time was shorter with propofol (mean difference [MD] 16.3 minutes, 95% confidence interval [CI] 8.4 to 24.3 fewer minutes; high certainty), and patient satisfaction was better with ketamine-propofol (MD 1.5 points, 95% CI 0.3 to 2.6 points, high certainty). Regarding AEs, compared to midazolam-opioids, respiratory AEs were less frequent with ketamine (relative risk [RR] 0.55, 95% CI 0.32 to 0.96; high certainty) , gastrointestinal AEs were more common with ketamine-midazolam (RR 3.08, 95% CI 1.15 to 8.27; high certainty), and neurological AEs were more common with ketamine-propofol (RR 3.68, 95% CI 1.08 to 12.53; high certainty).

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

Clinical Trial Registration: Center for Open Science (https://osf.io/apx53).

INTRODUCTION

Procedural sedation and analgesia (PSA) refer 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 [58]. PSA is commonly performed in-hospital, particularly in the Emergency Department (ED) and Intensive Care Units (ICU) to facilitate a number of procedures such as bronchoscopy, tracheostomy, and emergent endoscopy in the ICU [59], or orthopedic manipulation, abscess incision and drainage, and electrical cardioversion in the ED [60]. There are a variety of medications that can be selected for PSA with propofol, fentanyl, and midazolam being the most commonly used [61]; however, etomidate, ketamine, and dexmedetomidine have seen increased use of late [61].

Despite the large number of randomized clinical trials (RCTs) comparing these medications, uncertainty persists regarding the optimal medication for both safety and efficacy [27]. Also, previous systematic reviews and meta-analyses have been limited to head-to-head pairwise comparisons between two drug regimes. Our objective was to perform a systematic review and network meta-analysis comparing the efficacy and safety of various intravenous PSA medications for emergent procedures in the ED and ICU.

METHODS

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement extension for network meta-analysis (Supplemental Appendix) [62, 63]. We registered the protocol with the Center for Open Science (https://osf.io/apx53).

Data Sources and Strategy

We searched four databases (Medline, EMBASE, Cochrane, and PubMed) from inception to March 2, 2023. The search strategy was developed by an expert health sciences librarian and peer-reviewed (Supplement Appendix 1-2). To search for unpublished studies, we reviewed conference proceedings from the following organizations 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 (Supplement Appendix 1-2).

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 intravenous 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) Non-invasive positive pressure ventilation (NIPPV)

(ii) As part of a strategy that included general anesthesia

(iii) For tracheal intubation

(iv) In combination with neuromuscular blockade

(v) Restraining and controlling aggression or delirium or

(vi) Procedures exceeding a duration longer than 1 hour as procedures of this length are not frequently undertaken in the ED or ICU

Our outcomes of interest include: 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 adverse events (AEs) related to PSA medications (as defined by study authors).

Data Extraction and Risk of Bias (RoB) 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 randomized, patient age and setting, procedure type and length categorization, and outcomes data. Pairs of investigators independently collected all study data in duplicate and assessed RoB of the included studies using the modified Cochrane RoB 2.0 tool [64]. We assessed each included

trial as either low, probably low, probably high, or high RoB examining the bias from the following domains: randomization 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 risk of bias 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). For dichotomous outcomes such as adverse events, we calculated the relative risk (RR) and the corresponding 95% CIs. We assessed statistical heterogeneity between trials using visual inspection of the forest plots, and the I^2 statistic. 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 DerSimonian and Laird random-effects model, for all comparisons with two RCTs or more [65].

We performed frequentist random-effects network meta-analysis using multivariate meta-analysis assuming a common heterogeneity parameter [66, 67]. 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 side-splitting method [68]. We also confirmed the coherence assumption in the entire network using 'design-by-treatment' model [69].

Following 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) [70].

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 [71]. First, we assessed certainty of evidence in direct estimates using traditional GRADE framework based on risk of bias, consistency, directness, and publication bias, followed by assessing certainty of indirect estimates using the lowest order loop and considering intransitivity. For the risk of bias determination, if most of the studies for a specific outcome were at probably high or high RoB, we lowered our certainty in that effect. We then rated the certainty in network estimates based on the certainty in direct and indirect estimates considering issues of incoherence and imprecision [71]. We used a minimally contextualized approach to evaluate certainty in effect estimates [72] using the null as the threshold for all outcomes except sedation recovery time. For sedation recovery time, we used 5 minutes as the threshold for clinically important effect. We used GRADE narrative statements to communicate the findings from our NMA (e.g., "probably", "may", etc.). [73].

Subgroup Analyses

We performed subgroup analysis regardless of the observed heterogeneity using network meta-regression model for the following a priori defined subgroups: (i) adults (18 years or older) versus pediatrics (under 18 years); (ii) short procedures versus long procedures (see the study protocol for procedure categorization); (iii) Patients admitted to the ICU versus those in the ED; (iv) high versus low RoB studies; and (v) PSA with opioids versus without opioids.

RESULTS

Search Results and Study Characteristics

We identified 15,341 citations (Figure 1) in the search. Of these, 168 underwent full-text review and we ultimately included 82 RCTs with a total of 8,105 patients. Characteristics of the included trials are in Appendix 3, Supplement Table 1. Seventy-eight studies were performed in the ED (n=7,822 patients) [39, 74-149] and four in the ICU (n=283 patients) [150-153]. Nineteen were determined to be at overall high or probably high RoB [77, 82, 83, 86, 90, 97, 99-101, 105, 107, 123, 128, 131, 142, 145, 148, 151, 152] and sixty-three were found to be at low or probably low RoB [39, 74-76, 78-81, 84, 85, 87-89, 91-96, 98, 102-104, 106, 108-122, 124-127, 129, 130, 132-141, 143, 144, 146, 147, 149, 150, 153, 154] (Appendix 3, Supplement Table 2). Fifty-two studies included adults only (n=4,850 patients) [39, 74-76, 78, 80, 81, 84, 86-88, 95-98, 100, 102, 105-108, 113-123, 125-128, 130, 131, 134, 136-142, 145, 146, 149-152, 154], twenty-three included pediatrics only (n=2,358 patients) [82, 83, 90-94, 99, 101, 103, 109-112, 124, 132, 133, 135, 143, 144, 148, 150, 153], and seven included a mix of both populations (n=897 patients) [77, 79, 85, 89, 104, 129, 147]. The most common comparators were midazolam-opioid (n=1,188 patients), ketamine-propofol (n=1,497 patients) and ketamine alone (n=894 patients). The opioids included were fentanyl, remifentanil, and alfentanil. Studies that examined non-synthetic opioids such as morphine as part of PSA were analyzed separately because of their vastly different pharmacokinetics. For instance, alfentanil and fentanyl are highly lipid soluble with a far more rapid onset of action than morphine [155]; combining these two classes of opioids wound introduce a significant amount of clinical heterogeneity. The definitions of all adverse events recorded from the 79 RCTs that reported them are provided in Appendix 3 (Supplement Table 3).

The dosing regimens of the PSA medications used in the included studies are provided in Appendix 3. The network maps for all the outcomes are in Appendix 5.

Sedation Recovery Time

Compared to midazolam-opioid, sedation recovery time was shorter with propofol (MD 16.3 minutes less, 95% CI 8.4 to 24.3 minutes less; high certainty), and probably shorter with propofol-opioid (MD 13.6 minutes less, 95% CI 6.6 to 20.7 minutes less; moderate certainty), ketamine-propofol (MD 10.5 minutes less, 95% CI 3.4 to 17.6 minutes less; moderate certainty), etomidate-opioid (MD 14.8 minutes less, 95% CI 3.5 to 26.0 minutes less; moderate certainty), and opioids (MD 12.1 minutes less, 95% CI 25.4 minutes less to 1.3 minutes more; moderate certainty) (Table 1; Appendix 3, Supplement Tables 4, 11). Compared to midazolam-opioid, sedation recovery time may be longer with the use of ketamine-midazolam (MD 8.3 minutes more, 95% CI 1.1 to 15.5 minutes more; low certainty) (Table 1; Appendix 3, Supplement Tables 4, 11).

Compared to ketamine-propofol, recovery time may be shorter with propofol (MD 5.8 minutes less, 95% CI 12.01 minutes less to 0.4 minutes more; low certainty) (Table 1; Appendix 3, Supplement Tables 4, 12). Compared to ketamine-propofol, there is probably no difference in sedation recovery time with the use of propofol-opioids (MD 3.1 minutes less, 95% CI 8.5 minutes less to 2.3 minutes more; moderate certainty) and may be no difference with the use of ketamine (MD 3.6 minutes more, 95% CI 2.7 minutes less to 9.8 minutes more; low certainty) (Table 1; Appendix 3, Supplement Tables 4, 12).

Compared to ketamine, recovery time is probably shorter with propofol (MD 9.4 minutes less, 95% CI 2.2 to 16.5 minutes less; moderate certainty), propofol-opioids (MD 6.7 minutes less, 95% CI 13.8 minutes less to 0.5 minutes more; moderate certainty), and etomidate-opioids (MD 7.8 minutes less, 95% CI 19.1 minutes less to 3.5 minutes more; moderate certainty) (Table 1; Appendix 3, Supplement Tables 4, 13). Compared to ketamine, there was a longer recovery time with the use of midazolam-ketamine (MD 15.2 minutes more, 95% CI 8.1 to 22.4 minutes more; high certainty) and may be no difference with etomidate (MD 0.2 minutes less, 95% CI 9.6 minutes less to 9.1 minutes more; low certainty) (Table 1; Appendix 3, Supplement Tables 4, 13).

Patient Satisfaction

Patient satisfaction was reported as a continuous outcome in 22 studies (involving 2,126 patients) and measured as number of patients satisfied with sedation/analgesia in 24 studies (involving 2,711 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 (Appendix 3). Compared to midazolam-opioids, patient satisfaction was higher using ketamine-propofol (MD 1.5 points higher, 95% CI 0.3 to 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) as well as propofol-opioids (MD 1.0 points higher, 95% CI 0.2 points lower to 2.2 points higher; low certainty) (Appendix 3, Supplement Tables 5, 11, 14). Compared to 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) (Appendix 3, Supplement Tables 5,

11, 14) while opioids may result in decreased patient satisfaction (MD 0.7 points lower, 95% 2.2 points lower to 0.8 points higher; low certainty) (Appendix 3, Supplement Tables 5, 11, 14).

Compared to 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) (Appendix 3, Supplement Tables 5, 12, 14). Compared to 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) (Appendix 3, Supplement Tables 5, 13, 14).

Compared to 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 to 1.19; moderate certainty) or ketamine-midazolam (RR 1.01, 95% CI 0.90 to 1.14; moderate certainty) (Appendix 3, Supplement Tables 6, 11, 15).

Compared to ketamine-propofol, patient satisfaction as a dichotomous outcome was probably worse with the use of ketamine (RR 0.89, 95% CI 0.79 to 1.02; moderate certainty), and propofol-opioids (RR 0.93, 95% CI 0.83 to 1.05; moderate certainty), and may be worse with propofol (RR 0.94, 95% CI 0.82 to 1.07, low certainty) (Appendix 3, Supplement Tables 6, 12, 15).

Compared to ketamine, there was probably no difference in patient satisfaction as a dichotomous outcome with propofol (RR 1.05, 95% CI 0.92 to 1.20; moderate certainty),

midazolam-ketamine (RR 1.07, 95% CI 0.94 to 1.23; moderate certainty), and propofol-opioids (RR 1.04, 95% CI 0.91 to 1.19; moderate certainty) (Appendix 3, Supplement Tables 6, 13, 15).

Respiratory Adverse Events

Respiratory AEs were defined variably by the included studies and included the following: apnea, laryngospasm, bag-valve mask ventilation, oxygen desaturation, intubation, aspiration, hypoxia (as defined by the authors) amongst others (Appendix 3, Supplement Table 3). 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 to 0.96; high certainty), ketamine-midazolam (RR 0.57, 95% CI 0.37 to 0.86; high certainty), ketamine-propofol (RR 0.52, 95% CI 0.31 to 0.87; high certainty), and may be fewer with the use of propofol (RR 0.71, 95% CI 0.43 to 1.16; low certainty) (Table 2, Figure 3; Appendix 3, Supplement Tables 7, 11). Compared to midazolam-opioids, there may be no effect on respiratory AEs with the use propofol-opioids (RR 1.05, 95% CI 0.61 to 1.81; low certainty), etomidate-opioids (RR 0.85, 95% CI 0.42 to 1.74; low certainty), midazolam (RR 0.49, 95% CI 0.14 to 1.67; low certainty) or dexmedetomidine-opioids (RR 0.84, 95% CI 0.15 to 4.83; low certainty) (Table 2, Figure 3; Appendix 3, Supplement Tables 7, 11). Compared to midazolam-opioids, there may be more respiratory AEs with the use of opioids (RR 1.22, 95% CI 0.57 to 2.60; low certainty) (Table 2, Figure 3; Appendix 3, Supplement Tables 7, 11).

Compared to ketamine-propofol, there were more respiratory AEs with the use of propofol-opioids (RR 2.03, 95% CI 1.32 to 3.13; high certainty) and probably more with propofol (RR 1.37, 95% CI 0.98 to 1.91; moderate certainty) (Table 2; Appendix 3, Supplement Tables 7,

12). Compared to ketamine-propofol, there was probably no difference in respiratory AEs with the use of ketamine (RR 1.07, 95% CI 0.76 to 1.49; moderate certainty) (Table 2; Appendix 3, Supplement Tables 7, 12).

Compared to ketamine, there were more respiratory AEs with the use of propofol-opioids (RR 1.90, 95% CI 1.15 to 3.15; high certainty), and may be more with etomidate (RR 1.43, 95% CI 0.73 to 2.79; low certainty) or propofol (RR 1.29, 95% CI 0.85 to 1.95; low certainty) (Table 2; Appendix 3, Supplement Tables 7, 13). Compared to ketamine, there may be no difference in respiratory AEs with the use of midazolam-ketamine (RR 1.03, 95% CI 0.63 to 1.67; low certainty), and dexmedetomidine-ketamine (RR 0.91, 95% CI 0.46 to 1.80; low certainty). There was an uncertain effect on respiratory AEs with midazolam (RR 0.89, 95% CI 0.26 to 2.98; very low certainty) (Table 2; Appendix 3, Supplement Tables 7, 13).

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 (Appendix 3, Supplement Table 3). Compared to midazolam-opioids, there may be fewer cardiac AEs with the use of ketamine-propofol (RR 0.38, 95% CI 0.10 to 1.44; low certainty) and an uncertain effect on cardiac AEs with the use of ketamine-midazolam (RR 0.83, 95% CI 0.25 to 2.81; very low certainty) (Table 3; Appendix 3, Supplement Tables 8, 11). Compared to midazolam-opioids, there was an uncertain effect on cardiac AEs with the use of opioids (RR 2.67, 95% CI 0.22 to 32.19; very low certainty), propofol (RR 1.89, 95% CI 0.44 to 8.04; very low certainty), propofol-opioids (RR 1.44, 95% CI 0.39 to 5.30; very low

certainty) and dexmedetomidine-opioids (RR 4.02, 95% CI 0.37 to 43.87; very low certainty) (Table 3; Appendix 3, Supplement Tables 8, 11).

Compared to ketamine-propofol, there were more cardiac AEs with the use of propofol-opioids (RR 3.80, 95% CI 2.02 to 7.16; high certainty) and propofol (RR 4.99, 95% CI 1.91 to 13.02; high certainty), and probably more cardiac AEs with ketamine (RR 2.56, 95% CI 0.72 to 9.08; moderate certainty) (Table 3; Appendix 3, Supplement Tables 8, 12).

Compared to ketamine, there was an uncertain effect on cardiac AEs with the use of propofol (RR 1.95, 95% CI 0.44 to 8.67; very low certainty), propofol-opioids (RR 1.48, 95% CI 0.39 to 5.48; very low certainty), midazolam-ketamine (RR 0.82, 95% CI 0.14 to 4.81; very low certainty) or dexmedetomidine-ketamine (RR 0.92, 95% CI 0.16 to 5.48; very low certainty) (Table 3; Appendix 3, Supplement Tables 8, 13).

Gastrointestinal (GI) Adverse Events

Almost all the included studies defined GI AEs as nausea and/or vomiting (Appendix 3, Supplement Table 3). Compared to midazolam-opioids, there were more GI AEs with ketamine-midazolam (RR 3.08, 95% CI 1.15 to 8.27; high certainty), and there may be more with ketamine-propofol (RR 1.97, 95% CI 0.58 to 6.66; low certainty) (Table 4; Appendix 3, Supplement Tables 9, 11). Compared to midazolam-opioids, there were probably fewer GI AEs with the use of dexmedetomidine-opioids (RR 0.07, 95% CI 0.00 to 0.97; moderate certainty) and an uncertain effect with the use of opioids (RR 0.32, 95% CI 0.04 to 2.30; very low certainty), etomidate-opioids (RR 1.35, 95% CI 0.44 to 4.15; very low certainty) and propofol (RR 1.99, 95% CI 0.30 to 13.21; very low certainty) (Table 4; Appendix 3, Supplement Tables 9, 11).

Compared to ketamine-propofol, there were probably more GI AEs with ketamine (RR 2.08, 95% CI 1.05 to 4.11; moderate certainty) and may be fewer with propofol-opioids (RR 0.66, 95% CI 0.32 to 1.37; low certainty) (Table 4; Appendix 3, Supplement Tables 9, 12). Compared to ketamine-propofol, propofol has an uncertain effect on GI AEs (RR 1.01, 95% CI 0.17 to 5.86; very low certainty) (Table 4; Appendix 3, Supplement Tables 9, 12).

Compared to ketamine, there were fewer GI AEs with the use of propofol-opioids (RR 0.32, 95% CI 0.13 to 0.74; high certainty) (Table 4; Appendix 3, Supplement Tables 9, 13). Compared to ketamine, there may be no effect on GI AEs with the use of midazolam-ketamine (RR 0.75, 95% CI 0.35 to 1.59; low certainty) and an uncertain effect with propofol (RR 0.49, 95% CI 0.08 to 2.85; very low certainty) (Table 4; Appendix 3, Supplement Tables 9, 13).

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 (Appendix 3, Supplement Table 3). Compared to midazolam-opioids, there were more neurological AEs with the use of ketamine-propofol (RR 3.68, 95% CI 1.08 to 12.53; high certainty), etomidate-opioids (RR 5.88, 95% CI 1.96 to 17.62; high certainty), and ketamine-midazolam (RR 5.97, 95% CI 2.15 to 16.62; high certainty) (Appendix 3, Supplement Tables 10, 11, 16). Compared to midazolam-opioids, there was an uncertain effect on neurological AEs with the use of opioids (RR 0.34, 95% CI 0.07 to 1.72; very certainty) (Appendix 3, Supplement Tables 10, 11, 16).

Compared to ketamine-propofol, there were more neurological AEs with ketamine (RR 2.38, 95% CI 1.33 to 4.23; high certainty) (Appendix 3, Supplement Tables 10, 12, 16) and may be

no difference in neurological AEs with the use of propofol-opioids (RR 1.00, 95% CI 0.35 to 2.80; low certainty) or propofol (RR 0.79, 95% CI 0.38 to 1.63; low certainty) (Appendix 3, Supplement Tables 10, 12, 16).

Compared to ketamine, there were fewer neurological AEs with the use of propofol (RR 0.33, 95% CI 0.15 to 0.71; high certainty), and probably fewer with propofol-opioids (RR 0.42, 95% CI 0.15 to 1.15; moderate certainty) and dexmedetomidine-ketamine (RR 0.37, 95% CI 0.12 to 1.17; moderate certainty). Compared to ketamine, there may be no difference in neurological AEs with the use of midazolam-ketamine (RR 0.68, 95% CI 0.32 to 1.45; low certainty) (Appendix 3, Supplement Tables 10, 13, 16).

Additional Analyses

We explored the impact of age (adults vs pediatrics), duration of procedure (long vs short), and risk of bias on network estimates using network meta-regression but found no evidence of important subgroup effect in relative effects across outcomes of interest (Appendix 3, Supplement Tables 17-53). We didn't have enough studies to perform subgroup analysis for the comparison of ICU vs ER admission. Ranking probabilities and SUCRA values are provided in Appendix 3.

DISCUSSION

This systematic review and network meta-analysis highlights the strengths and weaknesses of various PSA medications. Specifically, our analysis demonstrates that compared to midazolam-opioids for PSA in the ED and ICU, ketamine has fewer respiratory AEs. Furthermore, compared to 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 higher with ketamine-propofol. Moreover, compared to 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). This airway protective feature is likely due to the physiological properties of ketamine that allows the preservation of patient's airway reflexes [10]. It is also a key reason as to why ED policies endorse its use [11]. In contrast, healthcare providers may want to avoid propofol, propofol-opioids, and opioid-midazolam in these very same patients given their association with more respiratory AEs. This is likely a result of the respiratory depression associated with the use of these medications [156].

Healthcare providers providing PSA for patients undergoing procedures such as emergent endoscopies may want to use combination midazolam-opioids as our analysis found that this regimen had the fewest GI AEs. Conversely, ketamine should perhaps be avoided in this clinical circumstance given it is on the other end of the spectrum with the most GI AEs; of note, the most

common ketamine associated GI AE is post-procedure vomiting, when patients are alert [157]. In circumstances where healthcare providers want to 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. This may be due to the anti-emetic properties of propofol [158].

Despite our analysis not having many critically ill patients to draw conclusions from, these patients often require PSA in either the ED or the ICU. Amongst their complex clinical factors, many of them are often hypotensive due to shock of various etiologies. In these instances, healthcare providers may wish to avoid propofol and propofol-opioids as they were associated with the most cardiac AEs. This is likely due to the bradycardia and hypotension that can be caused by these drugs; in particular, propofol is associated with peripheral vasodilation and negative inotropy [156]. A plausible alternative in these circumstances would be using either midazolam-opioid and 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 shown to require lower doses of each individual drug, perhaps abrogating negative sequelae [159]. With respect to ketamine having fewer cardiac AEs, this may be related to its sympathomimetic effects off-setting the cardiac depressant effects of propofol [156].

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 characterized by euphoria, vivid dreams, illusions, and hallucinations [160]. On the other hand, etomidate is associated with myoclonic jerks which can

explain the increase in noted neurological AEs [161]. Suitable alternatives with the fewest neurological AEs in these patients include propofol, midazolam-opioids, and propofol-opioids.

The time it takes for a patient to recover from PSA is important from a resource utilization 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. Having a patient recover earlier would allow healthcare providers to tend to other critically ill patients sooner. 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. As a result, these medications may be preferable for shorter procedures. This is consistent with data showing that propofol and opioids have shorter recovery times [162] whereas ketamine use can be associated with a more prolonged sedative period [163]. 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 optimizing benefit while minimizing potential adverse effects associated with higher doses.

We did not identify any relative subgroup effect when comparing children versus adults (Appendix 4). The majority of patients included in this analysis were ED patients and were not critically ill. In lower risk patients, the decision around sedative agent may be less likely to show

subgroup effect as opposed to those that are at higher risk. Furthermore, of the 23 studies that focused on a pediatric population alone, 21 examined ketamine alone or in combination with another drug. Ketamine has a good safety profile [12], 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 pediatric populations. Similarly, we did not identify subgroup effect comparing studies done in the ICU versus those conducted in the ED (Appendix 4). There were 4 studies that examined PSA in critically ill patients with 2 in a pediatric population. One of the pediatric studies examined sedation for the insertion central venous catheters [150] whereas the other examined sedation for procedures such as a lumbar puncture and bone marrow aspiration [153]. Of the adult ICU studies, one examined the sedation of burn patients for the purpose of dressing changes [151] and the other assessed sedating post coronary artery bypass graft patients for synchronized cardioversion for atrial fibrillation [152]. With the small number of ICU studies included in the analysis, it was extremely challenging to evaluate for subgroup effects, and imprecision almost certainly contributed to this lack of effect seen.

Overall, these data illustrate that decisions around optimal PSA medication need to consider patient and procedure characteristics. Ultimately, each healthcare provider will need to use an individualized approach based upon the risk profile of the specific patient they are treating. That being said, this analysis provides the best possible summary for clinicians in making these decisions and evaluating comparative efficacy and safety. Based on these findings, clinicians may want to avoid ketamine for patients with a psychiatric history or those with profound nausea and/or vomiting. Furthermore, clinicians may want to use propofol-opioid

combinations for shorter procedures and may want to avoid this drug combination in patients at higher risk for respiratory compromise.

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 generalizable understanding of the various PSA medications used.

LIMITATIONS

First, there were only 4 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 due to imprecision and wide confidence intervals, it is clear further RCTs are still needed. Third, many of the included studies used different definitions for AEs which introduced some heterogeneity into our findings. These limitations were considered when using the GRADE approach assessing the certainty of evidence. Fourth, given the large number of indirect comparisons, our results likely have a degree of intransitivity.

CONCLUSIONS

Compared to midazolam-opioids for PSA in the acute care setting, ketamine has fewer respiratory AEs, sedation recovery time is shortest with propofol, and patient satisfaction is highest using a

combination of ketamine-propofol. Compared to ketamine-propofol, propofol-opioids may be associated with higher rates of respiratory and cardiac AEs, and probably fewer gastrointestinal AEs.

AUTHOR'S CONTRIBUTIONS

SS, BR designed the study. JK, FR, BF, MH, AG, and SS collected the data. SS, BR, BS analyzed and interpreted the data. SS, BR, BS, SMF, LM, ME, RS, MD, MB, LB, JP, AP, GM, PP, and MW contributed to the writing of the manuscript.

DECLARATIONS OF INTEREST

Dr. Sameer Sharif holds a McMaster University Department of Medicine Internal Career Research Award.

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FUNDING

None

DATA AVAILABILITY

Figure 1. Study Flowchart.

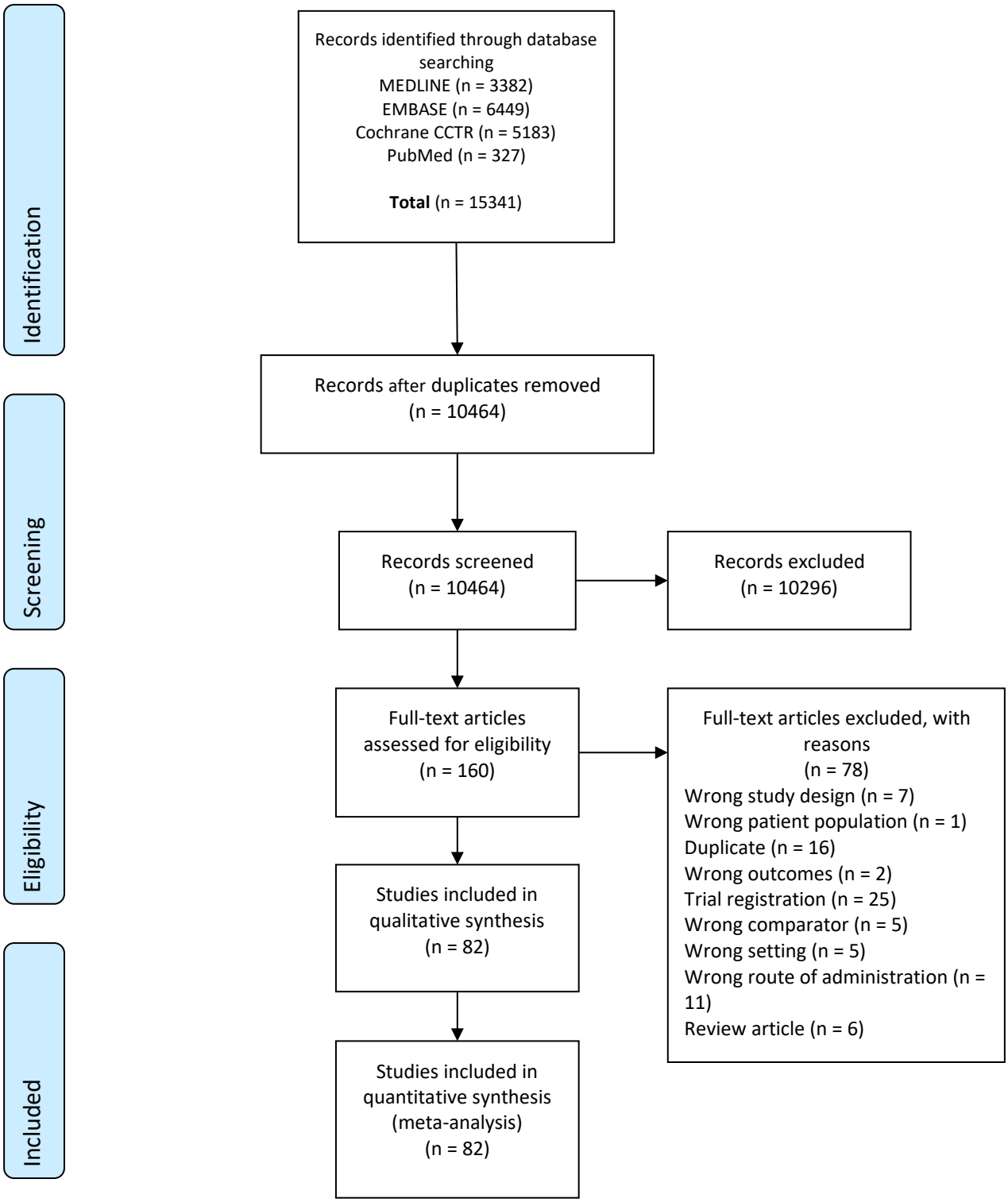


Figure 2. Network map for respiratory adverse events for x-node analysis. The size of the node corresponds to the number of patients randomized to that intervention. The thickness of the line and the associated numbers correspond to the number of studies comparing the two linked interventions.

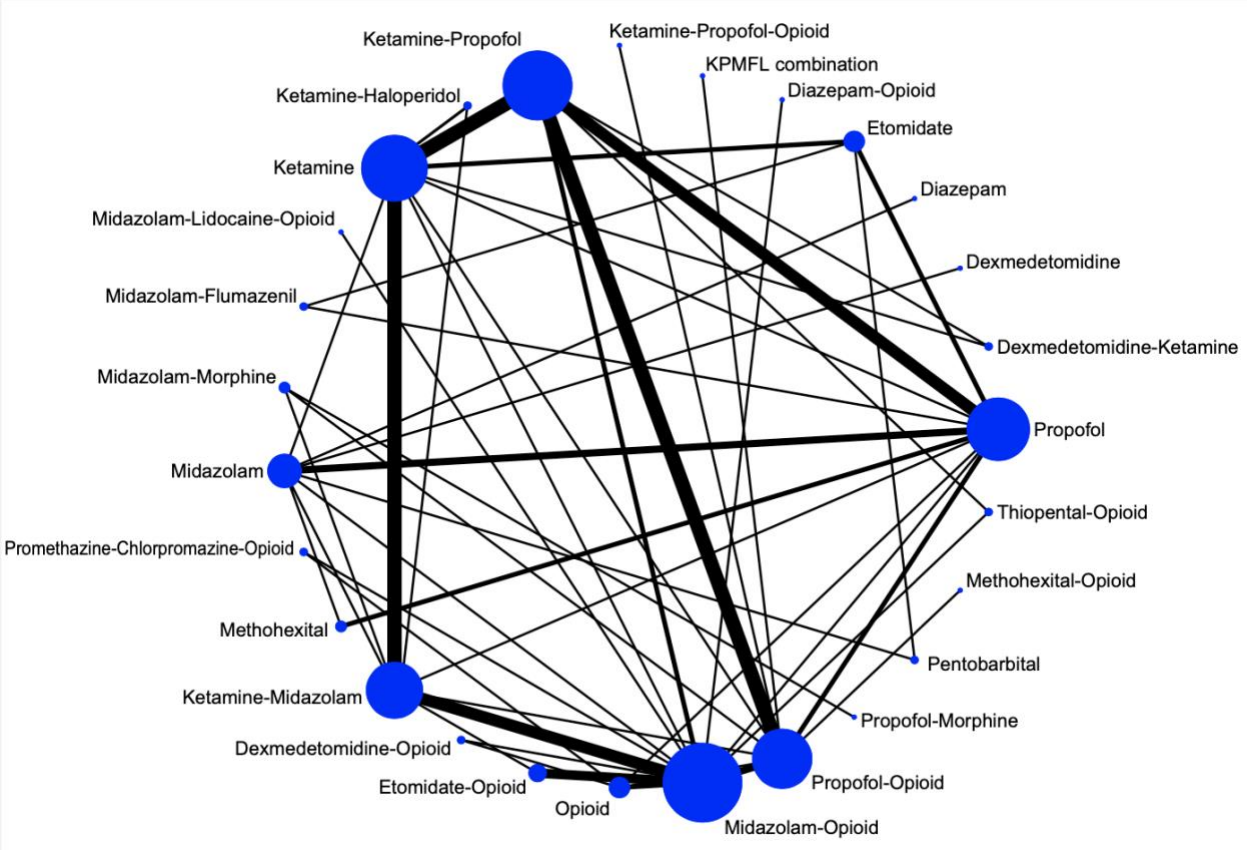
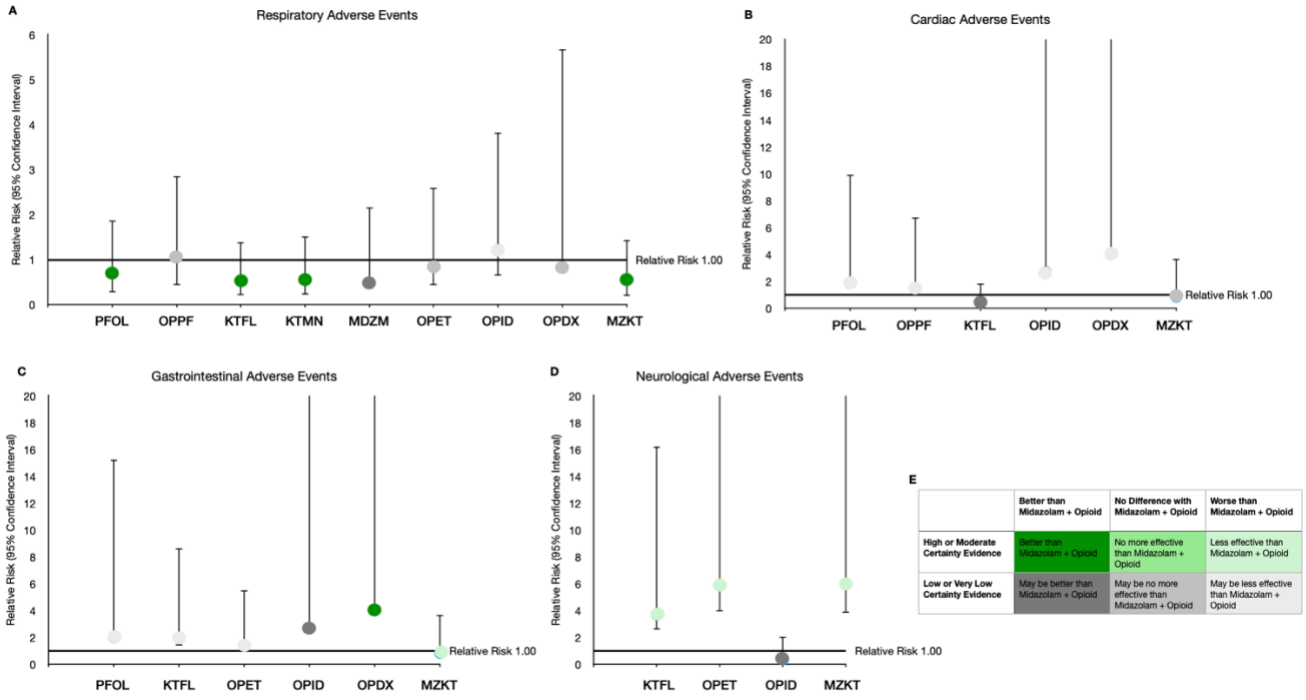


Figure 3. Network meta-analysis results based on GRADE certainty of evidence and treatment effectiveness for the comparisons of active treatments versus midazolam-opioid for the outcome of adverse events. A: Respiratory Adverse Events; B: Cardiac Adverse Events; C: Gastrointestinal Adverse Events; D: Neurological Adverse Events; E: GRADE certainty of evidence table and figure legend.



Abbreviations: PFOL, propofol; OPPF, opioid-propofol; KTFL, ketamine-propofol; KTMN, ketamine; MDZM, midazolam; OPET, opioid-etomidate; OPID, opioid; OPDX, opioid-dexmedetomidine; MZKT, midazolam-ketamine

Table 1. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for recovery time

Comparison	Direct Estimate MD (95% CI)	Indirect Estimate MD (95% CI)	Network Estimate[1] MD (95% CI)	GRADE	Narrative Summary
OPMZ v PFOL	21.7 (3.67,39.73)	14.72 (5.41,24.03)	16.34 (8.39,24.29)	High	Midazolam-opioids has a longer recovery time when compared to propofol
OPID v OPMZ	-5 (-25.23,15.23)	-18.59 (-37.34,0.16)	-12.06 (-25.38,1.27)	Moderate[2]	Opioids probably have a shorter recovery time when compared to midazolam with opioids
OPET v OPMZ	-9.94 (-27.03,7.14)	-18.49 (-34.64,-2.35)	-14.76 (-25.98,-3.53)	Moderate[2]	Etomidate-opioids probably has a shorter recovery time when compared to midazolam-opioids
MZKT v OPMZ	2.74 (-7.6,13.07)	14.33 (3.9,24.76)	8.29 (1.08,15.51)	Low[2,3]	Midazolam-ketamine may have a longer recovery time when compared to midazolam-opioids
KTFL v OPMZ	-6.93 (-23.99,10.13)	-11.34 (-19.68,-2.99)	-10.52 (-17.61,-3.43)	Moderate[2]	Ketamine-propofol probably has a shorter recovery time when compared to midazolam-opioids
KTFL v PFOL	8.35 (-0.17,16.87)	2.12 (-7.81,12.04)	5.82 (-0.37,12.01)	Low[3,4]	Ketamine-propofol may have a longer recovery time when compared to propofol
KTFL v OPPF	0.46 (-6.45,7.36)	11.03 (0.56,21.49)	3.10 (-2.29,8.48)	Moderate[2]	Ketamine-propofol probably has no difference in recovery time when compared to propofol-opioids
KTFL v KTMN	-3.59 (-13.69,6.52)	-5.04 (-15.32,5.24)	-3.57 (-9.85,2.71)	Low[2,3]	Ketamine-propofol may have no difference in recovery time when compared to ketamine
KTMN v PFOL	10.13 (-7.39,27.65)	9.97 (1.28,18.66)	9.39 (2.25,16.53)	Moderate[2]	Ketamine probably has a longer recovery time when compared to propofol
KTMN v OPPF	1.20 (-15.54, 17.94)	7.95 (-0.10, 15.99)	6.67 (-0.51,13.84)	Moderate[2]	Ketamine probably has a longer recovery time when compared to propofol-opioids
KTMN v OPET	4.9 (-12.97,22.77)	10.9 (-4.88,26.67)	7.81 (-3.50,19.12)	Moderate[2]	Ketamine probably has a longer recovery time when

					compared to etomidate-opioids
KTMN v MZKT	-8.14 (-18.35,2.08)	-21.6 (-32.1,-11.09)	-15.24 (-22.38,-8.09)	High	Ketamine has a shorter recovery time when compared to ketamine-midazolam
ETMD v KTMN	6.58 (-6.02,19.18)	-9.59 (-23.73,4.55)	-0.25 (-9.65,9.14)	Low[4]	Etomidate may have no difference in recovery time when compared to ketamine

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference; CI, confidence interval; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid; MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision
[3] Lowered for inconsistency
[4] Lowered two levels for very serious imprecisions

Table 2. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for respiratory adverse events

Comparison	Direct Estimate RR (95% CI)	Indirect Estimate RR (95% CI)	Network Estimate[1] RR (95% CI)	GRADE	Narrative Summary
KTFL v OPMZ	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 to opioid-midazolam
KTMN v OPMZ	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 to opioid-midazolam
MZKT v OPMZ	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 to opioid-midazolam
OPDX v OPMZ	1 (0.02,52.41)	0.84 (0.12,6.14)	0.84 (0.15,4.83)	Low[3]	Opioid-Dexmedetomidine may have no effect on respiratory adverse events compared to opioid-midazolam
OPID v OPMZ	0.88 (0.22,3.61)	1.5 (0.58,3.91)	1.22 (0.57,2.60)	Low[3]	Opioids may have more respiratory adverse events compared to opioid-midazolam
OPMZ v PFOL	0.69 (0.22,2.13)	1.71 (0.95,3.06)	1.41 (0.86,2.32)	Moderate[2]	Opioid-Midazolam probably has more respiratory adverse events compared to propofol
OPMZ v OPPF	0.81 (0.22,2.9)	0.85 (0.44,1.63)	0.95 (0.55,1.64)	Low[3]	Opioid-Midazolam may have no effect on respiratory adverse events compared to opioid-propofol
MDZM v OPMZ	0.09 (0.01, 0.89)	0.7 (0.19, 2.59)	0.49 (0.14, 1.67)	Low[3]	Midazolam may have no effect on respiratory adverse events compared opioid-midazolam
KTFL v PFOL	0.83 (0.53,1.29)	0.54 (0.29,0.99)	0.73 (0.52,1.02)	Moderate[2]	Ketamine-Propofol probably has fewer respiratory adverse events compared to propofol
KTFL v KTMN	1.03 (0.6,1.77)	1.18 (0.59,2.34)	0.94 (0.67,1.31)	Moderate[2]	Ketamine-Propofol probably has no difference in respiratory adverse events compared to ketamine
KTFL v OPPF	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 to opioid-propofol
DXKT v KTFL	0.71 (0.15, 3.39)	1.06 (0.47, 2.43)	0.97 (0.49,1.93)	Moderate[2]	Dexmedetomidine-Ketamine probably has no effect on respiratory adverse events when compared to ketamine-propofol
ETMD v KTMN	4.84 (1.8,12.99)	0.84 (0.45,1.58)	1.43 (0.73,2.79)	Low[2,4]	Etomidate may have more respiratory adverse events compared to ketamine
KTMN v PFOL	1.6 (0.89,2.87)	0.53 (0.33,0.85)	0.78 (0.51,1.18)	Low[2,4]	Ketamine may have fewer respiratory adverse events compared to propofol
KTMN v MDZM	0.96 (0.02,49.82)	0.97 (0.26,3.58)	1.13 (0.34,3.79)	Low[3]	Ketamine may have no difference in respiratory adverse events compared to midazolam
KTMN v MZKT	0.72 (0.37,1.42)	1.1 (0.5,2.44)	0.97 (0.60,1.58)	Moderate[2]	Ketamine probably has no difference in respiratory adverse events compared to midazolam-ketamine
KTMN v OPMZ	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 to opioid-midazolam
DXKT v KTMN	1.28 (0.25, 6.42)	0.85 (0.38, 1.88)	0.91 (0.46,1.80)	Moderate[2]	Dexmedetomidine-Ketamine probably has no effect on respiratory adverse events when compared to ketamine
KTMN v OPPF	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 to propofol-opioid

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk; CI, confidence interval; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid; MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate; OPDX, dexmedetomidine with opioids; DXKT, dexmedetomidine with ketamine

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision
[3] Lowered two levels for very serious imprecisions
[4] Lowered for incoherence

Table 3. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for cardiac adverse events

Comparison	Direct Estimate RR (95% CI)	Indirect Estimate RR (95% CI)	Network Estimate[1] RR (95% CI)	GRADE	Narrative Summary
KTFL v OPMZ	0.333 (0.014,7.88)	0.387 (0.088,1.694)	0.38 (0.10,1.43)	Low[3]	Ketamine-Propofol may have fewer cardiac adverse events compared to opioid-midazolam
MZKT v OPMZ	0.967 (0.236,3.964)	0.552 (0.051,5.909)	0.80 (0.24,2.69)	Low[3]	Midazolam-Ketamine may have no effect on cardiac adverse events compared to opioid-midazolam
OPDX v OPMZ	7.001 (0.373,131.382)	1.334 (0.021,83.063)	4.02 (0.37,43.87)	Very Low[4]	Opioid-Dexmedetomidine has an uncertain effect on cardiac adverse events compared to opioid-midazolam
OPMZ v PFOL	3.77 (0.158,90.033)	0.305 (0.06,1.555)	0.53 (0.12,2.25)	Very Low[4]	Opioid-Midazolam has an uncertain effect on cardiac adverse events compared to propofol
OPMZ v OPPF	0.441 (0.06,3.249)	1.142 (0.202,6.473)	0.69 (0.19,2.55)	Very Low[4]	Opioid-Midazolam has an uncertain effect on cardiac adverse events compared to opioid-propofol
KTFL v PFOL	0.155 (0.05,0.483)	0.345 (0.056,2.117)	0.20 (0.08,0.52)	High	Ketamine-Propofol has fewer cardiac adverse events compared to propofol
KTFL v KTMN	0.167 (0.02,1.412)	0.305 (0.016,5.766)	0.39 (0.11,1.38)	Moderate[2]	Ketamine-Propofol probably has fewer cardiac adverse events compared to ketamine
KTFL v OPPF	0.32 (0.159,0.643)	0.119 (0.017,0.83)	0.26 (0.14,0.50)	High	Ketamine-Propofol has fewer cardiac adverse events compared to opioid-propofol
DXKT v KTFL	2.00 (0.19, 20.93)	4.03 (0.04, 425.10)	2.37 (0.34,16.34)	Very Low[4]	DXKT has an uncertain effect on cardiac adverse events when compared to ketamine-propofol
KTMN v PFOL	1.063 (0.022,52.527)	0.912 (0.111,7.486)	0.51 (0.12,2.29)	Very Low[4]	Ketamine has an uncertain effect on cardiac adverse events when compared to propofol
KTMN v MZKT	0.969 (0.02,48.05)	2.986 (0.272,32.82)	1.21 (0.21,7.07)	Very Low[4]	Ketamine has an uncertain effect on cardiac adverse

					events when compared to midazolam-ketamine
KTMN v OPPF	0.16 (0.01, 2.46)	1.00 (0.23, 4.46)	0.67 (0.18,2.59)	Very Low[4]	Ketamine has an uncertain effect on cardiac adverse events when compared to opioid-propofol

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk; CI, confidence interval; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid; MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate; OPDX, dexmedetomidine with opioids; DXKT, dexmedetomidine with ketamine

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision
[3] Lowered two levels for very serious imprecisions
[4] Lowered three levels for very serious imprecisions

Table 4. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for gastrointestinal adverse events

Comparison	Direct Estimate RR (95% CI)	Indirect Estimate RR (95% CI)	Network Estimate[1] RR (95% CI)	GRADE	Narrative Summary
KTFL v OPMZ	1 (0.02,52.41)	2.13 (0.57,7.94)	1.97 (0.58,6.66)	Low[3]	Ketamine-Propofol may have more GI adverse events compared to opioid-midazolam
MZKT v OPMZ	3.07 (0.93,10.09)	3.11 (0.45,21.55)	3.08 (1.15,8.27)	High	Midazolam-Ketamine has more GI adverse events compared to opioid-midazolam
OPDX v OPMZ	1 (0.02,52.21)	0.01 (0,0.27)	0.07 (0.00,0.97)	Moderate[2]	Opioid-Dexmedetomidine probably has fewer GI adverse events compared to opioid-midazolam
OPET v OPMZ	1.17 (0.34,4.03)	3.15 (0.17,60.32)	1.35 (0.44,4.15)	Very Low[4]	Opioid-Etomidate has an uncertain effect on GI adverse events compared to opioid-midazolam
OPID v OPMZ	0.14 (0.02,1.25)	18.99 (0.14,2505.57)	0.32 (0.04,2.30)	Very Low[4]	Opioids have an uncertain effect on GI adverse events compared to opioid-midazolam
OPMZ v PFOL	0.42 (0.02,10.93)	0.58 (0.06,6.16)	0.50 (0.08,3.32)	Very Low[4]	Opioid-Midazolam has an uncertain effect on GI adverse events compared to propofol
KTFL v PFOL	1 (0.02,50.69)	1.03 (0.14,7.48)	0.99 (0.17,5.72)	Very Low[4]	Ketamine-Propofol has an uncertain effect on GI adverse events compared to propofol
KTFL v KTMN	0.44 (0.19,0.99)	0.62 (0.09,4.37)	0.48 (0.24,0.95)	Moderate[5]	Ketamine-Propofol probably has fewer GI adverse events compared to ketamine
KTFL v OPPF	1.7 (0.71,4.11)	1.68 (0.19,15.14)	1.52 (0.73,3.16)	Low[3]	Ketamine-Propofol may have more GI adverse events compared to opioid-propofol
KTMN v PFOL	1.06 (0.02,56.48)	2.67 (0.35,20.3)	2.06 (0.35,12.05)	Very Low[4]	Ketamine has an uncertain effect on GI adverse events compared to propofol
KTMN v MZKT	1.37 (0.58,3.22)	1.59 (0.21,11.9)	1.33 (0.63,2.82)	Low[3]	Ketamine may have more GI adverse events compared to midazolam-ketamine

KTMN v OPPF	2.18 (0.36, 13.25)	3.60 (1.29, 10.02)	3.16 (1.34,7.43)	High	Ketamine has more GI adverse events compared to Propofol-Opioid

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk; CI, confidence interval; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid; MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate; OPDX, dexmedetomidine with opioids; DXKT, dexmedetomidine with ketamine

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision
[3] Lowered two levels for very serious imprecisions
[4] Lowered three levels for very serious imprecisions
[5] Lowered for inconsistency

APPENDIX: SUPPLEMENTARY DATA & PRISMA NMA CHECKLIST

Pilot Study Protocol – Adjunctive ketamine sedation in critically ill patients (KANINE): a pilot randomized controlled trial

Objective of Pilot Study: Is it feasible to perform a large randomized controlled trial (RCT) in mechanically ventilated critically ill patients requiring sedation to investigate whether an adjunctive ketamine infusion versus placebo improves ventilator free days and other patient important outcomes?

Project Design, Methodology, & Analysis

Research question for the KANINE Pilot RCT

Is it feasible to perform a large RCT in mechanically ventilated critically ill patients requiring sedation to investigate whether an adjunctive ketamine infusion versus placebo improves ventilator free days and other patient important outcomes?

PICOT Question for Pilot

Population: Adults (≥ 18 years of age) in the ICU who are receiving invasive mechanical ventilation.
Intervention: Adjunctive ketamine infusion.
Control: Placebo (normal saline).
Outcomes: For the pilot RCT, the main outcomes are feasibility (consent rate, recruitment, protocol adherence). We will also examine all the clinical outcomes relevant for the larger RCT.
Type of study: Randomized, concealed, blinded, parallel-group feasibility pilot RCT

Research Question for the Main KANINE RCT

In adults (≥18 years of age) who have been intubated for longer than 24 hours, does the use of an adjunct intravenous ketamine infusion in addition to any non-ketamine first-line sedation agent versus placebo increase the primary outcome of VFDs at 28 days, and decrease the secondary outcomes of mortality at 28 days, delirium, delirium-free/coma-free days, sedation and analgesic requirements, ICU LOS, vasopressor requirements, tracheostomy, unplanned extubations, use of anti-psychotics for agitated delirium, and adverse events?

PICOT Question for Main KANINE RCT

Population: Adults (≥ 18 years of age) in the ICU who are receiving invasive mechanical ventilation.
Intervention: Adjunctive ketamine infusion
Control: Placebo (normal saline).
Outcomes: VFD at 28 days, 28-day mortality, delirium, delirium-free/coma-free days, sedation and analgesic requirements, ICU LOS, vasopressor requirements, tracheostomy, unplanned extubations, use of anti-psychotics for agitated delirium, and adverse events?

Pilot Study Design & Study Centers

This is a multi-centre, stratified, allocation-concealed, blinded parallel-group pilot randomized controlled trial. The primary outcome for this pilot trial will be feasibility as assessed by three outcomes of consent rate, recruitment parameters and protocol adherence. We plan to enroll patients at 3 study centers which are all academic teaching hospitals associated with McMaster University in Hamilton, Ontario (St Joseph's Hospital, Juravinski Hospital and the Hamilton General Hospital).

Patients

All patients will be screened for study eligibility 24 hours following their ICU admission. A dedicated research coordinator will be physically present in the ICU and will screen every admission for potential inclusion. On weekends or after-hours ICU clinical staff will perform

screening as availability allows. A screening log will be kept at each study center with all patients reviewed and reasons for study exclusion documented. All study centers have ICUs with at least 15 funded ICU beds providing considerable capacity and potential patients.

Inclusion Criteria

1. Adult patients (≥ 18 years of age) admitted to the ICU
2. Patients intubated for at least 24 hours
3. Patients have been mechanically ventilated for fewer than 5 days
4. Patients receiving any non-ketamine continuous sedative infusion and/or analgesic infusion

Exclusion Criteria

1. Pregnancy
2. Patients on neuromuscular blocking agent
3. End-stage Liver Failure (Child-Pugh C)
4. Patients undergoing palliation or comfort care
5. Patients with a pre-existing tracheostomy
6. Hypersensitivity to Ketamine
7. Patients admitted with intracranial hemorrhage or stroke

Informed Consent

When an eligible patient is identified, research coordinators will approach the patient's SDM to explain the objectives of the trial along with its potential risks and benefits. The informed consent will also include the study protocol description, potential benefits, expected length of the study, and the option to withdraw from the study at any time. The informed consent document will be presented at a grade eight level of language and will be available in multiple languages. Verbal consent from an SDM will be sufficient to enrol the patient into the study if written consent cannot be obtained. Furthermore, the research coordinator will be present to answer any questions prior to obtaining consent.

If we cannot find the appropriate SDM, we will enroll patients into the study using the deferred consent model. As ketamine is already extensively used in healthcare and has an excellent track record of safety, we believe deferred consent is an ethically sound model for this study [164]. Once the patients are extubated and are able to communicate, they will also be informed about the study that they were enrolled in by their substitute decision maker. Patients and SDMs will have the option to opt out at any point in the study. Should patients or SDMs choose to opt out of the trial, we will use the data collected up until that point unless requested otherwise. Once the study is complete, the participants will be informed of the results as part of the dissemination plan. This type of deferred consent model has been successfully used in critical care research [165].

Allocation & Randomization

Once the research coordinators have identified an eligible patient, they will log into our centralized data center. Once connected, computerized prompts will be given for preliminary identifying data. If eligibility criteria are met, the patient will be randomly allocated in a 1:1 ratio to either adjunctive ketamine or placebo (Figure 1).

Patients will be allocated using undisclosed variable block sizes through a central computer system on REDCap (www.project-redcap.org). Randomization will be stratified by site, and type of patient (medical versus surgical). REDCap will be used for randomization and it will automatically generate patient allocation. Research coordinators will screen eligible patients on a daily basis and will be blinded to treatment assignment. Once an eligible patient has been identified, consented, enrolled, and randomized, they will be started on intervention or placebo depending on allocation. The study drug and placebo will be prepared by the local pharmacist.

Experimental Interventions

All eligible patients assigned to the treatment group will receive an adjunct continuous ketamine infusion at a fixed dose of 0.50 mg/kg/hour. This will be added to the subject's existing sedative and/or analgesic regime that was selected by the bedside clinician (e.g. propofol and/or midazolam and/or dexmedetomidine and/or fentanyl). The dosing of the first-line sedative and/or analgesic infusion of choice will be titrated to achieve the desired Richmond Agitation Sedation Scale (RASS) at the discretion of the healthcare team (Figure 2).

If the patient's RASS is lower than the goal, the first-line sedative drug will be titrated down (Figure 3). If the goal RASS has still not been achieved after the first-line sedative agent has been stopped, the study drug will be discontinued (Figure 3). If the RASS remains lower than the goal, the healthcare team will re-assess the patient to rule out other causes for their decreased level of consciousness.

If the patient's RASS is higher than the goal, the first-line sedative drug will be titrated up as needed at the direction of the healthcare team. If the goal RASS has still not been achieved after the first-line sedative agent has been optimized (based on the discretion of the healthcare team), the study drug dose will not be adjusted (Figure 3). If additional sedation is needed, the healthcare team will have the option of using boluses of their primary sedative agent. If the goal RASS has still not been achieved, a third sedative or analgesic infusion may be added that is not ketamine.

The study drug would continue in this instance for a maximum of 28 days or until the patient is extubated or has died, whichever occurs first. If patients are re-intubated or re-admitted to the ICU, they would not be eligible to resume the trial or study drug. The drug will only run for 28 days as a maximum as most intubated patients at that point in time have either been extubated or transitioned to a tracheostomy [166]. If a patient undergoes a tracheostomy, the study drug will stop.

Control Interventions

The placebo used in this study will be normal saline in a 150mL saline bag that will look identical to ketamine infusion. As ketamine is colourless, the two will be visually indistinguishable. Healthcare providers will follow the same sedation titration chart outlined in Figure 3 and in the Experimental Interventions section.

If control patients inadvertently receive ketamine, they will still be analyzed as part of the intention-to-treat analysis plan. If the healthcare team chooses to use an open-label ketamine infusion as part of their treatment plan, the study drug would be held in that circumstance until the open-label ketamine had been stopped. If the healthcare team chooses to use open-label bolus dosing of ketamine, the study drug would continue.

Blinding

Patient allocation will be blinded to treating physicians, nurses, patients, the statisticians, site investigators, and the research coordinators collecting the data. The group allocation will be stored in an electronic case report form that will be password protected. As ketamine is colourless, it will be indistinguishable to the placebo upon visual inspection; this will minimize the ability of the healthcare team to discern which treatment their patient is allocated to. Moreover, study adjudicators and data analysts will also be blinded to further reduce bias.

At periodic intervals, the drug labelling processes will be audited by the Methods Center to confirm its accuracy and to ensure that blinding is maintained. This information will help determine whether our blinding technique is working effectively and whether it needs further adjustments for the larger RCT.

An emergency phone number to the 24-hour Methods Center will be available at all centers should emergent unblinding be required. This will only be allowed if the treating physician is sure that the results will change the clinical management of the patient.

Outcomes

Pilot Study Primary Feasibility Outcomes

The primary outcome for the KANINE Pilot Trial is feasibility, which will be judged by 3 outcomes of recruitment parameters, consent rate, and protocol adherence.

Enrolment/Recruitment rate: We define a successful recruitment rate of 1 patient per centre per month over the duration of the trial. The recruitment will be reviewed weekly and the records will be screened monthly. This will be done to ensure that enrolment is being maximized and that any barriers are being addressed. A recruitment metric will be measured and interpreted at the end of the trial. Excluded patients and eligible non-randomized patients will be reviewed to determine whether any modifications to the protocol may be warranted, or to address implementation challenges. Barriers to enrolment will be discussed and strategies to improve enrolment will be operationalized, if needed.

Consent rate: We will define >75% consent rate as successful. This will be calculated as the overall proportion of patients/substitute decisions makers (SDMs) who consented to the trial out of everyone who was approached. As we are planning for deferred consent, there will be a lag time between study enrolment and consent. If a patient or SDM chooses to withdraw from the study but allows for the data that had been collected up until that point to be used for analysis, they will still be counted as not providing consent. Reasons for withdrawal will be recorded. The consent rate will be reviewed weekly and any barriers to consent that are identified will be addressed to improve the consent process.

Protocol adherence: We will define ≥75% protocol adherence as successful. The adherence will be calculated as the number of patients who received ketamine as an adjunctive sedation per study day over all the patients enrolled in the experimental arm of the study. Minor deviations, such as physicians holding sedation for clinical reasons, will be deemed to be adherent to the protocol. The research coordinator will review the chart to determine the actual compliance, and document all the reasons for non-compliance of both the control and experimental arms of the study. Receiving open-label ketamine as a bolus will not be deemed as a protocol violation. Furthermore, the study drug being discontinued in a patient no longer requiring sedation and then re-started in the same patient would also not be deemed a protocol violation. If the study drug is stopped outside the parameters of drug titration as allowed by the protocol, this would constitute as a protocol violation. Adherence will also be reviewed monthly and the reasons for compliance failure will be investigated and recorded as a protocol violation. Further behavioural strategies will be employed to improve adherence, if needed.

Pilot Study Secondary Clinical Outcomes

In the main KANINE trial, we will aim to determine whether the use of an adjunctive ketamine infusion to any first-line sedative infusion compared to placebo in mechanically ventilated ICU patients has an impact on patient important outcomes. These outcomes will be captured in this pilot study but we will not have enough patients and therefore will not analyze based on allocated group.

- Ventilator-free days at 28 days
- 28-day mortality
- ICU mortality
- Hospital mortality
- Delirium using the validated the Confusion Assessment Method for the ICU (CAM-ICU) score [167]
- Delirium-Free/Coma-Free Days
- Sedation requirements over ICU stay (total dosage and weight-based dosage)
- Analgesic requirements over ICU stay (total dosage and weight-based dosage)
- ICU length of stay
- Hospital length of stay
- Adverse events (Arrhythmias [atrial flutter/fibrillation, ventricular fibrillation, ventricular tachycardia], vomiting)
- Tracheostomy

- Unplanned extubation
- Use of anti-psychotics for agitated delirium
- Vasopressor requirement (weight-based mean dose)

Pilot Study Adjudication

An adjudication committee composed of ICU clinicians will be formed for this pilot trial. This committee will adjudicate situations in which uncertainty exists regarding protocol violations (our primary feasibility outcome). These situations will be identified by the steering committee or the individual site research coordinators. Clinical charts will be reviewed to better clarify whether violations occurred.

Subgroups

The following are the proposed subgroup populations:

1. Patients with respiratory failure (defined as the failure of the gas exchange functions of the lungs resulting in hypoxemia [PaO2 < 80mmHg] and/or hypercapnia[PaCO2 > 45mmHg]) [168] versus those without respiratory failure. We hypothesize that ketamine would have a more pronounced treatment effect in patients with respiratory failure because of its mechanism of causing bronchodilation [10].
2. Patients admitted with shock (defined as requiring vasopressor or inotropic support) versus those without shock. We hypothesize that ketamine would have a more pronounced treatment effect in patients with shock because of its sympathomimetic properties allowing for the preservation of cardiac output [10].
3. Age ≥ 70 years versus those younger than 70 years of age. We hypothesize that ketamine will have a more pronounced treatment effect in patients older than 70 years of age as there is evidence that the use of ketamine can lower the doses of narcotics used in patients [169]
4. Acute physiology and chronic health evaluation (APACHE II) score ≥ 20 versus APACHE II score < 20. We hypothesize that ketamine will have a more pronounced treatment effect in patients with APACHE II scores ≥ 20 due to its anti-inflammatory properties [42].

Pilot Study Data Collection

Trained research coordinators at each site will screen and log patients admitted to the ICU on a daily basis. They will record the following on pre-established data abstraction forms that will be transcribed into a web-based case report form on REDCap (http://www.project-redcap.org) that will be encrypted and password protected: 1) Number eligible; 2) Number eligible and enrolled; 3) Number eligible but not enrolled (including the reason why); 4) Number excluded (including the reason why); 5) Number lost to follow-up; 6) Admission diagnosis; 7) Baseline demographic data. The online database we plan to use fully complies with FDA and Health Canada rules for electronic data management. No data that could lead to study patient identification will be entered. The paper data abstraction form will be stored in a locked facility at each center for safe storage.

For up to 28 days post randomization, local research coordinators will review the charts of the patients enrolled into the study and collect the following data: baseline characteristics (demographics, admission diagnosis, sedative medication use and dose, analgesic medication use and dose, vasopressor use and dose), daily clinical data (duration of mechanical ventilation, mortality, delirium (defined by the CAM-ICU score), tracheostomy, unplanned extubations).

The electronic case report forms will be tested for clarity and ease of use prior to the commencement of the trial. This web-based form will allow for data validation, consistency checks and frequent audits of entered data to ensure they are complete and accurate. The paper forms will always be available as backup or to check against potential errors. Furthermore, these forms will be subjected to frequent data audits to ensure data is complete and entered accurately. The methods centre at McMaster will manage the database and quality assurance using anomaly searches and logic checks. Real-time data entry will ensure missing data is identified quickly and issues are resolved in a timely manner. Inquiries will be made to study centres that are slow to enter data or enter inconsistent data with helpful remediation recommendations offered. Records and paper forms will be kept for the duration as required by local regulatory bodies.

Statistical Analysis

KANINE Sample Size

The sample size for the pilot was calculated using a 95% confidence interval approach for examining protocol adherence. Protocol adherence is defined as the number of patients who received ketamine as an adjunctive sedation per study day over all the patients enrolled in the experimental arm of the study. The lower bound for the confidence interval was set at the threshold for feasibility (75%) and an expected adherence rate (90%) was selected based on previously published RCT [170]. Using a power of 80%, the require sample size is at least 48 patients. To be conservative, we will plan for 54 patients (approximately 27 per study arm). We performed similar calculations for the consent rate outcome using a feasibility threshold of 75% and an expected consent rate of 90% leading to an identical sample size number.

KANINE Pilot Study Analysis

Calculation of the three feasibility outcomes for the KANINE trial are noted in the outcomes section above. No interim analyses are planned for the pilot study due to the short duration and small number of patients planned.

Full KANINE Study Analysis

The analysis performed for this trial will be according to the intention-to-treat (ITT) principle and will be done by a blinded statistician. This is the suggested analytical method for RCTs as per the CONSORT statement [171]. The baseline characteristics comparing the ketamine and placebo groups will be reported using means (and standard deviations), medians (and inter-quartile ranges) or proportions, as indicated.

For the outcome of VFDs, we will use the Wilcoxon test to compare their distribution between two treatment groups. We will assume that the probability of death and the extubation

are constant over the first 28 days of treatment. The mean mortality of the patients will be assumed to be 30% based on prior clinical trials examining critically ill patients [172]. For the continuous secondary outcomes of ICU LOS, sedation and analgesic requirements, and vasopressor requirements, we will test the null hypothesis that the means of both groups are equal for each outcome using the independent two-sample two-sided t-test (H_0: $\mu_{control}=\mu_{intervention}$). For the secondary outcome of mortality, Kaplan-Meier curves will be plotted to assess the time from randomization to death, censored at 28 days. Between group comparisons will be assessed with the log-rank test.

For the categorical variables of delirium, physical restraint use, tracheostomy, unplanned extubation, and adverse events, we will calculate the association using the Chi-squared (χ^2) test. The Fischer's exact test will be used if an expected value of less than 5 in more than 20% of cells in the chi squared table. The analyses will be reported as odds ratios with 95% confidence intervals. A P value of less than 0.05 will indicate statistical significance for all analyses.

Pilot Study Data & Safety Monitoring

The trial steering committee will be responsible for reviewing any identified severe adverse events (SAEs). Our plan is for the same DSMB to carry over to the larger KANINE trial.

Pilot Study Trial Administration

Dr. Sameer Sharif is the principal investigator of this trial and will lead the steering committee with his mentors and research manager. Members of the steering committee will include world renowned health research methodologists, experienced individuals who have performed large-scale multi-centre, international ICU clinical trials, as well as expert clinical biostatisticians. In addition to being clinical experts, many of individuals on the steering committee will have performed Canadian Institutes of Health Research (CIHR) funded clinical trials. Dr. Bram Rochwerg has agreed to being part of the steering committee. Dr. Rochwerg has multiple CIHR funded RCTs currently being performed.

The trial steering committee will meet every 3 months via teleconference and will review all pertinent details including but not limited to: site recruitment, enrolment, screening logs, blinded data to ensure completeness, any issues that have arisen. Dr. Sharif will meet with the study co-ordinator weekly, and will be responsible for overall start-up and study management.

Dr. Sharif will be responsible for starting the clinical trial and recruiting local site principal investigators (PIs) who will manage the trial at the local level. This includes local REB approval, hospital approval, ensuring pharmacy cooperation and ensuring all parties are properly trained. Once the contracts are signed, the respective site will receive a written confirmation from Dr. Sharif that they can begin to enrol patients. The steering committee and central Methods Center staff will closely support local PIs. At the time of center initiation all relevant paperwork and standard operating procedures (SOPs) will be supplied to the local PI. Dr. Sharif and the study co-ordinator will provide on-site training sessions for the local PIs and study co-ordinators in terms of study protocols and data collection procedures. Educational material will be offered to the local PI and research staff to facilitate education of other clinicians at participating hospitals.

Additional meetings with local site investigators and research coordinators will be planned at least every 6 months to review study updates and recruitment numbers. A study delegate will be available to answer any questions 24 hours a day, 7 days a week. The KANINE pilot trial will be registered on clinicaltrials.gov.

Pilot Trial Feasibility & Funding

Dr. Sharif is a co-applicant on a CIHR funded RCT examining the role of dexmedetomidine in critically ill patients undergoing non-invasive positive pressure ventilation. He has also led systematic reviews and meta-analyses, some of which examined the role of ketamine in acutely ill patients (see Appendix). He is a research fellow, practicing intensive care clinician and has significant protected research time to dedicate to completing this trial. He has completed a Master's degree in Health Research Methodology at McMaster University with a focus on RCTs, meta-analyses and clinical practice guideline methodology.

The co-investigators who will be part of the steering committee will include experienced ICU trialists with a plethora of experience conducting pilot RCTs like this [173]. They will act as mentors and provide guidance for the principle investigator throughout the trial. The centers which we plan to recruit to participate in KANINE have all previously participated in trials administered by members of the steering committee and have established research infrastructure and teams. Our centralized data center has collaborated on many ICU trials. We have extensive experience using REDCap and will work with our statisticians and data analysts closely.

Ethical Considerations

This trial will adhere to the Helsinki Declaration and all local and national laws for each participating centre. The protocol will be submitted for approval at each participating centre's institutional review board as well as Clinical Trials Ontario. Center enrolment will only begin after approval by each local REB. The vast majority of patients will be unable to provide consent at the time of enrolment. Patients will be enrolled using deferred consent; however, patients will only be continued in the trial if they or a suitable SDM provides consent in a timely manner. If consent is not obtained then the patient will be removed from the trial, although data will be retained up until this point. Given that most patients will be unconscious at the time of enrolment they represent a potentially vulnerable population. This trial could not be performed in conscious patients and excluding these patients from studies would have a deleterious effect on our ability to treat this condition at a population level. All study personnel will complete the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics to review health records. All personal information will be safeguarded within the confines of a locked room and there will be no personal information on REDCap.

Knowledge Translation

The early knowledge translation plan for KANINE will include engaging all multi-disciplinary groups at the participating centers (physicians, pharmacists, nurses, etc) via email

and presentation of research rounds on the importance of this topic and the protocol of the study planned. An abstract and information poster will be circulated to all participaiting centers.

The later knowledge translation plan will involve the production of a manuscript summarizing the results which we will disseminate in a high-impact peer-reviewed scientific journal. We will present our results locally, in conferences nationally and internationally. We will also present our findings through social media and online medical education blogs. If deemed feasible, the pilot trial will inform a large-scale RCT designed to inform clinical practice. The trial will also have its own website and twitter account providing updates on trial progress.

Figure 1. Flowchart outlining the trial design.

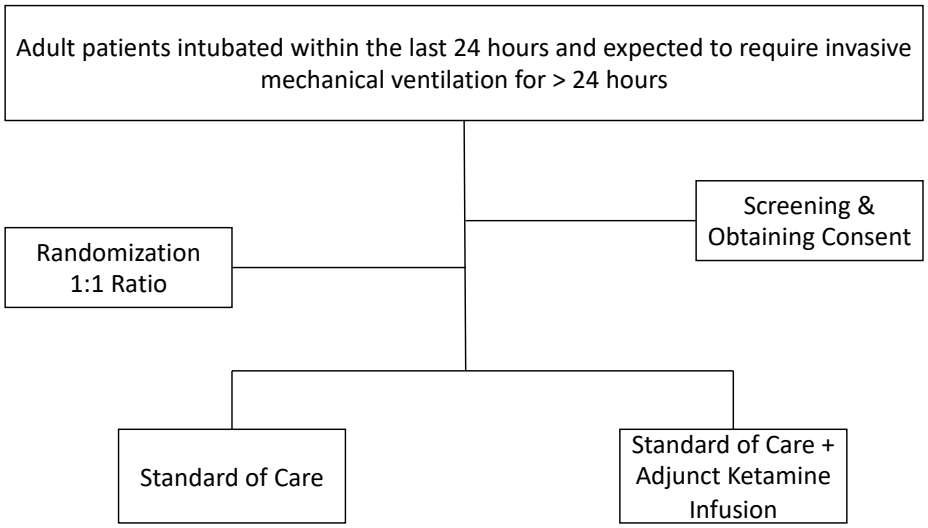
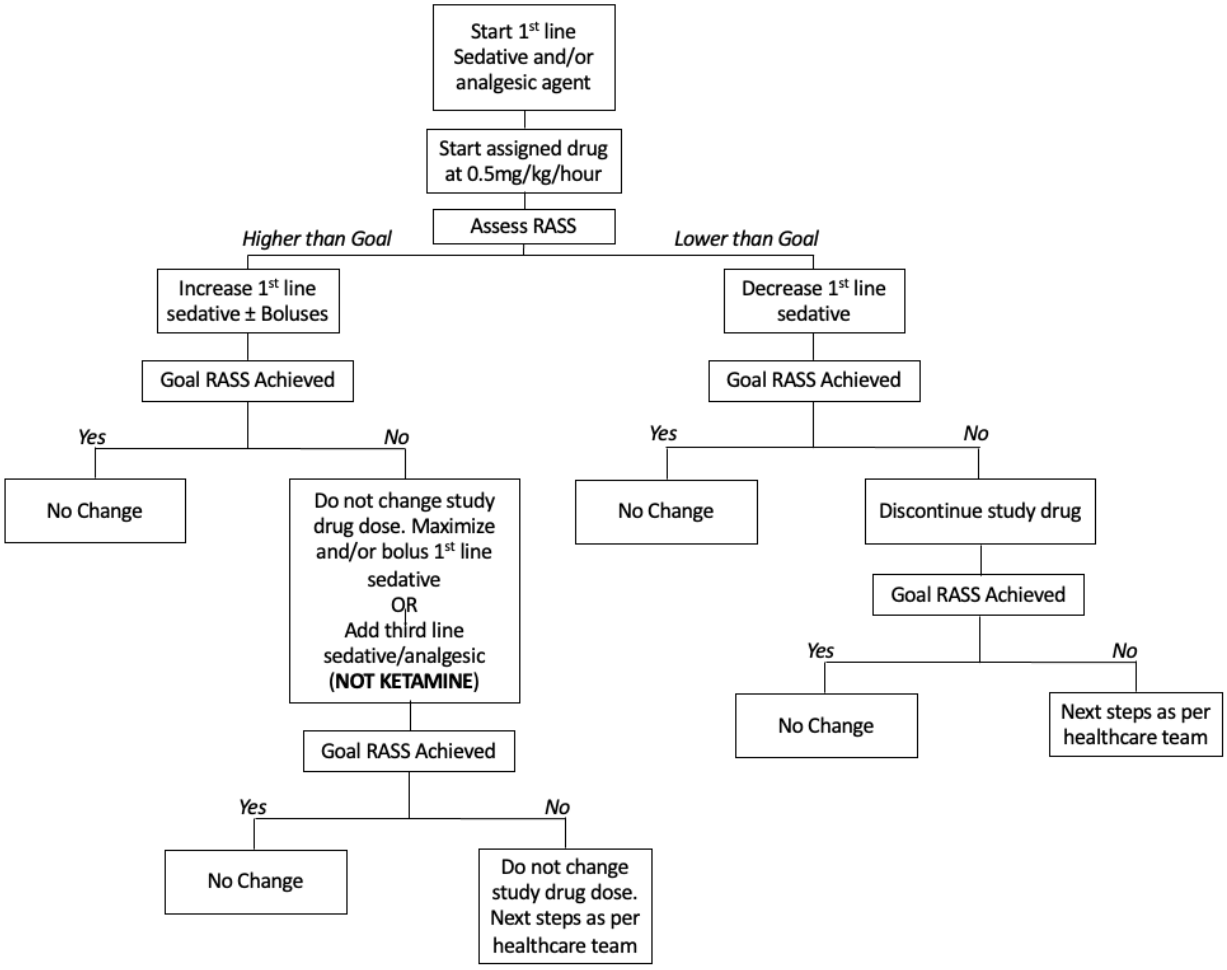


Figure 2. Richmond Agitation and Sedation Scale.

RASS (Richmond Agitation Sedation Scale)		
4	Combative	Overtly combative, violent, immediate danger to staff
3	Very agitated	Pulls or removes tubes or catheters; aggressive
2	Agitated	Frequent non-purposeful mvmt, fights ventilator
1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Sustained awakening to voice (≥10sec)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)
-3	Moderate sedation	Movement or eye opening to voice but no eye contact
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
-5	Cannot be aroused	No response to voice or physical stimulation

Figure 3. Sedation protocol flowchart for all patients included in the trial.



Abbreviations: RASS (Richmond Agitation Sedation Scale)

DISCUSSION – METHOGOLODICAL ISSUES & THESIS CONCLUSIONS

Manuscript # 1

Given the lack of data examining the use of ketamine as a continuous sedative infusion in the ICU, particularly in Canada, it was important to get a national perspective on this important question. In this manuscript, we highlight the values and preferences of Canadian Intensivists with respect to the use of ketamine in the ICU. This first step was necessary to lay the groundwork of our planned RCT evaluating the topic and to understand which outcomes clinicians think that patients value.

In performing this survey, we had to deal with a number of important methodological issues. The response rate for the survey was low at 22%. The initial response rate was even lower (16.2%) and we were able to address this limitation by redistributing the survey multiple times (more than initially planned) which included a prolonged period of survey response. The reasons for the low response rate were likely multifactorial, although primarily related to increased burnout amongst intensivists during the pandemic (39), a phenomenon that has been well noted with declines in post-pandemic survey response rates (40). Given the concern about temporal changes in beliefs, especially during the evolving pandemic, we compared the initial survey responses to the re-sent responses which were completed 8 months later, and did not note any important differences. However, given the insufficient numbers, it is possible that there was an important trend that we were not able to see due to imprecision.

One other limitation of this survey was that it was distributed to clinicians, and as a result, the outcomes that were reported to be of interest for a future RCT were those most thought to be important to patients. This is in contrast to outcomes selected by patients that they deem to be most important. This is a limitation as there is a push in the Critical Care literature to select outcomes that are patient-important [174]; moreover, despite clinicians selecting outcomes that they think are most important, getting patient perspectives serves as a gold standard. To remedy this, our RCT outcomes were selected in accordance with the SCEPTER-III recommendations which were created with patient partners [175].

Also, there may have been response bias, including the over-representation of academic ICU physicians. In this survey, 72% of respondents reported practicing in an academic ICUs which at first seemed high however, based on census data we found this is only slightly higher than a Canadian medical Association poll reporting that 59% of all intensivists in Canada work at an academic teaching hospital (38).

Manuscript #2

In this manuscript (Manuscript #2), we summarize the evidence examining ketamine for periprocedural sedation. As is evident from Manuscript #1, there is a lack of direct evidence of ketamine use as a continuous sedative in the ICU; as such this manuscript evaluates indirect evidence of ketamine in acutely ill patients.

There were a few methodological issues noted with this review. From a data interpretation perspective, there were a multitude of nodes and comparisons that made it challenging to present the data in such a way that readers could use this information at the bedside. For instance, for the outcome of respiratory adverse events, there were 27 nodes and 44 comparisons. To address this, we employed the use of a NMA summary of findings table as recommended by the GRADE group [176]. In addition to creating these tables, we created novel figures that incorporated the relative risks, confidence intervals, as well as the GRADE certainty of evidence. This unique figure serves as a valuable tool to use at the bedside when managing patients.

From an outcome perspective, despite adhering to GRADE standards and initially selecting 6 outcomes in our NMA protocol, the sheer volume of the results made it a challenging endeavour to present comprehensively. As a result, we reported the most relevant patient-important outcomes by focusing on adverse events and patient satisfaction. Furthermore, we also planned to perform 6 subgroup analyses. Given the sheer volume of data, interpreting these results were a challenge. To remedy this, we used the ICEMAN tool and decided what constituted a credible subgroup effect when performing our analyses [177].

Given that this NMA included multiple comparisons as outlined above, and some of the medications used in the study were used in combination with variable populations and definitions of certain outcomes, intransitivity was introduced. Intransitivity specifically arises from important differences in population, intervention, comparator, and outcome characteristics between studies that inform an indirect comparison of the intervention effects [178]; given our NMA had 82 studies, there were notable differences in all the aforementioned characteristics. As a result, our indirect estimates may have been biased. We addressed this by identifying potential effect modifiers and judging their credibility, strength, and how they were distributed across the contributing direct evidence [178]. Importantly, we took the other GRADE domains into account in addition to intransitivity when evaluating the certainty of the evidence to avoid double counting the limitations of the evidence.

Other notable limitations of this NMA include the lack of critically ill patients. There were only 4 ICU studies included in the review. As such, we were unable to draw conclusions in the critically ill population. Additionally, a pre-planned subgroup analysis could not be conducted when comparing ICU patients to non-ICU patients due to a lack of available data. In addition, many of the outcomes had either low or very low certainty of evidence due to imprecision and wide confidence intervals. However, we accounted for this limitation by using the GRADE approach to assess the certainty of evidence.

KANINE Pilot Protocol

Our survey study demonstrated that although ketamine is used as a continuous sedative under certain clinical circumstances, many physicians are not comfortable with its use and have particular concerns regarding possible psychotropic side-effects and delirium. There are no RCTs

examining the safety and efficacy or ketamine as continuous sedative in the ICU; as such, we evaluated all the indirect evidence available on procedural sedative drugs in acutely ill patients. Ketamine was associated with the fewest respiratory adverse events but did have more neurological and gastrointestinal adverse events. Given that the use of ketamine as a continuous sedative is very different from its one-time use for procedural purposes, we present a protocol for a pilot RCT addressing this question. This pilot is being planned as an initial step to demonstrate feasibility to inform a larger RCT. This pilot proposal will be submitted for peer-reviewed funding in the fall of 2023.

The following methodological issues of this pilot RCT need to be addressed:

1. Feasibility Design – the primary outcome of the pilot study will be feasibility. This will be assessed by the three outcomes of consent rate, protocol adherence, and recruitment rate. Large scale RCTs examining continuous sedatives in the ICU have successfully been conducted around the globe; given our centers have not done this locally, we felt it was important to prove feasibility before moving on to a large-scale RCT. Furthermore, successfully completing this pilot will improve our chances of getting funded for a larger study.
2. Powering a Pilot Study – there are several ways to calculate a sample size for a pilot study, and unfortunately, there is no gold standard. Given our aim for this pilot study was to examine protocol adherence, we used a 95% confidence interval approach. Specifically, the lower bound for the confidence interval was set at the threshold for feasibility and we used a previously published RCT to determine an expected adherence rate (90%) [170]. We then used a power of 80% to determine our sample size and utilized this same method for the outcome of consent rate.
3. Pragmatism & Limiting Bias – We opted to create a blinded study to limit bias. As a result, we had to create a protocolized way for participating centers to utilize ketamine as an adjunctive sedative medication. With protocolized care comes added complexity which limits the pragmatism of this trial. In an effort to balance limiting bias and increasing pragmatism, we created a clinician friendly protocol that would mimic the use of sedative infusions at the bedside. As such, with a simplified protocol for use at the bedside along with the use of a placebo, we were able to balance introducing bias and limited pragmatism in this study.
4. Outcome Selection – with respect to the selected clinical outcomes, we selected patient-important outcomes guided by the SCEPTER-III recommendations for designing studies assessing sedation in critically ill patients [175]. Given our population of interest were patients in receipt of invasive mechanical ventilation, we opted to assess the effect of ketamine on their ability to be liberated from the ventilation. Specifically, we chose to measure ventilator-free days, a composite outcome, as opposed to duration of mechanical ventilation. We selected this composite outcome as it incorporates death whereas the outcome of duration of mechanical ventilation is at risk of providing us with skewed results as patients who die on mechanical ventilation would have a shorter duration of mechanical ventilation. This outcome is inherently at odds with itself, as early

mortality would show a favourably short duration of mechanical ventilation, but so too would being extubated early in their clinical course.

5. Protocol Adherence – ketamine is used as a continuous sedative by some ICU physicians based on certain clinical circumstances. Despite the practical design of this study protocol, violations are possible. We will be strictly documenting when any violations occur and try to determine their reasons. Prior to initiating our study at a specific site, we will discuss the project with the attending physicians to ensure they have a good understanding of the protocol. We are also planning for in-grant knowledge translation to educate practitioners and ensure study compliance and understanding. Furthermore, safety criteria are built into the protocol whereby if a patient needs to be sedated rapidly, the healthcare team has the option of blousing their first-line sedative or even adding a third agent as needed. Our hope is that the built in safety criteria will limit protocol violations.
6. Knowledge Translation – the results of this trial will be disseminated using a multimodal approach that is above and beyond the traditional conference presentation and manuscript publication. Specifically, we will create online medical educational content on popular blogs, create podcasts, and use social media (i.e. twitter) to disseminate our findings. Moreover, we will also liaise with critical care societies to incorporate our findings in the next clinical practice guidelines on the topic. We are already in the midst of applying for specific knowledge translation grants to achieve our goal.

Final Conclusions

The objective of this thesis was to gather and evaluate available evidence on ketamine to inform the start-up of a pilot RCT examining the safety and efficacy of ketamine as a continuous sedative infusion in the ICU. We employed a comprehensive approach by surveying ICU physicians in Canada and then performed a systematic review and network meta-analysis to find indirect evidence on the safety and efficacy of ketamine as there is limited direct evidence. Finally, we propose a pilot study that will investigate the feasibility of a larger RCT attempting to address this question.

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Supplementary Appendix

Supplement to: Sharif S, Kang J, Sadeghirad B, Rizvi F, Forestell B, Greer A, Hewitt M, Fernando SM, Eltorki M, Siemieniuk R, Duffett M, Bhatt M, Burry L, Perry J, Petrosoniak A, Mehta G, Pandharipande P, Welsford M, Rochwerg B. Procedural sedation and analgesia in the emergency department and intensive care unit: A Systematic Review and Network Meta-analysis.

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Abbreviations

Treatment	***Abbreviations***
Dexmedetomidine	DXMT
Diazepam	DZPM
Etomidate	ETMD
Diazepam-Fentanyl	FNDZ
Ketamine-Midazolam-Fentanyl	KMDF
Fentanyl (LD), Propofol, Midazolam, Ketamine and lidocaine combination	KPMF
Ketamine-Propofol-Fentanyl	KPRF
Ketamine-Propofol (ketofol)	KTFL
Haloperidol-Ketamine	KTHL
Ketamine	KTMN
Midazolam-Fentanyl-Lidocaine	LMDF
Midazolam (with Flumazenil)	MDFM
Midazolam-morphine	MDMO
Midazolam	MDZM
Meperidine-promethazine-chlorpromazine	MPCL
Methohexital	MTHX
Ketamine-Midazolam	MZKT
Dexmedetomidine-Opioid	OPDX
Etomidate-Opioid	OPET
Opioid	OPID
Midazolam-Opioid	OPMZ
Propofol-Opioid	OPPF
Propofol-lidocaine	PFLD
Propofol-morphine	PFMP
Propofol	PFOL
Pentobarbital	PNTB
Methohexital + remifentanil	RMMT
Thiopental-Fentanyl	TPFN

Appendix 1. MEDLINE, EMBASE Search Strategy

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:
---
1 Conscious Sedation/ (9149)
2 sedation.mp. (44204)
3 or/1-2 (44204)
4 critical care/ or early goal-directed therapy/ (54836)
5 Critical Illness/ (31882)
6 intensive care units/ or burn units/ or coronary care units/ or recovery room/ or respiratory care units/ (67241)
7 Intubation, Gastrointestinal/ (9841)
8 monitoring, physiologic/ or hemodynamic monitoring/ (56467)
9 exp Cardiac Surgical Procedures/ (225791)
10 exp Shock/ (78152)
11 exp Multiple Trauma/ (13103)
12 Resuscitation/ (26878)
13 exp Ventilators, Mechanical/ (9475)
14 ((critical* or intensive or tertiary) adj3 (care or ill* or therap*)).mp. (341168)
15 (serious* adj injur*).mp. (4905)
16 (severe adj (traum* or shock)).mp. (9883)
17 ((preoperative or intraoperative or perioperative) adj (care or procedure* or period)).tw. (17056)
18 ventilat*.mp. (198611)
19 ((cardiac or thoracic or heart) adj3 (surgery or surgical)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (128980)
20 ((severe or serious or critical*) adj3 (ill* or injur* or trauma*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (140899)
21 (shock or ICU or polytrauma).mp. (298785)
22 ((digestive* or gastro* or gastric* or nasogastr*) adj3 intubate*).mp. (68)
23 ((physiologic* or hemodynamic* or hemo-dynamic* or haemodynamic* or haemo-dynamic*) adj3 monitor*).mp. (63717)
24 or/4-23 (1152570)

25 exp Emergency Service, Hospital/ (84306)
26 Emergency Medical Services/ (44241)
27 (emergency or emergencies).af. (480566)
28 (trauma adj3 (center* or unit*)).mp. (22930)
29 or/25-28 (495060)
30 24 or 29 (1558015)
31 Propofol/ (15241)
32 (Propofol* or 2,6 diisopropylphenol or anepol or anesia or cryotol or diisoprofol or diprivan or diprofol or disoprivan* or disoprofol or fresofol or gobbifol or hiremon or ici 35 868 or ici 35,868 or ici 35868 or ivifol or plofed or pofol or profast or propocam or propolipid or propoven or provive or rapinovet or rapiva or recofol or ripol or safol or spifol or spiva or unifol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23503)
33 Fentanyl/ (13958)
34 (Fentanyl or ap 48 or ap48 or duragesic or durogesic or epufen or fentalis or fentamat or fentamyl or fentanex or fentanyl or fentanest or fetanex or fentanyl or fentora or leptanal or mezolar matrix or pecfent or phentanyl or r 4263 or r4263 or rapinyl or recuvyra or sublimaze or subsys or tanyl or tilotrans or transfenta).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23591)
35 Midazolam/ (9056)
36 (Midazolam or adv 6209 or adv6209 or "af 0901" or af0901 or buccolam or dalam doricum or dormicum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or iti 111 or iti111 or midacum or midafresa or midazo or midazol or midolam or miloz or nayzilam or nvd 301 or nvd301 or ro 21 3981 or "ro 21 3981 003" or ro 21-3981 or ro 21-3981-003 or ro 213981 or "ro 213981003" or ro21 3981 or "ro21 3981 003" or ro21-3981 or ro21-3981-003 or ro213981 or ro213981003 or seizalam or shp 615 or shp615 or "suda 003" or suda003 or usl 261 or usl261 or versed).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (16011)
37 Etomidate/ (1938)
38 (amidate or ethomidate or etomidat* or hypnomidate or r 16659 or r 26 490 or r 26490 or r 7405 or r16659 or r26490 or r7405 or radenarcon or radenarkon).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3168)
39 Dexmedetomidine/ (4037)
40 (dexmedetomidine or cepedex or dexamedetomidine or dexdomitor or dexdor or mpv 1440 or mpv1440 or precedex or primadex or sedadex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading

word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6844)
41 exp "Hypnotics and Sedatives"/ (124820)
42 (Alprazolam or Amobarbital or Azaperone or Barbital or Bromisovalum or Chloral Hydrate or Chloralose or Chlordiazepoxide or Chlormethiazole or Dexmedetomidine or Diazepam or Diphenhydramine or Eszopiclone or Ethchlorvynol or Etomidate or Etorphine or Flurazepam or Glutethimide or Hexobarbital or Lorazepam or Medazepam or Medetomidine or Mephobarbital or Meprobamate or Methapyrilene or Methaqualone or Midazolam or Nitrazepam or Oxazepam or Paraldehyde or Pentobarbital or Phenobarbital or Propofol or Secobarbital or Temazepam or Thiamylal or Thiopental or Xylazine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (153487)
43 (Opiate* or opioid* or opium or morphine* or alfentanil* or fentanyl* or fentanyl* or remifentanil or sufentanil or lofentanil or hydromorphone* or ketamine* or esketamin* or ketanest* or ketalar* or ketaset*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (208320)
44 (buprenorphine or butorphanol or codeine or cyclazocine or dextropropoxyphene or dextrorphan or diamorphine or ethylketazocine or ethylmorphine or etorphine or hydrocodone or levorphanol or methadone or nalbuphine or oxycodone or oxymorphone or pentazocine or pethidine or phencyclidine or piritramide or tramadol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (56116)
45 (Sublimaze or Actiq or Durogesic or Duragesic or Fentora or Matrifen or Haldid or Onsolis or Instanyl or Abstral or Lazanda or Alfenta or Dilaudid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (252)
46 or/31-44 (376065)
47 30 and 46 (39776)
48 3 and 30 and 46 (6936)
49 random:.tw. or placebo:.mp. or double-blind:.tw. (1329849)
50 ((treatment or control) adj3 group*).ab. (641839)
51 (allocat* adj5 group*).ab. (27666)
52 ((clinical or control*) adj3 trial).ti,ab,kw. (308969)
53 or/49-52 (1850723)
54 randomized controlled trial.pt. (530983)
55 controlled clinical trial.pt. (94165)
56 randomized.ab. (520289)
57 placebo.ab. (218146)
58 drug therapy.fs. (2318433)

59 randomly.ab. (357530)
60 trial.ab. (552159)
61 groups.ab. (2194683)
62 or/54-61 (5002641)
63 exp animals/ not humans.sh. (4830343)
64 62 not 63 (4349639)
65 53 not 63 (1595966)
66 64 or 65 (4709748)
67 48 and 66 (3014)

EMBASE

Search Strategy:
---
1 conscious sedation/ (8355)
2 sedation.mp. (98481)
3 1 or 2 (98481)
4 intensive care/ or exp artificial feeding/ or exp artificial ventilation/ or early goal-directed therapy/ or exp intensive care nursing/ or exp patient monitoring/ or resuscitation/ (692518)
5 critical illness/ (31330)
6 intensive care unit/ or burn unit/ or exp coronary care unit/ or medical intensive care unit/ or neurological intensive care unit/ or stroke unit/ or surgical intensive care unit/ (195150)
7 tertiary health care/ or tertiary care center/ (112737)
8 exp heart surgery/ (385340)
9 exp shock/ (139554)
10 multiple trauma/ (15299)
11 perioperative period/ (53624)
12 exp artificial ventilation/ or exp ventilator weaning/ (187126)
13 ((critical* or intensive or tertiary) adj3 (care or ill*)).mp. (582954)
14 (serious* adj injur*).mp. (6026)
15 (severe adj (traum* or shock)).mp. (13689)
16 ((preoperative or intraoperative or perioperative) adj (care or procedure* or period)).tw. (24258)
17 ventilat*.mp. (342006)
18 ((severe or serious or critical*) adj3 (ill* or injur* or trauma*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (202294)
19 ((cardiac or thoracic or heart) adj3 (surgery or surgical)).mp. (171920)
20 (shock or ICU or polytrauma).mp. (458494)
21 ((physiologic* or hemodynamic* or hemo-dynamic* or haemodynamic* or haemo-dynamic*) adj3 monitor*).mp. (31463)
22 ((digestive* or gastro* or gastric* or nasogastr*) adj3 intubat*).mp. (5116)
23 or/4-22 (2021868)

24 exp emergency health service/ (109276)
25 (emergency or emergencies).af. (714752)
26 (trauma adj3 (center* or unit*)).mp. (22785)
27 or/24-26 (723007)
28 23 or 27 (2557646)
29 3 and 28 (33569)
30 propofol/ (57328)
31 (Propofol* or 2,6 diisopropylphenol or anepol or anesia or cryotol or diisoprofol or diprivan or diprofol or disoprivan* or disoprofol or fresofol or gobbifol or hiremon or ici 35 868 or ici 35,868 or ici 35868 or ivifol or plofed or pofol or profast or propocam or propolipid or propoven or provive or rapinovet or rapiva or recofol or ripol or safol or spifol or spiva or unifol).mp. (59696)
32 fentanyl/ (65430)
33 (Fentanyl or ap 48 or ap48 or duragesic or durogesic or epufen or fentalis or fentamat or fentamyl or fentanex or fentanyl or fentanest or fetanex or fentanyl or fentora or leptanal or mezolar matrix or pecfent or phentanyl or r 4263 or r4263 or rapinyl or recuvyra or sublimaze or subsys or tanyl or tilotrans or transfenta).mp. (70622)
34 midazolam/ (49604)

35 (Midazolam or adv 6209 or adv6209 or "af 0901" or af0901 or buccolam or dalam doricum or dormicum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or iti 111 or iti111 or midacum or midafresa or midazo or midazol or midolam or miloz or nayzilam or nvd 301 or nvd301 or ro 21 3981 or "ro 21 3981 003" or ro 21-3981 or ro 21-3981-003 or ro 213981 or "ro 213981003" or ro21 3981 or "ro21 3981 003" or ro21-3981 or ro21-3981-003 or ro213981 or ro213981003 or seizalam or shp 615 or shp615 or "suda 003" or suda003 or usl 261 or usl261 or versed).mp. (53151)
36 etomidate/ (8053)
37 (amidate or ethomidate or etomidat* or hypnomidate or r 16659 or r 26 490 or r 26490 or r 7405 or r16659 or r26490 or r7405 or radenarcon or radenarkon).mp. (8565)
38 dexmedetomidine/ (12875)
39 (dexmedetomidine or cepedex or dexamedetomidine or dexdomitor or dexdor or mpv 1440 or mpv1440 or precedex or primadex or sedadex).mp. (13228)
40 exp hypnotic sedative agent/ (393057)
41 (Alprazolam or Amobarbital or Azaperone or Barbital or Bromisovalum or Chloral Hydrate or Chloralose or Chlordiazepoxide or Chlormethiazole or Dexmedetomidine or Diazepam or Diphenhydramine or Eszopiclone or Ethchlorvynol or Etomidate or Etorphine or Flurazepam or Glutethimide or Hexobarbital or Lorazepam or Medazepam or Medetomidine or Mephobarbital or Meprobamate or Methapyrilene or Methaqualone or Midazolam or Nitrazepam or Oxazepam or Paraldehyde or Pentobarbital or Phenobarbital or Propofol or Secobarbital or Temazepam or Thiamylal or Thiopental or Xylazine).mp. (347200)

42 (Opiate* or opioid* or opium or morphine* or alfentanil* or fentanyl* or fentanyl* or remifentanil or sufentanil or lofentanil or hydromorphone* or ketamine* or esketamin* or ketanest* or ketalar* or ketaset*).mp. (367050)

43 (buprenorphine or butorphanol or codeine or cyclazocine or dextropropoxyphene or dextrorphan or diamorphine or ethylketazocine or ethylmorphine or etorphine or hydrocodone or levorphanol or methadone or nalbuphine or oxycodone or oxymorphone or pentazocine or pethidine or phencyclidine or piritramide or tramadol).mp. (155895)

44 (Sublimaze or Actiq or Durogesic or Duragesic or Fentora or Matrifen or Haldid or Onsolis or Instanyl or Abstral or Lazanda or Alfenta or Dilaudid).mp. (2629)

45 or/30-44 (805572)

46 29 and 45 (19048)

47 random:.tw. or placebo:.mp. or double-blind:.tw. (1921631)

48 ((treatment or control) adj3 group*).ab. (931241)

49 (allocat* adj5 group*).ab. (36299)

50 ((clinical or control*) adj3 trial).ti,ab,kw. (456349)

51 or/47-50 (2690944)

52 randomized controlled trial/ (656042)

53 Controlled clinical study/ (463256)

54 random$.ti,ab. (1660915)

55 randomization/ (90674)

56 intermethod comparison/ (271118)

57 placebo.ti,ab. (323417)

58 (compare or compared or comparison).ti. (536518)

59 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2298375)

60 (open adj label).ti,ab. (87265)

61 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (244063)

62 double blind procedure/ (183748)

63 parallel group$1.ti,ab. (27415)

64 (crossover or cross over).ti,ab. (110699)

65 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (354110)

66 (assigned or allocated).ti,ab. (417281)

67 (controlled adj7 (study or design or trial)).ti,ab. (377780)

68 (volunteer or volunteers).ti,ab. (256906)

69 human experiment/ (542522)

70 trial.ti. (328450)

71 or/52-70 (5382714)

72 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8556)

73 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (268458)

74 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (18458)

75 (Systematic review not (trial or study)).ti. (173992)

76 (nonrandom$ not random$).ti,ab. (16936)

77 "Random field$".ti,ab. (2505)

78 (random cluster adj3 sampl$).ti,ab. (1354)

79 (review.ab. and review.pt.) not trial.ti. (886329)

80 "we searched".ab. and (review.ti. or review.pt.) (36523)

81 "update review".ab. (116)

82 (databases adj4 searched).ab. (42488)

83 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1105803)

84 Animal experiment/ not (human experiment/ or human/) (2321302)

85 or/72-84 (3691235)

86 71 not 85 (4781871)

87 51 not 85 (2238792)

88 86 or 87 (5228692)

89 46 and 88 (5470)

Appendix 2. COCHRANE CENTRAL Search Strategy

ID	Search	Hits
#1	MeSH descriptor: [Conscious Sedation] explode all trees	1421
#2	sedation	19555
#3	#1 or #2	19555
#4	MeSH descriptor: [Critical Care] explode all trees	2104
#5	MeSH descriptor: [Early Goal-Directed Therapy] explode all trees	9
#6	MeSH descriptor: [Critical Illness] explode all trees	2354
#7	MeSH descriptor: [Intensive Care Units] explode all trees	3719
#8	MeSH descriptor: [Burn Units] explode all trees	45
#9	MeSH descriptor: [Coronary Care Units] explode all trees	145
#10	MeSH descriptor: [Recovery Room] explode all trees	91
#11	MeSH descriptor: [Respiratory Care Units] explode all trees	13
#12	MeSH descriptor: [Intubation, Gastrointestinal] explode all trees	685
#13	MeSH descriptor: [Monitoring, Physiologic] explode all trees	12429
#14	MeSH descriptor: [Hemodynamic Monitoring] explode all trees	16
#15	MeSH descriptor: [Cardiac Surgical Procedures] explode all trees	12976
#16	MeSH descriptor: [Shock] explode all trees	2345
#17	MeSH descriptor: [Multiple Trauma] explode all trees	233
#18	MeSH descriptor: [Resuscitation] explode all trees	5135
#19	MeSH descriptor: [Ventilators, Mechanical] explode all trees	272
#20	((critical* or intensive or tertiary) near/3 (care or ill* or therap*))	61274

#21 serious* near/1 injur*268

#22 (severe near/1 (traum* or shock)) 1196

#23 ((preoperative or intraoperative or perioperative) near/1 (care or procedure* or period)) 18389

#24 ventilat* 35135

#25 ((cardiac or thoracic or heart) near/3 (surgery or surgical)) 21359

#26 ((severe or serious or critical*) near/3 (ill* or injur* or trauma*)) 16053

#27 shock or ICU or polytrauma 25022

#28 ((digestive* or gastro* or gastric* or nasogastr*) near/3 intubate*) 22

#29 ((physiologic* or hemodynamic* or hemo-dynamic* or haemodynamic* or haemo-dynamic*) near/3 monitor*) 4309

#30 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 149028

#31 MeSH descriptor: [Emergency Service, Hospital] explode all trees 2467

#32 MeSH descriptor: [Emergency Medical Services] explode all trees 3989

#33 emergency or emergencies 33118

#34 (trauma near/3 (center* or unit*)) 1592

#35 #30 or #31 or #32 or #33 or #34 174088

#36 #3 and #35 6509

#37 MeSH descriptor: [Propofol] explode all trees 4967

#38 Propofol* or 2,6 diisopropylphenol or anepol or anesia or cryotol or diisoprofol or diprivan or diprofol or disoprivan* or disoprofol or fresofol or gobbifol or hiremon or ici 35 868 or ici 35,868 or ici 35868 or ivifol or plofed or pofol or profast or propocam or propolipid or propoven or provive or rapinovet or rapiva or recofol or ripol or safol or spifol or spiva or unifol 14551

#39 MeSH descriptor: [Fentanyl] explode all trees 5621

#40 Fentanyl or ap 48 or ap48 or duragesic or durogesic or epufen or fentalis or fentamat or fentamyl or fentanex or fentanyl or fentanest or fetanex or fentanyl or fentora or leptanal or mezolar matrix or pecfent or phentanyl or r 4263 or r4263 or rapinyl or recuvyra or sublimaze or subsys or tanyl or tilotrans or transfenta 16596

#41 MeSH descriptor: [Midazolam] explode all trees 3089

#42 Midazolam or buccolam or dalam doricum or dormicum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or iti 111 or iti111 or midacum or midafresa or midazo or midazol or midolam or miloz or nayzilam or seizalam or versed 9093

#43 MeSH descriptor: [Etomidate] explode all trees 381

#44 amidate or ethomidate or etomidat* or hypnomidate or r 16659 or r 26 490 or r 26490 or r 7405 or r16659 or r26490 or r7405 or radenarcon or radenarkon 1579

#45 MeSH descriptor: [Dexmedetomidine] explode all trees 1827

#46 dexmedetomidine or cepedex or dexamedetomidine or dexdomitor or dexdor or mpv 1440 or mpv1440 or precedex or primadex or sedadex 5523

#47 MeSH descriptor: [Hypnotics and Sedatives] explode all trees 3728

#48 Alprazolam or Amobarbital or Azaperone or Barbital or Bromisovalum or Chloral Hydrate or Chloralose or Chlordiazepoxide or Chlormethiazole or Dexmedetomidine or Diazepam or Diphenhydramine or Eszopiclone or Ethchlorvynol or Etomidate or Etorphine or Flurazepam or Glutethimide or Hexobarbital or Lorazepam or Medazepam or Medetomidine or Mephobarbital or Meprobamate or Methapyrilene or Methaqualone or Midazolam or Nitrazepam or Oxazepam or Paraldehyde or Pentobarbital or Phenobarbital or Propofol or Secobarbital or Temazepam or Thiamylal or Thiopental or Xylazine 36540

#49 Opiate* or opioid* or opium or morphine* or alfentanil* or fentanyl* or fentanyl* or remifentanil or sufentanil or lofentanil or hydromorphone* or ketamine* or esketamin* or ketanest* or ketalar* or ketaset* 53843

#50 buprenorphine or butorphanol or codeine or cyclazocine or dextropropoxyphene or dextrorphan or diamorphine or ethylketazocine or ethylmorphine or etorphine or hydrocodone or levorphanol or methadone or nalbuphine or oxycodone or oxymorphone or pentazocine or pethidine or phencyclidine or piritramide or tramadol 17102

#51 Sublimaze or Actiq or Durogesic or Duragesic or Fentora or Matrifen or Haldid or Onsolis or Instanyl or Abstral or Lazanda or Alfenta or Dilaudid 201

#52 #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 84835

#53 #36 and #52 in Trials 4484

Appendix 3. Supplementary Tables

Supplement Table 1. Baseline Characteristics of Included Studies

Study author and year	Study design	Study Arms and no. of patients	Age of Patients (years; mean ± SD unless otherwise specified)	Adult or Pediatrics	Study Setting	Inclusion Criteria	Exclusion criteria
Abdolrazaghnejad 2017	Single site RCT	Midazolam-ketamine: 41 Fentanyl-midazolam: 40	31.7 ± 20.6	Adult	ER	Closed reduction of fracture or dislocation	SBP <90 mmHg, HR <60 bpm, ASA I to II, chronic renal failure, liver failure, known history of sensitivity to ketamine, midazolam, or fentanyl
Afzalimoghaddam 2021	Single site RCT	Diazepam-Fentanyl: 42 Midazolam-Fentanyl: 39	DPF: 30.8 ± 11.5 MPF: 32.5 ± 9.8	Adult	ER	18-65yrs old, reduction of anterior shoulder dislocation	Severe underlying disease that precludes ED PSA (ASA >II); allergy or sensitivity to benzodiazepines or opioids; pregnancy; hemodynamic instability; presence of any fracture in the dislocated joint (based on local ED protocols, in this case we consulted with orthopedic surgeons); using analgesics, recreational drugs, or alcohol 12h before the incident; refusal to participate
Akhlaghi 2019	Single site RCT	Placebo-ketamine: 63 Midazolam-ketamine: 61 Haloperidol-ketamine: 61	37.5 ± 12.00	Adult	ER	>18yrs old who required PSA	Any contraindication to ketamine, midazolam, or haloperidol
Amini 2018	Single site RCT	Low-dose fentanyl, propofol, midazolam, ketamine and lidocaine combination: 63	37.8 ± 14.3	Adult/Pediatric	ER	15-60yrs old, pain score equal to or higher than 7 (based on numeric analog scale)	Refusal to participate, previous allergy to drugs used in the study, allergy to protein products such as egg and soy, hemodynamic instability, increased intracranial pressure, lactating and pregnant women

		Regular dose of propofol and fentanyl combination: 62					
Aminiahidashti 2018	Single site RCT	Propofol-fentanyl: 70 Propofol-ketamine: 66	PF 33.77 ± 9.22 PK 31.71 ± 8.76	Adult	ER	Trauma patients who required PSA	Patients <18 and >60yrs old, ASA 3 or above, intoxicated trauma patients, patients with head trauma, patients with addiction history, pregnant women, patients with blood pressure <90mmHg, pulse oximetry <90%, HR <60 and patients with allergies or contraindications for fentanyl, propofol and ketamine
Andolfatto 2012	Single site RCT	Ketamine-propofol: 142 Propofol: 142	Median (IQR), years: Ketofol 48 (25–66); propofol 54 (35–68)	Adult/ Pediatric	ER	Requirement for procedural sedation, aged 14 years or older, and ASA class 1 to 3 status	Unable to give informed consent, pregnant, known allergy to either study medication
Arhami Dolatabadi 2018	Multisite RCT	Dexmedetomidine-fentanyl: 40 Midazolam-fentanyl: 40	42.08 ± 12.17	Adult	ER	Patients with distal radius fractures aged between 18 and 60 years	Patients with history of using antihypertensive or antihistamine medications, patients with head trauma and loss of consciousness, severe chest trauma, cervical vertebra trauma with unstable fracture, mental retardation, those who could not verbally communicate, hemodynamically unstable patients, history of allergic reaction to drugs, addicts and those who had a history of drug abuse, pregnant women, and those with a history of cardiac disease (cardiac block and bradycardia)
Arhami Dolatabadi 2018b	Multisite RCT	Midazolam-fentanyl: 50 Midazolam-fentanyl-lidocaine: 50	MF 27.7 ± 8.7; MFL 27.0 ± 9.2	Adult	ER	Patients with anterior shoulder dislocation candidate for reduction	Patients with altered level of consciousness at the time of presentation, those who had a fracture in their shoulder joint along with shoulder dislocation (apart from Lesion Sachs-Hill), patients with a history of surgery on the same shoulder joint or fracture of the shoulder joint, history of seizure, those who had received analgesic drugs before presenting, patients with history of cardiac diseases and dysrhythmia, history of taking digoxin, and patients with a history of allergy to lidocaine, midazolam, or fentanyl
Azizkhani 2021	Multisite RCT	Ketamine-dexmedetomidine: 31	Ketamine-dexmedetomidine: 39 ± 18	Adult	ER	Patients >=18 years old who were candidates for painful procedures in the ED. Inclusion criteria were also	Unable to give informed consent, received any sedative or analgesic agents within the previous 24 h; had a known allergy to ketamine, dexmedetomidine, or propofol; had a previous

		Propofol-ketamine: 31 Ketamine: 31	Propofol-ketamine: 42 ± 17 Ketamine: 34 ± 12			pain score over 5 that was measured by the Visual Analogue Scale and ASA class 1 to 3 status. The duration of procedure was ≤15 min in all patients	history of severe systemic illness, organ dysfunction, or psychiatric disorder; had a permanent instability in hemodynamic state; who was pregnant, and had a contraindication to study drugs (e.g. hypersensitivity)
Bahreini 2020	Single site RCT	sodium thiopental–fentanyl: 49 ketamine–propofol: 47	TF 37.00 ± 17.70; KP 35.97 ± 16.59	Adult	ER	Adult patients of 18 years or older with ASA class I–II who were planned to undergo painful procedures requiring procedural sedation. Patients mainly necessitated moderate sedation for fracture or dislocation reductions and percutaneous pinning. Other procedures include hernia reduction, chest tube insertion and lumbar puncture	ASA class III–V, haemodynamic instability, pregnancy, the history of cardiovascular disease or moderate to severe asthma attack, present pneumonia, uncontrolled diabetes mellitus, sepsis, neurological or psychiatric disease, the consumption of neurological/ psychiatric drugs, moderate to severe obesity, cardiac/renal/liver/ pulmonary/endocrine insufficiency, porphyria, allergy to soya or egg and patients who did not fill the consent form
Barcelos 2015	Single site RCT	Ketamine-midazolam: 13 Morphine-midazolam: 12	ketamine 90.7±34.1 months morphine 102.1±48.5 months	Pediatric	ER	Patients aged 3 years to 14 years, with dislocation or closed fracture that required orthopedic reduction maneuvers	(a) class III or higher ASA (b) fractures for more than 24 hours (c) allergies or (d) contraindication to any medication used in the study and (e) parent or guardians who did not consent to participate in the study
Bauman 2002	Single site RCT	Methohexital-remifentanil 6.6: 27 Methohexital-remifentanil 10: 30 Methohexital-remifentanil 13.4: 30 Propofol-fentanyl 1: 28	N/A	Pediatric	ER	Paediatric patients, with a gestational age of >=52 weeks to <=12 years	Unstable cardiovascular status, severe craniofacial disease, upright positioning requirements, no consent, parental refusal, intravenous access difficulties, or were not NPO (6 h for solids, 3 h for milk, 2 h for clear liquids). 27 children excluded after randomization due to failure of their peripheral IV catheter or the infusion pump

		Propofol-fentanyl: 1.5: 30 Propofol-fentanyl: 30					
Burton 2002	Single site RCT	Etomidate-fentanyl: 19 Midazolam-fentanyl: 22	etomidate 47±23; midazolam 34±14	Adult	ER	Adult patients presenting to the ED and requiring PSA for suspected acute anterior shoulder dislocation	Age younger than 18 years, inability to give informed consent, pregnancy, patients seen without the emergency physician attending staff and managed solely by the orthopedic service, and weight more than 100 kg
Cevik 2013	Single site RCT	Ketamine-midazolam: 31 Midazolam-fentanyl: 30	Mean (SD/min-max), years: KM 34.1 (21.2/4-74); MF 36.5 (21.0/9-75)	Adult/ Pediatric	ER	Patients requiring urgent reduction either for a fracture or for a dislocation	SBP <90 mm Hg, pulse rate less than 60 beats/min, ASA class other than 1 to 2, chronic renal or liver failure, and known allergy to study drugs
Chan 2008	Single site RCT	Midazolam-fentanyl: 38 Etomidate-fentanyl: 42	Midazolam 57 ± 23; Etomidate 56 ± 21	Adult	ER	Age >=18 years who required PSA, most commonly for closed reduction of joint dislocation or closed reduction of bony fracture	<18 or >80 years old, patient unable to give informed consent, pregnancy, hemodynamic instability, underlying uncontrolled cardiopulmonary illness, neurologically unstable, patients who require analgesia for pain control only without sedatives, sedation solely for purpose of managing behavioural emergencies, known allergy to fentanyl, etomidate, or midazolam, refusal to participate or withdrawal
Cimilli Ozturk 2014	Single site RCT	Midazolam-fentanyl: 37 Propofol-fentanyl: 38	Midazolam 43.5 ± 19.4 (95% CI 37.0-50.0); Propofol 40.0 ± 18.4 (95% CI 34.0-46.1).	Adult	ER	Adult patients with isolated anterior shoulder dislocation	1. ASA 3, 4, 5 patients (moderate and severe systemic disease and moribund); 2. patients <18 years; 3. head trauma; 4. pregnancy; 5. known allergic reactions with the drugs; 6. associated fracture at the site of injury
Coll-Vinent 2003	Single site RCT	Etomidate: 9 Propofol: 9 Midazolam: 8 Midazolam-flumazenil: 6	Median (range) years: etomidate 63 (44–79); propofol 65 (29–81); midazolam 62 (52–78); midazolam + flumazenil 58 (15–71); total 62.5 (15–81)	Adult	ER	Adult patients (>18 years) undergoing cardioversion at the ED for a supraventricular arrhythmia (flutter or atrial fibrillation)	Clinical signs of behavior, memory, or consciousness disorders; evidence of hepatic or renal illness; known allergy or secondary reaction to egg or benzodiazepines; chronic treatment with benzodiazepines or H2 inhibitors; history of sleep apnea; or hemodynamic instability

David 2011	Single site RCT	Ketamine-propofol-fentanyl: 97 Propofol-fentanyl: 96	Median (range) years: KP: 20 (2–83); Propofol: 22 (2–75)	Adult/ Pediatric	ER	Patients selected for procedural sedation and analgesia	Patients who were pregnant or who were younger than 1 year and those with a history of an adverse reaction to anesthesia, underlying cardiac or pulmonary disease, hepatic dysfunction, porphyria, psychiatric illness, allergy to eggs or soybeans, increased intracranial or intraocular pressure, abnormal airway pathology, or ASA III or greater
Del Pizzo 2011	Single site RCT	Total number of patients: 53	N/A	Pediatric	ER	Children 3-18 years with forearm fracture requiring closed reduction	N/A
Derakhshanfar 2015	Single site RCT	Midazolam: 50 Dexmedetomidine: 50	5.3 ± 2.5	Pediatric	ER	Children 2 to 12 years who complained of head trauma and needed to have brain CT performed	Patients who suffered from unstable vital signs, or trauma in the areas except head, fracture and/or uncontrollable bleeding, deep tissues injury such as tendon, main arteries, patients with respiratory infection, allergy to the drugs used in the current study, and patients who used pain killers
Di Liddo 2006	Single site RCT	Etomidate-fentanyl: 50 Midazolam-fentanyl: 50	Mean age (SD), months: Etomidate: 108 (45.6); Midazolam: 100 (42.7)	Pediatric	ER	Healthy children ASA I or II, aged 2 to 18 years, and presenting to the hospital with a displaced extremity fracture requiring procedural sedation and analgesia for closed reduction	Respiratory tract infection, hemodynamic instability, significant recent head injury, known seizure disorder, significant underlying heart or lung disease or craniofacial anomaly, underlying adrenocortical dysfunction, pregnancy, allergy to study drugs, fasting criteria not met (solids less than 6 hours and clear liquids less than 2 hours earlier), or inability to obtain IV access
Dilli 2008	Single site RCT	Ketamine: 51 Ketamine-Midazolam: 48	6.5 ± 3.7	Pediatric	ER	Children 2-14 years requiring lumbar puncture for suspected meningitis who were hemodynamically and neurologically stable	Children with a history of an adverse reaction to midazolam or ketamine, psychiatric or behavioral disorder, risk of raised intracranial or intraocular pressure, thyroid disorder, porphyria, blocked nose, or who had been sedated within 4 h of presentation
Disel 2016	Single site RCT	Etomidate-fentanyl: 24 Ketamine: 20	Mean (SD, minimum-maximum): 12.3 (4.1, 7–18) years	Pediatric	ER	Children 7 to 18 years with separated limb fractures and/or dislocations requiring closed reduction and/or whose main treatment was surgical, preceded by necessary emergency stabilization with reduction and splinting	ASA score other than class I or who had unseparated fractures, contraindications for the study drugs to be used (previous seizures, epilepsy, cardiopulmonary disease, adrenocortical insufficiency), difficulty in consciousness evaluation (mental retardation, head trauma), contraindications for sedation, and/or analgesia; injuries that required general anesthesia and surgical measures for emergency treatment, respiratory infections, a maxillofacial trauma or anomaly, known allergies to the study drugs, or difficulty in venous access in the large antecubital veins

Dunn 2010	Single site RCT	Remifentanil-propofol: 20 Morphine-midazolam: 20	Mean (years): remifentanil-propofol: 39; morphine-midazolam: 35	Adult	ER	Patients with shoulder dislocation between the ages of 16 and 65. We considered patients with anterior glenohumeral dislocation including those with avulsion fracture of the greater tuberosity or of the glenoid labrum	ASA physical status greater than II, those with more major fracture dislocations, other major injuries, posterior shoulder dislocations, a history of drug abuse, and those who were intoxicated
Ferguson 2016	Multisite RCT	Propofol: 292 Ketamine-propofol: 281	Median (IRQ), range: Propofol: 46 (30–62), 19-86 years; Ketofol: 50 (31–65), 18-95 years	Adult	ER	Patients aged 18 years or older who required deep procedural sedation to facilitate the performance of a painful procedure in the ED	Unable to provide informed consent; pregnant; allergic to ketamine, soy products, or eggs; reduced level of consciousness or known raised intracranial pressure; uncontrolled hypertension (BP >160/90 mm Hg), abdominal aortic aneurysm, or symptomatic ischemic heart disease; heart failure or recent myocardial infarction; other severe systemic disease (ASA class IV or greater)
Gale 1993	Single site RCT	Propofol: 10 Methohexital: 10 Midazolam: 10	propofol 64.3 ± 4.4; methohexital 72.4 ± 7.9; midazolam 64.1 ± 12.5	Adult	ER	Age <18yrs and ASA II or III who underwent elective direct-current cardioversion for the treatment of atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia	Patients who required emergent cardioversion or who had allergies to the drug classes used
Genzlinger 2012	Single site RCT	Ketamine: 27 Etomidate: 25	N/A	Adult	ER	Patients requiring procedural sedation for urgent reduction of orthopedic dislocations	Pregnancy, age <14, altered mental status, and patients with suspected cocaine abuse
Gharavifard 2016	Single site RCT	Fentanyl-Midazolam: 48 Remifentanil: 48	remifentanil 39.7 ± 10.3; fentanyl and midazolam 39.8 ± 9.9	Adult	ER	Patients aged 18–64 years and ASA I and II with anterior shoulder dislocation and requiring closed reduction	All subjects with history of allergy to benzodiazepines and narcotics; prolonged use of opioids or alcohol; consumption of sedative or analgesic drugs before presenting to ED; sleep obstructive apnea syndrome; maxillofacial malformations with high probability of airway maintenance failure; pregnant; anterior dislocation requiring referral to orthopedic operating room; severe trauma and unstable hemodynamics; advanced heart disease; kidney failure; pneumonia; uncontrolled seizures; and finally patients not willing to participate in the study

Godambe 2003	Single site RCT	Ketamine-midazolam: 54 Propofol-fentanyl: 59	Range 3.1-16.3 years; Median 9.0 years; Mean 9.2 years	Pediatric	ER	Children aged 3 years to 18 years that required PSA for emergency orthopedic procedures	ASA class III or greater, fractures >24 hours old, and known allergy to any of the study medications or eggs
Gumus 2012	Single site RCT	Dexmedetomidine: 21 Remifentanil: 20	Mean +/- SD (range): Dexmedetomidine: 56.4 +/- 7.4 (41-70); Remifentanil 55.0 +/- 12.9 (30-77) years	Adult	ER	Patients who underwent elective isolated coronary bypass surgery	Lack of ability to understand and speak the Turkish language, ejection fraction <40%, or had left bundle branch block, hepatic, renal, or pulmonary failure. Neurological disorder, chronic opioid usage, allergies to opioids or paracetamol, a prolonged need for mechanical ventilation, or the need for vasoactive drug support. Patients <30 or >90 years old
Hart 1997	Single site RCT	Fentanyl: 20 Fentanyl-midazolam: 13 Meperidine-promethazine-chlorpromazine (MPC): 9	Mean +/- SD (range): 4.8 +/- 2 (2-11)	Pediatric	ER	Children between 24 months and 18 years requiring analgesia and sedation for painful ED procedures	Prior history of severe systemic illness; hepatic or renal failure; prior adverse reactions to narcotics, hypnotics, sedatives, or general anesthetics; or were currently using tranquilizers, antipsychotics, or monoamine oxidase inhibitors
Hatamabadi 2015	Single site RCT	Propofol-fentanyl: 19 Midazolam-fentanyl: 29	31.9 ± 8.8	Adult	ER	Patients with ASD in an age range of 18 - 60 with anterior dislocation of the shoulder	Hypersensitivity to midazolam, propofol, or fentanyl; other injury (fracture around shoulder or other limb); intake of food or fluid during last 4 hours; presence of airway difficulty; sensory problems; motor problems, vascular problems; consumption of alcohol or other recreational drug during past 6 hours; allergic to eggs and/or certain medications
Havel 1999	Single site RCT	Propofol-morphine: 43 Midazolam-morphine: 46	Mean +/- SD (range), years: Propofol 9.0 +/- 3.8 (2–18); midazolam 8.6 +/- 4.2 (2–16)	Pediatric	ER	Patients 2–18 years of age presenting to the ED with an isolated extremity injury necessitating procedural sedation for closed reduction	1) hemodynamic compromise; 2) a history of cardiac disease; 3) a known allergy to any study medication, eggs, or soybeans; and 4) inability to obtain informed consent from a parent or guardian
Hunt 2005	Single site RCT	Etomidate-morphine/fentanyl: 23	etomidate 43.3 ± 23; midazolam 53.4 ± 26	Adult/ Pediatric	ER	Age above 10 years; dislocation of the shoulder, hip, knee, elbow, or wrist; and any displaced/angulated long bone fractures	Age below 10 years, previous adverse reaction to midazolam or etomidate, and hemodynamic instability

		Midazolam-morphine/fentanyl: 21				requiring procedural sedation for reduction	
Holger 2005	Single site RCT	Midazolam: 17 Propofol: 15	N/A	Adult	ER	(1) age 18 to 65 and competent to give informed consent, (2) expected procedure length of 15 minutes or less, and (3) ASA class I or II	(1) evidence of alcohol or drug intoxication; (2) pregnancy; (3) allergy to midazolam, fentanyl, or propofol; and (4) evidence of significant hypovolemia or severe cardiac or pulmonary disease
Jamal 2011	Single site RCT	Midazolam-fentanyl: 23 Ketamine: 18	Median (range), years: MF 36 (18-81); ketamine 28 (18-54)	Adult	ER	Patients aged between 18 and 60 years who presented to the ED with fractures and dislocations requiring reductions	Patients with hemodynamic instability, alcohol influence, known or suggestive renal and liver disease, pregnant or lactating, ASA III and above, a previous history of allergy to opioids, benzodiazepines or ketamine and hypertensive (SBP > 145 mmHg and DBP > 100mmHg)
Kennedy 1998	Single site RCT	Fentanyl-Midazolam: 130 Ketamine-Midazolam: 130	FM 9.7 ± 3.01; KM 9.7 ± 3.27	Pediatric	ER	Patients between 5 and 15 years of age requiring fracture reduction/joint relocation and meeting ASA class I or II criteria	Abnormalities of airway, cardiorespiratory, hepatic, renal, or central nervous systems; history of psychoses; ethanol, psychotropic, or nonprescribed narcotic drug use within 6 hours of the procedure; and adverse reaction to the study drugs, opiates, or benzodiazepines
Khutia 2012	Single site RCT	Ketamine-propofol: 48 Propofol-fentanyl: 44	PK 8.44 ± 2.39; PF 8.75 ± 2.89	Pediatric	ER	Children aged 3–14 years, of ASA physical status IE-IIE, posted for emergency short surgical procedures like reduction of fracture dislocation, incision and drainage of abscess and dressing-debridement of wounds	Known allergy or contraindication to either study drug, patient's/parent's refusal, head injury, seizure disorder, psychological disorders, ingestion of psychotropic or sedative medication, congenital heart disease, severe obesity (body mass index >35 kg/m2) and full stomach patients
Kienstra 2004	Single site RCT	Etomidate: 24 Pentobarbital: 33	Mean (SD), months: etomidate 24.2 (12.2), pentobarbital 26.5 (10.9)	Pediatric	ER	Children 6 months to 6 years of age who required a head or neck CT scan and in whom sedation was deemed necessary for effective imaging, ASA I or II	History of barbiturate hypersensitivity (allergy), presence of hemodynamic instability (ie, shock or hypotension), presence of congestive heart failure, respiratory depression, airway obstruction (including status asthmaticus), impaired level of consciousness (GCS < 10), concomitant administration of narcotics or other respiratory depressants, history of liver or renal dysfunction, severe anemia, myasthenia gravis, porphyria, adrenal insufficiency, or focal seizure disorder

Lee-Jayaram 2010	Single site RCT	Ketamine-midazolam: 11 Etomidate-fentanyl: 12	Mean (SD) (median), years: KM 9.64 (2.9) (10.0); EF 8.5 (2.6) (8.0)	Pediatric	ER	ASA class I or II patients	Non-English speaking, Pregnancy, Multiple injuries, Fracture in >1 extremity, History of allergy or adverse drug reaction to study medications, History of psychoses, Developmental delay
Lemoel 2017	Multisite RCT	Ketamine: 76 Ketamine-Propofol: 76	Median (IQR), years: ketamine 47 (25–68); ketofol 49 (28–65)	Adult	ER	Adult patients (>18 years) presenting with an orthopedic injury and needing a procedural sedation	ASA physical status greater than 2; known hypersensitivity to either study product; sustained a thoracic, abdominal, spinal, or head injury; hemodynamic instability; intoxicated or schizophrenic. Pregnant women, prisoners, intravenous (IV) drug users, patients unable to give consent, porphyria, glaucoma
LucasdaSilva 2007	Single site RCT	Midazolam-fentanyl: 28 Midazolam-ketamine: 29	Median (IQR), months: MF 20 (8.2-78.7); MK 21 (6-78)	Pediatric	ICU	Patients from 3 months to 14 years of age requiring central venous catheters	Patients under 3 months of age; abnormalities in the airways; serious impairment of the central nervous system; intracranial hypertension; glaucoma; hyperthyroidism; severe respiratory disease; history of psychosis; use of ethanol or nonprescribed psychotropic or narcotic drugs within 6 h prior to the procedure and known adverse reaction to the drugs used in the study or to opioids, benzodiazepines or ketamine
Maltepe 2006	Single site RCT	Propofol-fentanyl: 33 Propofol-remifentanil: 30	fentanyl 65 ± 11; remifentanil 64 ± 12	Adult	ER	Ambulatory patients with atrial fibrillation of less than 24 hours duration, who were scheduled for external DC cardioversion after fasting for 5 hours	Patients less than 18 years of age, or ASA physical status >3, or with potentially difficult airway problems or a body mass index (BMI)>35 kg/m2
Masoumi 2019	Single site RCT	Dexmedetomidine: 30 Midazolam-fentanyl: 30	dex 30.8 ± 6.02; MF 29.57 ± 5.78	Adult	ER	Patients with age range of 18 to 70 years with shoulder dislocations	Patients with decreased consciousness, trauma with damage to other organs, cardiovascular diseases, respiratory problems, metabolic disease, pregnancy, inability to speak for any reason, impaired vital signs such as BP <90mmHg and respiratory rate less than 10-12, analgesic intake before entering the emergency room, drug sensitivity to opioid or any history of drug-related anaphylaxis and those who declined to participate in the study
Massaeli 2022	Single site RCT	Ketamine: 50 Propofol-ketamine: 50	23.02 ± 3.22	Adult/ Pediatric	ER	Age 15-40 years, willingness for the study participation, presence of orthopedic dislocation, and normal neuromuscular examination.	Patients with underlying disease (e.g., hypertension or hypotension), diabetes, cardiac diseases, insensitivity to sedative medications, cardiovascular instability, multiple trauma, head trauma, and allergy to eggs, lecithin, and soybean seeds, as well

		Propofol-fentanyl: 50					as the presence of low oxygen saturation from the beginning of the visit, the administration of sedative and hypnotic medicines and opiates, the risk of bleeding into the abdomen or chest, and the loss of consciousness.
Messenger 2008	Single site RCT	Ketamine-propofol: 32 Fentanyl-propofol: 31	ketamine 35.6 ± 17.0; fentanyl 43.2 ± 17.4	Adult	ER	Patients presenting with a fracture or dislocation requiring reduction, or with an abscess requiring incision and drainage, and for whom administration of PSA was deemed appropriate	Age < 14 or > 65 years; ASA Class III or greater; history of significant active cardiac, pulmonary, hepatic, or renal disease; weight > 130 kg; history of physician-diagnosed obstructive sleep apnea; chronic use of opioids; history of recent substance abuse or prior opioid dependence; acute intoxication with drugs or alcohol; history of psychotic disorder; or history of allergy or sensitivity to any study medication
Miner 2003	Single site RCT	Methohexital: 52 Propofol: 51	Age (95% CI), years: methohexital 44.2 (39.8, 48.6); propofol 41.3 (36.6, 46.1)	Adult	ER	All adult (age >=18) ED patients who were going to receive PS in the ED for the reduction of a fracture or dislocation	Unable to give consent, known hypersensitivity to either medication, pregnant, or clinical evidence of intoxication before the start of the procedure
Miner 2007	Single site RCT	Etomidate: 105 Propofol: 109	Age (SD), years: etomidate 36.9 (3.1) (Range 18–74); propofol 40.4 (14.5) (Range 18–78)	Adult	ER	All adult (age >18 years) ED patients who were to receive procedural sedation using either propofol or etomidate	Unable to give consent, ASA greater than 2, known hypersensitivity to either medication, pregnant, or clinical evidence of intoxication before the start of the procedure
Miner 2009	Single site RCT	Propofol: 74 Propofol-alfentanil: 71	Median (range), years: propofol 39 (18-87); PA 38 (18-80)	Adult	ER	All adult (age >=18 years) ED patients who were to receive deep procedural sedation using propofol	Unable to give consent, ASA >2, known hypersensitivity to either study medication, pregnant, or clinical evidence of intoxication prior to the start of the procedure
Miner 2010	Single site RCT	Ketamine: 47 Propofol: 50	Median (range), years: ketamine 30 (18–73); propofol 34.5 (18–85)	Adult	ER	All adult (age >=18 years) ED patients who were to receive moderate procedural sedation using propofol	Unable to give consent, ASA >2, known hypersensitivity to either study medication, pregnant, or clinical evidence of intoxication prior to the start of the procedure. Patients were not eligible for this study if the treating physician planned to use deep procedural sedation rather than moderate sedation
Miner 2013	Single site RCT	Propofol: 10 Propofol-alfentanil: 10	Median (range), years: propofol 34 (18–60); PA 36 (20–58)	Adult	ER	All adult (age >=18 years) ED patients who were to receive deep PS for fracture or dislocation reduction using propofol	Unable to give consent, ASA > 2, known hypersensitivity to either study medication, pregnant, or clinical evidence of intoxication prior to the start of the procedure

Miner 2015	Single site RCT	Propofol: 90 Propofol-ketamine 1:1: 85 Propofol-ketamine 4:1: 96	Median age (IQR, range), years: propofol - 40 (28 to 51, 18 to 83); PK 1:1 - 39 (27 to 51, 18 to 80); PK 4:1 - 36 (26 to 47.5, 18 to 84)	Adult	ER	We enrolled adult (aged >18 years) ED patients chosen to receive deep procedural sedation	Unable to give consent, ASA physical status greater than 2, known hypersensitivity to either study medication, pregnant, or showed evidence of intoxication
Miner 2017	Single site RCT	Alfentanil: 52 Propofol: 56	Median age (IQR, range), years: Alfentanil 32 (21–62, 18–82); propofol 36 (23–56, 18–64)	Adult	ER	Adult (age ≥ 18 years) ED patients chosen to receive moderate procedural sedation	Unable to give consent, ASA >2, known hypersensitivity to either study medication, pregnant, prisoners, or showed evidence of intoxication
Mofidi 2018	Multisite RCT	Propofol-fentanyl: 55 Propofol-ketamine: 55	PF 37.71 ± 12.21; PK: 33.82 ± 11.26	Adult	ER	Patients aged 18 to 70 years, presenting to the ED and needing closed reduction	Unwillingness to participate in the study, known psychiatric disorders, chronic opiate users, known hypersensitivity to the drugs under assessment, a BMI higher than 30 kg/m2, active infection in the upper respiratory tract or any anatomical abnormality in the upper airways
MonsefKasmaee 2019	Single site RCT	Remifentanil: 32 Propofol-fentanyl: 32	remifentanil 34.28 ± 10.84; PF 35.43 ± 14.25	Adult	ER	Patients with acute anterior shoulder dislocation aged between 15-60 years	Fracture-dislocation of the shoulder joint and history of surgery, except for patients with Hill-Sachs lesions, decreased consciousness and unstable hemodynamic status, hypotension (SBP <90), history of heart disease, and allergy to soy and eggs
Moro-Sutherland 2000	Single site RCT	Midazolam: 26 Pentobarbital: 29	Mean +/- SD, months: midazolam 26.0 +/- 15.8; pentobarbital 26.4 +/- 12.4	Pediatric	ER	Children 6 months to 6 years of age requiring CT of the head	History of adverse reaction to barbiturates, benzodiazepines, or flumazenil, a known seizure disorder on chronic benzodiazepines, the presence of hemodynamic instability in the ED, the presence of congestive heart failure, respiratory depression in the ED, airway obstruction, a history of respiratory tract infection, an impaired level of consciousness (defined as a GCS < 10), concomitant administration of opioids or other respiratory depressants, multiple drug overdose, history of liver dysfunction or uremia
Nashibi 2017	Single site RCT	Ketamine-propofol: 30	KF 31.83 ± 6.5 years; FM 32.13 ± 5.9	Adult	ER	20 to 40 year-old males with Colle's fracture, candidates for outpatient closed reduction	ASA physical status III or more, history of allergy to ketamine, propofol, midazolam, fentanyl and egg, increased intracranial pressure, multiple trauma, impaired mental status, cognitive disorders, and

		Fentanyl-midazolam: 30					patients who were opium abusers or had a history of psychoactive drugs use
Nejati 2011	Single site RCT	Ketamine-Propofol: 31 Fentanyl-midazolam: 31	Median (IQR), years): ketofol 25 (23–37); FM 25 (20–32)	Adult	ER	Patients aged 18 years or older requiring PSA for repair of deep traumatic lacerations and reduction of bone fractures in the ED	ASA physical status >=3; a positive history for adverse reaction to ketamine, propofol, midazolam, fentanyl, or egg; pregnancy; increased intracranial pressure; multiple trauma; and patients with a major psychiatric disease (e.g., psychosis) who were unable to complete the Visual Analog Scale (VAS)
Parlak 2006	Single site RCT	Midazolam: 37 Propofol: 33	67.91 ± 11.39	Adult	ER	Patients at least 18 years of age, had 90% or higher peripheral oxygen saturation while breathing room air and were free from any respiratory problems, had a sufficient preprocedural fasting period, were undergoing an elective cardioversion because of atrial fibrillation, and were able to provide a written informed consent	Uncooperative patients, those with liver and renal insufficiency, electrolyte imbalance, acute respiratory symptoms, chronic obstructive pulmonary disease, blood pressure less than 90/60 mm Hg, or obscure cardiac rhythms, and those who were taking digoxin, beta blockers, or heparin
Phillips 2010	Single site RCT	Propofol: 14 Propofol-ketamine: 14	N/A	Adult	ER	Patients undergoing joint dislocation reduction or fracture manipulation. All patients were over the age of 21 and GCS 15	No participant was clinically intoxicated and there was no history of psychiatric problems or opioid use/dependency. All patients were hemodynamically stable prior to sedation and did not demonstrate signs of a potentially difficult airway
Rahman 2011	Single site RCT	Propofol-fentanyl: 20 Fentanyl-midazolam: 20	Age, years: PF 40.6 (95% CI 38.2-43.3); FM 35.0 (95% CI 33.2-37.6)	Adult/ Pediatric	ER	(1) all trauma (except head injury) and nontrauma adult patients; (2) all patients aged 12 years and above who gave verbal and written consent to participate in the study. Parental consent was obtained if the patient's age was between 12 and 18 years; (3) all patients who were indicated for procedural sedation; (4) all patients with a physical status of ASA I and II	N/A

Salen 2016	Single site RCT	Ketamine: 46 Etomidate: 34	ketamine 46.4 ± 24.4; etomidate 51.6 ± 22.6	Adult	ER	All adult (age > 18 years) ED patients in need of PS for the purposes of reduction of a dislocated large joint (shoulder, hip, knee, ankle, and elbow)	Age < 18 years, inability to give informed consent, altered mental status, suspected cocaine or other illicit drug abuse, an ASA Physical Assessment Score of > 2, allergy to etomidate or ketamine, pregnancy, or evidence of illicit drug intoxication prior to the start of the PS
Sawas 2013	Single site RCT	Ketamine-Propofol: 48 Propofol: 51	Mean: 45 +/- 18 years	Adult	ER	N/A	N/A
Sener 2011	Single site RCT	IV ketamine-placebo: 45 IV ketamine-midazolam: 45 IM ketamine-placebo: 47 IM ketamine-midazolam: 45	Median (IQR), years: IV K - 35 (24–40); IV KM - 29 (25–38); IM K - 27 (22–33); IM KM - 31 (22.5–37)	Adult	ER	Patients selected for ketamine administration who were between the ages of 18 and 50 years and in good health or with only mild systemic disease (ASA I or II)	Patients with significant cardiovascular disease, central nervous system lesions or injuries, psychiatric disorders, pregnancy, ocular pathology, thyroid disease, acute pulmonary infections, conditions requiring stimulation of the posterior pharynx, and who had ingested solid food in the previous 4 hours or clear liquids in the previous 2 hours
Seol 2015	Single site RCT	Ketamine-propofol: 25 Propofol-remifentanil: 25	Median (range), months: PK 19 (12–36); PR 18 (12–33)	Pediatric	ER	Patients (ASA physical status I and II, aged 12–36 months, with second-degree burns; total burn surface area of 5–25%) scheduled for the first burn dressing change after skin graft surgery	Cardiovascular, cerebrovascular, pulmonary, renal or hepatic disease, upper respiratory infection or were at risk of aspiration
Shah 2011	Single site RCT	Ketamine: 69 Ketamine-propofol: 67	Median (IQR), years: ketamine 11 (7–13); KP 11 (7–14)	Pediatric	ER	ASA class I and II children aged 2 to 17 years with an isolated orthopedic injury that required procedural sedation and analgesia	Hemodynamic instability; seizure disorder; significant heart or lung disease; pregnancy; intoxication; an allergy to eggs, soy, or the study drugs; and other traditional ketamine contraindications
Sheik 2017	Single site RCT	Ketamine-propofol 0.5:1: 50 Ketamine: 50	ketofol 31.1 ± 8.4; ketamine 30.4 ± 11.9	Adult	ER	Patients aged 14 years old or older, and ASA class 1 to 2 status and patients of any country of origin	Hemodynamic instability; pregnancy; head injury; intoxication; an allergy to egg, soy and study medicine; and other traditional ketamine contraindication
Sherwin 2000	Single site RCT	ketamine-midazolam: 53	Median (IQR), years: midazolam 7.3 (4.1 to 10.9);	Pediatric	ER	Children aged 12 months to 15 years for ketamine sedation if they required short painful procedures	Age ≤3 mo; History of airway instability, tracheal surgery, or tracheal stenosis; procedures involving stimulation of the posterior pharynx; active pulmonary infection or disease (including upper-

		ketamine-placebo: 51	placebo 6.1 (2.2 to 10.7)			(especially procedures in which immobilization was required) or examinations likely to produce emotional distress	respiratory infection); full meal in 3 hours preceding procedure; cardiovascular disease including angina, heart failure, and hypertension; head injury associated with loss of consciousness, altered mental status, or emesis; central nervous system masses, abnormalities, or hydrocephalus; poorly controlled seizure disorder; glaucoma or acute globe injury; psychosis, porphyria, thyroid disorder, or thyroid medication
Soysal 2004	Single site RCT	Fentanyl-Midazolam: 36 Meperidine-Midazolam: 34	fentanyl 45.58±16.51, meperidine 42.94±16.88	Adult	ER	Adult patients with extremity fracture or dislocation	Patients younger than 16 years or older than 60; pregnant women; patients with coronary artery disease, hypertension, respiratory depression, or neuropsychiatric disorders; patients using sedative drugs; and patients with a history of previous opioid use. Patients experiencing cardiovascular complications or failing to achieve effective analgesic relief despite the administration of additional doses were also excluded from the study
Stronati 2020	Single site RCT	Propofol: 34 Midazolam: 35	66.5 ± 12.0	Adult	ER	Age > 18 years old and admission for high rate atrial fibrillation or atrial flutter requiring urgent/emergency cardioversion	Documented or suspected allergy or intolerance to midazolam or propofol
Tajoddini 2020	Single site RCT	Ketamine-Propofol: 98 Propofol-fentanyl: 98	31.42 ± 8.54	Adult	ER	ASA physical status 1 and patients who needed a painful procedure in the ED	Patients with clinically significant cardiovascular/hepatic diseases, epileptic disease, respiratory disease, O2 saturation less than 92%, SBP <100 mmHg, and GCS score less than 15. Procedure longer than 1 h, hypersensitivity to the drugs
Taylor 2005	Multisite RCT	Propofol: 48 Midazolam-Fentanyl: 38	Mean, 95% CI, years: propofol 40.9 (34.7, 47.1); MF 45.2 (37.3, 53.1)	Adult	ER	Anterior dislocation of the shoulder and aged 18 years or older	Presence of any other injury (including a fracture around the shoulder), known allergy or hypersensitivity to any of the study drugs, contraindication to sedation (<4 hours since food/fluid intake, <6 hours since recreational drug or alcohol use, anticipated airway difficulty), pregnant
Uri 2011	Single site RCT	Propofol: 30 Midazolam-ketamine: 30	45 ± 17	Adult	ER	Patients with orthopaedic injuries requiring painful manipulation (reduction of a fracture or dislocation, suture of an extensive laceration) Inclusion criteria	N/A

						were (1) an age of 18 to 65 years, (2) ASA score of 1 or 2, (3) SBP of >90 mmHg before the initiation of sedation, (4) willingness and ability to provide informed consent, (5) no known hypersensitivity to any of the study medications, (6) no evidence of intoxication, (7) no solid food two hours before the induction of sedation, and (8) a nonpregnant status (for women)	
Vahidi 2018	Multisite RCT	Midazolam-fentanyl: 35 Thiopental-fentanyl: 35	midazolam 25.77 ± 3.69; thiopental 27.94 ± 5.56	Adult	ER	Patients aged >18 years old who were diagnosed with anterior shoulder dislocation	Patients with other types of shoulder dislocation, severe neurovascular injury, dislocation longer than 24 hours, fracture dislocation, multiple trauma mechanism, no consent to participate in the study, decreased level of consciousness, systolic hypotension <90 mmHg, drugs hypersensitivity, illicit drug use, age<18 years, pregnancy or hepatorenal disorders
Vardi 2002	Single site RCT	Ketamine-midazolam-fentanyl: 47 Propofol-lidocaine: 58	7.25 ± 5.73	Pediatric	ER	Fasting required - solid food (including milk) was withheld for at least 8 hrs in children over 36 months of age, for 6 hrs in children between 6 and 36 months of age, and for 4 hrs in younger patients. All the children were allowed clear liquids up to 3 hrs before the procedure	N/A
Venkatakrishnan 2011	Single site RCT	Propofol-fentanyl: 20 Ketamine-Midazolam: 20	Mean, years: KM 34.5, PF 37.6	Adult	ER	Patients aged > 18 years, with isolated limb injury, having a pain score of 7 or more on VAS, and fasting for at least 4 h	Patients with respiratory compromise, hemodynamic instability, head injury or raised intracranial pressure, psychiatric history, pregnancy, allergy to drugs used in the study, or inability to understand VAS pain score
Wathen 2000	Single site RCT	Ketamine: 129	Mean (IQR), years: K 6.8 (4.4,	Pediatric	ER	Children 4 months to 18 years receiving pediatric ED procedures	Age younger than 4 months, hypertension, glaucoma, globe injury, increased intracranial pressure or central nervous system mass lesion,

		Ketamine-Midazolam: 137	10.3); KM 5.6 (3.4, 9.6)				active upper or lower respiratory tract infection, procedures of the pharynx/larynx or trachea, congenital or anatomic airway abnormalities, major psychiatric disorder, porphyria, or previous adverse reaction to ketamine. ASA class I and II
Weisz 2017	Single site RCT	Ketamine: 96 Ketamine-propofol: 91	Median (IQR), years: ketamine 8.3 (6); KP 9.3 (5)	Pediatric	ER	Patients between 3 and 21 years of age who had an ASA physical status classification of I/IE or II/ IIE	Hypertension (BP > 95th percentile for age); glaucoma or acute globe injury; increased intracranial pressure or central nervous system mass lesion; porphyria; previous allergic reaction to ketamine; previous allergic reaction to propofol or its components, including soybean oil, glycerol, egg lecithin, and disodium edentate; disorders of lipid metabolism, including primary hyperlipoproteinemia, diabetic hyperlipemia, or pancreatitis; mitochondrial myopathies or disorders of electron transport; and pregnancy
Wright 1993	Multisite RCT	Midazolam: 36 Diazepam: 33	M 30 ± 8; D 32 ± 11	Adult	ER	Patients requiring one of the following painful procedures: abscess incision and drainage, joint or fracture reduction, extensive suturing or soft tissue repair, burn debridement, chest tube insertion, or lumbar puncture	Pregnant and lactating women, history of allergy or adverse reactions to one of the study drugs or similar agents, altered level of consciousness, multiple trauma victims, hemodynamic instability, history of chronic obstructive pulmonary disease, dehydration, recent narcotic or benzodiazepine use, inability to obtain informed consent
Yang 2018	Single site RCT	Dexmedetomidine-remifentanil: 20 Remifentanil: 20	N/A	Adult	ICU	Patients hospitalized in our burn intensive care unit	N/A
Yildirim 2007	Single site RCT	Propofol-remifentanil: 30 Midazolam-remifentanil: 30	PR 56.53 ± 9.56; MR 56.10 ± 9.90	Adult	ICU	Sixty patients who presented with atrial fibrillation after coronary artery bypass grafting, and who underwent cardioversion after not responding to medical treatment that was given to restore sinus rhythm	Hemodynamic instability; ASA grade IV physical status classification; clinical signs of behavior, memory, or consciousness disorder; evidence of hepatic or renal illness; known allergy or secondary reaction to eggs or benzodiazepines; long-term treatment with benzodiazepines or H2 inhibitors; history of sleep apnea

Yldzdas 2004	Single site RCT	Midazolam: 26 Ketamine: 25 Ketamine-Midazolam: 25 Ketamine-Fentanyl: 25 Propofol: 25	8.3 ± 3.7	Pediatric	ICU	Children who needed sedation/analgesia for minor procedures	Patients with severe systemic illness, pulmonary disease, hepatic or renal failure, prior adverse reactions to sedative/analgesic drugs, intolerance to the nasal cannula, and injury that precluded placement of nasal cannulas and need for oxygen

Abbreviations: RCT – randomized clinical trial; ASA - American Society of Anesthesiology; PSA - procedural sedation and analgesia; GCS - Glasgow coma scale; SBP - systolic blood pressure; DBP - diastolic blood pressure; BP - blood pressure

Supplement Table 2. Risk of Bias Assessment

Author, Year	Bias arising from the randomization process	Bias due to protocol deviations	Bias in measurement of the outcome	Bias due to missing outcome data	Bias in selection of the reported result	Overall ROB
Abdolrazaghnejad 2017	probably low	low	low	probably low	probably low	probably low
Afzalimoghaddam 2021	low	low	low	low	probably low	probably low
Akhlaghi 2019	low	low	low	probably low	probably low	probably low
Amini 2018	low	probably low	probably low	probably low	probably low	probably low
Aminiahidashti 2018	low	low	low	low	probably low	low
Andolfatto 2012	low	low	low	low	low	low
Arhami Dolatabadi 2018	probably low	probably low	probably low	probably low	probably low	probably low
Arhami Dolatabadi 2018b	low	low	low	low	low	low
Azizkhani 2021	low	low	low	low	low	low
Bahreini 2020	low	low	low	probably low	low	low
Barcelos 2015	probably low	probably low	probably low	probably low	probably low	probably low
Bauman 2002	probably low	probably low	probably low	probably low	probably low	probably low
Burton 2002	low	probably low	low	probably low	low	probably low
Cevik 2013	low	low	low	low	low	low
Chan 2008	low	low	low	probably low	probably low	probably low
Cimilli Ozturk 2014	low	low	probably low	low	low	low
Coll-Vinent 2003	low	low	probably low	low	low	low
David 2011	low	low	low	low	low	low
Del Pizzo 2011	probably low	probably low	probably low	probably low	probably low	probably low

Derakhshanfar 2015	probably low	probably low	probably low	probably low	probably low	probably low
Di Liddo 2006	low	low	probably low	probably low	probably low	probably low
Dilli 2008	low	low	probably low	probably low	low	probably low
Disel 2016	probably low	low	probably low	low	low	probably low
Dunn 2010	probably low	low	probably low	low	low	probably low
Ferguson 2016	low	low	low	low	low	low
Gale 1993	probably low	low	probably low	low	low	probably low
Genzlinger 2012	probably low	probably low	probably low	probably low	probably low	probably low
Gharavifard 2016	low	low	low	low	probably low	low
Godambe 2003	probably low	low	probably low	probably low	low	probably low
Gumus 2012	probably low	low	low	probably low	probably low	probably low
Hart 1997	probably low	probably low	probably low	probably low	probably low	probably low
Hatamabadi 2015	low	low	low	low	low	low
Havel 1999	low	low	probably low	probably low	low	probably low
Hunt 2005	low	low	low	probably low	low	low
Holger 2005	probably low	low	probably low	probably low	probably low	probably low
Jamal 2011	probably low	probably low	probably low	probably low	probably low	probably low
Kennedy 1998	low	probably low	probably low	low	low	probably low
Khutia 2012	probably low	low	low	probably low	low	probably low
Kienstra 2004	probably low	probably low	probably low	probably low	probably low	probably low
Lee-Jayaram 2010	probably low	low	probably low	low	low	probably low
Lemoel 2017	low	low	probably low	low	probably low	probably low
LucasdaSilva 2007	low	probably low	probably low	low	low	probably low
Maltepe 2006	probably low	low	low	low	low	low
Masoumi 2019	low	low	probably low	probably low	low	low
Massaeli 2022	probably low	low	low	low	low	low
Messenger 2008	low	low	probably low	low	low	low
Miner 2003	probably low	low	low	probably low	low	probably low
Miner 2007	low	probably low	probably low	low	low	probably low

Miner 2009	low	probably low	probably low	low	low	probably low
Miner 2010	low	probably low	probably low	low	low	probably low
Miner 2013	low	probably low	probably low	low	low	probably low
Miner 2015	low	low	low	low	low	low
Miner 2017	low	probably low	low	low	low	low
Mofidi 2018	low	low	low	low	low	low
MonsefKasmaee 2019	low	low	low	low	low	low
Moro-Sutherland 2000	low	probably low	probably low	low	low	probably low
Nashibi 2017	probably low	low	low	low	low	low
Nejati 2011	low	low	probably low	low	low	low
Parlak 2006	low	low	low	low	low	low
Phillips 2010	probably low	low	probably low	probably low	probably low	probably low
Rahman 2011	low	low	probably low	low	low	low
Salen 2016	probably low	low	probably low	low	low	probably low
Sawas 2013	probably low	probably low	probably low	probably low	probably low	probably low
Sener 2011	low	low	probably low	low	low	low
Seol 2015	probably low	low	low	low	low	low
Shah 2011	probably low	low	low	probably low	low	probably low
Sheik 2017	probably low	probably low	probably low	low	low	probably low
Sherwin 2000	low	low	low	low	low	low
Soysal 2004	probably low	low	low	low	low	low
Stronati 2020	probably low	low	probably low	low	low	probably low
Tajoddini 2020	low	low	low	low	probably low	low
Taylor 2005	low	low	probably low	low	low	low
Uri 2011	probably low	low	probably low	probably low	low	probably low
Vahidi 2018	low	low	low	low	low	low
Vardi 2002	probably low	low	probably low	low	low	probably low

Venkatakrishnan 2011	probably low	probably low	probably low	probably low	probably low	probably low
Wathen 2000	low	low	low	low	low	low
Weisz 2017	low	low	probably low	low	low	low
Wright 1993	probably low	low	low	low	low	low
Yang 2018	probably low	probably low	probably low	probably low	probably low	probably low
Yildirim 2007	probably low	low	probably low	probably low	probably low	probably low
Yldzdas 2004	low	probably low	probably low	low	low	probably low

Supplement Table 3. Adverse Event Definitions

Study author and year	Respiratory Adverse Events	Cardiac Adverse Events	Gastrointestinal Adverse Evets	Neurologic Adverse Events	Other Adverse Events
Abdolrazaghnejad 2017	Intubation, BMV	NA	Nausea, vomiting	Vertigo, recovery agitation, fasciculations	Hiccups
Afzalimoghaddam 2021	Hypoxia (O2 saturation <94%)	Hypotension (SBP <90mmHg)	NA	NA	NA
Akhlaghi 2019	Laryngospasm, hypoxia	Cardiovascular events, change in BP	Nausea, vomiting	Severe agitation	NA
Amini 2018	Apnea	Hemodynamic instability	Nausea, vomiting	NA	NA
Aminiahidashti 2018	Change in RR, change in O2 saturation, intervention required to maintain respiratory status	Change in BP, change in HR	NA	NA	NA
Andolfatto 2012	NA	Bradycardia, hypotension	Vomiting	Procedural agitation, recovery agitation	Rash
Arhami Dolatabadi 2018	Apnea	Hypotension, bradycardia	Nausea, vomiting	NA	NA
Arhami Dolatabadi 2018b	Apnea, hypoxia	Dysrhythmia	Nausea, vomiting	NA	NA
Azizkhani 2021	O2 desaturation, BMV, neck repositioning, supplemental O2	Hypotension, bradycardia	NA	Hallucination, nightmare, disorientation	NA
Bahreini 2020	Hypoxia, hypoventilation, apnea, use of airway maneuvers, orotracheal intubation, cough	Bradycardia, hypotension	Nausea, vomiting	Emergence phenomena, recovery agitation, myoclonus	NA
Barcelos 2015	Fall in O2 saturation, apnea, laryngospasm	Tachycardia, hypotension	Vomiting	Agitation, hallucination	Use of reversal (flumazenil, naloxone)
Bauman 2002	NA	Hypotension	Nausea, vomiting	NA	Stiff chest
Burton 2002	O2 saturation <90%, apnea, BMV	NA	Vomiting	Myoclonus	Pain with injection, use of reversal (flumazenil)
Cevik 2013	Hypoxia, O2 required	NA	Nausea, vomiting	Vertigo, recovery agitation, fasciculation	Hiccups
Chan 2008	O2 desaturation, BMV, intubation	Hypotension, use of inotropic agent	Nausea, vomiting	NA	Pain at injection site, use of reversal (flumazenil, naloxone)
Cimilli Ozturk 2014	Apnea >30s, O2 saturation <90%, airway maneuvers, BMV, intubation	NA	NA	NA	NA

Coll-Vinent 2003	Apnea >20s, O2 saturation <90%, bronchospasm	NA	Nausea, vomiting	Myoclonus	Pain at injection site, procedure recall, resedation, spontaneous complaint of patient
David 2011	ETCO2 increase >5mmHg of >=10s duration, RR<8 breaths/min of >=10s duration, O2 saturation <90% of >=10s duration, apnea >15s, airway manipulation (jaw repositioning, BMV)	NA	NA	NA	NA
Del Pizzo 2011	NA	NA	NA	NA	NA
Derakhshanfar 2015	Hypoxia	NA	NA	Agitation	NA
Di Liddo 2006	Desaturation (O2 saturation <93% for >10s), apnea	NA	Nausea, vomiting	Myoclonus	Pain with injection
Dilli 2008	Apnea, O2 saturation <90%	Hypotension	Nausea, vomiting	Nightmares, dizziness	Crying spells
Disel 2016	Hypoxemia (O2 saturation <96% for >10s), pulmonary aspiration, respiratory arrest	Cardiac arrest, hypotension	Nausea, vomiting, excessive secretions	Myoclonus	Urticaria, pain at injection site, anaphylaxis
Dunn 2010	O2 desaturation, apnea	Hypotension	Nausea	Dizziness	Fainting, use of reversal
Ferguson 2016	Hypoxia (O2 saturation <93%), RR <=8 breaths/min, apnea, laryngospasm, aspiration, rescue intervention (increased O2 flow rate, airway repositioning, BMV, intubation), aspiration	Hypotension (SBP <90mmHg)	Vomiting	NA	NA
Gale 1993	Apnea >30s, O2 saturation <90%	NA	NA	Confusion, agitation lasting >10min	Pain with injection, procedure recall
Genzlinger 2012	Laryngospasm, intubation, BMV, chin lift, jaw thrust	Change in vital signs	Vomiting, hypersalivation	Emergence reactions, myoclonus	NA
Gharavifard 2016	Required supplemental O2, BMV, use of rescue maneuver, insertion of airway, respiratory stimulation, O2 saturation <92%, cough, bronchospasm, laryngospasm, stridor, apnea, aspiration	NA	Nausea, vomiting	Dysphoria, headache, myoclonus, seizures, restlessness, agitation	Stiffness, rash
Godambe 2003	O2 saturation <90%, required supplemental O2, airway repositioning, suction, laryngospasm, apnea	Hypotension,	Vomiting	Agitation, nightmares	Pain, behavioural change
Gumus 2012	NA	NA	NA	NA	NA

Hart 1997	O2 saturation <90% for >1min, ETCO2 >=50, required supplemental O2	NA	NA	NA	Use of reversal
Hatamabadi 2015	Apnea	Bradycardia	NA	NA	NA
Havel 1999	Hypoxemia	Signs of hypoperfusion (e.g. delayed peripheral pulses, cool and pale distal extremities)	Vomiting	Agitation	Pain with medication administration, procedure recall, oversedation, fever
Hunt 2005	Desaturation, apnea	Hypotension	NA	Myoclonus, agitation	Use of reversal
Holger 2005	NA	NA	Vomiting	NA	Procedure recall
Jamal 2011	O2 saturation <90%	Arrhythmia	Nausea	Dizziness, emergence delirium	NA
Kennedy 1998	Stridor, laryngospasm	NA	Nausea, vomiting, dry mouth	Emergence, pleasant dreams, nightmares, dizziness, headache, hallucinations	Sleepiness, crying
Khutia 2012	Desaturation	Hypotension	Nausea, vomiting	Hallucinations, agitation	Pain
Kienstra 2004	Apnea, hypoxia (O2 saturation <93%), laryngospasm, cough	Bradycardia, hypotension	Vomiting	Headache, agitation, myoclonus	Histamine reaction, hiccups, pain with injection
Lee-Jayaram 2010	Hypoxemia (O2 saturation <93%)	NA	Vomiting	Myoclonus, emergence reaction (e.g. dysphoria, hallucination, outbursts)	Pain at injection site
Lemoel 2017	Apnea >20s, upper airway obstruction, hypoxia (O2 saturation <92%), ETCO2 >50mmHg	Hypotension	Nausea, vomiting	NA	NA
LucasdaSilva 2007	Need for manual airway manipulation, BMV, tracheal intubation, desaturation	Alteration in vital signs (>20% variation from baseline), hypotension	NA	NA	Use of reversal
Maltepe 2006	Apnea, cough	NA	Nausea, vomiting	NA	Abnormal movement
Masoumi 2019	NA	NA	NA	NA	NA
Massaeli 2022	Desaturation, apnea, RR<8, airway obstruction, respiratory events	Hypotension	Vomiting	Agitation, delusion, delirium	NA
Messenger 2008	Desaturation, supplemental O2 required, use of rescue maneuvers, rise in ETCO2, BMV, artificial airway required	Hypotension, dysrhythmia, use of vasoactive agent	Vomiting prior to recovery of verbal response	NA	Use of reversal (naloxone)
Miner 2003	Respiratory depression, aspiration, intubation, assisted ventilation (e.g. BMV)	Hypotension, arrhythmia	Vomiting	NA	Transfer to higher level of care after procedure

Miner 2007	Subclinical respiratory depression, use of supplemental O2, BMV, airway repositioning, stimulation to induce breathing	NA	NA	Myoclonus	NA
Miner 2009	Subclinical respiratory depression, use of supplemental O2, BMV, airway repositioning, stimulation to induce breathing, aspiration, intubation	Hypotension, arrhythmia	Vomiting	NA	Transfer to higher level of care after procedure
Miner 2010	Subclinical respiratory depression, aspiration, intubation	Hypotension, arrhythmia	Vomiting	Recovery agitation	Transfer to higher level of care after procedure
Miner 2013	Subclinical respiratory depression, aspiration, intubation	Hypotension, arrhythmia	Vomiting	NA	Transfer to higher level of care after procedure
Miner 2015	Respiratory adverse event leading to an intervention, intubation	Arrhythmia, bradycardia, hypotension	NA	Procedural agitation, recovery agitation (restlessness, confusion, dysphoria, hallucinations)	NA
Miner 2017	Respiratory adverse event leading to an intervention, intubation	Arrhythmia, bradycardia, hypotension	NA	Procedural agitation, recovery agitation (restlessness, confusion, dysphoria, hallucinations)	NA
Mofidi 2018	Desaturation, apnea	Hypotension, bradycardia	NA	NA	NA
MonsefKasmaee 2019	Apnea	NA	NA	Agitation	NA
Moro-Sutherland 2000	Desaturation, assisted ventilation, intubation	Resuscitation required	NA	NA	Inadequate sedation
Nashibi 2017	Apnea, cough	Bradycardia	Vomiting	Agitation, myoclonus, delirium, seizure, nystagmus	Rash, itching
Nejati 2011	Apnea, desaturation, cough	Bradycardia	NA	Emergence reaction, restlessness, vertigo	Involuntary movements, hiccups
Parlak 2006	Desaturation (O2 saturation <95%), apnea (respiratory arrest >=20s)	NA	NA	NA	NA
Phillips 2010	NA	NA	NA	Delirium, vivid dreams, disorientation	NA
Rahman 2011	Hypoxemia, hypoventilation, apnea	NA	NA	NA	NA
Salen 2016	Laryngospasm, respiratory depression	NA	Vomiting, hypersalivation	Recovery agitation, myoclonus	Use of additional doses of nonstudy sedative agents

Sawas 2013	Clinical respiratory depression (placement of an airway, airway maneuvers, BMV, intubation), subclinical respiratory depression	NA	NA	NA	NA
Sener 2011	Desaturation, apnea, laryngospasm	NA	Nausea, vomiting	Recovery agitation	NA
Seol 2015	Hypoxia, respiratory depression	Hypotension, bradycardia	Nausea, vomiting	NA	Movement during procedure
Shah 2011	Upper airway obstruction, desaturation	NA	Nausea, vomiting, hypersalivation	Agitation, hallucination, delirium, diplopia	Muscle rigidity, rash, pain on injection
Sheik 2017	Hypoxia	NA	Vomiting	Emergence reaction	Muscle hypertonicity, drowsiness
Sherwin 2000	Airway complications	NA	Emesis while sedated or during recovery, hypersalivation	NA	NA
Soysal 2004	Dyspnea, apnea, respiratory distress	Hypotension, bradycardia, tachycardia	Nausea, vomiting	Seizures, euphoria	NA
Stronati 2020	Hypoxia (O2 saturation <85%), orotracheal intubation	Bradycardia, hypotension, stroke, transient ischemic attack	NA	NA	NA
Tajoddini 2020	NA	Hypotension, bradycardia	Vomiting	Procedural agitation, recovery agitation	Rash
Taylor 2005	Respiratory depression, aspiration	Hypotension	Vomiting	NA	Moaning, procedure recall, pain at IV site
Uri 2011	Apnea, hypoxemia	Hypotension, bradycardia	NA	Agitation, euphoria	NA
Vahidi 2018	Apnea	NA	Nausea, vomiting	NA	NA
Vardi 2002	Airway repositioning, apnea, BMV, intubation	Hypotension	NA	Hallucinations	Allergic reactions
Venkatakrishnan 2011	Airway intervention	NA	NA	NA	NA
Wathen 2000	Apnea, laryngospasm, O2 saturation <90%	NA	Vomiting	Emergence phenomena (agitation, dysphoria, euphoria, dreaming, nightmares, hallucination)	NA
Weisz 2017	Apnea, laryngospasm, aspiration, desaturation	Hypotension, bradycardia	NA	NA	NA
Wright 1993	Apnea	Hypotension	Nausea, vomiting	Dizziness, headache	Phlebitis, diaphoresis, eyelid swelling
Yang 2018	Respiratory depression	Hypotension, bradycardia	Nausea, vomiting	NA	NA
Yildirim 2007	Apnea, desaturation, cough	NA	Nausea, vomiting	NA	Abnormal movement

Yldzdas 2004	Respiratory depression	NA	NA	NA	NA

Abbreviations: BMV - bag and mask ventilation; SBP - systolic blood pressure; DBP - diastolic blood pressure; BP - blood pressure; HR - heart rate; RR - respiratory rate; O2 - oxygen; ETCO2 - end-tidal CO2.

Supplement Table 4. Surface Under the Cumulative Ranking curve (SUCRA), pairwise and loop incoherence estimates for recovery time

SUCRA and ranking probabilities for treatments

Treatment	SUCRA	PrBest	MeanRank
Propofol	85.5	3.2	4.2
Methohexital-Opioid	83.0	21.5	4.7
Methohexital	82.5	21.3	4.9
Propofol-Morphine	79.9	32.7	5.4
Etomidate-Opioid	79.8	6.5	5.5
Propofol-Opioid	77.8	0.4	5.9
Opioid	72.6	3.6	7.0
KPMFL combination	71.1	8.2	7.4
Ketamine-Propofol	67.7	0.0	8.1
Thiopental-Opioid	58.7	0.6	10.1
Etomidate	58.2	0.2	10.2
Dexmedetomidine-Opioid	56.8	1.5	10.5
Ketamine	56.4	0.0	10.6
Midazolam-Opioid	40.7	0.0	14.0
Midazolam	34.5	0.0	15.4
Dexmedetomidine	31.9	0.2	16.0
Diazepam-Opioid	29.9	0.0	16.4
Ketamine-Midazolam	26.9	0.0	17.1
Midazolam-Morphine	17.5	0.0	19.2
Midazolam-Flumazenil	15.3	0.0	19.6
Ketamine-Haloperidol	10.7	0.0	20.7
Pentobarbital	10.1	0.0	20.8
Promethazine-Chlorpromazine-Opioid	2.6	0.0	22.4

Direct and indirect estimates of effect and P value for pairwise incoherence

Treatment/Comparison	Direct MD	Indirect MD	dif	sedif	p value	Tau
ETMD vs PFOL*	3.38 (-7.85, 14.60)	18.64 (4.19, 33.08)	-15.259	9.333	0.102	7.958
ETMD vs KTMN	6.64 (-5.66, 18.93)	-8.62 (-22.17, 4.93)	15.259	9.333	0.102	7.958
ETMD vs MDFM*	-29.25 (-48.47, -10.03)	-12.36 (-49.87, 25.15)	-16.890	20.477	0.409	8.309
KTFL vs PFOL	8.35 (0.09, 16.60)	2.53 (-6.90, 11.95)	5.820	6.394	0.363	8.290
KTFL vs KTMN	-3.07 (-11.53, 5.39)	-4.27 (-14.04, 5.50)	1.201	6.594	0.855	8.421
KTFL vs OPMZ	-6.93 (-23.43, 9.57)	-11.38 (-19.37, -3.38)	4.446	9.355	0.635	8.393
KTFL vs OPPF	0.35 (-5.84, 6.54)	10.29 (0.23, 20.35)	-9.938	6.030	**0.099**	8.074
KTFL vs TPFN	-1.08 (-18.01, 15.85)	-6.43 (-24.59, 11.74)	5.345	12.671	0.673	8.397
KTHL vs KTMN*	30.67 (13.64, 47.70)	27.58 (-5.83, 60.99)	3.092	18.983	0.871	8.414
KTHL vs MZKT*	14.17 (-2.92, 31.26)	17.26 (-16.05, 50.58)	-3.092	18.983	0.871	8.414
KTMN vs PFOL	10.13 (-6.84, 27.10)	9.24 (1.19, 17.28)	0.894	9.581	0.926	8.417
KTMN vs MZKT*	-8.16 (-18.04, 1.71)	-21.98 (-31.62, -12.33)	13.812	7.044	**0.050**	7.921
KTMN vs OPET	4.90 (-12.46, 22.26)	10.06 (-5.16, 25.28)	-5.161	11.777	0.661	8.373
KTMN vs OPPF	1.20 (-15.54, 17.94)	7.95 (-0.10, 15.99)	-6.750	9.476	0.476	8.355
MDFM vs PFOL*	32.50 (13.44, 51.56)	49.39 (11.64, 87.13)	-16.890	20.477	0.409	8.309
MPCL vs OPID*	45.00 (27.31, 62.69)	70.94 (19.88, 122.00)	-25.937	27.393	0.344	8.289
MPCL vs OPMZ*	40.00 (19.74, 60.26)	14.06 (-34.04, 62.17)	25.938	27.393	0.344	8.289
MZKT vs PFOL	22.90 (5.97, 39.83)	25.15 (15.99, 34.31)	-2.254	9.821	0.819	8.411
MZKT vs OPET	36.70 (14.41, 58.99)	18.20 (4.92, 31.48)	18.498	13.237	0.162	8.191
MZKT vs OPMZ	2.72 (-7.41, 12.86)	13.80 (3.70, 23.89)	-11.074	7.294	0.129	8.146
MZKT vs OPPF	40.44 (28.61, 52.28)	13.83 (6.26, 21.40)	26.615	7.173	**0.000**	6.799
OPET vs OPMZ	-10.05 (-26.67, 6.57)	-18.93 (-34.55, -3.31)	8.877	11.657	0.446	8.386
OPID vs OPMZ*	-5.00 (-24.79, 14.79)	-17.97 (-36.10, 0.16)	12.969	13.697	0.344	8.289
OPID vs OPPF	-3.37 (-19.93, 13.19)	9.60 (-11.53, 30.73)	-12.969	13.697	0.344	8.289
OPMZ vs PFOL	21.70 (4.19, 39.21)	14.92 (5.91, 23.94)	6.776	10.051	0.500	8.330
OPMZ vs OPPF	11.71 (-0.63, 24.06)	14.61 (5.82, 23.40)	-2.898	7.727	0.708	8.384
OPMZ vs TPFN	4.60 (-11.92, 21.12)	9.95 (-8.60, 28.49)	-5.347	12.671	0.673	8.397
OPPF vs PFOL	-0.25 (-18.78, 18.28)	3.25 (-4.67, 11.18)	-3.501	10.281	0.733	8.374
all the evidence about these contrasts comes from the trials which directly compare them.						

Loop-specific incoherence

Loop				IF	SE IF	p_value	Loop Heterogeneity (tau2)
KTMN	MZKT	OPPF		30.869	12.185	**0.011**	69.425
MZKT	OPMZ	OPPF		25.136	12.859	**0.051**	109.479
MZKT	OPET	OPMZ		23.701	14.415	**0.100**	58.737
KTMN	MZKT	OPET		23.643	14.980	0.114	64.031
PFOL	MZKT	OPPF		19.014	5.938	**0.001**	0.000
PFOL	OPMZ	OPPF		16.505	5.693	**0.004**	0.000
KTHL	KTMN	MZKT		14.223	3.491	**0.000**	0.000
PFOL	ETMD	KTMN		13.14	13.925	0.345	83.089
PFOL	KTMN	OPPF		9.18	5.146	**0.074**	0.000
PFOL	KTFL	OPPF		8.163	8.231	0.321	34.054
OPET	KTMN	OPMZ	OPPF	7.876	25.490	0.757	189.065
PFOL	KTFL	OPMZ		6.542	6.869	0.341	15.888
PFOL	KTMN	MZKT		4.613	12.722	0.717	64.031
PFOL	KTMN	OPET	OPMZ	4.566	5.642	0.418	0.000
KTFL	OPMZ	OPPF		4.373	10.587	0.680	64.830
OPID	OPMZ	OPPF		3.815	6.222	0.540	0.000
KTFL	KTMN	OPET	OPMZ	3.139	6.523	0.630	7.495
KTFL	KTMN	OPPF		2.421	7.451	0.745	35.857
KTFL	KTMN	MZKT	OPMZ	2.075	8.828	0.814	34.379
PFOL	MZKT	OPMZ		1.5	12.743	0.906	61.307
PFOL	KTFL	KTMN		1.282	4.846	0.791	12.042
KTFL	OPMZ	TPFN		1.25	2.259	0.580	0.000
PFOL	ETMD	MDFM		0.25	7.298	0.973	0.000
*MPCL	OPID	OPMZ		0	9.173	1.000	0.000
* These loops are formed only by multi-arm trial(s)							

Supplement Table 5. Surface Under the Cumulative Ranking curve (SUCRA), pairwise and loop incoherence estimates for Patient Satisfaction as a Continuous Outcome

SUCRA and ranking probabilities for treatments

Treatment	SUCRA	PrBest	MeanRank
Diazepam-Opioid	84.1	42.2	3.2
Ketamine-Midazolam	69.3	6.5	5.3
Ketamine-Propofol	68.6	1.7	5.4
Propofol	68.0	2.6	5.5
Ketamine	66.5	11.9	5.7
Etomidate	65.9	13.6	5.8
Dexmedetomidine-Opioid	55.6	9.7	7.2
Dexmedetomidine	53.4	1.9	7.5
Propofol-Opioid	51.0	0.5	7.9
Midazolam	50.7	7.0	7.9
Promethazine-Chlorpromazine-Opioid	40.8	2.5	9.3
Thiopental-Opioid	27.4	0.1	11.2
Etomidate-Opioid	22.1	0.0	11.9
Midazolam-Opioid	19.3	0.0	12.3
Opioid	7.3	0.0	14.0

Direct and indirect estimates of effect and P value for pairwise incoherence

Treatment/Comparison	Direct MD	Indirect MD	dif	sedif	p value	Tau
DXMT vs OPID	2 (0.25,3.75)	1.1 (-1.6,3.8)	0.900	1.639	0.583	0.860
DXMT vs OPMZ	0.73 (-1.04,2.5)	1.63 (-1.05,4.31)	-0.900	1.639	0.583	0.860
KTFL vs PFOL	0.09 (-1.23,1.4)	-0.37 (-3.09,2.34)	0.459	1.539	0.766	0.890
KTFL vs KTMN	0 (-1.65,1.65)	-0.37 (-5.72,4.99)	0.367	2.859	0.898	0.822
KTFL vs OPMZ	1.6 (-0.43,3.63)	1.42 (-0.15,2.99)	0.180	1.310	0.891	0.875
KTFL vs OPPF	0 (-1.8,1.8)	0.94 (-0.8,2.67)	-0.935	1.273	0.463	0.829
KTFL vs TPFN	1.43 (-0.41,3.27)	1.05 (-1.22,3.31)	0.384	1.489	0.797	0.881
KTMN vs OPET	1.8 (-3.31,6.91)	1.43 (-0.87,3.74)	0.367	2.859	0.898	0.822
MPCL vs OPID*	1.14 (-0.91,3.19)	2.94 (-3.23,9.11)	-1.800	3.278	0.583	0.860
MPCL vs OPMZ*	0.77 (-1.38,2.92)	-1.03 (-7.09,5.03)	1.800	3.278	0.583	0.860
MZKT vs PFOL	-0.12 (-1.95,1.71)	0.34 (-2.06,2.74)	-0.459	1.539	0.765	0.890
MZKT vs OPET	3.25 (1.41,5.09)	-0.28 (-1.87,1.32)	3.525	1.240	**0.004**	0.516
MZKT vs OPPF	-0.43 (-1.12,1.98)	1.73 (-3.54,0.08)	2.160	1.215	**0.076**	0.693
OPET vs OPMZ	0.72 (-0.35,1.79)	-2.6 (-4.67,-0.54)	3.322	1.187	**0.005**	0.515
OPID vs OPMZ*	-0.37 (-2.4,1.66)	-1.27 (-3.76,1.22)	0.900	1.639	0.583	0.860
OPMZ vs OPPF	0.27 (-0.14,0.68)	-2.18 (-2.97,-1.38)	2.446	0.455	**0.000**	0.000

OPMZ vs TPFN	-0.35 (-2.09,1.39)	0.03 (-2.31,2.37)	-0.384	1.489	0.797	0.881
all the evidence about these contrasts comes from the trials which directly compare them.						

Loop-specific incoherence

Loop				IF	SE IF	p_value	Loop Heterogeneity (tau2)
MZKT	OPET	OPMZ	OPPF	4.662	0.980	**0.000**	0.000
KTFL	OPMZ	OPPF		1.87	0.711	**0.008**	0.000
KTFL	KTMN	OPET	OPMZ	0.912	2.573	0.723	0.000
DXMT	OPID	OPMZ		0.9	0.683	0.188	0.000
PFOL	KTFL	MZKT	OPPF	0.306	0.620	0.622	0.000
KTFL	OPMZ	TPFN		0.18	0.659	0.785	0.000
*MPCL	OPID	OPMZ		0	1.074	1.000	0.000
* These loops are formed only by multi-arm trial(s)							

Supplement Table 6. Surface Under the Cumulative Ranking curve (SUCRA), pairwise and loop incoherence estimates for Patient Satisfaction as a Dichotomous Outcome

SUCRA and ranking probabilities for treatments

Treatment	SUCRA	PrBest	MeanRank
Ketamine-Propofol	75.6	13.8	4.2
Ketamine-Midazolam	62.9	4.7	5.8
Opioid	60.0	9.7	6.2
Midazolam-Opioid	57.3	3.4	6.6
Propofol	54.3	0.4	6.9
Etomidate	52.6	13.0	7.2
Midazolam-Flumazenil	52.5	13.6	7.2
KPMFL combination	50.7	9.2	7.4
Methohexital	50.3	10.8	7.5
Propofol-Opioid	49.4	0.7	7.6
Midazolam	46.7	9.1	7.9
Ketamine	34.9	0.1	9.5
Etomidate-Opioid	29.8	3.3	10.1
Midazolam-Morphine	23.0	8.4	11.0

Direct and indirect estimates of effect and P value for pairwise incoherence

Treatment/Comparison	Direct RR	Indirect RR	dif	sedif	p value	Tau
KPMF vs OPPF*	1.00 (0.83, 1.21)	1.02 (0.00, 731.68)	-0.018	80.893	1.000	0.093
KTFL vs PFOL	0.99 (0.78, 1.25)	1.11 (0.93, 1.32)	-0.117	0.151	0.440	0.100
KTFL vs KTMN	1.16 (0.99, 1.35)	1.04 (0.82, 1.32)	0.106	0.142	0.457	0.099
KTFL vs OPPF	1.05 (0.92, 1.20)	1.17 (0.91, 1.51)	-0.105	0.145	0.471	0.097
KTMN vs PFOL	1.00 (0.82, 1.23)	0.91 (0.75, 1.10)	0.094	0.141	0.504	0.102
KTMN vs MZKT	0.93 (0.80, 1.09)	0.90 (0.61, 1.32)	0.035	0.210	0.868	0.103
KTMN vs OPPF	1.00 (0.81, 1.24)	0.93 (0.76, 1.12)	0.077	0.146	0.598	0.102
MZKT vs OPMZ	1.02 (0.89, 1.16)	0.98 (0.67, 1.45)	0.035	0.210	0.868	0.103
OPID vs PFOL	1.03 (0.80, 1.33)	1.00 (0.72, 1.38)	0.035	0.210	0.868	0.103
OPID vs OPMZ	1.00 (0.81, 1.23)	1.04 (0.72, 1.48)	-0.035	0.210	0.868	0.103
OPPF vs PFOL	0.98 (0.80, 1.21)	0.99 (0.81, 1.22)	-0.010	0.147	0.946	0.103
all the evidence about these contrasts comes from the trials which directly compare them.						

Loop-specific incoherence

Loop			**ROR**	**p_value**	**RoR 95% CI**	**Loop Heterogeneity (tau2)**
PFOL	KTFL	KTMN	1.22	0.550	(1.00,2.33)	0.041
KTFL	KTMN	OPPF	1.20	0.538	(1.00,2.15)	0.039
PFOL	KTMN	OPPF	1.02	0.778	(1.00,1.14)	0.000
PFOL	KTFL	OPPF	1.02	0.893	(1.00,1.27)	0.000
*PFOL	ETMD	MDFM	1.00	1.000	(1.00,1.44)	0.000
* These loops are formed only by multi-arm trial(s)						

Supplement Table 7. Surface Under the Cumulative Ranking curve (SUCRA), pairwise and loop incoherence estimates for Respiratory Adverse Events

SUCRA and ranking probabilities for treatments

Treatment	SUCRA	PrBest	MeanRank
Ketamine-Propofol	74.1	0.1	7.7
Dexmedetomidine-Ketamine	72.1	1.2	8.3
Midazolam-Flumazenil	70.5	3.5	8.7
Midazolam	70.3	1.9	8.7
Ketamine	69.7	0.2	8.9
Ketamine-Midazolam	68.4	0.1	9.2
Promethazine-Chlorpromazine-Opioid	61.7	6.8	10.9
Dexmedetomidine	60.0	23.3	11.4
Diazepam	58.2	21.3	11.9
Thiopental-Opioid	56.3	0.3	12.4
Ketamine-Haloperidol	55.6	14.5	12.5
Propofol	55.5	0.0	12.6
Methohexital	50.5	0.1	13.9
Etomidate	49.1	0.0	14.2
Ketamine-Propofol-Opioid	49.1	0.3	14.2
Dexmedetomidine-Opioid	48.2	3.1	14.5
Etomidate-Opioid	46.2	0.2	15.0
KPMFL combination	45.9	12.2	15.1
Diazepam-Opioid	45.7	6.2	15.1
Midazolam-Lidocaine-Opioid	44.3	2.7	15.5
Midazolam-Opioid	36.4	0.0	17.5
Propofol-Opioid	33.6	0.0	18.3
Propofol-Morphine	30.5	1.3	19.1
Midazolam-Morphine	29.9	0.2	19.2
Opioid	29.0	0.0	19.5
Methohexital-Opioid	20.0	0.0	21.8
Pentobarbital	19.1	0.5	22.0

Direct and indirect estimates of effect and P value for pairwise incoherence

Treatment/Comparison	Direct RR	Indirect RR	dif	sedif	p value	Tau
DXKT vs KTFL*	0.71 (0.15, 3.39)	1.06 (0.47, 2.43)	0.408	0.909	0.653	0.347
DXKT vs KTMN*	1.28 (0.25, 6.42)	0.85 (0.38, 1.88)	-0.408	0.909	0.653	0.347
ETMD vs PFOL*	4.83 (1.82, 12.80)	0.76 (0.51, 1.13)	-1.847	0.529	**0.000**	0.119

ETMD vs KTMN	0.74 (0.46, 1.21)	4.78 (1.86, 12.28)	1.864	0.539	**0.001**	0.116
ETMD vs MDFM*	6.64 (0.63, 69.54)	0.89 (0.21, 3.76)	-2.012	1.416	0.155	0.333
ETMD vs PNTB	0.18 (0.01, 4.63)	0.45 (0.02, 11.34)	0.899	2.324	0.699	0.318
KTFL vs PFOL	0.57 (0.32, 1.00)	0.83 (0.55, 1.26)	0.376	0.355	0.289	0.347
KTFL vs KTMN*	1.06 (0.56, 2.01)	0.90 (0.60, 1.36)	-0.159	0.388	0.681	0.349
KTFL vs OPMZ	0.57 (0.33, 0.97)	0.21 (0.04, 1.13)	-0.978	0.893	0.273	0.304
KTFL vs OPPF	0.57 (0.32, 1.01)	0.42 (0.22, 0.77)	-0.313	0.428	0.464	0.317
KTFL vs TPFN	0.58 (0.19, 1.75)	1.04 (0.30, 3.62)	0.594	0.852	0.486	0.335
KTHL vs KTMN*	1.02 (0.00, 1033.13)	1.03 (0.02, 53.83)	0.009	4.066	0.998	0.319
KTHL vs MZKT*	1.01 (0.00, 1020.34)	1.00 (0.02, 52.13)	-0.009	4.066	0.998	0.319
KTMN vs PFOL	0.66 (0.43, 1.01)	1.60 (0.90, 2.84)	0.886	0.367	**0.016**	0.210
KTMN vs MDZM	1.15 (0.32, 4.10)	0.96 (0.02, 49.21)	-0.172	2.109	0.935	0.319
KTMN vs MZKT*	1.38 (0.67, 2.81)	0.75 (0.40, 1.43)	-0.604	0.475	0.203	0.317
KTMN vs OPMZ	0.62 (0.37, 1.07)	0.08 (0.01, 0.71)	-2.007	1.116	**0.072**	0.294
KTMN vs OPPF	0.43 (0.25, 0.75)	2.37 (0.60, 9.40)	1.704	0.758	**0.025**	0.324
MDFM vs PFOL*	4.21 (0.28, 64.25)	0.56 (0.17, 1.87)	-2.012	1.416	0.155	0.333
MDMO vs MZKT	1.84 (0.04, 96.58)	3.25 (0.36, 29.72)	0.568	2.315	0.806	0.319
MDMO vs OPPF	1.77 (0.18, 17.22)	1.00 (0.02, 50.56)	-0.568	2.315	0.806	0.319
MDZM vs PFOL	0.19 (0.03, 1.35)	1.21 (0.32, 4.65)	1.849	1.163	0.112	0.307
MDZM vs MTHX	0.87 (0.19, 4.00)	0.34 (0.04, 2.70)	-0.938	1.262	0.457	0.321
MDZM vs MZKT	0.90 (0.25, 3.25)	0.66 (0.05, 8.76)	-0.306	1.338	0.819	0.329
MDZM vs OPMZ	0.71 (0.20, 2.56)	0.09 (0.01, 0.83)	-2.063	1.150	**0.073**	0.299
MDZM vs PNTB	0.30 (0.01, 9.83)	0.12 (0.01, 2.34)	-0.899	2.324	0.699	0.318
MPCL vs OPID*	0.22 (0.01, 7.52)	0.56 (0.07, 4.74)	0.938	1.757	0.593	0.328
MPCL vs OPMZ*	1.23 (0.04, 38.79)	0.48 (0.05, 4.32)	-0.938	1.757	0.593	0.328
MTHX vs PFOL*	4.87 (0.03, 713.38)	1.05 (0.53, 2.07)	-1.533	2.579	0.552	0.317
MZKT vs PFOL	0.80 (0.47, 1.36)	0.75 (0.16, 3.53)	-0.068	0.834	0.935	0.327
MZKT vs OPET	0.72 (0.31, 1.69)	0.22 (0.01, 4.35)	-1.207	1.589	0.448	0.318
MZKT vs OPMZ	0.60 (0.26, 1.36)	0.55 (0.33, 0.91)	-0.079	0.488	0.872	0.335
MZKT vs OPPF	0.67 (0.37, 1.19)	0.23 (0.07, 0.74)	-1.068	0.663	0.108	0.292
OPDX vs OPID	0.82 (0.01, 45.95)	0.67 (0.11, 4.00)	-0.213	2.246	0.925	0.320
OPDX vs OPMZ	0.81 (0.12, 5.68)	1.00 (0.02, 51.73)	0.213	2.246	0.925	0.320
OPET vs OPMZ	2.66 (0.13, 55.03)	0.80 (0.38, 1.66)	-1.207	1.589	0.448	0.318
OPID vs PFOL	2.65 (0.97, 7.28)	1.17 (0.45, 3.03)	-0.815	0.707	0.249	0.312
OPID vs OPMZ*	1.41 (0.56, 3.53)	0.88 (0.22, 3.50)	-0.469	0.845	0.579	0.328
OPID vs OPPF	0.75 (0.32, 1.73)	3.33 (0.89, 12.45)	1.498	0.799	**0.061**	0.285
OPMZ vs PFOL	1.70 (0.98, 2.96)	0.69 (0.23, 2.03)	-0.903	0.620	0.145	0.307
OPMZ vs OPPF	0.99 (0.54, 1.84)	0.81 (0.23, 2.86)	-0.205	0.716	0.775	0.329
OPMZ vs TPFN	2.17 (0.55, 8.54)	1.20 (0.46, 3.13)	-0.594	0.852	0.486	0.335
OPPF vs PFOL	1.58 (0.89, 2.78)	1.36 (0.72, 2.59)	-0.145	0.438	0.741	0.334
OPPF vs RMMT*	2.30 (0.00, .)	0.63 (0.31, 1.29)	-1.295	704.932	0.999	0.317

all the evidence about these contrasts comes from the trials which directly compare them.

Loop-specific incoherence

Loop				ROR	p_value	RoR 95% CI	Loop Heterogeneity (tau2)
KTMN	OPMZ	OPPF		49.80	**0.020**	(1.85,1340.90)	0.000
PFOL	KTMN	OPMZ		36.08	**0.018**	(1.83,709.63)	0.000
PFOL	MDZM	OPMZ		21.83	0.231	(1.00,3375.62)	1.660
KTMN	MZKT	OPPF		19.55	**0.020**	(1.59,240.71)	0.377
PFOL	ETMD	KTMN		9.82	**0.000**	(3.41,28.33)	0.000
KTMN	MZKT	OPMZ		8.32	0.146	(1.00,144.64)	0.000
KTFL	KTMN	OPPF		7.02	**0.010**	(1.61,30.65)	0.000
PFOL	MDZM	MZKT		6.68	0.479	(1.00,1280.02)	1.660
PFOL	ETMD	MDZM	PNTB	6.20	0.536	(1.00,2017.16)	0.029
PFOL	MDZM	MTHX		6.19	0.318	(1.00,221.18)	0.000
PFOL	KTFL	OPMZ		6.00	**0.058**	(1.00,38.26)	0.000
OPID	OPMZ	OPPF		4.54	0.154	(1.00,36.39)	0.000
KTFL	OPMZ	TPFN		4.16	0.172	(1.00,32.15)	0.000
PFOL	OPID	OPPF		3.79	**0.072**	(1.00,16.15)	0.000
KTFL	KTMN	OPMZ		3.70	0.452	(1.00,111.34)	0.000
PFOL	KTMN	MZKT		3.59	0.299	(1.00,40.01)	0.377
MZKT	OPET	OPMZ		3.37	0.429	(1.00,68.33)	0.000
KTMN	MDZM	MZKT		3.37	0.652	(1.00,654.18)	0.382
PFOL	MZKT	OPPF		2.44	0.325	(1.00,14.44)	0.000
KTFL	OPMZ	OPPF		2.37	0.486	(1.00,26.97)	0.311
PFOL	KTMN	OPPF		2.23	0.256	(1.00,8.92)	0.000
MZKT	OPMZ	OPPF		2.17	0.332	(1.00,10.32)	0.000
PFOL	OPID	OPMZ		1.94	0.447	(1.00,10.67)	0.000
MDZM	MZKT	OPMZ		1.84	0.771	(1.00,112.37)	0.000
PFOL	MZKT	OPMZ		1.82	0.488	(1.00,9.91)	0.000
OPDX	OPID	OPMZ		1.71	0.813	(1.00,142.21)	0.000
KTHL	KTMN	MZKT		1.70	0.859	(1.00,614.02)	0.430
PFOL	KTMN	MDZM		1.65	0.862	(1.00,470.74)	1.660
PFOL	KTFL	KTMN		1.63	**0.074**	(1.00,2.78)	0.000
PFOL	ETMD	MDFM		1.63	0.569	(1.00,8.62)	0.000
PFOL	OPMZ	OPPF		1.62	0.533	(1.00,7.35)	0.000
PFOL	KTFL	OPPF		1.47	0.284	(1.00,2.97)	0.000
MDMO	MZKT	OPPF		1.34	0.900	(1.00,124.24)	0.000
ETMD	KTMN	MDZM	PNTB	1.25	0.940	(1.00,432.03)	0.000
DXKT	KTFL	KTMN		1.18	0.698	(1.00,2.73)	0.022
MPCL	OPID	OPMZ		1.15	0.954	(1.00,151.53)	0.000

*KTMN	MDZM	OPMZ		1.00	1.000	(1.00,259.05)	0.000
* These loops are formed only by multi-arm trial(s)							

Supplement Table 8. Surface Under the Cumulative Ranking curve (SUCRA), pairwise and loop incoherence estimates for Cardiac Adverse Events

SUCRA and ranking probabilities for treatments

Treatment	SUCRA	PrBest	MeanRank
Ketamine-Propofol	82.8	5.4	4.4
Etomidate-Opioid	66.4	8.2	7.7
Ketamine-Midazolam	62.0	0.7	8.6
Methohexital-Opioid	59.2	0.6	9.2
Pentobarbital	56.5	18.0	9.7
Dexmedetomidine-ketamine	56.2	2.4	9.8
Ketamine-Haloperidol	55.4	10.5	9.9
Ketamine	55.3	0.2	9.9
Midazolam-Opioid	55.2	0.2	10.0
Diazepam-Opioid	54.1	15.7	10.2
Etomidate	52.9	7.2	10.4
Midazolam-Fentanyl-Lidocaine	52.9	6.8	10.4
Midazolam-Morphine	51.1	5.3	10.8
FPMKL combination	46.6	8.2	11.7
Propofol-Opioid	42.8	0.0	12.4
Diazepam	41.2	8.2	12.8
Midazolam	37.1	0.0	13.6
Propofol	34.6	0.0	14.1
Opioid	33.7	1.2	14.3
Thiopental-Opioid	30.0	1.2	15.0
Dexmedetomidine-Opioid	23.9	0.3	16.2

Direct and indirect estimates of effect and P value for pairwise incoherence

Treatment/Comparison	Direct RR	Indirect RR	log dif	sedif	p value	Tau
DXKT vs KTFL*	2.00 (0.19, 20.93)	4.03 (0.04, 425.10)	-0.701	2.843	0.805	0.000
DXKT vs KTMN*	1.00 (0.15, 6.66)	0.50 (0.00, 93.71)	0.701	2.843	0.805	0.000
KTFL vs PFOL	0.16 (0.05, 0.48)	0.38 (0.06, 2.25)	-0.888	1.080	0.411	0.000
KTFL vs KTMN*	0.33 (0.08, 1.42)	0.64 (0.05, 7.83)	-0.665	1.480	0.653	0.000
KTFL vs OPMZ	0.33 (0.01, 7.88)	0.39 (0.09, 1.69)	-0.156	1.779	0.930	0.000
KTFL vs OPPF	0.30 (0.15, 0.59)	0.10 (0.02, 0.67)	1.072	1.026	0.296	0.000
KTHL vs KTMN*	1.03 (0.02, 51.22)	0.59 (0.00, 1483.44)	0.563	4.466	0.900	0.000
KTHL vs MZKT*	1.00 (0.02, 49.60)	1.76 (0.00, 4436.54)	-0.563	4.466	0.900	0.000
KTMN vs PFOL	1.06 (0.02, 52.49)	0.45 (0.09, 2.29)	0.851	2.154	0.693	0.000
KTMN vs MZKT*	0.97 (0.02, 48.07)	1.28 (0.18, 9.28)	-0.282	2.233	0.900	0.000
KTMN vs OPPF	0.16 (0.01, 2.46)	1.00 (0.23, 4.46)	-1.858	1.559	0.233	0.000
MDMO vs MZKT	1.08 (0.02, 50.43)	1.86 (0.03, 117.30)	-0.549	2.884	0.849	0.000
MDMO vs OPPF	1.00 (0.02, 48.09)	0.58 (0.01, 35.46)	0.549	2.884	0.849	0.000
MZKT vs PFOL	0.20 (0.01, 4.00)	0.55 (0.09, 3.43)	-1.014	1.790	0.571	0.028
MZKT vs OPMZ	0.97 (0.24, 3.96)	0.48 (0.05, 5.02)	0.708	1.401	0.613	0.000
MZKT vs OPPF	0.36 (0.02, 8.74)	0.62 (0.13, 3.02)	-0.531	1.812	0.769	0.000
OPDX vs OPID	1.33 (0.34, 5.21)	7.00 (0.05, 920.26)	-1.658	2.584	0.521	0.000
OPDX vs OPMZ	7.00 (0.37, 131.28)	1.33 (0.02, 82.99)	1.658	2.584	0.521	0.000
OPID vs OPMZ	1.00 (0.02, 49.40)	5.25 (0.21, 133.06)	-1.658	2.584	0.521	0.000
OPMZ vs PFOL	3.77 (0.16, 89.99)	0.32 (0.06, 1.60)	2.481	1.819	0.173	0.000
OPMZ vs OPPF	0.44 (0.06, 3.24)	0.97 (0.17, 5.42)	-0.791	1.344	0.556	0.000
OPPF vs PFOL	1.02 (0.07, 15.72)	0.72 (0.23, 2.30)	0.345	1.515	0.820	0.000
all the evidence about these contrasts comes from the trials which directly compare them.						

Loop-specific incoherence

Loop				ROR	p_value	RoR 95% CI	Loop Heterogeneity (tau2)
PFOL	MZKT	OPMZ		18.22	0.215	(1.00,1787.28)	0.000
PFOL	OPMZ	OPPF		8.38	0.369	(1.00,868.33)	0.000
PFOL	KTFL	OPMZ		8.10	0.375	(1.00,823.69)	0.000
PFOL	KTMN	MZKT		5.48	0.595	(1.00,2924.34)	0.000
KTFL	KTMN	MZKT	OPPF	5.45	0.547	(1.00,1351.01)	0.000
OPDX	OPID	OPMZ		5.25	0.521	(1.00,831.88)	0.000
MDMO	MZKT	OPPF		2.55	0.771	(1.00,1414.61)	0.000
KTFL	OPMZ	OPPF		2.18	0.688	(1.00,97.85)	0.000
KTFL	KTMN	MZKT	OPMZ	2.13	0.792	(1.00,599.93)	0.000
PFOL	KTFL	OPPF		2.11	0.632	(1.00,44.11)	0.000

PFOL	MZKT	OPPF		1.86	0.814	(1.00,321.04)	0.000
MZKT	OPMZ	OPPF		1.17	0.938	(1.00,64.67)	0.000
PFOL	KTFL	KTMN		1.14	0.955	(1.00,112.52)	0.000
*KTHL	KTMN	MZKT		1.00	1.000	(1.00,864.69)	0.000

Supplement Table 9. Surface Under the Cumulative Ranking curve (SUCRA), pairwise and loop incoherence estimates for Gastrointestinal Adverse Events

SUCRA and ranking probabilities for treatments

Treatment	SUCRA	PrBest	MeanRank
Dexmedetomidine-Opioid	96.1	65.3	1.7
Opioid	85.1	5.3	3.8
Midazolam-Opioid	69.8	0.0	6.7
Propofol-Opioid	64.0	0.1	7.8
Diazepam-Opioid	62.7	10.1	8.1
Etomidate-Opioid	60.6	0.2	8.5
KPMFL combination	58.3	3.8	8.9
Methohexital-Opioid	56.6	8.5	9.2
Midazolam	54.5	3.5	9.6
Ketamine-Haloperidol	52.8	0.4	10.0
Ketamine-Propofol	51.0	0.0	10.3
Propofol	50.3	0.0	10.4
Thiopental-Opioid	46.6	0.7	11.1
Ketamine-Midazolam	36.8	0.0	13.0
Etomidate	33.1	0.6	13.7
Ketamine	27.9	0.0	14.7
Midazolam-Morphine	26.8	0.0	14.9
Pentobarbital	25.7	1.2	15.1
Diazepam	25.2	0.4	15.2
Propofol-Morphine	16.2	0.0	16.9

Direct and indirect estimates of effect and P value for pairwise incoherence

Treatment/Comparison	Direct RR	Indirect RR	dif	sedif	p value	Tau
KTFL vs PFOL	1.00 (0.02, 50.40)	0.98 (0.14, 6.98)	0.018	2.235	0.994	0.344
KTFL vs KTMN	0.44 (0.20, 0.93)	0.78 (0.13, 4.74)	-0.578	0.993	0.561	0.376
KTFL vs OPMZ	1.00 (0.02, 51.39)	2.11 (0.59, 7.61)	-0.748	2.117	0.724	0.343
KTFL vs OPPF	1.49 (0.66, 3.38)	1.56 (0.23, 10.75)	-0.044	1.073	0.967	0.366
KTFL vs TPFN	3.13 (0.12, 80.93)	0.23 (0.01, 6.07)	2.607	2.351	0.267	0.348
KTHL vs KTMN*	0.41 (0.07, 2.39)	0.65 (0.02, 20.74)	-0.447	1.829	0.807	0.367

KTHL vs MZKT*	0.67 (0.10, 4.44)	0.43 (0.02, 11.04)	0.447	1.829	0.807	0.367
KTMN vs PFOL	1.06 (0.02, 55.69)	2.43 (0.34, 17.61)	-0.828	2.259	0.714	0.349
KTMN vs MZKT*	1.34 (0.59, 3.04)	1.40 (0.20, 9.67)	-0.044	1.053	0.967	0.362
KTMN vs OPPF	2.18 (0.36, 13.25)	3.60 (1.29, 10.02)	-0.505	1.059	0.633	0.385
MDMO vs MZKT	3.25 (0.36, 29.81)	0.38 (0.01, 21.85)	2.152	2.364	0.363	0.339
MDMO vs OPPF	1.00 (0.02, 50.40)	8.58 (0.74, 99.48)	-2.151	2.364	0.363	0.339
MZKT vs OPET	1.09 (0.07, 16.63)	2.94 (0.59, 14.69)	-0.991	1.618	0.540	0.344
MZKT vs OPMZ	3.10 (0.96, 9.96)	3.06 (0.45, 20.84)	0.007	1.146	0.995	0.356
MZKT vs OPPF	11.94 (0.62, 230.34)	1.89 (0.62, 5.81)	1.846	1.613	0.252	0.355
OPDX vs OPID	0.05 (0.00, 0.91)	7.03 (0.08, 625.35)	-4.890	2.714	**0.072**	0.318
OPDX vs OPMZ	1.00 (0.02, 51.39)	0.01 (0.00, 0.27)	4.890	2.714	**0.072**	0.318
OPET vs OPMZ	1.17 (0.35, 3.94)	3.16 (0.17, 58.58)	-0.991	1.618	0.540	0.344
OPID vs OPMZ	0.14 (0.02, 1.23)	18.92 (0.15, 2442.34)	-4.890	2.714	**0.072**	0.318
OPMZ vs PFOL	0.42 (0.02, 10.84)	0.55 (0.05, 5.66)	-0.272	2.039	0.894	0.347
OPMZ vs TPFN	0.14 (0.01, 2.85)	1.94 (0.06, 63.42)	-2.607	2.351	0.267	0.348
OPPF vs PFOL	1.02 (0.06, 16.50)	0.48 (0.05, 4.75)	0.756	1.836	0.680	0.344
all the evidence about these contrasts comes from the trials which directly compare them.						

Loop-specific incoherence

Loop				ROR	p_value	RoR 95% CI	Loop Heterogeneity (tau2)
OPDX	OPID	OPMZ		133.00	**0.066**	(1.00,24318.70)	0.000
MDMO	MZKT	OPPF		39.00	0.173	(1.00,7568.49)	0.000
KTFL	OPMZ	TPFN		21.88	0.298	(1.00,7312.84)	0.000
KTMN	MZKT	OPPF	PFOL	15.83	0.347	(1.00,5028.52)	0.166
MZKT	OPMZ	OPPF	PFOL	9.25	0.400	(1.00,1653.84)	0.000
KTMN	MZKT	OPPF	KTFL	4.16	0.419	(1.00,131.88)	0.294
PFOL	KTFL	KTMN		2.67	0.746	(1.00,1022.08)	0.564
MZKT	OPET	OPMZ		2.53	0.553	(1.00,53.88)	0.000
PFOL	KTFL	OPMZ		2.39	0.787	(1.00,1337.52)	0.000
MZKT	OPMZ	OPPF	KTFL	2.17	0.762	(1.00,318.72)	0.000
PFOL	KTFL	OPPF		1.79	0.811	(1.00,211.38)	0.000
KTMN	MZKT	OPMZ	KTFL	1.72	0.813	(1.00,149.11)	0.350
KTMN	MZKT	OPMZ	PFOL	1.55	0.870	(1.00,289.63)	0.056
KTHL	KTMN	MZKT		1.46	0.761	(1.00,17.10)	0.000

Supplement Table 10. Surface Under the Cumulative Ranking curve (SUCRA), pairwise and loop incoherence estimates for Neurological Adverse Events

SUCRA and ranking probabilities for treatments

Treatment	SUCRA	PrBest	MeanRank
Opioid	89.0	11.1	3.4
Dexmedetomidine-Opioid	80.1	27.7	5.4
Midazolam-Opioid	77.4	0.3	6.0
Ketamine-Haloperidol	72.5	8.8	7.1
Dexmedetomidine	72.1	23.4	7.1
Diazepam-Opioid	69.7	14.7	7.7
Thiopental-Opioid	62.3	0.7	9.3
Propofol	57.3	0.0	10.4
Dexmedetomidine-Ketamine	53.5	0.0	11.2
Methohexital	52.8	3.5	11.4
Midazolam	51.8	0.6	11.6
Propofol-Opioid	50.3	0.0	11.9
Ketamine-Propofol	50.2	0.0	12.0
Methohexital-Opioid	49.5	4.0	12.1
KPMFL combination	49.3	4.5	12.2
Etomidate-Opioid	39.0	0.0	14.4
Midazolam-Flumazenil	37.8	0.6	14.7
Ketamine-Midazolam	36.4	0.0	15.0
Propofol-Morphine	36.2	0.2	15.0
Midazolam-Morphine	26.9	0.0	17.1
Ketamine	26.4	0.0	17.2
Etomidate	6.6	0.0	21.5
Pentobarbital	2.9	0.0	22.4

Direct and indirect estimates of effect and P value for pairwise incoherence

Treatment/Comparison	Direct RR	Indirect RR	dif	sedif	p value	Tau
DXKT vs KTFL*	1.17 (0.28, 4.91)	0.39 (0.03, 4.75)	1.104	1.490	0.459	0.541
DXKT vs KTMN*	0.32 (0.09, 1.13)	0.96 (0.06, 15.33)	-1.104	1.490	0.459	0.541
ETMD vs PFOL*	10.38 (2.34, 45.96)	60.83 (10.53, 351.45)	-1.768	1.174	0.132	0.494
ETMD vs KTMN	16.20 (3.43, 76.52)	2.77 (0.51, 15.11)	1.768	1.174	0.132	0.494
ETMD vs MDFM*	8.10 (0.42, 156.64)	65.48 (0.07, 59270.07)	-2.090	3.289	0.525	0.522
KTFL vs PFOL	0.94 (0.37, 2.37)	65.48 (0.07, 59270.07)	-0.855	0.796	0.283	0.531
KTFL vs KTMN*	0.42 (0.21, 0.83)	0.44 (0.13, 1.51)	-0.041	0.723	0.955	0.555
KTFL vs OPMZ	13.20 (1.61, 108.01)	2.03 (0.51, 8.10)	1.870	1.284	0.145	0.449
KTFL vs OPPF	1.17 (0.33, 4.12)	0.77 (0.12, 4.98)	0.417	1.135	0.713	0.533

KTHL vs KTMN*	0.08 (0.00, 1.61)	7.72 (0.01, 5670.25)	-4.577	3.163	0.148	0.486
KTHL vs MZKT*	1.00 (0.02, 55.63)	0.01 (0.00, 1.15)	4.577	3.163	0.148	0.486
KTMN vs PFOL	4.52 (1.05, 19.42)	2.57 (1.01, 6.51)	0.566	0.882	0.521	0.534
KTMN vs MZKT*	1.84 (0.70, 4.82)	0.85 (0.19, 3.73)	0.774	0.901	0.390	0.556
KTMN vs OPPF	1.52 (0.41, 5.61)	4.44 (0.98, 20.15)	-1.072	1.009	0.288	0.525
MDFM vs PFOL*	1.11 (0.02, 57.71)	8.98 (0.06, 1452.13)	-2.090	3.289	0.525	0.522
MDMO vs MZKT	2.17 (0.35, 13.36)	0.56 (0.01, 36.41)	1.353	2.323	0.560	0.521
MDMO vs OPPF	1.00 (0.02, 54.90)	3.87 (0.44, 33.73)	-1.353	2.323	0.560	0.521
MZKT vs PFOL	22.00 (2.52, 191.77)	1.16 (0.37, 3.69)	2.939	1.252	**0.019**	0.492
MZKT vs OPET	0.36 (0.04, 3.78)	1.68 (0.33, 8.71)	-1.532	1.459	0.294	0.517
MZKT vs OPMZ	4.68 (1.24, 17.63)	8.64 (1.73, 43.16)	-0.612	1.063	0.565	0.513
MZKT vs OPPF	7.64 (0.34, 170.52)	1.30 (0.39, 4.30)	1.774	1.699	0.296	0.510
OPET vs OPMZ	4.47 (1.33, 15.04)	20.69 (1.55, 276.75)	-1.532	1.459	0.294	0.517
OPID vs OPMZ	0.40 (0.06, 2.66)	0.19 (0.01, 5.49)	0.726	1.962	0.711	0.525
OPID vs OPPF	0.06 (0.00, 1.17)	0.12 (0.01, 1.36)	-0.726	1.962	0.711	0.525
all the evidence about these contrasts comes from the trials which directly compare them.						

Loop-specific incoherence

Loop				ROR	p_value	RoR 95% CI	Loop Heterogeneity (tau2)
PFOL	KTFL	MZKT	OPMZ	59.93	**0.038**	(1.25,2872.65)	0.606
KTFL	MZKT	OPMZ	OPPF	16.56	0.202	(1.00,1239.68)	0.390
MDMO	MZKT	OPPF		16.55	0.280	(1.00,2687.86)	0.000
KTMN	MZKT	OPPF		11.11	0.241	(1.00,622.80)	0.699
KTHL	KTMN	MZKT		10.90	0.335	(1.00,1394.39)	0.000
PFOL	KTMN	MZKT		10.62	0.176	(1.00,323.96)	0.699
MZKT	OPID	OPMZ	OPPF	10.46	0.366	(1.00,1703.16)	0.422
PFOL	ETMD	KTMN		6.99	**0.075**	(1.00,59.44)	0.000
KTFL	KTMN	MZKT	OPMZ	4.79	0.229	(1.00,61.45)	0.124
PFOL	KTFL	MZKT	OPPF	4.42	0.544	(1.00,536.04)	0.816
MZKT	OPET	OPMZ		2.62	0.466	(1.00,34.73)	0.000
PFOL	KTFL	KTMN		1.96	0.443	(1.00,10.95)	0.211
KTFL	KTMN	OPPF		1.81	0.377	(1.00,6.77)	0.000
DXKT	KTFL	KTMN		1.77	0.394	(1.00,6.62)	0.000
KTFL	OPID	OPMZ	OPPF	1.59	0.839	(1.00,133.30)	0.362
PFOL	ETMD	MDFM		1.21	0.939	(1.00,167.72)	0.000
*PFOL	MDZM	MTHX		1.00	1.000	(1.00,760.07)	0.000
* These loops are formed only by multi-arm trial(s)							

Supplement Table 11. Network meta-analysis results sorted based on GRADE certainty of evidence and treatments effectiveness for the comparisons of active treatments vs. midazolam-opioid for primary and secondary outcomes

Drugs	Recovery Time MD (95% CI)	Patient Satisfaction (Continuous) MD (95% CI)	Patient Satisfaction (Dichotomous) RR (95% CI)	Respiratory Adverse Events RR (95% CI)	Cardiac Adverse Events RR (95% CI)	GI Adverse Events RR (95% CI)	Neuro Adverse Events RR (95% CI)
Dexmedetomidine		1.00 (-0.39, 2.39)					
Propofol	-16.34 (-24.29, -8.39)			0.71 (0.43, 1.16)	1.89 (0.44, 8.04)	1.99 (0.30, 13.21)	
Propofol + Opioid	-13.62 (-20.69, -6.55)	0.98 (-0.25, 2.21)		1.05 (0.61, 1.81)	1.44 (0.39, 5.30)		
Ketamine + Propofol	-10.52(-17.61, -3.43)	1.47 (0.30, 2.63)		0.52 (0.31, 0.87)	0.38 (0.10, 1.44)	1.97 (0.58, 6.66)	3.68 (1.08, 12.53)
Ketamine				0.55 (0.32, 0.96)			
Midazolam				0.49 (0.14, 1.67)			
Etomidate + Opioid	-14.76 (-25.98, -3.53)	0.01 (-1.20, 1.22)		0.85 (0.42, 1.74)		1.35 (0.44, 4.15)	5.88 (1.96, 17.62)
Opioid	-12.06 (-25.38, 1.27)	-0.74 (-2.23, 0.76)	1.01 (0.86, 1.19)	1.22 (0.57, 2.60)	2.67 (0.22, 32.19)	0.32 (0.04, 2.30)	0.34 (0.07, 1.72)
Opioid + Dexmedetomidine				0.84 (0.15, 4.83)	4.02 (0.37, 43.87)	0.07 (0.00, 0.97)	
Ketamine + Midazolam	8.29 (1.08, 15.51)		1.01 (0.90, 1.14)	0.57 (0.37, 0.86)	0.83 (0.25 2.81)	3.08 (1.15, 8.27)	5.97 (2.15, 16.62)

	Statistically Better than Midazolam + Opioid	Statistically No Difference with Midazolam + Opioid	Statistically Worse than Midazolam + Opioid
High or Moderate Certainty Evidence	Better than Midazolam + Opioid	No more effective than Midazolam + Opioid	Less effective than Midazolam + Opioid
Low or Very Low Certainty Evidence	May be better than Midazolam + Opioid	May be no more effective than Midazolam + Opioid	May be less effective than Midazolam + Opioid

Supplement Table 12. Network meta-analysis results sorted based on GRADE certainty of evidence and treatments effectiveness for the comparisons of active treatments vs. ketamine-propofol for primary and secondary outcomes

Drugs	Recovery Time MD (95% CI)	Patient Satisfaction (Continuous) MD (95% CI)	Patient Satisfaction (Dichotomous) RR (95% CI)	Respiratory Adverse Events RR (95% CI)	Cardiac Adverse Events RR (95% CI)	GI Adverse Events RR (95% CI)	Neuro Adverse Events RR (95% CI)
Opioid + Midazolam	10.52 (3.43, 17.61)	-1.47 (-2.63, -0.30)		1.94 (1.15, 3.27)	2.64 (0.70, 9.99)	0.51 (0.15, 1.72)	0.27 (0.09, 0.92)
Ketamine	3.57 (-2.71, 9.85)	0.03 (-1.51, 1.58)	0.89 (0.79, 1.02)	1.07 (0.76, 1.49)	2.56 (0.72, 9.08)	2.08 (1.05, 4.11)	2.38 (1.33, 4.23)
Propofol + Opioid	-3.10 (-8.48, 2.29)	-0.49 (-1.70, 0.72)	0.93 (0.83, 1.05)	2.03 (1.32, 3.13)	3.80 (2.02, 7.16)	0.66 (0.32, 1.37)	1.00 (0.35, 2.80)
Propofol	-5.82 (-12.01, 0.37)	-0.01 (-1.09, 1.07)	0.94 (0.82, 1.07)	1.37 (0.98, 1.91)	4.99 (1.91, 13.02)	1.01 (0.17, 5.86)	0.79 (0.38, 1.63)

	Statistically Better than KTFL	Statistically No Difference with KTFL	Statistically Worse than KTFL
High or Moderate Certainty Evidence	Better than KTFL	No more effective than KTFL	Less effective than KTFL
Low or Very Low Certainty Evidence	May be better than KTFL	May be no more effective than KTFL	May be less effective than KTFL

Supplement Table 13. Network meta-analysis results sorted based on GRADE certainty of evidence and treatments effectiveness for the comparisons of active treatments vs. ketamine for primary and secondary outcomes

Drugs	Recovery Time MD (95% CI)	Patient Satisfaction (Continuous) MD (95% CI)	Patient Satisfaction (Dichotomous) RR (95% CI)	Respiratory Adverse Events RR (95% CI)	Cardiac Adverse Events RR (95% CI)	GI Adverse Events RR (95% CI)	Neuro Adverse Events RR (95% CI)
Opioid + Midazolam				1.82 (1.04, 3.16)			
Etomidate	-0.25 (-9.65, 9.14)			1.43 (0.73, 2.79)			
KTFL	-3.57 (-9.85, 2.71)	-0.03 (-1.58, 1.51)	1.12 (0.98, 1.27)	0.94 (0.67, 1.31)	0.39 (0.11, 1.38)	0.48 (0.24, 0.95)	0.42 (0.24, 0.75)
Propofol	-9.39 (-16.53, -2.25)		1.05 (0.92, 1.20)	1.29 (0.85, 1.95)	1.95 (0.44, 8.67)	0.49 (0.08, 2.85)	0.33 (0.15, 0.71)
Opioid + Etomidate	-7.81 (-19.12, 3.50)	-1.49 (-3.55, 0.58)					
Midazolam + Ketamine	15.24 (8.09, 22.38)		1.07 (0.94, 1.23)	1.03 (0.63, 1.67)	0.82 (0.14, 4.81)	0.75 (0.35, 1.59)	0.68 (0.32, 1.45)
OPPF	-6.67 (-13.84, 0.51)		1.04 (0.91, 1.19)	1.90 (1.15, 3.15)	1.48 (0.39, 5.68)	0.32 (0.13, 0.74)	0.42 (0.15, 1.15)
DXKT				0.91 (0.46, 1.80)	0.92 (0.16, 5.48)		0.37 (0.12, 1.17)
Midazolam				0.89 (0.26, 2.98)			

	Statistically Better than KTMN	Statistically No Difference with KTMN	Statistically Worse than KTMN

High or Moderate Certainty Evidence	Better than KTMN	No more effective than KTMN	Less effective than KTMN
Low or Very Low Certainty Evidence	May be better than KTMN	May be no more effective than KTMN	May be less effective than KTMN

Supplement Table 14. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for patient satisfaction as a continuous outcome

Comparison	Direct Estimate MD (95% CI)	Indirect Estimate MD (95% CI)	Network Estimate[1] MD (95% CI)	GRADE	Narrative Summary
DXMT v OPMZ	0.73 (-1.04,2.5)	1.63 (-1.05,4.31)	1.00 (-0.39,2.39)	Low[2,4]	Dexmedetomidine may result in better patient satisfaction as a continuous outcome when compared to Opioid-Midazolam
KTFL v OPMZ	1.6 (-0.43,3.63)	1.42 (-0.15,2.99)	1.47 (0.30,2.63)	High	Ketamine-Propofol results in better patient satisfaction as a continuous outcome when compared to Opioid-Midazolam
OPET v OPMZ	0.72 (-0.35,1.79)	-2.6 (-4.67,-0.54)	0.01 (-1.20,1.22)	Low[2,5]	Opioid-Etomidate may have no effect on patient satisfaction as a continuous outcome when compared to opioid-midazolam
OPID v OPMZ	-0.37 (-2.4,1.66)	-1.27 (-3.76,1.22)	-0.74 (-2.23,0.76)	Low[2,4]	Opioids may result in worse patient satisfaction as a continuous outcome when compared to opioid-midazolam
OPMZ v OPPF	0.27 (-0.14,0.68)	-2.18 (-2.97,-1.38)	-0.98 (-2.21,0.25)	Low[2,5]	Opioid-Midazolam may result in worse patient satisfaction as a continuous outcome when compared to Opioid-Propofol
KTFL v PFOL	0.09 (-1.23,1.4)	-0.37 (-3.09,2.34)	0.01 (-1.07,1.09)	Low[3]	Ketamine-Propofol may have no effect on patient satisfaction as a continuous outcome when compared to propofol
KTFL v KTMN	0 (-1.65,1.65)	-0.37 (-5.72,4.99)	-0.03 (-1.58,1.51)	Low[3]	Ketamine-Propofol may have no effect on patient satisfaction as a continuous outcome when compared to ketamine

KTFL v OPPF	0 (-1.8,1.8)	0.94 (-0.8,2.67)	0.49 (-0.72,1.70)	Low[3]	Ketamine-Propofol may result in better patient satisfaction as a continuous outcome when compared to Opioid-Propofol
KTMN v OPET	1.8 (-3.31,6.91)	1.43 (-0.87,3.74)	1.49 (-0.58,3.55)	Moderate[2]	Ketamine probably results in better patient satisfaction as continuous outcome compared to opioid-etomidate

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MD, mean difference; CI, confidence interval; DXMT, dexmedetomidine; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid; MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision
[3] Lowered two levels for very serious imprecisions
[4] Lowered for risk of bias
[5] Lowered for incoherence

Supplement Table 15. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for patient satisfaction as a dichotomous outcome

Comparison	Direct Estimate RR (95% CI)	Indirect Estimate RR (95% CI)	Network Estimate[1] RR (95% CI)	GRADE	Narrative Summary
MZKT v OPMZ	1.02 (0.88,1.18)	0.95 (0.61,1.48)	1.01 (0.90,1.14)	Moderate[2]	Midazolam-Ketamine probably has no difference in patient satisfaction as a dichotomous outcome when compared to opioid-midazolam
OPID v OPMZ	1 (0.79,1.27)	1.07 (0.71,1.61)	1.01 (0.86,1.19)	Moderate[2]	Opioids probably have no difference in patient satisfaction as a dichotomous outcome when compared to opioid-midazolam
KTFL v PFOL	0.99 (0.76,1.28)	1.18 (0.96,1.45)	1.06 (0.93,1.22)	Moderate[2]	Ketamine-Propofol probably increases patient satisfaction as a dichotomous outcome when compared to propofol
KTFL v KTMN	1.31 (1.07,1.61)	1.03 (0.8,1.31)	1.12 (0.98,1.27)	Moderate[2]	Ketamine-Propofol probably increases patient satisfaction as a dichotomous outcome when compared to ketamine
KTFL v OPPF	1.09 (0.89,1.33)	1.13 (0.84,1.54)	1.07 (0.96,1.21)	Moderate[2]	Ketamine-Propofol probably increases patient satisfaction as a dichotomous outcome when compared to propofol-opioid
KTMN v PFOL	1 (0.8,1.24)	0.84 (0.66,1.06)	0.95 (0.84,1.08)	Moderate[2]	Ketamine probably decreases patient satisfaction as a dichotomous outcome when compared to propofol
KTMN v MZKT	0.93 (0.78,1.1)	0.87 (0.56,1.34)	0.93 (0.81,1.07)	Moderate[2]	Ketamine probably decreases patient satisfaction as a dichotomous outcome when compared to midazolam-ketamine

KTMN v OPPF	1.00 (0.81, 1.24)	0.93 (0.76, 1.12)	0.96 (0.84,1.10)	Moderate[2]	Ketamine probably has no effect on patient satisfaction as a dichotomous outcome when compared to opioid-propofol

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk; CI, confidence interval; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid; MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision

Supplement Table 16. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for gastrointestinal adverse events

Comparison	Direct Estimate RR (95% CI)	Indirect Estimate RR (95% CI)	Network Estimate[1] RR (95% CI)	GRADE	Narrative Summary
KTFL v OPMZ	1 (0.02,52.41)	2.13 (0.57,7.94)	1.97 (0.58,6.66)	Low[3]	Ketamine-Propofol may have more GI AEs compared to midazolam-opioid
MZKT v OPMZ	3.07 (0.93,10.09)	3.11 (0.45,21.55)	3.08 (1.15,8.27)	High	Midazolam-Ketamine has more GI AEs compared to opioid-midazolam
OPDX v OPMZ	1 (0.02,52.21)	0.01 (0,0.27)	0.07 (0.00,0.97)	Moderate[2]	Opioid-Dexmedetomidine probably has fewer GI AEs compared to opioid-midazolam
OPET v OPMZ	1.17 (0.34,4.03)	3.15 (0.17,60.32)	1.35 (0.44,4.15)	Very Low[4]	Opioid-Etomidate has an uncertain effect on GI AEs compared to opioid-midazolam
OPID v OPMZ	0.14 (0.02,1.25)	18.99 (0.14,2505.57)	0.32 (0.04,2.30)	Very Low[4]	Opioids have an uncertain effect on GI AEs compared to midazolam-opioid
OPMZ v PFOL	0.42 (0.02,10.93)	0.58 (0.06,6.16)	0.50 (0.08,3.32)	Very Low[4]	Opioid-Midazolam has an uncertain effect on GI AEs compared to propofol
KTFL v PFOL	1 (0.02,50.69)	1.03 (0.14,7.48)	0.99 (0.17,5.72)	Very Low[4]	Ketamine-Propofol has an uncertain effect on GI AEs compared to propofol
KTFL v KTMN	0.44 (0.19,0.99)	0.62 (0.09,4.37)	0.48 (0.24,0.95)	Moderate[5]	Ketamine-Propofol probably has fewer GI AEs compared to ketamine
KTFL v OPPF	1.7 (0.71,4.11)	1.68 (0.19,15.14)	1.52 (0.73,3.16)	Low[3]	Ketamine-Propofol may have more GI AEs compared to opioid-propofol
KTMN v PFOL	1.06 (0.02,56.48)	2.67 (0.35,20.3)	2.06 (0.35,12.05)	Very Low[4]	Ketamine has an uncertain effect on GI AEs compared to propofol
KTMN v MZKT	1.37 (0.58,3.22)	1.59 (0.21,11.9)	1.33 (0.63,2.82)	Low[3]	Ketamine may have more GI AEs compared to midazolam-ketamine
KTMN v OPPF	2.18 (0.36, 13.25)	3.60 (1.29, 10.02)	3.16 (1.34,7.43)	High	Ketamine has more GI AEs compared to Propofol-Opioid

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk; CI, confidence interval; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid;

MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate; OPDX, dexmedetomidine with opioids; DXKT, dexmedetomidine with ketamine; AE, adverse events

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision
[3] Lowered two levels for very serious imprecisions
[4] Lowered three levels for very serious imprecisions
[5] Lowered for inconsistency

Supplement Table 17. Network estimates evaluating the efficacy of various procedural sedation and analgesia medication regimens for neurological adverse events

Comparison	Direct Estimate RR (95% CI)	Indirect Estimate RR (95% CI)	Network Estimate[1] RR (95% CI)	GRADE	Narrative Summary
MZKT v OPMZ	4.89 (1.21,19.87)	9.17 (1.67,50.26)	5.97 (2.15,16.62)	High	Midazolam-Ketamine increases neurologic adverse events compared to opioid-midazolam
OPID v OPMZ	0.4 (0.06,2.91)	0.08 (0,3.2)	0.34 (0.07,1.72)	Very Low[4]	Opioids have an uncertain effect on neurological adverse events compared to opioid-midazolam
KTFL v PFOL	0.93 (0.34,2.55)	2.86 (0.67,12.21)	1.27 (0.61,2.63)	Low[3]	Ketamine-Propofol may have no effect on neurological adverse events compared to propofol
KTFL v KTMN	0.48 (0.17,1.38)	0.43 (0.11,1.64)	0.42 (0.24,0.75)	High	Ketamine-Propofol has fewer neurological adverse events than ketamine
KTFL v OPMZ	13.2 (1.53,113.75)	2.62 (0.54,12.73)	3.68 (1.08,12.53)	High	Ketamine-Propofol has more neurological adverse events compared to opioid-midazolam
KTFL v OPPF	4.34 (0.37,51.34)	1.35 (0.13,14.41)	1.00 (0.36,2.83)	Low[3]	Ketamine-Propofol may have more neurological adverse events compared to opioid-propofol
DXKT v KTFL	1.17 (0.28, 4.91)	0.39 (0.03, 4.75)	0.88 (0.27,2.89)	Moderate[2]	Dexmedetomidine-Ketamine probably has no effect on neurological adverse events compared to ketamine-propofol
ETMD v KTMN	16.2 (3.2,82.09)	2.68 (0.42,17.07)	7.23 (2.28,22.90)	High	Etomidate has more neurological adverse events compared to ketamine
KTMN v PFOL	4.52 (0.91,22.56)	2.43 (0.81,7.3)	3.02 (1.40,6.49)	High	Ketamine probably increases neurologic adverse events compared to propofol
KTMN v MZKT	1.98 (0.68,5.77)	1.01 (0.17,5.84)	1.47 (0.69,3.11)	Low[3]	Ketamine may increase neurologic adverse events compared to midazolam-ketamine
KTMN v OPPF	1.52 (0.41, 5.61)	4.44 (0.98, 20.15)	2.39 (0.87,6.55)	Moderate[2]	Ketamine probably increases neurologic

					adverse events compared to opioid-propofol

Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RR, relative risk; CI, confidence interval; OPMZ, midazolam with opioids; PFOL, propofol; KTFL, ketamine with propofol; OPID, opioid; MZKT, midazolam with ketamine; OPPF, propofol with opioid; KTMN, ketamine; OPET, opioid with etomidate; ETMD, etomidate; OPDX, dexmedetomidine with opioids; DXKT, dexmedetomidine with ketamine

[1] Imprecision only incorporated at network level, not at direct or indirect
[2] Lowered for imprecision
[3] Lowered two levels for very serious imprecisions
[4] Lowered three levels for very serious imprecisions

Supplement Table 18. Patient Satisfaction Scales of Included Studies

Study author and year	Patient Satisfaction Scale Used
Abdolrazaghnejad 2017	Likert scale (very poor, poor, moderate, good, excellent)
Afzalimoghaddam 2021	5-point Likert scale (1 = very dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, 5 = completely satisfied)
Akhlaghi 2019	NA
Amini 2018	Likert scale (dissatisfied, partial, complete)
Aminiahidashti 2018	Likert scale (good, moderate, poor)
Andolfatto 2012	10-point scale (1 = not satisfied, 10 = extremely satisfied)
Arhami Dolatabadi 2018	NA
Arhami Dolatabadi 2018b	NA
Azizkhani 2021	NA
Bahreini 2020	10-point scale (0 = completely dissatisfied, 10 = completely satisfied)
Barcelos 2015	5-point Likert scale (1 = very pleased, 5 = very dissatisfied)
Bauman 2002	NA
Burton 2002	100mm VAS
Cevik 2013	Likert scale (excellent, good, moderate, poor, very poor)
Chan 2008	100mm VAS
Cimilli Ozturk 2014	100mm VAS
Coll-Vinent 2003	Likert scale (not satisfied, moderately satisfied, satisfied, very satisfied)
David 2011	NA
Del Pizzo 2011	NA
Derakhshanfar 2015	NA
Di Liddo 2006	5-point Likert scale
Dilli 2008	Presence of patient amnesia
Disel 2016	Pain during procedure (0 = lowest, 10 = highest)
Dunn 2010	Pain during procedure (0 = nil, 1 = mild, 2 = moderate, 3 = severe)
Ferguson 2016	10-point scale (0 = completely dissatisfied, 10 = completely satisfied)
Gale 1993	NA
Genzlinger 2012	NA
Gharavifard 2016	Likert scale (excellent, good, average, poor)
Godambe 2003	Parental perception of patient's pain - 100mm VAS Presence of patient amnesia
Gumus 2012	Pain at 10th minute after chest tube removal (0 = no pain, 10 = unbearable pain)
Hart 1997	Mean peak pain - 10-point scale (0 = no pain, 10 = severe pain) Mean peak anxiety - 4-point scale
Hatamabadi 2015	NA
Havel 1999	NA
Hunt 2005	Presence of patient amnesia
Holger 2005	100mm VAS
Jamal 2011	Percentage reduction of pain score
Kennedy 1998	Presence of patient amnesia
Khutia 2012	NA
Kienstra 2004	NA
Lee-Jayaram 2010	5-point Likert scale (very dissatisfied to very satisfied)
Lemoel 2017	NA
LucasdaSilva 2007	NA
Maltepe 2006	NA
Masoumi 2019	VAS
Massaeli 2022	Likert scale (moderate, high, very high)
Messenger 2008	10-point scale
Miner 2003	100mm VAS
Miner 2007	100mm VAS
Miner 2009	Satisfaction with procedure (yes/no)

Miner 2010	Satisfaction with procedure (yes/no)
Miner 2013	Satisfaction with procedure (yes/no)
Miner 2015	Satisfaction with procedure (yes/no)
Miner 2017	Satisfaction with procedure (yes/no)
Mofidi 2018	5-point Likert scale (excellent, very good, good, fair, poor)
MonsefKasmaee 2019	NA
Moro-Sutherland 2000	NA
Nashibi 2017	5-point scale (1 = strongly unsatisfied, 2 = unsatisfied, 3 = acceptable, 4 = satisfied, 5 = strongly satisfied)
Nejati 2011	NA
Parlak 2006	Likert scale
Phillips 2010	Degree of recall and pain (0 = low/nonexistent, 10 = high/maximum)
Rahman 2011	NA
Salen 2016	NA
Sawas 2013	NA
Sener 2011	5-point Likert scale (1 = least satisfied, 5 = most satisfied)
Seol 2015	NA
Shah 2011	7-point Likert scale (1 = not satisfied, 7 = extremely satisfied) If patient was 5-9 years old - 5-point facial hedonic scale
Sheik 2017	10-point scale (0=unsatisfied; 10=satisfied)
Sherwin 2000	NA
Soysal 2004	NA
Stronati 2020	NA
Tajoddini 2020	10-point Likert scale (1 = not satisfied, 10 = extremely satisfied)
Taylor 2005	NA
Uri 2011	100mm VAS
Vahidi 2018	5-point scale (1 = very good, 2 = good, 3 = average, 4 = bad, 5 = very bad)
Vardi 2002	10-point scale (1 = poor, 10 = highly satisfactory)
Venkatakrishnan 2011	NA
Wathen 2000	Likert scale (very satisfied, satisfied, unsatisfied)
Weisz 2017	10-point scale (1 = unsatisfied, 10 = extremely satisfied)
Wright 1993	NA
Yang 2018	NA
Yildirim 2007	NA
Yldzdas 2004	NA

Unless otherwise specified, scale used was a direct measure of patient satisfaction
Abbreviations: NA - not available; VAS - visual analogue scale

Supplement Table 19. Doses of Medications used for Procedural Sedation and Analgesia.

Study author & year	Sedative Dose Arm 1	Sedative Dose Arm 2	Sedative Dose Arm 3	Analgesic Dose Arm 1	Analgesic Dose Arm 2	Analgesic Dose Arm 3
Abdolrazaghnejad 2017	Midazolam*	Midazolam*	NA	Ketamine*	Fentanyl*	NA
Afzalimoghaddam 2021	Diazepam 0.1 mg/kg	Midazolam 0.1 mg/kg	NA	Fentanyl 1 ug/kg	Fentanyl 1 ug/kg	NA
Akhlaghi 2019	Placebo	Midazolam 0.05 mg/kg	Haloperidol 5 mg	Ketamine 1 mg/kg	Ketamine 1 mg/kg	Ketamine 1 mg/kg
Amini 2018	Propofol 0.5 mg/kg Midazolam 0.1-0.02 mg/kg	Propofol 1 mg/kg	NA	Fentanyl 0.5-1 ug/kg Ketamine 0.2-0.25 mg/kg Lidocaine 0.5 mg/kg	Fentanyl 1 ug/kg	NA
Aminiahidashti 2018	Propofol 0.5 mg/kg	Propofol 0.5 mg/kg	NA	Fentanyl 1 ug/kg	Ketamine 1 mg/kg	NA
Andolfatto 2012	Propofol 0.375 mg/kg	Propofol 0.75 mg/kg	NA	Ketamine 0.375 mg/kg	NA	NA
Arhami Dolatabadi 2018	Dexmedetomidine 1 µg/kg	Midazolam 0.01 mg/kg	NA	Fentanyl 3 µg/kg	Fentanyl 3 µg/kg	NA
Arhami Dolatabadi 2018b	Midazolam*	Midazolam*	NA	Fentanyl*	Fentanyl*	NA
Azizkhani 2021	Dexmedetomidine 0.7 ug/kg	Propofol 0.5 mg/kg	Ketamine 1 mg/kg	Ketamine 1 mg/kg	Ketamine 0.5 mg/kg	NA
Bahreini 2020	Thiopental 1 mg/kg	Propofol 0.5 mg/kg	NA	Fentanyl 1 ug/kg	Ketamine 0.5 mg/kg	NA
Barcelos 2015	Midazolam 0.2 mg/kg, max 10mg	Midazolam 0.2 mg/kg, max 10mg	NA	Ketamine 2 mg/kg, max 70mg	Morphine 0.1 mg/kg, max 5mg	NA
Bauman 2002	Methohexital four boluses 200 ug/kg, infusion 150 ug/kg/min, additional boluses 200 ug/kg as needed	Propofol and 0.1% lidocaine four boluses 500 ug/kg, infusion 180 ug/kg/min, additional boluses as needed	NA	Remifentanil loading doses of 0.53, 0.80 and 1.1 ug/kg, infusion 0.1, 0.15 and 0.20 ug/kg/min	Fentanyl 1.0, 1.5, or 2.0 ug/kg	NA
Burton 2002	Etomidate 0.1 mg/kg	Midazolam 0.033 mg/kg	NA	Fentanyl 1.5-2.0 µg/kg	Fentanyl 1.5-2.0 µg/kg	NA
Cevik 2013	Midazolam 0.2 mg/kg	Midazolam 0.1 mg/kg	NA	Ketamine 2 mg/kg	Fentanyl*	NA
Chan 2008	Midazolam 0.05 mg/kg	Etomidate 0.1 mg/kg	NA	Fentanyl 1 ug/kg	Fentanyl 1 ug/kg	NA

Cimilli Ozturk 2014	Midazolam 0.1 mg/kg, additional 0.05 mg/kg to desired sedation level	Propofol 1 mg/kg, additional 0.5 mg/kg if needed	NA	Fentanyl 1.5 mcg/kg	Fentanyl 1.5 mcg/kg	NA
Coll-Vinent 2003	Etomidate 0.2 mg/kg	Propofol 1.5 mg/kg	Midazolam 0.2 mg/kg	NA	NA	NA
David 2011	Ketamine 0.5 mg/kg Propofol 1 mg/kg	Propofol 1 mg/kg	NA	Fentanyl 0.5-1.0 ug/kg	Fentanyl 0.5-1.0 ug/kg	NA
Del Pizzo 2011	Propofol 1 mg/kg	Propofol 1 mg/kg	Propofol 0.3 mg/kg	NA	Ketamine 0.3 mg/kg	Ketamine 0.3 mg/kg
Derakhshanfar 2015	Midazolam 0.05 mg/kg	Dexmedetomidine 2 µg/kg	NA	NA	NA	NA
Di Liddo 2006	Etomidate 0.2 mg/kg, max 10mg	Midazolam 0.1 mg/kg, max 5mg		Fentanyl 1 ug/kg, max 50ug	Fentanyl 1 ug/kg, max 50ug	
Dilli 2008	Ketamine 1 mg/kg	Midazolam 0.1 mg/kg	NA	NA	Ketamine 1 mg/kg	NA
Disel 2016	Etomidate 0.2 mg/kg	Ketamine 1 mg/kg	NA	Fentanyl 1 ug/kg	NA	NA
Dunn 2010	Propofol 0.5 mg/kg, subsequent doses 0.25 mg/kg	Midazolam 0.15 mg/kg, max 10mg	NA	Remifentanil 0.5 ug/kg, subsequent doses 0.5 ug/kg	Morphine until analgesia achieved or 0.15 mg/kg	
Ferguson 2016	Propofol 0.5 mg/kg, additional 0.25 mg/kg as needed	Propofol 0.25 mg/kg, additional 0.125 mg/kg as needed	NA	NA	Ketamine 0.25 mg/kg, additional 0.125 mg/kg as needed	NA
Gale 1993	Propofol (mean 1.69 ± 0.46 mg/kg)	Methohexital (mean 1.07 ± 0.34 mg/kg)	Midazolam (mean 0.16 ± 0.06 mg/kg)	NA	NA	NA
Genzlinger 2012	Ketamine 1 mg/kg	Etomidate 0.1 mg/kg	NA	NA	NA	NA
Gharavifard 2016	Midazolam 0.1 mg/kg	NA	NA	Fentanyl 1.5 ug/kg	Remifentanil 1 ug/kg	NA
Godambe 2003	Midazolam 0.05 mg/kg	Propofol 1 mg/kg	NA	Ketamine 1-2 mg/kg	Fentanyl 1-2 ug/kg	NA
Gumus 2012	NA	NA	NA	Dexmedetomidine 1 µg/kg	Remifentanil 0.5 ug/kg	NA
Hart 1997	NA	Midazolam 0.07 mg/kg	NA	Fentanyl 2 ug/kg	Fentanyl 2 ug/kg	0.08ml/kg (max dose 2ml) intramuscular meperidine 25 mg/ml, promethazine 6.25 mg/mL, chlorpromazine 6.25 mg/mL

Hatamabadi 2015	Propofol 0.5 mg/kg	Midazolam 0.5 mg/kg	NA	Fentanyl 1 ug/kg	Fentanyl 1 ug/kg	NA
Havel 1999	Propofol 1 mg/kg, infusion 67-100 ug/kg/min, additional bolus 1 mg/kg as needed	Midazolam 0.1 mg/kg, additional bolus 0.05-0.1 mg/kg as needed	NA	Morphine sulfate 0.05-0.1 mg/kg (max single dose 5mg), additional 0.05–0.1 mg/kg as required	Morphine sulfate 0.05-0.1 mg/kg (max single dose 5mg), additional 0.05–0.1 mg/kg as required	NA
Hunt 2005	Etomidate 0.1 mg/kg, max 3 doses	Midazolam 0.035 mg/kg, max 3 doses	NA	Morphine sulfate 0.1-0.15 mg/kg pre-procedure, fentanyl 50 ug increments during procedure	Morphine sulfate 0.1-0.15 mg/kg pre-procedure, fentanyl 50 ug increments during procedure	NA
Holger 2005	Midazolam 1 mg, additional doses 1 mg as needed	Propofol 0.5 mg/kg, additional bolus 0.25 mg/kg as needed	NA	NA	NA	NA
Jamal 2011	Midazolam 0.05 mg/kg, max 7.5mg	Ketamine 0.5 mg/kg, max 2 mg/kg	NA	Fentanyl 1 ug/kg	NA	NA
Kennedy 1998	Midazolam ≤0.1 mg/kg (max 2.5 mg) until speech slurred or eyes became glassy or until a max first dose of 0.3 mg/kg (max 7.5 mg)	Midazolam ≤0.1 mg/kg (max 2.5 mg) until speech slurred or eyes became glassy or until a max first dose of 0.3 mg/kg (max 7.5 mg)	NA	Fentanyl ≤0.5 ug/kg until a decreased response to verbal or painful stimuli occurred or a max first dose of 2 ug/kg (max 100 ug)	Ketamine ≤0.5 mg/kg until a decreased response to verbal or painful stimuli occurred or a max first dose of 2 mg/kg	NA
Khutia 2012	Propofol 1 mg/kg, infusion 50 ug/kg/min	Propofol 1 mg/kg, infusion 50 ug/kg/min	NA	Ketamine 0.5 mg/kg	Fentanyl 1.5 ug/kg	NA
Kienstra 2004	Etomidate 0.1-0.2 mg/kg	Pentobarbital up to 5 mg/kg	NA	NA	NA	NA
Lee-Jayaram 2010	Midazolam 0.05 mg/kg, max 2mg	Etomidate 0.2 mg/kg	NA	Ketamine 1 mg/kg	Fentanyl 1 ug/kg	NA
Lemoel 2017	NA	Propofol 0.5 mg/kg	NA	Ketamine 1 mg/kg	Ketamine 0.5 mg/kg	NA
LucasdaSilva 2007	Midazolam 0.15 mg/kg, max 5mg	Midazolam 0.15 mg/kg, max 5mg	NA	Fentanyl 1 ug/kg, max 100ug	Ketamine 0.5 mg/kg	NA
Maltepe 2006	Propofol (mean 0.88 ± 0.48 mg/kg)	Propofol (mean 0.9 ± 0.43 mg/kg)	NA	Fentanyl 1 ug/kg	Remifentanil 0.25 ug/kg	NA
Masoumi 2019	Dexmedetomidine 1 µg/kg, infusion 2 µg/kg/h	Midazolam 0.05 mg/kg	NA	NA	Not Comprehensively Reported	NA
Massaeli 2022	Ketamine 1-2 mg/kg	Propofol 1-2 mg/kg	Propofol 0.5 mg/kg	NA	Ketamine 1-2 mg/kg	Fentanyl 1 ug/kg

Messenger 2008	Propofol 0.4 mg/kg, additional bolus 0.1 mg/kg as needed	Propofol 0.4 mg/kg, additional bolus 0.1 mg/kg as needed	NA	Ketamine 0.3 mg/kg	Fentanyl 1.5 ug/kg	NA
Miner 2003	Methohexital 1 mg/kg, additional bolus 0.5 mg/kg as needed	Propofol 1 mg/kg, additional bolus 0.5 mg/kg as needed	NA	Morphine 0.1 mg/kg, additional bolus 0.05 mg/kg as needed	Morphine 0.1 mg/kg, additional bolus 0.05 mg/kg as needed	NA
Miner 2007	Etomidate 0.1 mg/kg, bolus 0.05 mg/kg as needed	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	NA	NA	NA	NA
Miner 2009	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	NA	NA	Alfentanil 10 ug/kg	NA
Miner 2010	Ketamine 1 mg/kg, bolus 0.5 mg/kg as needed	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	NA	NA	NA	NA
Miner 2013	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	NA	NA	Alfentanil 10 ug/kg	NA
Miner 2015	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	Propofol 0.5 mg/kg, bolus 0.25 mg/kg as needed	Propofol 0.8 mg/kg, bolus 0.4 mg/kg as needed	NA	Ketamine 0.5 mg/kg, bolus 0.25 mg/kg as needed	Ketamine 0.2 mg/kg, bolus 0.1 mg/kg as needed
Miner 2017	Alfentanil 10 ug/kg, bolus 5 ug/kg as needed	Propofol 1 mg/kg, bolus 0.5 mg/kg as needed	NA	NA	NA	NA
Mofidi 2018	Propofol 1 mg/kg	Propofol 1 mg/kg	NA	Fentanyl 1 ug/kg	Ketamine 0.5 mg/kg	NA
MonsefKasmaee 2019	NA	Propofol 1 mg/kg	NA	Remifentanil 1 ug/kg	Fentanyl 1 ug/kg	NA
Moro-Sutherland 2000	Midazolam 0.2 mg/kg, max 7.5mg	Pentobarbital 5 mg/kg, max 100mg	NA	NA	NA	NA
Nashibi 2017	Propofol 0.5 mg/kg	Midazolam 0.4 mg/kg	NA	Ketamine 0.5 mg/kg	Fentanyl 2 ug/kg	NA
Nejati 2011	Propofol (median 1.125 mg/kg)	Midazolam (median 0.04 mg/kg)	NA	Ketamine (median 1.125 mg/kg)	Fentanyl (median 2 ug/kg)	NA
Parlak 2006	Midazolam 2 mg, then 1 mg every 2 min	Propofol 20 mg, then 20 mg every 2 min	NA	Fentanyl 0.5-1 ug/kg	Fentanyl 0.5-1 ug/kg	NA
Phillips 2010	Propofol 0.5-1.5 mg/kg	Propofol 0.75 mg/kg	NA	NA	Ketamine 0.5-1 mg/kg	NA
Rahman 2011	Propofol 1 mg/kg, additional bolus 0.5 mg/kg if needed	Midazolam 0.1 mg/kg, additional	NA	Fentanyl 3 ug/kg	Fentanyl 3 ug/kg	NA

		bolus 0.1 mg/kg if needed				
Salen 2016	Ketamine 0.5 mg/kg, additional bolus 0.5 mg/kg if needed	Etomidate 0.1 mg/kg, additional bolus 0.1 mg/kg if needed	NA	NA	NA	NA
Sawas 2013	NA	NA	NA	NA	NA	NA
Sener 2011	Placebo 0.03 mg/kg	Midazolam 0.3 mg/kg	Arm 3: Placebo 0.03 mg/kg Arm 4: Midazolam 0.3 mg/kg	Ketamine 1.5 mg/kg	Ketamine 1.5 mg/kg	Arm 3: IM Ketamine 4 mg/kg Arm 4: IM Ketamine 4 mg/kg
Seol 2015	Propofol 2 mg/kg	Propofol 2 mg/kg	NA	Ketamine 1 mg/kg	Remifentanil 1 ug/kg, infusion 0.05 ug/kg/min	NA
Shah 2011	Ketamine 1 mg/kg, additional 0.25 mg/kg as needed	Ketamine 0.5 mg/kg	NA	NA	Propofol 0.5 mg/kg, additional 0.5 mg/kg as needed	NA
Sheik 2017	Ketamine 0.5 mg/kg	Ketamine 1 mg/kg	NA	Propofol 1 mg/kg	NA	NA
Sherwin 2000	Midazolam 0.05 mg/kg, max 2mg	NA	NA	Ketamine 1.5 mg/kg	Ketamine 1.5 mg/kg	NA
Soysal 2004	Midazolam 0.02 mg/kg	Midazolam 0.02 mg/kg	NA	Fentanyl 1 ug/kg	Meperidine 0.5 mg/kg	NA
Stronati 2020	Propofol 1 mg/kg, additional 0.5 mg/kg as needed	Midazolam 3mg, followed by 2 mg bolus as needed	NA	NA	NA	NA
Tajoddini 2020	Propofol 1 mg/kg	Propofol 1 mg/kg	NA	Ketamine 0.5 mg/kg	Fentanyl 1 ug/kg	NA
Taylor 2005	Propofol (mean 1.8 mg/kg)	Midazolam (mean 0.06 mg/kg)	NA	NA	Fentanyl 1.25 ug/kg	NA
Uri 2011	Propofol 10 mg bolus until adequate sedation, max 200mg	Midazolam 0.1 mg/kg until adequate sedation, max 5mg	NA	NA	Ketamine 1 mg/kg, max 100mg	NA
Vahidi 2018	Midazolam 0.1 mg/kg	Thiopental 2 mg/kg	NA	Fentanyl 2 ug/kg	Fentanyl 2 ug/kg	NA
Vardi 2002	Midazolam 0.1 mg/kg Ketamine 2 mg/kg	Propofol 2-3 mg/kg, infusion 200 ug/kg/min	NA	Fentanyl 2 ug/kg	Lidocaine 1mg prior to propofol injection	NA
Venkatakrishnan 2011	NA	NA	NA	NA	NA	NA
Wathen 2000	NA	Midazolam 0.1 mg/kg	NA	Ketamine 1 mg/kg	Ketamine 1 mg/kg	NA
Weisz 2017	Ketamine 1 mg/kg	Ketamine 0.5 mg/kg	NA	NA	Propofol 0.5 mg/kg	NA

Wright 1993	Midazolam, max 5mg	Diazepam, max 12.5mg	NA	NA	NA	NA
Yang 2018	Dexmedetomidine*	NA	NA	Remifentanil (mean 282 ± 19 ug)	Remifentanil (mean 340 ± 31 ug)	NA
Yildirim 2007	Propofol 1 mg/kg	Midazolam 0.05 mg/kg	NA	Remifentanil 0.1 ug/kg	Remifentanil 0.1 ug/kg	NA
Yldzdas 2004	Arm 1: Midazolam 0.15 mg/kg	Arm 2: Propofol 2 mg/kg	Arm 3: Midazolam 0.1 mg/kg + fentanyl 2 ug/kg	Arm 4: Ketamine 1 mg/kg	Arm 5: Ketamine 1 mg/kg + Midazolam 0.1 mg/kg	NA

*Not Comprehensively Reported
Unless otherwise specified, route of administration is IV

Appendix 4. Subgroup Analyses

Supplement Table 20. Subgroup Analysis for Recovery Time: Low Risk of Bias versus High Risk of Bias

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Low RoB	33.50	13.88	53.12	0.001
ETMD	test of interaction	-12.34	-11421.10	11396.41	0.998
	Low RoB	9.76	1.88	17.64	0.015
FNDZ	test of interaction	.			
	Low RoB	24.40	9.37	39.43	0.001
KPMF	test of interaction	.			
	Low RoB	0.44	-1415.39	1416.26	1.000
KTFL	test of interaction	0.78	-13.80	15.36	0.916
	Low RoB	6.22	0.79	11.64	0.025
KTHL	test of interaction	.			
	Low RoB	36.55	23.46	49.64	0.000
KTMN	test of interaction	-5.62	-11414.38	11403.13	0.999
	Low RoB	8.04	2.00	14.08	0.009
MDFM	test of interaction	.			
	Low RoB	35.64	20.38	50.90	0.000
MDMO	test of interaction	.			
	Low RoB	34.29	19.40	49.18	0.000
MDZM	test of interaction	-21.90	-43.61	-0.19	**0.048**
	Low RoB	30.90	16.33	45.47	0.000
MPCL	test of interaction	.			
	Low RoB	40.61	-1375.27	1456.49	0.955
MTHX	test of interaction	.			
	Low RoB	-1.40	-14.39	11.59	0.833
MZKT	test of interaction	19.31	-1396.55	1435.18	0.979
	Low RoB	20.17	13.08	27.26	0.000
OPDX	test of interaction	.			
	Low RoB	11.20	-3.32	25.72	0.131
OPET	test of interaction	.			
	Low RoB	0.83	-9.50	11.16	0.875
OPID	test of interaction	.			
	Low RoB	-4.39	-1420.22	1411.44	0.995

OPMZ	test of interaction	-16.69	-1432.54	1399.16	0.982
	Low RoB	17.30	10.31	24.29	0.000
OPPF	test of interaction	-5.31	-1421.12	1410.50	0.994
	Low RoB	4.29	-2.20	10.77	0.195
PFMP	test of interaction	.			
	Low RoB	-0.31	-24.10	23.48	0.980
PNTB	test of interaction	.			
	Low RoB	41.06	24.71	57.41	0.000
RMMT	test of interaction	.			
	Low RoB	-4.85	-1420.70	1411.00	0.995
TPFN	test of interaction	.			
	Low RoB	10.11	-0.58	20.80	0.064

Supplement Table 21. Subgroup Analysis for Recovery Time: Long Procedure versus Other Duration of Procedure

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Procedure long	1.30	-5110.06	5112.66	1.000
ETMD	test of interaction	-12.58	-33.73	8.56	0.244
	Procedure long	15.96	-1.53	33.45	0.074
FNDZ	test of interaction	.			
	Procedure long	26.27	6.38	46.15	0.010
KPMF	test of interaction	.			
	Procedure long	6.03	-15.01	27.07	0.574
KTFL	test of interaction	3.76	-9.68	17.19	0.584
	Procedure long	4.56	-5.54	14.66	0.376
KTHL	test of interaction	.			
	Procedure long	38.92	19.11	58.74	0.000
KTMN	test of interaction	2.10	-14.93	19.14	0.809
	Procedure long	9.44	-2.37	21.24	0.117
MDFM	test of interaction	.			
	Procedure long	32.56	14.22	50.90	0.001
MDMO	test of interaction	.			
	Procedure long	31.17	11.29	51.05	0.002
MDZM	test of interaction	21.98	-5089.39	5133.36	0.993
	Procedure long	-1.30	-5112.66	5110.06	1.000
MPCL	test of interaction	.			
	Procedure long	49.37	22.18	76.55	0.000
MTHX	test of interaction	.			
	Procedure long	-1.40	-18.16	15.36	0.870
MZKT	test of interaction	-5.00	-24.35	14.34	0.612
	Procedure long	26.42	16.09	36.74	0.000
OPDX	test of interaction	.			
	Procedure long	13.06	-6.44	32.56	0.189
OPET	test of interaction	.			
	Procedure long	3.13	-11.08	17.34	0.666
OPID	test of interaction	6.57	-26.72	39.86	0.699
	Procedure long	-2.20	-21.88	17.48	0.826
OPMZ	test of interaction	-9.80	-30.42	10.82	0.351
	Procedure long	19.17	8.87	29.47	0.000
OPPF	test of interaction	3.41	-13.07	19.88	0.685
	Procedure long	1.17	-9.00	11.33	0.822
PFMP	test of interaction	.			

	Procedure long	-3.43	-32.62	25.75	0.818
PNTB	test of interaction	.			
	Procedure long	47.26	22.29	72.23	0.000
RMMT	test of interaction	.			
	Procedure long	0.74	-20.36	21.85	0.945
TPFN	test of interaction	.			
	Procedure long	10.21	-4.84	25.27	0.184

Supplement Table 22. Subgroup Analysis for Recovery Time: Short Procedure versus Other Duration of Procedures

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Procedure short	11.60	-12.51	35.71	0.346
ETMD	test of interaction	8.46	-10.56	27.49	0.383
	Procedure short	3.25	-12.63	19.13	0.688
FNDZ	test of interaction	.			
	Procedure short	25.57	7.78	43.36	0.005
KPMF	test of interaction	.			
	Procedure short	4.40	-12.61	21.41	0.612
KTFL	test of interaction	-2.76	-1540.95	1535.43	0.997
	Procedure short	8.40	-1529.77	1546.58	0.991
KTHL	test of interaction	.			
	Procedure short	40.31	24.93	55.70	0.000
KTMN	test of interaction	.			
	Procedure short	10.12	3.11	17.12	0.005
MDFM	test of interaction	.			
	Procedure short	32.50	14.20	50.80	0.000
MDMO	test of interaction	.			
	Procedure short	32.94	15.44	50.44	0.000
MDZM	test of interaction	-21.90	-46.83	3.03	0.085
	Procedure short	30.90	13.95	47.85	0.000
MPCL	test of interaction	.			
	Procedure short	53.21	34.72	71.71	0.000
MTHX	test of interaction	.			
	Procedure short	-1.40	-17.02	14.22	0.861
MZKT	test of interaction	21.46	-1516.92	1559.84	0.978
	Procedure short	4.20	-1534.16	1542.57	0.996
OPDX	test of interaction	.			
	Procedure short	12.36	-5.00	29.73	0.163
OPET	test of interaction	.			
	Procedure short	2.98	-8.86	14.82	0.621
OPID	test of interaction	.			
	Procedure short	5.18	-8.60	18.96	0.461
OPMZ	test of interaction	20.92	-1517.31	1559.16	0.979
	Procedure short	-2.46	-1540.67	1535.76	0.998
OPPF	test of interaction	7.04	-1531.13	1545.20	0.993
	Procedure short	-4.10	-1542.25	1534.05	0.996
PFMP	test of interaction	.			

	Procedure short	-1.66	-28.60	25.27	0.904
PNTB	test of interaction	.			
	Procedure short	43.01	23.26	62.77	0.000
RMMT	test of interaction	.			
	Procedure short	-7.93	-1546.14	1530.29	0.992
TPFN	test of interaction	.			
	Procedure short	10.40	-2.24	23.03	0.107

Supplement Table 23. Subgroup Analysis for Recovery Time: Mixed Procedure versus Other Duration of Procedures

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Procedure short/long	33.50	8.20	58.80	0.009
ETMD	test of interaction	6.20	-14.95	27.35	0.566
	Procedure short/long	3.50	-13.57	20.57	0.688
FNDZ	test of interaction	.			
	Procedure short/long	22.93	2.92	42.94	0.025
KPMF	test of interaction	.			
	Procedure short/long	9.09	-14.39	32.57	0.448
KTFL	test of interaction	-3.93	-17.20	9.34	0.561
	Procedure short/long	7.89	-1.29	17.06	0.092
KTHL	test of interaction	.			
	Procedure short/long	41.21	19.96	62.46	0.000
KTMN	test of interaction	-5.98	-22.84	10.87	0.487
	Procedure short/long	12.89	-0.23	26.01	0.054
MDFM	test of interaction	.			
	Procedure short/long	35.66	16.91	54.41	0.000
MDMO	test of interaction	.			
	Procedure short/long	30.40	10.42	50.38	0.003
MDZM	test of interaction	21.90	-5.05	48.85	0.111
	Procedure short/long	9.00	-10.66	28.66	0.370
MPCL	test of interaction	.			
	Procedure short/long	33.81	-7657.82	7725.45	0.993
MTHX	test of interaction	.			
	Procedure short/long	-1.40	-18.62	15.82	0.873
MZKT	test of interaction	-0.35	-21.75	21.04	0.974
	Procedure short/long	24.65	5.74	43.57	0.011
OPDX	test of interaction	.			
	Procedure short/long	9.73	-9.90	29.36	0.331
OPET	test of interaction	.			
	Procedure short/long	0.36	-13.57	14.28	0.960
OPID	test of interaction	8.22	-7683.44	7699.88	0.998
	Procedure short/long	-11.19	-7702.82	7680.45	0.998
OPMZ	test of interaction	22.02	-7669.63	7713.67	0.996
	Procedure short/long	-6.19	-7697.83	7685.46	0.999
OPPF	test of interaction	-7.23	-26.02	11.55	0.451
	Procedure short/long	7.63	-8.52	23.78	0.354
PFMP	test of interaction	.			

	Procedure short/long	-4.20	-33.71	25.32	0.780
PNTB	test of interaction	.			
	Procedure short/long	41.00	18.88	63.11	0.000
RMMT	test of interaction	.			
	Procedure short/long	-3.43	-23.06	16.20	0.732
TPFN	test of interaction	.			
	Procedure short/long	8.21	-6.83	23.24	0.285

Supplement Table 24. Subgroup Analysis for Recovery Time: Adults versus Other

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Adults	1.31	-5115.78	5118.40	1.000
ETMD	test of interaction	-26.39	-8104.28	8051.49	0.995
	Adults	8.28	-1.69	18.25	0.104
FNDZ	test of interaction	.			
	Adults	24.89	4.81	44.96	0.015
KPMF	test of interaction	.			
	Adults	-1.59	-24.44	21.25	0.891
KTFL	test of interaction	-0.64	-15.45	14.18	0.933
	Adults	5.95	-2.42	14.33	0.164
KTHL	test of interaction	.			
	Adults	38.75	21.35	56.16	0.000
KTMN	test of interaction	2.48	-15.60	20.56	0.788
	Adults	7.53	-2.05	17.11	0.124
MDFM	test of interaction	.			
	Adults	34.96	16.61	53.32	0.000
MDMO	test of interaction	-19.01	-17918.67	17880.65	0.998
	Adults	35.73	15.92	55.53	0.000
MDZM	test of interaction	-21.95	-5139.05	5095.16	0.993
	Adults	20.66	7.23	34.09	0.003
MPCL	test of interaction	.			
	Adults	57.88	29.05	86.71	0.000
MTHX	test of interaction	.			
	Adults	-1.40	-18.58	15.78	0.873
MZKT	test of interaction	-0.63	-21.30	20.04	0.952
	Adults	25.15	14.36	35.93	0.000
OPDX	test of interaction	.			
	Adults	11.69	-8.01	31.38	0.245
OPET	test of interaction	.			
	Adults	2.38	-17.32	22.09	0.813
OPID	test of interaction	10.52	-24.07	45.12	0.551
	Adults	2.36	-17.25	21.96	0.814
OPMZ	test of interaction	0.09	-22.20	22.38	0.994
	Adults	17.79	7.81	27.77	0.000
OPPF	test of interaction	-8.78	-26.62	9.07	0.335
	Adults	5.73	-3.55	15.00	0.226

PFMP	test of interaction	.			
	Adults	-17.89	-17917.53	17881.76	0.998
PNTB	test of interaction	.			
	Adults	13.18	-8064.70	8091.07	0.997
RMMT	test of interaction	.			
	Adults	-6.88	-29.79	16.02	0.556
TPFN	test of interaction	.			
	Adults	10.18	-4.42	24.79	0.172

Supplement Table 25. Subgroup Analysis for Recovery Time: Pediatrics versus Other

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Pediatrics	1.30	-5117.99	5120.59	1.000
ETMD	test of interaction	26.16	-8062.57	8114.88	0.995
	Pediatrics	-18.12	-8106.84	8070.60	0.996
FNDZ	test of interaction	.			
	Pediatrics	26.23	7.92	44.55	0.005
KPMF	test of interaction	.			
	Pediatrics	7.40	-10.14	24.94	0.408
KTFL	test of interaction	-1.09	-18.78	16.60	0.904
	Pediatrics	7.00	-9.35	23.35	0.402
KTHL	test of interaction	.			
	Pediatrics	37.25	21.35	53.15	0.000
KTMN	test of interaction	-7.26	-28.21	13.68	0.497
	Pediatrics	14.24	-5.11	33.58	0.149
MDFM	test of interaction	.			
	Pediatrics	34.84	17.48	52.20	0.000
MDMO	test of interaction	19.22	-18177.88	18216.32	0.998
	Pediatrics	16.72	-18180.37	18213.81	0.999
MDZM	test of interaction	22.05	-5097.26	5141.36	0.993
	Pediatrics	-1.30	-5120.59	5117.99	1.000
MPCL	test of interaction	.			
	Pediatrics	56.40	25.79	87.01	0.000
MTHX	test of interaction	.			
	Pediatrics	-1.40	-17.31	14.51	0.863
MZKT	test of interaction	-5.05	-27.79	17.68	0.663
	Pediatrics	27.73	7.02	48.44	0.009
OPDX	test of interaction	.			
	Pediatrics	13.03	-4.87	30.93	0.154
OPET	test of interaction	25.87	-32.47	84.22	0.385
	Pediatrics	3.26	-19.28	25.80	0.777
OPID	test of interaction	-8.83	-43.97	26.32	0.623
	Pediatrics	11.40	-18.91	41.71	0.461
OPMZ	test of interaction	2.74	-22.14	27.61	0.829
	Pediatrics	16.40	-6.94	39.74	0.169
OPPF	test of interaction	11.46	-9.26	32.19	0.278
	Pediatrics	-5.52	-24.74	13.70	0.573
PFMP	test of interaction	.			

	Pediatrics	-17.88	-18214.97	18179.21	0.998
PNTB	test of interaction	.			
	Pediatrics	13.18	-8075.54	8101.90	0.997
RMMT	test of interaction	.			
	Pediatrics	-9.35	-34.24	15.53	0.461
TPFN	test of interaction	.			
	Pediatrics	10.86	-2.24	23.97	0.104

Supplement Table 26. Subgroup Analysis for Recovery Time: Mixed Population versus Other

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Mixed	23.28	1.89	44.68	0.033
ETMD	test of interaction	.			
	Mixed	9.61	0.17	19.04	0.046
FNDZ	test of interaction	.			
	Mixed	22.29	3.30	41.29	0.021
KPMF	test of interaction	.			
	Mixed	5.51	-23.34	34.36	0.708
KTFL	test of interaction	2.14	-15.80	20.08	0.815
	Mixed	3.75	-12.81	20.31	0.657
KTHL	test of interaction	.			
	Mixed	40.71	24.19	57.22	0.000
KTMN	test of interaction	5.16	-19.72	30.05	0.684
	Mixed	5.25	-18.40	28.90	0.664
MDFM	test of interaction	.			
	Mixed	35.61	17.62	53.61	0.000
MDMO	test of interaction	.			
	Mixed	32.14	13.34	50.95	0.001
MDZM	test of interaction	.			
	Mixed	20.68	7.52	33.84	0.002
MPCL	test of interaction	.			
	Mixed	51.04	31.42	70.65	0.000
MTHX	test of interaction	.			
	Mixed	-1.40	-18.16	15.36	0.870
MZKT	test of interaction	29.88	-10000.54	10060.30	0.995
	Mixed	-3.72	-10034.14	10026.69	0.999
OPDX	test of interaction	.			
	Mixed	9.09	-9.51	27.69	0.338
OPET	test of interaction	-12.30	-10042.85	10018.25	0.998
	Mixed	13.15	-10017.39	10043.69	0.998
OPID	test of interaction	.			
	Mixed	3.50	-11.29	18.30	0.642
OPMZ	test of interaction	12.05	-10018.37	10042.46	0.998
	Mixed	3.15	-10027.26	10033.56	1.000
OPPF	test of interaction	-1.91	-26.79	22.98	0.881
	Mixed	4.05	-19.56	27.66	0.737
PFMP	test of interaction	.			

	Mixed	-2.46	-30.92	26.00	0.866
PNTB	test of interaction	.			
	Mixed	40.91	20.75	61.06	0.000
RMMT	test of interaction	.			
	Mixed	-1.69	-20.11	16.74	0.858
TPFN	test of interaction	.			
	Mixed	8.83	-4.85	22.51	0.206

Supplement Table 27. Subgroup Analysis for Patient Satisfaction as a Continuous Outcome: Low Risk of Bias versus High Risk of Bias

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Low RoB	0.80	-280.37	281.97	0.996
ETMD	test of interaction	.	.	.	.
	Low RoB	0.05	-1.58	1.68	0.952
FNDZ	test of interaction	.	.	.	.
	Low RoB	0.34	-2.23	2.92	0.794
KTFL	test of interaction	0.68	-1.70	3.05	0.577
	Low RoB	-0.48	-1.95	1.00	0.527
KTMN	test of interaction	.	.	.	.
	Low RoB	-0.44	-2.56	1.67	0.681
MDZM	test of interaction	.	.	.	.
	Low RoB	-0.50	-2.56	1.56	0.634
MPCL	test of interaction	.	.	.	.
	Low RoB	0.36	-280.81	281.54	0.998
MZKT	test of interaction	-0.64	-1242.61	1241.34	0.999
	Low RoB	0.41	-1.12	1.94	0.598
OPDX	test of interaction	.	.	.	.
	Low RoB	0.89	-280.29	282.06	0.995
OPET	test of interaction	2.38	-278.81	283.56	0.987
	Low RoB	-1.93	-3.88	0.02	0.053
OPID	test of interaction	.	.	.	.
	Low RoB	-0.94	-282.11	280.23	0.995
OPMZ	test of interaction	1.73	-279.45	282.91	0.990
	Low RoB	-1.93	-3.72	-0.15	0.034
OPPF	test of interaction	1.61	-1240.37	1243.58	0.998
	Low RoB	-1.40	-3.35	0.54	0.158
TPFN	test of interaction	.	.	.	.
	Low RoB	-1.73	-3.67	0.21	0.080

Supplement Table 28. Subgroup Analysis for Patient Satisfaction as a Continuous Outcome: Long Procedure versus Mixed Duration of Procedures

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Procedure long	-0.87	-3.86	2.12	0.569
ETMD	test of interaction	.	.	.	.
	Procedure long	0.05	-2.03	2.13	0.962
FNDZ	test of interaction	.	.	.	.
	Procedure long	0.68	-2.41	3.76	0.667
KTFL	test of interaction	-0.13	-2.92	2.67	0.930
	Procedure long	0.13	-1.77	2.02	0.896
KTMN	test of interaction	.	.	.	.
	Procedure long	0.14	-2.53	2.80	0.920
MDZM	test of interaction	.	.	.	.
	Procedure long	-0.50	-2.93	1.93	0.686
MPCL	test of interaction	.	.	.	.
	Procedure long	0.34	-440.22	440.91	0.999
MZKT	test of interaction	.	.	.	.
	Procedure long	-0.05	-1.88	1.77	0.954
OPDX	test of interaction	.	.	.	.
	Procedure long	1.03	-439.53	441.59	0.996
OPET	test of interaction	.	.	.	.
	Procedure long	-1.60	-3.86	0.66	0.166
OPID	test of interaction	2.07	-438.50	442.65	0.993
	Procedure long	-2.87	-6.52	0.78	0.124
OPMZ	test of interaction	1.17	-439.40	441.74	0.996
	Procedure long	-1.60	-3.70	0.50	0.136
OPPF	test of interaction	0.79	-2.99	4.58	0.681
	Procedure long	-0.79	-3.10	1.51	0.499
TPFN	test of interaction	.	.	.	.
	Procedure long	-1.28	-3.64	1.09	0.291

Supplement Table 29. Subgroup Analysis for Patient Satisfaction as a Continuous Outcome: Adults versus Pediatrics

		MD	95% CI		P value
DXMT	test of interaction	.	.	.	.
	Adults	-0.31	-2.06	1.44	0.732
ETMD	test of interaction	.	.	.	.
	Adults	0.05	-1.07	1.17	0.930
FNDZ	test of interaction	.	.	.	.
	Adults	1.24	-0.67	3.15	0.204
KTFL	test of interaction	-0.35	-561.15	560.46	0.999
	Adults	0.07	-0.79	0.93	0.869
KTMN	test of interaction	.	.	.	.
	Adults	-0.27	-561.08	560.53	0.999
MDZM	test of interaction	.	.	.	.
	Adults	-0.50	-2.18	1.18	0.559
MPCL	test of interaction	.	.	.	.
	Adults	0.78	-959.35	960.91	0.999
MZKT	test of interaction	1.30	-559.51	562.10	0.996
	Adults	-0.12	-1.33	1.09	0.845
OPDX	test of interaction	.	.	.	.
	Adults	-0.48	-2.89	1.93	0.695
OPET	test of interaction	-1.76	-562.56	559.05	0.995
	Adults	-0.32	-2.00	1.36	0.711
OPID	test of interaction	1.95	-958.18	962.08	0.997
	Adults	-2.31	-4.41	-0.21	0.031
OPMZ	test of interaction	1.05	-959.08	961.18	0.998
	Adults	-1.04	-2.31	0.24	0.111
OPPF	test of interaction	2.32	-558.49	563.13	0.994
	Adults	-0.71	-2.05	0.62	0.295
TPFN	test of interaction	.	.	.	.
	Adults	-0.98	-2.28	0.33	0.142

Supplement Table 30. Subgroup Analysis for Patient Satisfaction as a Dichotomous Outcome: Low Risk of Bias versus High Risk of Bias

		RR	95% CI		P value
ETMD	test of interaction	.	.	.	.
	Low RoB	1.00	0.76	1.31	1.000
KPMF	test of interaction	.	.	.	.
	Low RoB	1.00	0.00	187.00	1.000
KTFL	test of interaction	.	.	.	.
	Low RoB	1.06	0.93	1.22	0.359
KTMN	test of interaction	.	.	.	.
	Low RoB	0.95	0.84	1.08	0.458
MDFM	test of interaction	.	.	.	.
	Low RoB	0.99	0.75	1.32	0.967
MDMO	test of interaction	.	.	.	.
	Low RoB	0.88	0.00	660.00	0.999
MDZM	test of interaction	.	.	.	.
	Low RoB	0.97	0.77	1.23	0.830
MTHX	test of interaction	.	.	.	.
	Low RoB	0.98	0.78	1.24	0.871
MZKT	test of interaction	1.09	0.00	820.00	0.999
	Low RoB	1.02	0.86	1.21	0.790
OPET	test of interaction	.	.	.	.
	Low RoB	0.91	0.70	1.20	0.513
OPID	test of interaction	.	.	.	.
	Low RoB	1.02	0.84	1.23	0.858
OPMZ	test of interaction	.	.	.	.
	Low RoB	1.01	0.84	1.21	0.924
OPPF	test of interaction	1.01	0.00	189.00	0.999
	Low RoB	0.99	0.87	1.13	0.891

* only two studies at high risk of bias - low power

Supplement Table 31. Subgroup Analysis for Patient Satisfaction as a Dichotomous Outcome: Long Procedure versus Mixed Duration of Procedures

		RR	95% CI		P value
ETMD	test of interaction	.	.	.	.
	Procedure long	1.00	0.75	1.33	1.000
KPMF	test of interaction	.	.	.	.
	Procedure long	0.98	0.72	1.33	0.912
KTFL	test of interaction	1.06	0.55	2.05	0.857
	Procedure long	1.07	0.57	1.99	0.841
KTMN	test of interaction	0.91	0.47	1.78	0.792
	Procedure long	0.99	0.52	1.87	0.976
MDFM	test of interaction	.	.	.	.
	Procedure long	0.99	0.74	1.34	0.969
MDMO	test of interaction	.	.	.	.
	Procedure long	0.97	0.41	2.26	0.940
MDZM	test of interaction	.	.	.	.
	Procedure long	0.97	0.76	1.25	0.842
MTHX	test of interaction	.	.	.	.
	Procedure long	0.98	0.76	1.26	0.880
MZKT	test of interaction	0.72	0.34	1.50	0.379
	Procedure long	1.23	0.62	2.43	0.554
OPET	test of interaction	.	.	.	.
	Procedure long	1.09	0.53	2.26	0.811
OPID	test of interaction	0.85	0.40	1.85	0.689
	Procedure long	1.21	0.58	2.49	0.612
OPMZ	test of interaction	.	.	.	.
	Procedure long	1.21	0.60	2.42	0.596
OPPF	test of interaction	0.98	0.51	1.88	0.958
	Procedure long	1.00	0.54	1.84	1.000

Supplement Table 32. Subgroup Analysis for Patient Satisfaction as a Dichotomous Outcome: Adults versus Other

		RR	95% CI		P value
ETMD	test of interaction	.	.	.	.
	Adults	1.00	0.72	1.38	1.000
KPMF	test of interaction	.	.	.	.
	Adults	1.00	0.00	209.00	1.000
KTFL	test of interaction	0.94	0.00	196.00	0.998
	Adults	1.11	0.92	1.35	0.271
KTMN	test of interaction	1.11	0.00	232.00	0.997
	Adults	0.88	0.71	1.09	0.234
MDFM	test of interaction	.	.	.	.
	Adults	0.99	0.71	1.38	0.972
MDMO	test of interaction	.	.	.	.
	Adults	0.81	0.00	170.00	0.993
MDZM	test of interaction	.	.	.	.
	Adults	0.97	0.73	1.30	0.864
MTHX	test of interaction	.	.	.	.
	Adults	0.98	0.73	1.31	0.896
MZKT	test of interaction	0.99	0.00	206.00	1.000
	Adults	1.05	0.74	1.49	0.799
OPET	test of interaction	.	.	.	.
	Adults	0.90	0.00	188.00	0.997
OPID	test of interaction	.	.	.	.
	Adults	1.05	0.80	1.37	0.737
OPMZ	test of interaction	0.94	0.00	195.00	0.998
	Adults	1.06	0.77	1.47	0.728
OPPF	test of interaction	1.00	0.00	208.00	1.000
	Adults	1.00	0.83	1.22	0.970

Supplement Table 33 Subgroup Analysis for Patient Satisfaction as a Dichotomous Outcome: Pediatrics versus Other

		RR	95% CI		P value
ETMD	test of interaction	.	.	.	.
	Pediatrics	1.00	0.73	1.37	1.000
KPMF	test of interaction	.	.	.	.
	Pediatrics	0.98	0.73	1.32	0.902
KTFL	test of interaction	0.94	0.00	702.00	0.999
	Pediatrics	1.13	0.00	843.00	0.998
KTMN	test of interaction	0.95	0.00	707.00	0.999
	Pediatrics	0.98	0.00	732.00	1.000
MDFM	test of interaction	.	.	.	.
	Pediatrics	0.99	0.72	1.37	0.971
MDMO	test of interaction	.	.	.	.
	Pediatrics	0.82	0.00	610.00	0.997
MDZM	test of interaction	.	.	.	.
	Pediatrics	0.97	0.74	1.29	0.858
MTHX	test of interaction	.	.	.	.
	Pediatrics	0.98	0.74	1.30	0.892
MZKT	test of interaction	1.05	0.00	781.00	0.999
	Pediatrics	1.04	0.00	773.00	1.000
OPET	test of interaction	0.90	0.00	672.00	0.999
	Pediatrics	0.99	0.00	738.00	1.000
OPID	test of interaction	.	.	.	.
	Pediatrics	1.05	0.82	1.36	0.684
OPMZ	test of interaction	1.08	0.00	808.00	0.999
	Pediatrics	0.99	0.00	737.00	1.000
OPPF	test of interaction	.	.	.	.
	Pediatrics	0.98	0.83	1.16	0.825

Supplement Table 34. Subgroup Analysis for Patient Satisfaction as a Dichotomous Outcome: Mixed Population versus Other

		RR	95% CI		P value
ETMD	test of interaction	.	.	.	.
	Mixed	1.00	0.73	1.37	1.000
KPMF	test of interaction	.	.	.	.
	Mixed	1.00	0.00	207.00	1.000
KTFL	test of interaction	1.09	0.00	225.00	0.998
	Mixed	1.02	0.00	211.00	1.000
KTMN	test of interaction	0.92	0.00	192.00	0.998
	Mixed	1.00	0.00	207.00	1.000
MDFM	test of interaction	.	.	.	.
	Mixed	0.99	0.72	1.37	0.971
MDMO	test of interaction	.	.	.	.
	Mixed	0.79	0.45	1.38	0.401
MDZM	test of interaction	.	.	.	.
	Mixed	0.97	0.74	1.29	0.858
MTHX	test of interaction	.	.	.	.
	Mixed	0.98	0.74	1.30	0.892
MZKT	test of interaction	0.95	0.00	167.00	0.999
	Mixed	1.05	0.00	186.00	0.999
OPET	test of interaction	1.18	0.00	208.00	0.998
	Mixed	0.84	0.00	149.00	0.998
OPID	test of interaction	.	.	.	.
	Mixed	1.01	0.80	1.27	0.932
OPMZ	test of interaction	0.98	0.00	173.00	1.000
	Mixed	1.01	0.00	179.00	1.000
OPPF	test of interaction	1.00	0.00	208.00	1.000
	Mixed	1.00	0.00	207.00	1.000

Supplement Table 35. Subgroup Analysis for Respiratory Adverse Events: Low Risk of Bias versus High Risk of Bias

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Low RoB	0.81	0.43	1.55	0.528
DXMT	test of interaction	.	.	.	.
	Low RoB	0.70	0.01	41.90	0.865
DZPM	test of interaction	.	.	.	.
	Low RoB	1.05	0.00	.	1.000
ETMD	test of interaction	1.89	0.00	.	0.999
	Low RoB	0.98	0.60	1.59	0.929
FNDZ	test of interaction	.	.	.	.
	Low RoB	1.45	0.09	24.35	0.795
KPMF	test of interaction	.	.	.	.
	Low RoB	0.72	0.00	1719.00	0.999
KPRF	test of interaction	.	.	.	.
	Low RoB	1.18	0.54	2.59	0.682
KTFL	test of interaction	0.79	0.33	1.87	0.589
	Low RoB	0.81	0.59	1.11	0.189
KTHL	test of interaction	.	.	.	.
	Low RoB	0.96	0.03	29.38	0.979
KTMN	test of interaction	0.23	0.00	.	0.998
	Low RoB	0.91	0.61	1.36	0.660
LMDF	test of interaction	.	.	.	.
	Low RoB	1.57	0.20	11.97	0.666
MDFM	test of interaction	.	.	.	.
	Low RoB	0.67	0.23	1.97	0.461
MDMO	test of interaction	0.36	0.00	870.00	0.996
	Low RoB	1.53	0.03	77.29	0.831
MDZM	test of interaction	1.37	0.00	.	1.000
	Low RoB	0.70	0.23	2.18	0.541
MPCL	test of interaction	.	.	.	.
	Low RoB	1.36	0.00	3212.00	0.999
MTHX	test of interaction	.	.	.	.
	Low RoB	1.06	0.60	1.88	0.837
MZKT	test of interaction	0.17	0.00	4119.00	0.994
	Low RoB	0.97	0.60	1.57	0.895
OPDX	test of interaction	1.05	0.00	2519.00	1.000
	Low RoB	1.57	0.03	81.58	0.824
OPET	test of interaction	1.81	0.00	4419.00	0.998

	Low RoB	1.34	0.59	3.08	0.486
OPID	test of interaction	2.06	0.00	4919.00	0.997
	Low RoB	1.19	0.51	2.76	0.685
OPMZ	test of interaction	1.81	0.00	4319.00	0.998
	Low RoB	1.57	0.96	2.54	0.070
OPPF	test of interaction	0.48	0.00	1119.00	0.997
	Low RoB	1.53	1.03	2.28	0.036
PFMP	test of interaction	.	.	.	.
	Low RoB	1.64	0.03	100.64	0.814
PNTB	test of interaction	.	.	.	.
	Low RoB	3.66	0.39	34.80	0.258
RMMT	test of interaction	.	.	.	.
	Low RoB	1.17	0.00	2819.00	0.999
TPFN	test of interaction	.	.	.	.
	Low RoB	1.09	0.50	2.36	0.825

Supplement Table 36. Subgroup Analysis for Respiratory Adverse Events: Long Procedure versus Other Duration of Procedures

		RR	.		P value
DXKT	test of interaction	.	.	.	.
	Procedure long	0.63	0.29	1.36	0.235
DXMT	test of interaction	.	.	.	.
	Procedure long	0.90	0.00	328.70	0.973
DZPM	test of interaction	.	.	.	.
	Procedure long	1.14	0.02	66.91	0.949
ETMD	test of interaction	0.23	0.07	0.77	0.017
	Procedure long	3.31	1.05	10.47	0.041
FNDZ	test of interaction	.	.	.	.
	Procedure long	0.88	0.05	14.58	0.929
KPMF	test of interaction	.	.	.	.
	Procedure long	1.55	0.03	78.61	0.826
KPRF	test of interaction	.	.	.	.
	Procedure long	1.21	0.64	2.29	0.551
KTFL	test of interaction	1.28	0.62	2.63	0.507
	Procedure long	0.65	0.33	1.29	0.219
KTHL	test of interaction	.	.	.	.
	Procedure long	2.08	0.07	63.71	0.675
KTMN	test of interaction	2.04	0.95	4.37	0.068
	Procedure long	0.70	0.35	1.38	0.299
LMDF	test of interaction	.	.	.	.
	Procedure long	0.95	0.13	7.13	0.959
MDFM	test of interaction	.	.	.	.
	Procedure long	0.61	0.23	1.65	0.333
MDMO	test of interaction	.	.	.	.
	Procedure long	1.71	0.24	12.05	0.593
MDZM	test of interaction	1.16	0.01	113.48	0.949
	Procedure long	0.90	0.01	75.26	0.964
MPCL	test of interaction	.	.	.	.
	Procedure long	1.44	0.18	11.46	0.730
MTHX	test of interaction	1.92	0.43	8.62	0.394
	Procedure long	0.98	0.66	1.46	0.924
MZKT	test of interaction	5.11	1.69	15.40	**0.004**
	Procedure long	0.58	0.31	1.08	0.088
OPDX	test of interaction	1.14	0.01	87.46	0.953
	Procedure long	0.95	0.02	49.00	0.979
OPET	test of interaction	.	.	.	.

	Procedure long	0.82	0.35	1.93	0.644
OPID	test of interaction	0.45	0.10	1.94	0.282
	Procedure long	3.63	0.99	13.34	0.053
OPMZ	test of interaction	5.76	1.76	18.80	**0.004**
	Procedure long	0.95	0.51	1.76	0.866
OPPF	test of interaction	1.28	0.60	2.73	0.526
	Procedure long	1.23	0.65	2.35	0.524
PFMP	test of interaction	.	.	.	.
	Procedure long	1.82	0.19	17.78	0.605
PNTB	test of interaction	.	.	.	.
	Procedure long	7.31	0.25	210.81	0.246
RMMT	test of interaction	.	.	.	.
	Procedure long	2.50	1.47	4.25	0.001
TPFN	test of interaction	.	.	.	.
	Procedure long	0.74	0.32	1.70	0.473

Supplement Table 37. Subgroup Analysis for Respiratory Adverse Events: Short Procedure versus Other Duration of Procedures

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure short	0.72	0.34	1.52	0.384
DXMT	test of interaction	.	.	.	.
	Procedure short	0.16	0.00	16.81	0.443
DZPM	test of interaction	.	.	.	.
	Procedure short	0.18	0.00	18.16	0.464
ETMD	test of interaction	2.64	0.67	10.45	0.168
	Procedure short	0.50	0.15	1.69	0.264
FNDZ	test of interaction	.	.	.	.
	Procedure short	1.26	0.07	21.95	0.874
KPMF	test of interaction	.	.	.	.
	Procedure short	1.42	0.03	76.18	0.862
KPRF	test of interaction	.	.	.	.
	Procedure short	1.11	0.45	2.78	0.817
KTFL	test of interaction	6.03	0.00	2227.00	0.996
	Procedure short	0.12	0.00	4527.00	0.995
KTHL	test of interaction	.	.	.	.
	Procedure short	0.80	0.03	25.11	0.898
KTMN	test of interaction	.	.	.	.
	Procedure short	0.78	0.52	1.18	0.244
LMDF	test of interaction	.	.	.	.
	Procedure short	1.36	0.17	10.95	0.774
MDFM	test of interaction	.	.	.	.
	Procedure short	0.56	0.17	1.85	0.345
MDMO	test of interaction	.	.	.	.
	Procedure short	2.23	0.31	16.11	0.426
MDZM	test of interaction	0.13	0.01	2.12	0.153
	Procedure short	1.24	0.32	4.83	0.758
MPCL	test of interaction	.	.	.	.
	Procedure short	0.80	0.10	6.50	0.833
MTHX	test of interaction	0.49	0.09	2.79	0.420
	Procedure short	2.01	0.42	9.69	0.384
MZKT	test of interaction	5.22	0.00	.	0.998
	Procedure short	0.15	0.00	.	0.998
OPDX	test of interaction	2.16	0.00	.	0.999
	Procedure short	0.63	0.00	.	1.000
OPET	test of interaction	.	.	.	.

	Procedure short	1.16	0.48	2.78	0.741
OPID	test of interaction	1.80	0.00	.	0.999
	Procedure short	0.94	0.00	.	1.000
OPMZ	test of interaction	1.74	0.00	.	0.999
	Procedure short	0.78	0.00	.	1.000
OPPF	test of interaction	1.70	0.00	6227.00	0.999
	Procedure short	0.85	0.00	3127.00	1.000
PFMP	test of interaction	.	.	.	.
	Procedure short	2.39	0.22	25.89	0.474
PNTB	test of interaction	.	.	.	.
	Procedure short	1.89	0.14	24.85	0.628
RMMT	test of interaction	.	.	.	.
	Procedure short	1.35	0.00	4927.00	0.999
TPFN	test of interaction	.	.	.	.
	Procedure short	0.95	0.41	2.20	0.904

Supplement Table 38. Subgroup Analysis for Respiratory Adverse Events: Mixed Procedure versus Other Duration of Procedure

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure short/long	0.43	0.21	0.89	0.022
DXMT	test of interaction	.	.	.	.
	Procedure short/long	0.99	0.02	58.54	0.995
DZPM	test of interaction	.	.	.	.
	Procedure short/long	0.40	0.00	52.08	0.710
ETMD	test of interaction	1.47	0.64	3.38	0.362
	Procedure short/long	0.81	0.58	1.15	0.237
FNDZ	test of interaction	.	.	.	.
	Procedure short/long	0.69	0.04	11.26	0.792
KPMF	test of interaction	.	.	.	.
	Procedure short/long	1.52	0.03	76.76	0.836
KPRF	test of interaction	.	.	.	.
	Procedure short/long	1.18	0.63	2.24	0.602
KTFL	test of interaction	0.55	0.28	1.06	0.076
	Procedure short/long	0.83	0.67	1.03	0.091
KTHL	test of interaction	.	.	.	.
	Procedure short/long	2.07	0.07	63.43	0.678
KTMN	test of interaction	0.34	0.17	0.68	0.002
	Procedure short/long	1.41	1.00	1.99	0.047
LMDF	test of interaction	.	.	.	.
	Procedure short/long	0.74	0.10	5.49	0.767
MDFM	test of interaction	.	.	.	.
	Procedure short/long	0.67	0.25	1.81	0.431
MDMO	test of interaction	.	.	.	.
	Procedure short/long	1.30	0.19	9.07	0.790
MDZM	test of interaction	2.71	0.11	65.24	0.539
	Procedure short/long	0.36	0.02	6.90	0.501
MPCL	test of interaction	.	.	.	.
	Procedure short/long	1.29	0.16	10.38	0.810
MTHX	test of interaction	.	.	.	.
	Procedure short/long	1.03	0.70	1.51	0.887
MZKT	test of interaction	0.15	0.05	0.45	0.001
	Procedure short/long	2.92	1.15	7.43	0.024
OPDX	test of interaction	.	.	.	.
	Procedure short/long	1.56	0.24	10.26	0.645

OPET	test of interaction	.	.	.	.
	Procedure short/long	0.64	0.28	1.46	0.285
OPID	test of interaction	1.73	0.42	7.16	0.449
	Procedure short/long	1.55	0.78	3.07	0.208
OPMZ	test of interaction	0.16	0.05	0.55	0.004
	Procedure short/long	4.50	1.54	13.16	0.006
OPPF	test of interaction	0.63	0.31	1.31	0.220
	Procedure short/long	1.54	1.03	2.30	0.036
PFMP	test of interaction	.	.	.	.
	Procedure short/long	1.39	0.14	13.42	0.775
PNTB	test of interaction	.	.	.	.
	Procedure short/long	4.84	0.51	46.24	0.171
RMMT	test of interaction	.	.	.	.
	Procedure short/long	1.54	0.77	3.12	0.225
TPFN	test of interaction	.	.	.	.
	Procedure short/long	0.56	0.25	1.24	0.153

Supplement Table 39. Subgroup Analysis for Respiratory Adverse Events: Adults versus Other

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Adults	0.68	0.28	1.65	0.389
DXMT	test of interaction	.	.	.	.
	Adults	0.18	0.00	28.67	0.505
DZPM	test of interaction	.	.	.	.
	Adults	1.16	0.02	76.93	0.943
ETMD	test of interaction	0.56	0.00	132.53	0.837
	Adults	1.16	0.62	2.16	0.648
FNDZ	test of interaction	.	.	.	.
	Adults	0.98	0.05	18.33	0.991
KPMF	test of interaction	.	.	.	.
	Adults	1.98	0.03	128.12	0.748
KPRF	test of interaction	.	.	.	.
	Adults	1.55	0.33	7.26	0.579
KTFL	test of interaction	1.46	0.56	3.80	0.436
	Adults	0.64	0.41	0.99	0.043
KTHL	test of interaction	.	.	.	.
	Adults	0.76	0.02	24.82	0.875
KTMN	test of interaction	1.02	0.30	3.43	0.978
	Adults	0.79	0.46	1.37	0.403
LMDF	test of interaction	.	.	.	.
	Adults	1.06	0.12	9.37	0.959
MDFM	test of interaction	.	.	.	.
	Adults	0.73	0.21	2.49	0.614
MDMO	test of interaction	2.41	0.02	277.03	0.716
	Adults	1.34	0.02	72.08	0.885
MDZM	test of interaction	0.17	0.01	5.19	0.307
	Adults	1.07	0.28	4.10	0.922
MPCL	test of interaction	.	.	.	.
	Adults	1.08	0.08	15.18	0.956
MTHX	test of interaction	.	.	.	.
	Adults	1.15	0.53	2.51	0.721
MZKT	test of interaction	1.42	0.31	6.47	0.650
	Adults	0.70	0.29	1.70	0.431
OPDX	test of interaction	.	.	.	.
	Adults	1.19	0.19	7.40	0.849
OPET	test of interaction	1.46	0.14	15.25	0.752

	Adults	1.17	0.22	6.30	0.853
OPID	test of interaction	1.05	0.11	9.92	0.963
	Adults	1.84	0.79	4.28	0.158
OPMZ	test of interaction	2.11	0.44	10.09	0.349
	Adults	1.06	0.54	2.08	0.868
OPPF	test of interaction	1.50	0.39	5.74	0.553
	Adults	1.34	0.80	2.25	0.267
PFMP	test of interaction	.	.	.	.
	Adults	3.46	0.18	64.94	0.407
PNTB	test of interaction	.	.	.	.
	Adults	1.44	0.02	111.14	0.869
RMMT	test of interaction	.	.	.	.
	Adults	3.19	0.71	14.35	0.131
TPFN	test of interaction	.	.	.	.
	Adults	0.77	0.30	1.98	0.583

Supplement Table 40. Subgroup Analysis for Respiratory Adverse Events: Pediatrics versus Other

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Pediatrics	0.84	0.45	1.58	0.597
DXMT	test of interaction	.	.	.	.
	Pediatrics	0.11	0.00	2214.00	0.989
DZPM	test of interaction	.	.	.	.
	Pediatrics	1.18	0.02	72.65	0.938
ETMD	test of interaction	2.75	0.00	561.00	0.995
	Pediatrics	0.39	0.00	814.00	0.996
FNDZ	test of interaction	.	.	.	.
	Pediatrics	1.00	0.06	17.00	0.998
KPMF	test of interaction	.	.	.	.
	Pediatrics	1.23	0.02	63.72	0.918
KPRF	test of interaction	.	.	.	.
	Pediatrics	0.96	0.45	2.07	0.920
KTFL	test of interaction	1.49	0.00	2914.00	0.998
	Pediatrics	0.52	0.00	1143.00	0.997
KTHL	test of interaction	.	.	.	.
	Pediatrics	0.84	0.03	25.93	0.923
KTMN	test of interaction	2.93	0.00	581.00	0.995
	Pediatrics	0.35	0.00	681.00	0.995
LMDF	test of interaction	.	.	.	.
	Pediatrics	1.08	0.14	8.39	0.941
MDFM	test of interaction	.	.	.	.
	Pediatrics	0.68	0.23	1.99	0.482
MDMO	test of interaction	0.83	0.00	1714.00	0.999
	Pediatrics	1.51	0.00	314.00	0.998
MDZM	test of interaction	10.10	0.00	214.00	0.989
	Pediatrics	0.11	0.00	214.00	0.989
MPCL	test of interaction	.	.	.	.
	Pediatrics	0.75	0.00	1514.00	0.999
MTHX	test of interaction	.	.	.	.
	Pediatrics	1.08	0.62	1.88	0.793
MZKT	test of interaction	1.45	0.00	2914.00	0.998
	Pediatrics	0.47	0.00	911.00	0.996
OPDX	test of interaction	.	.	.	.
	Pediatrics	1.13	0.21	6.14	0.890
OPET	test of interaction	0.50	0.00	981.00	0.997

	Pediatrics	1.47	0.00	2914.00	0.998
OPID	test of interaction	1.26	0.00	2514.00	0.999
	Pediatrics	1.35	0.00	2716.00	0.999
OPMZ	test of interaction	0.69	0.00	1414.00	0.998
	Pediatrics	1.56	0.00	3115.00	0.998
OPPF	test of interaction	0.57	0.00	1117.00	0.997
	Pediatrics	2.20	0.00	434.00	0.996
PFMP	test of interaction	.	.	.	.
	Pediatrics	1.62	0.00	3221.00	0.998
PNTB	test of interaction	.	.	.	.
	Pediatrics	0.87	0.00	1718.00	0.999
RMMT	test of interaction	.	.	.	.
	Pediatrics	3.48	0.00	681.00	0.994
TPFN	test of interaction	.	.	.	.
	Pediatrics	0.84	0.38	1.84	0.663

Supplement Table 41. Subgroup Analysis for Respiratory Adverse Events: Mixed Population versus Other

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Mixed	0.61	0.26	1.43	0.257
DXMT	test of interaction	.	.	.	.
	Mixed	0.68	0.01	42.77	0.855
DZPM	test of interaction	.	.	.	.
	Mixed	0.74	0.01	46.18	0.886
ETMD	test of interaction	.	.	.	.
	Mixed	1.10	0.60	2.00	0.760
FNDZ	test of interaction	.	.	.	.
	Mixed	1.30	0.07	23.57	0.857
KPMF	test of interaction	.	.	.	.
	Mixed	0.55	0.01	42.94	0.789
KPRF	test of interaction	.	.	.	.
	Mixed	0.43	0.06	3.16	0.408
KTFL	test of interaction	0.69	0.28	1.74	0.438
	Mixed	0.93	0.41	2.14	0.873
KTHL	test of interaction	.	.	.	.
	Mixed	0.70	0.02	22.65	0.843
KTMN	test of interaction	0.43	0.09	2.15	0.304
	Mixed	1.50	0.32	6.92	0.606
LMDF	test of interaction	.	.	.	.
	Mixed	1.40	0.17	11.92	0.756
MDFM	test of interaction	.	.	.	.
	Mixed	0.71	0.21	2.40	0.587
MDMO	test of interaction	.	.	.	.
	Mixed	2.20	0.29	16.43	0.443
MDZM	test of interaction	.	.	.	.
	Mixed	0.68	0.21	2.20	0.519
MPCL	test of interaction	.	.	.	.
	Mixed	0.84	0.10	7.07	0.869
MTHX	test of interaction	.	.	.	.
	Mixed	1.11	0.52	2.35	0.791
MZKT	test of interaction	2.25	0.03	192.27	0.721
	Mixed	0.33	0.00	27.23	0.623
OPDX	test of interaction	.	.	.	.
	Mixed	1.23	0.20	7.37	0.822
OPET	test of interaction	7.14	0.06	831.29	0.418

	Mixed	0.20	0.00	21.41	0.504
OPID	test of interaction	.	.	.	.
	Mixed	1.79	0.84	3.80	0.129
OPMZ	test of interaction	2.50	0.03	196.36	0.680
	Mixed	0.56	0.01	42.41	0.793
OPPF	test of interaction	2.92	0.47	18.29	0.253
	Mixed	0.56	0.10	3.30	0.523
PFMP	test of interaction	.	.	.	.
	Mixed	2.35	0.20	27.10	0.493
PNTB	test of interaction	.	.	.	.
	Mixed	3.79	0.38	37.86	0.257
RMMT	test of interaction	.	.	.	.
	Mixed	2.59	1.00	6.74	0.051
TPFN	test of interaction	.	.	.	.
	Mixed	0.92	0.37	2.28	0.854

Supplement Table 42. Subgroup Analysis for Cardiac Adverse Events: Low Risk of Bias versus High Risk of Bias

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Low RoB	0.43	0.05	3.59	0.435
DZPM	test of interaction	.	.	.	.
	Low RoB	0.98	0.00	.	1.000
ETMD	test of interaction	0.85	0.00	.	1.000
	Low RoB	1.13	0.00	.	1.000
FNDZ	test of interaction	.	.	.	.
	Low RoB	0.47	0.01	30.45	0.723
KPMF	test of interaction	.	.	.	.
	Low RoB	1.19	0.00	.	1.000
KTFL	test of interaction	5.61	0.10	300.24	0.396
	Low RoB	0.18	0.07	0.48	0.001
KTHL	test of interaction	.	.	.	.
	Low RoB	0.45	0.01	16.78	0.666
KTMN	test of interaction	1.91	0.00	.	1.000
	Low RoB	0.47	0.10	2.12	0.325
LMDF	test of interaction	.	.	.	.
	Low RoB	0.51	0.02	11.46	0.668
MDMO	test of interaction	0.70	0.00	.	1.000
	Low RoB	0.68	0.01	38.18	0.852
MDZM	test of interaction	0.93	0.00	.	1.000
	Low RoB	0.97	0.41	2.29	0.947
MZKT	test of interaction	1.05	0.00	.	1.000
	Low RoB	0.42	0.08	2.25	0.312
OPDX	test of interaction	0.30	0.00	.	0.999
	Low RoB	3.54	0.13	94.72	0.451
OPET	test of interaction	3.29	0.00	.	1.000
	Low RoB	0.25	0.01	4.33	0.338
OPID	test of interaction	1.56	0.00	.	0.999
	Low RoB	0.51	0.01	32.84	0.749
OPMZ	test of interaction	1.87	0.00	.	1.000
	Low RoB	0.51	0.11	2.24	0.369
OPPF	test of interaction	1.78	0.00	.	0.999
	Low RoB	0.68	0.23	2.05	0.494
PNTB	test of interaction	.	.	.	.
	Low RoB	0.83	0.00	.	1.000
RMMT	test of interaction	.	.	.	.

	Low RoB	0.74	0.00	.	1.000
TPFN	test of interaction	.	.	.	.
	Low RoB	1.54	0.07	32.91	0.782

* limited within node variability leading to low statistical power

Supplement Table 43. Subgroup Analysis for Cardiac Adverse Events: Long Procedure versus Other Duration of Procedures

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure long	0.78	0.05	13.09	0.864
DZPM	test of interaction	.	.	.	.
	Procedure long	1.06	0.02	56.90	0.978
ETMD	test of interaction	.	.	.	.
	Procedure long	0.94	0.01	91.34	0.978
FNDZ	test of interaction	.	.	.	.
	Procedure long	1.17	0.01	93.75	0.945
KPMF	test of interaction	.	.	.	.
	Procedure long	0.37	0.01	23.06	0.639
KTFL	test of interaction	0.46	0.04	4.88	0.517
	Procedure long	0.31	0.04	2.49	0.272
KTHL	test of interaction	.	.	.	.
	Procedure long	1.10	0.00	273.39	0.974
KTMN	test of interaction	1.22	0.01	120.71	0.932
	Procedure long	0.87	0.08	9.86	0.911
LMDF	test of interaction	.	.	.	.
	Procedure long	1.25	0.04	37.75	0.896
MDMO	test of interaction	.	.	.	.
	Procedure long	1.28	0.05	33.45	0.883
MDZM	test of interaction	.	.	.	.
	Procedure long	0.97	0.41	2.29	0.947
MZKT	test of interaction	1.77	0.00	660.71	0.850
	Procedure long	0.62	0.07	5.29	0.661
OPDX	test of interaction	0.13	0.00	.	0.998
	Procedure long	8.78	0.25	307.85	0.231
OPET	test of interaction	.	.	.	.
	Procedure long	0.72	0.04	12.95	0.823
OPID	test of interaction	0.67	0.00	.	1.000
	Procedure long	1.25	0.02	101.11	0.919
OPMZ	test of interaction	0.91	0.00	390.63	0.974
	Procedure long	1.25	0.17	9.41	0.826
OPPF	test of interaction	0.15	0.01	1.62	0.119
	Procedure long	2.47	0.35	17.35	0.362
PNTB	test of interaction	.	.	.	.
	Procedure long	0.68	0.00	140.29	0.888
RMMT	test of interaction	.	.	.	.

	Procedure long	0.23	0.04	1.19	0.080
TPFN	test of interaction	.	.	.	.
	Procedure long	2.70	0.08	95.10	0.585

Supplement Table 44. Subgroup Analysis for Cardiac Adverse Events: Short Procedure versus Other Duration of Procedures

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure short	0.47	0.06	3.90	0.485
DZPM	test of interaction	.	.	.	.
	Procedure short	0.78	0.00	.	1.000
ETMD	test of interaction	.	.	.	.
	Procedure short	0.55	0.01	35.09	0.776
FNDZ	test of interaction	.	.	.	.
	Procedure short	0.57	0.01	38.16	0.791
KPMF	test of interaction	.	.	.	.
	Procedure short	0.76	0.01	43.39	0.893
KTFL	test of interaction	.	.	.	.
	Procedure short	0.20	0.08	0.53	0.001
KTHL	test of interaction	.	.	.	.
	Procedure short	0.43	0.01	16.17	0.647
KTMN	test of interaction	.	.	.	.
	Procedure short	0.51	0.11	2.27	0.375
LMDF	test of interaction	.	.	.	.
	Procedure short	0.61	0.03	14.57	0.759
MDMO	test of interaction	.	.	.	.
	Procedure short	0.54	0.03	10.58	0.683
MDZM	test of interaction	0.73	0.00	.	1.000
	Procedure short	0.97	0.41	2.29	0.947
MZKT	test of interaction	0.35	0.00	.	0.999
	Procedure short	1.00	0.00	.	1.000
OPDX	test of interaction	4.61	0.00	.	0.998
	Procedure short	0.92	0.00	.	1.000
OPET	test of interaction	.	.	.	.
	Procedure short	0.35	0.03	4.78	0.430
OPID	test of interaction	0.88	0.00	.	1.000
	Procedure short	0.69	0.00	.	1.000
OPMZ	test of interaction	0.59	0.00	.	1.000
	Procedure short	1.03	0.00	.	1.000
OPPF	test of interaction	0.98	0.00	.	1.000
	Procedure short	0.79	0.00	.	1.000
PNTB	test of interaction	.	.	.	.
	Procedure short	0.40	0.00	57.42	0.716
RMMT	test of interaction	.	.	.	.

	Procedure short	0.48	0.00	.	0.999
TPFN	test of interaction	1.75	0.08	36.86	0.720
	Procedure short	2.70	.	.	0.585

* limited within node variability leading to low statistical power

Supplement Table 45. Subgroup Analysis for Cardiac Adverse Events: Mixed Procedure versus Other Duration of Procedures

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure short/long	0.73	0.04	12.09	0.826
DZPM	test of interaction	.	.	.	.
	Procedure short/long	0.96	0.00	.	1.000
ETMD	test of interaction	.	.	.	.
	Procedure short/long	0.88	0.01	84.86	0.955
FNDZ	test of interaction	.	.	.	.
	Procedure short/long	0.96	0.01	71.93	0.985
KPMF	test of interaction	.	.	.	.
	Procedure short/long	0.37	0.01	23.06	0.639
KTFL	test of interaction	2.04	0.19	21.48	0.552
	Procedure short/long	0.14	0.05	0.45	0.001
KTHL	test of interaction	.	.	.	.
	Procedure short/long	1.10	0.00	273.39	0.974
KTMN	test of interaction	0.77	0.01	75.22	0.910
	Procedure short/long	1.06	0.02	52.49	0.976
LMDF	test of interaction	.	.	.	.
	Procedure short/long	1.03	0.04	28.39	0.986
MDMO	test of interaction	.	.	.	.
	Procedure short/long	1.41	0.06	36.10	0.835
MDZM	test of interaction	1.10	0.00	.	1.000
	Procedure short/long	0.88	0.00	.	1.000
MZKT	test of interaction	0.72	0.00	249.20	0.914
	Procedure short/long	1.10	0.00	273.40	0.974
OPDX	test of interaction	.	.	.	.
	Procedure short/long	4.14	0.20	85.68	0.358
OPET	test of interaction	.	.	.	.
	Procedure short/long	0.59	0.04	9.58	0.711
OPID	test of interaction	.	.	.	.
	Procedure short/long	2.75	0.12	61.62	0.523
OPMZ	test of interaction	.	.	.	.
	Procedure short/long	1.03	0.16	6.63	0.975
OPPF	test of interaction	6.19	0.59	64.79	0.128
	Procedure short/long	0.38	0.10	1.43	0.152
PNTB	test of interaction	.	.	.	.
	Procedure short/long	0.64	0.00	130.48	0.868
RMMT	test of interaction	.	.	.	.

	Procedure short/long	1.42	0.16	12.39	0.750
TPFN	test of interaction	.	.	.	.
	Procedure short/long	2.52	0.07	87.83	0.611

Supplement Table 46. Subgroup Analysis for Cardiac Adverse Events: Adults versus Pediatrics

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Adults	0.54	0.06	4.85	0.585
DZPM	test of interaction	.	.	.	.
	Adults	1.06	0.02	56.90	0.978
ETMD	test of interaction	1.63	0.00	.	1.000
	Adults	0.73	0.01	50.77	0.882
FNDZ	test of interaction	.	.	.	.
	Adults	0.66	0.01	46.34	0.847
KPMF	test of interaction	.	.	.	.
	Adults	1.57	0.00	.	0.999
KTFL	test of interaction	3.09	0.00	.	0.998
	Adults	0.17	0.06	0.47	0.001
KTHL	test of interaction	.	.	.	.
	Adults	0.52	0.01	21.43	0.732
KTMN	test of interaction	0.85	0.00	.	1.000
	Adults	0.67	0.12	3.77	0.653
LMDF	test of interaction	.	.	.	.
	Adults	0.71	0.03	17.93	0.834
MDMO	test of interaction	0.71	0.00	.	0.999
	Adults	1.26	0.02	78.36	0.912
MDZM	test of interaction	.	.	.	.
	Adults	0.97	0.41	2.29	0.947
MZKT	test of interaction	2.13	0.00	.	0.998
	Adults	0.39	0.05	3.37	0.393
OPDX	test of interaction	.	.	.	.
	Adults	2.84	0.15	53.67	0.486
OPET	test of interaction	0.75	0.00	.	0.999
	Adults	0.61	0.01	42.83	0.819
OPID	test of interaction	.	.	.	.

	Adults	1.89	0.09	38.69	0.679
OPMZ	test of interaction	1.32	0.00	.	0.999
	Adults	0.71	0.13	3.90	0.692
OPPF	test of interaction	1.27	0.00	.	0.999
	Adults	1.26	0.30	5.26	0.748
PNTB	test of interaction	.	.	.	.
	Adults	0.86	0.00	.	1.000
RMMT	test of interaction	.	.	.	.
	Adults	0.97	0.00	.	1.000
TPFN	test of interaction	.	.	.	.
	Adults	1.51	0.07	32.22	0.792

* limited within node variability leading to low statistical power

Supplement Table 47. Subgroup Analysis for Gastrointestinal Adverse Events: Low Risk of Bias versus High Risk of Bias

		RR	95% CI		P value
DZPM	test of interaction	.	.	.	.
	Low RoB	4.81	0.14	165.94	0.384
ETMD	test of interaction	0.38	0.00	.	1.000
	Low RoB	2.72	0.03	224.19	0.657
FNDZ	test of interaction	.	.	.	.
	Low RoB	0.44	0.01	37.90	0.718
KPMF	test of interaction	.	.	.	.
	Low RoB	0.07	0.00	.	0.996
KTFL	test of interaction	1.02	0.01	81.27	0.995
	Low RoB	0.99	0.14	7.07	0.988
KTHL	test of interaction	.	.	.	.
	Low RoB	0.88	0.07	11.15	0.924
KTMN	test of interaction	0.48	0.00	.	1.000
	Low RoB	2.02	0.29	14.31	0.480
MDMO	test of interaction	3.97	0.00	.	0.998
	Low RoB	0.68	0.01	54.93	0.863
MDZM	test of interaction	.	.	.	.
	Low RoB	0.88	0.06	14.08	0.929
MZKT	test of interaction	0.58	0.00	.	0.999
	Low RoB	1.44	0.19	10.79	0.720
OPDX	test of interaction	0.21	0.00	.	0.998

	Low RoB	0.47	0.01	40.74	0.742
OPET	test of interaction	1.42	0.00	.	1.000
	Low RoB	0.66	0.07	6.72	0.729
OPID	test of interaction	28.10	0.00	.	0.995
	Low RoB	0.07	0.00	1.34	0.077
OPMZ	test of interaction	2.32	0.00	.	1.000
	Low RoB	0.47	0.06	3.67	0.474
OPPF	test of interaction	0.10	0.00	.	0.997
	Low RoB	0.68	0.10	4.80	0.698
PFMP	test of interaction	.	.	.	.
	Low RoB	1.21	0.01	113.60	0.934
PNTB	test of interaction	.	.	.	.
	Low RoB	5.99	0.03	1423.75	0.521
RMMT	test of interaction	.	.	.	.
	Low RoB	0.07	0.00	.	0.997
TPFN	test of interaction	.	.	.	.
	Low RoB	1.12	0.06	20.79	0.940

Supplement Table 48. Subgroup Analysis for Gastrointestinal Adverse Events: Long Procedure versus Mixed Duration of Procedures

		RR	95% CI		P value
DZPM	test of interaction	.	.	.	.
	Procedure long	4.81	0.14	169.17	0.387
ETMD	test of interaction	.	.	.	.
	Procedure long	2.65	0.07	103.96	0.603
FNDZ	test of interaction	.	.	.	.
	Procedure long	0.48	0.00	48.28	0.755
KPMF	test of interaction	.	.	.	.
	Procedure long	0.46	0.01	30.07	0.717
KTFL	test of interaction	0.56	0.01	26.25	0.766
	Procedure long	1.09	0.11	10.73	0.942
KTHL	test of interaction	.	.	.	.
	Procedure long	1.04	0.03	34.19	0.981
KTMN	test of interaction	1.07	0.02	51.50	0.973
	Procedure long	2.20	0.20	23.67	0.515
MDMO	test of interaction	.	.	.	.
	Procedure long	3.12	0.16	62.75	0.458

MDZM	test of interaction	.	.	.	.
	Procedure long	0.88	0.05	14.26	0.930
MZKT	test of interaction	1.11	0.02	61.20	0.960
	Procedure long	1.57	0.13	18.31	0.718
OPDX	test of interaction	0.19	0.00	.	0.998
	Procedure long	0.52	0.01	51.89	0.778
OPET	test of interaction	.	.	.	.
	Procedure long	0.70	0.05	9.39	0.786
OPID	test of interaction	25.80	0.00	.	0.995
	Procedure long	0.07	0.00	1.83	0.112
OPMZ	test of interaction	.	.	.	.
	Procedure long	0.52	0.05	5.44	0.581
OPPF	test of interaction	0.69	0.02	31.10	0.847
	Procedure long	0.68	0.07	6.70	0.744
PFMP	test of interaction	.	.	.	.
	Procedure long	5.56	0.22	139.94	0.297
PNTB	test of interaction	.	.	.	.
	Procedure long	5.84	0.04	782.55	0.480
RMMT	test of interaction	.	.	.	.
	Procedure long	0.47	0.00	71.55	0.771
TPFN	test of interaction	.	.	.	.
	Procedure long	1.23	0.06	26.48	0.896

Supplement Table 49. Subgroup Analysis for Gastrointestinal Adverse Events: Adults versus Pediatrics

		RR	95% CI		P value
DZPM	test of interaction	.	.	.	.
	Adults	4.81	0.14	165.90	0.384
ETMD	test of interaction	0.17	0.00	.	0.999
	Adults	3.50	0.11	106.40	0.472
FNDZ	test of interaction	.	.	.	.
	Adults	0.47	0.00	44.56	0.745
KPMF	test of interaction	.	.	.	.
	Adults	0.49	0.00	1123.00	0.998
KTFL	test of interaction	0.88	0.00	1923.00	1.000
	Adults	0.93	0.15	5.84	0.942
KTHL	test of interaction	.	.	.	.
	Adults	1.37	0.10	17.91	0.810

KTMN	test of interaction	0.52	0.00	1123.00	0.998
	Adults	2.91	0.41	20.77	0.287
MDMO	test of interaction	4.39	0.00	960.00	0.996
	Adults	0.56	0.01	43.95	0.795
MDZM	test of interaction	.	.	.	.
	Adults	0.88	0.06	14.08	0.929
MZKT	test of interaction	0.30	0.00	650.00	0.996
	Adults	2.52	0.30	21.16	0.395
OPDX	test of interaction	.	.	.	.
	Adults	0.03	0.00	1.13	0.059
OPET	test of interaction	0.31	0.00	680.00	0.997
	Adults	1.00	0.03	28.93	0.999
OPID	test of interaction	.	.	.	.
	Adults	0.16	0.01	3.25	0.234
OPMZ	test of interaction	0.51	0.00	1123.00	0.998
	Adults	0.50	0.05	4.80	0.552
OPPF	test of interaction	0.88	0.00	1923.00	1.000
	Adults	0.56	0.09	3.69	0.548
PFMP	test of interaction	.	.	.	.
	Adults	4.40	0.00	950.00	0.996
PNTB	test of interaction	.	.	.	.
	Adults	1.30	0.00	.	1.000
RMMT	test of interaction	.	.	.	.
	Adults	0.50	0.00	1123.00	0.998
TPFN	test of interaction	.	.	.	.
	Adults	1.13	0.07	19.52	0.933

* limited within node variability leading to low statistical power

Supplement Table 50. Subgroup Analysis for Neurological Adverse Events: Low Risk of Bias versus High Risk of Bias

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Low RoB	1.21	0.28	5.17	0.801
DXMT	test of interaction	.	.	.	.
	Low RoB	0.20	0.00	33.79	0.539
ETMD	test of interaction	0.10	0.00	.	0.997
	Low RoB	18.63	5.00	69.44	0.000

FNDZ	test of interaction	.	.	.	.
	Low RoB	0.32	0.00	24.01	0.608
KPMF	test of interaction	.	.	.	.
	Low RoB	0.29	0.00	.	0.998
KTFL	test of interaction	0.74	0.01	44.41	0.884
	Low RoB	1.36	0.60	3.06	0.461
KTHL	test of interaction	.	.	.	.
	Low RoB	0.33	0.01	7.88	0.495
KTMN	test of interaction	0.05	0.00	.	0.996
	Low RoB	3.22	1.38	7.50	0.007
MDFM	test of interaction	.	.	.	.
	Low RoB	2.10	0.09	51.33	0.648
MDMO	test of interaction	3.58	0.00	.	0.998
	Low RoB	1.36	0.02	96.52	0.886
MDZM	test of interaction	.	.	.	.
	Low RoB	1.00	0.02	54.29	1.000
MTHX	test of interaction	.	.	.	.
	Low RoB	1.00	0.02	54.29	1.000
MZKT	test of interaction	1.09	0.00	.	1.000
	Low RoB	2.06	0.70	6.09	0.190
OPDX	test of interaction	.	.	.	.
	Low RoB	0.02	0.00	.	0.992
OPET	test of interaction	0.40	0.00	.	1.000
	Low RoB	2.42	0.44	13.39	0.312
OPID	test of interaction	0.12	0.00	.	0.996
	Low RoB	0.14	0.01	1.58	0.111
OPMZ	test of interaction	3.24	0.00	.	1.000
	Low RoB	0.35	0.08	1.47	0.151
OPPF	test of interaction	0.22	0.00	.	0.997
	Low RoB	1.36	0.35	5.32	0.654
PFMP	test of interaction	.	.	.	.
	Low RoB	0.97	0.01	111.21	0.991
PNTB	test of interaction	.	.	.	.
	Low RoB	54.21	3.48	845.03	0.004
RMMT	test of interaction	.	.	.	.
	Low RoB	0.30	0.00	.	0.998
TPFN	test of interaction	.	.	.	.
	Low RoB	0.78	0.11	5.54	0.805

Supplement Table 51. Subgroup Analysis for Neurological Adverse Events: Long Procedure versus Other Duration of Procedures

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure long	7.18	0.57	90.20	0.127
DXMT	test of interaction	.	.	.	.
	Procedure long	0.34	0.00	.	1.000
ETMD	test of interaction	0.03	0.00	0.80	0.036
	Procedure long	307.59	18.67	5068.59	0.000
FNDZ	test of interaction	.	.	.	.
	Procedure long	1.97	0.02	185.32	0.769
KPMF	test of interaction	.	.	.	.
	Procedure long	0.10	0.00	15.67	0.369
KTFL	test of interaction	0.12	0.01	1.29	0.079
	Procedure long	8.66	0.89	84.05	0.063
KTHL	test of interaction	.	.	.	.
	Procedure long	0.39	0.02	9.28	0.558
KTMN	test of interaction	0.21	0.02	2.74	0.233
	Procedure long	18.98	1.82	197.49	0.014
MDFM	test of interaction	.	.	.	.
	Procedure long	1.26	0.05	30.89	0.886
MDMO	test of interaction	.	.	.	.
	Procedure long	21.83	1.79	266.01	0.016
MDZM	test of interaction	0.59	0.00	.	1.000
	Procedure long	1.68	0.00	.	1.000
MTHX	test of interaction	.	.	.	.
	Procedure long	1.00	0.02	51.37	1.000
MZKT	test of interaction	0.20	0.02	2.10	0.179
	Procedure long	11.67	1.70	80.10	0.012
OPDX	test of interaction	.	.	.	.
	Procedure long	1.00	0.00	.	1.000
OPET	test of interaction	.	.	.	.
	Procedure long	12.19	1.22	121.64	0.033
OPID	test of interaction	1.29	0.00	.	1.000
	Procedure long	0.77	0.06	10.47	0.847
OPMZ	test of interaction	.	.	.	.
	Procedure long	2.12	0.25	18.12	0.491
OPPF	test of interaction	0.01	0.00	0.47	0.019
	Procedure long	10.31	1.00	106.86	0.050
PFMP	test of interaction	.	.	.	.

	Procedure long	15.57	0.65	375.31	0.091
PNTB	test of interaction	.	.	.	.
	Procedure long	894.81	23.57	33972.22	0.000
RMMT	test of interaction	.	.	.	.
	Procedure long	0.10	0.00	16.15	0.375
TPFN	test of interaction	.	.	.	.
	Procedure long	4.98	0.30	82.88	0.263

Supplement Table 52. Subgroup Analysis for Neurological Adverse Events: Short Procedure versus Other Duration of Procedures

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure short	1.16	0.30	4.51	0.834
DXMT	test of interaction	.	.	.	.
	Procedure short	0.33	0.00	.	1.000
ETMD	test of interaction	2.84	0.11	71.38	0.525
	Procedure short	9.00	0.46	175.30	0.147
FNDZ	test of interaction	.	.	.	.
	Procedure short	0.33	0.00	22.74	0.606
KPMF	test of interaction	.	.	.	.
	Procedure short	1.27	0.02	85.60	0.911
KTFL	test of interaction	.	.	.	.
	Procedure short	1.30	0.62	2.75	0.487
KTHL	test of interaction	.	.	.	.
	Procedure short	0.32	0.01	7.17	0.471
KTMN	test of interaction	.	.	.	.
	Procedure short	3.13	1.43	6.85	0.004
MDFM	test of interaction	.	.	.	.
	Procedure short	1.11	0.02	57.71	0.958
MDMO	test of interaction	.	.	.	.
	Procedure short	3.68	0.54	24.95	0.181
MDZM	test of interaction	1.67	0.00	.	1.000
	Procedure short	1.00	0.02	52.68	1.000
MTHX	test of interaction	.	.	.	.
	Procedure short	1.00	0.02	52.68	1.000
MZKT	test of interaction	.	.	.	.
	Procedure short	2.11	0.78	5.71	0.141
OPDX	test of interaction	.	.	.	.
	Procedure short	1.00	0.00	.	1.000

OPET	test of interaction	.	.	.	.
	Procedure short	2.07	0.42	10.27	0.371
OPID	test of interaction	0.12	0.00	.	0.999
	Procedure short	1.00	0.00	.	1.000
OPMZ	test of interaction	.	.	.	.
	Procedure short	0.35	0.09	1.33	0.123
OPPF	test of interaction	1.33	0.00	.	1.000
	Procedure short	0.97	0.00	.	1.000
PFMP	test of interaction	.	.	.	.
	Procedure short	2.63	0.16	42.41	0.496
PNTB	test of interaction	.	.	.	.
	Procedure short	74.44	5.14	1078.15	0.002
RMMT	test of interaction	.	.	.	.
	Procedure short	0.99	0.00	.	1.000
TPFN	test of interaction	.	.	.	.
	Procedure short	0.75	0.12	4.86	0.763

Supplement Table 53. Subgroup Analysis for Neurological Adverse Events: Mixed Procedure versus Other Duration of Procedures

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Procedure short/long	2.26	0.24	21.32	0.475
DXMT	test of interaction	.	.	.	.
	Procedure short/long	0.20	0.00	32.64	0.536
ETMD	test of interaction	5.08	0.33	78.13	0.244
	Procedure short/long	10.90	1.85	64.17	0.008
FNDZ	test of interaction	.	.	.	.
	Procedure short/long	0.86	0.01	77.43	0.947
KPMF	test of interaction	.	.	.	.
	Procedure short/long	0.10	0.00	16.58	0.374
KTFL	test of interaction	2.90	0.35	24.22	0.326
	Procedure short/long	0.99	0.41	2.39	0.989
KTHL	test of interaction	.	.	.	.
	Procedure short/long	0.39	0.02	9.99	0.571
KTMN	test of interaction	1.45	0.15	14.09	0.749
	Procedure short/long	3.93	1.24	12.48	0.020
MDFM	test of interaction	.	.	.	.
	Procedure short/long	5.54	0.17	182.09	0.336
MDMO	test of interaction	.	.	.	.

	Procedure short/long	10.20	0.90	115.12	0.060
MDZM	test of interaction	.	.	.	.
	Procedure short/long	1.00	0.02	53.10	1.000
MTHX	test of interaction	.	.	.	.
	Procedure short/long	1.00	0.02	53.10	1.000
MZKT	test of interaction	2.71	0.26	28.02	0.403
	Procedure short/long	2.17	0.48	9.75	0.312
OPDX	test of interaction	.	.	.	.
	Procedure short/long	0.31	0.00	34.96	0.629
OPET	test of interaction	.	.	.	.
	Procedure short/long	5.53	0.62	49.03	0.124
OPID	test of interaction	.	.	.	.
	Procedure short/long	0.31	0.03	3.72	0.358
OPMZ	test of interaction	.	.	.	.
	Procedure short/long	0.92	0.13	6.77	0.938
OPPF	test of interaction	35.79	0.82	1568.13	0.064
	Procedure short/long	0.10	0.00	2.36	0.153
PFMP	test of interaction	.	.	.	.
	Procedure short/long	7.27	0.31	172.19	0.219
PNTB	test of interaction	.	.	.	.
	Procedure short/long	161.11	6.86	3783.29	0.002
RMMT	test of interaction	.	.	.	.
	Procedure short/long	3.56	0.04	332.86	0.583
TPFN	test of interaction	.	.	.	.
	Procedure short/long	1.66	0.12	22.23	0.703

Supplement Table 54. Subgroup Analysis for Neurological Adverse Events: Adults versus Other

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Adults	1.76	0.70	4.43	0.230
DXMT	test of interaction	.	.	.	.
	Adults	0.33	0.00	.	1.000
ETMD	test of interaction	0.02	0.00	.	0.997
	Adults	27.59	10.33	73.66	0.000
FNDZ	test of interaction	.	.	.	.
	Adults	0.14	0.00	9.43	0.356
KPMF	test of interaction	.	.	.	.
	Adults	0.37	0.01	22.07	0.632

KTFL	test of interaction	0.24	0.08	0.72	0.011
	Adults	1.69	0.91	3.14	0.097
KTHL	test of interaction	.	.	.	.
	Adults	0.49	0.03	9.05	0.631
KTMN	test of interaction	0.13	0.03	0.45	0.002
	Adults	5.47	2.89	10.37	0.000
MDFM	test of interaction	.	.	.	.
	Adults	3.18	0.17	59.24	0.438
MDMO	test of interaction	1.20	0.01	198.21	0.944
	Adults	1.23	0.01	140.13	0.931
MDZM	test of interaction	1.65	0.00	.	1.000
	Adults	1.00	0.02	46.05	1.000
MTHX	test of interaction	.	.	.	.
	Adults	1.00	0.02	46.05	1.000
MZKT	test of interaction	0.26	0.05	1.24	0.090
	Adults	2.67	0.94	7.61	0.066
OPDX	test of interaction	.	.	.	.
	Adults	0.06	0.00	5.16	0.217
OPET	test of interaction	1.91	0.07	54.14	0.704
	Adults	0.63	0.04	10.91	0.753
OPID	test of interaction	.	.	.	.
	Adults	0.06	0.01	0.53	0.011
OPMZ	test of interaction	1.71	0.17	17.21	0.650
	Adults	0.15	0.03	0.78	0.024
OPPF	test of interaction	0.30	0.02	6.02	0.434
	Adults	1.23	0.08	18.74	0.880
PFMP	test of interaction	.	.	.	.
	Adults	1.06	0.08	14.01	0.967
PNTB	test of interaction	.	.	.	.
	Adults	1.38	0.00	.	1.000
RMMT	test of interaction	.	.	.	.
	Adults	0.38	0.01	22.77	0.641
TPFN	test of interaction	.	.	.	.
	Adults	0.97	0.22	4.39	0.971

Supplement Table 55. Subgroup Analysis for Neurological Adverse Events: Pediatrics versus Other

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Pediatrics	1.21	0.36	4.05	0.762
DXMT	test of interaction	.	.	.	.
	Pediatrics	0.33	0.00	.	1.000
ETMD	test of interaction	49.73	0.00	.	0.997
	Pediatrics	0.48	0.00	.	0.999
FNDZ	test of interaction	.	.	.	.
	Pediatrics	0.12	0.00	8.43	0.326
KPMF	test of interaction	.	.	.	.
	Pediatrics	1.79	0.03	114.57	0.784
KTFL	test of interaction	1.91	0.00	462.00	0.998
	Pediatrics	0.59	0.00	1423.00	0.999
KTHL	test of interaction	.	.	.	.
	Pediatrics	0.35	0.02	7.36	0.499
KTMN	test of interaction	3.90	0.00	930.00	0.996
	Pediatrics	0.93	0.00	2223.00	1.000
MDFM	test of interaction	.	.	.	.
	Pediatrics	2.66	0.13	56.19	0.530
MDMO	test of interaction	0.96	0.00	2323.00	1.000
	Pediatrics	1.89	0.00	452.00	0.998
MDZM	test of interaction	0.60	0.00	.	1.000
	Pediatrics	1.67	0.00	.	1.000
MTHX	test of interaction	.	.	.	.
	Pediatrics	1.00	0.02	50.24	1.000
MZKT	test of interaction	2.33	0.00	560.00	0.998
	Pediatrics	0.87	0.00	2122.00	1.000
OPDX	test of interaction	.	.	.	.
	Pediatrics	0.06	0.00	5.18	0.218
OPET	test of interaction	0.42	0.00	1239.00	0.998
	Pediatrics	1.79	0.00	432.00	0.998
OPID	test of interaction	.	.	.	.
	Pediatrics	0.06	0.01	0.45	0.006
OPMZ	test of interaction	0.29	0.00	723.00	0.997
	Pediatrics	0.43	0.00	1239.00	0.998
OPPF	test of interaction	22.35	0.00	542.00	0.991
	Pediatrics	0.08	0.00	1923.00	0.993
PFMP	test of interaction	.	.	.	.

	Pediatrics	1.35	0.00	323.00	0.999
PNTB	test of interaction	.	.	.	.
	Pediatrics	1.38	0.00	.	1.000
RMMT	test of interaction	.	.	.	.
	Pediatrics	0.08	0.00	223.00	0.993
TPFN	test of interaction	.	.	.	.
	Pediatrics	0.65	0.11	3.72	0.632

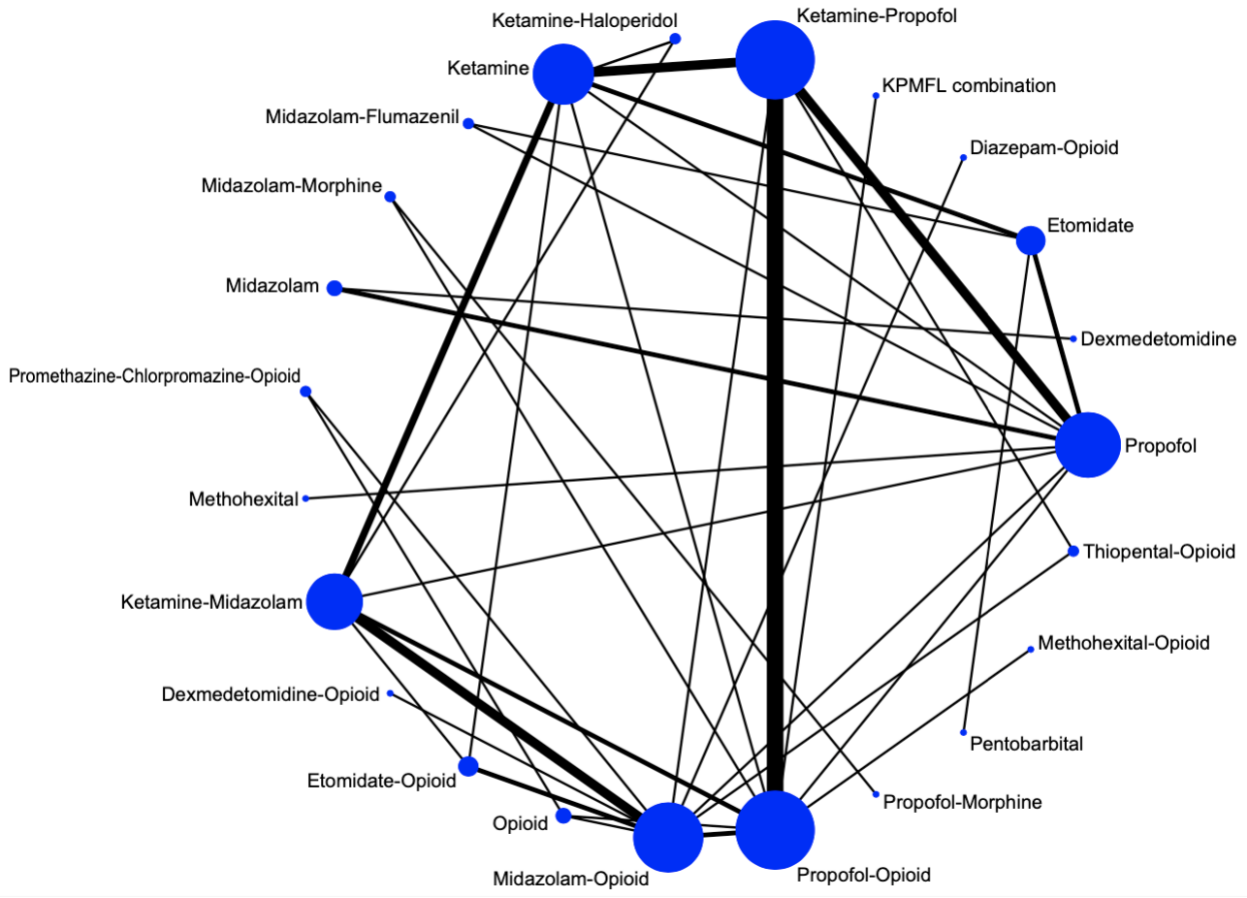
Supplement Table 56. Subgroup Analysis for Neurological Adverse Events: Mixed Population versus Other

		RR	95% CI		P value
DXKT	test of interaction	.	.	.	.
	Mixed	1.63	0.47	5.69	0.446
DXMT	test of interaction	.	.	.	.
	Mixed	0.20	0.00	29.74	0.528
ETMD	test of interaction	.	.	.	.
	Mixed	25.77	8.58	77.37	0.000
FNDZ	test of interaction	.	.	.	.
	Mixed	0.49	0.01	33.04	0.740
KPMF	test of interaction	.	.	.	.
	Mixed	0.53	0.01	40.93	0.772
KTFL	test of interaction	4.97	1.16	21.33	0.031
	Mixed	0.40	0.12	1.35	0.140
KTHL	test of interaction	.	.	.	.
	Mixed	0.42	0.02	8.99	0.582
KTMN	test of interaction	5.46	0.83	35.83	0.077
	Mixed	0.80	0.14	4.43	0.798
MDFM	test of interaction	.	.	.	.
	Mixed	2.88	0.14	60.65	0.496
MDMO	test of interaction	.	.	.	.
	Mixed	4.47	0.68	29.41	0.120
MDZM	test of interaction	.	.	.	.
	Mixed	1.00	0.02	50.03	1.000
MTHX	test of interaction	.	.	.	.
	Mixed	1.00	0.02	50.03	1.000
MZKT	test of interaction	1.37	0.00	.	1.000
	Mixed	2.03	0.00	.	0.999
OPDX	test of interaction	.	.	.	.
	Mixed	0.15	0.00	12.20	0.393

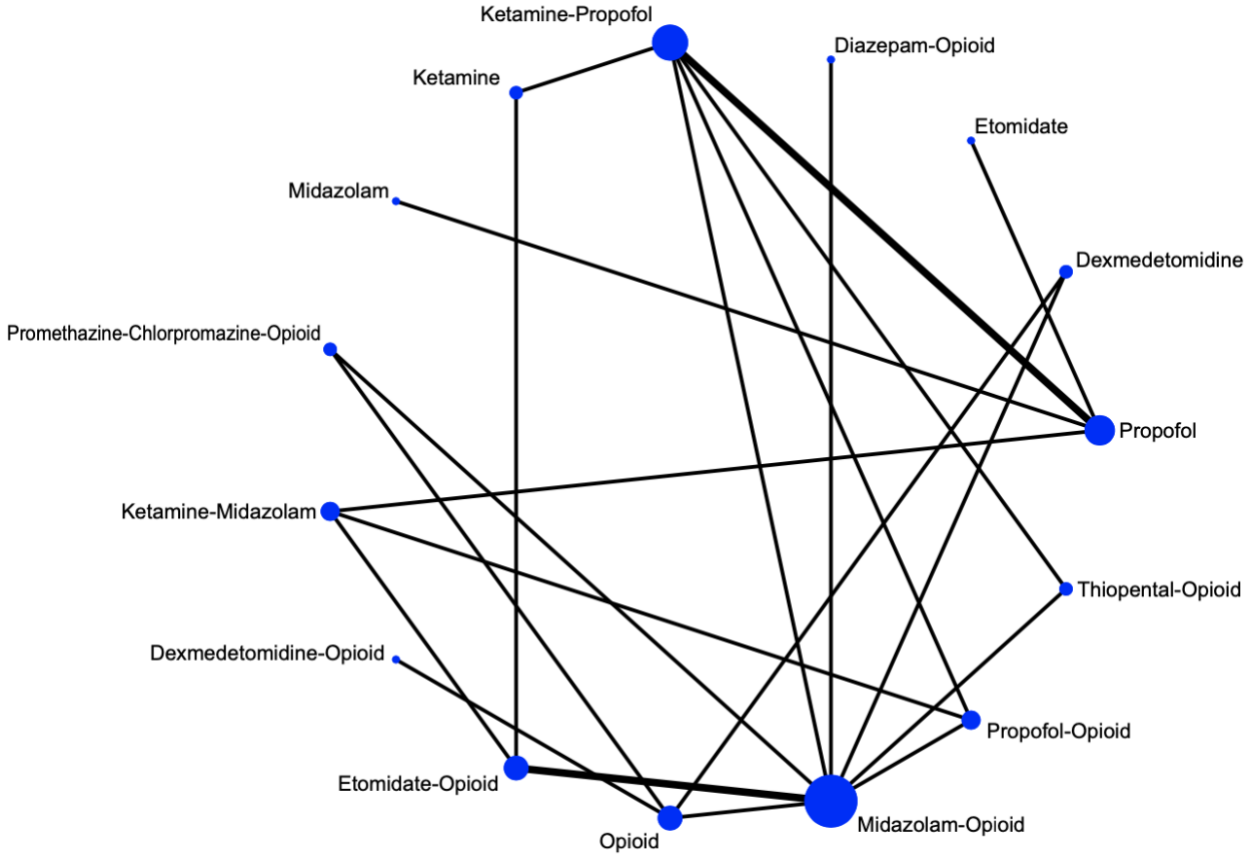
OPET	test of interaction	1.69	0.00	.	0.999
	Mixed	1.62	0.00	.	0.999
OPID	test of interaction	.	.	.	.
	Mixed	0.15	0.02	1.07	0.059
OPMZ	test of interaction	3.27	0.00	.	0.998
	Mixed	0.16	0.00	.	0.997
OPPF	test of interaction	1.69	0.14	20.15	0.678
	Mixed	0.53	0.09	3.09	0.483
PFMP	test of interaction	.	.	.	.
	Mixed	3.19	0.22	46.81	0.398
PNTB	test of interaction	.	.	.	.
	Mixed	74.96	6.00	936.27	0.001
RMMT	test of interaction	.	.	.	.
	Mixed	0.91	0.01	71.04	0.967
TPFN	test of interaction	.	.	.	.
	Mixed	1.14	0.19	6.78	0.883

Appendix 5. Supplementary Figures

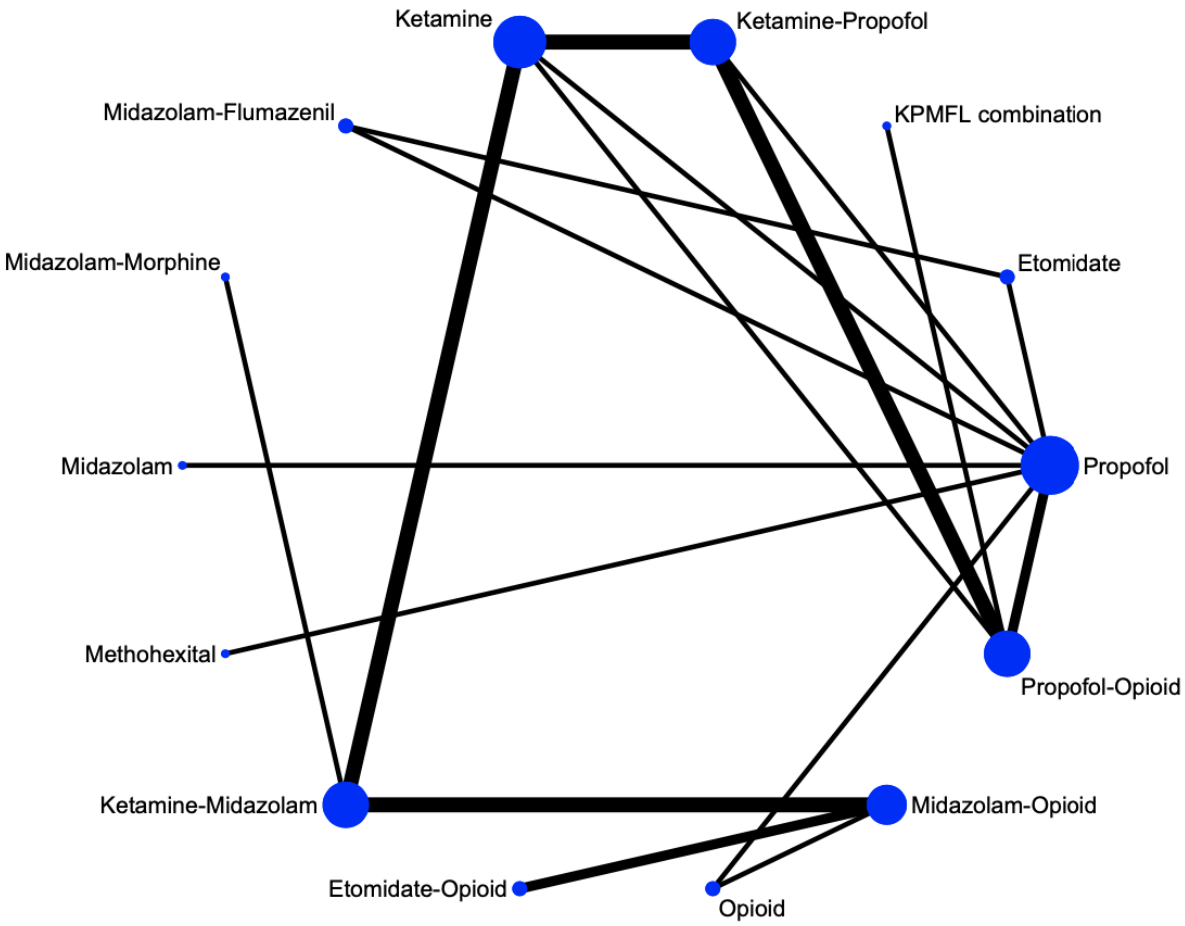
Supplement Figure 1. Network Map for Sedation Recovery Time for 23-node analysis



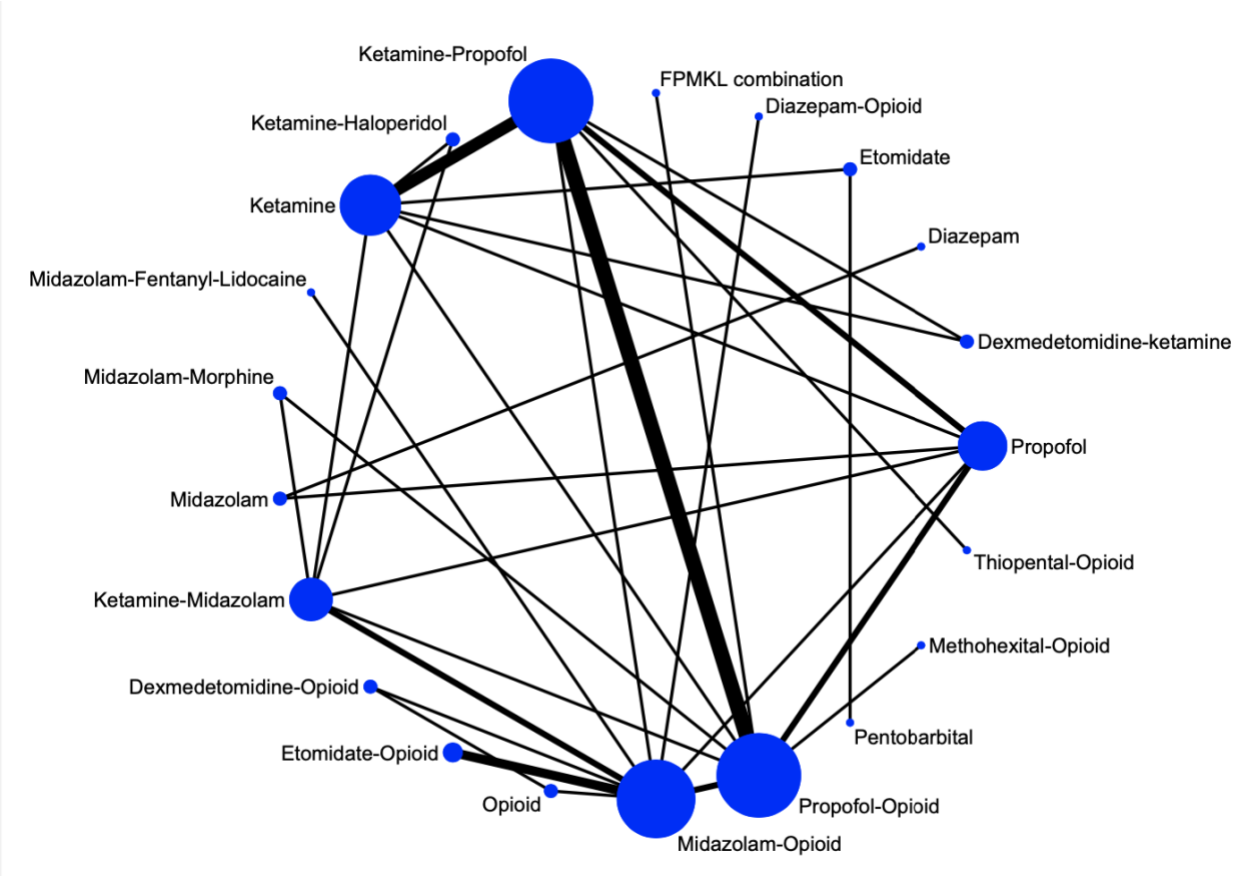
Supplement Figure 2. Network Map for Patient Satisfaction as a continuous outcome for 11-node analysis



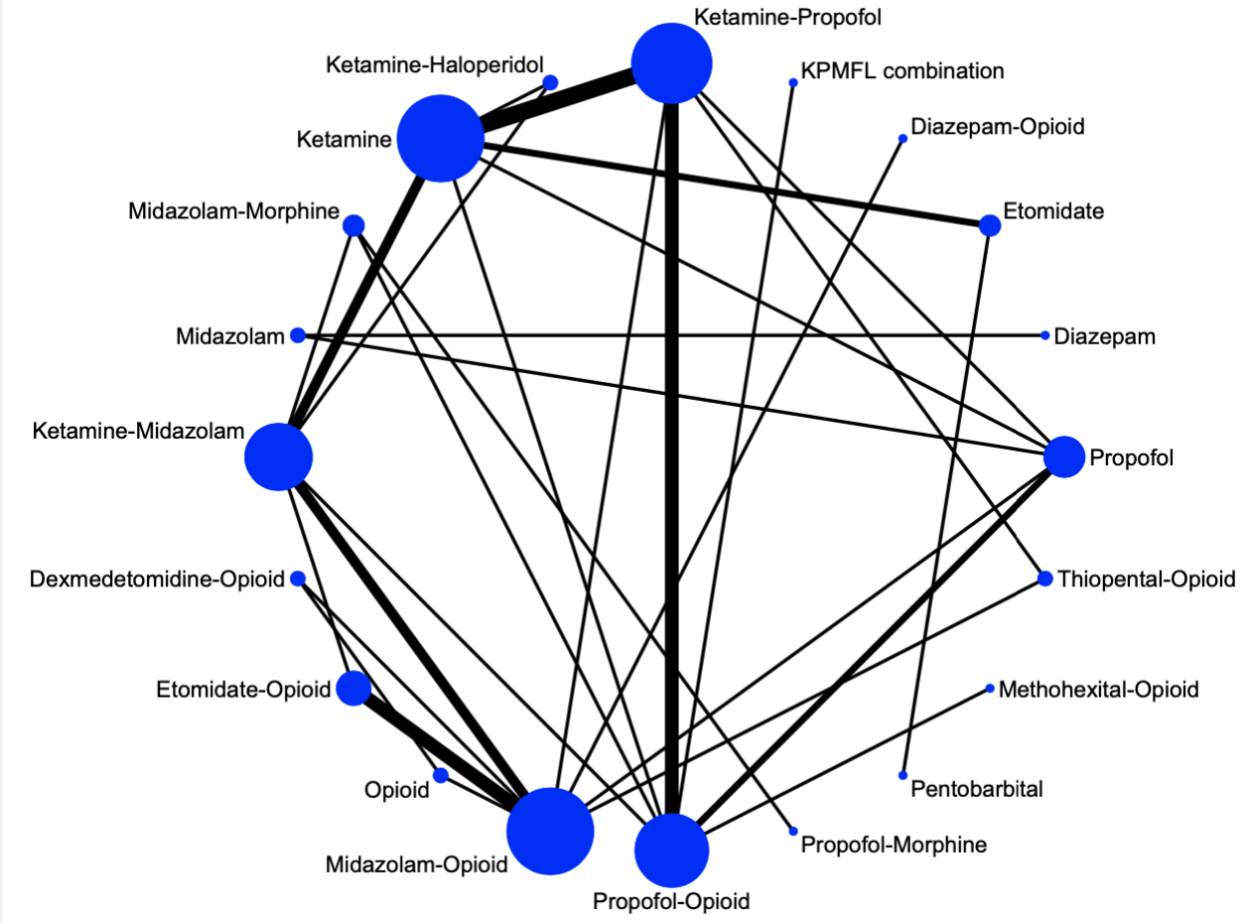
Supplement Figure 3. Network Map for Patient Satisfaction as a dichotomous outcome for 14-node analysis



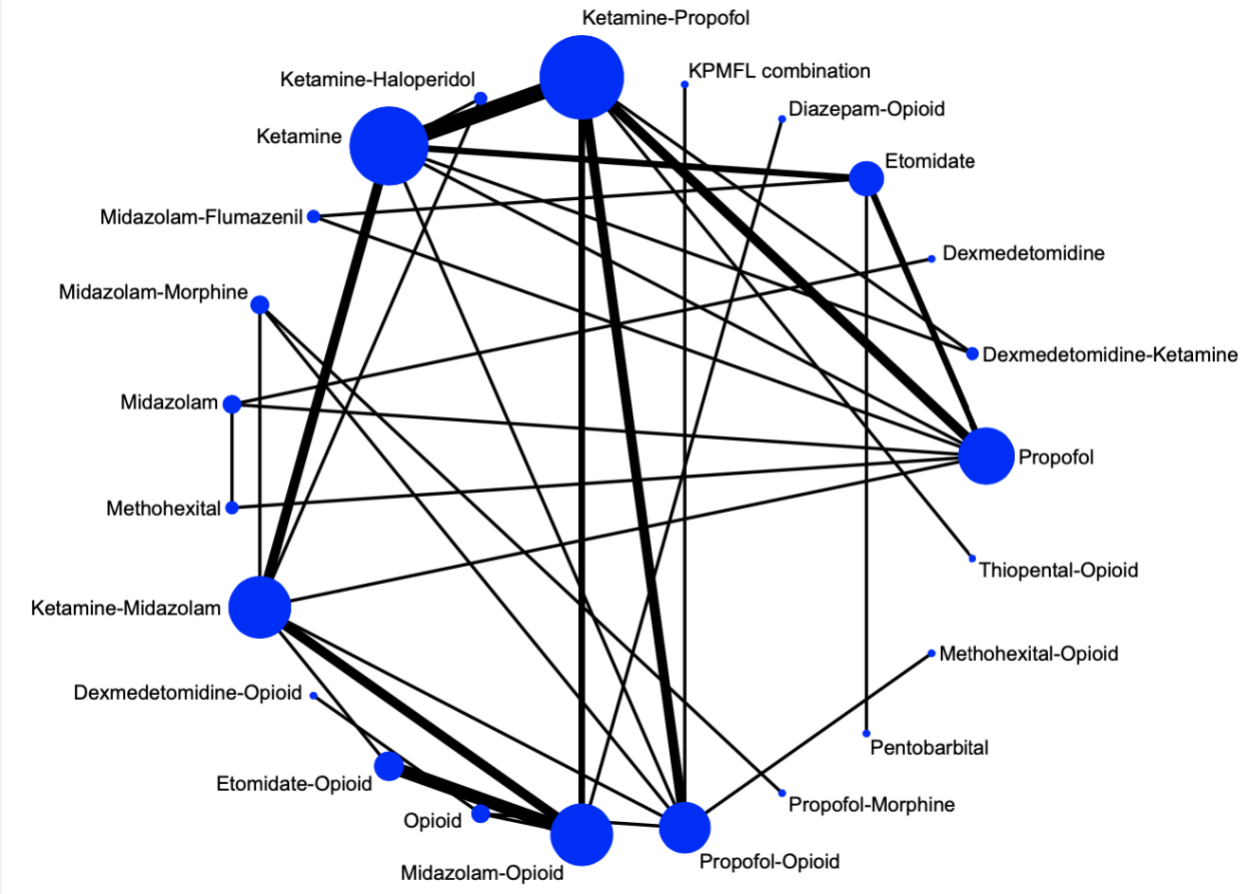
Supplement Figure 4. Network Map for Cardiac Adverse Events for 21-node analysis


Ketamine-Propofol
FPMKL combination
Diazepam-Opioid
Ketamine-Haloperidol
Etomidate
Ketamine
Diazepam
Midazolam-Fentanyl-Lidocaine
Dexmedetomidine-ketamine
Midazolam-Morphine
Propofol
Midazolam
Thiopental-Opioid
Ketamine-Midazolam
Methohexital-Opioid
Dexmedetomidine-Opioid
Pentobarbital
Etomidate-Opioid
Opioid
Propofol-Opioid
Midazolam-Opioid

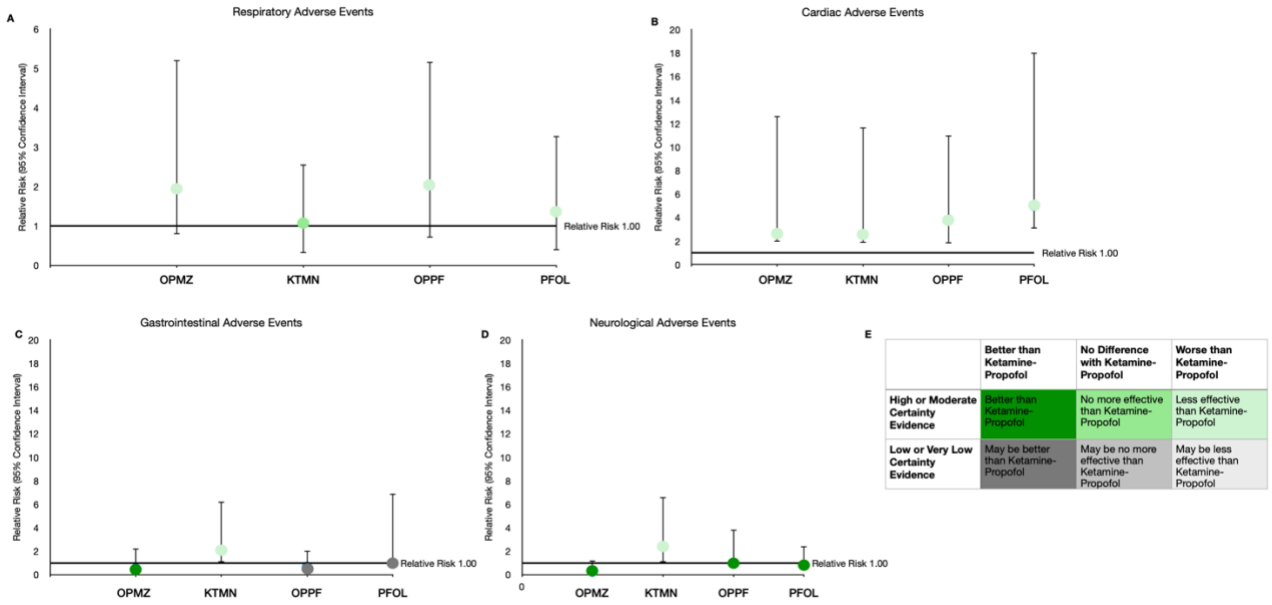
Supplement Figure 5. Network Map for Gastrointestinal Adverse Events for 20-node analysis



Supplement Figure 6. Network Map for Neurological Adverse Events for 23-node analysis

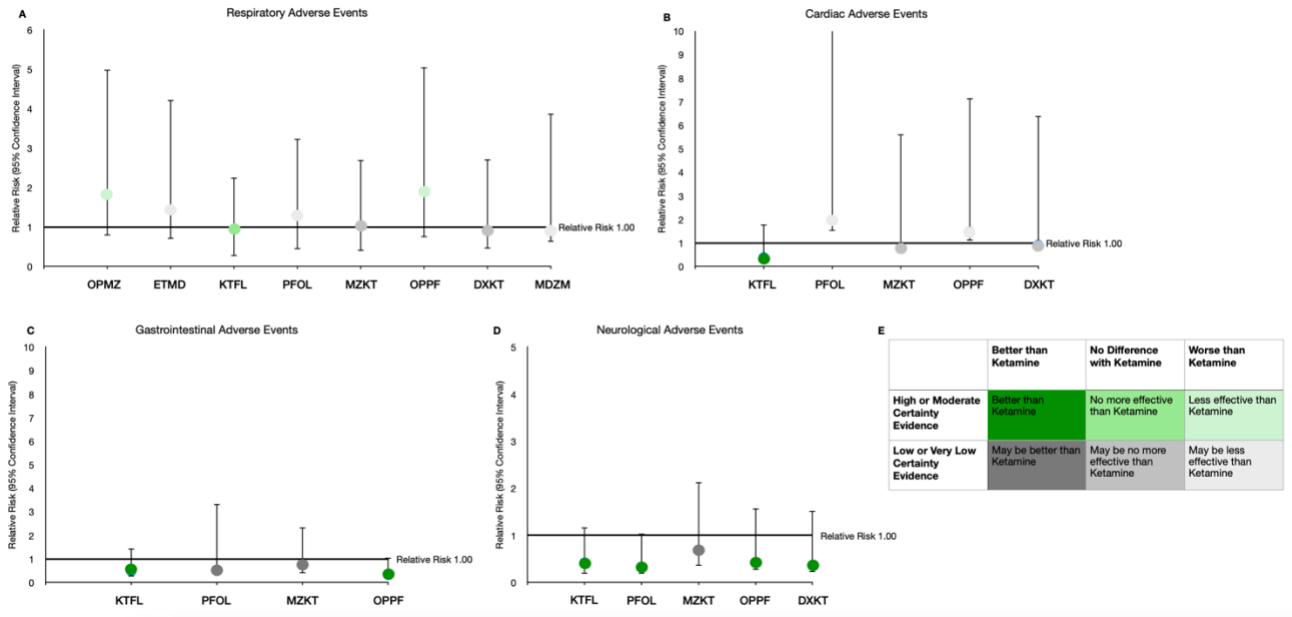


Supplement Figure 7. Network meta-analysis results based on GRADE certainty of evidence and treatment effectiveness for the comparisons of active treatments versus ketamine-propofol for the outcome of adverse events. A: Respiratory Adverse Events; B: Cardiac Adverse Events; C: Gastrointestinal Adverse Events; E: GRADE certainty of evidence table and figure legend.



Abbreviations: OPMZ, midazolam-opioids; KTMN, ketamine; OPPF, opioid-propofol; PFOL, propofol

Supplement Figure 8. Network meta-analysis results based on GRADE certainty of evidence and treatment effectiveness for the comparisons of active treatments versus ketamine for the outcome of adverse events. A: Respiratory Adverse Events; B: Cardiac Adverse Events; C: Gastrointestinal Adverse Events; E: GRADE certainty of evidence table and figure legend.



Abbreviations: OPMZ, midazolam-opioids; ETMD, etomidate; KTFL, ketamine-propofol; PFOL, propofol; MZKT, midazolam-ketamine; OPPF, opioid-propofol; DXKT, dexmedetomidine-ketamine; MDZM, midazolam