Systematic Review

Effects of Ketamine on Chronic Postsurgical Pain in Patients Undergoing Surgery: A Systematic Review and Meta-analysis

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Background: Chronic postsurgical pain (CPSP) has become a common complication during the perioperative period. The efficacy of one of the most potent strategies, ketamine, remains unclear.

Objectives: The aim of this meta-analysis was to evaluate the effect of ketamine on CPSP in patients undergoing common surgeries..

Study Design: Systematic review and meta-analysis.

Methods: English-language randomized controlled trials (RCTs) published in MEDLINE, Cochrane Library, and EMBASE from 1990 through 2022 were screened. RCTs with a placebo control group that evaluated the effect of intravenous ketamine on CPSP in patients undergoing common surgeries were included. The primary outcome was the proportion of patients who experienced CPSP 3 – 6 months postsurgery. The secondary outcomes included adverse events, emotional evaluation, and 48 hour postoperative opioid consumption. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Pooled effect sizes were measured using the common-effects model or random-effects model, and several subgroup analyses were conducted.

Results: Twenty RCTs were included with 1,561 patients. Our pooled meta-analysis showed a significant difference between ketamine and placebo in the treatment of CPSP (Relative Risk [RR] = 0.86; 95% CI, 0.77 – 0.95; $P = 0.02$; $I^2 = 44\%$). In the subgroup analyses, our results indicated that compared with placebo, intravenous ketamine might decrease the prevalence of CPSP 3 – 6 months postsurgery (RR = 0.82; 95% CI, 0.72 – 0.94; $P = 0.03$; $I^2 = 45\%$). For adverse events, we observed that intravenous ketamine might lead to hallucinations (RR = 1.61; 95% CI, 1.09 – 2.39; $P = 0.27$; $I^2 = 20\%$) but did not increase the incidence of postoperative nausea and vomiting (RR = 0.98; 95% CI, 0.86 – 1.12; $P = 0.66$; $I^2 = 0\%$).

Limitations: Inconsistent assessment tools and follow-up for chronic pain may contribute to the high heterogeneity and limitation of this analysis.

Conclusions: We discovered that intravenous ketamine may reduce the incidence of CPSP in patients undergoing surgery, especially 3 – 6 months postsurgery. Because of the small sample size and high heterogeneity of the included studies, the effect of ketamine in the treatment of CPSP still needs to be explored in future large-sample, standardized-assessment studies.

Key words: Ketamine, chronic postsurgical pain, perioperative period, meta-analysis, randomized controlled trial

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Chronic postsurgical pain (CPSP), an important complication following surgery, is defined as pain that persists past the normal healing time after surgery, usually for more than 3 months (1). According to previous research, the prevalence of CPSP is 10% – 50% across all surgeries (2). Once a patient

develops CPSP, many other complications can emerge. Experiencing CPSP might impair cognitive function (3) and may increase the risk of senile dementia in elderly patients (4). Persistent pain can also influence the emotional and mental health of the patient, which could in turn yield an unfavorable prognosis for the patient (5,6). However, no effective treatment for CPSP has yet been found.

The mechanism underlying the development of CPSP is believed to be closely related to the release of inflammatory factors due to injury at the surgical site and nearby nerves, which are thought to mediate peripheral and central sensitization (7). N-methyl-D-aspartate (NMDA) receptors notably seem to play a critical role in the development of CPSP (8). Consequently, ketamine and one of its enantiomers, S-ketamine, as an NMDA receptor antagonist, have taken on a competitive role in the treatment of CPSP. The effect of perioperative intravenous ketamine/S-ketamine on acute postsurgical pain (APSP) has been confirmed in many previous studies (9,10). Nevertheless, in the past few years, few studies have focused on the preventive efficacy of ketamine on CPSP.

In 2013, a meta-analysis suggested that ketamine could decrease the risk of CPSP at 3 months postoperatively (11). One year later, another meta-analysis emphasized that intravenous ketamine, rather than epidural ketamine, might prevent the occurrence of CPSP (12). However, because of the small sample sizes, limited number, and high heterogeneity of the included studies, the conclusion was unreliable. In 2020, an updated, large-scale meta-analysis including 110 studies performed 15 meta-analyses on the role of ketamine but returned a negative conclusion (13). Because of the various regimens for administering ketamine and the different assessment methods, the results could only suggest a general impression, especially regarding whether intravenous ketamine could play a role in preventing CPSP.

Thus, the objective of our systematic review and meta-analysis was to examine the efficacy of intravenous ketamine/S-ketamine in the treatment of CPSP in patients undergoing common surgeries and to observe the influence of different interventional regimens on preventing CPSP. These findings may provide new ideas for preventing CPSP to help improve the quality of life of patients undergoing surgery.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol of the systematic review was registered with PROSPERO (CRD42021227332) and published elsewhere.

Search Strategy and Data Source

We selected relevant studies published from 1990 through 2022 by searching Embase, MEDLINE (PubMed), and the Cochrane Library. We used the following combined text and MeSH terms as search words: ("Ketamine"[MeSH] OR "ketamine hydrochloride" OR "NMDA Receptor antagonist") AND (("Pain, Postoperative"[MeSH] OR "Chronic Pain"[MeSH] OR "Neuralgia"[MeSH] OR ("operation" OR "surgery")). The search results were limited to randomized controlled trials (RCTs). The details of the entire search strategy are in the eMethods Supplement.

Eligibility Criteria

We selected RCTs in accordance with the following inclusion criteria: 1) patients from any surgical population undergoing general anesthesia; 2) intravenous administration of a bolus and/or continuous infusion, or via a patient-controlled analgesia device of ketamine/S-ketamine during the perioperative period with no restrictions of dosage and duration; 3) a placebo-control group in RCTs; and 4) the proportion of patients with CPSP 3 – 6 months postoperatively as one of the study outcomes, evaluated by any relative scale. Studies on animals, reviews, and case reports were excluded. We also excluded papers not reported in the English language.

Study Selection

Two independent reviewers (W.S. and Y.Z.) screened the study titles and abstracts to identify potential articles. Subsequently, 2 reviewers (W.S. and Y.Z.) read the articles thoroughly to make a final decision. Both reviewers independently determined whether to include the study. In cases of conflicts, a third researcher (J.W.) was involved in the discussion. The process and details of study selection are shown in Fig. 1.

Data Extraction

Reference data, populations, and outcomes were extracted from the articles into a prespecified table form by 2 authors (W.S. and Y.Z.) independently. Original information included the studies' general characteristics (first author's last name, publication year, etc.),

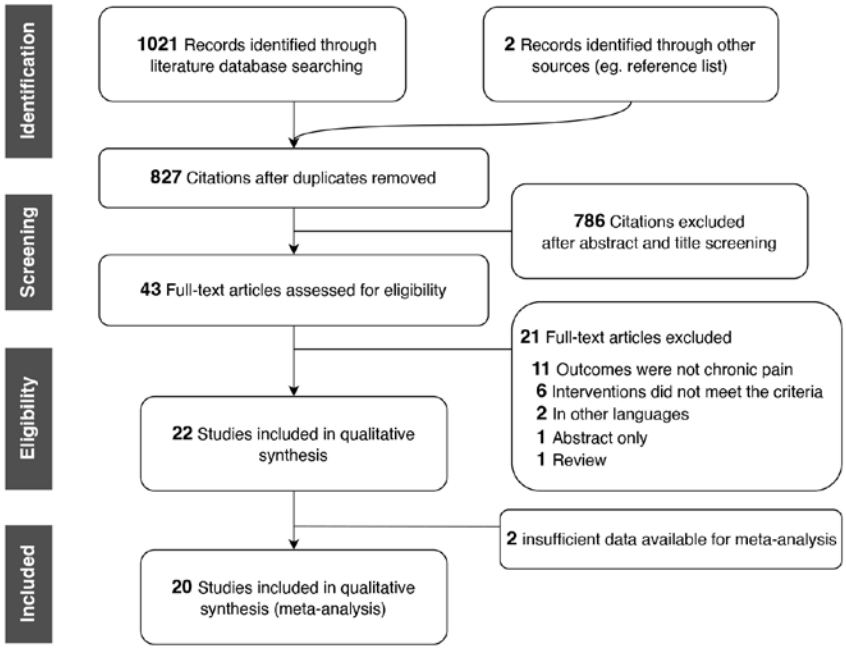

Fig 1. *Study Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.*

patients (demographic characteristics, sample size, type of surgery, etc.), intervention (dosage and duration of experimental drug administration, groups, etc.), and outcomes (prevalence of CPSP, assessment tools, time points of follow-up, adverse events, opioid consumption, etc.). The researchers attempted to contact the authors of these studies when they needed more information about their analyses or reported results.

Study Quality Assessment

Study quality was assessed by 2 independent researchers (W.S. and J.W.) Based on the Cochrane Collaboration's Risk of Bias (RoB) one tool, the following 7 key domains were examined: adequate random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcomes, incomplete outcome data, selective outcome reporting, and other biases.

The Jadad scale was used to assess the methodological quality of the selected RCTs. We defined RCTs with a score between 4 and 5 points as medium quality; those with a score between 6 and 7 were regarded as high-quality studies.

Outcome Measures and Data Synthesis

The diagnostic criteria for CPSP could depend on any relative assessment scale, such as the Visual Analog Scale (VAS), Numeric Rating Scales (NRS-11), Douleur Neuropathique 4 questionnaire (DN4), or even self-designed scales.

The number of patients with CPSP in the 2 groups at each time point was extracted, as well as the total number of patients in each group. The primary outcome was the proportion of patients undergoing surgery who experienced CPSP in the ketamine/S-ketamine group and control group 3 – 6 months postoperatively. The secondary outcomes included total opioid consumption within 48 hours postoperatively; the incidence of adverse events, including postoperative nausea and vomiting (PONV) and hallucinations; and the prevalence of depression and anxiety postoperatively. The included counting data are presented as relative risks (RRs) with 95% CIs, and the continuous data are presented as the mean differences (MD) with 95% CIs.

Statistical Analysis

The primary outcome was assessed with R version 4.1.3 with the meta package, version 5.2.0 (The R Foundation). Quantitative pooling analyses for the prevalence of CPSP were performed with the Mantel-Haenszel fixed-effects model, and trial weights were estimated by the inverse variance method. The effects of

ketamine on CPSP prognostic outcomes were assessed by pooled RRs for dichotomous variables and MDs for continuous variables, and the 95% CIs were estimated. Statistical heterogeneity in this meta-analysis was assessed by using the I^2 statistic. A random-effects model was used for pooled analyses with significant heterogeneity ($I^2 \geq 50\%$), and the fixed-effects (common effects) model was only used for analyses with moderate or low heterogeneity ($I^2 < 50\%$).

For the primary outcome, predefined subgroup analyses were conducted to detect the influence of certain trial design factors on heterogeneity between the included studies. Subgroups included type of surgery, CPSP assessment methods, length of follow-up for CPSP, and duration or dosage of ketamine infusion. Sensitivity analysis was performed by iteratively omitting each study from the pooled results. For publication bias analysis, a funnel plot and Egger's test were performed to assess the effects of small studies. A contour-enhanced funnel plot was inspected for asymmetry, and 2-sided *P* values < 0.05 for Egger's test indicated statistical significance.

Trial sequential analysis (TSA) was performed to determine whether the current sample size reached the threshold for statistical significance with TSA Version 0.9.5.10 (Copenhagen Trial Unit). The primary TSA was conducted by setting α to 0.05, power to 80%; estimated diversity and variances were estimated by the included trials.

Results

Literature Search

A total of 1,023 studies were identified through the initial search. We removed duplicate records and then selected relevant publications by screening abstracts and titles; the full texts of 43 studies were subsequently read. An additional 21 studies were excluded due to failure to meet the inclusion criteria, as listed in Fig. 1. Because of insufficient data available for the meta-analysis, 2 articles were excluded. Finally, 20 studies with 1,561 patients were included in the final analysis.

Study Characteristics

All included RCTs assessed the incidence of CPSP between ketamine/S-ketamine and placebo for patients undergoing any surgical procedure for 3 – 6 months postoperatively; 3 studies used S-ketamine as the interventional drug, and the others used ketamine. Among the trials, 6 enrolled patients undergoing thoracotomy (14-19); 6 included patients scheduled for orthopedic surgery: 3 reported on patients undergoing total hip/knee arthroplasty (20-22), 2 enrolled patients undergoing spinal surgery (23,24), and one described an amputation (25); 2 included patients prior to breast surgery (26,27); and the other 6 trials included thyroidectomy (28), rectal adenocarcinoma surgery (29), hemorrhoidectomy (30), open nephrectomy (31), abdominal or thoracic surgery (32), and cesarean delivery (33).

Among the 1,561 patients, 58.4% were women. The age of the patients was 45.9 ± 7.9 years. The sample size of the included studies ranged from 16 to 184. Fifteen percent of the studies had a sample size of less than 50, 50% had between 50 and 100 patients, and 35% had more than 100 patients. Regarding the interventions of the included studies, 2 of the trials had 3 groups, including ketamine, placebo, and other drugs (20,31); and 2 trials included an intravenous ketamine group, epidural ketamine group, and placebo group, for which we extracted only the data of the intravenous (IV) ketamine and placebo groups (16,29). According to the different dosages and routes, one trial was designed to have 4 arms (33), and one trial had 5 arms (29).

Risk of Bias Assessment

Quality assessment of the RCTs was based on the Cochrane Collaboration's RoB 1 tool (Supplemental Figs. 10 and 11). Five studies did not describe the method of random sequence generation (15,20,22,31,32). Regarding allocation concealment, 8 trials did not mention its implementation (15-17,19,20,25,29,33), and one trial prepared study medications by number (24). For blinding, 5 trials did not indicate blinding of the patients and investigators (15,17,19,20,22), and 3 studies did not introduce assessment blinding (15,19,22). Two trials yielded bias in incomplete outcome data (32,33), and 4 trials had biases in selective outcome reporting (17,20,29,33). Based on the Jadad scale, 8 trials were of medium quality, and the others were of high quality; the details are shown in Table 1.

Primary Outcome

All 20 RCTs reported the number of patients with CPSP in the 2 groups (ketamine and placebo) 3 – 6 months postsurgery. Nine studies (14,16,17,19,26-28,30,31) evaluated CPSP 3 months postoperatively, and the other studies evaluated CPSP occurring after 3 months but within 6 months. For the assessment standard, 4 trials (20,24,26,31) used a DN4 score of ≥ 4, 10

Table 1. *Included trials characteristics.*

Study	Year	Type of Surgery	Sample Size	Number of Groups	Infusion Regimen	Dosage of Ketamine/S-ketamine	Duration of Ketmaine	Assessment of CPSP	Time Points of Follow-up	JADAD
Dekock	2001	Rectal surgery	98	5	EP/IV	Bolus 0.25 mg/kg + 0.125 mg/kg/h or 0.5 mg/kg + 0.25 mg/kg/h	During surgery	self-designed	1 m, 6 m, 12 m	5
Hayes	2004	Knee amputation	45	2	IV	bolus 0.5 mg/kg + 0.15 mg/kg/h	72 h	self-designed	6 m	6
Suzuki	2006	Thoracotomy	49	2	IV	Bolus 0 mg/kg + 0.05 mg/kg/h	72 h	NRS	1 m, 3 m, 6 m	5
Duale	2009	Thoracotomy	86	2	IV	Bolus 1 mg/kg + 1 mg/kg/h (during surgery) + 1 mg/kg (post 24 h)	24 h	NPSI	1.5 m, 4 m	7
Remerand	2009	THA	154	2	IV	Bolus 0.5 mg/kg + 0.12 mg/kg/h	24 h	self-designed	1 m, 3 m, 6 m	7
Perrin	2009	TKA	16	2	IV	Bolus 0.5 mg/kg + 0.24 mg/kg/h	During surgery	WPS	6.5 m	5
Spreng	2010	Haemorrhoidectomy	77	2	IV	Bolus 0.35 mg/kg + 0.3 mg/kg/h	During surgery	NRS	3 m	7
Mendola	2012	Thoracotomy	62	2	IV	Bolus 0 mg/kg + 0.1 mg/kg/h	60 h	NRS	1 m, 3 m, 6 m	5
Bligen	2012	Cesarean delivery	140	4	IV	Bolus 0.25 mg/kg or Bolus 0.5 mg/kg or Bolus 1 mg/kg	Only bolus	Self-designed	1 m, 6 m, 12 m	5
Hu	2014	Thoracotomy	78	2	IV	Bolus 1 mg/kg + 0.12 mg/kg/h	72 h	NRS	2 m, 6 m	4
Tena	2014	Thoracotomy	104	3	EP/IV	Bolus 0.5 mg/kg + 0.25 mg/kg/h	48 h	VAS	3 m, 6 m	6
Aveline	2014	TKA	69	3	IV	Bolus 0.2 mL/kg + 0.12 mg/kg/h (during surgery) + 0.06 mg/kg/h (post 48 h)	48 h	DN4	6 m, 12 m	4
Nielsen	2017	Lumbar spinal fusion surgery	147	2	IV	Bolus 0.5 mg/kg + 0.25 mg/kg/h	During surgery	VAS	6 m, 12 m	7
Jendoubi	2017	Elective open nephrectomy	63	3	IV	Bolus 0.15 mg/kg + 0.1 mg/kg/h	24 h	DN4	3 m	6
Peyton	2017	Abdominal or thoracic surgery	80	2	IV	Bolus 0.5 mg/kg + 0.25 mg/kg/h (during surgery) + 0.1 mg/kg/h (post 24 h)	24 h	NRS	6 m	6
Lee	2018	Thyroidectomy	64	2	IV	Bolus 0.15 mg/kg + 0.12 mg/kg/h	During surgery	NRS	3 m	7
Chumbley	2019	Thoracotomy	70	2	IV	Bolus 0.1 mg/kg + 0.1 mg/kg/h	96 h	NPS	1 m, 3 m, 6 m, 12 m	7
Kang	2020	Breast cancer surgery	184	2	IV	Bolus 0.5 mg/kg + 0.12 mg/kg/h	During surgery	NRS	1 m, 3 m, 6 m	7
Czarnetzki	2020	Lower back surgery	160	2	IV	Bolus 0.25 mg/kg + 0.25 mg/kg/h (during surgery) +0.1 mg/kg/h (PACU)	During surgery	DN4	6 m, 12 m	5
Zhao	2021	Modied radial mastectomy	100	2	IV	Bolus 0.5 mg/kg + 0.25 mg/kg/h	During surgery	DN4	3 m	7

Abbreviations: EP, epidural; IV, intravenous; NRS-11, Numeric Rating Scale; NPSI, Neuropathic Pain Symptoms Inventory; VAS, Visual Analog Scale; DN4, Douleur Neuropathique 4 questionnaire; NPS, Numeric Pain Score; WPS, Womac pain subscale; TKA, Total knee arthroplasty; THA, Total hip arthroplasty; PACU, Postanesthesia Care Unit.

trials (14-17,19,23,27,28,30,32) used the NRS-11, VAS, or Numeric Pain Scores (NPS) to evaluate pain intensity, 4 trials (21,25,29,33) had self-designed scales, one trial (18) used the Neuropathic Pain Symptoms Inventory (NPSI) scale, and one trial (22) assessed CPSP with the Womac pain subscale.

In the analysis of these 20 RCTs with 1,561 patients, the pooled results indicate that 3 – 6 months postoperatively, compared with placebo, IV ketamine might decrease the incidence of CPSP (RR = 0.86; 95% CI, 0.77 – 0.95; P = 0.02; I^2 = 44%, Fig. 2). The funnel plot is presented in Fig. 3, showing that publication bias was not observed in any study. Egger's test also showed no publication bias (P = 0.66).

Secondary Outcomes

Adverse Events

Fourteen of the 20 trials reported the incidence of adverse events during the postoperative period. Meta-analysis of the data revealed that compared with placebo, IV ketamine did not increase the incidence of PONV (RR = 0.98; 95% CI, 0.86 – 1.12; P = 0.66; I^2 = 0%) (Supplemental Fig. 1). However, the pooled data showed that IV ketamine might increase the risk of postoperative hallucinations (RR = 1.61; 95% CI, 1.09 – 2.39; P = 0.27; I^2 = 20%) (Supplemental Fig 2). In addition, we also summarized the incidence of adverse drug reactions in the 20 included studies; details are in the Supplementary Table.

Opioid Consumption 48 Hours Postoperatively

Fourteen trials (14,15,17-19,21-25,27,31-33) observed the total postsurgery opioid consumption; 2 trials (17,19) performed postoperative analgesia via patient-controlled epidural analgesia , so their results were based on the epidural dosage. Six studies (14,18,24,25,27,32) are presented as the median (IQR). One study (15) only reported the total opioid consumption at 72 hours. Finally, only 5 studies (21-23,31,33) were included in the analysis; no difference was observed between the 2 groups in opioid consumption (Mean Difference = -7.37; 95% CI. -20.06 to 5.33; P < 0.01; I^2 = 93%) (Supplemental Fig. 3).

Depression and Anxiety

Only one study (27) focused on the postsurgical emotional assessment of patients. Kang et al (27) found that the prevalence of depression was nearly 13 – 14% in patients after breast surgery from one to 6 months

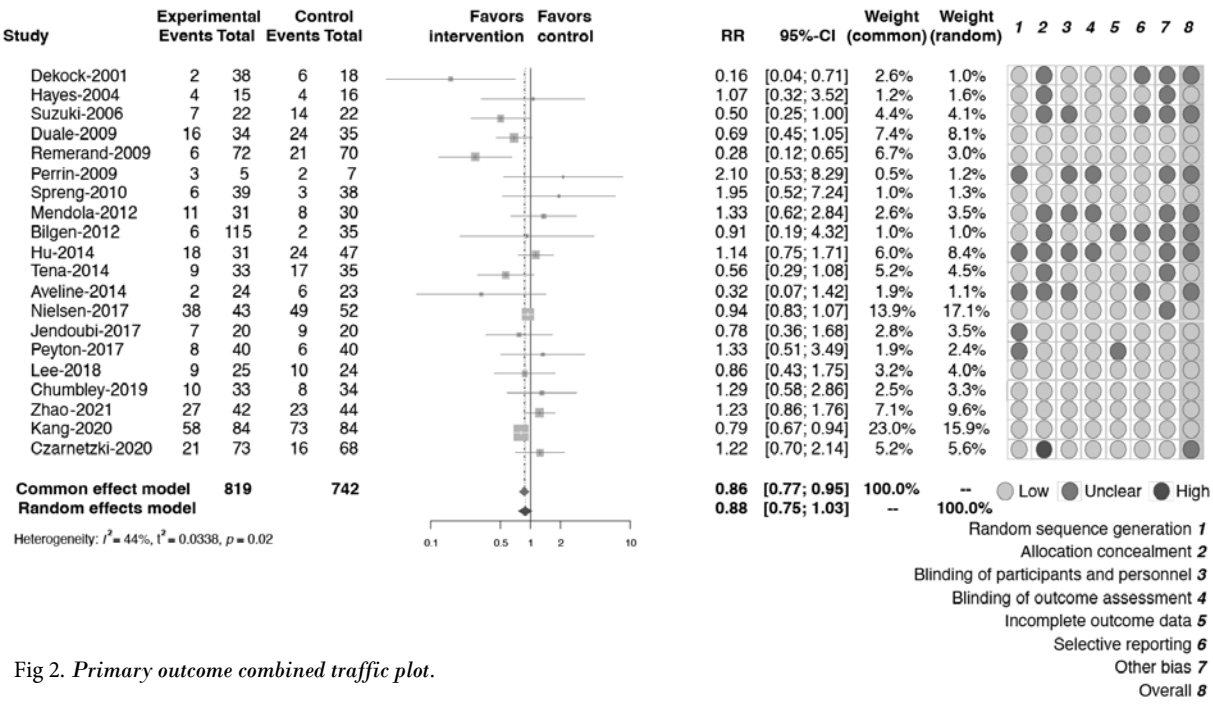

Fig 2. *Primary outcome combined traffic plot.*

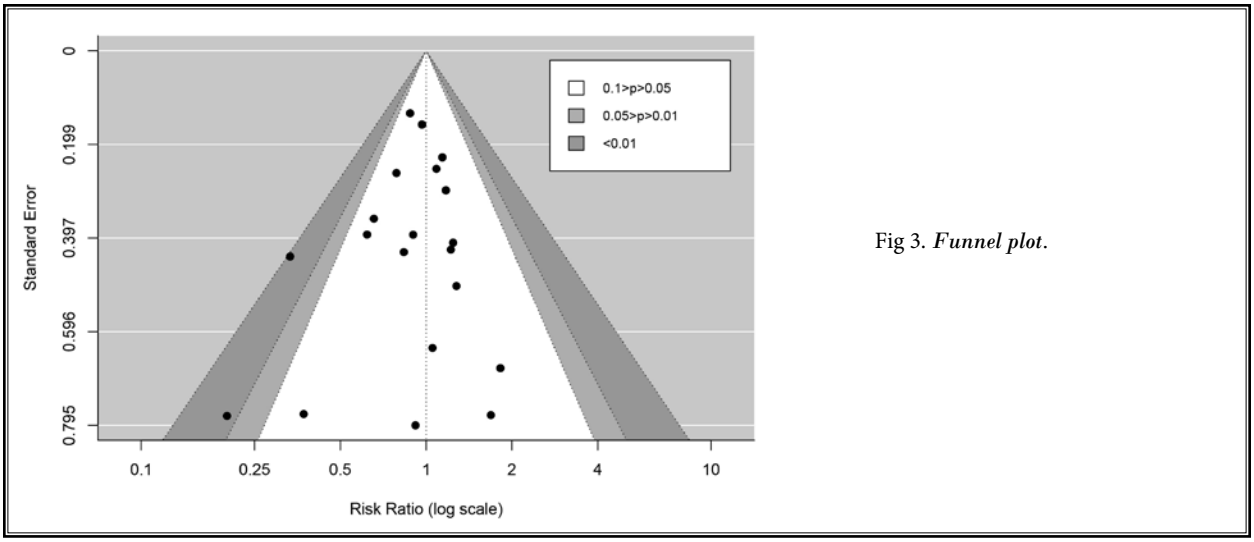

Fig 3. *Funnel plot*.

postoperatively; there were no significant differences between the 2 groups (one month: $P = 0.635$; 3 months: $P = 0.311$; 6 months: $P = 0.801$). This study also evaluated anxiety within 24 hours postoperative and did not observe a difference ($P = 0.682$).

Subgroup Analyses and Sensitivity Analysis

For the primary outcome, the I^2 statistic was 44% for the meta-analysis of intravenous ketamine from 20 RCTs. These outcomes indicated the presence of a moderate degree of heterogeneity. Many factors might cause this heterogeneity, including the type of surgery, assessment method, follow-up time points, and variations in the infusion regimen and placebo. To explore the sources of heterogeneity, we conducted 4 subgroup analyses and a sensitivity analysis. No significant differences were shown in the subgroup analyses for different surgical types, including orthopedic surgery, thoracotomy, abdominal surgery, thyroid surgery, or breast surgery (Supplemental Fig. 4).

One study enrolled a mixed surgery population, including thoracotomy, abdominal surgery, and breast surgery, so this trial was analyzed in different subgroups 3 times. Moreover, the various interventional regimens were estimated. Unfortunately, we found no significant differences among the following groups: infusion rate ≤ 0.125 mg/kg/h vs > 0.125 mg/kg/h; duration of intervention only during surgery; within 24 hours vs more than 24 hours; and a bolus dose of IV ketamine ≥ 0.5 mg/kg vs < 0.5 mg/kg (Supplemental Fig. 5). We also investigated the different time periods for assessing CPSP, including < 3 months, at 3 months, > 3 months, ≤ 6 months, > 6 months, and ≤ one year. Finally, we observed significant differences between > 3 and ≤ 6 months (RR = 0.82; 95% CI, 0.72 to 0.94; $P = 0.03$; $I^2 = 45\%$) (Supplemental Fig. 6). Moreover, we evaluated the different assessment methods for CPSP; we placed similar scales in the same subgroup, including VAS/NRS-11, DN4, self-designed scale (DIY) and NPSI. The results showed that under the same or similar scales, the effect of ketamine/S-ketamine could be observed more easily (Supplemental Fig. 7).

A sensitivity analysis was performed by sequentially removing each individual trial and evaluating how its removal affected the pooled estimate of the primary outcome. The results showed that omitting the study of Zhao (26) might have little influence on the outcomes (RR = 0.85; 95% CI, 0.74 to 0.98) (Supplemental Fig. 8).

Trial Sequential Analysis (TSA)

TSA for the effect of ketamine on CPSP was inconclusive, and the cumulative z-curve did not cross the benefit, harm, or futility threshold. The current evidence was not sufficient to clarify the effect of ketamine on CPSP. (Supplemental Fig. 9)

Discussion

This systematic review and meta-analysis of 20 RCTs evaluated intravenous ketamine/S-ketamine infusions versus placebo for CPSP in patients undergoing any type of surgery during the perioperative period. The results revealed that IV ketamine/S-ketamine use during the perioperative period could reduce the risk of CPSP in patients undergoing surgery. In the subgroup analysis, we found that standard assessment could help decrease the heterogeneity of the pooled results. Ad-

ditionally, regarding adverse events, the incidence of hallucinations with IV ketamine/S-ketamine was higher than that with placebo, but no effect was observed on the incidence of PONV.

Because of the associated economic burden and substantial functional impairment, CPSP is becoming an important issue in the field of perioperative medicine. In a previous study (34), the average prevalence of CPSP was almost 10% in the population undergoing surgery. Additionally, more than 320 million people require surgical treatment for their disease (7).

Based on the current severe situation, researchers have been seeking better ways to prevent or treat CPSP for the past few years. It is hypothesized that the development of CPSP and central sensitization requires high-concentration bombardment and blockade of NMDA receptors, which are intimately involved in neuroplasticity. Ketamine is a traditional intravenous anesthetic that exerts its analgesic effect by antagonizing NMDA receptors. As a result, ketamine and S-ketamine, one of its enantiomers, have become some of the most competitive drugs for alleviating CPSP. In 2014, McNicol et al (12) conducted a meta-analysis and demonstrated that perioperative IV ketamine reduces the risk of developing CPSP between 3 and 6 months postsurgery. The effect of ketamine has also been confirmed for other chronic pain populations, such as those with complex regional pain syndrome (both Type 1 and Type 2) (35) or chronic pain (36).

In 2020, an updated meta-analysis showed that ketamine might not prevent CPSP well (13), which seems to contradict our conclusions. However, their inclusion criteria were different from ours: they included all ketamine infusions, not only intravenous but also epidural administration, and they also included combinations of ketamine and other drugs, which might result in a higher heterogeneity of outcome, which might explain why the effect of ketamine/S-ketamine on CPSP was not observed in their study. On the other hand, we only enrolled studies that used intravenous ketamine/S-ketamine administration, which might explain the dissimilarity.

Pain and depression are reciprocally related (37-39). CPSP might increase the risk of depressive symptoms in patients who have had surgery. Once patients with CPSP suffer from depression, their prognosis worsens, so it is vital for clinicians to identify patients who have had surgery with depressive symptoms in time. According to one study (40), a subanaesthetic infusion of ketamine/S-ketamine had an obvious effect on depression. Moreover, our research team found that subanaesthetic ketamine could effectively decrease depressive symptoms in patients undergoing neurosurgical procedures (41). The conclusions seem to suggest that appropriate doses of ketamine could effectively address pain and depression.

However, IV ketamine might cause more significant dissociative symptoms and transient cardiovascular reactions (blood pressure elevations and/or higher heart rates). These side effects might limit the use of ketamine in patients with depression during the perioperative period. Concerns include the following: 1) intraoperative administration may alter the depth of anesthesia, and patients undergoing surgery who have depression often have a decreased tolerance to anesthesia; 2) continuous postsurgery IV ketamine could cause dissociative symptoms and hallucinations in patients with depression, which might further aggravate anxiety and depression; and 3) patients with depression usually need to take antidepressants to control the disease. How to balance the effects of antidepressants on perioperative management and the control of patients' depression is a crucial challenge for anesthesiologists. Thus, the most appropriate delivery strategy of ketamine needs to be clear as soon as possible.

According to a previous study, the incidence and intensity of CPSP are different among different patients undergoing surgery (7). Therefore, we performed subgroup analyses for different surgeries; ultimately, however, the data did not show differences between the 2 groups for each type of surgery. The results are consistent with those of previous studies (12,13).

Few previous related systematic reviews and meta-analyses have focused on the dosage or duration of the ketamine infusion regimen, despite it having a substantial effect on the analgesic effect of ketamine. Based on previous opinions, poorly controlled APSP is an independent risk factor for CPSP (42) and could increase the risk of CPSP 3-fold (43). We considered that a higher dosage and longer duration might result in better control of acute postoperative pain, influencing the development of CPSP. Our subgroup analysis of the infusion regimen was divided into 3 parts: the infusion rate, the bolus dosage, and the continuous duration. A previous updated review showed that the duration of ketamine administration was not related to the risk of CPSP in 3 – 6 months, which was opposite to their previous review (13). However, our results are consistent with these new observations. In addition, we also designed a secondary outcome of 48-hour opioid consumption to

explore the relationship between APSP and CPSP, but due to the excessive heterogeneity and little accurate data, we could not find meaningful results.

Moreover, none of the previous studies observed whether different assessment tools affected the evaluation of CPSP. Therefore, we performed a subgroup analysis to examine this issue. According to our results, we found that under the same scale, we could decrease the heterogeneity and find differences between the 2 groups. In other words, a unified evaluation helped us observe the results more clearly and obtain a conclusion more easily. Therefore, it is very important for future studies to use standard evaluation methods and fixed follow-up points.

The adverse effects of intravenous ketamine/S-ketamine were also evaluated in our meta-analysis. PONV is one of the most common postoperative complications of intravenous ketamine/S-ketamine. Our pooled data indicates that there were no significant differences in the incidence of PONV between the 2 groups. The same results were reported in a meta-analysis investigating the effect of IV ketamine on early APSP (9). Moreover, we assessed the proportion of hallucinations in all of the included studies, which is a specific adverse reaction of ketamine and its enantiomer administration. Finally, we found that IV ketamine seemed to produce a greater proportion of hallucinations than placebo. According to our secondary outcomes, we also planned to investigate the proportion of depression and anxiety in these populations. Depression and anxiety are common complications of CPSP and always lead to a poor prognosis (44,45). Unfortunately, only one study reported postsurgery emotional assessment, but we still think that it is very important to explore the relationship and influence between mood and CPSP. We suggest that future studies pay more attention to this field.

Our systematic review and meta-analysis has several limitations. First, there was possible publication bias in our review because of the exclusion of non-English papers. However, in our analysis, which consisted of a funnel plot and Egger's test, we did not observe any publication bias. Second, the incidence of CPSP was not the primary outcome in all included articles, which meant that the outcome of CPSP in some enrolled studies had insufficient power, potentially reducing the reliability of the results in our meta-analysis. At the same time, the sample size of some included papers was small, which might also have increased the reporting bias. Combined with the TSA results, these limitations indicate that further large-population and high-quality research is needed. Finally, the inconsistent assessment tools for the primary outcome possibly increased the heterogeneity of the results and made additional analysis difficult. Therefore, investigators should consider using a unified method to assess the prevalence of CPSP in the future to discuss effective drugs to prevent this severe problem.

Conclusions

Perioperative IV ketamine likely reduces the incidence of CPSP in patients undergoing surgery, especially 3 – 6 months postsurgery, while increasing the occurrence of hallucinations but not PONV. However, because of the high heterogeneity of the interventional regimens and assessment methods, our confidence in this analgesic effect is limited. Moreover, we found that using a uniform scale could decrease the heterogeneity and observe the effect of ketamine on CPSP more obviously. Therefore, additional standardized assessments and large-scale studies are needed to confirm this conclusion in the future.

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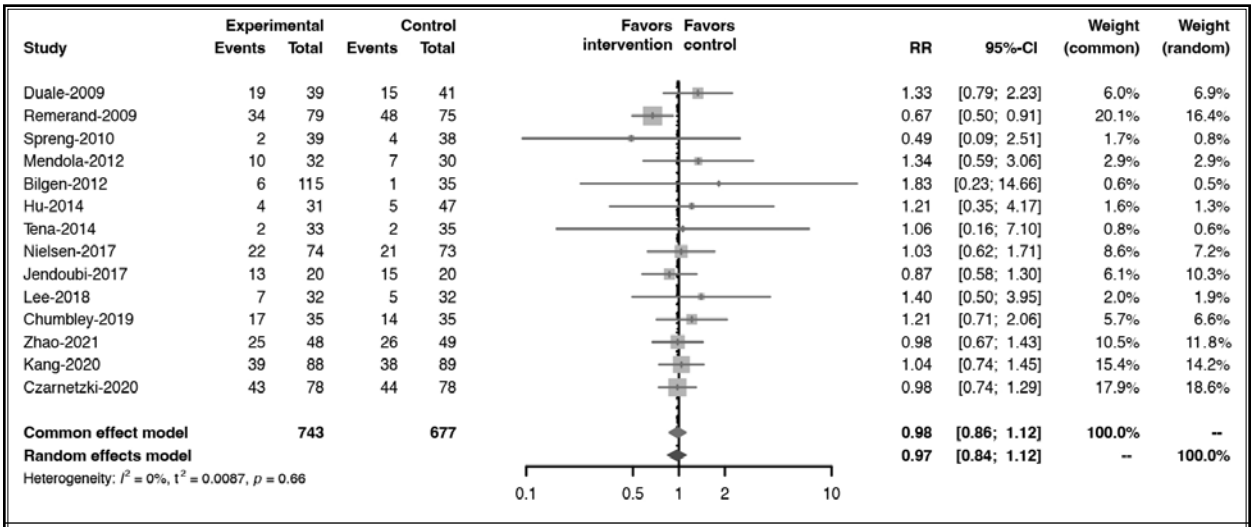
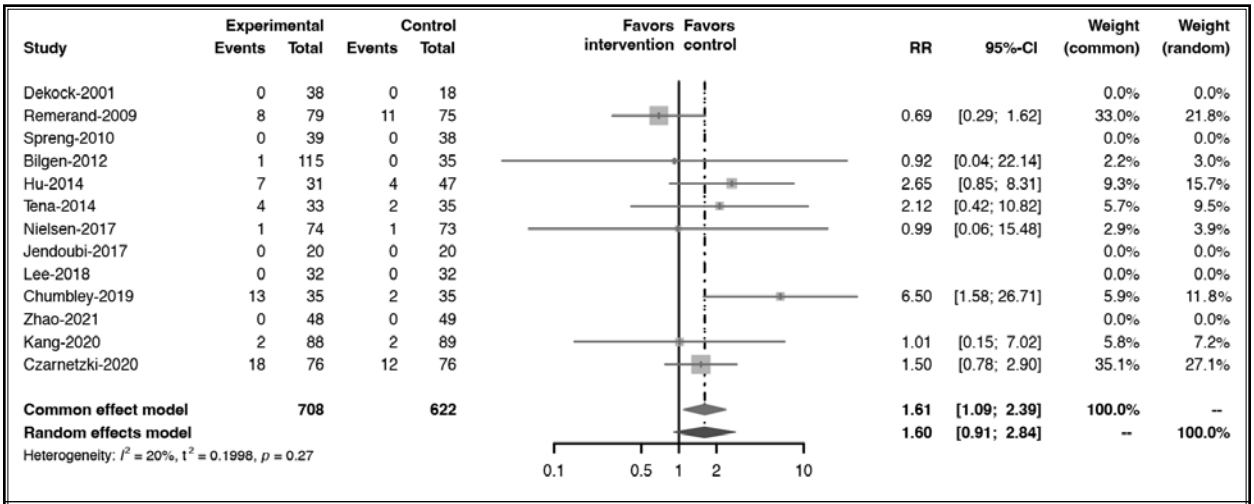
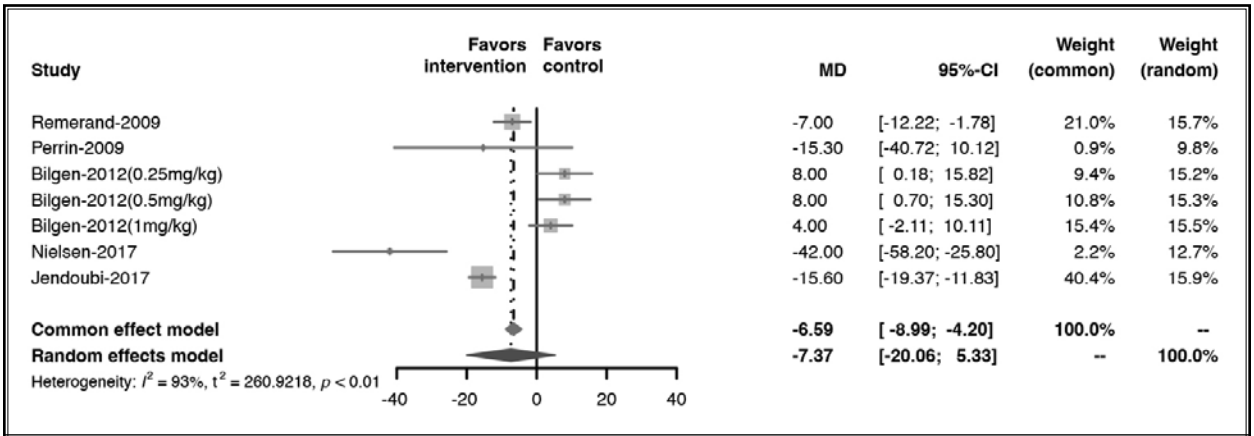


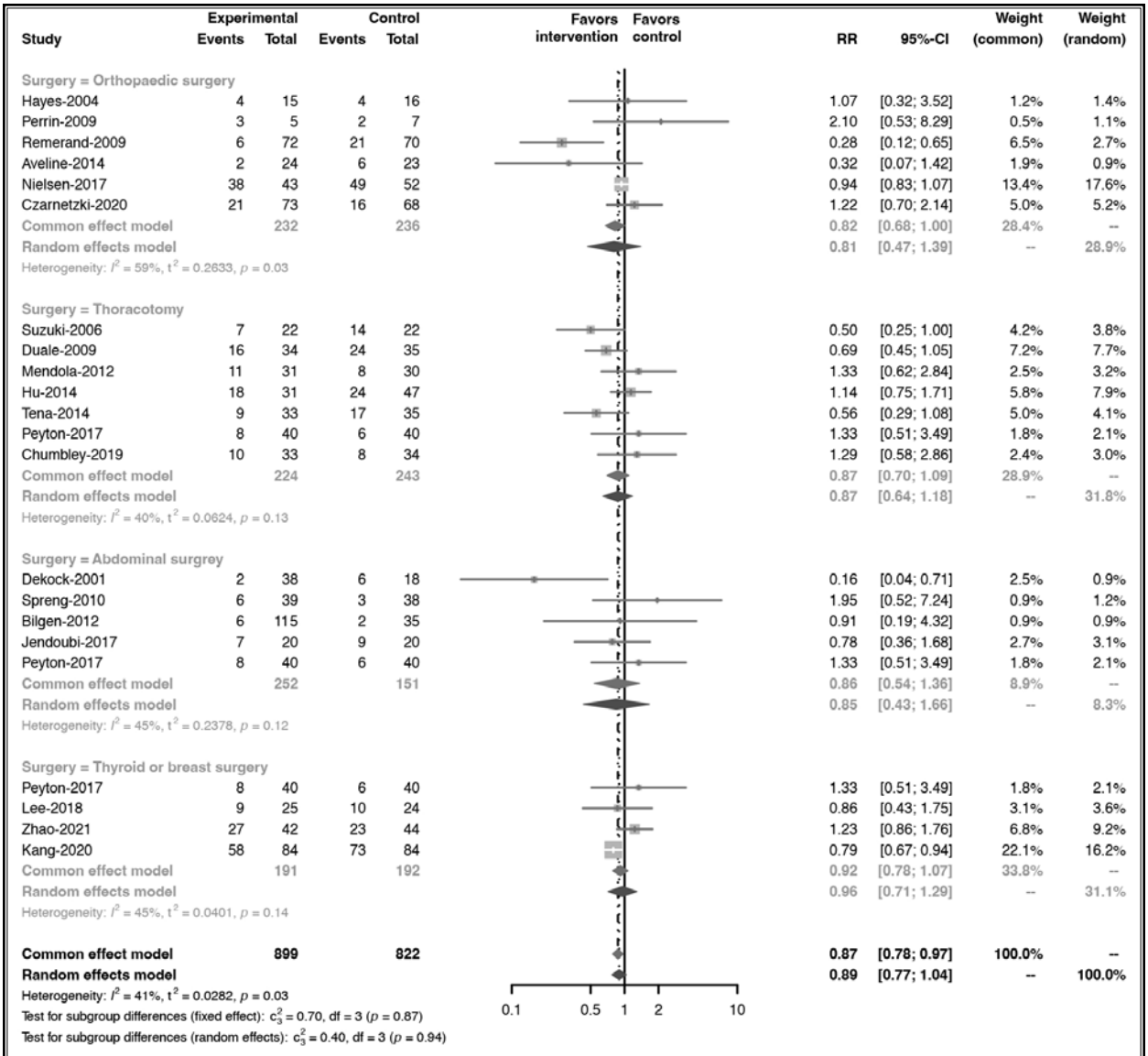
Supplemental Fig. 1. *Secondary outcome-PONV.*
PONV: Postoperative nausea and vomiting.



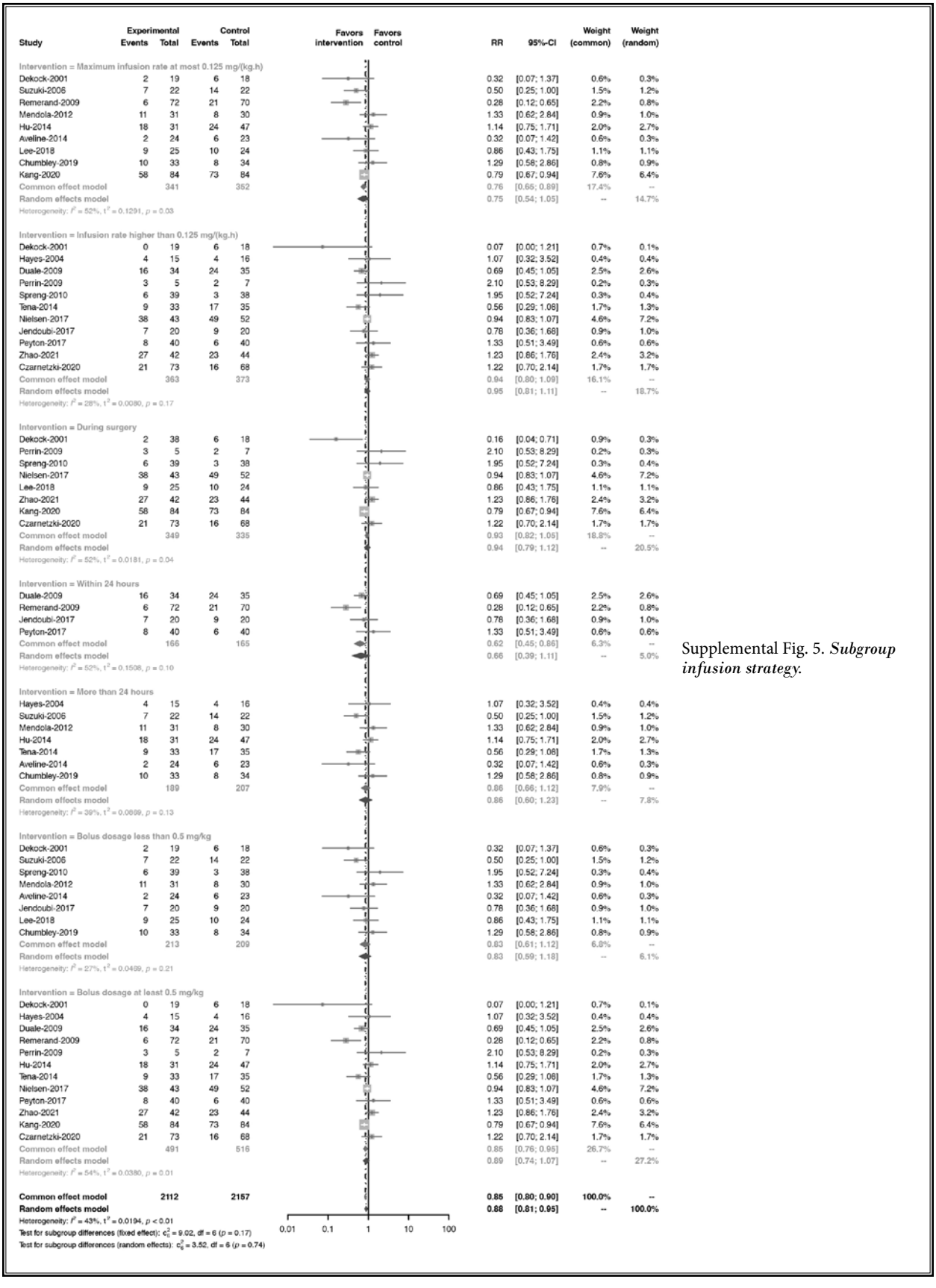
Supplemental Fig. 2. *Secondary outcome-hallucinations.*



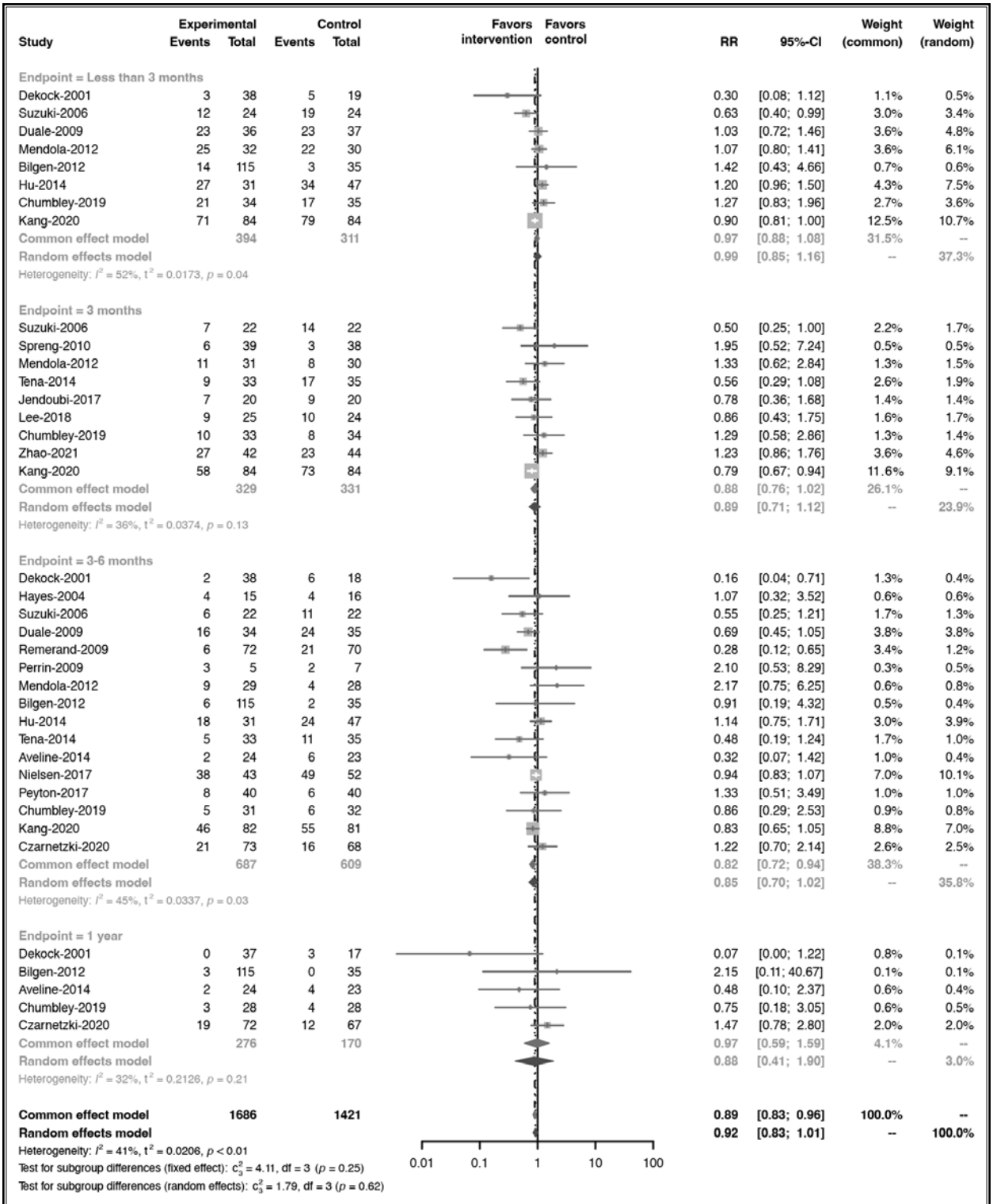
Supplemental Fig. 3. *Secondary outcome-48 hours postoperative opioid consumption.*



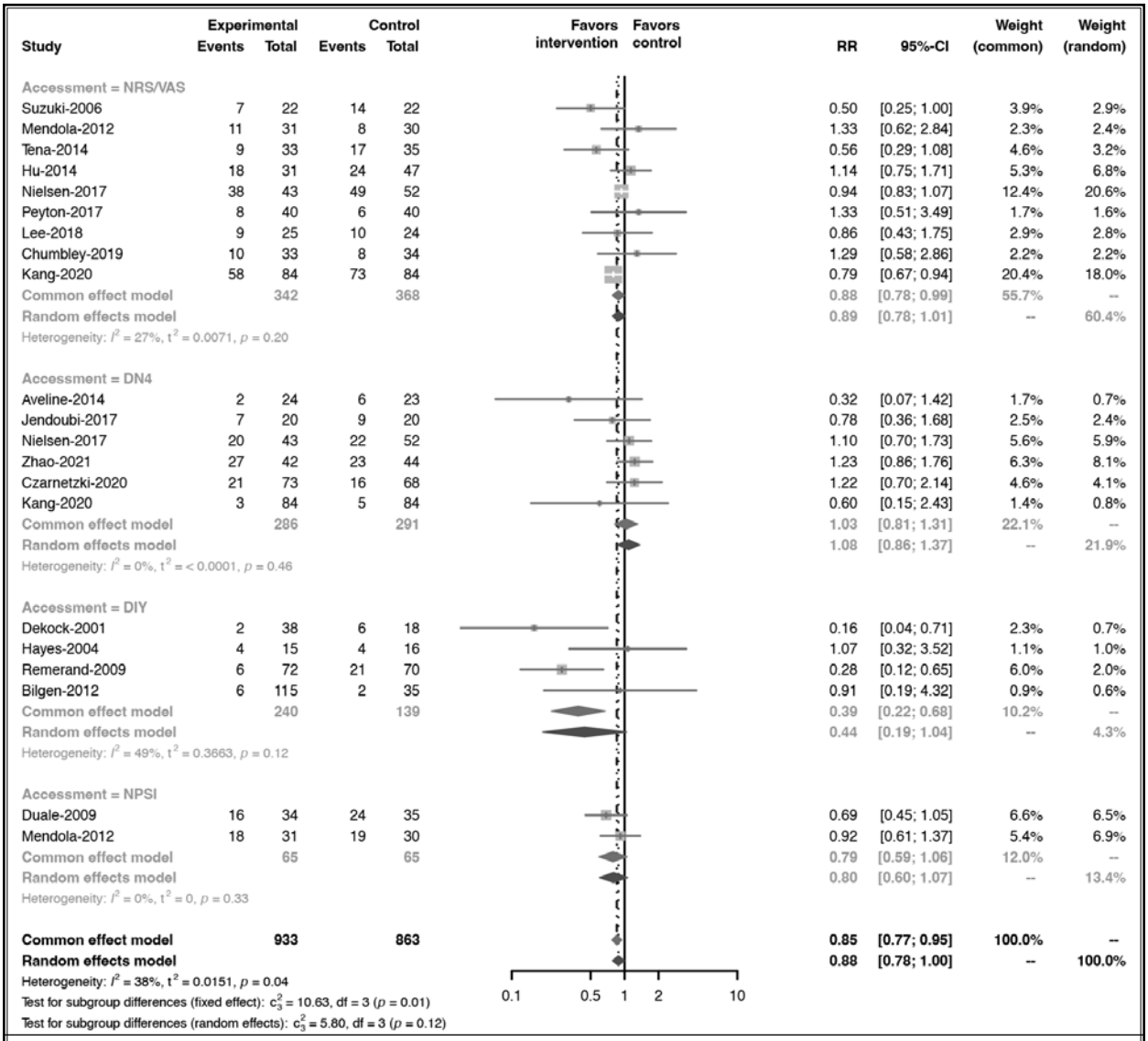
Supplemental Fig. 4. *Subgroup-surgery type.*



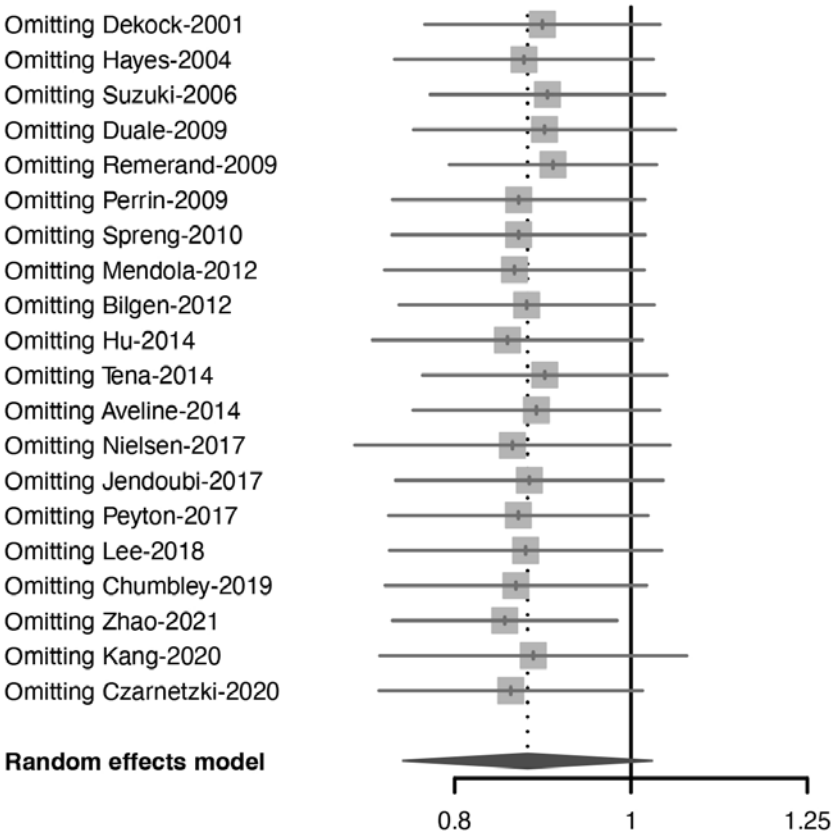
Supplemental Fig. 5. ***Subgroup infusion strategy.***



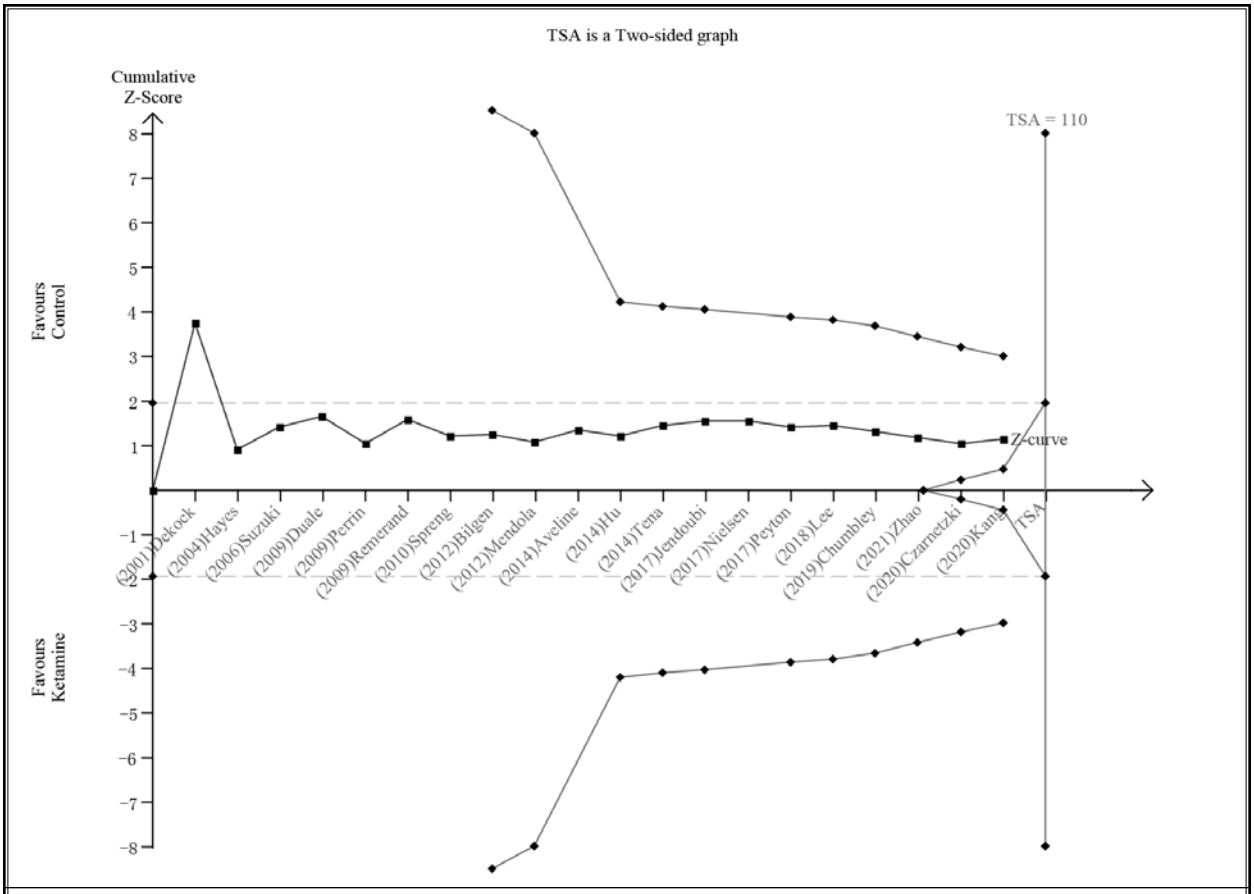
Supplemental Fig. 6. *Subgroup endpoints*.



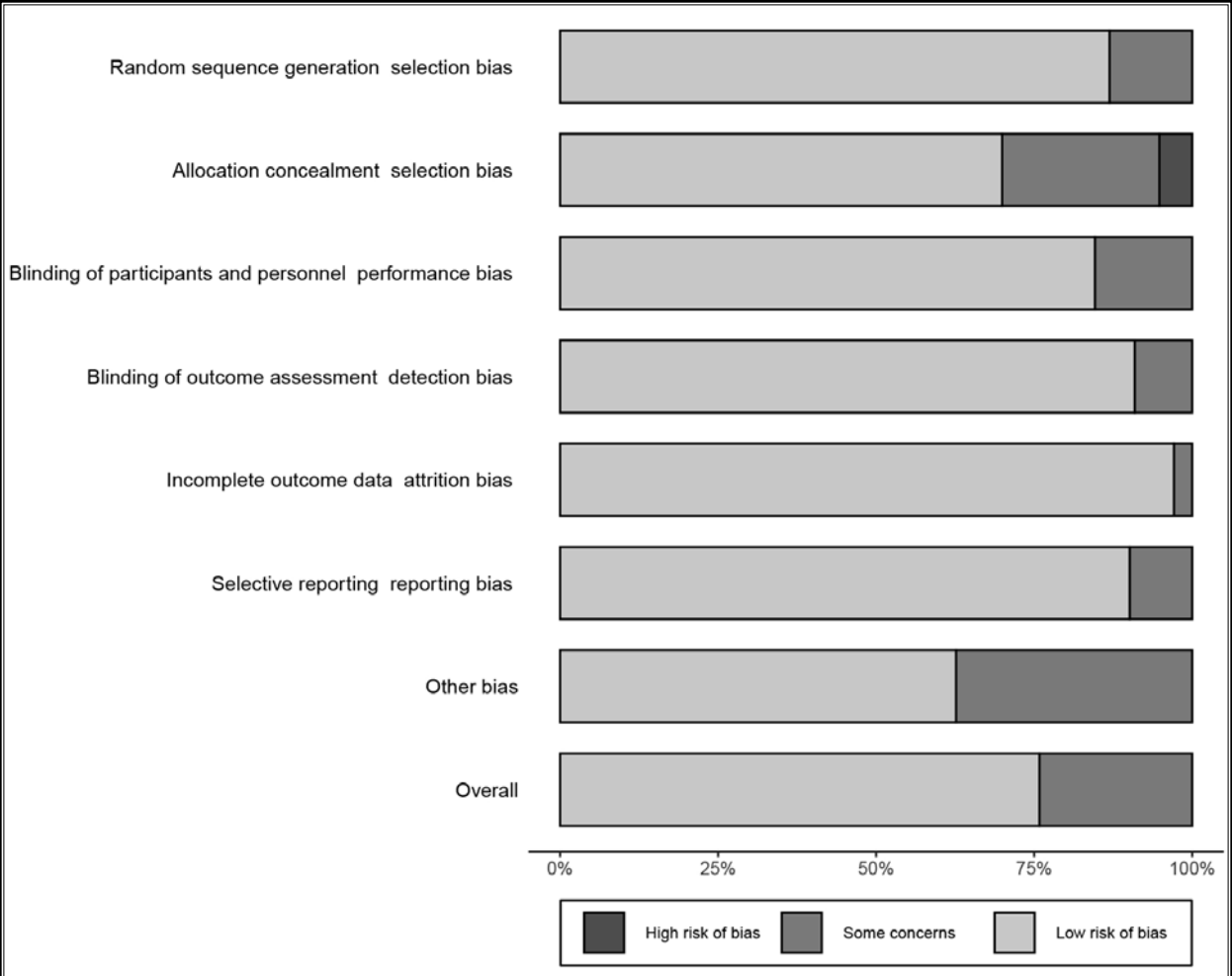
Supplemental Fig. 7. ***Subgroup-assessment scale.***
NRS-11: Numeric Rating Scale. VAS: Visual Analog Scale. DN4: Douleur Neuropathique 4 questionnaire. DIY: "design it yourself", means self-designed scale. NPSI: Neuropathic Pain Symptoms Inventory.



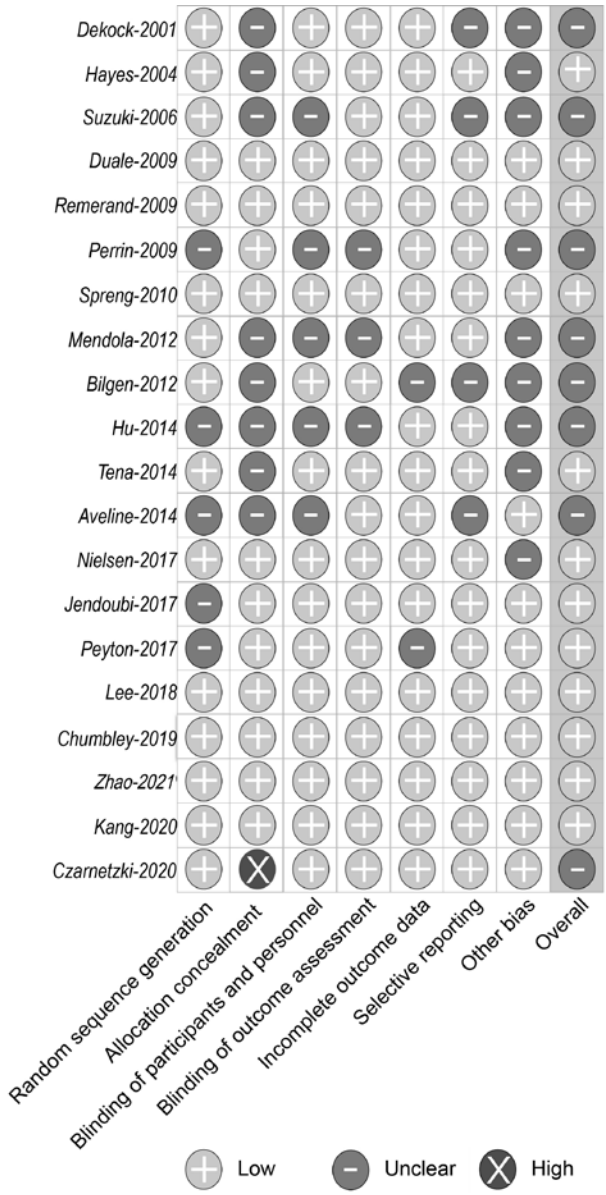
Supplemental Fig. 8. *Sensitivity analysis*.



Supplemental Fig. 9. ***Trial sequential analysis (TSA) plot.***



Supplemental Fig. 10. *Risk of Bias (RoB) Summary.*



Supplemental Fig. 11. ***Risk of Bias (RoB) plot***.

Supplemental Table. *The incidence of ADRs based on the included studies.*

ADRs	Events/Total	Incidence(%)	Study ID
PONV	243/743	32.7	Duale 2009, Remerand 2009, Spreng 2010, Mendola 2012, Bligen 2012, Hu 2014, Tena 2014, Nielsen 2017, Jendoubi 2017, Lee 2018, Chumbley 2019, Zhou 2021, Kang 2020, Czarnetzki 2020
Hallucinations	54/708	7.6	Dekock 2001, Remerand 2009, Spreng 2010, Bligen 2012, Hu 2014, Tena 2014, Nielsen 2017, Jendoubi 2017, Lee 2018, Chumbley 2019, Zhou 2021, Kang 2020, Czarnetzki 2020
Nightmares	23/359	6.4	Dekock 2001, Remerand 2009, Nielsen 2017, Lee 2018, Zhou 2021, Kang 2020
Sedation or Drowsiness	49/298	16.4	Duale 2009,Tena 2014, Nielsen 2017, Chumbley 2019, Zhou 2021, Czarnetzki 2020
Trouble with vision	27/298	9.1	Remerand 2009, Spreng 2010, Bligen 2012, Tena 2014, Lee 2018
Hemodynamic side effects	13/104	12.5	Duale 2009,Mendola 2012, Tena 2014
Neurologic side effects	5/113	4.4	Mendola 2012, Tena 2014, Zhou 2021
Dizziness	22/74	29.7	Duale 2009, Chumbley 2019

Abbreviations: ADRs, adverse drug reactions; PONV, postoperative nausea and vomiting.