Pharmacological interventions for improving the postoperative pain intensity in adults after opioid-based anesthesia: a systematic review and network meta-analysis

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Abstract

Background: Opioid-induced hyperalgesia (OIH) is an adverse event after exposure to opioids which would increase pain intensity. The optimal drug to prevent these adverse effects is still unclear. We aimed to perform a network meta-analysis to compare different pharmacological interventions in preventing the increase in postoperative pain caused by OIH. Methods: Several databases were searched independently for randomized-controlled trials (RCTs) comparing different pharmacological interventions in preventing OIH. The primary outcomes were postoperative pain intensity at rest at 24h and the incidence of postoperative nausea and vomiting (PONV). Secondary outcomes included pain thresholds at 24h after surgery, cumulative morphine consumption over 24h, time to first postoperative analgesic requirement, and the incidence of shivering. Results: In all, 33 RCTs comprising 1711 patients were identified. In terms of postoperative pain intensity, amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine, and S (+)-ketamine plus methadone were associated with milder pain intensity than placebo, with amantadine ranked the most effective (SUCRA values =96.2). In terms of the incidence of PONV, intervene with dexmedetomidine or flurbiprofen plus dexmedetomidine means a lower incidence placebo and dexmedetomidine showed the best result (SUCRA values =90.3). Conclusions: Amantadine was identified as the best in postoperative pain intensity as well as non-inferior to placebo in the incidence of PONV. Dexmedetomidine was the only intervention that is superior to placebo in all indicators.

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Abstract

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a network meta-analysis to compare different pharmacological interventions in preventing the increase in postoperative pain caused by OIH.

Methods: Several databases were searched independently for randomized-controlled trials (RCTs) comparing different pharmacological interventions in preventing OIH. The primary outcomes were postoperative pain intensity at rest at 24h and the incidence of postoperative nausea and vomiting (PONV). Secondary outcomes included pain thresholds at 24h after surgery, cumulative morphine consumption over 24h, time to first postoperative analgesic requirement, and the incidence of shivering.

Results: In all, 33 RCTs comprising 1711 patients were identified. In terms of postoperative pain intensity, amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine, and S (+)-ketamine plus methadone were associated with milder pain intensity than placebo, with amantadine ranked the most effective (SUCRA values =96.2). In terms of the incidence of PONV, intervene with dexmedetomidine or flurbiprofen plus dexmedetomidine means a lower incidence placebo and dexmedetomidine showed the best result (SUCRA values =90.3).

Conclusions : Amantadine was identified as the best in postoperative pain intensity as well as non-inferior to placebo in the incidence of PONV. Dexmedetomidine was the only intervention that is superior to placebo in all indicators.

Clinical trial registration: CRD42021225361 (PROSPERO).

Keywords: opioid-induced hyperalgesia; pharmacological interventions; general anesthesia; network meta-analysis; postoperative pain; postoperative nausea and vomiting

What is Already Known about this Subject

Opioid-induced hyperalgesia is highly prevalent in surgery patients, contributing to many undesirable events, such as more severe postoperative pain, extra opioids demand, high incidence of side effects, etc.

Multiple medications with different kinds of mechanisms were proved to prevent the increase in postoperative pain caused by OIH in clinical routines. However, the comparative effects of different kinds of pharmacologic interventions are urgently needed for a better guideline for individualized anesthesia protocol.

What this Study Adds

Amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine, and S (+)-ketamine plus methadone show statistically significantly milder pain intensity than placebo. Amantadine ranked the most effective while failed to demonstrate superiority in the incidence of postoperative nausea and vomiting when compared to placebo.

Dexmedetomidine is not the best but the most well-balanced choice for it is the only intervention that is superior to placebo in all indicators.

1. Introduction

As a component of balanced anesthesia, opioids are the main analgesics used during the perioperative period. Timely opioid administration during surgery lessens the requirement of general anesthetics, leading to faster recovery[1], and post-surgery patient-controlled opioid analgesia enhances patient comfort and satisfaction[2]. However, a reduction in nociceptive thresholds and a paradoxical increase in pain after exposure to opioids during surgery[3], referred to as opioid-induced hyperalgesia (OIH), had been demonstrated in animal models[4], human volunteers[5] and surgical patients[6]. Suffering more severe postoperative pain due to nociceptive sensitization may render patients obliged to accept more opioids, unless alternatives are considered[7]. Also, opioid-related adverse drug events have been associated with increased inpatient mortality, prolonged length of stay and high cost of hospitalization[8].

Although the precise molecular mechanism underlying OIH remains unclear, it is commonly suggested to be triggered by neuroplastic altering in the peripheral and central nervous systems[9]. Previous electrophysiolog-

ical studies using slices of rat spinal cord revealed a cellular mechanism concerning the rapid and persistent up-regulation of N-methyl-D-aspartate (NMDA) receptor function by clinically relevant concentrations of remifentanil through μ- and δ-opioid receptor pathway; mirroring the role of pathologic activation of NMDA receptor in the development of OIH[10, 11]. Therefore, to prevent the development of OIH, clinical explorers mainly followed the idea of manipulating the glutaminergic system through modulation of the NMDA receptor, either directly or indirectly. In light of these, multiple drugs have been shown the potential to attenuate the pain intensity and reduce the demand for postoperative analgesics, such as ketamine, dexmedetomidine and flurbiprofen[12]. Regretfully, limited by small sample sizes and various medication dosages in existing literature, clinical routines are still controversial about the optimal intervention strategy to prevent the increase in postoperative pain intensity due to OIH[13]. Importantly, comparative efficacy of diverse drugs of the prevention and comparisons involving non-NMDA receptor antagonists are urgently needed. As such, the comparative effects of different kinds of medications remains undetermined.

Given these uncertainties, we performed a systematic review and network meta-analysis evaluating different pharmacologic interventions for preventing the increase in postoperative pain intensity caused by OIH in adults after general anesthesia, with the hope to better guide clinical practice for more individualized general anesthesia protocol.

2. Methods

This network meta-analysis was registered on*https://www.crd.york.ac.uk/PROSPERO*. The registration number is: CRD42021225361.

2.1. Search strategy and selection criteria

According to PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses[14], MEDLINE, Embase, The Cochrane Central Register of Controlled Trials and Web of Science were searched with language restrictions in English. The search strategy combined free text words and MeSH terms to maximize the results yielded. Search terms were used as follows: (1) opioid, (2) hyperalgesia and (3) magnesium, naloxone, buprenorphine, ketamine, dexmedetomidine, butorphanol, propofol, flurbiprofen, morphine, methadone, lornoxicam, nitrous oxide, parecoxib, clonidine, amantadine, nalbuphine, paracetamol, pregabalin, nefopam, acetazolamide.

2.2. Selection of studies and data extraction

Two investigators (WJX and HFC) reviewed all titles, abstracts, and then full texts sequentially. Finally, eligible trials were determined and eligibility, quality, and outcomes data were retrieved independently. Disagreements on eligibility between two reviewers were resolved via mutual discussion, when needed, a third reviewer (YCL) was requested for final decision. Relevant data were extracted from eligible literature with a standard extraction formula with subsequent cross-checking.

Data retrieved included: (1) first author, year of publication, study location, study design, sample size, gender, age, ASA status, types of surgery, premedication, anesthesia maintenance, intervention description, control description, dose of opioids, postoperative analgesic strategines, and (2) pain intensity in the form of the various pain scores during the 0 to 24 postoperative hours, pain threshold or normalized area of hyperalgesia during the 0 to 48 postoperative hours, cumulative morphine consumption at 24h after surgery, time to first rescue analgesic, and incidence of postoperative opioid-related side-effects, such as postoperative nausea and vomiting (PONV), shivering, dizziness and hypotension. Dichotomous data were extracted as the number of patients (%). Continuous data were extracted in the form of mean ± standard deviations (SDs).

When the target data in the article were incomplete, we attempted to contact the author via e-mail twice, but no responses were received. When the standard deviation was missing, range and median estimation[15] were used for the conversion.

2.3. Type of outcome measures

Our primary outcomes were postoperative pain intensity at rest at 24h and the incidence of PONV. Postoperative pain intensity was evaluated by pain scores scaling from 0 (no pain) to 10 (worst possible pain). Intensity scores reported on a visual analogue scale (VAS: 0: no pain to 100: worst possible pain) were transformed to a 0-to-10 scale. PONV, the most common adverse event with an incidence as high as 80% in high-risk cohorts[16], contribute to the highly distressing experience and severe patient dissatisfaction[17, 18].

Our secondary outcomes include pain thresholds at 24h after surgery, cumulative morphine consumption over the 24h, the time to first postoperative analgesic requirement and the incidence of shivering.

2.4. Assessment of risk of bias

Two investigators (WJX and HFC) independently read the eligible articles and assessed their methodological validity using the Cochrane Collaboration's tool of Review Manager (RevMan version 5.4, Cochrane Community, London, England) software for assessing the risk of bias in randomized-controlled trials (RCTs) and resolved disagreements through discussion[19]. The tool consists of seven items describing random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. A judgment of high, low, or unclear risk of material bias for each item were assigned.

2.5. Statistical analysis

The odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes and standardized mean differences (SMDs) or mean differences (MDs) with 95% CIs for continuous outcomes were calculated.

This network meta-analysis was performed within a frequentist framework using the STATA 16.0 (StataCorp, Texas, USA) command 'mvmeta'[20]. Firstly, the network geometry plot for each outcome was established, which provided a visual and concise description between pairs of interventions[21]. Secondly, statistical consistency was evaluated by the node-splitting method and loop inconsistency model. P-value [?] 0.05 or the 95% CI for each closed-loop contained 0 means direct comparison and indirect comparison were considered consistent[22]. Thirdly, a comparison-adjusted funnel plot was used to evaluate publication bias. A symmetrical graph indicated a low influence of publication bias and an asymmetric graph meant possible publication bias. Finally, the forest plot was constructed to report the results for the mixed comparison between interventions and placebo, and the league table was performed to illustrate all head-to-head comparisons. We assumed that 95% CIs not containing 0 were considered statistically significant for SMDs or MDs, and those not containing 1 were considered statistically significant for ORs. The two-dimensional graph is presented to visualize the comprehensive comparisons of drugs to placebo. The point which lies to the lower-left portion of the coordinate system and does not intersect with the dark grey dashed line indicates that this pharmacological intervention is superior to placebo in terms of both postoperative pain intensity and the incidence of PONV. Additionally, the ranking probabilities were estimated for all interventions of being at each possible rank of each intervention[21]. By using the ranking probabilities, the treatment hierarchy was summarized and reported as the surface under the cumulative ranking curve (SUCRA)[21]. The larger the SUCRA value is, the better are the rank of the treatment for outcomes.

2.6. Inclusion and exclusion criteria

RCTs that matched the following criteria were considered eligible: (1) anesthesia was induced and maintained with opioids; (2) pharmacological interventions were given to patients at any dose before or during the operative period; and (3) a comparison was conducted between pharmacological interventions and placebo.

Articles were excluded based on the following considerations: (1) combination with regional nerve block during the anesthesia induction or maintenance period, and (2) data from healthy volunteer or children's studies, abstracts, letters, or reviews.

3. Results

3.1. Study selection and characteristics

We identified a total of 1602 potentially relevant studies. After adjusting for duplicates and reviewing title/abstract, the remaining 39 full-text manuscripts were reviewed. Consistent with the study protocol, 6 trials were excluded due to lack of outcome of interest (n=4) and combination with regional nerve block (n=2). In total, 33 RCTs (comprising 1711 patients) were identified. The process of literature selection is listed in **Figure. 1** .

3.2. Risk of bias assessment

The details for the risk of bias assessment are displayed in**Appendix2** . The random sequence generation was specified in 24 trials (72.7%). 18 trials (54.5%) reported the allocation concealment but one trial has high risk of bias for it. Only one trial lack of blinding methods. Selective reporting was identified in 8 trials (24.2%). No trials were found in high risk of bias for incomplete outcome data addressed and other bias. Overall, the quality of the included studies was considered relatively high.

3.3. Study characteristics and network geometry

In total, 960 subjects were randomly assigned to pharmacological intervention and 751 to placebo. The included RCTs were published from 2002 to 2020 and involved orthopedic(n=2), urinary(n=4), abdominal (n=10), gynecologic (n=9), thyroid surgery (n=5), thoracic(n=1) and ear-nose-throat surgery (n=2). The basic characteristics of enrolled studies are described in **Table 1** .

The network geometry plot (**Figure 2**) shows the network of eligible comparisons for postoperative pain intensity at rest at 24h (A) and the incidence of PONV (B). Of the 33 enrolled studies, 28 studies involving 20 treatments reported the postoperative pain intensity at rest at 24h after surgery, and 27 studies involving 17 treatments reported the incidence of PONV. All treatments had at least one placebo-controlled trial. Each treatment was represented by a node and linked by an edge when a direct comparison was performed. More sample sizes, bigger node. Similarly, more studies involved, thicker edge.

3.4. Results of primary outcomes

The forest plot (**Figure 3**) reveals the network meta-analysis' results for the primary outcomes. In terms of postoperative pain intensity, amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine and S (+)-ketamine plus methadone were associated with milder pain intensity than placebo, with SMDs ranging between -3.06 (95% CI: -4.67, -1.45) for amantadine and -0.62 (95% CI: -1.23, -0.01) for magnesium sulphate. In terms of the incidence of PONV, intervene with dexmedetomidine (OR=0.25, 95% CI: 0.11, 0.54) or flurbiprofen plus dexmedetomidine (OR=0.27, 95% CI: 0.08, 0.87) means lower incidence of PONV than placebo.

The league table (**Figure 4**) illustrates head-to-head comparisons for postoperative pain intensity (lower left portion) and the incidence of PONV (upper right portion) of all pharmacological intervention strategies and placebo. The pairwise comparison outcome are expressed as SMD (95%CI) and OR (95%CI) respectively. The two-dimensional graph (**Figure 5**) shows that only dexmedetomidine and flurbiprofen plus dexmedetomidine are superior to placebo in terms of both postoperative pain intensity and the incidence of PONV.

In the ranking probability plot (**Appendix4 Figure 4**), for postoperative pain intensity, amantadine seemed to be the best agent among all 20 treatments whose SUCRA values was 96.2. In terms of the incidence of PONV, it was proved that dexmedetomidine appeared to be the best option among all 17 treatments for PONV with an SUCRA value of 90.3.

3.5. Results of secondary outcomes

3.5.1 Pain thresholds at 24h after surgery

A total of 10 studies involved 11 interventions reported pain thresholds at 24h after surgery (measured by any type of QST and in g) (**Appendix4 Figure 4.1.1**). Compared with placebo, butorphanol (SMD=2.43, 95% CI:1.65, 3.22), magnesium sulphate (SMD=1.01, 95% CI:0.14, 1.88) and dexmedetomidine (SMD=1.01,

95% CI:0.14, 1.88) mean higher pain thresholds at 24h after surgery (**Appendix4 Figure 4.1.2**). The league table (**Appendix4 Figure 4.1.3**) illustrates the results of each intervention compared to each other. In the ranking probability plot (**Appendix4 Figure 4.1.4**), flurbiprofen plus dexmedetomidine was ranked highest among 11 interventions whose SUCRA values was 98.1.

3.5.2 Cumulative morphine consumption over the 24h

A total of 14 studies involved 11 interventions reported cumulative morphine consumption over the 24h (**Appendix4 Figure 4.2.1**). Compared with placebo, flurbiprofen (SMD= -17.36, 95% CI: -22.13, -12.59) and dexmedetomidine (SMD= -11.83, 95% CI: -17.77, -5.90) mean more morphine consumption at 24h after surgery (**Appendix4 Figure 4.2.2**). The league table (**Appendix4 Figure 4.2.3**) illustrates the results of each intervention compared to each other. In the ranking probability plot (**Appendix4 Figure 4.2.4**), flurbiprofen plus dexmedetomidine was ranked highest among 11 interventions whose SUCRA values was 100.

3.5.3 The time to first postoperative analgesic requirement

A total of 14 studies involved 13 interventions reported the time to first postoperative analgesic requirement (**Appendix4 Figure 4.3.1**). Compared with placebo, flurbiprofen plus dexmedetomidine (MD=43.05, 95% CI: 28.49, 57.60), adenosine (MD=26.90, 95% CI:11.98, 41.82), magnesium sulphate (MD=23.29, 95% CI:12.27, 34.30) and dexmedetomidine (MD=11.39, 95% CI:0.93, 21.84) mean longer time to require first postoperative analgesic (Appendix5 Figure 5.3.2). The league table (**Appendix4 Figure 4.3.3**) illustrates the results of each intervention compared to each other. In the ranking probability plot (**Appendix4 Figure 4.3.4**), flurbiprofen plus dexmedetomidine was ranked highest among 13 interventions whose SUCRA values was 98.5.

3.5.4 Incidence of Shivering

A total of 9 studies involved 9 interventions reported the incidence of shivering (**Appendix4 Figure 4.4.1**). Compared with placebo, dexmedetomidine (OR=0.16, 95% CI:0.06, 0.43), flurbiprofen plus dexmedetomidine (OR =0.12, 95% CI:0.03, 0.49), magnesium sulphate (OR =0.07, 95% CI:0.02, 0.36) and S(+)-ketamine (OR =0.05, 95% CI:0.00, 0.99) mean lower incidence of shivering (**Appendix4 Figure 4.4.2**). The league table (**Appendix4 Figure 4.4.3**) illustrates the results of each intervention compared to each other. In the ranking probability plot (**Appendix4 Figure 4.4.4**), S(+)-ketamine was ranked highest among 9 interventions whose SUCRA values was 82.0.

4. Discussion

Since the morbidity concealment, complex pathogenesis and treatment uncertainty for OIH, the best strategy is to prevent its occurrence. This is the first systematic review and network meta-analysis to compare different pharmacological interventions and explore the best strategy for preventing the increase in postoperative pain due to OIH in adults after general anesthesia. Twenty treatments were compared and analyzed from following aspects: pain intensity, opioid-related adverse effects, pain threshold, time to first rescue analgesic and morphine consumption. We found that no such perfect drug that ranked the best in all indicators. This seems to highlight the importance of individualized treatment selection and multimodal approach.

Our results reveal that amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine and S (+)-ketamine plus methadone all show their potential to prevent the increase of postoperative pain intensity, and amantadine seems to be the best option among all 20 interventions included in the analysis. Although the mechanisms for the development of OIH are not completely understood, preclinical models implicate the glutaminergic system and pathologic activation of NMDA receptors in the development of central sensitization[23-25]. Among these effective interventions, amantadine, magnesium sulphate, methadone and S (+)-ketamine are known to be antagonists of NMDA receptor, where its primary effects are thought to occur. Wu L et al. reported that perioperative administration of NMDA receptor antagonists could effectively prevent the increase of postoperative pain intensity and morphine consumption[13]. However, our works draw a partially consistent

conclusion that amantadine may be the best option but either ketamine or S (+)-ketamine fails to show significant superiority in deterring the raise of postoperative pain intensity. Possible factors responsible for this discrepancy could be that the conclusion of Wu L et al.'s needs an extraordinary prudent interpretation due to a high heterogeneity even after subgroup analysis; the studies involved were small (only 14 studies included 3 drugs which directly act on NMDA receptors), with possible overestimation of the risk of Type II statistical error. On the other hand, the effect of an intervention may be affected by others to different extents in NMA. Thus, we suggest that future studies should consider confirming our meta-analysis results.

Ibuprofen, flurbiprofen and parecoxib belong to non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used worldwide with potent anti-inflammatory, analgesic and antipyretic activity. It is well known that one of their main mechanisms of action is the inhibition of cyclo-oxygenase (COX), the enzyme involved in biosynthesing prostaglandins and thromboxane[26]. Interestingly, prostaglandins have been proved to modulate nociceptive processing[27] and stimulate the release of the excitatory amino acid glutamate in spinal cord dorsal horns[28]. Furthermore, the antagonize function of COX inhibitors to NMDA receptor in central nervous system also has been revealed[29, 30]. Clinical study or meta-analysis about the effect of COX inhibitors on OIH is still lacking although it has been proved in animal models[31, 32]and human volunteers[33, 34].

It has been indicated that pronociceptive effects caused by opioids result from the central and peripheral nervous system sensitization, which is similar to the mechanism of hyperalgesia associated with nerve injury[35]. Pregabalin is a 3-substituted analogue of γ-aminobutyric acid and treatment of neuropathic pain[36] which shares a close structure and similar mechanism of action with gabapentin but has fewer side effects[37]. The effect of pregabalin to reduce hyperalgesia and allodynia in human volunteers[38]and rat models[39] are acknowledged. However, A J Lederer et al. reviewed the effects of pregabalin on OIH and concluded that, while strongly supported by theoretical considerations, the recommendation as a clinical routine still lack of clinical evidence[40]. Stoicia et al. also draw a similar conclusion that the application of gabapentin in mitigating OIH still needs support from large-scale standardized patient studies[41].

Dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties[42]. Its anti-hyperalgesia effects are closely related to NMDA receptors. Animal experiments reveal that dexmedetomidine modulates spinal cord NMDA receptors activation via suppressing tyrosine phosphorylation of NR2B in the superficial spinal cord, which was found up-regulated when remifentanil-induced hyperalgesia happens[43], [44]. Likewise, its anti-hyperalgesia effect in clinical routine requires more evaluation of further studies.

The results of this meta-analysis also revealed that, compared with placebo, dexmedetomidine and flurbiprofen plus dexmedetomidine are the only two strategies that are associated with a lower incidence of PONV. It is interesting to note that flurbiprofen alone has no superior effect. This seems to infer that it is dexmedetomidine plays a significant role in preventing PONV. This finding is in line with past studies[45-47]. Jin S et al.[46] investigated the effect of dexmedetomidine on PONV on patients during general anesthesia and reported that dexmedetomidine (irrespective of administration mode) had a significantly lower incidence of PONV than placebo. It was through that this added antiemetic effect may be explained by α2 agonists through inhibition of catecholamine by parasympathetic tone, although the biologic basis remains obscure. Alternatively, consumption of intraoperative anesthetics and opioids, which have been considered risk factors for PONV[48], may be reduced with the use of dexmedetomidine.

Consideration of treatment risk/benefit ratio is an important factor in clinical decision-making. Our results show that, although there is the best option in every index, dexmedetomidine is the only pharmacological intervention that demonstrated superiority to placebo in all indicators. In addition, the multifarious benefit of dexmedetomidine in improving quality of emergence from anesthesia[49], reducing postoperative delirium incidence[50], enhancing recovery after surgery[51] and organ-protective effects[52] has been already fully proved and widely accepted. It is difficult to deny that dexmedetomidine is an attractive anesthetic adjuvant notwithstanding the side effects of hypotension and bradycardia[53].

This network meta-analysis had several possible limitations. First, since multiple interventions were included in the analysis, several had data from only one study and therefore a relatively small sample size, which may have led to possible bias and overestimation of treatment effect. Second, some non-pharmacological interventions were not involved to compare, such as gradual withdrawal of remifentanil[54], opioid rotation[55] and combination with a regional nerve block[56]. Third, variation was presented in the opioid dosage, timing, administration regimens, surgery duration and maintenance of anesthesia. These disparities restrict the amount of data that can be pooled in meta-analysis which present major challenges in interpretation and applicability of the results. Overall, this systematic review and network meta-analysis provides the best summary of the comparative effect of different pharmacological interventions on improving the postoperative pain intensity caused by OIH.

5. Conclusions

In summary, meta-analysis of the eligible RCTs suggests that amantadine was identified as the best in preventing the increase in postoperative pain as well as non-inferior to placebo in the incidence of PONV and dexmedetomidine was the only intervention that is superior to placebo in all indicators.

Abbreviations

OIH: Opioid-induced Hyperalgesia

RCT: Randomized-controlled Trial

PONV: Postoperative Nausea and Vomiting

NMDA: N-methyl-D-aspartate

SD: Standard Deviation

VAS: Visual Analogue Scale

OR: Odds Ratio

CI: Confidence Interval

SMD: Standardized Mean Difference

MD: Mean Difference

SUCRA: Surface Under the Cumulative Ranking Curve

NSAID: Non-steroidal Anti-inflammatory Drug

COX: Cyclo-oxygenase

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Author's contributions

WJX: This author was involved in study design, literature search, results screening, data extraction, statistical analysis and drafting the manuscript.

YCL: This author was involved in study design, results screening, data extraction and article revision.

SYW: This author was involved in study design, literature search and article revision.

HFC: This author was involved in study design, results screening, data extraction and article revision.

JSH: This author was involved in study design, literature search and article revision.

CFF: This author was involved in article revision.

WL: This author was involved in conducting the study and article revision.

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Tables and figures

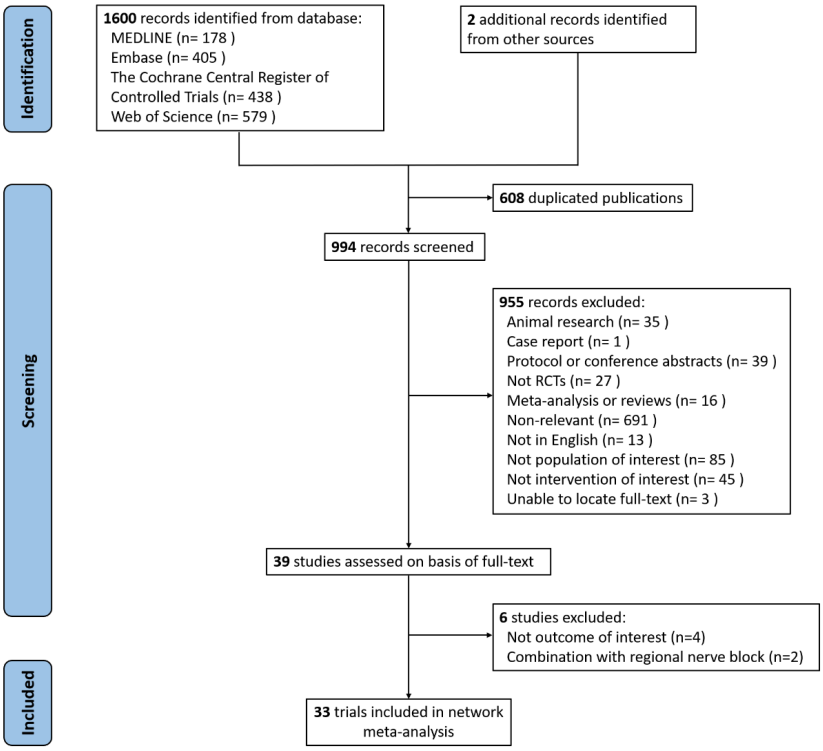


Figure 1. Flow chart of search strategy to identify the eligible randomized controlled trials.

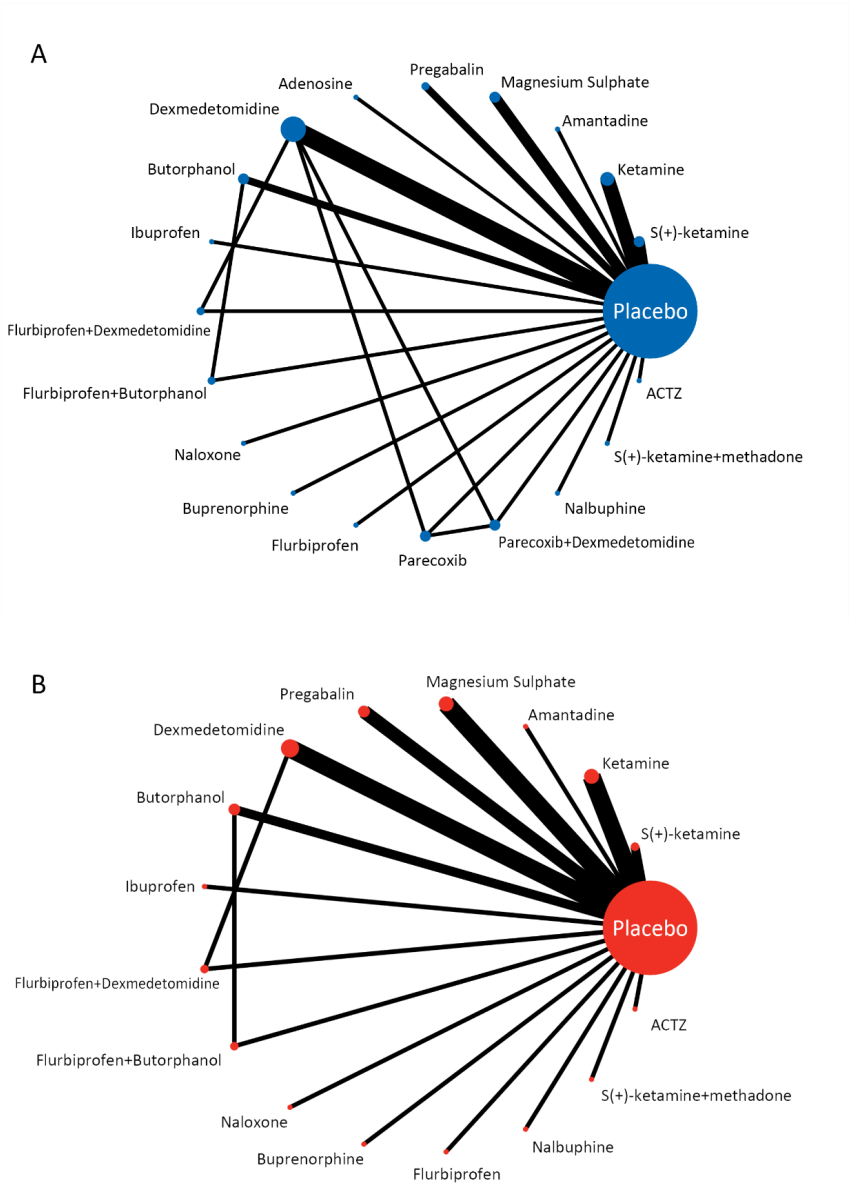


Figure 2. Network meta-analysis of eligible comparisons for postoperative pain intensity at rest at 24h (A) and the incidence of PONV (B).

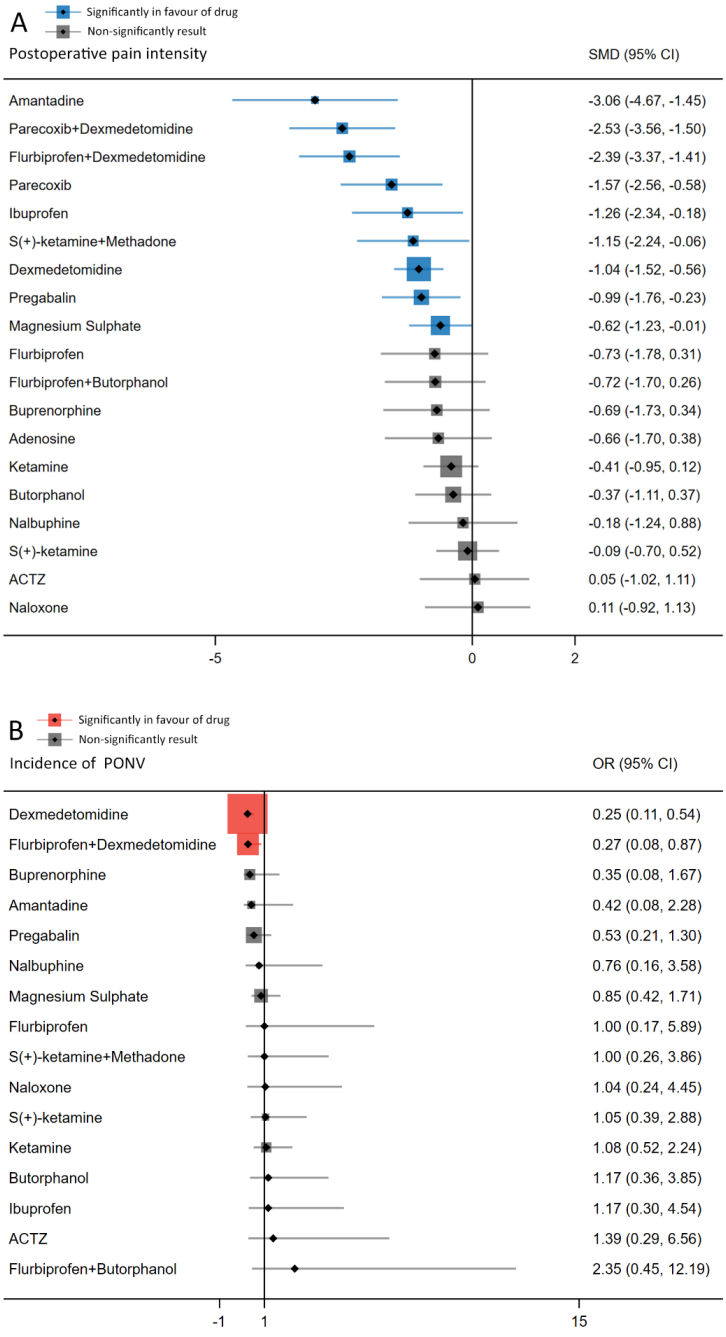


Figure 3. Forest plots of network meta-analysis of all trials for postoperative pain intensity at rest at 24h (A) and the incidence of PONV (B)

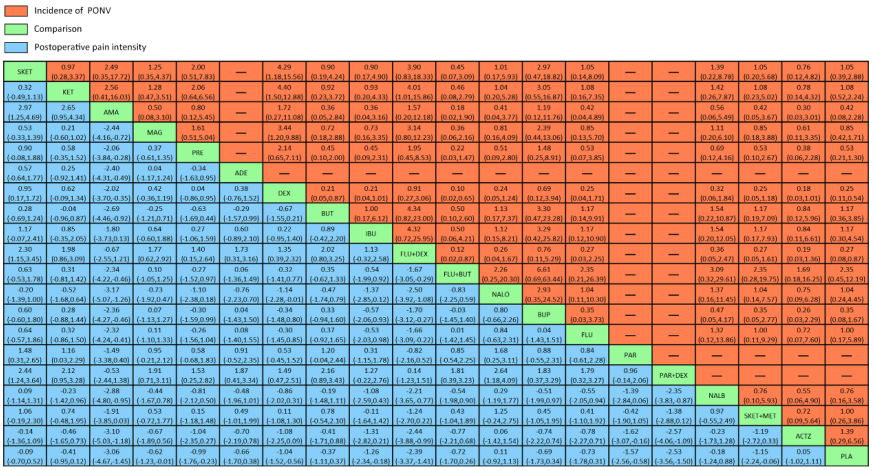


Figure4. League table of head-to-head comparisons for postoperative pain intensity at rest at 24h and the incidence of PONV of all pharmacological interventions and placebo.

PLA=placebo. SKET=S (+)-ketamine. KET= ketamine. AMA=amantadine. MAG=magnesium sulphate. PRE=pregabalin. ADE=adenosine. DEX=dexmedetomidine. BUT=butorphanol. IBU=ibuprofen. FLU+DEX=flurbiprofen+dexmedetomidine. FLU+BUT=flurbiprofen+butorphanol. NALO=naloxone. BUP=buprenorphine. FLU=flurbiprofen. PAR=parecoxib. PAR+DEX=parecoxib+dexmedetomidine. NALB =nalbuphine. SKET+MET =S (+)-ketamine+methadone.

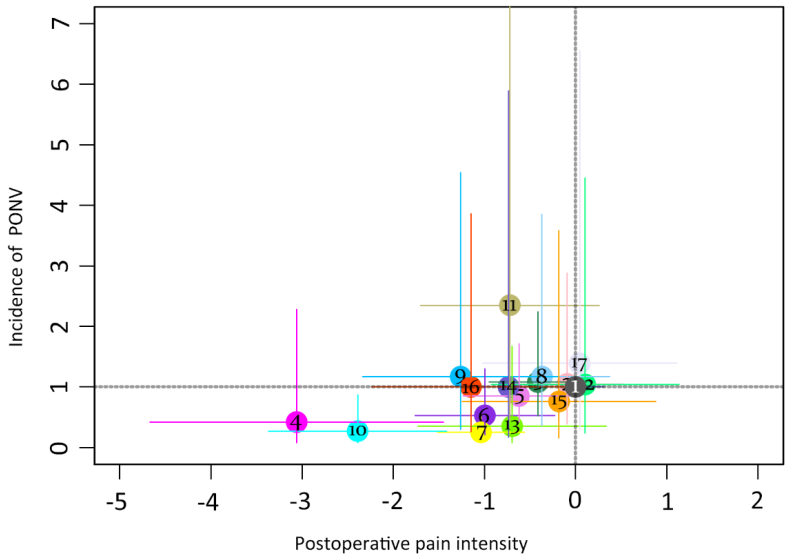


Figure 5. Two-dimensional graphs for postoperative pain intensity at rest at 24h and the incidence of PONV.

1=placebo; 2=S (+)-ketamine; 3=ketamine; 4=amantadine; 5=magnesium sulphate; 6=pregabalin; 7=dexmedetomidine; 8=butorphanol; 9=ibuprofen; 10=flurbiprofen+dexmedetomidine; 11=flur-

biprofen+butorphanol; 12=naloxone; 13=buprenorphine; 14=flurbiprofen; 15=nalbuphine; 16=S(+)-ketamine+methadone; 17=ACTZ.

Table 1. Characteristics of studies

Study (author/year)	Study (author/year)	Country	Sample Size (intervention/control)	Sample Size (intervention/control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery
W. Jaksch 2002	Austria	Austria	Austria	15/15	15/15	31.5	NA	S(+)-ketamine 0. 5 mg/kg IV + 2.0 μg/kg·min continuous infusion	arthroscopic anterior cruciate ligament repair
B. Guignard 2002	France	France	France	25/25	14/16	62.5	9/35/7	ketamine 0. 15 mg/kg IV + 2.0 μg/kg·min continuous infusion	open colorectal surgery
A. Sahin 2004	Turkey	Turkey	Turkey	17/16	16/17	47.4	NA	ketamine 0. 5 mg/kg IV	Lumbar disk operation
A. C. Van Elstraete 2004	France	France	France	20/20	20/20	29.0	NA	ketamine 0. 5 mg/kg IV + 2.0 μg/kg·min continuous infusion	elective electrodissection tonsillectom

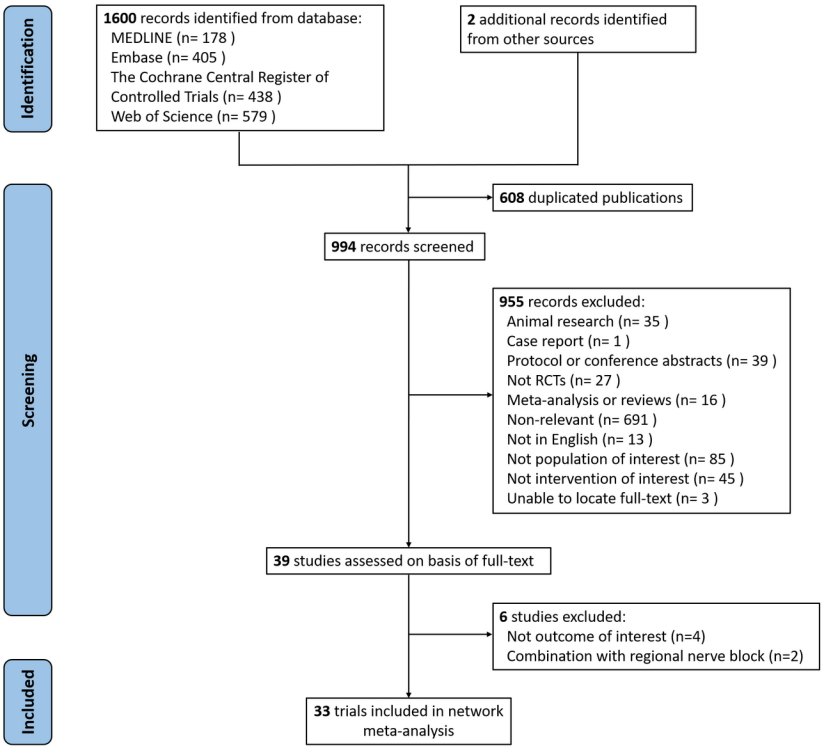
Study (author/year)	Study (author/year)	Country	Sample Size (intervention/control)	Sample Size (intervention/control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery
D. G. Snijdelaar 2004	Canada	Canada	Canada	11/10	21/0	60.0	8/12/1	amantadine 200mg orally at night and at 1h before surgery and 100mg at 8, 20, and 32 h after surgery	radical prostatecton
V. Joly 2005	France	France	France	24/25	18/32	57.5	21/22/7	ketamine 0. 5 mg/kg IV + 5.0 μg/kg· min continuous infusion+ 2.0 μg/kg· min for 48h after surgery	abdominal surgery
J. H. Ryu 2008	Korea	Korea	Korea	25/25	0/50	42.4	37/13/0	magnesium sulphate 50 mg/kg IV + 15 mg/kg· h continuous infusion	total abdominal hysterectom
S. Kaya 2009	Turkey	Turkey	Turkey	20/20	NA	50	NA	magnesium sulphate 30 mg/kg IV + 500 mg/ h continuous infusion	elective abdominal hysterectom

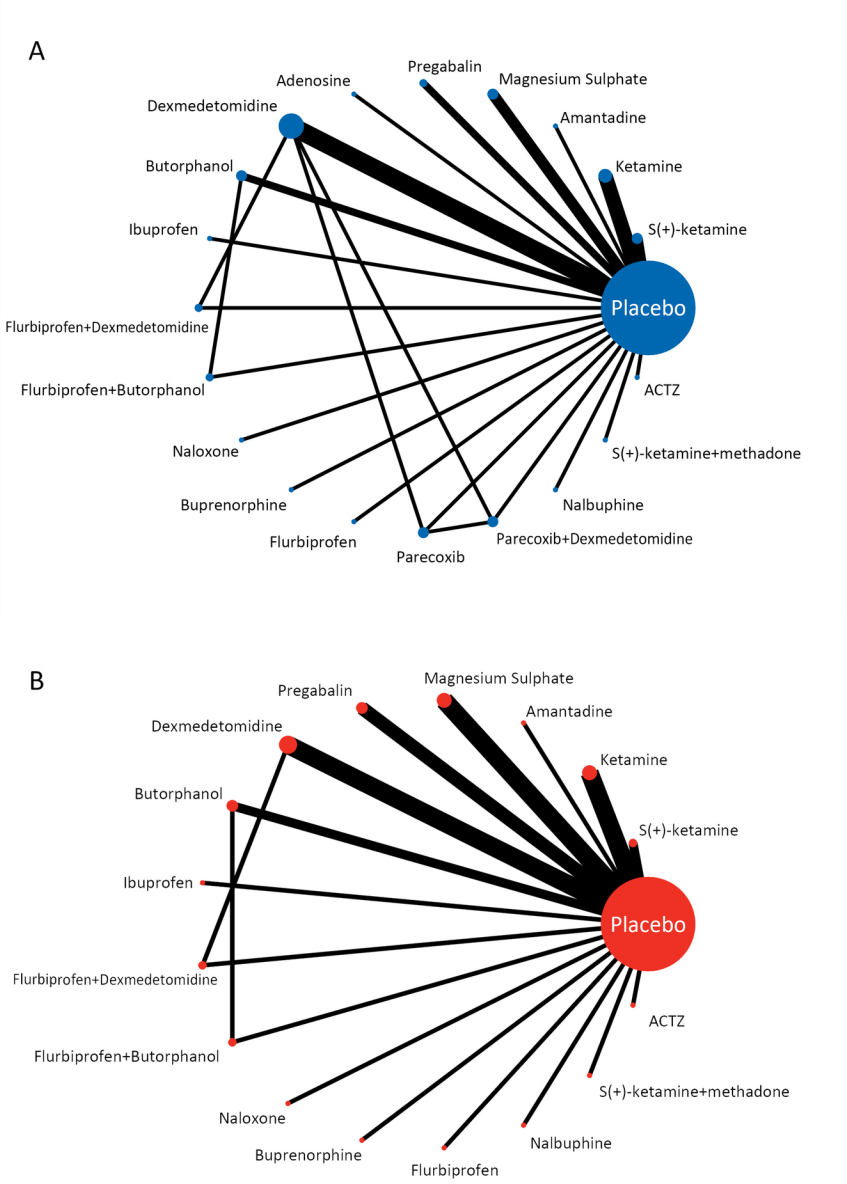
Study (author/year)	Study (author/year)	Country	Sample Size (intervention/control)	Sample Size (intervention/control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery
H. R. Jo 2011	Korea	Korea	Korea	20/20	0/40	46.1	34/6/0	pregabalin 150 mg orally	non-malignant total abdominal hysterectomy
C. Lee 2011	Korea	Korea	Korea	25/25	50/0	63.4	NA	magnesium sulfate 80 mg/kg IV	robot-assisted laparoscopic prostatectomy
C. Lee* 2011	Korea	Korea	Korea	30/30	38/22	38.2	NA	adenosine 80 μg/kg· min continuous infusion	tonsillectomy
J. W. Song 2011	Korea	Korea	Korea	28/28	11/45	46.0	NA	magnesium sulphate 30 mg/kg IV + 10 mg/kg· h continuous infusion	thyroidectomy
H. Bornemann-Cimenti 2012	Germany	Germany	Germany	13/13	11/15	56.9	NA	pregabalin 300 mg orally	elective transperitoneal nephr
C. Lee 2013	Korea	Korea	Korea	28/29	0/57	48.7	NA	dexmedetomidine 1.0 μg/kg IV + 0.7 μg/kg· h continuous infusion	laparoscopic assisted vaginal hysterectomy
C. Lee* 2013	Korea	Korea	Korea	31/29	31/29	50.7	NA	pregabalin 300 mg orally	laparoendoscopic single-site urologic surgery
S. Treskatsch 2014	Germany	Germany	Germany	16/17	8/25	66	NA	amantadine 200 mg/500 ml solution	intra-abdominal surgery

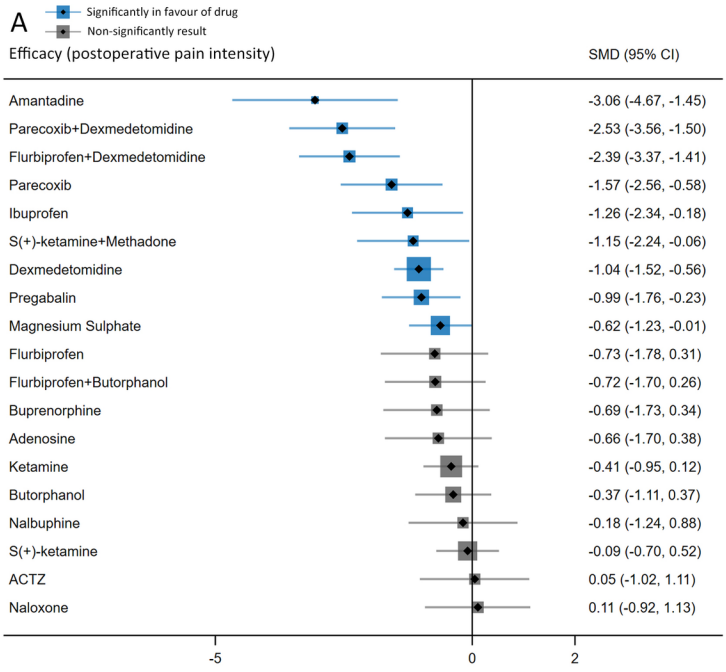
Study (author/year)	Study (author/year)	Country	Sample Size (intervention/control)	Sample Size (intervention/control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery
E. Choi 2015	Korea	Korea	Korea	25/25	0/50	44.1	NA	ketamine 0. 5 mg/kg IV + 5.0 μg/kg· min continuous infusion	elective laparoscopic gynecological surgery
P. C. Leal 2015	Brazil	Brazil	Brazil	28/28	9/47	44.6	28/28/0	ketamine 5.0 μg/kg· min continuous infusion	Laparoscopic cholecystect
H. Bornemann-Cimenti 2016	Austria	Austria	Austria	37/19	31/25	60.5	4/24/28	S(+)-ketamine 0. 25 mg/kg IV + 0.125 mg/kg· h continuous infusion or S(+)-ketamine 0.015 mg/kg· h continuous infusion	elective major abdominal surgery
M. Kong 2016	China	China	China	25/25	32/18	51.5	NA	butorphanol 0. 2 μg/kg IV + 0.02 μg/kg· min continuous infusion	laparoscopic cholecystect
C.-H. Koo 2016	Korea	Korea	Korea	27/26	33/20	63.7	NA	ibuprofen 800mg IV over 30 minutes	pancreaticod

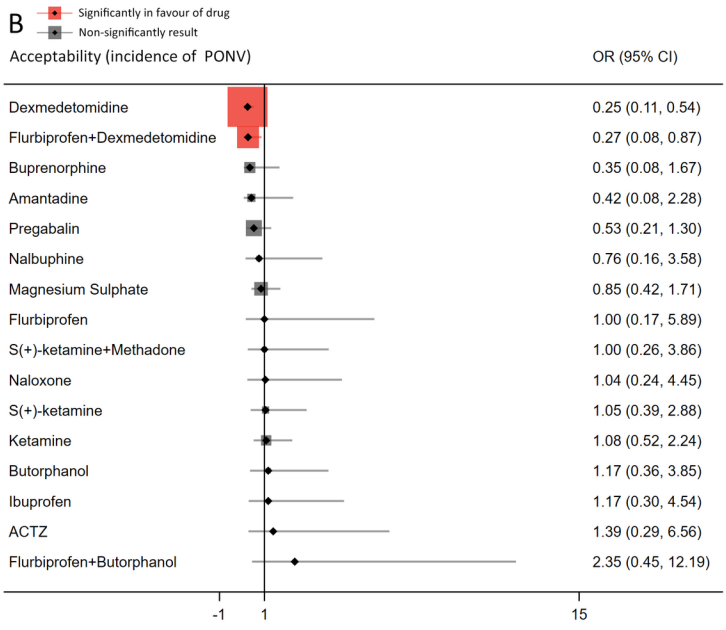
Study (author/year)	Study (author/year)	Country	Sample Size (intervention/control)	Sample Size (intervention/control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery
Z. Yu 2016	China	China	China	57/29	0/86	46.1	NA	dexmedetomidine 0.5 μg/kg IV + 0.6 μg/kg· h continuous infusion or flurbiprofen 1.5 mg/kg combination with dexmedetomidine infusion	laparoscopic assisted vaginal hysterectomy
L. Zhang 2016	China	China	China	56/28	0/84	46.0	67/NA/NA	butorphanol 20 μg/kg IV or butorphanol 20 μg/kg combined with flurbiprofen 0.5 mg/kg	elective laparoscopic gynaecological surgery
C. H. Koo 2017	Korea	Korea	Korea	30/31	20/41	47.0	50/11/0	naloxone 0.05 μg/kg· min continuous infusion	thyroid surgery
M. Mercieri 2017	Italy	Italy	Italy	31/32	34/29	64.5	6/42/15	buprenorphine 25 μg/h continuous infusion	lateral thora
L. Zhang 2017	China	China	China	28/28	0/56	44.8	45/11/0	flurbiprofen 1.0 mg/kg IV	elective laparoscopic gynecologic surgery
H. Qiu 2018	China	China	China	32/16	24/24	NA	NA	dexmedetomidine 0.2 μg/kg IV or 0.6 μg/kg	thyroidecton

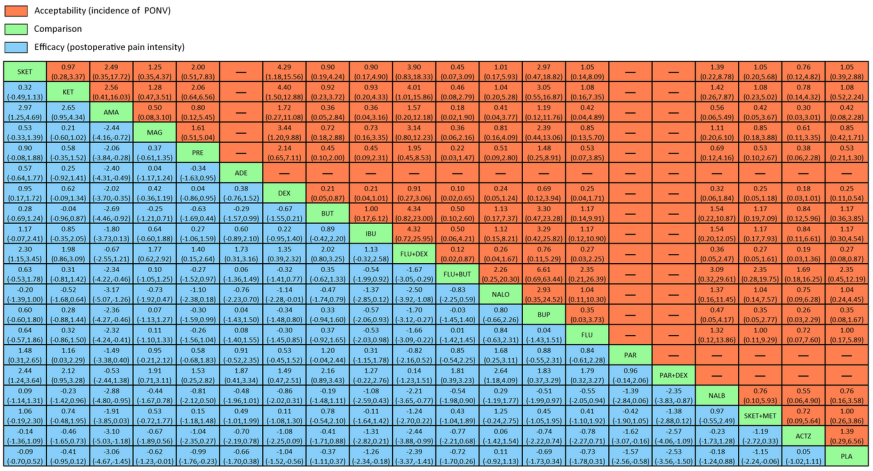
Study (author/year)	Study (author/year)	Country	Sample Size (intervention/control)	Sample Size (intervention/control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery
B. Sng 2018	Singapore	Singapore	Singapore	45/44	0/89	48.1	NA	S(+)-ketamine 0. 25 mg/kg IV	open abdominal hysterectom
X. Du 2019	China	China	China	60/20	NA	NA	NA	parecoxib 40 mg IV or dexmedetomidine 0.6 µg/kg· h continuous infusion or both	laparoscopic cholecystect
R. Gutiérrez 2019	Chile	Chile	Chile	23/24	4/43	44.5	18/29/0	ACTZ 250mg IV	total thyroidectomy without neck dissection
J. Hu 2020	China	China	China	24/24	11/37	50.2	24/24/0	nalbuphine 0. 2 mg/kg IV	laparoscopic cholecystect
E. Tognoli 2020	Italy	Italy	Italy	24/24	29/19	58.6	19/24/5	S(+)-ketamine 5.0 and 2.5 and 2µg/kg· min continuous infusion + methadone 2.0 mg IV	open laparotomy for anterior resection of the rectum
Z. Wu 2020	China	China	China	60/29	28/61	40.0	74/15/0	dexmedetomidine 0.2 µg/kg continuous infusion or 0.5 µg/kg	thyroidecton

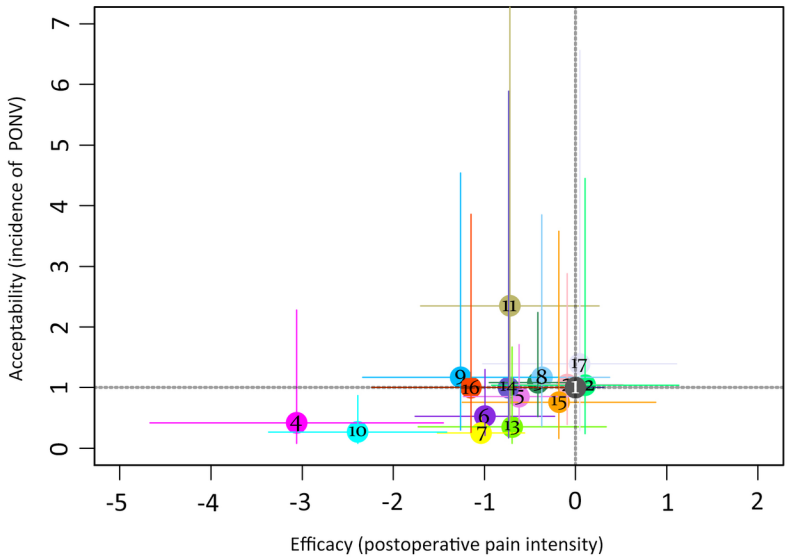












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