Systematic Review

Optimization of Postoperative Intravenous Patient-Controlled Analgesia with Opioid-Dexmedetomidine Combinations: An Updated Meta-Analysis with Trial Sequential Analysis of Randomized Controlled Trials

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Background: It is still a challenge to optimize postoperative pain management. The effects of adding dexmedetomidine (DEX) to opioid-based postoperative intravenous patient-controlled analgesia (PCA) are not fully understood.

Objectives: The aim of this study is to assess the efficacy and safety of opioid-DEX combinations for postoperative PCA, and a trial sequential analysis (TSA) is utilized to evaluate the robustness of the current evidence.

Study Design: A systematic review and meta-analysis.

Setting: Randomized controlled trials that compared opioid-DEX combinations with opioid-only for PCA in adult surgical patients.

Methods: MEDLINE, EMBASE, and CENTRAL databases were searched for relevant articles. The main outcomes analyzed were postoperative pain intensity, opioid requirement, and opioid-related adverse events. The random-effects model was used to estimate mean differences (MDs) or relative risks (RRs) with 95% confidence intervals (CIs). A TSA was performed to test whether the evidence was reliable and significant. The quality of evidence for the main outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: Eighteen studies involving 1,284 patients were included. The meta-analysis indicated that opioid-DEX combinations were associated with lower postoperative pain intensity (at rest: MD [24 hours] = -0.48, 95% CI [-0.75, -0.21], $P = 0.0005$), lower morphine-equivalent requirement (MD [0 – 24 hours] = -12.16 mg [-16.12, -8.21], $P < 0.00001$), and lower adverse events (nausea: RR = 0.66 [0.52, 0.83]; vomiting: RR = 0.65 [0.49, 0.87]; and pruritus: RR = 0.57 [0.40, 0.81]). For the above results, the TSA revealed that the cumulative Z-curve exceeded both the traditional boundary and the trial sequential monitoring boundary for benefit. DEX had no effect on the incidence of hypotension or bradycardia, which was also confirmed by the TSA. The GRADE level of evidence was high for postoperative nausea, moderate for pain intensity at rest at 24 hours postoperatively, morphine-equivalent requirement during 0 – 24 hours postoperatively, and postoperative vomiting, pruritus, and bradycardia, and low for postoperative hypotension.

Limitations: The risk of introducing potentially significant heterogeneity exists, and this study did not evaluate the effects of DEX combined with opioids on long-term outcomes including chronic pain and patients' satisfaction after hospital discharge.

Conclusions: Postoperative PCA strategies with opioid-DEX combinations decreased postoperative pain, opioid requirement, and opioid-related adverse events. DEX is a useful adjuvant to opioid-based PCA.

Key words: Dexmedetomidine, pain, postoperative analgesia, opioid, patient-controlled

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Acute postoperative pain increases patient morbidity and may even lead to chronic postsurgical pain (1,2). Opioids remain the cornerstone of intraoperative and postoperative analgesia, particularly, for moderate-to-severe pain. Patient-controlled analgesia (PCA) with systemic opioids provides greater pain relief after surgery and higher patient satisfaction than analgesia given as required by medical staff (3). However, it is still a challenge to minimize or prevent opioid-related side effects—the most serious of which is respiratory depression (4). Emphasis on multimodal strategies for postoperative pain management has grown recently, but an ideal protocol has not been defined (5,6).

Dexmedetomidine (DEX), a selective $\alpha 2$ adrenergic receptor agonist, has analgesic, sedative, and sympatholytic properties without respiratory depression (7,8). The preoperative or intraoperative use of DEX has been shown to potentiate analgesia and reduce postoperative opioid requirements (9,10). A previous meta-analysis has suggested the benefits of DEX for postoperative PCA, but it included limited data and was underpowered to achieve determinate conclusions (11). To date, it remains unclear to what extent opioid-DEX combinations decrease postoperative pain intensity, opioid requirement, and incidence of opioid-related adverse effects. In addition, concerns with respect to DEX-related hemodynamic changes, including bradycardia and hypotension, still exist, especially for prolonged postsurgical infusions.

In recent years, more well-conducted randomized controlled trials (RCTs) with adequate power have been published, providing new evidence for the use of opioid-DEX combination therapy for postoperative intravenous PCA. Thus, we undertook an updated meta-analysis to assess the efficacy and safety of these treatments and utilized a trial sequential analysis (TSA) to evaluate the robustness of the current evidence.

Methods

Literature Search

This meta-analysis was based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12). The PRISMA checklist is shown in Supplementary Table 1. All analyses were based on published data; thus, ethical approval or patient consent was not necessary for this report.

Two authors independently searched the MEDLINE, EMBASE, and CENTRAL databases using MeSH terms combined with text words (Supplementary Table 2). The literature search was completed on December 30, 2016, without language and publication date restrictions. In addition, we manually checked the references and previous reviews for other potentially eligible trials.

Eligibility Criteria

The inclusion and exclusion criteria were determined a priori. The inclusion criteria were as follows: RCTs, adult patients undergoing surgical procedures, treatment with a combination of opioid and DEX compared to treatment with opioid only in a postoperative PCA system, and studies that reported on postoperative pain-related outcomes, such as pain intensity, opioid consumption, and need for rescue analgesics, and PCA-related adverse events, such as nausea and vomiting, excessive sedation, hypotension, and bradycardia. The exclusion criteria were as follows: DEX administered only before anesthesia induction or during the maintenance period, pediatric patients, studies not reporting primary or secondary outcomes, and lack of access to the full text.

Two authors independently screened article titles and abstracts for appropriate studies and then reviewed the full texts to identify eligible studies. Any discrepancy over study selection was resolved by group discussion.

Data Extraction

All relevant data were extracted by one author and confirmed by 2 other authors. The following data were included: first author, publication year, number of patients, surgical setting, anesthesia, intraoperative analgesia, postoperative pain treatment, and PCA protocol. The corresponding authors of the selected studies were contacted to verify the extracted data or to request any missing data, if necessary. Any discrepancy over data extraction was resolved by group discussion.

Primary and Secondary Outcomes

The primary outcomes of this study were pain-related outcomes after surgery, including pain intensity, opioid consumption, and need for rescue analgesics. Pain intensity was assessed using a visual analog scale, numerical analog scale, or numeric rating scale from 0 to 10 (0 means no pain at all and 10 represents the worst pain imaginable). The pain scores at rest at 9 time-points (postoperative 1, 2, 4, 6, 8, 12, 16, 24, and

48 hours) and upon movement at 6 time-points (postoperative 1, 2, 6, 12, 24, and 48 hours) were analyzed. Opioid consumption during 7 time intervals (postoperative 0 to 1, 0 to 4, 0 to 6, 0 to 8, 0 to 12, 0 to 24, and 0 to 48 hours) was assessed using previously published data on opioid conversion factors (equivalent doses: morphine 10 mg, meperidine 100 mg, tramadol 100 mg, oxycodone 6.67 mg, fentanyl 0.1 mg, sufentanil 10 μg; intravenously administered doses for all analgesics) (13-15).

The secondary outcomes investigated were PCA-related adverse effects, such as postoperative nausea and vomiting (PONV), Ramsay sedation scores at postoperative 4, 8, 24, and 48 hours, somnolence, pruritus, hypoxemia, respiratory depression, hypotension, bradycardia, and dizziness. Patient satisfaction with pain management was also evaluated. The patients were asked to either report whether or not they were satisfied with their pain-management protocol ("yes" or "no") or to grade their satisfaction with the protocol as follows: very satisfied, satisfied, neutral, unsatisfied, or very unsatisfied. Answers of "yes," "very satisfied," or "satisfied" were considered to indicate satisfactory pain relief.

Study Quality Assessment

Two authors independently evaluated the risk of bias for all of the included studies with the Cochrane Collaboration tool (16). For each domain in this tool, the risk of bias was judged to be "high," "low," or "unclear." A trial was considered to have a high risk of bias when one or more key domains were found to be at a high risk of bias. Trials were considered to have a low risk of bias, if all domains were found to have a low risk of bias. Otherwise, the trial was judged to have an unclear risk of bias. Any discrepancy over bias assessment was resolved by group discussion.

Quality of Evidence Assessment

Two authors independently assessed the quality of evidence for the main outcomes and generated summary tables using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADEpro GDT, GRADEpro Guideline Development Tool, https://gradepro.org) (17). A judgment of "high," "moderate," "low," or "very low" was made for each outcome according to 5 criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Any discrepancy over evidence quality assessment was resolved by group discussion.

Statistical Analysis

Data synthesis was conducted with RevMan 5.0 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark). For continuous data, weighted mean differences (MDs) with 95% confidence intervals (CIs) were reported, and for dichotomous data, risk ratios (RRs) with 95% CIs were used. Standard deviations not stated were estimated as range/4 (range = maximum value – minimum value) or interquartile range/1.35 (interquartile range = the third quartile – the first quartile) (13,18).

A random-effects model was applied for individual endpoints due to clinical heterogeneity. Heterogeneity was evaluated with the I^2 statistic, with $I^2 > 50\%$ indicating significant heterogeneity (19). A funnel plot using one of the main outcomes as an end-point was constructed to detect publication bias. A *P*-value < 0.05 indicated statistical significance. In order to achieve robust results, data were reported when an outcome was reported by at least 3 studies simultaneously.

Subgroup analyses were performed for the primary outcomes, based on the following: type of surgery (major vs. minor), type of anesthesia (general vs. regional or local), allocation concealment (adequate vs. unclear), non-steroidal anti-inflammatory drugs (NSAIDs; not used vs. used), intraoperative DEX (not used vs. used), DEX administration (PCA system vs. infusion), and PCA DEX dosage (< 25 μg/h vs. ≥ 25 μg/h).

TSA

The main outcomes were analyzed using TSA 0.9.5.5 beta (www.ctu.dk/tsa) to quantify the reliability of the results (20). In a meta-analysis, sparse data and repetitive testing of accumulating data may increase random errors and the risk of type I error (21). Trial sequential monitoring boundaries in the TSA were introduced in order to reduce the risk of random errors and to determine the reliability and significance of the meta-analysis (21,22). If the cumulative Z-curve crosses the trial sequential monitoring boundary or enters below the futility curve, the evidence for reaching a solid conclusion may be sufficient and no further study is needed. Otherwise, the evidence may be insufficient. The TSA was conducted using $\alpha = 0.05$ (2-sided) and $\beta = 0.20$ (power 80%).

Results

Study Selection

The PRISMA flow diagram is shown in Fig. 1. The

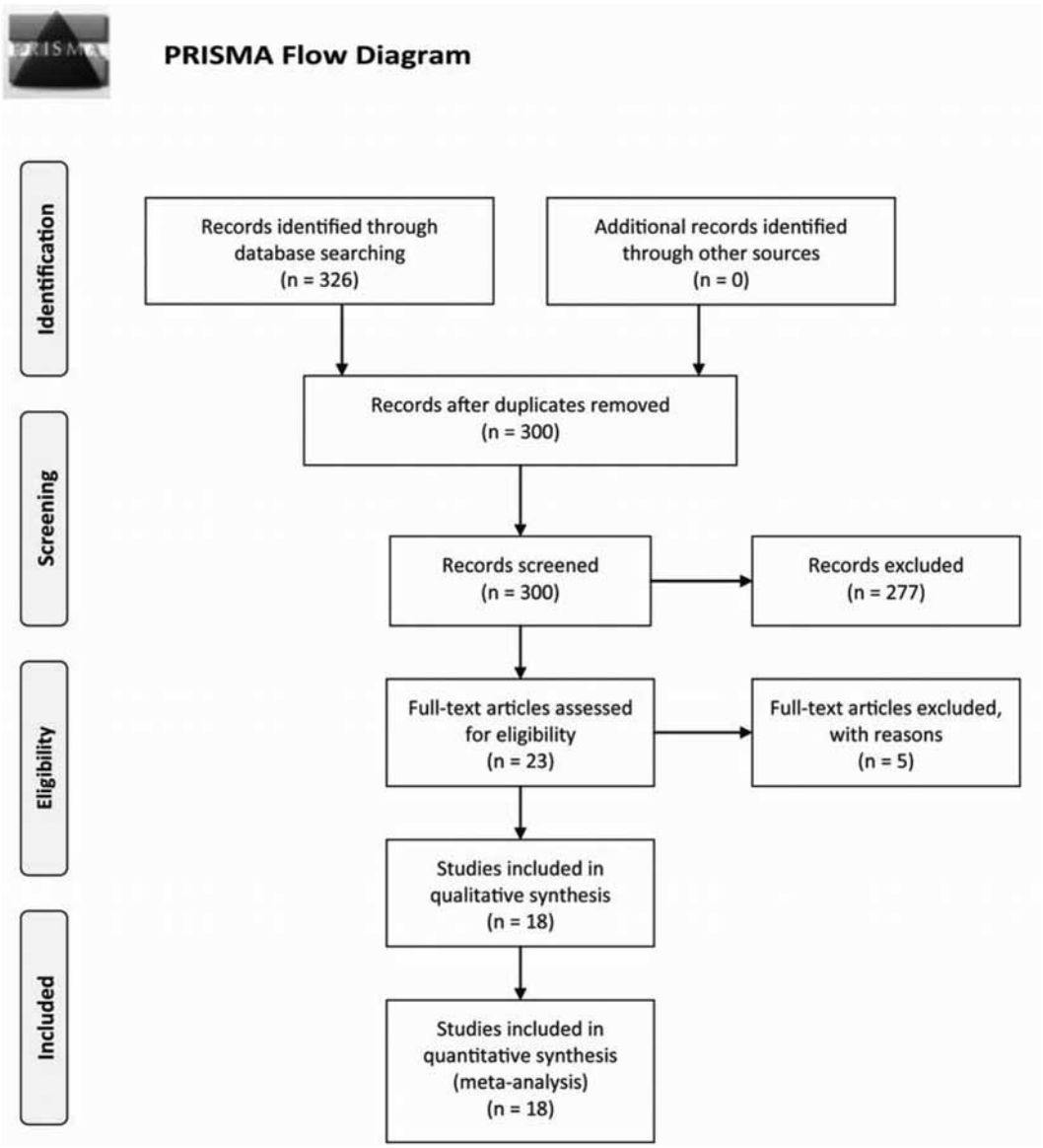

Fig. 1. *PRISMA flow diagram.*

initial literature search identified 326 studies. After the removal of duplicates and the screening of titles and abstracts, 23 studies met the inclusion criteria. After verifying the contents of each study, 18 studies were finally included in the analysis. Of those excluded, 2 studies were ineligible for inclusion and 3 were conference abstracts. These 18 publications reported on a combined subject population of 1,284 patients (23-40).

Study Characteristics

The study characteristics are presented in Table 1. The included studies were published from 2004 to 2016 with population sizes ranging from 34 to 152 patients. In the 18 studies included in this meta-analysis, PCA protocols were used in abdominal surgeries (6 studies), thoracic surgeries (4 studies), spine surgeries (3 studies), orthopedic surgery (1 study), coronary artery bypass grafting (1 study), and 3 minor procedures (1 study each). All of the studies were RCTs comparing the effects of adding DEX to an opioid-based PCA with opioid alone and included at least one of the outcomes listed in the inclusion criteria.

Table 1. *Study characteristics*.

Study (Reference)	Groups (No. of Patients)	Surgical Setting	Anesthesia	Intraoperative Analgesia	Pain Titration or Analgesics at the End of Surgery	PCA with or without DEX
Abdelmageed 2011 (23)	Control (19) DEX (20)	Uvulopalato-pharyngoplasty	Sevoflurane + nitrous oxide	Morphine	Titration with 2 mg morphine at 10-min intervals DEX 1 μg/kg, titration with 2 mg morphine at 10-min intervals	Morphine PCA with morphine + DEX infusion
Altindis 2008 (24)	Control (20) DEX (20)	Lower abdominal surgery	Sevoflurane + nitrous oxide	Fentanyl	Titration with 0.25 mg/kg bolus + 10 mg meperidine at 5-min intervals DEX 0.5 μg/kg, titration with 0.25 mg/kg bolus + 10 mg meperidine at 5-min intervals	Meperidine Meperidine-DEX combination
Arain 2004 (25)	Control (17) DEX (17)	Major inpatient surgery	Sevoflurane	Fentanyl	Titration with 0.08 mg/kg + 2 mg morphine at 5-min intervals DEX 1 μg/kg, titration with 0.08 mg/kg + 2 mg morphine at 5-min intervals	Morphine PCA with morphine + DEX infusion
Demirhan 2011 (26)	Control (15) DEX (15)	Thoracotomy	Sevoflurane	Remifentanil	Tramadol 50 mg DEX 1 μg/kg + tramadol 50 mg	Tramadol PCA with tramadol + DEX infusion
Gunes 2008 (27)	Control (32) DEX (32)	Laminectomy	Isoflurane	Remifentanil	Morphine 0.15 mg/kg Morphine 0.15 mg/kg	Morphine Morphine-DEX combination
Kim 2013 (28)	Control (25) DEX (25)	Uterine artery embolization	Local anesthesia	Tramadol, ketorolac	Tramadol 75 mg Tramadol 75 mg + DEX 0.2 μg/kg/h	Fentanyl PCA with fentanyl + DEX infusion
Korkmaz 2013 (29)	Control (20) DEX (20)	Coronary artery bypass grafting	No details provided	No details provided	Morphine 0.05 mg/kg Morphine 0.05 mg/kg	Morphine Morphine-DEX combination
Lee 2013 (30)	Control (30) DEX (30)	Gynecological abdominal surgery	No details provided	No details provided	Fentanyl 0.5 μg/kg + ketorolac 30 mg Fentanyl 0.5 μg/kg + ketorolac 30 mg	Fentanyl Fentanyl-DEX combination
Lin 2009 (31)	Control (48) DEX (50)	Abdominal total hysterectomy	Isoflurane + nitrous oxide	Fentanyl	PCA 2 mL (morphine 1 mg/mL) at 5-min intervals titration PCA 2 mL (morphine 1 mg/mL + DEX 5 μg/mL) at 5-min intervals titration	Morphine Morphine-DEX combination
Nie 2014 (32)	Control 1 (38) Control 2 (40) DEX (38)	Caesarean section	Spinal anesthesia	Bupivacaine	Saline DEX 0.5 μg/kg bolus DEX 0.5 μg/kg bolus	Sufentanil Sufentanil Sufentanil-DEX combination
Ramsay 2014 (33)	Control (19) DEX (19)	Thoracotomy	Sevoflurane	Fentanyl	Paravertebral block with 0.5% ropivacaine 5 mL Paravertebral block with 0.5% ropivacaine 5 mL	Morphine PCA with morphine + DEX infusion
Ren 2015(1) (34)	Control (41) DEX 1 (41) DEX 2 (43)	Thoracic surgery	Propofol	Sufentanil	DEX 0.1 μg/kg/h DEX 0.1 μg/kg/h DEX 0.1 μg/kg/h	Sufentanil Sufentanil-DEX combination Sufentanil-DEX combination

Table 1 (cont.). *Study characteristics*.

Study (Reference)	Groups (No. of Patients)	Surgical Setting	Anesthesia	Intraoperative Analgesia	Pain Titration or Analgesics at the End of Surgery	PCA with or without DEX
Ren 2015(2) (35)	Control (27) DEX 1 (28) DEX 2 (27)	Hysterectomy	Sevoflurane	Sufentanil	Saline infusion DEX 0.3 μg/kg/h DEX 0.3 μg/kg/h	Sufentanil Sufentanil-DEX combination Sufentanil-DEX combination
Song 2016 (36)	Control (52) DEX (53)	Posterior lumbar spinal fusion	Sevoflurane	Remifentanil	Fentanyl 0.5 μg/kg Fentanyl 0.5 μg/kg + DEX 0.5 μg/kg	Fentanyl Fentanyl-DEX combination
Wang 2015 (37)	Control (77) DEX (75)	Spine surgery	Propofol	Remifentanil	Sufentanil 0.05 μg/kg, Sufentanil 0.05 μg/kg	Sufentanil Sufentanil-DEX combination
Wang 2016 (38)	Control (40) DEX (40)	Video-assisted thoracoscopic lobectomy	Propofol or sevoflurane	Fentanyl	Oxycodone 2 mg titration Oxycodone 2 mg titration + DEX 0.5 μg/kg	Oxycodone Oxycodone-DEX combination
Wu 2011 (39)	Control (20) DEX (20)	Total hip replacement	Sevoflurane + propofol	Fentanyl	Fentanyl 1 μg/kg Fentanyl 1 μg/kg	Fentanyl PCA with fentanyl + DEX infusion
Zhang 2014 (40)	Control (43) DEX (48)	Amputated finger replantation	Brachial plexus blockade	Ropivacaine	Fentanyl PCA Fentanyl + DEX PCA	Fentanyl Fentanyl-DEX combination

Control = opioid only for postoperative PCA; DEX = dexmedetomidine; PCA = patient-controlled analgesia

Table 2. *PCA systems*.

Studies	Groups (Analgesics in PCA)	Background Infusion with or without DEX Infusion	Bolus Dose	Lockout Interval
Abdelmageed 2011 (23)	Control (morphine, no other details) DEX (morphine, no other details)	No background, saline infusion No background, DEX 0.6 μg/kg/h infusion	Morphine 1 mg Morphine 1 mg	5 min
Altindis 2008 (24)	Control (meperidine, no other details) DEX (meperidine + DEX, no other details)	No background No background	Meperidine 5 mg Meperidine 5 mg + DEX 10 μg	15 min
Arain 2004 (25)	Control (morphine, no other details) DEX (morphine, no other details)	No details provided DEX 0.4 μg/kg/h	No details provided	No details provided
Demirhan 2011 (26)	Control (tramadol 400 mg in 100 mL saline) DEX (tramadol 400 mg in 100 mL saline)	Tramadol 0.3 mg/kg/h, saline infusion Tramadol 0.3 mg/kg/h, DEX 0.4 μg/kg/h	Tramadol 10 mg Tramadol 10 mg	20 min
Gunes 2008 (27)	Control (morphine 40 mg, no other details) DEX (morphine 40 mg + DEX 200 μg, no other details)	No background No background	Morphine 0.02 mg/kg Morphine 0.02 mg/kg + DEX 0.1 μg/kg	15 min
Kim 2013 (28)	Control (fentanyl 1.5 g + ketorolac 90 mg in 150 mL saline) DEX (fentanyl 1.5 g + ketorolac 90 mg in 150 mL saline)	Fentanyl 10 μg/h, saline infusion Fentanyl 10 μg/h, DEX 0.4 μg/kg/h	Fentanyl 20 μg Fentanyl 20 μg	10 min
Korkmaz 2013 (29)	Control (morphine 100 mg in 100 mL saline) DEX (morphine 50 mg + DEX 250 μg in 100 mL saline)	Morphine 1 mg/h Morphine 0.5 mg/h + DEX 2.5 μg/h	Morphine 1 mg Morphine 0.5 mg + DEX 2.5 μg	15 min

Table 2 (cont.). *PCA systems*.

Studies	Groups (Analgesics in PCA)	Background Infusion with or without DEX Infusion	Bolus Dose	Lockout Interval
Lee 2013 (30)	Control (fentanyl 20 μg/kg + ketorolac 180 mg in 100 mL saline) DEX (fentanyl 20 μg/kg + ketorolac 180 mg + DEX 500 μg in 100 mL saline)	Fentanyl 0.4 μg/kg/h Fentanyl 0.4 μg/kg/h + DEX 10 μg/h	Fentanyl 0.4 μg/kg Fentanyl 0.4 μg/kg + DEX 10 μg	10 min
Lin 2009 (31)	Control (morphine 100 mg in 100 mL saline) DEX (morphine 100 mg + DEX 500 μg in 100 mL saline)	No background No background	Morphine 1 mg Morphine 1 mg + DEX 5 μg	5 min
Nie 2014 (32)	Control 1 (sufentanil 100 μg in 100 mL saline) Control 2 (DEX 0.5 μg/kg bolus, sufentanil 100 μg in 100 mL saline) DEX (sufentanil 100 μg + DEX 300 μg in 100 mL saline)	Sufentanil 0.015 μg/kg/h Sufentanil 0.015 μg/kg/h Sufentanil 0.015 μg/kg/h + DEX 0.045 μg/kg/h	Sufentanil 0.023 μg/kg Sufentanil 0.023 μg/kg Sufentanil 0.023 μg/kg + DEX 0.07 μg/kg	8 min
Ramsay 2014 (33)	Control (morphine, no other details) DEX (morphine, no other details)	No details provided DEX 0.1 – 0.5 μg/kg/h	No details provided	No details provided
Ren 2015(1) (34)	Control (sufentanil, no other details) DEX 1 (sufentanil + DEX, no other details) DEX 2 (sufentanil + DEX, no other details)	Sufentanil 0.02 μg/kg/h Sufentanil 0.02 μg/kg/h + DEX 0.02 μg/kg/h Sufentanil 0.02 μg/kg/h + DEX 0.04 μg/kg/h	Sufentanil 0.02 μg/kg Sufentanil 0.02 μg/kg + DEX 0.02 μg/kg Sufentanil 0.02 μg/kg + DEX 0.04 μg/kg	5 min
Ren 2015(2) (35)	Control (sufentanil, no other details) DEX 1 (sufentanil + DEX, no other details) DEX 2 (sufentanil + DEX, no other details)	Sufentanil 0.02 μg/kg/h Sufentanil 0.02 μg/kg/h + DEX 0.02 μg/kg/h Sufentanil 0.02 μg/kg/h + DEX 0.05 μg/kg/h	Sufentanil 0.02 μg/kg Sufentanil 0.02 μg/kg + DEX 0.02 μg/kg Sufentanil 0.02 μg/kg + DEX 0.05 μg/kg	8 min
Song 2016 (36)	Control (fentanyl 10 μg/kg + ketorolac 120 mg in 100 mL saline) DEX (fentanyl 10 μg/kg + ketorolac 120 mg + DEX 10 μg/kg in 100 mL saline)	Fentanyl 0.2 μg/kg/h Fentanyl 0.2 μg/kg/h + DEX 0.02 μg/kg/h	Fentanyl 0.1 μg/kg Fentanyl 0.1 μg/kg + DEX 0.01 μg/kg	15 min
Wang 2015 (37)	Control (sufentanil 2 μg/kg in 100 mL saline) DEX (sufentanil 2 μg/kg + DEX 3 μg/kg in 100 mL saline)	Sufentanil 0.04 μg/kg/h Sufentanil 0.04 μg/kg/h + DEX 0.06 μg/kg/h	Sufentanil 0.01 μg/kg Sufentanil 0.01 μg/kg + DEX 0.015 μg/kg	15 min
Wang 2016 (38)	Control (oxycodone 50 mg in 100 mL saline) DEX (oxycodone 50 mg + DEX 5 μg/kg in 100 mL saline)	Oxycodone 0.5 mg/h Oxycodone 0.5 mg/h + DEX 0.05 μg/kg/h	Oxycodone 1 mg Oxycodone 1 mg + DEX 0.1 μg/kg	15 min
Wu 2011 (39)	Control (fentanyl 1g in 100 mL saline) DEX (fentanyl 1g in 100 mL saline)	Fentanyl 10 μg/h, saline infusion Fentanyl 10 μg/h, DEX 0.2 μg/kg/h	Fentanyl 10 μg Fentanyl 10 μg	5 min
Zhang 2014 (40)	Control (fentanyl 1g + dezocine 10 mg in 100 mL saline) DEX (fentanyl 1g + dezocine 10 mg + DEX 200 μg in 100 mL saline)	Fentanyl 20 μg/h Fentanyl 20 μg/h + DEX 4 μg/h	Fentanyl 5μ g Fentanyl 5 μg + DEX 1μg	15 min

Control = opioid only for postoperative PCA; DEX = dexmedetomidine; PCA = patient-controlled analgesia

The detailed protocols for PCA are presented in Table 2. The doses of DEX added to the PCA solution ranged from 200 μg to 500 μg, and 6 studies applied continuous DEX administration at 0.1–0.6 μg/kg/h postoperatively (23,25,26,28,33,39). The PCA system was set as: background infusion rate of 0 – 2 mL/h, 0.5 – 2 mL bolus on-demand, and a lockout interval of 5 – 20 minutes.

Primary Outcomes

The primary outcomes are shown in Table 3. At all of the time-points at rest, the patients who received opioid-DEX combinations for postoperative PCA reported significantly lower pain scores than did those receiving opioids alone. Pooled data from 13 studies found a MD of -0.48 (95% CI: -0.75 to -0.21, $P = 0.005$, $I^2 = 83\%$) at 24 hours postoperatively (n = 1,029) (26,28-32,34-40)

Table 3. *Postoperative pain intensity, morphine-equivalent consumption, and rescue analgesia.*

Time-Points/Intervals	References	No. of Patients	MD or RR [95% CI]	*P*-Value	I^2 test (%)
Pain Intensity at Rest					
1 h postoperatively	25, 28, 30, 31, 34-37	706	MD = -0.73 points [-1.18, -0.27]	0.002	79
2 h postoperatively	25, 26, 28, 29, 31, 35, 37	466	MD = -0.55 points [-1.00, -0.10]	0.02	69
4 h postoperatively	28, 31, 32, 34, 35, 38, 39	551	MD = -0.79 points [-1.10, -0.48]	0.00001	66
6 h postoperatively	28-30, 36-38, 40	577	MD = -0.98 points [-1.19, -0.77]	0.00001	3
8 h postoperatively	26, 28, 32, 34, 35, 39	403	MD = -0.71 points [-1.06, -0.35]	0.0001	61
12 h postoperatively	28, 30, 36, 37, 39, 40	488	MD = -0.70 points [-1.12, -0.29]	0.001	74
16 h postoperatively	26, 34, 35	237	MD = -0.39 points [-0.71, -0.07]	0.02	0
24 h postoperatively	26, 28-32, 34-40	1029	MD = -0.48 points [-0.75, -0.21]	0.0005	83
48 h postoperatively	29, 30, 33-38, 40	773	MD = -0.48 points [-0.96, -0.01]	0.05	92
Pain Intensity upon Movement					
1 h postoperatively	30, 31, 34-37	622	MD = -0.62 points [-1.17, -0.08]	0.02	78
2 h postoperatively	31, 35, 37	332	MD = -0.63 points [-1.22, -0.04]	0.04	66
6 h postoperatively	30, 36-38	397	MD = -0.98 points [-1.26, -0.71]	0.00001	0
12 h postoperatively	30, 36, 37	307	MD = -0.42 points [-0.82, -0.02]	0.04	5
24 h postoperatively	30, 31, 34-38	702	MD = -0.66 points [-1.25, -0.08]	0.03	88
48 h postoperatively	30, 34-38	604	MD = -0.23 points [-0.53, 0.06]	0.12	55
Morphine-Equivalent Consumption					
0–1 h postoperatively	23–25, 31, 34-36	523	MD = -2.32 mg [-3.48, -1.16]	0.0001	95
0–4 h postoperatively	31, 32, 34, 35, 38	501	MD = -4.61 mg [-6.93, -2.29]	0.0001	96
0–6 h postoperatively	24, 28, 36, 38	275	MD = -3.07 mg [-4.68, -1.47]	0.0002	91
0–8 h postoperatively	32, 34, 35	323	MD = -9.48 mg [-11.76, -7.20]	0.00001	60
0–12 h postoperatively	23, 24, 36, 39	224	MD = -5.99 mg [-9.40, -2.58]	0.0006	76
0–24 h postoperatively	23, 24, 26-28, 31, 32, 34-39	1021	MD = -12.16 mg [-16.12, -8.21]	0.00001	96
0–48 h postoperatively	34, 35, 38	287	MD = -10.15 mg [-14.05, -6.26]	0.00001	79
Others					
Rescue analgesia	23, 28, 31, 34, 35, 38, 39	514	RR = 0.38 [0.20, 0.73]	0.004	45

Opioid-dexmedetomidine combination versus opioid alone for all comparisons. Pain intensity was assessed with a VAS, numerical analog scale, or NRS, where 0 = no pain and 10 = the most severe pain imaginable. Morphine-equivalents were calculated as: morphine 10 mg = tramadol 100 mg = meperidine 100 mg = oxycodone 6.67 mg = fentanyl 0.1 mg = sufentanil 10 μg, intravenously. MD: mean difference; RR: risk ratio; CI: confidence interval

(Fig. 2A). The TSA revealed that the cumulative Z-curve exceeded both the traditional boundary and the TSA boundary for benefit, establishing sufficient and firm evidence and suggesting that no further studies were needed. The calculation for required information size identified 667 patients with $\alpha = 0.05$ (2-sided), $\beta = 0.20$ (power 80%), and a MD of -0.48 (Fig. 2B).

Significantly lower pain scores upon movement for up to 24 hours postoperatively were also reported by patients treated with PCA strategies containing DEX. The data from 7 studies showed a MD of -0.66 (95% CI: -1.25 to -0.08, $P = 0.03$, $I^2 = 88\%$) at 24 hours postoperatively (n = 702) (30,31,34-38) (Supplementary Fig. 1A). However, the TSA found that the Z-curve crossed the traditional boundary but failed to cross the TSA boundary, indicating that the consolidated result was not reliable and more studies are needed (Supplementary Fig. 1B).

The patients who received DEX for intravenous PCA required fewer analgesics up to 48 hours postoperatively. During 0 – 24 hours after surgery, a MD of -12.16mg (95% CI: -16.12 to -8.21, $P < 0.00001$, $I^2 = 96\%$) was found (23,24,26-28,31,32,34-39) (Fig. 3A). This result was further supported by the TSA results (Fig. 3B). Patients receiving opioid-DEX combinations reported

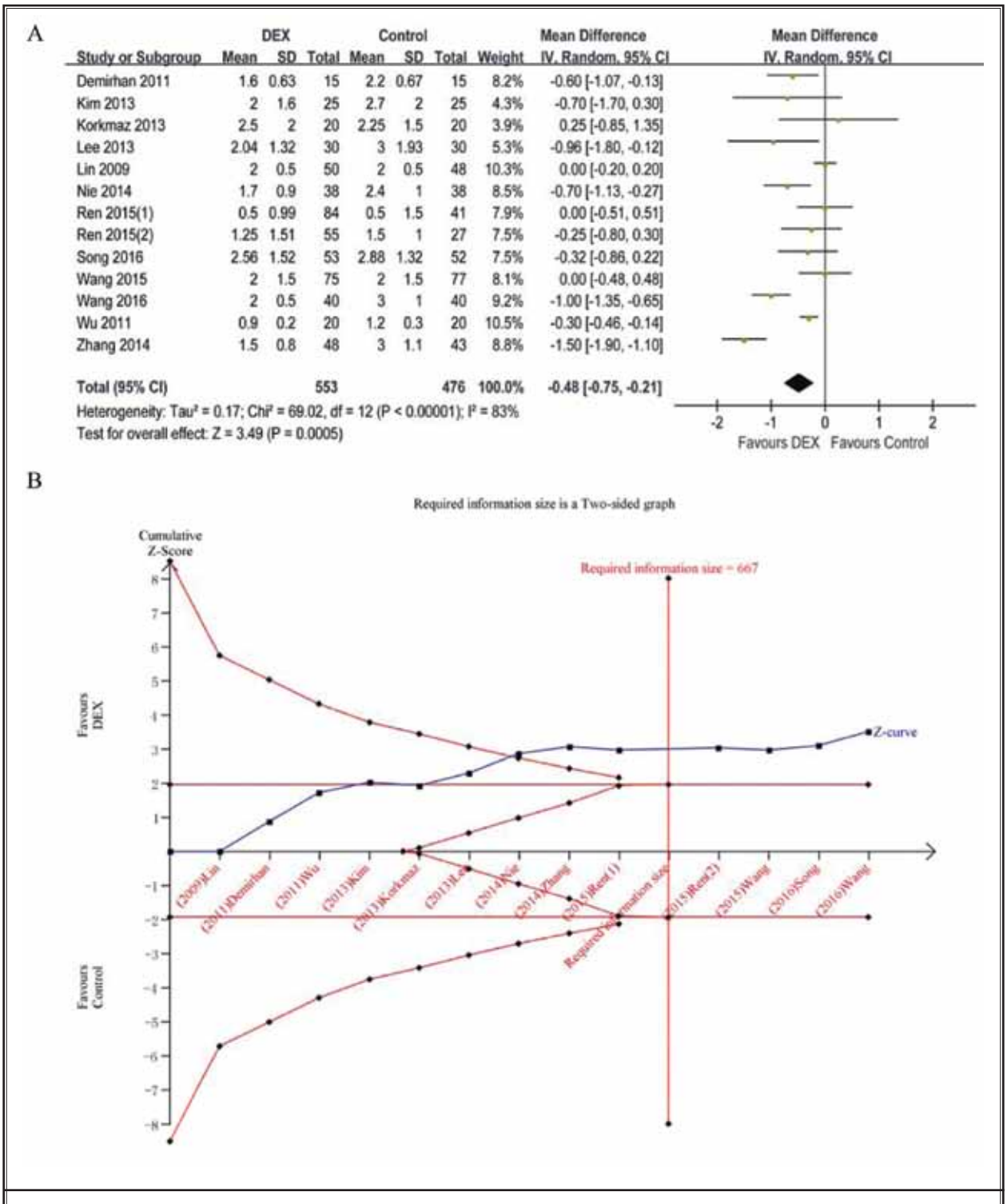

Fig. 2. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) pain intensity at rest at 24 hours postoperatively and (B) TSA.*
DEX = dexmedetomidine; SD = standard deviation; CI = confidence interval

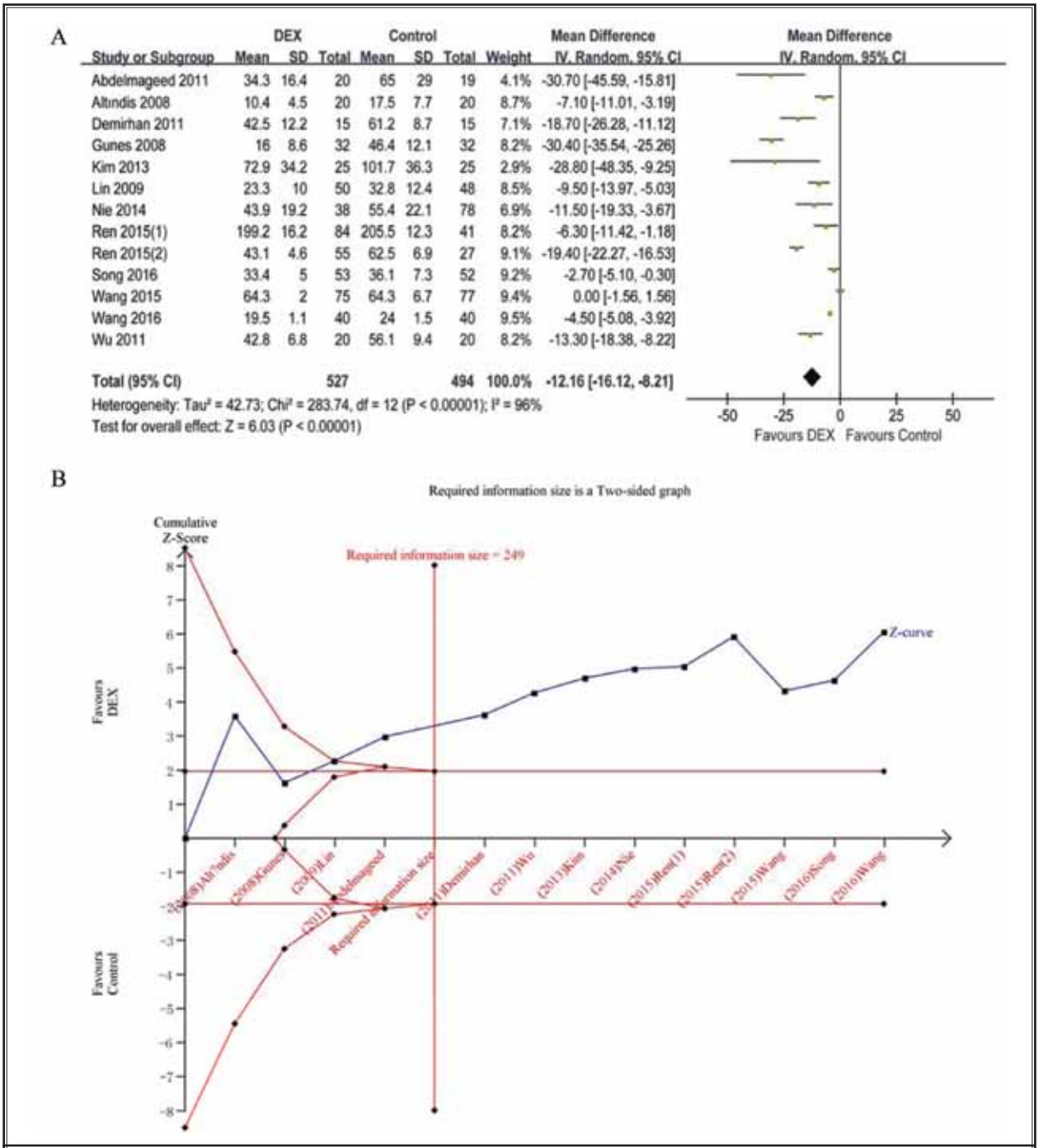

Fig. 3. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) morphine-equivalent consumption during 0 – 24 hours postoperatively and (B) TSA.*
DEX = dexmedetomidine; SD = standard deviation; CI = confidence interval.

less postoperative need for rescue analgesia (RR = 0.38 [0.20 to 0.73], $P = 0.004$, $I^2 = 4\%$) (23,28,31,34,35,38,39).

As shown in Supplementary Table 3, subgroup analyses found the pain intensity at rest at 24 hours postoperatively significantly differed with the type of surgery (major vs. minor) and the type of anesthesia (general vs. regional or local). Subgroup analyses based on the type of surgery (major vs. minor) and

Table 4. *Postoperative sedation scores, adverse events, and patient satisfaction.*

Outcomes	References	No. of Patients	MD or RR [95% CI]	*P*-Value	I^2 test (%)
Sedation					
Ramsay scores at 4 h	32, 38, 39	196	MD = 0.00 points [-0.00, 0.00]	0.99	0
Ramsay scores at 8 h	26, 32, 39	146	MD = 0.17 points [-0.09, 0.42]	0.20	72
Ramsay scores at 24 h	26, 32, 38-40	317	MD = 0.04 points [-0.05, 0.14]	0.37	26
Ramsay scores at 48 h	33, 38, 40	209	MD = 0.00 points [-0.04, 0.04]	0.97	0
Adverse Events					
Nausea	23, 24, 26-40	1250	RR = 0.66 [0.52, 0.83]	0.0005	45
Vomiting	26-32, 34-36, 38-40	981	RR = 0.65 [0.49, 0.87]	0.003	0
Pruritus	23, 28, 30, 31, 33-35, 38, 39	612	RR = 0.57 [0.40, 0.81]	0.002	0
Hypoxemia	23, 27-29, 32, 38	349	RR = 0.40 [0.19, 0.86]	0.02	0
Respiratory depression	27, 29-32, 34, 35, 38	625	RR = 0.33 [0.01, 7.72]	0.49	0
Hypotension	26, 28, 29, 31-33, 36-40	800	RR = 1.99 [0.88, 4.48]	0.10	0
Bradycardia	26, 28, 29, 31-33, 35-37, 39, 40	802	RR = 1.45 [0.72, 2.91]	0.30	0
Dizziness	28, 30, 35, 36, 39, 40	428	RR = 0.94 [0.61, 1.44]	0.77	0
Somnolence	29, 31, 37, 40	381	RR = 1.89 [0.49, 7.27]	0.35	0
Others					
Patient satisfaction	25, 31, 32, 37, 38	480	RR = 1.38 [1.06, 1.80]	0.02	84

Opioid-dexmedetomidine combination versus opioid alone for all comparisons. MD: mean difference; RR: risk ratio; CI: confidence interval.

DEX administration (PCA system vs. infusion) showed significant differences in morphine-equivalent consumption 0 – 24 hours postoperatively.

Secondary Outcomes

As shown in Table 4, no significant differences in the sedation levels were detected between patients receiving opioid-DEX combinations and those receiving opioids alone (26,32,33,38-40).

The incidence of the following adverse events was lower among patients who received DEX combined with opioid-based PCA than among those receiving opioids alone: postoperative nausea (RR = 0.66 [0.52 to 0.83], P = 0.0005, I^2 = 45%) (23,24,26-40) (Fig. 4A, 4B), vomiting (RR = 0.65 [0.49 to 0.87], P = 0.003, I^2 = 0%) (26-32,34-36,38-40) (Supplementary Fig. 2A, 2B), and pruritus (RR = 0.57 [0.40 to 0.81], P = 0.002, I^2 = 0%) (23,28,30,31,33-35,38,39) (Supplementary Fig. 3A, 3B). The TSA indicated that these results were reliable as the Z-curve exceeded both the traditional and the TSA boundary for benefit.

Eleven studies reported the incidence of postoperative bradycardia (26,28,29,31-33,35-37,39,40) (Fig. 5A). No significant difference in this parameter was found between the opioid-DEX combination group and the opioid-only group (RR = 1.45 [0.72 to 2.91], P = 0.30, I^2 = 0%). The cumulative Z-curve exceeded below the futility curve, establishing significant evidence and suggesting that no further trials were required. The required information size was 1,500 patients by calculation with α = 0.05 (2-sided), β = 0.20 (power 80%), an anticipated incidence of 6.00% in the intervention arm, and an incidence of 3.00% in the control arm (Fig. 5B). There was no significant difference in hypotension (Supplementary Fig. 4A, 4B), respiratory depression, dizziness, or somnolence between the opioid-DEX combination group and the opioid-only group.

More patients were satisfied when the opioid-DEX combination was used for postoperative intravenous PCA (RR = 1.38 [1.06 to 1.80], P = 0.02, I^2 = 84%) (25,31,32,37,38) (Supplementary Fig. 5A). However, the TSA revealed that the Z-curve exceeded the traditional boundary but did not cross the TSA boundary, indicating that the consolidated result was not reliable and that more studies were needed (Supplementary Fig. 5B).

Risk of Bias Assessment

The risk assessment is presented in Table 5. Overall, all of the studies were double-blinded and randomized. Fourteen studies adequately reported the random sequence generation (23-25,28,29,31-38,40) and 13 trials clearly reported the allocation concealment (23,24,28,29,31-38,40). The funnel plot with pain intensity at rest at 24 hours postoperatively as an end-point indicated no substantial publication bias (Fig. 6).

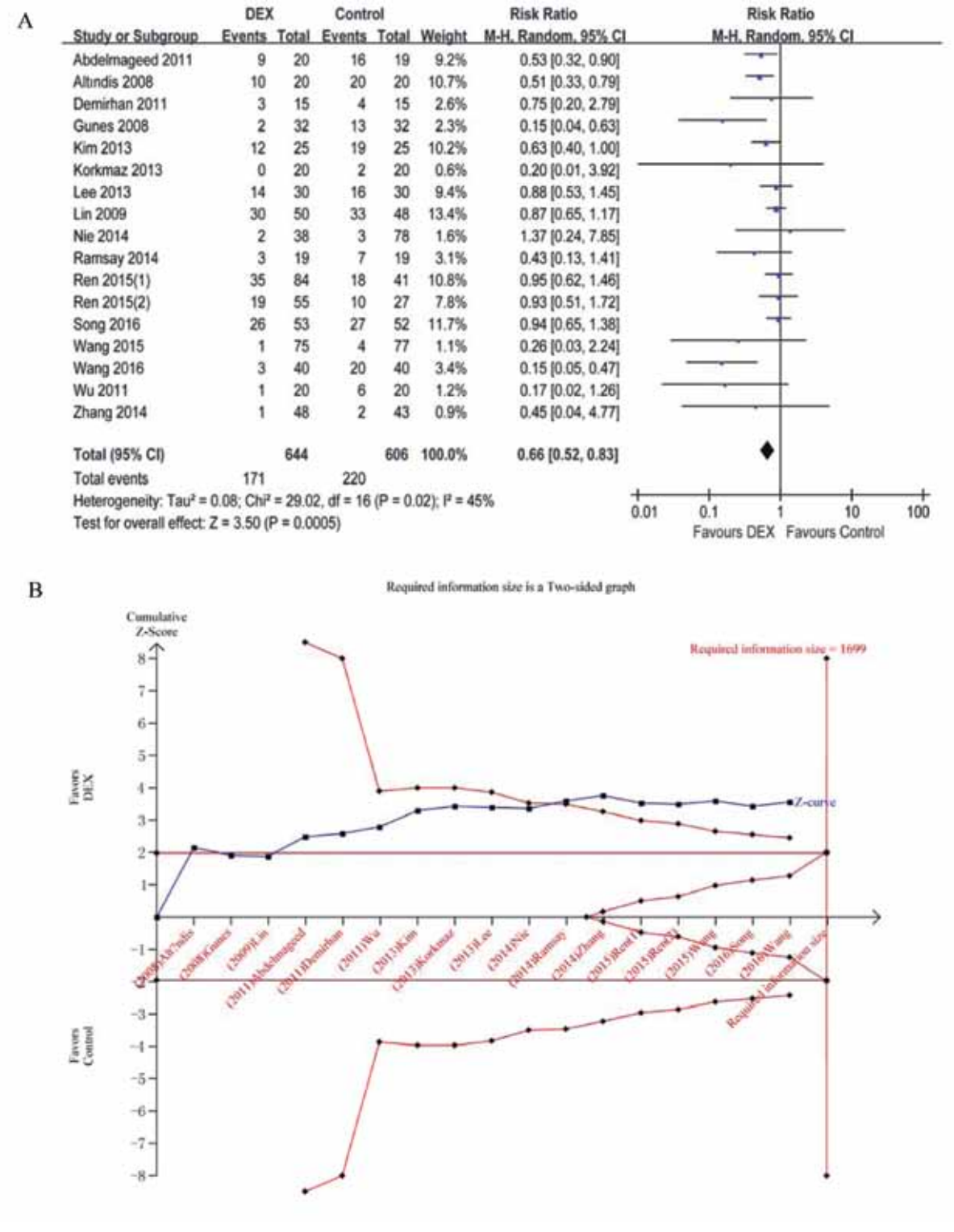

Fig. 4. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) incidence of postoperative nausea and (B) TSA.*
DEX = dexmedetomidine; CI = confidence interval

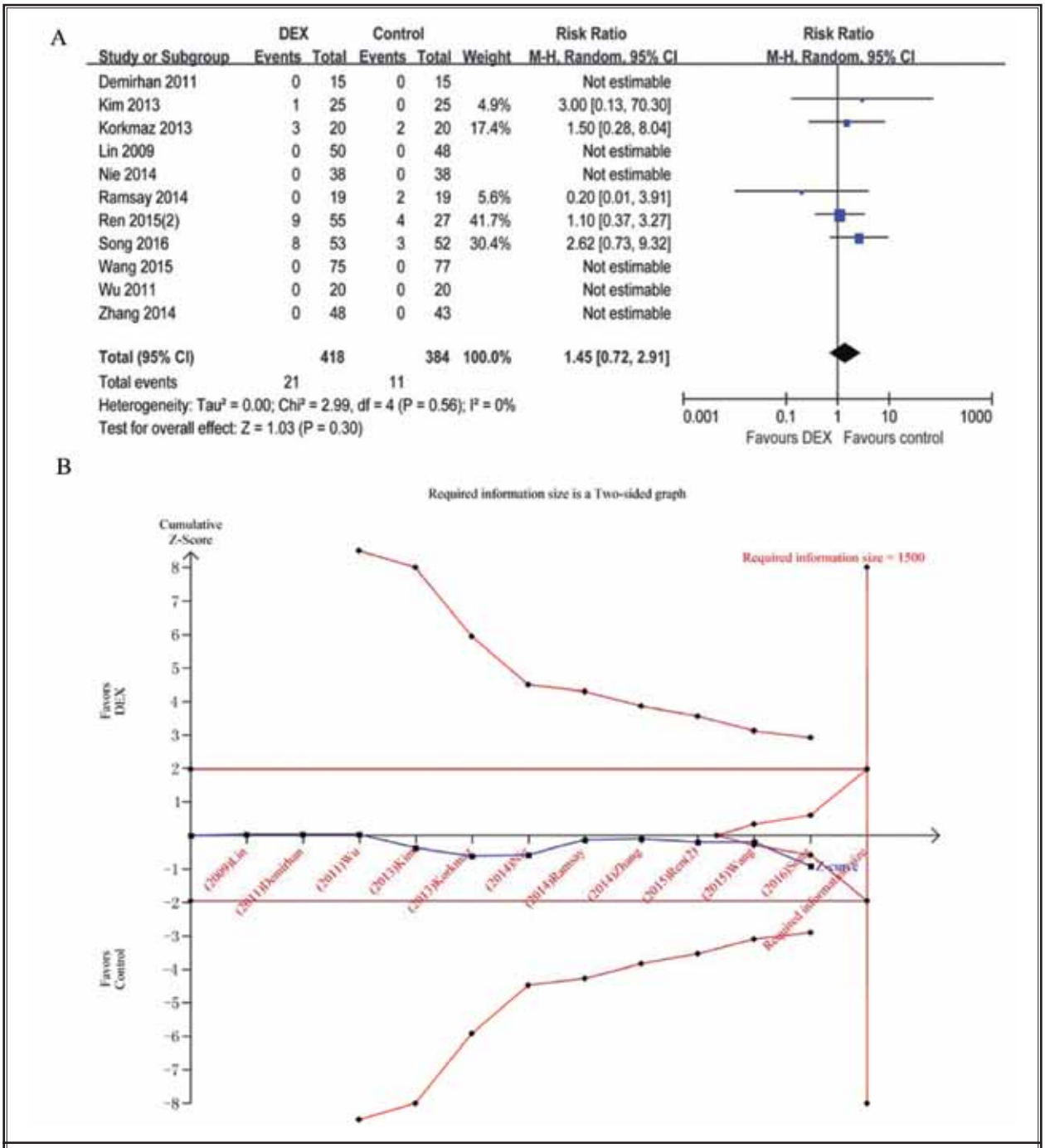

Fig. 5. *Opioid-DEX combination compared with opioid-only for intravenous patient-controlled analgesia: (A) incidence of postoperative bradycardia and (B) TSA.*
DEX = dexmedetomidine; CI = confidence interval

Level of Evidence Assessment

The GRADE evidence profiles were established for the outcomes in Table 6. The GRADE level of evidence was high for postoperative nausea, moderate for pain intensity at rest at 24 hours postoperatively, morphine-equivalent requirement during 0 – 24 hours postoperatively, and postoperative vomiting, pruritus, and bradycardia, and low for postoperative hypotension.

Table 5. *Risk of bias of the included studies.*

Studies	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Patients and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)
Abdelmageed 2011 (23)	Low	Low	Low	Low	Low	Low
Altindis 2008 (24)	Low	Low	Low	Low	Unclear	Unclear
Arain 2004 (25)	Low	Unclear	Low	Low	Unclear	Unclear
Demirhan 2011 (26)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gunes 2008 (27)	Unclear	Unclear	Low	Low	Unclear	Unclear
Kim 2013 (28)	Low	Low	Low	Low	Low	Low
Korkmaz 2013 (29)	Low	Low	Low	Low	Unclear	Unclear
Lee 2013 (30)	Unclear	Unclear	Low	Low	Unclear	Unclear
Lin 2009 (31)	Low	Low	Low	Low	Low	Low
Nie 2014 (32)	Low	Low	Low	Low	Low	Low
Ramsay 2014 (33)	Low	Low	Low	Low	Low	Low
Ren 2015(1) (34)	Low	Low	Low	Low	Low	Low
Ren 2015(2) (35)	Low	Low	Low	Low	Low	Low
Song 2016 (36)	Low	Low	Low	Low	Low	Low
Wang 2015 (37)	Low	Low	Low	Low	Low	Low
Wang 2016 (38)	Low	Low	Low	Low	Low	Low
Wu 2011 (39)	Unclear	Unclear	Low	Low	Low	Low
Zhang 2014 (40)	Low	Low	Low	Low	Unclear	Unclear

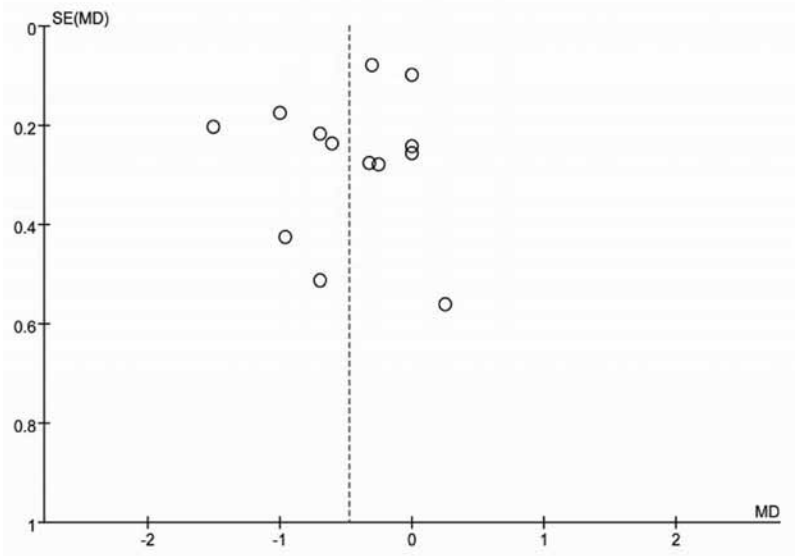

Fig. 6. ***Funnel plot for pain intensity at rest at 24 hours postoperatively.***
MD = weighted mean difference; SE = standard error

Table 6. *GRADE evidence profile.*

Quality Assessment							No. of Patients		Effect		Quality	Importance
No. of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Opioid + DEX**	**Opioid Alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain Intensity at Rest at 24 h Postoperatively												
13	RCT	Not serious	Serious(a)	Not serious	Not serious	None	553	476	-	MD: 0.48 lower (0.75 lower to 0.21 lower)	⊕⊕⊕◯ Moderate	Critical
Morphine-Equivalent Consumption during 0-24 h Postoperatively												
13	RCT	Not serious	Serious(b)	Not serious	Not serious	None	527	494	-	MD: 12.16 lower (16.12 lower to 8.21 lower)	⊕⊕⊕◯ Moderate	Critical
Incidence of Postoperative Nausea												
17	RCT	Not serious	Not serious	Not serious	Not serious	None	171/644 (26.6%)	220/606 (36.3%) 32.6% (c)	RR: 0.66 (0.52 to 0.83)	123 fewer per 1,000 (from 62 fewer to 174 fewer) 111 fewer per 1,000 (from 55 fewer to 157 fewer)	⊕⊕⊕⊕ High	Critical
Incidence of Postoperative Vomiting												
13	RCT	Not serious	Not serious	Not serious	Serious(d)	None	57/510 (11.2%)	79/471 (16.8%) 13.3% (c)	RR: 0.65 (0.49 to 0.87)	59 fewer per 1,000 (from 22 fewer to 86 fewer) 47 fewer per 1,000 (from 17 fewer to 68 fewer)	⊕⊕⊕◯ Moderate	Critical
Incidence of Postoperative Pruritus												
9	RCT	Not serious	Not serious	Not serious	Serious(e)	None	41/343 (12.0%)	50/269 (18.6%) 15.0% (c)	RR: 0.57 (0.40 to 0.81)	80 fewer per 1,000 (from 35 fewer to 112 fewer) 65 fewer per 1,000 (from 28 fewer to 90 fewer)	⊕⊕⊕◯ Moderate	Important
Incidence of Postoperative Hypotension												
11	RCT	Not serious	Not serious	Not serious	Very serious(f)	None	19/403 (4.7%)	8/397 (2.0%) 2.2%(c)	RR: 1.99 (0.88 to 4.48)	20 more per 1,000 (from 2 fewer to 70 more) 22 more per 1,000 (from 3 fewer to 77 more)	⊕⊕◯◯ Low	Important
Incidence of Postoperative Bradycardia												
11	RCT	Not serious	Not serious	Not serious	Serious(g)	None	21/418 (5.0%)	11/384 (2.9%) 3.0%(c)	RR: 1.45 (0.72 to 2.91)	13 more per 1,000 (from 8 fewer to 55 more) 13 more per 1,000 (from 8 fewer to 57 more)	⊕⊕⊕◯ Moderate	Important

DEX = dexmedetomidine; MD = mean difference; RR = risk ratio; CI = confidence interval; RCT = randomized controlled trial. GRADE Working Group grades of evidence: High quality = further research is very unlikely to change our confidence in the estimate of effect. Moderate quality = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality = we are very uncertain about the estimate. a) Heterogeneity (I^2 = 83%) was found; b) Heterogeneity (I^2 = 96%) was found; c) Possible trend of effect as calculated by GRADEpro; d) RR with 95% CI for one trial was 3.00 (0.13 – 68.26); e) RR with 95% CI for one trial was 5.00 (0.25 – 99.95); f) RR with 95% CI was 7.00 (0.39 – 124.83) for one trial and 9.00 (0.51 – 158.85) for another; g. RR with 95% CI for one trial was 3.00 (0.13 – 70.30).

Discussion

This meta-analysis comprehensively reviewed the current literature and demonstrated that compared with opioids alone, the opioid-DEX combination significantly decreased postoperative pain intensity, opioid requirement, and incidence of opioid-related adverse effects. The evidence of the benefits of combination therapy was confirmed by the TSA. In addition, the prolonged use of DEX after surgery did not increase the risk of hypotension or bradycardia, which was also confirmed by the TSA.

The results of this meta-analysis reinforced and updated the current understanding on this topic (11). Our previous meta-analysis included only 7 trials involving 427 patients. In contrast, the present meta-analysis includes 18 trials and 1,284 patients, which added statistical power. We conducted subgroup analyses for the primary outcomes to investigate the influence of various interventional factors. Notably, the TSA was applied to achieve more statistically significant estimates, indicating the current evidence obtained from this meta-analysis was sufficient and conclusive. We also provide GRADE level of evidence in order that healthcare workers may make more accurate decisions in clinical settings. Thus, this meta-analysis provides the most up-to-date and convincing evidence for the use of DEX in a PCA system.

Patients who received an opioid-DEX combination for a PCA system reported significantly better pain relief than those who received opioids alone. At postoperative 24 hours, the reduction in pain scores was 0.48 U at rest and 0.66 U on movement. In addition, the morphine-sparing effect of DEX was estimated to be 12.16 mg over 24 hours. This effect is greater than that obtained with cyclo-oxygenase 2 inhibitors (10.92 mg), NSAIDs (10.18 mg), tramadol (6.91 mg), and paracetamol (6.34 mg), when these analgesic adjutants are combined with morphine for postoperative pain management (41,42). Moreover, it is notable that improved postoperative analgesia achieved with DEX was also accompanied by a reduction in postoperative opioid-related adverse events, including PONV and pruritus.

DEX infusions can potentially induce hemodynamic changes such as hypotension and bradycardia; it is therefore essential to determine the safety of the prolonged use of DEX in a PCA system. This meta-analysis found that the use of DEX for postoperative PCA did not increase the risk of hypotension or bradycardia. Furthermore, the TSA confirmed that this result was reliable and that no additional trial was needed. A study has reported that stable hemodynamics was found when the loading dose of DEX was omitted, without compromising on sedation and analgesia (43). In our study, the relatively low doses of DEX administered (ranging from 2 μg/h to 10 μg/h) may have helped avoid clinically significant hypotension or bradycardia.

This meta-analysis has several limitations. First, the risk of introducing potentially significant heterogeneity exists; subgroup analyses revealed that the type of surgery, type of anesthesia, and method of DEX administration contributed to this heterogeneity. Second, this study did not evaluate the effects of DEX combined with opioids on long-term outcomes after hospital discharge, including chronic pain, rehabilitation, and patient satisfaction. Finally, the current results could not provide information on the dose-response effects, if any, of DEX used in PCA systems; thus, the optimal dose of DEX for PCA systems warrants further research.

In conclusion, there is sufficient evidence to show that PCA with opioid-DEX combinations offers satisfactory postoperative pain relief with decreased opioid consumption and adverse events. Therefore, DEX is recommended as an analgesic adjuvant for opioid-based intravenous PCA. Future dose-finding and larger outcome studies may be required.

Acknowledgement

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Supplementary Table 1. *PRISMA checklist*.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1–2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3–5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3–4, not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data-collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6–7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Fig. 1

Supplementary Table 1 con't. *PRISMA checklist*.

Section/topic	#	Checklist item	Reported on page #
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7–8, Table 1,2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, Table 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	8–9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8–9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8–9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome levels (e.g., risk of bias) and at review level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11–12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; 6(6):e1000097. doi:10.1371/journal.pmed1000097.
For more information, visit: www.prisma-statement.org.

Supplementary Table 2. *Search strategies*.

PubMed **Searched on: Dec 29, 2016** **Results: 61**	
Search	**Query**
#1	"dexmedetomidine"[mh]
#2	(MPV-1440) OR (MPV 1440) OR (MPV1440) OR (Precedex) OR (Hospira brand of dexmedetomidine hydrochloride) OR (dexmedetomidine hydrochloride) OR (hydrochloride, dexmedetomidine)
#3	#1 OR #2
#4	"analgesia, patient controlled"[mh]
#5	(analgesia, patient controlled) OR (patient-controlled analgesia) OR (patient controlled analgesia)
#6	#4 OR #5
#7	#3 AND #6
#8	"randomized controlled trials as topic"[mh]
#9	"randomized controlled trial"[pt]
#10	"controlled clinical trial"[pt]
#11	"random*"[tiab]
#12	#8 OR #9 OR #10 OR #11
#13	#7 AND #12

EMBASE **Searched on: Dec 29, 2016** **Results: 78**	
Search	**Query**
#1	'dexmedetomidine'/exp
#2	dexmedetomidine:ab,ti
#3	#1 OR #2
#4	'patient controlled analgesia'/exp
#5	'patient controlled analgesia':ab,ti
#6	#4 OR #5
#7	#3 AND #6
#8	'randomized controlled trial (topic)'/exp
#9	'randomized controlled trial'/exp
#10	'controlled clinical trial'/exp
#11	random*:ab,ti
#12	#8 OR #9 OR #10 OR #11
#13	#7 AND #12

CENTRAL **Searched on: Dec 29, 2016** **Results: 187**	
Search	**Query**
#1	MeSH descriptor: [dexmedetomidine]
#2	MeSH descriptor: [analgesia, patient-controlled]
#3	dexmedetomidine:ti,ab,kw
#4	patient controlled analgesia:ti,ab,kw
#5	#1 OR #3
#6	#2 OR #4
#7	#5 AND #6
#8	MeSH descriptor: [randomized controlled trial]
#9	MeSH descriptor: [randomized controlled trials as topic]
#10	MeSH descriptor: [controlled clinical trial]
#11	random*:ti,ab,kw
#12	#8 OR #9 OR #10 OR #11
#13	#7 AND #12

Supplementary Table 3. *Subgroup analyses of opioid-DEX combination versus opioid-only for intravenous PCA: pain intensity at rest at 24 hours postoperatively and morphine-equivalent requirement during 0 – 24 hours postoperatively.*

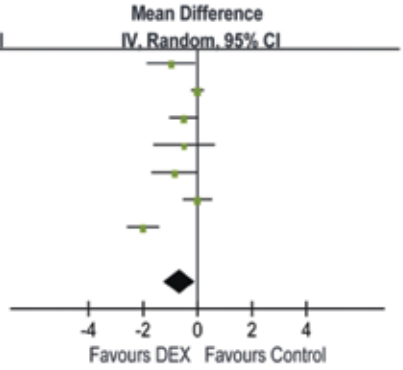
Subgroup	Pain Intensity at Rest at 24 hours Postoperatively				Morphine-Equivalent Requirement during 0 – 24 hours Postoperatively			
	No. of Trials	MD [95% CI]	*P*-value	Test of Interaction, *P*	No. of Trials	RR [95% CI]	*P*-value	Test of Interaction, *P*
Total	13	-0.48 points [-0.75, -0.21]	0.0005	N/A	13	-12.16 mg [-16.12, -8.21]	0.00001	N/A
Type of Surgery								
Major	11	-0.36 points [-0.59, -0.14]	0.002	0.03	11	-10.82 mg [-14.83, -6.82]	0.00001	0.003
Minor	2	-1.24 points [-1.97, -0.50]	0.001		2	-30.00 mg [-41.85, -18.16]	0.00001	
Type of Anesthesia								
General	10	-0.33 points [-0.56, -0.09]	0.007	0.04	11	-11.68 mg [-15.84, -7.52]	0.00001	0.48
Regional or local	3	-1.02 points [-1.64, -0.40]	0.001		2	-17.74 mg [-34.02, -1.46]	0.03	
Allocation Concealment								
Adequate	10	-0.45 points [-0.83, -0.07]	0.02	0.95	10	-8.96 mg [-12.67, -5.25]	0.00001	0.05
Unclear	3	-0.46 points [-0.78, -0.15]	0.004		3	-20.85 mg [-31.99, -9.72]	0.0002	
NSAIDs Use								
No	10	-0.45 points [-0.76, -0.14]	0.004	0.72	11	-12.7 mg [-17.23, -8.20]	0.00001	0.93
Yes	3	-0.54 points [-0.96, -0.13]	0.01		2	-13.87 mg [-39.18, 11.44]	0.28	
Intraoperative DEX Use								
No	7	-0.53 points [-0.81, -0.24]	0.0003	0.74	4	-13.17 mg [-26.26, -0.08]	0.05	0.84
Yes	6	-0.44 points [-0.88, 0.00]	0.05		9	-11.78 mg [-16.59, -6.97]	0.00001	
DEX Administration								
PCA system	10	-0.47 points [-0.85, -0.09]	0.02	0.53	9	-9.85 mg [-14.17, -5.52]	0.00001	0.03
Infusion	3	-0.34 points [-0.49, -0.19]	0.00001		4	-19.65 mg [-27.08, -12.23]	0.00001	
PCA DEX Dosage								
< 25 μg/h	8	-0.42 points [-0.80, -0.04]	0.03	0.65	7	-15.96 mg [-25.88, -6.05]	0.002	0.09
≥ 25 μg/h	5	-0.56 points [-1.06, -0.07]	0.02		6	-7.00 mg [-9.98, -4.02]	0.00001	

DEX = dexmedetomidine; PCA = patient-controlled analgesia; NSAID = nonsteroidal anti-inflammatory drug; MD = mean difference; RR = risk ratio; CI = confidence interval; N/A = not applicable

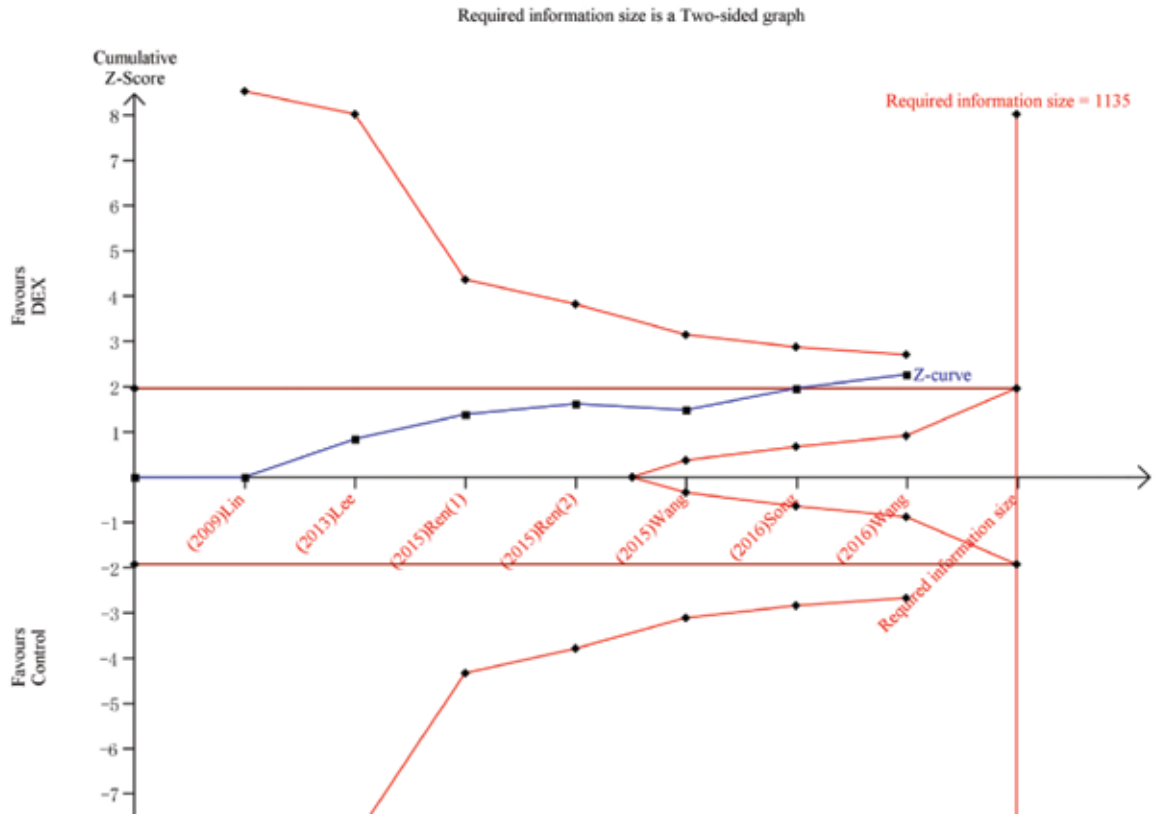
A

Study or Subgroup	DEX Mean	DEX SD	DEX Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Lee 2013	3.11	1.43	30	4.07	1.96	30	12.6%	-0.96 [-1.83, -0.09]
Lin 2009	4	0.5	50	4	0.5	48	17.2%	0.00 [-0.20, 0.20]
Ren 2015(1)	2.5	0.99	84	3	1.5	41	15.5%	-0.50 [-1.01, 0.01]
Ren 2015(2)	2.51	2.11	55	3	2.5	27	10.8%	-0.49 [-1.59, 0.61]
Song 2016	4.12	1.64	53	4.96	2.52	52	13.1%	-0.84 [-1.65, -0.03]
Wang 2015	3	2	75	3	1	77	15.5%	0.00 [-0.50, 0.50]
Wang 2016	2	1	40	4	1.5	40	15.1%	-2.00 [-2.56, -1.44]
Total (95% CI)			387			315	100.0%	**-0.66 [-1.25, -0.08]**

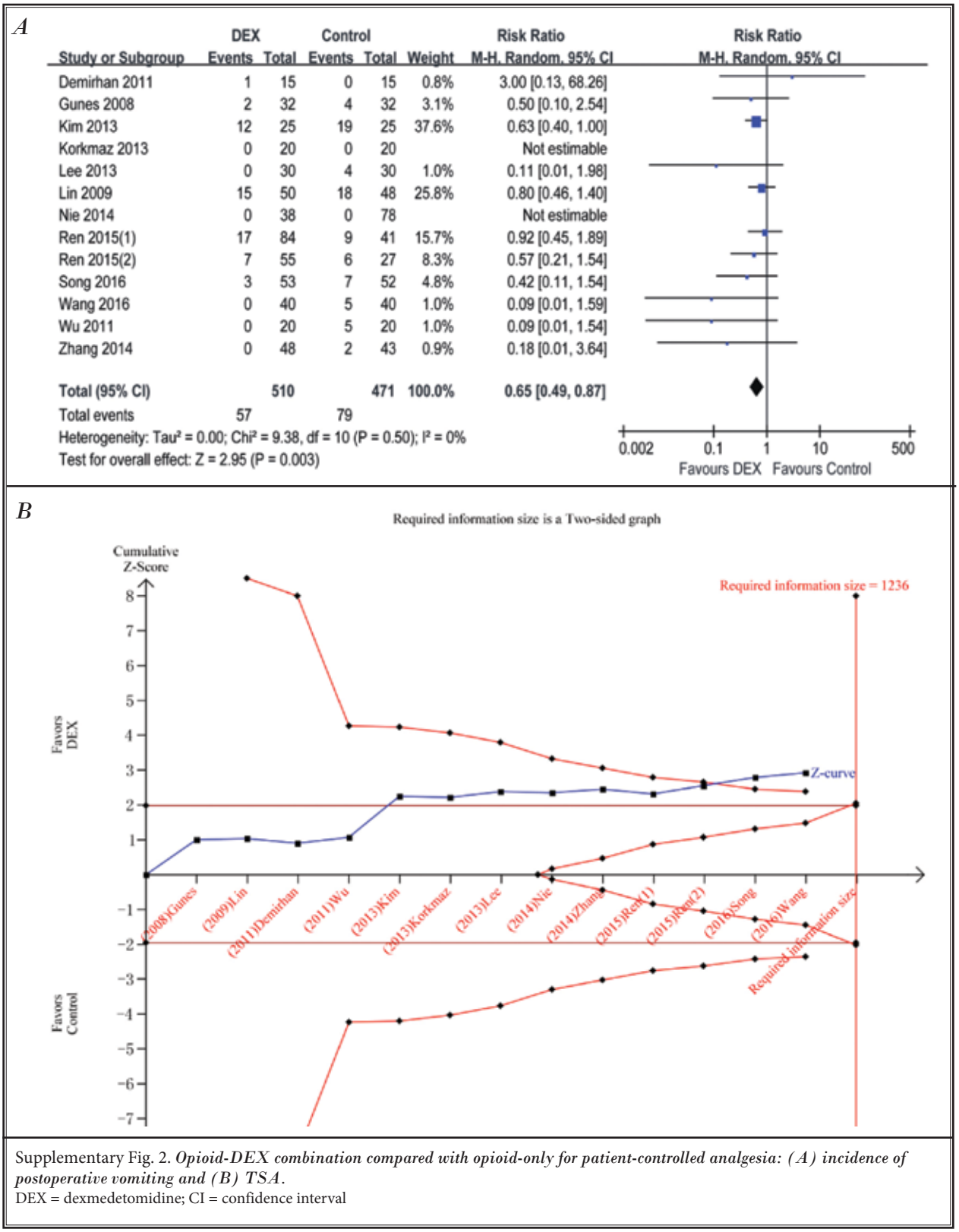
Heterogeneity: Tau² = 0.50; Chi² = 50.31, df = 6 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.23 (P = 0.03)



B



Supplementary Fig. 1. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) pain intensity on movement at 24 hours postoperatively and (B) TSA.*
DEX = dexmedetomidine; SD = standard deviation; CI = confidence interval



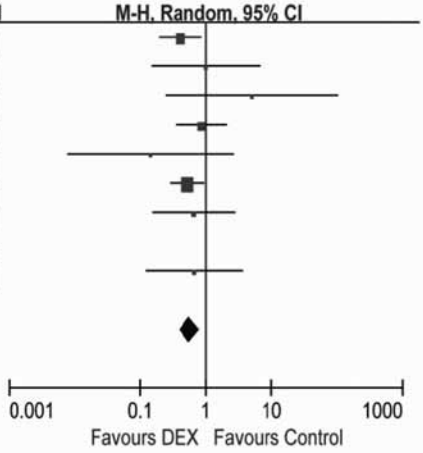
Supplementary Fig. 2. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) incidence of postoperative vomiting and (B) TSA.*
DEX = dexmedetomidine; CI = confidence interval

A

Study or Subgroup	DEX Events	DEX Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdelmageed 2011	6	20	14	19	25.0%	0.41 [0.20, 0.84]
Kim 2013	2	25	2	25	3.7%	1.00 [0.15, 6.55]
Lee 2013	2	30	0	30	1.5%	5.00 [0.25, 99.95]
Lin 2009	8	50	9	48	17.4%	0.85 [0.36, 2.03]
Ramsay 2014	0	19	3	19	1.6%	0.14 [0.01, 2.59]
Ren 2015(1)	17	84	16	41	39.9%	0.52 [0.29, 0.92]
Ren 2015(2)	4	55	3	27	6.4%	0.65 [0.16, 2.72]
Wang 2016	0	40	0	40		Not estimable
Wu 2011	2	20	3	20	4.6%	0.67 [0.12, 3.57]
Total (95% CI)		**343**		**269**	**100.0%**	**0.57 [0.40, 0.81]**
Total events	41		50			

Heterogeneity: Tau² = 0.00; Chi² = 5.14, df = 7 (P = 0.64); I² = 0%

Test for overall effect: Z = 3.08 (P = 0.002)



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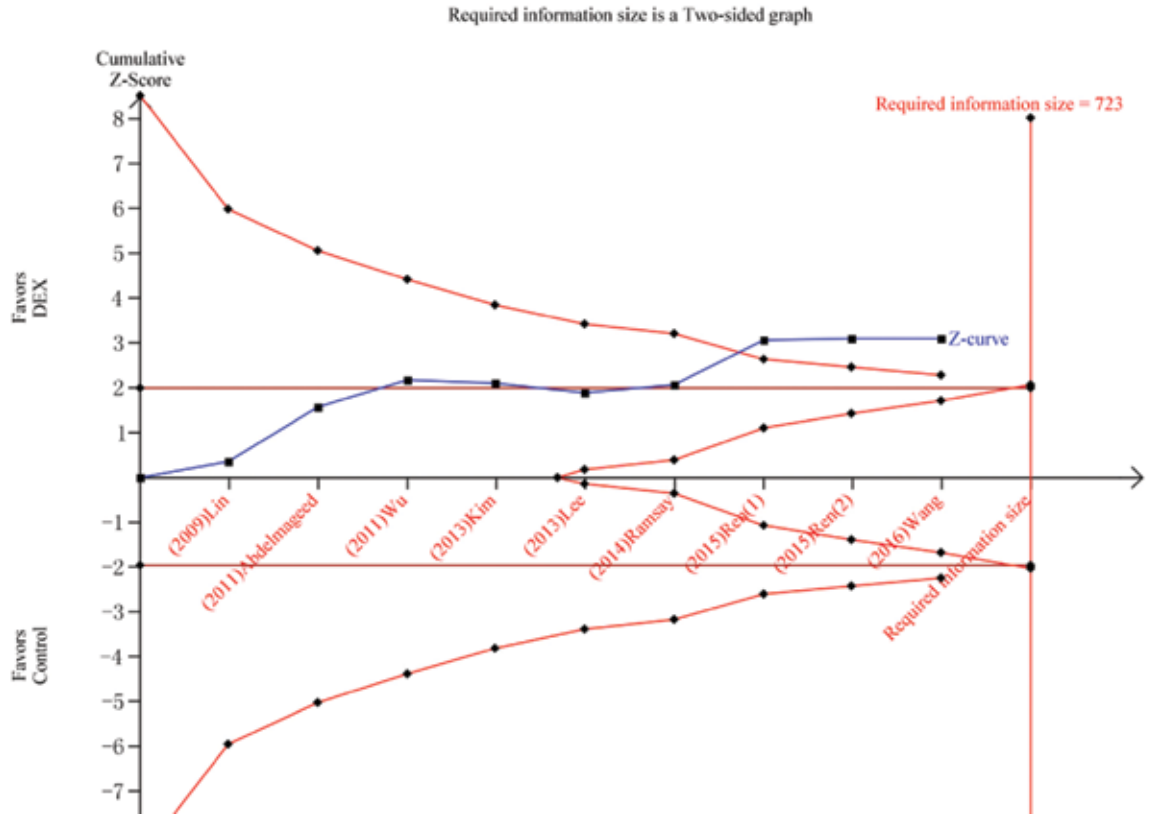
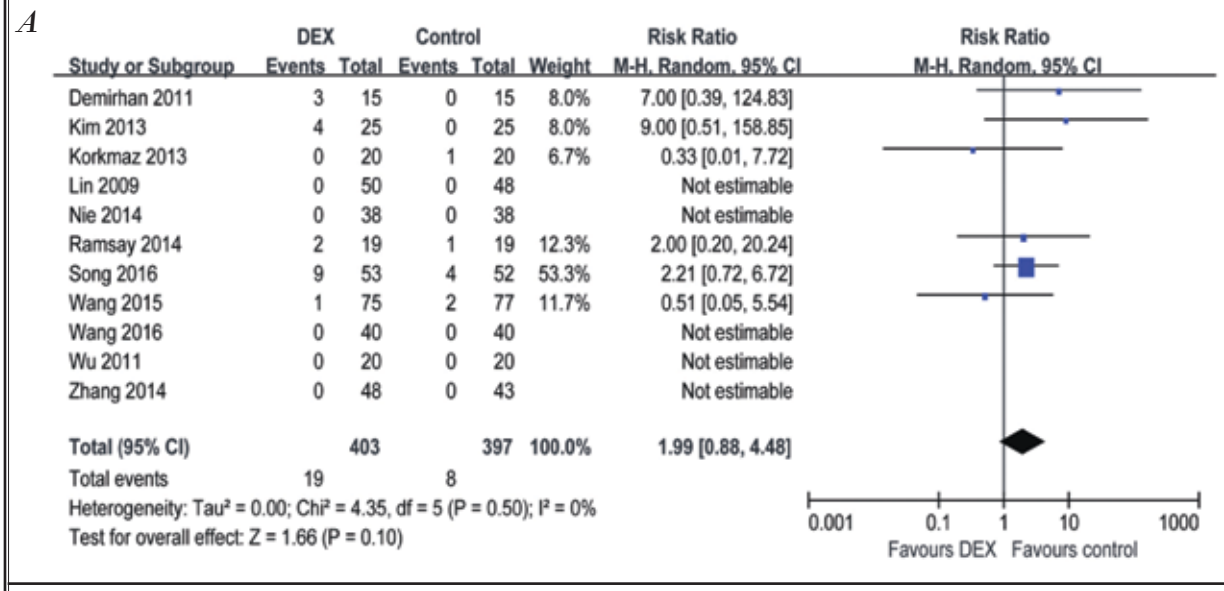
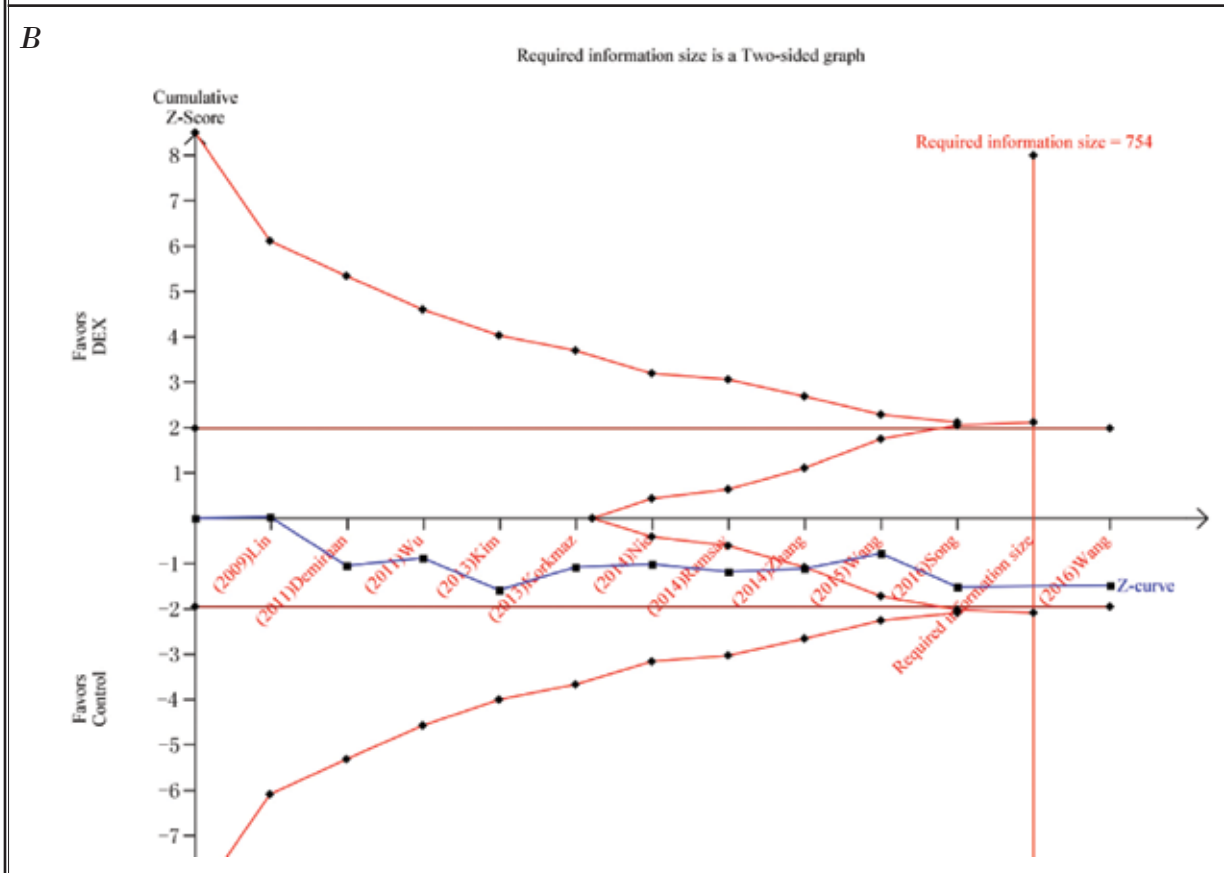
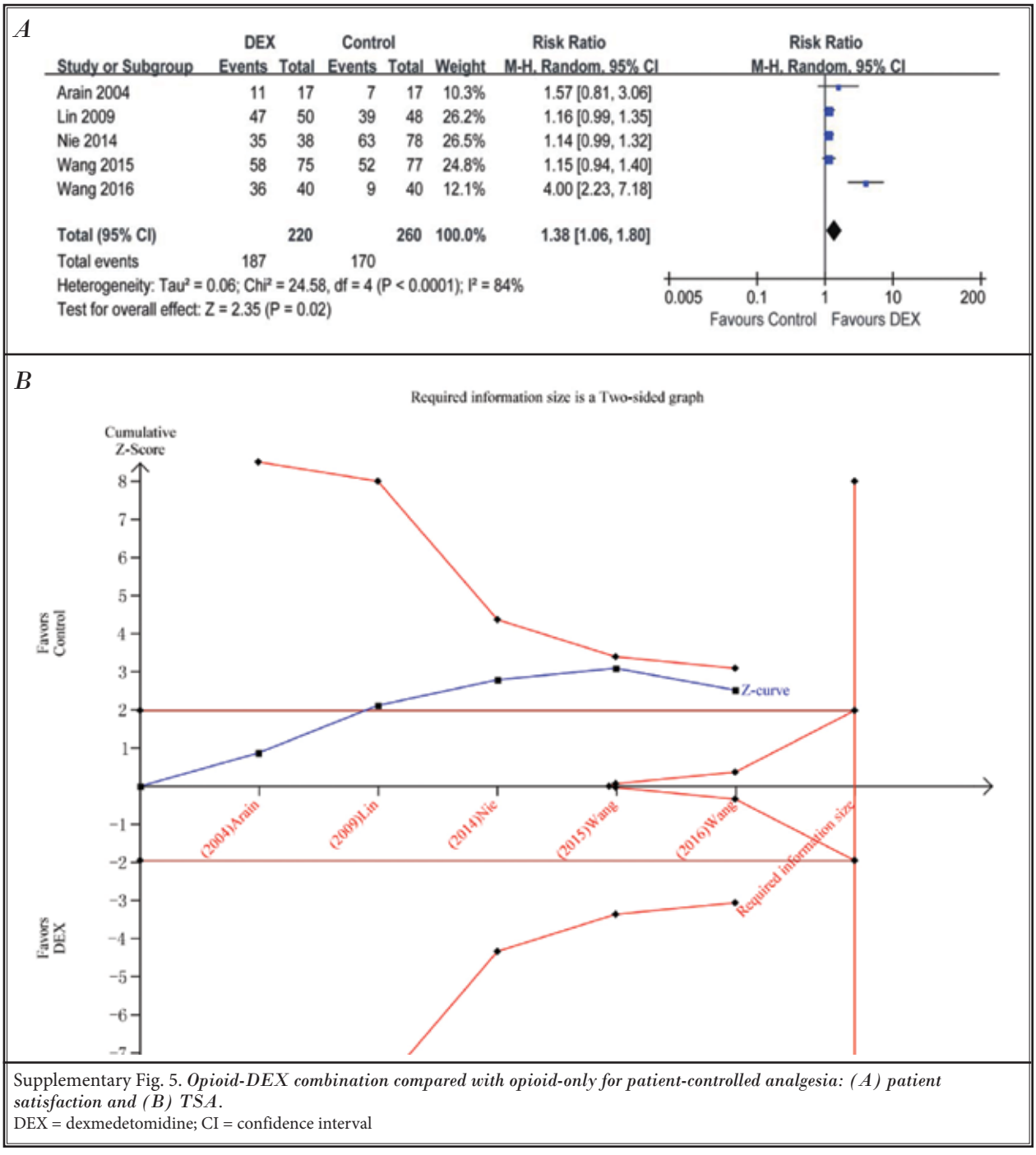


Supplementary Fig. 3. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) incidence of postoperative pruritus and (B) TSA.*
DEX = dexmedetomidine; CI = confidence interval





Supplementary Fig. 4. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) incidence of postoperative hypotension and (B) TSA.*
DEX = dexmedetomidine; CI = confidence interval



Supplementary Fig. 5. *Opioid-DEX combination compared with opioid-only for patient-controlled analgesia: (A) patient satisfaction and (B) TSA.*
DEX = dexmedetomidine; CI = confidence interval

References

1. Breivik H, Stubhaug A. Management of acute postoperative pain: Still a long way to go! *Pain* 2008; 137:233-234.
2. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006; 367:1618-1625.
3. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. *Cochrane Database Syst Rev* 2015; CD003348.
4. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology* 2010; 112:226-238.
5. Kharasch ED, Brunt LM. Perioperative opioids and public health. *Anesthesiology* 2016; 124:960-965.
6. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol* 2009; 22:588-593.
7. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. *Ann Pharmacother* 2009; 43:2064-2074.
8. Iirola T, Aantaa R, Laitio R, Kentala E, Lahtinen M, Wighton A, Garratt C, Ahtola-Sätilä T, Olkkola KT. Pharmacokinetics of prolonged infusion of high-dose dexmedetomidine in critically ill patients. *Crit Care* 2011; 15:R257.
9. Schnabel A, Meyer-Frießem CH, Reichl SU, Zahn PK, Pogatzki-Zahn EM. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. *Pain* 2013; 154:1140-1149.
10. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: Systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2012; 116:1312-1322.
11. Peng K, Liu HY, Wu SR, Cheng H, Ji FH. Effects of combining dexmedetomidine and opioids for postoperative intravenous patient-controlled analgesia: A systematic review and meta-analysis. *Clin J Pain* 2015; 31:1097-1104.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 2009; 151:264-269, W64.
13. Peng K, Liu HY, Wu SR, Liu H, Zhang ZC, Ji FH. Does propofol anesthesia lead to less postoperative pain compared with inhalation anesthesia? A systematic review and meta-analysis. *Anesth Analg* 2016; 123:846-858.
14. Turan A, Atim A, Dalton JE, Keeyapaj W, Chu W, Bernstein E, Fu A, Jae Ho L, Saager L, Sessler DI. Preoperative angiotensin-converting enzyme inhibitor use is not associated with increased postoperative pain and opioid use. *Clin J Pain* 2013; 29:1050-1056.
15. Von Korff M, Saunders K, Thomas RG, Boudreau D, Campbell C, Merrill J, Sullivan MD, Rutter CM, Silverberg MJ. De facto long-term opioid therapy for noncancer pain. *Clin J Pain* 2008; 24:521-527.
16. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0: The Cochrane Collaboration, 2011. Available from: http://handbook-5-1.cochrane.org/.
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924-926.
18. Paul JE, Arya A, Hurlburt L, Cheng J, Thabane L, Tidy A, Murthy Y. Femoral nerve block improves analgesia outcomes after total knee arthroplasty: A meta-analysis of randomized controlled trials. *Anesthesiology* 2010; 113:1144-1162.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557-560.
20. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark 2011: pp 1-115. Available from www.ctu.dk/tsa.
21. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive-- trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol* 2009; 38:287-298.
22. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008; 61:64-75.
23. Abdelmageed WM, Elquesny KM, Shabana RI, Abushama HM, Nassar AM. Analgesic properties of a dexmedetomidine infusion after uvulopalatopharyngoplasty in patients with obstructive sleep apnea. *Saudi J Anaesth* 2011; 5:150-156.
24. Altindis NT, Karaaslan D, Peker TT, Ozmen S, Bulbul M. Comparison of meperidine alone with meperidine plus dexmedetomidine for postoperative patient-controlled analgesia. *Neurosciences (Riyadh)* 2008; 13:117-121.
25. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. *Anesth Analg* 2004; 98:153-158.
26. Demirhan A, Gül R, Ganidağli S, Koruk S, Mizrak A, Şanli M, Öner Ü. [Combination of dexmedetomidine and tramadol in the treatment of pain after thoracotomy]. *GKD Anest Yog Bak Derneg* 2011; 17:34-41.
27. Gunes Y, Ozbek TH, Gunduz HM, Gedik YE, Erman T, Ozcengiz D. Patient-controlled analgesia comparison of morphine to dexmedetomidine plus morphine in patients undergoing laminectomy. *Neurosurg Quart* 2008; 18:178-181.
28. Kim SY, Chang CH, Lee JS, Kim YJ, Kim MD, Han DW. Comparison of the efficacy of dexmedetomidine plus fentanyl patient-controlled analgesia with fentanyl patient-controlled analgesia for pain control in uterine artery embolization for symptomatic fibroid tumors or adenomyosis: A prospective, randomized study. *J Vasc Interv Radiol* 2013; 24:779-786.
29. Korkmaz Dişli Z, Çelebi N, Canbay Ö, Çelebioğlu B. [Comparison of morphine and dexmedetomidine delivered by patient-controlled analgesia device during the postoperative period of coronary artery bypass surgery]. *Anestezi Dergisi* 2013; 21:29-36.
30. Lee W, Shin JD, Choe K, Kim MH. Comparison of dexmedetomidine and ketamine for the analgesic effect using intravenous patient-controlled analgesia after gynecological abdominal surgery. *Korean J Anesthesiol* 2013; 65(6 Suppl):S132-S134.
31. Lin TF, Yeh YC, Lin FS, Wang YP, Lin CJ, Sun WZ, Fan SZ. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* 2009; 102:117-122.
32. Nie Y, Liu Y, Luo Q, Huang S. Effect of

dexmedetomidine combined with sufentanil for post-caesarean section intravenous analgesia: A randomised, placebo-controlled study. *Eur J Anaesthesiol* 2014; 31:197-203.

33. Ramsay MA, Newman KB, Leeper B, Hamman BL, Hebeler RF Jr., Henry AC, Kourlis H Jr., Wood RE, Stecher JA, Tillmann Hein HA. Dexmedetomidine infusion for analgesia up to 48 hours after lung surgery performed by lateral thoracotomy. *Proc (Bayl Univ Med Cent)* 2014; 27:3-10.
34. Ren C, Zhang X, Liu Z, Li C, Zhang Z, Qi F. Effect of intraoperative and postoperative infusion of dexmedetomidine on the quality of postoperative analgesia in highly nicotine-dependent patients after thoracic surgery: A CONSORT-prospective, randomized, controlled trial. *Medicine (Baltimore)* 2015; 94:e1329.
35. Ren C, Chi M, Zhang Y, Zhang Z, Qi F, Liu Z. Dexmedetomidine in postoperative analgesia in patients undergoing hysterectomy: A CONSORT-prospective, randomized, controlled trial. *Medicine (Baltimore)* 2015; 94:e1348.
36. Song Y, Shim JK, Song JW, Kim EK, Kwak YL. Dexmedetomidine added to an opioid-based analgesic regimen for the prevention of postoperative nausea and vomiting in highly susceptible patients: A randomised controlled trial. *Eur J Anaesthesiol* 2016; 33:75-83.
37. Wang K, Li C, Shi J, Wei H. [Effects of patient-controlled intravenous analgesia with dexmedetomidine and sufentanil on postoperative cognition in elderly patients after spine surgery]. *Zhonghua Yi Xue Za Zhi* 2015; 95:2437-2441.
38. Wang X, Wang K, Wang B, Jiang T, Xu Z, Wang F, Yu J. Effect of oxycodone combined with dexmedetomidine for intravenous patient-controlled analgesia after video-assisted thoracoscopic lobectomy. *J Cardiothorac Vasc Anesth* 2016; 30:1015-1021.
39. Wu ZL, Zhou ZF, Xu LX, She SZ. [Effect of dexmedetomidine on patient-controlled intravenous analgesia with fentanyl in elderly patients after total hip replacement]. *Nan Fang Yi Ke Da Xue Xue Bao* 2011; 31:701-704.
40. Zhang Y, Zhang L, Zhang W. [Effect of postoperative analgesia with dexmedetomidine on the survival rate of amputated finger replantation]. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2014; 30:187-190.
41. McDaid C, Maund E, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction of morphine-related side-effects after major surgery: A systematic review. *Health Technol Assess* 2010; 14:1-153, iii-iv.
42. Martinez V, Guichard L, Fletcher D. Effect of combining tramadol and morphine in adult surgical patients: A systematic review and meta-analysis of randomized trials. *Br J Anaesth* 2015; 114:384-395.
43. Ickeringill M, Shehabi Y, Adamson H, Ruettimann U. Dexmedetomidine infusion without loading dose in surgical patients requiring mechanical ventilation: Haemodynamic effects and efficacy. *Anaesth Intensive care* 2004; 32:741-745.