Efficacy and safety of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia: A meta-analysis with trial sequential analysis of 23 randomised controlled trials

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Abstract
To further identify the real efficacy and safety of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia, we conducted this meta-analysis. The systematic search strategy was performed using PubMed, Embase, Cochrane Library, and Chinese databases. As a result, a total of 23 RCTs (1445 patients) were included. Patients receiving dexmedetomidine combined with local anaesthetics had a lower rescue analgesia rate [risk ratio (RR): 0.48; 95% confidence interval (CI): 0.36-0.65] and lower rescue analgesic consumption [weighted mean difference (WMD): −10.80 mg; 95%CI: −13.28 to −8.31 mg] than patients receiving local anaesthetics alone. The dexmedetomidine-related adverse reactions included bradycardia (RR: 1.33; 95%CI: 0.32-5.56) and hypotension (RR: 3.00; 95%CI: 0.49-18.42). In addition, the time to first analgesic request (WMD: 296.16 minutes; 95%CI: 165.69 minutes – 426.63 minutes), incidence of postoperative nausea and vomiting (PONV) and pain scores at 4 hours postoperatively were also significantly lower in patients receiving dexmedetomidine combined with local anaesthetics. This meta-analysis demonstrated that the use of dexmedetomidine as an adjuvant to wound infiltration is effective for reducing the rescue analgesia rate, rescue analgesic consumption and PONV. In addition, limited evidence shows that dexmedetomidine can prolong postoperative analgesia for approximately 5 hours. Further investigations on dexmedetomidine-related adverse reactions and the dose–response effect of dexmedetomidine in wound infiltration are warranted.

Keywords
adjuvant, dexmedetomidine, local wound infiltration, meta-analysis, trial sequential analysis

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1  |  INTRODUCTION

Postoperative pain and opioid-related adverse drug events are still among the principal factors affecting the rapid recovery and discharge of patients undergoing surgery.\(^1\) Wound pain at rest and on movement is one of the main sources of postoperative pain.\(^2\) In addition, skin traction stimulation, which can be caused by respiratory movement and the daily activities of patients after surgery, further aggravates the severity of wound pain, resulting in restlessness and insomnia and even inducing serious symptoms such as wound tear and infection. The technique of wound infiltration analgesia has been shown to play an active role in relieving postoperative pain and reducing opioid consumption.\(^2\)

Wound infiltration analgesia includes either local wound infiltration (LWI) or continuous wound infiltration (CWI) via a catheter. CWI has been shown to be effective but has also been found to be associated with increased difficulty in postoperative care, catheter detachment, and fluid leakage.\(^3\),\(^4\) While LWI with a single local anaesthetic can be used to overcome these complications, the analgesic time is unsatisfactory.\(^5\),\(^6\) By increasing the duration of action, dexmedetomidine (DEX), an \(\alpha_2\)-agonist, may help avoiding the need for catheters insertions.\(^7\)

In a previous meta-analysis conducted by our research team, the analgesic effect of DEX was not fully evaluated because of the small sample size and single analysis methods. Although this meta-analysis favoured DEX, the type of surgery examined was limited to abdominal surgery. In addition, DEX-related adverse reactions such as bradycardia and hypotension were not evaluated, and no trial sequential analysis (TSA) was conducted.\(^8\) These important topics have not been fully elucidated, and thus, it is important to further investigate the efficacy and safety of DEX in wound infiltration. Therefore, we conducted this meta-analysis to evaluate the analgesic effect of DEX as an adjuvant to local anaesthetics vs local anaesthetics alone in wound infiltration. Furthermore, we conducted a comprehensive investigation of the occurrence of adverse reactions with the aim of gaining greater insights into the safety of DEX.

2  |  METHODS

2.1  |  Search strategy

Based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the recommendations from the Cochrane Collaboration, a systematic search was performed using PubMed, Embase, the Cochrane Library, and Chinese databases [Chinese National Knowledge Infrastructure (CNKI) and Wan-Fang database]. In addition, Google Scholar was used to retrieve grey literature. This meta-analysis was registered in the PROSPERO database: CRD42020175117. The full search strategy is provided in the Appendix (Supplementary Search Strategies).

The search included studies published prior to May 2020. A manual search was also performed to select articles and published reviews. Because this study is a meta-analysis, there was no need for ethical approval and informed consent.

2.2  |  Study selection

Studies were included if they met the following criteria: (1) the study was a randomised controlled trial (RCT); (2) the study compared patients who received DEX as an adjuvant to local anaesthetics with patients who received local anaesthetics alone for local wound infiltration analgesia; (3) the study included a DEX group and placebo (PLA) group, at least; and (4) the full text of the study was available. There were no language restrictions. Studies were excluded if (1) they were abstracts, conference articles, and protocols, (2) they did not have complete data, or (3) DEX was given intravenously in the study.

2.3  |  Data retrieval

The extracted information included the name of the main author, the year of publication, the type of surgery, the sample size, the doses administered to the DEX group and the PLA group, and outcomes.

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**Key Messages**

- this meta-analysis investigated the real efficacy and safety of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia
- the results of trial sequential analysis showed that the evidences of dexmedetomidine used in wound infiltration to improve the analgesic effect of local anaesthetics are enough
- dexmedetomidine as an adjuvant can prolong postoperative analgesia for approximately 5 hours in local wound infiltration anaesthesia. Further studies should focus on the dexmedetomidine-related adverse reactions and dose–response effect of dexmedetomidine, rather than the analgesic effect
The following indexes were defined as primary outcomes: (1) the rescue analgesia rate within 24 hours after surgery, (2) the total rescue analgesic consumption in the 24-hour postoperative period, and (3) the incidence of DEX-related adverse reactions at 24 postoperative hours, that is, bradycardia and hypotension.

The secondary outcomes of this article include (1) the visual analogue score (VAS, ranging from 0 to 10; 0 corresponding to no pain and 10 representing the worst imaginable pain) at 1, 2, 4, 6, 8, 12, 24 and 48 hours postoperatively in the resting state, (2) the time of first rescue analgesia within 24 hours after surgery, and (3) the rescue analgesia of different frequencies. Other adverse events at 24 postoperative hours include postoperative nausea (PON), postoperative vomiting (POV), PONV, respiratory depression, shivering, dizziness, wound infection, sedation, and urinary retention.

Data reported in graphical form were derived by GetData Graph Digitizer Software (GetData Pty Ltd., Kogarah, Australia). The original data, which were represented by the median and interquartile range, were converted to the mean and standard deviation (SD) using the methods described by Wan et al.9 Using a published equivalence formula, cumulative opioid consumption with opioid drugs other than morphine was converted to morphine-equivalent doses, where 10 mg intravenous (i.v.) morphine = 0.01 mg i.v. sufentanil = 0.1 mg i.v. fentanyl = 100 mg i.v. tramadol = 2 mg i.v. butorphanol = 50 mg i.v. diclofenac = 100 mg i.v. pethidine. Finally, the time of first rescue analgesia and the total morphine consumption are continuous outcomes that are measured in units of minutes and milligrams, respectively.

2.4 | Qualitative assessment

The methodological quality of the included RCTs was reviewed by two reviewers (YFR and MLW) independently. The Cochrane Collaboration’s risk of bias assessment tool was used. They evaluated the quality of each article using seven domains. If there were some disagreements, they discussed the disagreements to reach consensus, or the issue was decided by two other reviewers (WS and HL). Finally, low bias, high bias, and unclear judgements were obtained.

2.5 | Statistical analysis

2.5.1 | Measures of treatment effects

Review Manager 5.3 was used for statistical analysis. The total rescue analgesic consumption and the time of the first rescue analgesia were expressed by the weight mean difference (WMD) and its 95% confidence interval (CI). Dichotomous outcomes were expressed by the risk ratio (RR) and its 95% CI. The continuity correction was applied for zero-event studies. A P value <.05 was considered statistically significant. VAS scores at different times after surgery are reported with 99% CIs (αcorrected = 0.01) because a Bonferroni correction was applied.10

2.5.2 | Heterogeneity, sensitivity and subgroup analyses

The I² statistics were used to assess the heterogeneity of the studies. If the I² < 50%, heterogeneity was considered not significant, and the fixed-effects model was applied; otherwise, we assumed that there was significant heterogeneity and used the random-effects model to calculate effect size.11 If an I² > 50% was observed, sensitivity analysis and subgroup analysis were performed to explore the sources of heterogeneity. Sensitivity analysis was conducted by excluding studies in which the quality was rated as “high risk”. The following subgroup analyses were performed if more than five trials were included for the outcome: the time of incision infiltration (before skin incision vs before skin closure), the type of local anaesthetic (ropivacaine vs bupivacaine), the DEX dose (≤1.0 μg/kg vs >1.0 μg/kg) and the anaesthesia mode (general anaesthesia vs regional anaesthesia). A two-sided P value <.05 was considered statistically significant.

2.5.3 | Assessment of publication biases

The funnel plot was used to assess the possibility of publication bias in the primary outcomes, including more than 10 trials.12 We estimated funnel plot asymmetry using Begg and Egger tests, and a one-sided P < .05 was considered to indicate significant publication bias. If a P value was less than .05, the trim-and-fill computation would be used to evaluate the effect of publication bias on the interpretation of the results. Stata 15.0 (StataCorp, College Station, TX) was used for assessment of publication biases.

2.5.4 | Trial sequential analysis

The repeated updating of a meta-analysis inevitably involves the repeated calculation of accumulated data, which results in the risk of random errors and false positives, especially in small sample sizes. Trial sequential analyses (TSA) can estimate and correct the potential
random errors and estimate the robustness and reliability of the accumulated combined data in a meta-analysis.\textsuperscript{13} Furthermore, TSA software can calculate the required information size (RIS). The RIS refers to the minimum sample size needed to achieve the maximum reliability on the basis of fully estimating the type I and type II errors. Therefore, a TSA was conducted to analyse the main outcomes by TSA software version 0.9 Beta (Copenhagen Trial Unit).

For dichotomous outcomes, a constant continuity correction was performed for zero-event trials. We calculated the RIS based on the low risk of bias studies. D\textsuperscript{2} was described as a heterogeneity correction. The risk for a type I error was 5%, and the risk for a type II error was 20% (80% power). (1) For the rescue analgesia rate, the relative risk reduction (RRR) = 44.18%, the incidence in the DEX group = 40.07%, and the incidence in the PLA group = 71.79%; (2) for the incidence of bradycardia, RRR = −18.56%, the incidence in the DEX group = 1.15%, and the incidence in the PLA group = 0.97%; (3) for the incidence of hypotension, RRR = −105.41%, the incidence in the DEX group = 0.76%, and the incidence in the PLA group = 0.37%.

For continuous outcomes, we set the effect measure as “WMD” and the model as “Random Effects (DL)” in TSA software. The risk for a type I error was 5%, and the risk for a type II error was 20% (80% power). We calculated the RIS based on the low risk of bias studies. WMD = −9.65 mg with SD = 6.92 mg.

In the graph drawn by TSA software, when the Z-curve crossed the conventional boundary and the TSA boundary value or directly crossed the RIS, we think that the current meta-analysis conclusion is stable and reliable enough, and further research would not reverse this conclusion\textsuperscript{13,14}; when the Z-curve crossed the invalid line and entered the invalid area, we think that there was no significant difference between the DEX group and PLA group; if the Z-curve did not meet the requirements of the above two lines, it indicates that further clinical studies are needed to determine the effectiveness of the DEX group.

\subsection*{2.5.5 Summary of findings}

GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) Profiler 3.6 software was also used to evaluate the evidence quality of primary outcomes in our study, which was classified as high, moderate, low, or very low. Judgements included risk of bias, inconsistency, indirectness, imprecision, and other considerations.\textsuperscript{15}

\section*{3 RESULTS}

\subsection*{3.1 Characteristics of the included studies}

The search identified 415 studies, of which 368 were eliminated from further review because they were animal studies, non-related studies, non-original articles, or duplicates. After reviewing the full texts of the articles, 24 trials were excluded. Finally, 23 RCTs were considered to be suitable for this meta-analysis,\textsuperscript{16-38} encompassing a total of 1445 adult patients. The search process is shown in Figure 1.

Of the 23 studies, patients underwent surgery under spinal anaesthesia in 2 studies,\textsuperscript{18,23} and other studies used general anaesthesia.\textsuperscript{16,17,19,22-38} Eight studies\textsuperscript{16,22,24,27,31,34,38} involved wound infiltration before skin incision, and 15 studies\textsuperscript{17-21,25,26,28-30,32,33,35-37} concerned wound infiltration before skin closure. The types of local anaesthetics include ropivacaine,\textsuperscript{18,20,22-26,28,30,33,36-38} bupivacaine\textsuperscript{16,17,19,21,29,31,32,34,35} and lidocaine.\textsuperscript{27} The concentrations of ropivacaine were 0.2%,\textsuperscript{20,22,23,30} 0.3%\textsuperscript{26,33,36} 0.375%\textsuperscript{25} 0.5%\textsuperscript{24,26,38} and 0.75%\textsuperscript{18,37}, the concentrations of bupivacaine were 0.25%\textsuperscript{17,19,21,29,31,32,34,35} and 0.5%\textsuperscript{16}, and the concentration of lidocaine was 2.0%.\textsuperscript{27} The doses of DEX were 0.5 μg/kg,\textsuperscript{28,30} 1.0 μg/kg,\textsuperscript{16,17,20,22-24,27,32,33,35,37,38} 1.5 μg/kg,\textsuperscript{18} 2.0 μg/kg,\textsuperscript{28,31} 5.0 μg/kg\textsuperscript{23,36} and 50 μg.\textsuperscript{19} In one study, adrenaline (1: 200 000) was given with lidocaine.\textsuperscript{27} Different non-opioid analgesics (tramadol, ketorolac, paracetamol, and diclofenac) were used for rescue analgesia in eight studies,\textsuperscript{16,18,19,21,28,30,31,35} and 15 trials\textsuperscript{17,20,22-27,29,32-34,36,38} reported that patients received only opioids for rescue analgesia. The detailed characteristics of all the included studies are shown in Table 1.

\subsection*{3.2 Study quality and risk of bias}

The risk-of-bias assessment for all included studies was performed by two independent reviewers (YFR and WML). All included studies provided clear inclusion and exclusion criteria. An adequate randomization method was used in all articles. Thirteen RCTs explicitly specified the method of allocation concealment (via opaque-sealed envelopes).\textsuperscript{16,18,20-23,26,29,32,34,35} Nine studies\textsuperscript{17,19,24,25,27,28,33,36,38} and 1 study,\textsuperscript{37} respectively, were assessed as having an unclear bias or high bias because of the absence of explicit or no mention of allocation concealment methods. Sixteen studies\textsuperscript{16,18,20-24,26-29,31,32,34,35,38} had a low risk of bias as a result of the blinding of participants and personnel; however, 3 trials\textsuperscript{25,33,37} were rated as being at a high risk of detection bias because there was no indication of how participants or personnel were blinded. Five trials\textsuperscript{18,21,32,33,35} were rated as an unclear risk because of incomplete outcome data. Most of the studies (13 out of 23)\textsuperscript{17,19,24,25,27,28,30,33,36-38} were assessed as
having an unclear risk of other bias because of the lack of sufficient methodological reports. Overall, seven studies\(^{16,20,22,23,26,29,34}\) had a low risk of bias, 13 studies\(^{17-19,21,24,27,28,30-32,35,36,38}\) had an unclear risk of bias, and 3 studies\(^{25,33,37}\) had a high risk of bias. The quality assessment for each study and the results of the included RCTs are shown in Figure 2.

### 3.3 Primary outcomes

#### 3.3.1 Total rescue analgesia rate within 24 hours after surgery

The total rescue analgesia rate was assessed by 16 studies.\(^{16-21,24,25,29-32,34-37}\) Patients in the DEX group required less rescue analgesia than patients receiving local anaesthetics alone (RR: 0.48; 95% CI: 0.36-0.65; \(P < .00001; I^2 = 91\%\)) (see Figure 3A).

Sensitivity analysis did not show any changes in heterogeneity (Table S1A). The subgroup analysis showed that compared with the control group, the DEX group had a significantly reduced the rate of total rescue analgesia regardless of the type of local anaesthetic, the DEX dose, the type of anaesthesia, and the type of incision infiltration. It should be noted that wound infiltration performed before skin closure led to a significant reduction in the total rescue analgesia rate (RR: 0.49; 95% CI: 0.35-0.69; \(P < .0001; I^2 = 90\%\)); however, no significant difference was observed when wound infiltration was performed before skin incision (RR: 0.43; 95% CI: 0.13-1.44; \(P = .17; I^2 = 90\%\)) (Table S1B).
| Studies (year) | Surgery                      | Groups (n): Treatment (total volume)                                                                 | Time of WI        | Analgesic   | Outcomes                                                                 |
|---------------|------------------------------|------------------------------------------------------------------------------------------------------|-------------------|-------------|--------------------------------------------------------------------------|
| Abdelnaim et al (2018) | Hernia repair               | DEX (15): 0.5% bupivacaine+1 μg/kg DEX+ NS (20 mL)                                                   | Before skin incision | Ketorolac   | Rescue analgesia rate VAS scores Bradycardia, hypotension, PON, POV, PONV, respiratory depression |
| Ahmed et al (2020) | Lower segment caesarean section | DEX (30): 0.25% bupivacaine+1 μg/kg DEX+ NS (25 mL)                                                 | Before skin closure | Morphine    | Rescue analgesia rate Rescue analgesic consumption Bradycardia, hypotension, PONV, dizzy |
| Bhardwaj et al (2017) | Lower segment caesarean section | DEX (30): 0.75% ropivacaine 3 mg/kg + 1.5 μg/kg DEX+ NS (40 mL)                                    | Before skin closure | Tramadol    | Rescue analgesia rate Rescue analgesic consumption Time to first request of analgesia VAS scores Bradycardia, hypotension, PONV, respiratory depression, wound infection, sedation |
| Bommalingappa et al (2016) | Lumbar spine surgery       | DEX (25): 0.25% bupivacaine +50 μg DEX+ NS (15 mL)                                                   | Before skin closure | Acetaminophen | Rescue analgesia rate Time to first request of analgesia VAS scores Bradycardia, PON, POV, respiratory depression, shivering, dizzy |
| Deshwal et al (2018) | Lumbar discectomy          | DEX (30): 0.2% ropivacaine+1 μg/kg DEX+ NS (30 mL)                                                   | Before skin closure | Fentanyl    | Rescue analgesia rate Rescue analgesic consumption Bradycardia, hypotension, PON, PONV, respiratory depression |
| Jyothi et al (2020) | Abdominal Surgeries        | DEX (30): 0.25% bupivacaine+2 μg/kg DEX+ NS (30 mL)                                                 | Before skin closure | Tramadol    | Rescue analgesia rate Rescue analgesic consumption Time to first request of analgesia VAS scores Bradycardia, hypotension, PON, respiratory depression, wound infection, sedation |
| Kang et al (2012) | Inguinal herniorrhaphy     | DEX (26): 0.2% ropivacaine+1 μg/kg DEX+ NS (10 mL)                                                   | Before skin incision | Fentanyl    | Rescue analgesic consumption VAS scores PON, POV, PONV, dizzy, sedation, urinary retention |
| Kim et al (2014) | Hemorrhoidectomy           | DEX (19): 0.2% ropivacaine+5 μg/kg DEX+ NS (20 mL)                                                   | Before skin incision | Fentanyl    | Rescue analgesic consumption VAS scores PONV, urinary retention |
| Li et al (2019) | Lumbar Fusion Surgery      | DEX (29): 0.5% ropivacaine+1 μg/kg DEX+ NS (20 mL)                                                   | Before skin incision | Morphine    | Rescue analgesia rate REScue analgesic consumption Bradycardia, hypotension, PONV, dizzy, wound infection |
| Li et al (2018) | Breast cancer              | DEX (40): 0.375% ropivacaine +1.0 μg/kg DEX+ NS (20 mL)                                              | Before skin closure | Sufentanil  | Rescue analgesia rate VAS scores Bradycardia, hypotension, PONV, respiratory depression, dizzy, wound infection, sedation, urinary retention |
| Luan et al (2017) | Open gastrectomy           | DEX (23): 0.3% ropivacaine+1.0 μg/kg DEX+ NS (22 mL)                                                | Before skin closure | Sufentanil  | Rescue analgesic consumption VAS scores PON, POV, PONV |

(Continues)
| Studies (year) | Surgery | Groups (n): Treatment (total volume) | Time of WI | Analgesic | Outcomes |
|---------------|---------|-------------------------------------|------------|-----------|----------|
| Mandal et al 27 (2016) | Reconstructive maxillofacial surgery | DEX (38): 2% lignocaine+1 μg/kg DEX+ NS (15 mL) PLA (38): 2% lignocaine+ NS (15 mL) | Before skin incision | Sufentanil | Rescue analgesic consumption Time to first request of analgesia Bradycardia, hypotension, PON, PO, PONV, dizzy, sedation, urinary retention |
| Mitra et al 28 (2017) | Lumbar discectomy | DEX (15): 0.5% ropivacaine+0.5 μg/kg DEX+ NS (22 mL) PLA (15): 0.5% ropivacaine+ NS (22 mL) | Before skin closure | Diclofenac | Rescue analgesic consumption Time to first request of analgesia VAS scores Bradycardia, hypotension, PON, PO, PONV, respiratory depression |
| Mohamed et al 29 (2018) | Abdominal hysterectomy | DEX (30): 0.25% bupivacaine+2 μg/kg DEX+ NS (40 mL) PLA (30): 0.25% bupivacaine+ NS (40 mL) | Before skin closure | Morphine | Rescue analgesia rate Rescue analgesic consumption Time to first request of analgesia VAS scores Bradycardia, hypotension, PON, PO, PONV, respiratory depression, sedation |
| Ranjita et al 30 (2016) | Total laparoscopic hysterectomy | DEX (40): 0.2% ropivacaine+0.5 μg/kg DEX+ NS (40 mL) PLA (40): 0.2% ropivacaine+ NS (40 mL) | Before skin closure | Diclofenac | Rescue analgesia rate Rescue analgesic consumption Time to first request of analgesia VAS scores Bradycardia, hypotension, PON, PO, PONV |
| Selvaraj et al 31 (2019) | Laparoscopic cholecystectomy | DEX (58): 0.25% bupivacaine+2 μg/kg DEX+ NS (24 mL) PLA (58): 0.25% bupivacaine+ NS (24 mL) | Before skin incision | Ketorolac | Rescue analgesia rate VAS scores PONV |
| Singh et al 32 (2017) | Abdominal hysterectomy | DEX (28): 0.25% bupivacaine +1.0 μg/kg DEX+ NS (30 mL) PLA (30): 0.25% bupivacaine+ NS (30 mL) | Before skin closure | Morphine | Rescue analgesia rate Rescue analgesic consumption VAS scores |
| Tan et al 33 (2018) | Laparoscopic cholecystectomy | DEX (20): 0.3% ropivacaine+1.0 μg/kg DEX+ NS (24 mL) PLA (20): 0.3% ropivacaine+ NS (24 mL) | Before skin closure | Butorphanol | Rescue analgesic consumption Time to first request of analgesia VAS scores PONV |
| Ülgey et al 34 (2015) | Total abdominal hysterectomy | DEX (25): 0.25% bupivacaine +2.0 μg/kg DEX+ NS (40 mL) PLA (25): 0.25% bupivacaine+ NS (40 mL) | Before skin incision | Pethidine | Rescue analgesia rate Rescue analgesic consumption VAS scores Bradycardia, hypotension, PON, PO, PONV, respiratory depression, wound infection |
| Vallapu et al 35 (2018) | Postcraniotomy | DEX (50): 0.25% bupivacaine+1 μg/kg DEX+ NS (20 mL) PLA (50): 0.25% bupivacaine+ NS (20 mL) | Before skin closure | Acetaminophen | Rescue analgesia rate Rescue analgesic consumption Time to first request of analgesia VAS scores |
| Wu et al 36 (2019) | Breast cancer | DEX (55): 0.3% ropivacaine+5.0 μg/kg DEX+ NS (250 mL) PLA (55): 0.3% ropivacaine+ NS (250 mL) | Before skin closure | Pethidine | Rescue analgesia rate VAS scores PONV, shivering, sedation |
| Xia et al 37 (2017) | Retroperitoneal laparoscopic | DEX (30): 0.75% ropivacaine +1.0 μg/kg DEX+ NS (11 mL) PLA (30): 0.75% ropivacaine+ NS (11 mL) | Before skin closure | Dezocine | Rescue analgesia rate VAS scores PONV, shivering |
TABLE 1 (Continued)

| Studies (year) | Surgery | Groups (n): Treatment (total volume) | Time of WI | Analgesic | Outcomes |
|---------------|---------|-------------------------------------|------------|-----------|----------|
| Yu et al38 (2016) | Laparoscopic cholecystectomy | DEX (35): 0.5% ropivacaine+1.0 μg/kg DEX+ NS (30 mL) PLA (35): 0.5% ropivacaine+ NS (30 mL) | Before skin incision | Pethidine | Rescue analgesic consumption VAS scores |

Abbreviations: DEX, dexmedetomidine; PLA, placebo; NS, normal saline; VAS, visual analogue scores; PON, postoperative nausea; POV, postoperative vomiting; PONV, Postoperative nausea and vomiting.

The TSA results showed that the cumulative Z-curve crossed both the traditional boundary and the TSA boundary. Therefore, the accumulated sample information of the current studies reached the expected value, indicating that the rescue analgesia rate of the DEX group was significantly lower than that of the PLA group (see Figure 3B).

Egger’s test showed that there was asymmetry in the funnel plot ($P = .000$). However, the adjusted effect estimate obtained via trim and fill analysis (with no study added) indicated that the data were unchanged (see Figure SP1). This finding suggests that publication bias does not significantly affect the stability of the pooled results.

We graded the quality of the evidence for the “total rescue analgesia rate” as “moderate” (downgraded because of publication bias).

3.3.2 | Total rescue analgesic consumption within 24 hours after surgery

Twenty studies16-24,26-35,38 investigated postoperative analgesic requirements within 24 hours after surgery, 2 trials21,35 reported insufficient graphical information to allow for extraction, and 3 studies16,19,31 were not included in the meta-analysis because their results were not reported. Thus, of the 20 studies, 1517,18,20,22-24,26-30,32-34,38 had complete data to allow statistical analysis. Compared with local anaesthetics alone, the addition of DEX significantly reduced the consumption of rescue analgesic (morphine equivalent, mg) by $10.83 \text{ mg}$ (95% CI: $-13.05$ to $-8.61 \text{ mg}$; $P < .00001$; $I^2 = 98\%$) (Tables S2A, S2B).

A TSA for postoperative equivalent consumption of morphine showed an RIS of 279 participants, and the cumulative Z-curve also crossed both the traditional boundary and the TSA boundary, demonstrating that firm evidence was established with respect to the sample size (see Figure 4B).

A funnel plot constructed using Egger’s test showed the presence of publication bias ($P = .009$). However, the adjusted effect estimate obtained via trim and fill analysis suggested that no trimming was performed, and the data were unchanged (see Figure SP2). So, it suggests no concern that the presence of publication bias has resulted in exaggerated summary effects.

We graded the quality of the evidence for the “analgesic requirement” as “moderate” (also downgraded because of publication bias).

3.3.3 | Incidence of bradycardia and hypotension

The most common adverse events following DEX administration, namely, bradycardia and hypotension, were reported by 11 (623 patients)16-18,20,21,24,25,27-29,34 and 10 (547 patients)16-18,20,21,24,25,28,29,34 of the included trials, respectively. Only one study27 reported that seven patients experienced bradycardia after surgery (4 in DEX group and 3 in PLA group) and there was no statistically significant difference between the groups ($P = .69$) (see Figure 5A). The results showed that the risk of hypotension was three-fold after receiving DEX (RR, 3.00; 95% CI: 0.49-18.42; $I^2 = 0\%$), but there was also no statistically significant difference ($P = .24$) (see Figure 5A).

Because heterogeneity was less than 50%, sensitivity and subgroup analyses were not needed.

The results of the TSA for bradycardia and hypotension showed that the current evidence was insufficient with respect to sample size (see Figure SP3).
We graded the quality of the evidence for 'bradycardia' and 'hypotension' as "low" (downgraded because of inconsistency and imprecision).

3.4 Secondary outcomes

3.4.1 Time of first rescue analgesia

Eleven studies\textsuperscript{16,18,19,21,24,27-30,33,35} reported the time of first rescue analgesia, and 2\textsuperscript{16,21} of these 11 trials were not included in the meta-analysis because the only data reported were the means. Compared with receiving local anaesthetics alone, the addition of DEX significantly prolonged the time to first analgesic request by an average of 296.16 minutes (95% CI: 165.69-426.63 minutes; \(P < .00001; I^2 = 100\%\)) (see Figure 6A).

As a result of the high statistical heterogeneity (\(I^2 = 100\%\)), the sensitivity analysis and subgroup analyses were also used to analyse the sources of heterogeneity. The effect estimates remained robust in a sensitivity analysis excluding high-risk trials (WMD: 268.26 minutes; 95% CI: 135.89-400.63 minutes; \(P < .0001; I^2 = 100\%\)) (Table S3A). Upon stratification of the data based on the type of local anaesthetic, compared with bupivacaine (WMD: 167.77 minutes; 95% CI: 110.22-225.33 minutes; \(P < .00001; I^2 = 69\%\)), it seems that ropivacaine is more effective in prolonging the time to first analgesic request (WMD: 392.37 minutes; 95% CI: 191.53-593.20 minutes; \(P = .0001; I^2 = 100\%\)) (Table S3B).

3.4.2 Rescue analgesia rate of different frequencies measurements within 24 hours after surgery

Considering that in some of the studies, the difference in the total rescue analgesia rate between the DEX group and the control group was not obvious, we tried to confirm the reliability of the postoperative analgesic consumption result through rescue analgesia of different frequencies measurement. Three studies\textsuperscript{18,24,29} evaluated the rescue analgesia rate of different frequency (once/twice/>twice). The results showed that the number of patients in the DEX group was higher than that in the control group in aspect of rescue analgesia of once (RR: 3.68; 95% CI: 1.80-7.51; \(P = .0003; I^2 = 0\%\)), but the number of patients in the DEX group was much lower than that in the control group when rescue analgesia was more than twice (RR: 0.18; 95% CI: 0.06-0.55; \(P = .003; I^2 = 63\%\)). No significant difference was observed when rescue analgesia was administered twice (RR: 1.26; 95% CI: 0.59-2.71; \(P = .55; I^2 = 48\%\)) (see Figure 6B). As a result of the limited number of included trials, sensitivity analyses, and funnel plot analyses were not performed.
Twenty trials\textsuperscript{16,18-20,22-26,28-38} investigated the outcome “the pain scores at different times postoperatively”. Four\textsuperscript{18,19,31,32} of these 20 trials were not included in the meta-analysis because the only data reported were the means or because the data could not be extracted. VAS scores were used as a pain scoring tool in all 16 RCTs. The data can be combined and analysed only when the number of studies is more than two for a given outcome.
−0.88 to −0.30; \( P < .0001; I^2 = 86\% \), 8 hours (WMD: −0.83 cm; 95% CI: −1.05 to −0.61; \( P < .00001; I^2 = 94\% \)), 12 hours (WMD: −0.81 cm; 95% CI: −1.02 to −0.59; \( P < .00001; I^2 = 96\% \)), 24 hours (WMD: −0.50 cm; 95% CI: −0.62 to −0.38; \( P < .00001; I^2 = 86\% \)) and 48 hours (WMD: −0.31 cm; 95% CI: −0.48 to −0.14; \( P = .0004; I^2 = 95\% \)) postoperatively (see Figure 7).

We conducted a sensitivity analysis by excluding high-risk bias trials, and the data remained robust (Table S4A). Next, we performed subgroup analyses with the remaining prespecified subgroups, but heterogeneity was not reduced below an \( I^2 \) of 50% in any of the subgroups with more than two trials (Table S4B).

### 3.5 Safety analysis

#### 3.5.1 Adverse events

All included studies reported various side effects, three32,35,38 of which were excluded because of a lack of
specific data. Thus, of the 23 studies, 20 had complete data to allow for statistical analysis.

The most commonly reported adverse events were postoperative nausea (PON), postoperative vomiting (POV), PONV, and respiratory depression. Compared with the control group, patients receiving DEX had a reduced incidence of PON (RR: 0.61; 95% CI: 0.43-0.86; \( P = .004; I^2 = 0\%\)), POV (RR: 0.51; 95% CI: 0.28-0.92; \( P = .03; I^2 = 0\%\)), and PONV (RR: 0.50; 95% CI: 0.37-0.69; \( P < .0001; I^2 = 0\%\)). None of the studies reported the outcome of respiratory depression in patients (Figure 8).

On the other hand, our meta-analysis focusing on shivering, dizziness, sedation, and urinary retention showed no significant differences between the DEX combined with local anaesthetics group and the local anaesthetics group. It is important to note that no patients with respiratory depression or wound infection were reported in any trial (Figure 8). Because of the low heterogeneity of all the results (\( I^2 < 50\%\)) in this analysis and the limited number of studies included for some indicators, sensitivity, and subgroup analyses were not conducted.

4 | DISCUSSION

The results of this meta-analysis indicate that DEX as a local anaesthetic adjuvant used in wound infiltration could reduce the rescue analgesia rate (by more than twice) and reduce analgesic requirements within 24 hours after surgery with firm evidence according to the TSA. Furthermore, DEX significantly prolonged the analgesia time of wound infiltration by approximately 5 hours and decreased the VAS score at 4 hours postoperatively (the magnitude of the decrease was 1). Our study also shows that DEX does not significantly increase the incidence of transient or reversible side effects but significantly reduces the incidence of PON, POV, and PONV. However, it is equally important to note that there is not enough evidence to confirm that DEX has nothing to do

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**FIGURE 5** Forest plot for the outcome “incidence of DEX related adverse reactions”. A, Bradycardia. B, Hypotension. DEX, dexmedetomidine; PLA, placebo
with the occurrence of postoperative bradycardia and hypotension according to the TSA results.

### 4.1 | Efficacy of local DEX in wound infiltration analgesia

In this meta-analysis, because VAS is greatly affected by subjective factors and there are few studies that have examined the time to first rescue analgesia, the more objective indicators of rescue analgesia rate and analgesic consumption were selected as the primary outcomes.12

This meta-analysis identified 23 RCTs that compared DEX combined with anaesthetic and anaesthetic alone in wound infiltration. The results of the rescue analgesia rate and analgesic consumption were consistent, especially that the rescue analgesia rate of more than twice in DEX group was significantly lower than that in the anaesthetic alone group. Nonetheless, we urge caution in interpreting the rescue analgesia of different frequencies measurement data given that only three trials were

| Study or Subgroup | DEX | PLA | Mean Difference | Mean Difference |
|-------------------|-----|-----|----------------|----------------|
|                   | Mean | SD  | Total | Mean | SD  | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Bharadwaj 2017   | 420 | 111 | 30    | 196.2| 121.8| 30    | 11.1% | 223.80 [164.83, 282.77] |
| Bommalapeta 2016 | 312.2| 16.1| 25    | 156.2| 12.7 | 25    | 11.3% | 156.00 [147.96, 164.04] |
| Li 2019          | 630 | 222 | 29    | 318  | 90   | 28    | 10.8% | 312.00 [224.59, 399.41] |
| Mandal 2016      | 804.8| 150.6| 38    | 612  | 144  | 38    | 11.0% | 192.80 [126.35, 258.85] |
| Mitra 2017       | 930 | 43.7| 15    | 270  | 15.47| 15    | 11.3% | 660.00 [636.54, 683.46] |
| Mohamed 2018     | 360 | 223.8| 30    | 252  | 67.8 | 30    | 10.8% | 108.00 [24.32, 191.6] |
| Ranjita 2016     | 487.7| 40.96| 40    | 242.5| 19.84| 40    | 11.3% | 245.20 [231.10, 259.30] |
| Tan 2018         | 927 | 45.6| 20    | 411  | 40.2 | 20    | 11.3% | 516.00 [489.36, 542.64] |
| Valliapu 2018    | 559.8| 183 | 50    | 319.8| 183  | 50    | 11.0% | 240.00 [168.27, 311.73] |

Total (95% CI) | 277 | 276 | 100.0% | 296.16 [165.69, 426.63] |

**FIGURE 6** A, Forest plot for the outcome “time of first rescue analgesia within 24 hours after surgery”. B, Forest plot for the outcome “rescue analgesia rate of different frequency”. DEX, dexmedetomidine; PLA, placebo.
included in this group. In addition, we demonstrated for the first time within the TSA that the evidence is powered sufficiently by a large number of RCTs so that studies do not need to investigate the effect of the rescue analgesia rate and analgesic consumption following DEX combined with local anaesthetics in the future.

In the subgroup analysis, we tried to explore the source of heterogeneity through the types of local anaesthetics, the doses of DEX and so on. Although the results are robust, we must admit that our exploration did not find substantial evidence of reduced heterogeneity. In these subgroup analyses, we focused on the dose of DEX.

The meta-analysis or RCTs examining the brachial plexus block\textsuperscript{12,41,42} showed that DEX had a dose-dependent effect on prolonging the analgesia time and reducing the consumption of analgesics; that is, increasing the dose of DEX would prolong the analgesia time and reduce the consumption of analgesics. Curiously, low-dose DEX (≤1.0 μg/kg) seems to be more effective than high-dose DEX (>1.0 μg/kg) in our subgroup analysis, but this result is only inferential and needs to be carefully explained. This result is consistent with the TSA results, further emphasising the need to focus on the dose–response effect of DEX in future research.\textsuperscript{12}

In terms of the pain score, the VAS was used as the evaluation method in all included studies, which is very important for reducing clinical heterogeneity.\textsuperscript{43} We analysed the VAS at eight time points in the resting state within 48 hours after surgery. Compared with local anaesthesia alone, DEX modestly reduced the resting VAS pain scores and benefit up to 48 hours after surgery. However, the reduction of the combined effect was inferior, and the magnitude of decrease was more than 1 point only at 4 hours postoperatively (typically, this is considered clinically significant).\textsuperscript{44}

4.2 | Safety of local DEX in wound infiltration analgesia

Because the local administration of DEX is an off-label use,\textsuperscript{45} it is important to fully report possible adverse events before using DEX as a local anaesthetic adjuvant to wound infiltration. We concluded that there were no significant differences in the side effects related to DEX (bradycardia, hypotension),\textsuperscript{12,41,42} respiratory inhibition, wound infection, and other adverse reactions between the DEX group and the placebo group. In contrast, the use of DEX reduced the incidence of PONV, an effect associated with reduced postoperative pain and opioid use. If we only analyse the research results, the local use of DEX seems to be relatively safe, and wound infiltration with DEX will not lead to wound infection. However, the TSA results showed that the total number of patients analysed is too low to clearly understand the evidence of side effects related to DEX; further research may overcome this limitation.
Therefore, after comprehensive consideration, the overall quality of evidence for DEX-related side effects was rated as 'low' according to the GRADE approach. It is necessary to carry out large-scale RCTs on these adverse events before DEX is formally used for wound infiltration in adult patients.

4.3 Strengths and limitations

Our research has several advantages and potential limitations. First, this research is based on a meta-analysis conducted by our team that is in previous study, and our interpretation of the results is cautious; the GRADE rating of the evidence base is conservative. Second, in this meta-analysis, we analysed the results by TSA, sensitivity analysis, subgroup analysis, publication bias (including trim-and-fill computation), and GRADE rating to further appraise the robustness of the results and provide ideas for future research directions. Last, compared with our previous meta-analysis, we comprehensively evaluated the safety of DEX in this study, which is profoundly significant for clinical medication.

The most important limitation of the study is the high heterogeneity of the primary outcomes. First, both sensitivity analysis and subgroup analysis cannot continuously reduce heterogeneity, which may have a negative impact on the external validity of our results. This indicates that in addition to our predetermined subgroup analysis, other potential sources of heterogeneity (such as the type of surgery, the depth of wound infiltration, and the type of postoperative analgesics) may affect the consistency of studies. The above factors, together with other internal factors, might lead to a high degree of heterogeneity in all RCTs.

Second, the trim-and-fill computation showed that the primary indicators are robust, and the TSA shows that the evidence of the main indicators is enough. However, there is a significant publication bias that cannot be ignored, which is one of the reasons why the two foremost pain indicators were rated as "moderate" by the GRADE approach. Finally, we were unable to explain why DEX's effect varies with local anaesthetics, and low-dose DEX seems to be better for prolonging postoperative analgesia. Although this may be related to the quality of the methodology in the included trials, future research should focus on the evaluation of the dose response of DEX.

4.4 Conclusions

In conclusion, the meta-analysis of 23 RCTs demonstrated that DEX combined with local anaesthetics
significantly reduced the rescue analgesia rate and analgesic consumption compared with local anaesthetics alone (both moderate-quality evidence). Other benefits of DEX included prolonged time to first rescue analgesia (approximately 5 hours), reduced early postoperative pain scores measured with the VAS (especially at 4 hours), and reduced PONV. As such, to optimise the analgesic effect of wound infiltration, DEX is a reasonable option as an adjuvant to local anaesthesia in clinical practice. However, as a result of the local injection of DEX currently being off-label in wound infiltration and the low-quality evidence of DEX-related side effects (bradycardia and hypotension), we must emphasise the importance of conducting the necessary trials focusing on the adverse events and dose–response effects of local DEX.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

REFERENCES

1. Shafi S, Collinsworth AW, Copeland LA, et al. Association of Opioid-Related Adverse Drug Events with Clinical and Cost Outcomes among Surgical Patients in a large integrated health care delivery system. JAMA Surg. 2018;153(8):757-763.
2. Paladini G, Di Carlo S, Musella G, et al. Continuous wound infiltration of local anesthetics in postoperative pain management: safety, efficacy and current perspectives. J Pain Res. 2020;13:285-294.
3. Loizides S, Gurusamy KS, Nagendran M, Rossi M, Guerrini GP, Davidson BR. Wound infiltration with local anaesthetic agents for laparoscopic cholecystectomy. Cochrane Database Syst Rev. 2014;12(3):Cd007049.
4. Liang SS, Ying AJ, Affan ET, et al. Continuous local anaesthetic wound infusion for postoperative pain after midline laparotomy for colorectal resection in adults. Cochrane Database Syst Rev. 2019;10:CD012310.
5. Taha T, Sionov BV, Rosenberg P, et al. Pain control after laparoscopic radical prostatectomy: comparison between unilateral Transversus Abdominis plane block and wound infiltration. Urol Int. 2019;103(1):19-24.
6. Loh JW, Taib NA, Cheong YT, Tin TS. A double-blind, randomized controlled trial of pre-incision wound infiltration using Diclofenac versus bupivacaine for post-operative pain relief in open thyroid and parathyroid surgery. World J Surg. 2020;44(8):2656-2666.
7. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anaesthetics: current understanding and future trends. World J Clin Cases. 2017;5(8):307-323.
8. Ren Y, Shi W, Chen C, et al. Efficacy of dexmedetomidine as an adjuvant to local wound infiltration anaesthesia in abdominal surgery: a meta-analysis of randomised controlled trials. Int Wound J. 2019;16(5):1206-1213.
9. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
10. Chong M, Berbenetz N, Kumar K, Lin C. The serratus plane block for postoperative analgesia in breast and thoracic surgery: a systematic review and meta-analysis. Reg Anesth Pain Med. 2019. https://doi.org/10.1136/rapm-2019-100982.
11. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect. 2014;20(2):123-129.
12. Schnabel A, Reichl SU, Weibel S, et al. Efficacy and safety of dexmedetomidine in peripheral nerve blocks: a meta-analysis and trial sequential analysis. Eur J Anaesthesiol. 2018;35(10):745-758.
13. van der Tweel I, Bollen C. Sequential meta-analysis: an efficient decision-making tool. Clin Trials. 2010;7(2):136-146.
14. 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(1):64-75.
15. Duan X, Coburn M, Rossaint R, Sanders RD, Wasenberge JV, Kowark A. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. Br J Anaesth. 2018;121(2):384-397.
16. Abdelnaim HE, Mohamed NN, Saleh AH, Youssef AN. Comparison between bupivacaine-dexmedetomidine mixture and bupivacaine-magnesium mixture when used for wound infiltration before skin incision in surgeries for hernia repair regarding their intraoperative and postoperative analgesic effects. Ain-Shams J Anaesthesiol. 2018;10:10.
17. Ahmed AE-H, Mohamed A, Mohamed AE-F. A comparison of the postoperative analgesic effects of intravenous dexmedetomidine with a combination of dexmedetomidine and bupivacaine wound infiltration for lower segment cesarean section: a prospective, randomized study. Ain-Shams J Anaesthesiol. 2016;9(2):235-239.
18. Bhardwaj S, Devgan S, Sood D, Katyal S. Comparison of local wound infiltration with Ropivacaine alone or Ropivacaine plus Dexmedetomidine for postoperative pain relief after lower segment cesarean section. Anesth Essays Res. 2017;11(4):940-945.
19. Bommalingappa B, Channabasappa SM. A comparative study of post-operative continuous wound infiltration with dexmedetomidine—ropivacaine mixture and plain ropivacaine in patients undergoing lumbar spine surgeries. J Evolution Med Dent Sci. 2016;5(92):6820-6824.
20. Deshwal R, Kumar N, Sharma JP, Kumar R. Efficacy of Dexmedetomidine added to Ropivacaine Infiltration on post-operative pain following spine surgeries: a randomized controlled study. Anesth Essays Res. 2018;12(3):700-704.
21. Jyothi B, Govindaraj K, Shaikh SI. Comparison of analgesic efficacy of levobupivacaine, levobupivacaine and clonidine, and levobupivacaine and dexmedetomidine in wound infiltration technique for abdominal surgeries: a prospective randomized controlled study. *Indian J Pain.* 2017;31(2):127-132.

22. Kang H. The effect of dexmedetomidine added to preemptive ropivacaine infiltration on post-operative pain after inguinal herniorrhaphy: a prospective, randomized, double-blind, placebo-controlled study. *Eur Surg.* 2012;44(4):274-280.

23. Kim BG, Kang H. The effect of preemptive perianal ropivacaine and ropivacaine with dexmedetomidine on pain after hemorrhoidectomy: a prospective, randomized, double-blind, placebo-controlled study. *Indian J Surg.* 2014;76(1):49-55.

24. Li J, Yang JS, Dong BH, Ye JM. The effect of Dexmedetomidine added to preemptive Ropivacaine infiltration on postoperative pain after lumbar fusion surgery: a randomized controlled trial. *Spine (Phila Pa 1976).* 2019;44(19):1333-1338.

25. Li SY, Li P. The effect of dexmedetomidine combined with ropivacaine on postoperative wound infiltration analgesia of breast cancer. *Jiangsu Med J.* 2018;44(6):700-701.

26. Luan H, Zhu P, Zhang X, et al. Effect of dexmedetomidine as an adjuvant to ropivacaine for wound infiltration in patients undergoing open gastrectomy: a prospective randomized controlled trial. *Medicine (Baltimore).* 2017;96(38):e7950.

27. Mandal D, Das A, Chhaule S, et al. The effect of dexmedetomidine added to preemptive (2% lignocaine with adrenaline) infiltration on intraoperative hemodynamics and postoperative pain after ambulatory maxillofacial surgeries under general anesthesia. *Anesth Essays Res.* 2016;10(2):324-331.

28. Mitra S, Purohit S, Sharma M. Postoperative analgesia after wound infiltration with tramadol and dexmedetomidine as an adjuvant to ropivacaine for lumbar discectomies: a randomized-controlled clinical trial. *J Neurosurg Anesthesiol.* 2017;29(3):433-438.

29. Mohamed SA, Sayed DM, El Sherif FA, Abd El-Rahman AM. Effect of local wound infiltration with ketamine versus dexmedetomidine on postoperative pain and stress after abdominal hysterectomy, a randomized trial. *Eur J Pain.* 2018;22(5):951-960.

30. Ranjita A, Karan D, Khetan M. Postoperative analgesia with intraperitoneal ropivacaine with and without dexmedetomidine after total laparoscopic hysterectomy: a randomized, double-blind, controlled trial. *Asian J Pharm Clin Res.* 2016;9(3):76-79.

31. Selvaraj V, Kamaraj R. Effect of Dexmedetomidine as an adjuvant to 0.25% bupivacaine for local infiltration of port site in laparoscopic cholecystectomy in terms of quality and duration of post-op analgesia. *JARSS.* 2019;27(3):210-216.

32. Singh S, Prasad C. Post-operative analgesic effect of dexmedetomidine administration in wound infiltration for abdominal hysterectomy: a randomised control study. *Indian J Anaesth.* 2017;61(6):494-498.

33. Tan SS, Hu TT, Yao ZM, Zhu SS. Effect of different doses of dexmedetomidine combined with ropivacaine intraperitoneal atomization and incision injection on postoperative analgesia after laparoscopic cholecystectomy. *Chin J Mod Drug Appl.* 2018;12(99):8-11.

34. Ülgey A, Gineş I, Bayram A, et al. The analgesic effects of incisional Levobupivacaine with Dexmedetomidine after Total abdominal hysterectomy. *Erciyes Med J/Erciyes Tip Dergisi.* 2015;37(2):64-68.

35. Vallapu S, Panda NB, Samagh N, Bharti N. Efficacy of Dexmedetomidine as an adjuvant to local anesthetic agent in scalp block and scalp infiltration to control Postcraniotomy pain: a double-blind randomized trial. *J Neurosci Rural Pract.* 2018;9(1):73-79.

36. Wu XF, Cheng B, Yu YC, Yang T, Su WD. Effects of ropivacaine wound infiltration combined with dexmedetomidine on postoperative analgesia and outcome of breast cancer. *Beijing Med J.* 2019;41(08):749-750+753.

37. Xia FF, Chen HP, Zhou JS, Bao NN, Shi KJ. Effect of dexmedetomidine combined with ropivacaine on laparoscopic analgesia after enhanced incision infiltration. *Chin Modern Doc.* 2017;55(18):108-111.

38. Yu JM, Sun H, Wu C, Dong CS, Lu Y, Zhang Y. The analgesic effect of Ropivacaine combined with Dexmedetomidine for incision infiltration after laparoscopic cholecystectomy. *Surg Laparosc Endosc Percutan Tech.* 2016;26(6):449-454.

39. Gordon DB. Acute pain assessment tools: let us move beyond simple pain ratings. *Curr Opin Anaesthesiol.* 2015;28(5):565-569.

40. Ford C. Adult pain assessment and management. *Br J Nurs.* 2019;28(7):421-423.

41. Hussain N, Grzywacz VP, Ferreri CA, et al. Investigating the efficacy of Dexmedetomidine as an adjuvant to local anesthesia in brachial plexus block: a systematic review and meta-analysis of 18 randomized controlled trials. *Reg Anesth Pain Med.* 2017;42(2):184-196.

42. Koraki E, Stachtari C, Kapsokalyvas I, Stergiouda Z, Katsanevakis A, Trikoupi A. Dexmedetomidine as an adjuvant to 0.5% ropivacaine in ultrasound-guided axillary brachial plexus block. *J Clin Pharm Ther.* 2018;43(3):348-352.

43. Sedgwick P. Meta-analyses: what is heterogeneity? *BMJ.* 2015;350:h1435.

44. Myles PS, Myles DB, Galagher W, et al. Measuring acute post-operative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state. *Br J Anaesth.* 2017;118(3):424-429.

45. Zhang P, Liu S, Zhu J, Rao Z, Liu C. Dexamethasone and dexmedetomidine as adjuvants to local anesthetic mixture in intercostal nerve block for thoracoscopic pneumonectomy: a prospective randomized study. *Reg Anesth Pain Med.* 2019. https://doi.org/10.1136/rapm-2018-100221.

**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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