Systematic Review and Meta-Analysis

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Comparing the effects of dexmedetomidine and dexamethasone as perineural adjuvants on peripheral nerve block

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Dexmedetomidine (Dexm), a selective alpha-2 adrenoceptor agonist, and dexamethasone (Dexa), a very potent and highly selective glucocorticoid, have both been proven effectively to prolong the duration of local anesthetics (LA) in regional anesthesia. However, data comparing the efficacy of Dexm and Dexa as perineural adjuvants are inconsistent. Therefore, this systematic review and meta-analysis of randomized and quasi-randomized controlled trials (RCTs) was conducted to compare the effects of Dexm and Dexa when used as LA adjuvants on peripheral nerve block (PNB).

Methods: We systematically searched PubMed, Cochrane Library, EMBASE, Web of Science, and ScienceDirect databases up to October, 2020. The primary outcome was the duration of analgesia. Secondary outcomes included incidence of rescue analgesia, cumulative opioid consumption, time required for onset of sensory and motor blockades, duration of sensory and motor blockades, incidence of postoperative nausea and vomiting (PONV), and side effect-associated outcomes (e.g., bradycardia, sedation, hypotension, rates of infection, and neurological complications). The study was registered on PROSPERO, number CRD42020188796.

Results: After screening of full-text relevant articles, 13 RCTs that met the inclusion criteria were retrieved for this systematic review. It was revealed that perineural Dexm provided equivalent analgesic duration to perineural Dexa. Besides, the intake of Dexm increased the incidence of rescue analgesia in limbs surgery, as well as the cumulative opioid consumption, and decreased the time required for onset of sensory and motor blockades for long-acting LA (all $P < .05$). Other analysis revealed insignificant difference between the 2 groups in terms of the incidence of PONV ($P > .05$). Additionally, 2 studies demonstrated that Dexm possesses more sedative properties than Dexa ($P < .05$).

Conclusions: This meta-analysis indicated that the analgesic duration of Dexm and Dexa as LA adjuvants in PNB is the same. Meanwhile, the effects of perineural Dexm and Dexa on some secondary outcomes, including the incidence of rescue analgesia, cumulative opioid consumption, and time required for onset of sensory and motor blockades, are associated with the surgical site and type of LA.

Abbreviations: Dexa = dexamethasone, Dexm = dexmedetomidine, LA =local anesthetics, PNB = peripheral nerve block, PONV = postoperative nausea and vomiting, RCTs = randomized controlled trials.

Keywords: anesthesia adjuvants, dexamethasone, dexmedetomidine, meta-analysis, nerve block, postoperative pain, systematic review

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CX, C-PH, and DZ contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Poor postoperative pain control may produce a series of detrimental acute and chronic effects on the body.[1] Compared with intravenous analgesia, regional anesthesia techniques not only provide excellent analgesia effects, but also possess fewer side effects. Peripheral nerve block (PNB) is currently one of the most commonly used regional anesthesia methods. Whether used alone or in combination with general anesthesia, it can accelerate a patient's recovery, relieve postoperative pain and reduce the use of intravenous drugs.[2,3] However, regarding the currently available local anesthetics (LA) for PNB, the duration of postoperative analgesia is a main challenge, and its effect often fades before the peak of postoperative pain.[4]

Addition of adjuvants including dexmedetomidine (Dexm),[5] dexamethasone (Dexa),[6] clonidine,[7] buprenorphine,[8] magnesium[9] and midazolam[10] to LA for regional anesthesia effectively prolongs the postoperative analgesia. Compared with commonly used continuous catheter-based nerve block, adjuvants in LA can reduce multiple postoperative complications.[11,12] To date, studies have shown that Dexm and Dexa are the 2 most frequently used adjuvants for LA. They can significantly prolong postoperative analgesic duration, reduce intake of opioids, and their use is associated with a limited number of side effects.[13–15] However, there are conflicting reports regarding the overall efficacy of the 2 additives as adjuvants in LA.[16–18]

Motivated by this controversy, this systematic review and meta-analysis aimed to assess the comparative analgesic efficacy of Dexm and Dexa to light. The primary outcome of this meta-analysis was the duration of analgesia.

2. Materials and methods

2.1. Registration and protocol

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] recommendations were followed in the preparation of this review. The protocol of this study was registered at International Prospective Register of Systematic Reviews (PROSPERO) (number CRD42020188796).

2.2. Search strategy

Two independent researchers (Chang Xiong and Cheng-peng Han) conducted the search process in PubMed, Cochrane Library, EMBASE, Web of Science, and ScienceDirect databases from inception of each database to October, 2020. The key search terminology was MeSH and its synonyms were "dexmedetomidine," "dexamethasone," and "regional anesthesia/nerve block/peripheral block". After filtering titles and abstracts, 13 relevant randomized and quasi-randomized controlled trials (RCTs) were retrieved for analysis. Potentially eligible trials were also manually searched. The retrieval strategy in PubMed database is shown in Supplementary Appendix S1, http://links.lww.com/MD/G380.

2.3. Selection criteria/eligibility

The inclusion criteria were as follows: (a) Intervention: perineural administration of Dexm (combined with LA) (Dexm group); (b) Control: perineural administration of Dexa (combined with LA) (Dexa group); (c) Population: adult patients (subjects who aged ≥18 years old) who underwent surgery with regional anesthesia; (d) Design: RCTs.

2.4. Data extraction

Relevant data, including the authors' full name, year of publication, the first author's country of residence, number of patients in each group, type of PNB, adjuvant, type and dose of LA, anesthesia and surgery, postoperative analgesia, and outcomes were extracted independently from eligible articles by 2 researchers.

Primary outcome was the duration of analgesia. Secondary outcomes included the incidence of rescue analgesia, cumulative opioid consumption, blockade-associated outcomes, such as time required for the onset of sensory and motor blockades, the corresponding duration of sensory and motor blockades, incidence of postoperative nausea and vomiting (PONV), and side effect-associated outcomes (e.g., bradycardia, sedation, hypotension, rates of infection, and neurological complications).

Opioid intake was equated into probable morphine consumption [morphine (10 mg) = tramadol (100 mg) = fentanyl (0.1 mg) = pethidine (75 mg) = diclofenac (140 mg), i.v.].[20,21]

Attempts were made to retrieve raw data for continuous variables from the eligible articles if variables in the full texts were presented as median and range; however, if data could not be extracted, then, the median and range were transformed to the mean ± standard deviation (SD).[22] Any disagreements arising from the entire process were arbitrated by a third experienced researcher (Dong Zhao).

2.5. Assessment of risk of bias

Risk of bias was assessed by 2 independent researchers (Chang Xiong and Cheng-peng Han) using the Cochrane Collaboration Risk of Bias tool.[23] Any disagreement was also arbitrated by a third researcher (Dong Zhao). The articles were evaluated under 6 bias-based parameters, including selection (random sequence generation and allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome assessment), attrition (incomplete outcome data), and reporting (selective reporting) bias. The risk of bias for each parameter was classified as "low," "unclear" or "high". The Egger test, as well as visual examination of the funnel plot were used to assess potential publication bias; besides, Duval & Tweedie's trim-and-fill analysis was employed to adjust the effect size accordingly when P-values of Egger test was <.1.

2.6. Statistical analysis

Continuous data on outcomes, including the duration of analgesia, time required for the onset of sensory and motor blockades, the corresponding duration of sensory and motor blockades, and cumulative opioid consumption were presented as mean difference (MD) at 95% confidence interval (CI). The dichotomous data on outcomes, such as incidence of rescue analgesia and PONV were expressed as the relative risk (RR) at 95% CI. The χ^2 test and I^2 statistic were employed to estimate statistical heterogeneity across studies. The I^2 statistic was stratified into 3 levels: low-level (0%–49%), moderate-level (50%–74%), and high-level (>75%). The fixed-effects model

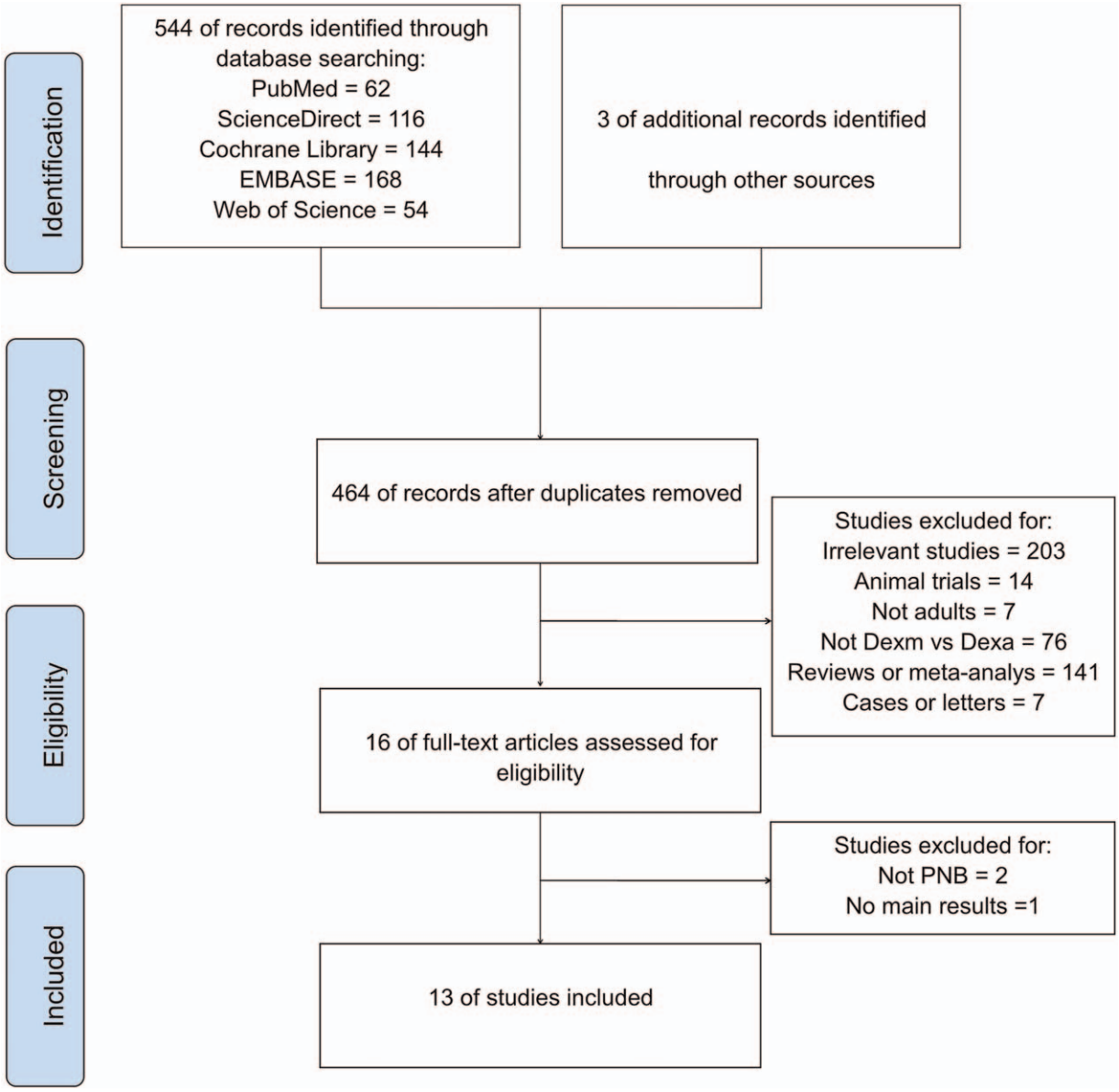

Figure 1. PRISMA flow diagram summarizing retrieved, included, and excluded RCTs. PRISMA indicates = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PNB = peripheral nerve block.

was used in the event of low-level heterogeneity; otherwise, a random-effect model was applied. For moderate-level and high-level of heterogeneity ($I^2 > 50\%$), subgroup analysis was planned based on the following priori hypotheses. RevMan (version 5.3; Cochrane Library, Oxford, UK) was used to perform meta-analyses, and STATA 14/MP (StataCorp., College Station, TX, USA) was used for conducting Egger's test (metabias module) and Duval & Tweedie's trim-and-fill analysis (metatrim module).

2.7. Priori hypotheses to explain heterogeneity subgroup analysis

The pre-identified hypotheses used to evaluate heterogeneity is that the effects of Dexm or Dexa on PNB depend on surgical site and the type of LA utilized. Specifically, all trials were divided into 2 subgroups according to the surgical site (limbs and thoracic surgeries), and 3 subgroups according to the type of LA (long-acting LA, intermediate + long-acting LA, and intermediate LA).

3. Results of the meta-analysis for outcomes

3.1. Characteristics of the included studies

Five hundred forty seven studies were identified during our first search, among which 83 duplicates were removed after assessment. Through thorough review of the titles, abstracts, and full texts, 13 RCTs[13–18,24–30] were eventually selected for the final analysis. The flowchart of the study selection is shown in Fig. 1. The selected studies were published between 2014 and 2020, and were carried out in different countries, such as India, China, Iran, Korea, Spain, and Chile. The surgeries that were documented in the studies included limbs surgery

Table 1

Characteristics of 13 included studies.

Study	Country	Group (N)	Type of peripheral nerve blockade	Local anesthetics	Adjuvant	Type of surgery	Anethesia	Postoperative analgesia	Outcomes
Aliste J 2019[17]	Chile	Dexm vs Dexa (56/53)	Ultrasound-guided infraclavicular block	1% lidocaine+0.25% bupivacaine 35ml	Dexm:100 μg Dexa:5 mg	Upper limb surgery	Nerve blockade	None	Duration of analgesia, duration of sensory and motor blockades
Gao Z 2019[18]	China	Dexm vs Dexa (30/30)	Ultrasound-guided erector spinae plane block	0.5% ropivacaine 30 ml	Dexm: 1 μg/kg Dexa:10 mg	Video-assisted thoracoscopic lobectomy surgery	General anesthesia	IV-PCA (250ml) contained 7.5 μg/kg sufentanil +250 mg flurbiprofen. Tramadol 100 mg intramuscularly injection if VAS > 4	Duration of analgesia, incidence of rescue analgesia, duration of sensory blockade, postoperative nausea and vomiting
Kataria S 2019[13]	India	Dexm vs Dexa (30/30)	Ultrasound-guided interscalene block	0.5% ropivacaine 20 ml	Dexm: 0.5 μg/kg (2ml) Dexa: 8 mg (2 mL)	Arthroscopic shoulder surgery	General anesthesia	IV-PCA boluses of 10 μg of fentanyl, with lock-out interval of 6 min, maximum 4-h dose of fentanyl being 400 μg.	Duration of analgesia, opioid consumption over 24h after surgery, time required for onset time of sensory and motor blockades, duration of motor blockade, postoperative nausea and vomiting
Kaur M 2018[24]	India	Dexm vs Dexa (50/50)	Peripheral nerve stimulator guided supraclavicular BPB	20 ml 2% lidocaine +18 mL 0.5% bupivacaine	Dexm: 50 μg (2 mL) Dexa: 8 mg (2mL)	Upper limb surgery	Nerve blockade	None	Duration of analgesia, time required for onset time of sensory and motor blockades, duration of sensory and motor blockades
Kumar AN 2014[25]	India	Dexm vs Dexa (30/30)	Interscalene BPB	40 mL 0.25% bupivacaine	Dexm: 50 μg (1 mL) Dexa: 8 mg (1 mL)	Upper limb surgery	Nerve blockade	Diclofenac sodium 75 mg IM. when VAS > 4, if analgesia is still inadequate after 30 minutes, pentazocine 30 mg IV given	Duration of analgesia, opioid consumption over 24h after surgery, time required for onset time of motor blockade, duration of sensory and motor blockades
Lee MJ 2016[16]	Korea	Dexm vs Dexa (17/17)	Ultrasound-guided axillary BPB	0.5% ropivacaine 20 mL	Dexm: 100 μg (2 mL) Dexa:10 mg (2 mL)	Forearm and hand surgery	Nerve blockade	None	Incidence of rescue analgesia, time required for onset time of sensory blockade, duration of sensory blockade
Ortiz-Gómez JR 2017[26]	Spain	①FNB+Dexm vs FNB+ Dexa (80/81) ②ACB+Dexm vs ACB+Dexa (78/81)	Ultrasound-guided FNB and ACB	0.375% levobupivacaine 20 ml in FNB and 30 mL in ACB	Dexm: 100 μg (1ml) Dexa: 4 mg (1 mL)	Knee surgery	Spinal anesthesia	Paracetamol 1g IV, morphine up to 6 mg	Incidence of rescue analgesia, opioid consumption over 24h after surgery
Shekar M 2020[27]	India	Dexm vs Dexa (46/46)	Ultrasound guided interscalene BPB	15 mL 0.2% ropivacaine	Dexm: 1 μg/kg Dexa: 100 μg/kg	Arthroscopic shoulder surgery	General anesthesia	None	Duration of analgesia, time required for onset time of sensory and motor blockades, duration of sensory and motor blockades
Siamak Y 2019[14]	Iran	Dexm vs Dexa (26/25)	Ultrasound-guided infraclavicular BPB	2% lidocaine 28 mL	Dexm: 1 μg/kg (2 mL) Dexa: 8 mg (2 mL)	Forearm surgery	Nerve blockade	Pethidine 25 mg IV if VAS > 4	Duration of analgesia, incidence of rescue analgesia, opioid consumption over 24h after surgery, time required for onset time of sensory and motor blockades, duration of sensory blockade, postoperative nausea and vomiting
Singh N 2020[28]	India	Dexm vs Dexa (20/20)	Ultrasound-guided supraclavicular BPB	0.5% ropivacaine 30 mL	Dexm: 1 μg/kg Dexa: 8 mg	Upper limb surgery	Nerve blockade	Tramadol 50 mg IV if VAS ≥ 4	Duration of analgesia, opioid consumption over 24h after surgery, time required for onset time of sensory and motor blockades, duration of sensory and motor blockades

(*continued*)

Table 1
(continued).

Study	Country	Group (N)	Type of peripheral nerve blockade	Local anesthetics	Adjuvant	Type of surgery	Anethesia	Postoperative analgesia	Outcomes
Niranjan KV 2016[29]	India	Dexm vs Dexa (50/50)	Supraclavicular BPB	0.5% ropivacaine 30 mL	Dexm: 50 μg (2 mL) Dexa: 8 mg (2 mL)	Upper limb surgeries	Nerve blockade	No details provided	Duration of analgesia, time required for onset time of sensory and motor blockades, duration of sensory and motor blockades
Vinisha A 2020[30]	India	Dexm vs Dexa (30/30)	Supraclavicular BPB	20 ml 2% lidocaine + 20 ml of 0.5% bupivacaine	Dexm: 20 μg Dexa: 4 mg	Upper limb surgeries	Nerve blockade	None	Duration of analgesia, time required for onset time of sensory and motor blockades, duration of sensory and motor blockades
Zhang P 2019[15]	China	Dexm vs Dexa (20/20)	Intercostal nerve block	0.5% ropivacaine 28 ml	Dexm: 1 μg/kg (2 mL) Dexa: 10 mg (2 mL)	Thoracoscopic pneumonectomy	General anesthesia	IV-PCA (100ml) contained 1 mg fentanyl	Duration of analgesia, opioid consumption over 24h after surgery, postoperative nausea and vomiting

ACB = adductor canal block, BPB = brachial plexus block, FNB = femoral nerve block, IM = intramuscularly, IV = intravenous, NRS = numerical rating scale, PCA = patient controlled analgesia, VAS = visual analogy scale.

(n = 11) [13,14,16,17,24–30] and thoracic surgery (n = 2).[15,18] Surgeries in 9 studies [13,15,16,18,25–29] involved the use of long-acting LA, such as ropivacaine, bupivacaine, and levobupivacaine. Three trials[17,24,30] reviewed herein used intermediate + long-acting LA, namely lidocaine + bupivacaine. In one study,[14] lidocaine was used for an intermediate-acting LA. The dose of Dexm ranged from 20 to 100 μg or 0.5 to 1 μg/kg, whereas that of Dexa ranged from 4 to 10 mg. Another study reported the use of 2 different trials, thus each experiment was analyzed separately in the meta-analysis, presented as Ortiz-Gómez JR 2017(a) and Ortiz-Gómez JR 2017(b).[26] The general characteristics of all the RCTs are summarized in Table 1.

3.2. Assessment of risk of bias within studies

Low risk of bias was found in 4 studies.[15–17,25] Three study[24,29,30] displayed high risk of bias arising from selection, performance, detection, and attrition. The remaining 6 articles had unclear risks of bias.[13,14,18,26–28] The outcomes of risk assessment are presented in Fig. 2.

Figure 2. Risks of bias (A summary and B graph) for the thirteen included studies. Notes: Red, high risk of bias; yellow, unclear risk of bias; green, low risk of bias.

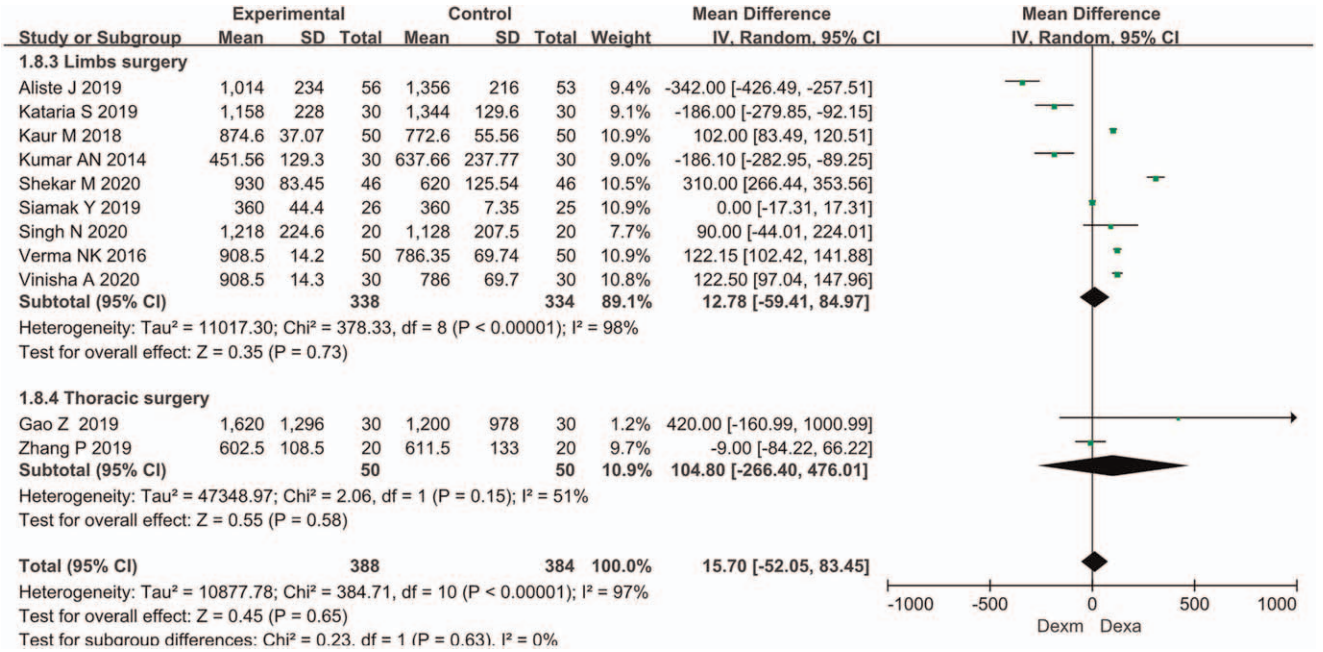

Figure 3. Forest plot (subgroup analysis of surgical site) comparing the effect of Dexm and Dexa on duration of analgesia.

3.3. Duration of analgesia

The duration of analgesia was reported in 11 of the 13 included trials[13–15,17,18,24,25,27–30] (n = 772 patients, of whom 388 received Dexm), and it was defined as the time required to administer the first analgesic supplement post-operatively. The random-effects model used in eleven studies showed that the MD between Dexm and Dexa was 15.7 minutes (95% CI: −52.05 to 83.45; $P = .65$; Figs. 3 and 4). However, regarding a great degree of heterogeneity

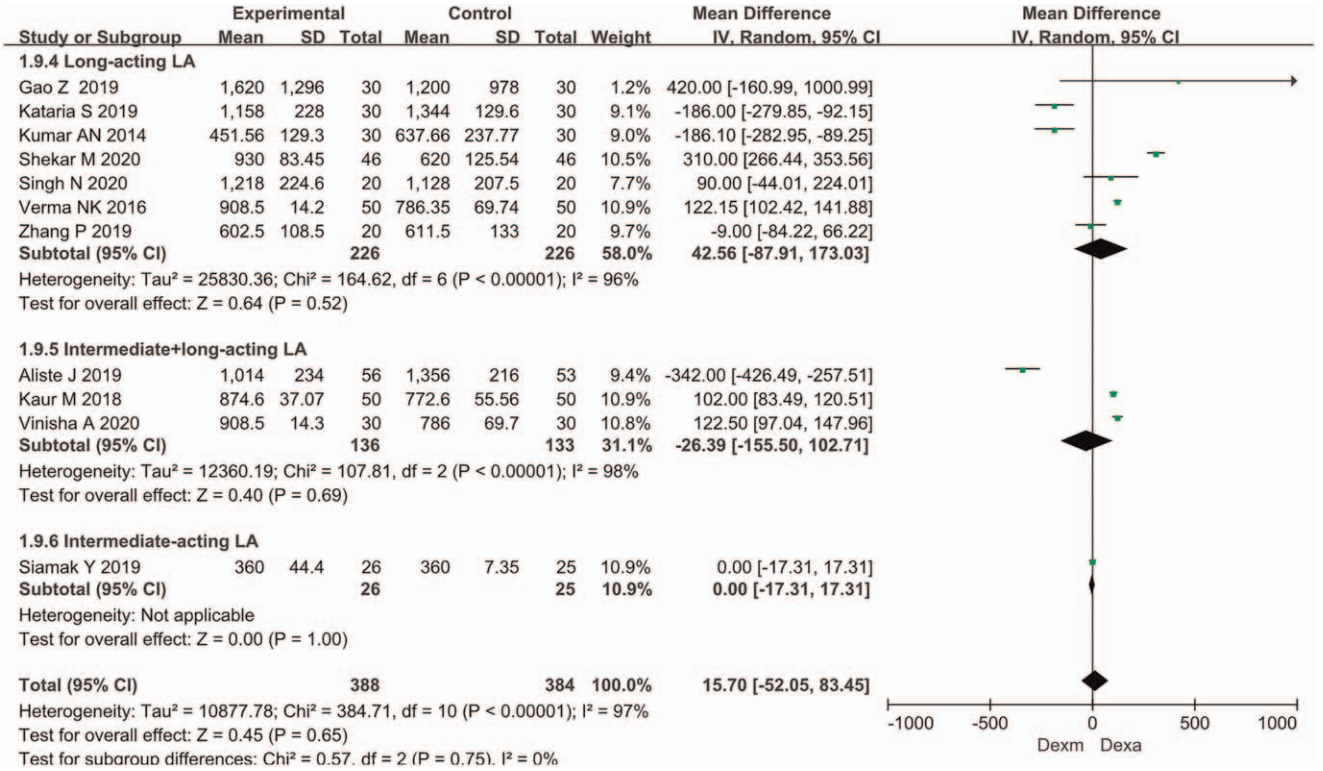

Figure 4. Forest plot (subgroup of various types of LA) comparing the effect of Dexm and Dexa on duration of analgesia; LA = local anesthetics.

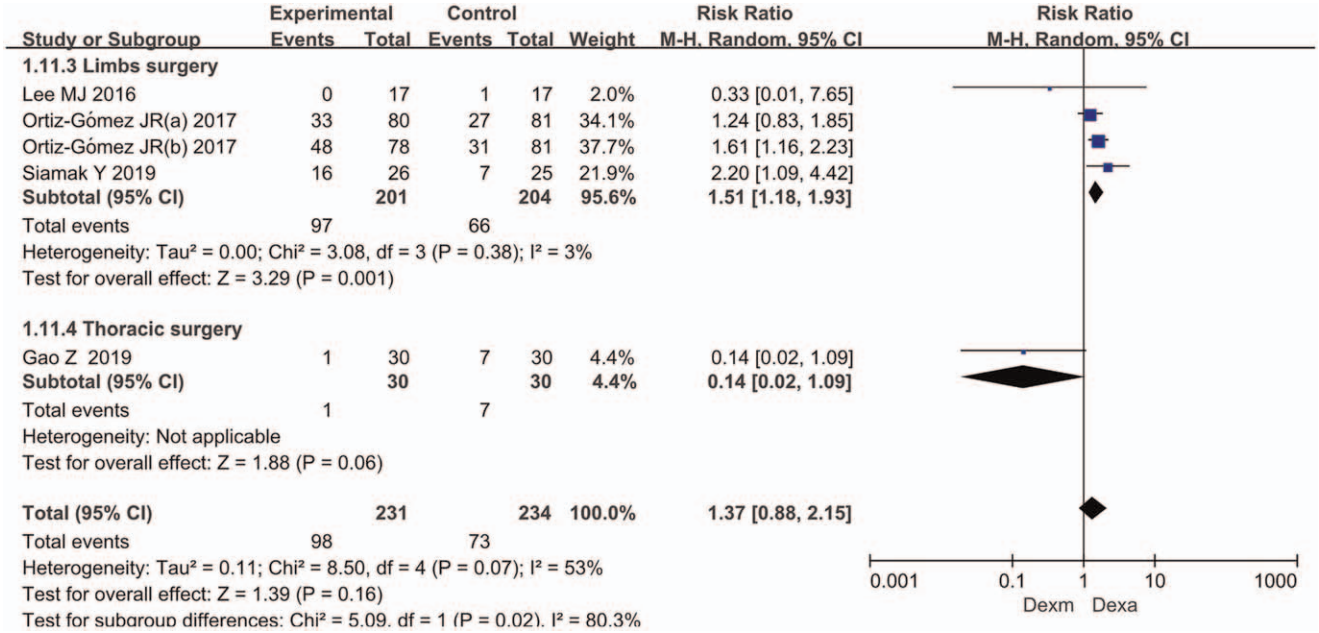

Figure 5. Forest plot (subgroup analysis of surgical site) comparing the effect of Dexm and Dexa on incidence of rescue analgesia.

($I^2 = 97\%$), we attempted to use the priori subgroup hypotheses to perform analysis. For the subgroup of surgical site, the pooled effect of limbs surgery or thoracic surgery demonstrated that Dexm and Dexa have similar analgesic durations ($P = .63$ and $I^2 = 0$ for subgroup differences). For the subgroup of various types of LA, the pooled effect of long, intermediate + long or intermediate-acting LA indicated that Dexm had an equivalent analgesic duration with Dexa ($P = .75$ and $I^2 = 0$ for subgroup differences). The data that compared peripheral Dexa and Dexm used in a surgical site at the limbs and thoracic surgeries, as well as mixed with different types of LA for long, intermediate + long, and intermediate-acting LA showed no significant difference in analgesic duration (Figs. 3 and 4). The findings of the sensitivity analysis did not significantly vary from these summarized results.

3.4. Incidence of rescue analgesia

Four trials[14,16,18,26] assessed incidence of rescue analgesia (one study[26] included 2 different trials). The synthetic analysis performed by using a random-effect model revealed a higher

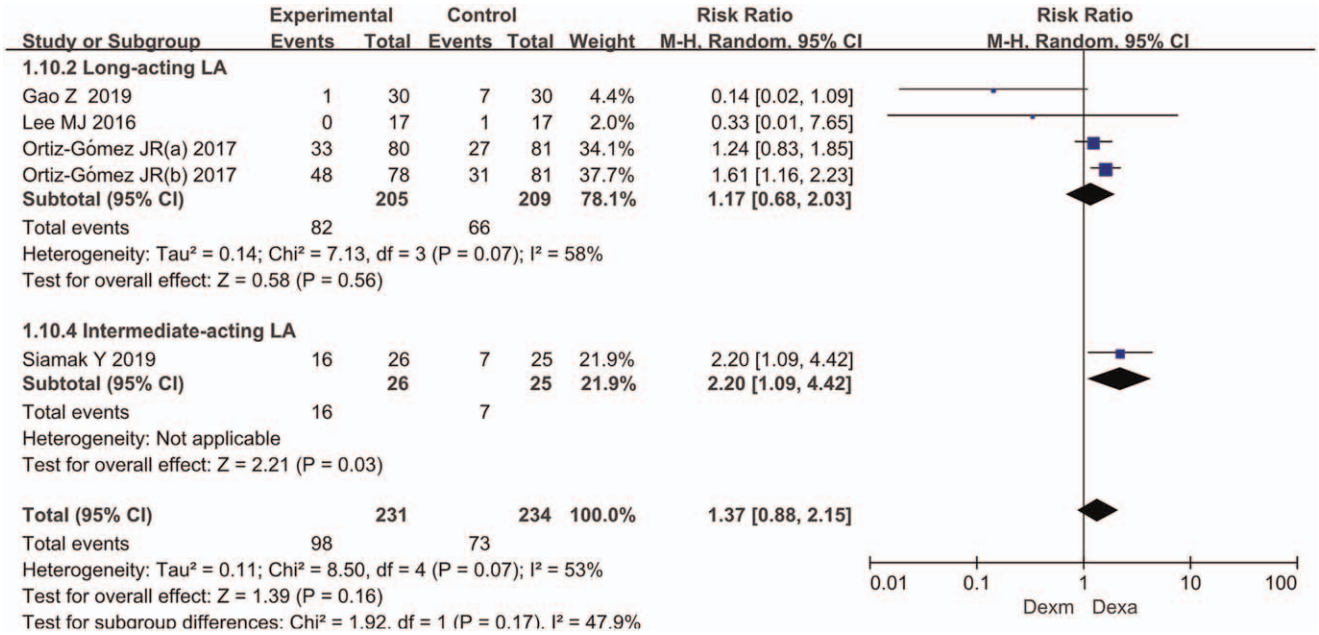

Figure 6. Forest plot (subgroup of various types of LA) comparing the effect of Dexm and Dexa on incidence of rescue analgesia; LA = local anesthetics.

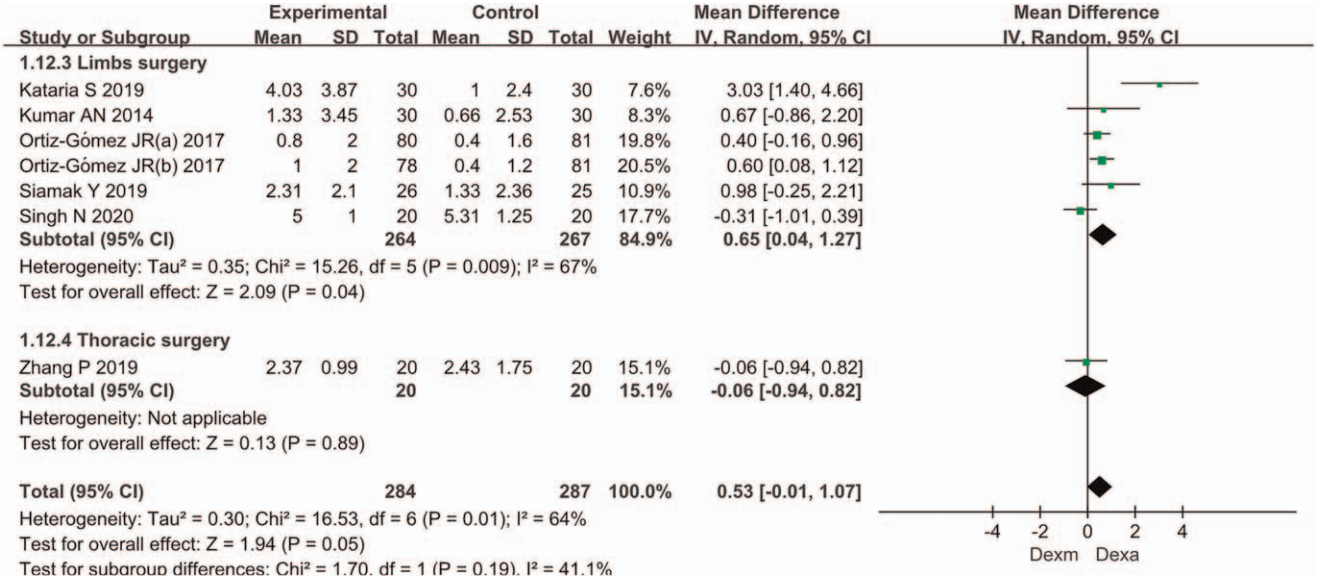

Figure 7. Forest plot (subgroup analysis of surgical site) comparing the effect of Dexm and Dexa on opioid consumption 24 hours after surgery.

incidence of rescue analgesia in the Dexm group compared with that in the Dexa group (RR: 1.37, 95% CI: 0.88–2.15, $I^2 = 53\%$; $P = .16$; Figs. 5 and 6), although the difference was not statistically significant. However, subgroup analysis of surgical site showed that in limbs surgery, the incidence of rescue analgesia in Dexm group was 1.51 times higher than that in Dexa group ($P < .05$), while there was no significant difference in thoracic surgery (Fig. 5). In addition, subgroup analysis of LA demonstrated that perineural Dexm increased the incidence of rescue analgesia for long-acting LA compared with Dexa, whereas no significant difference was noted in intermediate-acting LA between the 2 groups (Fig. 6).

3.5. Opioid consumption 24 hours after surgery

Six studies[13–15,25,26,28] reported 24-hours cumulative opioid intake (morphine equivalents) postoperation. Pooled results demonstrated that there was no significant increase in morphine intake in this period (24-hours) in individuals put on Dexm compared with those on Dexa (MD = 0.53; 95% CI: −0.01 to 1.07; $I^2 = 64\%$; $P = .05$; Figs. 7 and 8). Subgroup analysis revealed that compared with perineural Dexa, Dexm increased cumulative opioid consumption only in limbs surgery (MD = 0.65; 95% CI: 0.04–1.27; $I^2 = 67\%$; $P = .04$; Fig. 7), whereas no significant difference was found in other subgroups (thoracic surgery and long/intermediate-acting LA) (Figs. 7 and 8).

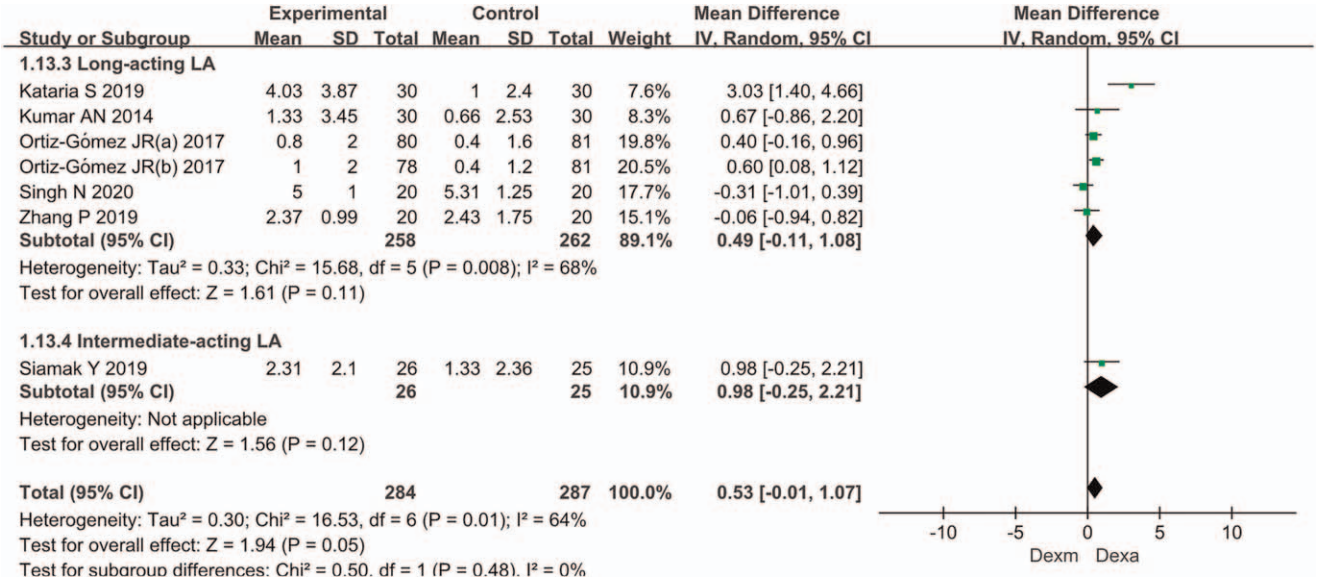

Figure 8. Forest plot (subgroup of various types of LA) comparing the effect of Dexm and Dexa on opioid consumption 24 hours after surgery; LA = local anesthetics.

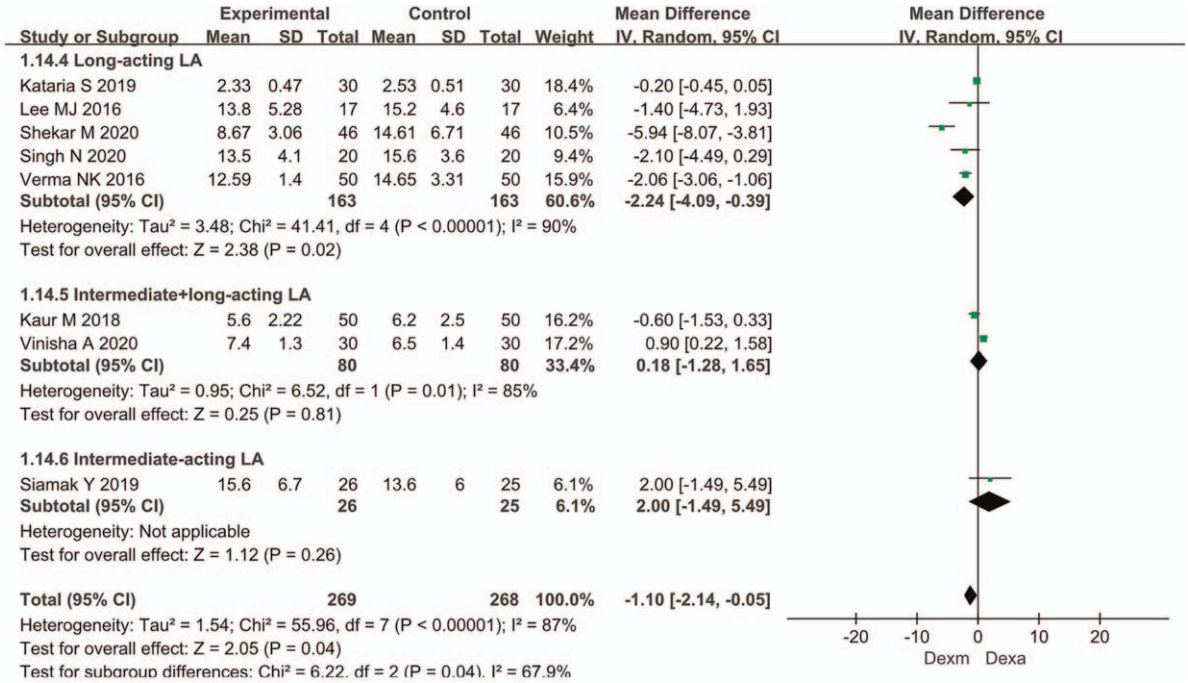

Figure 9. Forest plot (subgroup of various types of LA) comparing the effect of Dexm and Dexa on time required for the onset of sensory blockade; LA = local anesthetics.

3.6. Time required for the onset of sensory and motor blockades

Time required for onset of sensory and motor blockades was reported in 8 [13,14,16,24,27–30] and 8[13,14,24,25,27–30] studies, respectively. The pooled analysis indicated that onset time of sensory blockade was decreased by 1.1 minutes (95% CI: −2.14 to −0.05, $I^2 = 87\%$; $P = .04$) with Dexm intake compared with Dexa intake (Fig. 9), and there was no significant difference in onset time of motor blockade between intake of Dexa and Dexm (Fig. 10). Subgroup analysis showed that Dexm had a greater facilitative effect

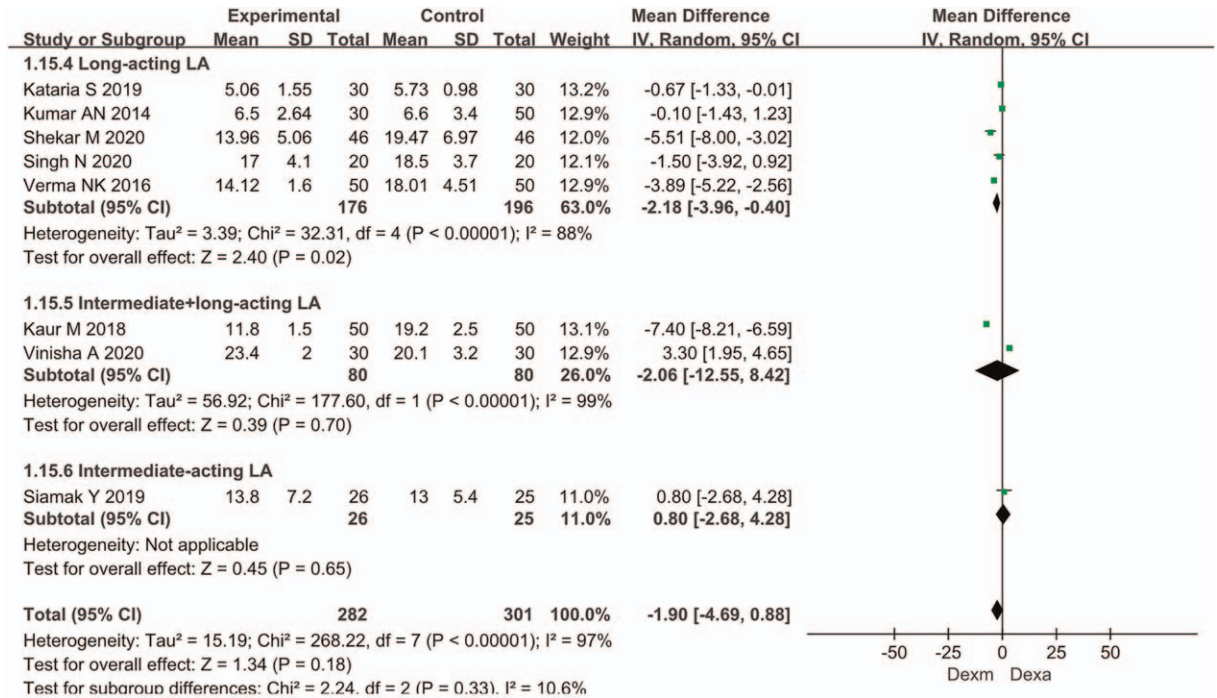

Figure 10. Forest plot (subgroup of various types of LA) comparing the effect of Dexm and Dexa on time required for the onset of motor blockade; LA = local anesthetics.

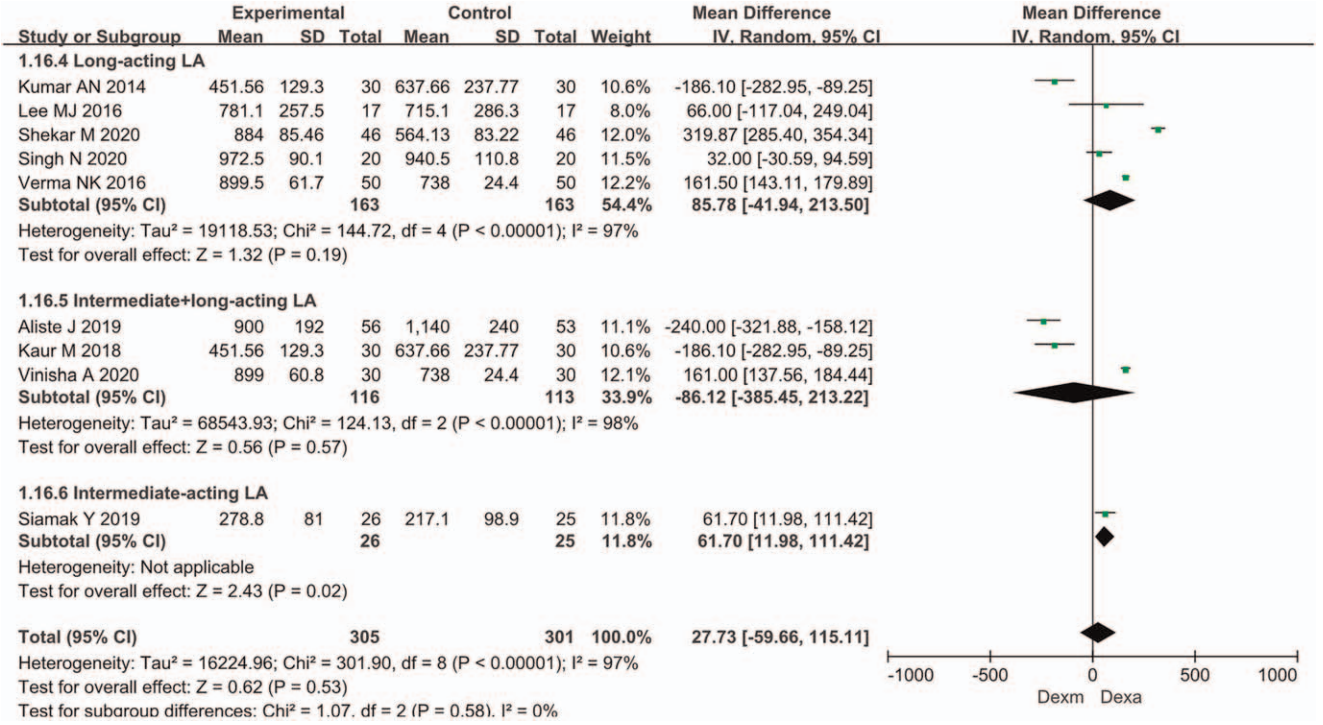

Figure 11. Forest plot (subgroup of various types of LA) comparing the effect of Dexm and Dexa on duration of sensory blockade; LA = local anesthetics.

on long-acting LA. Compared with Dexa, Dexm shortened the time required for the onset of sensory blockade by 2.24 minutes (95% CI: −4.09 to −0.39) and that of the motor blockade by 2.18 minutes (95% CI: −3.96 to −0.4) for long-acting LA (Figs. 9 and 10).

3.7. Duration of sensory and motor blockades

Nine[14,16,17,24,25,27–30] and 8[14,17,24,25,27–30] studies reported the durations of sensory and motor blockades, respectively. Random-effects model did not reveal any significant differences in the duration of sensory blockade (MD: 27.73; 95% CI: −59.66 to 115.11; $I^2=97\%$; $P=.53$; Fig. 11) between the 2 groups, while it was revealed that Dexm prolonged the duration of motor blockade by 82.6 minutes (95% CI: 15.95 to 149.24; $I^2=97\%$; $P=.02$) more than Dexa (Fig. 12). However, subgroup analysis showed that Dexm combined with intermediate-acting LA prolonged the duration of sensory blockade, which was longer than that of Dexa, whereas this result was not observed in long-acting or intermediate + long-acting LA (Fig. 11). Besides, it was revealed that in various types of LA, the 2 additives did not have a significant influence on the duration of motor blockade, which is different from the estimated overall effects (Fig. 12).

3.8. Incidence of postoperative nausea and vomiting

Four trials[13–15,18] investigated the incidence of PONV. The pooled analysis revealed that there was no significant difference between the 2 groups (RR: 0.44; 95% CI: 0.15–1.35; $I^2=0$; $P=.15$; Fig. 13), with no heterogeneity.

3.9. Publication bias

No substantial asymmetry was detected by visual examination of the funnel plot (Fig. 14). There was no evidence of publication bias for these outcomes among included trails except the Egger test for duration of motor blockades ($P<.1$). Thus, we performed a Duval & Tweedie's trim-and-fill analysis, which demonstrated that the effect size was not changed. The Egger test for clinical outcomes was displayed in Table 2.

3.10. Complications

A previous study[13] reported blockade-associated complications, including Horner's syndrome and dysphonia. Two studies[17,27] demonstrated that Dexm displayed more sedative properties than Dexa ($P<.05$). Other complications, such as bradycardia and hypotension, were also reported, while their incidence was low, with no significant difference between the 2 groups.

4. Discussion

To our knowledge, this is a pioneering systematic review and meta-analysis aiming to directly assess the comparative efficacies of Dexm and Dexa when they were separately utilized as adjuvants for PNB. This meta-analysis incorporated 13 RCTs encompassing 1126 patients. We found that there was no significant difference in duration of analgesia and incidence of PONV between Dexm and Dexa groups. Meanwhile, intake of Dexm increased the incidence of rescue analgesia in limbs surgery, as well as the cumulative opioid consumption, and shortened the time required for onset of sensory and motor blockades for long-acting LA, which indicated that the effects of the 2 adjuvants on PNB were interfered by the nature of pain and type of LA. Specifically, Dexa may be better in postoperative pain management, while Dexm possesses a number of advantages in terms of shortening the time required for onset of sensory and motor blockades. All the trials included in this meta-analysis did

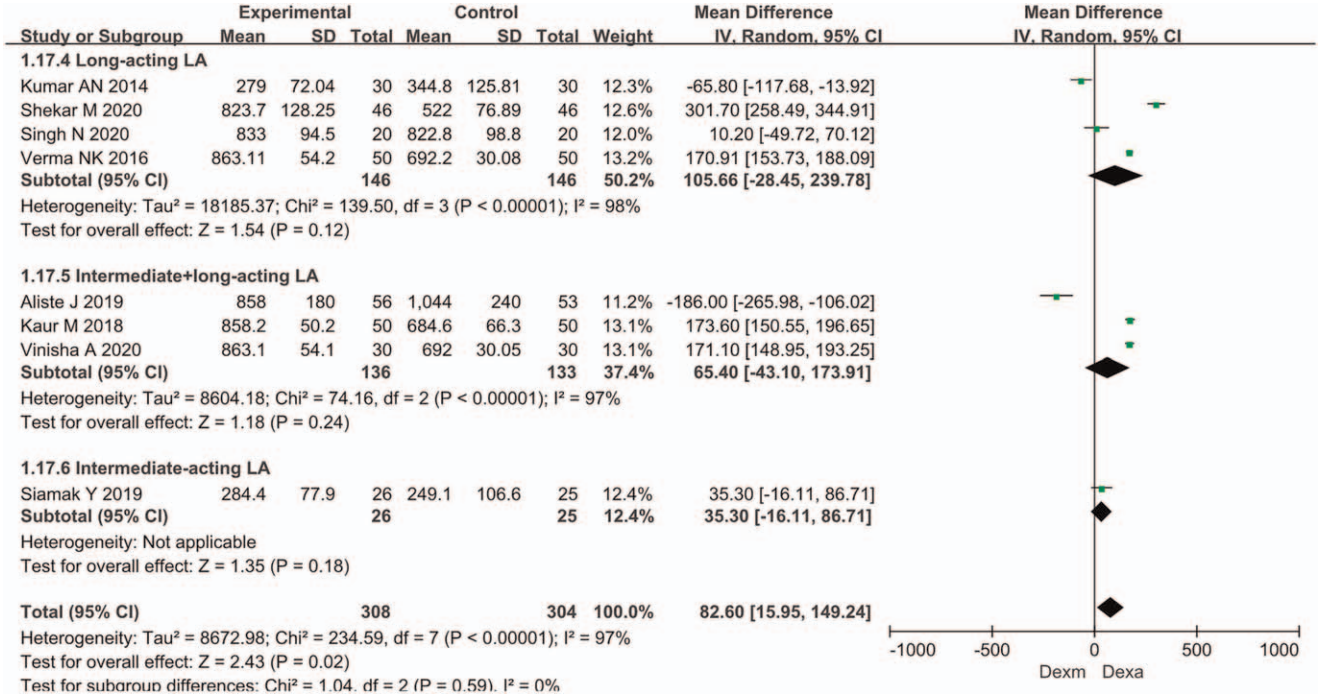

Figure 12. Forest plot (subgroup of various types of LA) comparing the effect of Dexm and Dexa on duration of motor blockade; LA = local anesthetics.

not report serious adverse effects of the 2 adjuvants. For Dexm, the postoperative sedation may be more efficacious than that of Dexa, which is also acceptable. In addition, the clinical meaningfulness of our results may be restricted in virtue of the high degree of heterogeneity found in the included trials, although we had used prior hypotheses to explain them.

Incorporation of adjuvants in LA has significantly attracted scholars' attention owing to their contribution in managing postoperative pain. Adjutants enhance the pain-relieving effect of analgesics, with relatively few side-effects. The first adjuvant was introduced in 1982, and since then, several other armamentariums (e.g., midazolam, buprenorphine, ketamine, clonidine, magnesium, epinephrine, Dexm, Dexa, etc.) have been discovered.[31–33] At present, Dexm and Dexa are the 2 most widely used additives in LA, however, their comparative advantages remain inconsistent. A recent meta-analysis suggested that Dexa may be a better adjuvant than Dexm in supraclavicular brachial plexus block,[34] because it significantly prolongs the duration of analgesia. The results of the present meta-analysis were slightly dissimilar to those findings, in the sense that, we found the duration of analgesia associated with Dexm was longer than that of Dexa, although the difference was not statistically significant. This discrepancy may be explained by the indirect comparison employed in a previous meta-analysis,[34] and as mentioned by the authors of the above meta-analysis, a head-to-head comparison is essential to effectively assess the efficacy of Dexm and Dexa.

To date, the precise mechanism with which dexmedetomidine and dexamethasone prolong the duration of nerve blocks is not fully understood, but it is thought to be multifactorial. One of the ways in which adjuvants mediate the aforementioned function is by increasing vasoconstriction of the surrounding blood vessels.[35,36] Dexmedetomidine, in particular, is thought to bind on locus ceruleus, thus interfering with norepinephrine release from the respective cells.[37] Dexamethasone on its part impairs inflammation[38] and transmission of sensory signals in unmy-

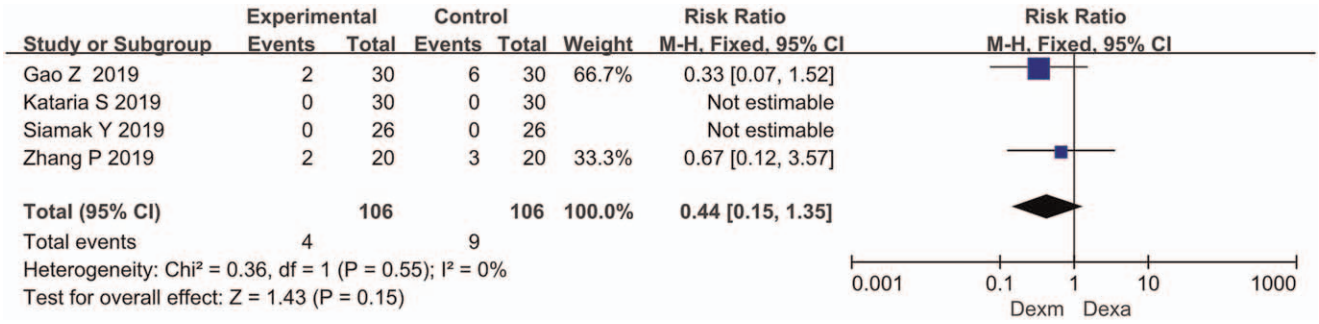

Figure 13. Forest plot comparing the effect of Dexm and Dexa on PONV; PONV, postoperative nausea and vomiting.

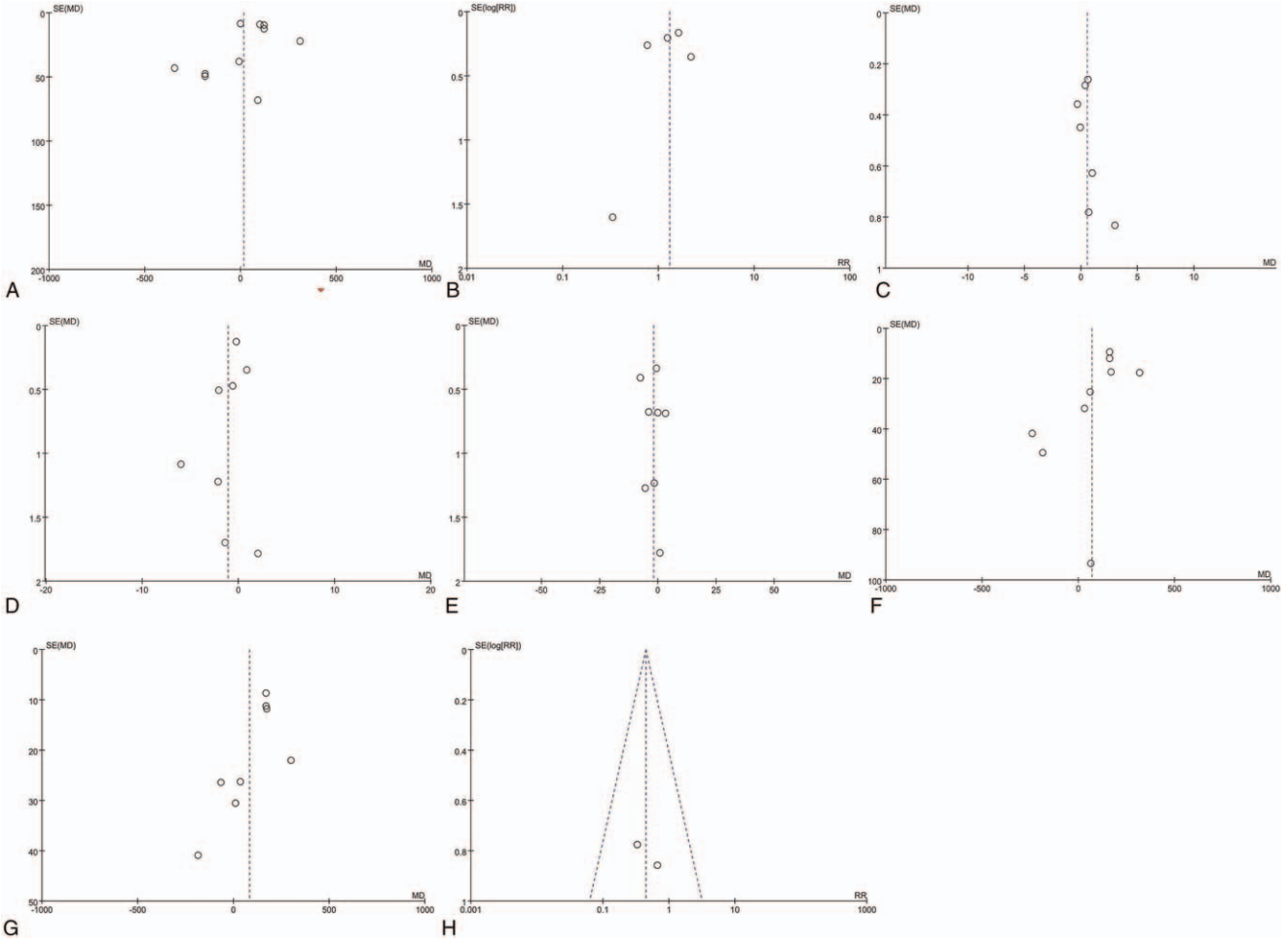

Figure 14. Publication bias assessed by funnel plot. Panel A presents the funnel plot for duration of analgesia, panel B for incidence of rescue analgesia, panel C for opioid consumption over 24 hours after surgery, panel D and E for time required for onset time of sensory and motor blockades, panel F and G for duration of sensory and motor blockades and panel H for PONV.

elinated C-fiber cells.[39] As far as these mechanisms are currently mastered, it has not been discovered that they can cause serious adverse consequences, especially whether this "off-label" method of perineural administration will cause potential neurological complications. In recent years, multiple studies from human and animal experiments have demonstrated the safety of both dexmedetomidine and dexamethasone as adjuvants in local anesthetics.[40–44] And in this review, except for dexmedetomidine-related bradycardia and a slightly higher degree of sedation, no other serious adverse reactions were found.

It is noteworthy that Dexm significantly reduces the time required for onset of sensory and motor blockades for long-acting LA. However, addition of both Dexm and Dexa to LA can shorten the time required for onset of the sensory and motor blockades compared with LA alone,[45,46] while this feature is not altered by the type of LA (intermediate-acting or long-acting). Thus, we hypothesized that Dexm and Dexa have either 2 pathways of action or a same pathway of action, whereas Dexm has a stronger effect, which is amplified in long-acting LA. In the current meta-analysis, we also found that the quality of postoperative analgesia (incidence of rescue analgesia and cumulative opioid consumption) using Dexm in limbs surgery is worse than that of Dexa; however, in thoracic surgery, the effects of the 2 additives are equivalent. This finding is consistent with result of a previous research,[47] in which Dexm provides superior postoperative analgesia in more painful surgeries.

Table 2

Publication bias on the association of each clinical outcome.

	Duration of analgesia	Incidence of rescue analgesia	Opioid consumption over 24h after surgery	Time required for onset time of sensory blockade	Time required for onset time of motor blockade	Duration of sensory blockade	Duration of motor blockade
Egger test (P)	0.517	0.265	0.301	0.299	0.752	0.115	0.071

Hence, further exploration of these mechanisms is warranted, and the difference between the 2 adjuvants in more types of surgery or pain should be studied as well.

Regarding limitations of the current meta-analysis, firstly, a limited number of reports were included herein and there was a high degree of clinical heterogeneity between included studies, which may increase the variability of outcomes and restrict the generalizability of our results. Second, this study was only based on 2 surgical sites and more types of surgery should be studied in future researches. Furthermore, it may be more meaningful to analyze the specific PNB. Finally, the majority of the articles included in this study were conducted in India and China, which may lead to publication bias. Besides, the lack of data from ongoing trials (i.e., at least one phase III trial) may further exacerbate publication bias. Therefore, further large-scale, multicenter, prospective, double-blinded RCTs are warranted to explicitly discern the effectiveness of Dexm and Dexa.

5. Conclusions

The present meta-analysis revealed that Dexm and Dexa provide comparable analgesic durations. However, there are several differences between the 2 adjuvants. For instance, Dexa is associated with a lower incidence of rescue analgesia and less cumulative opioid consumption, while this is also based on certain surgical sites; Dexm shortens the time required for onset of sensory and motor blockades and is unique to long-acting LA. To sum up, when choosing a perineural adjuvant for PNB, the results of this meta-analysis recommend that for limbs surgery, Dexa is the first choice, regardless of the type of LA; for thoracic surgery, Dexm is preferred when involving long-acting LA.

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