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Comparison of intravenous and perineural dexmedetomidine in prolongation of analgesia for peripheral nerve block: a meta-analysis and systematic review

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Abstract. – OBJECTIVE: We conducted a meta-analysis and systematic review to compare the efficacy of perineural vs. intravenous dexmedetomidine as local anesthetic adjuvant.

MATERIALS AND METHODS: Two researchers searched MEDLINE, OVID, PubMed, Embase, Cochrane Central, Web of Science and Wanfang data for randomized controlled trials comparing the effect of intravenous vs. perineural injection of dexmedetomidine as a local anesthetic adjuvant in prolongation of analgesia for peripheral nerve block, without any language restrictions.

RESULTS: We identified 14 randomized controlled trials. The results revealed that the duration of analgesia [Standard mean difference (SMD): -0.55, 95% CI, (-1.05, -0.05) p=0.032, I^2=85.4%] and the duration of sensory block [SMD: -2.68, 95% CI, (-4.53, -0.83) p=0.004, I^2=97.3%], were significantly longer, the onset time of motor block [SMD: 0.65, 95% CI, (0.02, 1.27) p=0.043, I^2=85.0%] was shorter in the perineural dexmedetomidine group, when compared with the systematic dexmedetomidine group. There was no significant difference in the duration of motor block [SMD: -0.32, 95% CI, (-1.11, -0.46) p=0.416, I^2=89.8%] and the onset time of sensory block [SMD: 0.09, 95% CI, (-0.33, 0.52) p=0.668, I^2=59.9%] between the two groups. Meanwhile, perineural dexmedetomidine reduced analgesic consumption in 24 hours [SMD: 0.43, 95% CI, (0.06, 0.80) p=0.022, I^2=58.7%] compared with the intravenous dexmedetomidine group.

CONCLUSIONS: Our meta-analysis currently generates the evidence that perineural dexmedetomidine administration offers advantages not only in prolonging the duration of analgesia and sensory block, but also in shortening the onset time of motor block, when compared with the intravenous administration.

Key Words:
Local anesthesia, Dexmedetomidine, Perineural, Intravenous, Analgesia, Nerve block.

Abbreviations

PNB: Peripheral nerve blocks; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; RCT: Randomized Controlled Trials; RSS: Ramsay Sedation Score; CI: Confidence interval; RR: Relative risk; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; SMD: Standard mean difference; AMP: Adenosine monophosphate; CNS: Central nervous system.

Introduction

Postoperative pain, as an unpleasant experience, negatively affects postoperative recovery, increases hospitalization costs, and the risk of postoperative adverse events and may result in chronic diseases[1]. There is numerous research on improving the prolongation of analgesia after surgery. Especially, several available options were applied to prolong the duration of analgesia of peripheral nerve blocks (PNBs) under regional anesthesia. For instance, continuously perineural catheters were applied for the infusion of local anesthetics or liposomal preparations of local anesthetics[2]. However, single drug treatment was not desirable. Combining local anesthetics with different adjuvants could prolong the duration of analgesia associated with PNBs[3]. Popular adjuvants, epinephrine and clonidine reportedly increased the duration of analgesia, but these drugs were limited in use for their neurotoxicity and cardiovascular side effects[4,5]. Dexmedetomidine, a highly selective a_2-adrenergic receptor agonist, is widely used in clinical anesthesia due to its sedation, anti-anxiety and analgesic properties[6,7]. Some studies[8-10] demonstrated that both perineural and intravenous injection of dexmedetomidine to PNBs with local anesthetics could effectively prolong the duration of analgesia. However, which route

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of dexmedetomidine administration tends to be superior remains controversial. With the present meta-analysis and systematic review, we integrated all the data to assess the duration of analgesia, duration and onset time of sensory block and motor block during dexmedetomidine injected intravenously or perineurally as an adjuvant with regional anesthesia in adult patients undergoing surgery.

Materials and Methods

This meta-analysis was registered with PROSPERO, the prospective international register of systematic reviews of the National Institute for Health Research (www.crd.york.ac.uk/PROSPERO/#index. php, registration number CRD42020201996). Our analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[11].

Literature Search

We conducted a comprehensive electronic literature search in the databases PubMed, MEDLINE, OVID, Embase, Cochrane Central, Web of Science, Wanfang data and www.chictr.org.cn from inception to December 1st, 2022, to identify randomized controlled trials comparing perineural with intravenous dexmedetomidine in prolonging the duration of analgesia after receiving regional anesthesia, without any language restrictions. The search strategies for the different databases are in **Supplementary File A**.

The program Endnote X9 (available at: https://endnote.com/) was employed to manage the studies identified by the search. After removing duplicate articles, two authors (Y.F., X.B.C) independently screened the search results for qualified trials. Additionally, we searched the clinical trials registry www.chictr.org.cn.

Inclusion and Exclusion Criteria

For inclusion, Randomized Controlled Trials (RCTs) should have the following characteristics:

Patients: adults under regional anesthesia alone or combined with general anesthesia for selective surgeries; Intervention: addition of dexmedetomidine to PNB at a single level with local anesthetics for perioperative analgesia (perineural dexmedetomidine group);

Comparison: addition of dexmedetomidine intravenously to PNB at a single level with local anesthetic for perioperative analgesia (intravenous dexmedetomidine group);

Outcomes: duration of analgesia, duration of sensory and motor block, onset time of sensory and motor block, analgesic consumption in 24 hours, Ramsay Sedation Score (RSS) after surgery, adverse events reported in the trials, such as hypotension, bradycardia, postoperative neurologic symptoms, respiratory depression, nausea, vomiting.

Exclusion criteria: patient age under 18 years old.

Assessment of Risks of Bias

The Cochrane Risk of Bias[12] tool was applied to analyze the methodological quality of the studies by Review Manager 5.3. (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and this analysis was completed by two authors independently (Y.F., X.B.C.). This tool allowed for an assessment of the risks of selection bias, including random sequence generation and allocation concealment, performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and other bias (the authenticity of clinical trials and whether the data are authentic and reliable; whether the evaluation results are appropriate and whether the baseline characteristics are the same between the experimental groups and the control groups included). These results are divided into three categories: low risk of bias, unclear bias, or high risk of bias. We considered a trial at low risk of bias if there was adequate random sequence generation, allocation concealment, and blinding of outcome assessment.

Data Extraction and Quality Assessment

Two reviewers (Y.F., X.B.C) selected qualified studies independently, extracted data, and recorded the trial characteristics with a standard data collection form. Any conflicts were settled by mutual negotiation. Data extracted included primary author, year of publication, comparative groups, sample size, surgical site, level of PNB, nerve localization technique, type and dose of local anesthesia, dose of perineural and intravenous dexmedetomidine, block characteristics, outcomes. We also extracted the means, standard deviations, standard mean difference, 95% confidence intervals (CIs), number of events, relative risk (RR). The authors of trials who failed to report the sample size or effective numerical results were contacted twice by e-mail to request the missing or raw data. Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

methodology was used to evaluate the overall evidence-based quality of each outcome.

Statistical Analysis

We decided to conduct a meta-analysis when at least three studies directly compared perineural and intravenous dexmedetomidine[13]. We used Stata/SE 12.1 (Stata Corp LP Lakeway Drive College Station, TX, USA) for meta-analysis. The duration of analgesia, duration of sensory and motor block, onset time of sensory and motor block are continuous data, so they were reported standard mean difference (SMD) with 95% CI. To assess the robustness of the results and to identify potential methodological biases and heterogeneity, we also conducted meta-regression and sensitivity analysis for the primary outcome. In meta-regression analysis, we focused on the dosage of dexmedetomidine (≥1 μg/kg or <1 μg/kg), level of PNBs, type of surgery and country. The I^2 coefficient was chosen to evaluate heterogeneity with predetermined thresholds for low (25-49%), moderate (50-74%), and high (>75%) levels. A random-effects model was applied when the I^2 coefficient was more than 50%; otherwise, a fixed-effects model was used[14]. Publication bias was evaluated by using Begg's test and Egger's test when at least ten studies were included in the meta-analysis. A p-value lower than 0.05 was considered statistically significant.

Results

Study Selection

Figure 1 showed the flow chart of our study selection. Of the 1,278 studies retrieved, a total of 14 randomized controlled trials involving 801 patients (401 received dexmedetomidine perineurally and 400 received dexmedetomidine intravenously) were potentially eligible to be included and were applied to an assessment of the methodological quality[15-28].

Study Characteristics

Table I contained the details of the included studies and the primary and secondary outcomes. Table II summarized the definitions used by the authors of the studies.

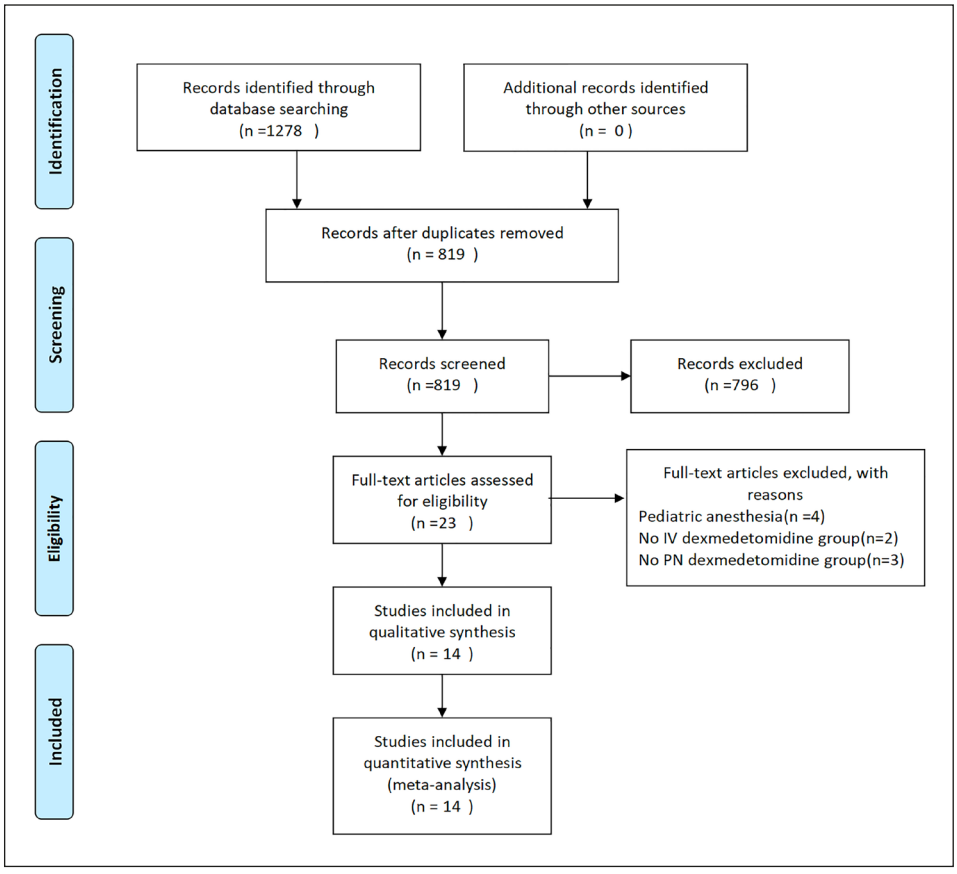

Figure 1. PRISMA flow diagram showing literature search results, fourteen randomized controlled trials were included in the analysis. IV: intravenous; PN: perineural; n: number of studies.

Table I. Details of the included trials.

Study	Number of patients		Type of surgery	Nerve block	Dex dose in IV group	Dex dose in PN group	Primary outcome of the study	Secondary outcomes	Other anesthesia techniques	Postoperative analgesia
	IV	PN								
Marhofer et al[15]	12	12	Volunteer study	Ultrasound-guided ulnar nerve block with 3 mL ropivacaine 0.75%	20 µg	20 µg	Duration of analgesia	Sensory and motor onset time; duration of sensory and motor block; adverse events: bradycardia, hypotension		
Kathuria et al[16]	20	20	Elective upper limb surgery	Ultrasound-guided supra-clavicular brachial plexus block with 30 mL of 0.5% ropivacaine	50 µg	50 µg	Duration of analgesia	Onset time and duration of sensory and motor block; onset time and duration of sensory and motor block; total analgesic consumption in 24 hours post-operatively; adverse events: respiratory depression, bradycardia, hypotension, skin rash, nausea, vomiting		Injection diclofenac sodium 75 mg intra-muscular was admini-stered when VAS score was≥4
Abdallah et al[17]	34	33	Elective unilateral arthroscopic shoulder surgery	Ultrasound-guided single-injection interscalene brachial plexus block with 15 mL ropivacaine, 0.5%	0.5 µg/kg	0.5 µg/kg	Duration of postoperative analgesia	Duration of motor block; opioid consumption; VAS; PSS; adverse events: bradycardia hypotension postoperative neurologic symptoms and/or 25 µg IV fentanyl	Premication: 1,000 mg oral acetaminophen and 400 mg celecoxib, all patients received 1 to 4 mg IV midazolam for anxiolysis and analgesia before block, GA:1 to 3 µg/kg IV fentanyl l, 2 to 4 mg/kg IV propofol, and 0.6 mg/kg IV rocuronium	VAS≥4: 25 to 50 µg IV fentanyl every 5 min followed by 2 to 4 mg IV morphine
Shashikala and Madhyastha[18]	30	30	Elective forearm surgeries	Nerve stimulator supraclavicular brachial plexus block with 28 mL 0.5% ropivacaine	50 µg	50 µg	The sensory and motor block duration, total duration of analgesia	Onset time of sensory and motor block; adverse event: bradycardia, hypotension; hemodynamic parameters: mean systolic blood pressure and heart rate.	Premication: orally alprazolam 0.5 mg on the night before the surgery and intra-venously midazolam 0.02 mg/kg before block	

Continued

Table I *(continued)*. Details of the included trials.

Study	Number of patients		Type of surgery	Nerve block	Dex dose in IV group	Dex dose in PN group	Primary outcome of the study	Secondary outcomes	Other anesthesia techniques	Postoperative analgesia
	IV	PN								
Ranjith et al[19]	38	40	Elective and emergency femur surgeries	Ultrasound-guided fascia iliaca compartment block with 40 mL of 0.25% bupivacaine with 2 mL of 0.9% saline	1 µg/kg	1 µg/kg	Mean duration of postoperative analgesia	Total consumption of morphine in 24 hours; total consumption of morphine in 24 hours; number of used PCA boluses f morphine; VAS; adverse events: nausea, vomiting	Premication: orally diazepam 5mg, 100 µg/kg morphine intravenously before theblock, GA:5 mg/kg Sodium thiopentone and 0.5mg/kg atracurium intravenously (IV)	PCA morphine, intravenous paracetamol of 1 g to ensure NRS below 4 at movement
Khan and Singh[20]	30	30	Unilateral upper limb surgery	Ultrasound-guided supraclavicular brachial plexus with 19.5 mL of 0.75% ropivacaine	0.75 µg/kg	0.75 µg/kg	Onset time and duration of sensory and motor block	Hemodynamic parameters: mean systolic blood pressure and heart rate; sedation score		
Andersen et al[21]	11	11	Volunteer study	Ultrasound–guided ulnar nerve block with 4 mL ropivacaine 5 mg/mL	100 µg	100 µg	Duration of nerve block by mechanical discrimination	Duration of sensory and motor block; onset time of sensory block; hemodynamic parameters: blood pressure and pulse rate at either 7.5 mg/mL	On the subsequent treatment day, 1 mL of normal saline plus 4 mL of ropivacaine (HiRopi) or 5 mg/mL (NoDex)	
Thapa et al[22]	35	35	Arthroscopic anterior cruciate ligament	Ultrasound-guided adductor canal block (ACB) using 15 mL of 0.5% ropivacaine	0.5 µg/kg	0.5 µg/kg	24 hours' total morphine consumption	VAS; RSS; hemodynamic parameters: mean systolic blood pressure and heart rate 1 g IV prior to	At the completion of surgery, all subjects received paracetamol Rescue analgesia was shifting into PACU	PCA (morphine and paracetamol 1 g) in the postoperative period. provided with IV diclofenac 75 mg if the patient experienced a VAS≥4
Zhang et al[23]	20	20	Thoracoscopic lobectomy	Intercostal nerve block	1 µg/kg	1 µg/kg	Duration of postoperative analgesia	Total consumption of morphine in 24 hours, VAS, RSS, adverse events: bradycardia, hypotension, respiratory rate depression, nausea, vomiting	GA: midazolam 0.05 mg/kg, fentanyl 4 µg/kg, etomidate 0.3 mg/kg, cisatracurium 0.2 mg/kg	PCA in the postoperative period

Continued

Table I *(continued)*. Details of the included trials.

Study	Number of patients		Type of surgery	Nerve block	Dex dose in IV group	Dex dose in PN group	Primary outcome of the study	Secondary outcomes	Other anesthesia techniques	Postoperative analgesia
	IV	P								
Somsunder et al[24]	30	30	Upper limb surgeries	Under nerve stimulator technique supraclavicular brachial plexus block with 20 mL of 0.5% levobupivacaine plus 10 mL of 2% lignocaine	1 µg/kg	1 µg/kg	Duration of analgesia	Onset time and duration of sensory and motor block; onset time and duration of sensory and motor block; ramsay sedation score; opioid consumption; adverse events	The patients were premedicated with 0.5 mg of tablet alprazolam and 150 g of tablet ranitidine on the previous night of surgery	Patients with VAS≥4 received injection diclofenac sodium 75 mg as rescue analgesia
Ahuja et al[25]	30	30	Below knee trauma surgery	Ultrasound-guided adductor canal block with 15 mL of 0.5% ropivacaine, sciatic popliteal block with 20 mL of 0.15% ropivacaine	1.0 µg/kg	0.5 µg/kg	Cumulative tramadol consumption, perioperatively	The cumulative postoperative tramadol consumption at 4, 6, 12, 18, 24, 30, 36, and 42 hours following surgery; median VAS; RSS; adverse events: nausea or vomiting; patient satisfaction score	Premication: orally alprazolam 0.25 mg, each patient was anesthetized with subarachnoid block with 3.2 mL of 0.5% bupivacaine heavy and 15 µg fentanyl	Tramadol PCA pump, VAS≥4: IV diclofenac 75 mg
Samar et al[26]	20	20	Upper extremity orthopedic surgery	Nerve stimulator-guided supraclavicular block with 40 mL solution containing 5 mg/kg lignocaine (2%) and 2 mg/kg of bupivacaine (0.5%)	1 µg/kg	1 µg/kg	Duration of analgesia	Onset and duration of sensory and motor block, hemodynamic parameters		Rescue analgesia was provided in the form of diclofenac 75 mg intravenously when VAS was >4
Yao et al[27]	50	50	Elective lumpectomy	Ultrasound-guided intercostal nerve block with 0.5% ropivacaine	0.5 µg/kg	0.5 µg/kg	Duration of postoperative analgesia	NRS; RSS; adverse events: dizziness, dry mouth, nausea, vomiting, and respiratory. Depression		Tramadol 1-2 mg/kg if the patients required
Lai et al[28]	40	40	Intentioned repair of inguinal hernia	Ultrasound-guided ilio-hypogastric nerve and ilioinguinal nerve block with15 mL of 0.375% ropivacaine 15 mL	1 µg/kg	1 µg/kg	Duration of postoperative analgesia	Onset time of sensory block; hemodynamic parameters: mean systolic blood pressure and heart rate at different time points; VAS; adverse events: dizziness, nausea, vomiting		

Dex: Dexmedetomidine. IV: Intravenous(ly). PN: Perineural(ly). PCA: Patient controll analgesia. VAS: Visual analogue scale. RSS: Ramsay sadation score. PSS: Patient satisfication score. GA: General anesthesia. NRS: Numerical rating scale.

Table II. Definitions used by the authors of the studies.

Author	Duration of analgesia	Duration of sensory block	Duration of motor block	Onset time of sensory block	Onset time of motor block	Analgesic consumption
Marhofer et al[15]	Time from performance of the block to pinprick 100% in all sensory areas	Time during pinprick 0% persisted in all areas	Time during motor score 0 persisted in all areas	Time from performance of the block to pinprick 0% in all sensory areas	Time from performance of the block to a motor score 0	
Kathuria et al[16]	The time between the end of local anesthetic administration and first rescue analgesic administration	The time interval between the end of study drug administration and complete resolution of sensation on all nerves	The time interval between the end of study drug administration and the recovery of complete motor power of the hand and forearm	The time interval between the end of total local anesthetic administration and complete sensory	The time interval between the end of total local anesthetic administration and complete motor block	Total amount of diclofenac sodium used in first 4 hours period postoperatively was noted
Abdallah et al[17]	Time from performance of the block to the first report of postoperative pain at the surgical site		Time from performance of the block to return to normal or presurgical strength in the arm			Intraoperative fentanyl requirements
Shashikala and Madhyastha[18]	Total duration of analgesia	The time taken for complete sensory blockade	The time taken for complete motor blockade	The time taken for complete sensory blockade	The time taken for complete motor blockade	
Sivakumar et al[19]	Time taken for the first analgesic requirement in the post-operative period					Total consumption of morphine in 24 hours was calculated
Andersen et al[21]	Time from block performance until tonic heat stimulation again elicited a painful response on a visual analog scale score (VAS>0)	Time from block completion until pinprick again was perceived as sharp	Time from block performance until MVIC>75% of baseline values	Time from block performance until pinprick ceased to feel sharp		Total consumption of fentanyl in PCIA

Continued

Table II *(continued)*. Definitions used by the authors of the studies.

Author	Duration of analgesia	Duration of sensory block	Duration of motor block	Onset time of sensory block	Onset time of motor block	Analgesic consumption
Zhang et al[23]	Time elapsed from the end of the block till the first report of postoperative pain at the surgical site					
Somsunder et al[24]	The time interval between completion of local anesthetic injection and the first analgesic request.	The time interval after the completion of local anesthetic injection to complete resolution of sensation	The interval between completion of local anesthetic injection and complete resolution of motor power	The time interval between the completion of local anesthetic injection and loss of touch sensation	The time interval between completion of local anesthetic injection and loss of complete motor power	Patients with VAS≥4 received injection diclofenac sodium 75 mg as rescue analgesia and the time was also noted
Ahuja et al[25]	Time to the first tramadol PCA					The cumulative post-operative tramadol consumption at 4, 6, 12, 18, 24, 30, 36, and 42 hours following surgery
Samar et al[26]	Time elapsed from the end of the block till the first request for analgesia	Time elapsed between injection of the drug and appearance of visual analogue score (VAS)>3	Time elapsed between injection of the drug to complete return of motor power	Time from injection to the onset of analgesia in each of the major peripheral nerve distribution	Time from injection to the complete loss of flexion	
Yao et al[27]	Duration of postoperative analgesia					
Lai et al[28]		The time interval after the completion of local anesthetic injection to appearance of visual analogue score (VAS)>0		The time interval between the completion of local anesthetic injection and loss of pain sensation		

MVIC: maximal voluntary isometric contraction. PCA: patient controlled analgesia. PCIA: Patient controlled intravenous analgesia. VAS: Visual analogue scale. PCA: Patient controlled analgesia.

Risk of Bias Within Studies

Figure 2 showed the methodological quality of the studies[15-28]. We assessed 5 as low risk of bias[16,17,19,22,23] and 9 as unclear risk of bias[15,18,20,21,24-28] of these 14 trials according to our pre-specified criteria. In our review, no consultation of a third author was required, as no disagreements between the authors existed.

Synthesis of Results

Primary outcome: duration of analgesia

Figure 3A showed the meta-analysis for analgesia duration, including twelve trials[15-19,21-27] that had data for this outcome. Compared with systematic dexmedetomidine, the duration of analgesia was significantly longer in the perineural group [SMD: -1.8, 95%CI, (-2.75, -0.86) $p<0.0001$, $I^2=96.1\%$] using a random-effect model. In meta-regression analysis, the dosage of dexmedetomidine ($p=0.529$), level of PNBs ($p=0.467$), type of surgery ($p=0.599$), country ($p=0.953$) did not correlate with the duration of analgesia.

Sensitivity analysis: three[18,21,27] of twelve studies[15-19,21-27] may have led the heterogeneity among studies. The definitions of primary and secondary outcomes in one study[18] was ambiguous, the dosage of local anesthetic in one study[21] was lower (4 mL ropivacaine 5 mg/mL) than other studies[15-19,22-26] and another study[27] did not refer the dosage of local anesthetic. After removing the studies, the heterogeneity of the remaining studies was reduced ($I^2=85.4\%$). Using a random-effect model, the results of meta-analysis (Figure 3B)[15-19,21-27] showed that the duration of analgesia was still statistically significantly longer in the perineural group [SMD: -0.55, 95% CI, (-1.05, -0.05) $p=0.032$, $I^2=85.4\%$].

Secondary outcomes: duration of sensory block (hour)

Eight studies[15,16,18,20,21,24,26,28] reported this variable. The meta-analysis is shown in Figure 4A. When comparing perineural with intravenous dexmedetomidine, the duration of sensory block was longer in the perineural group [SMD: -4.11, 95% CI, (-6.04, -2.19), $p<0.0001$, $I^2=97.7\%$]. Sensitivity analysis: after removing the studies[18,21] that may lead heterogeneity, the heterogeneity of the remaining studies was not significantly reduced ($I^2=97.3\%$). Using a random-effect model, the results of meta-analysis (Figure 4B)[15,16,20,24,26,28] showed that the duration of sensory block was still statistically longer in the perineural group [SMD: -2.68, 95% CI, (-4.53, -0.83) $p=0.004$, $I^2=97.3\%$].

Duration of motor block (hour)

This outcome was reported in eight studies[15-18,20,21,24,26]. When compared with systematic dexmedetomidine, the duration of motor block was longer in the perineural group [SMD: -1.65, 95% CI, (-2.87, -0.44) $p=0.007$, $I^2=95.7\%$] in Figure 5A[15-18,20,21,24,26]. Sensitivity analysis: after removing the low quality studies[18,21], the heterogeneity of the remaining studies[15-17,20,24,26] was reduced ($I^2=89.8\%$). Using a random-effect model, the results of meta-analysis (Figure 5B) showed that there was no significant difference between the two groups [SMD: -0.32, 95% CI, (-1.11, 0.46) $p=0.416$, $I^2=89.8\%$].

Onset time of sensory block (min)

This outcome was reported in seven studies[15,16,18,20,24,26,28], and a meta-analysis was shown in Figure 6A. Compared with intravenous dexmedetomidine, the onset time of sensory block was shorter in the perineural group [SMD: 1.57, 95% CI, (0.17, 2.97) $p=0.028$, $I^2=96.8\%$]. Sensitivity analysis: after removing the studies[18,28] that may lead heterogeneity, the heterogeneity of the remaining studies[15,16,20,24,26] was reduced ($I^2=59.9\%$). Using a random-effect model, the results of meta-analysis (Figure 6B) showed that there was no significant difference between the two groups [SMD: 0.09, 95% CI, (-0.33, 0.52) $p=0.668$, $I^2=59.9\%$].

Onset time of motor block (min)

This outcome was reported in seven studies[15,16,18,20,21,24,26], and a meta-analysis was shown in Figure 7. Compared with intravenous dexmedetomidine, the onset time of motor block was shorter in perineural group [SMD: 0.65, 95% CI, (0.02, 1.27) $p=0.043$, $I^2=85.0\%$] analyzed by a random-effect model.

Analgesic Consumption

Analgesic consumption in 24 hours was reported in six studies[16,17,19,22,23,25] in **Supplementary Figure 1A**, the cumulative analgesic consumption in 24 hours in perineural group was lower than that in the intravenous group [SMD: 0.37, 95% CI, (0.05, 0.69) $p=0.023$, $I^2=55.6\%$]. Sensitivity analysis: one study[25] with different doses of dexmedetomidine in the intravenous group and the perineural group may lead heterogeneity. After removing the study, the heterogeneity of the remaining studies[16,17,19,22,23] did not change significantly ($I^2=58.7\%$). Using a random-effect model, the results of meta-analysis (**Supplementary Figure 1B**) showed that the cumulative analgesic consumption in 24 hours in perineural group was

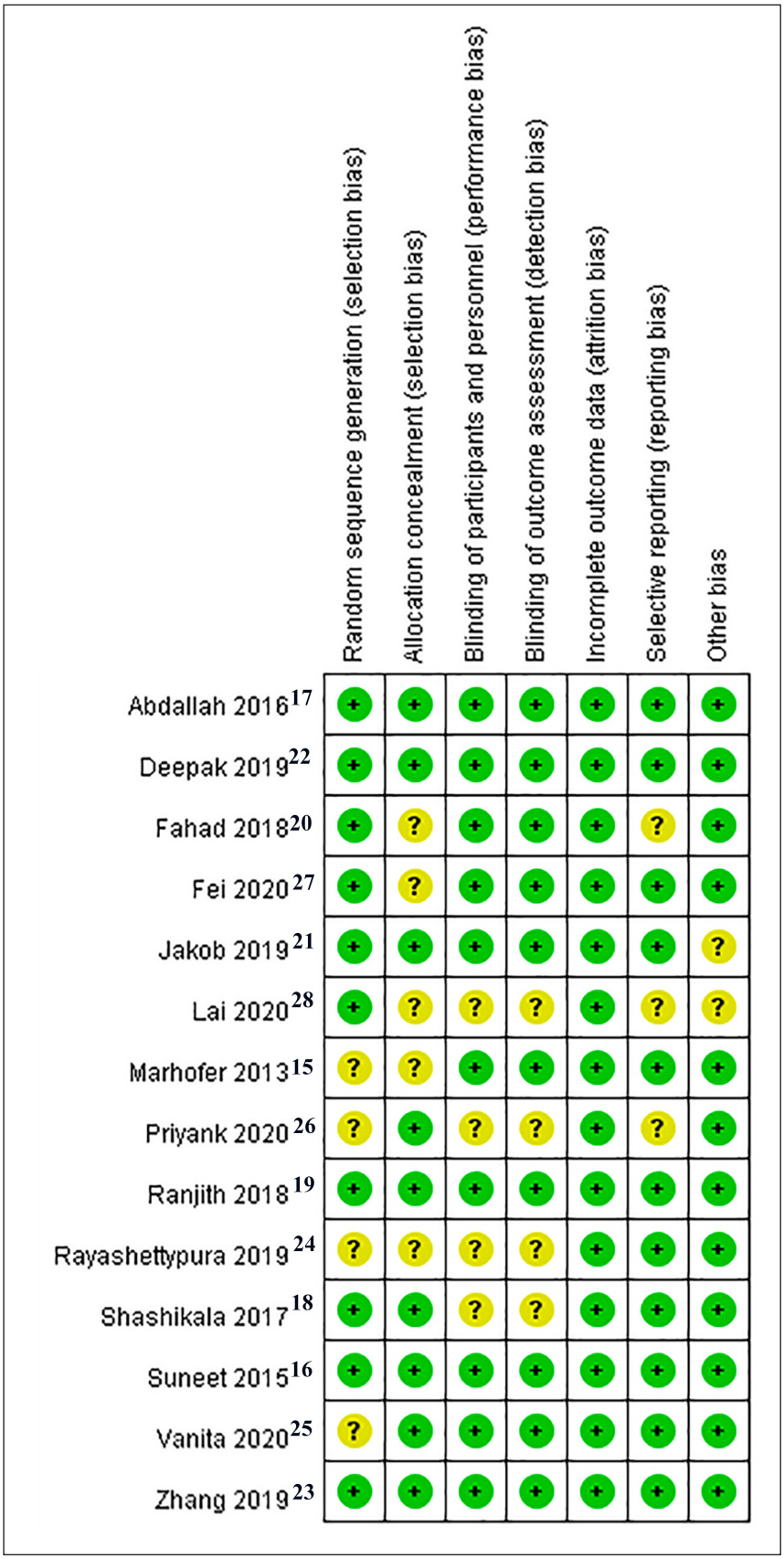

Figure 2. Risk of bias summary.

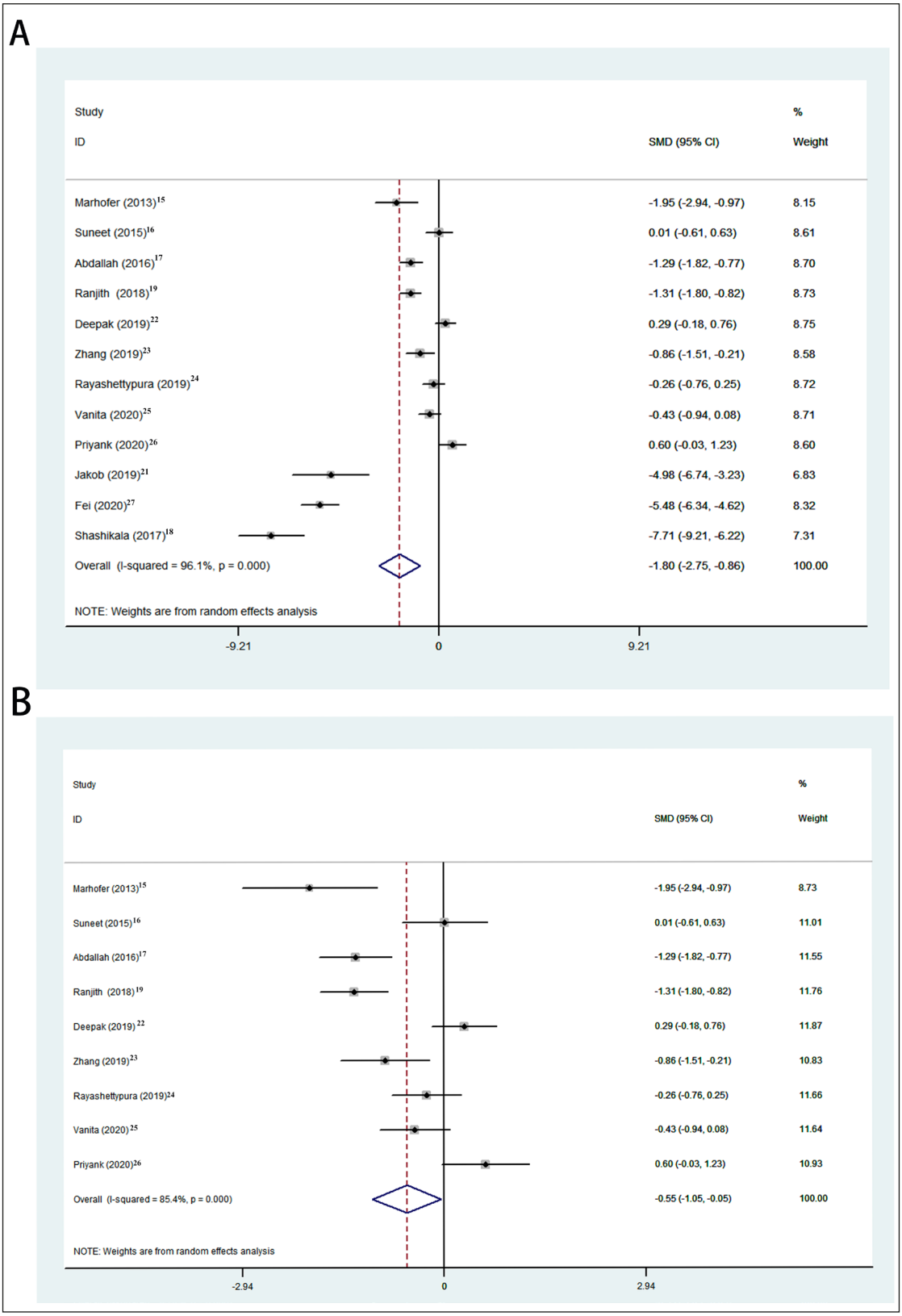

Figure 3. **A**, Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of analgesia. **B**, Forest plot for sensitivity analysis of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of analgesia. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval.

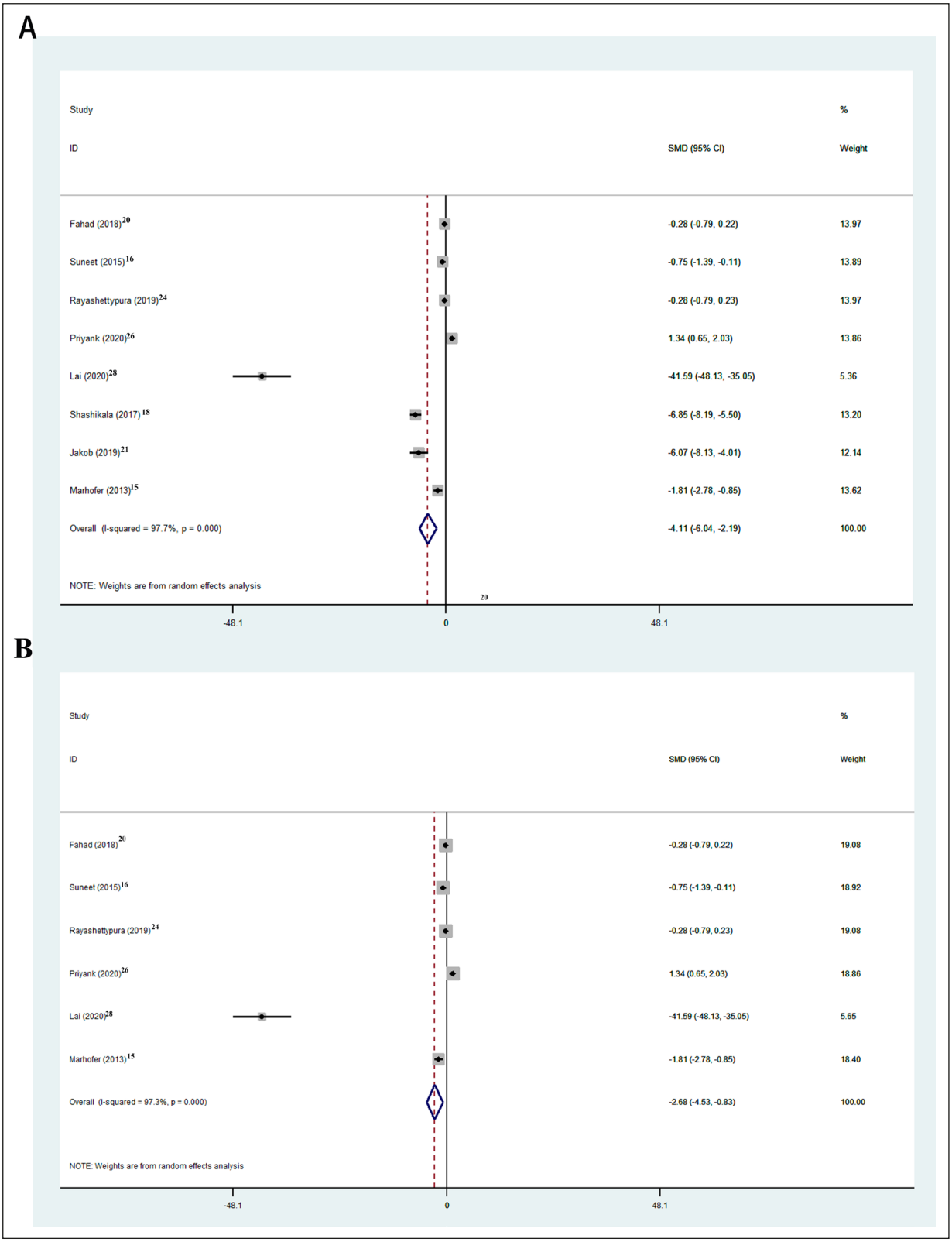

Figure 4. **A**, Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of sensory block. **B**, Forest plot for sensitivity analysis of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of sensory block. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval.

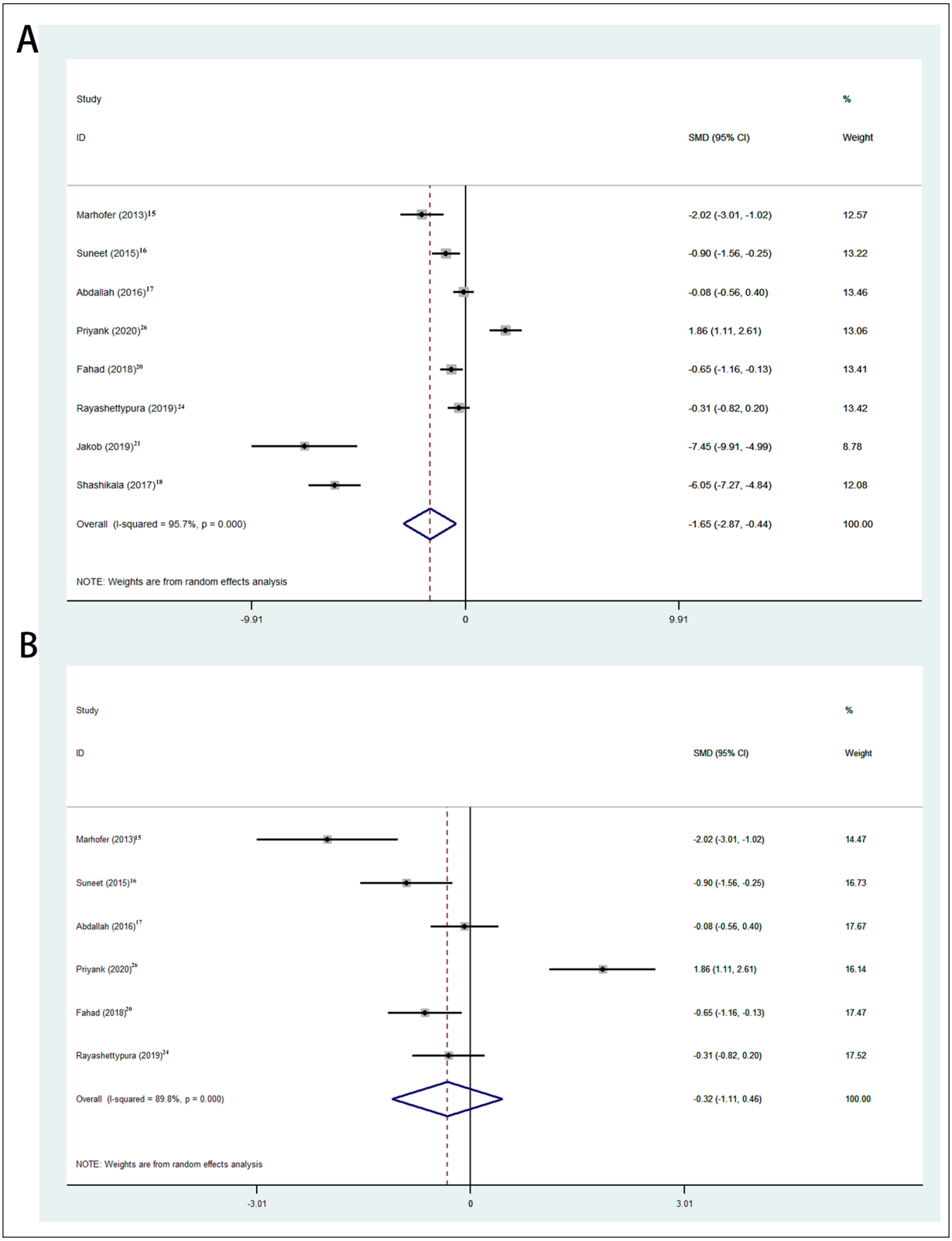

Figure 5. **A**, Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of motor block. **B**, Forest plot for sensitivity analysis of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of motor block. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval.

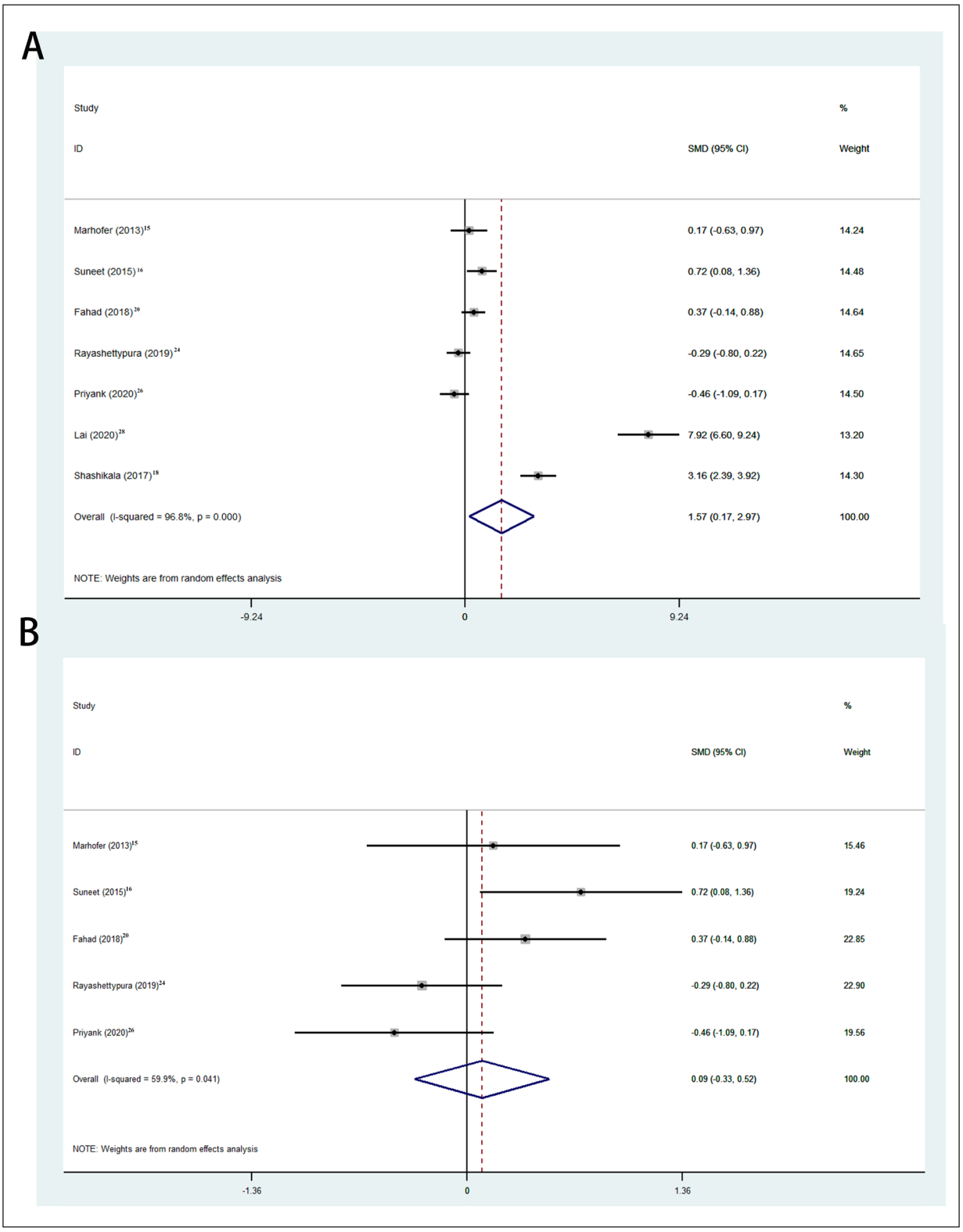

Figure 6. **A**, Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the onset time of sensory block. **B**, Forest plot for sensitivity analysis of perineural dexmedetomidine and intravenous dexmedetomidine on the onset time of sensory block. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval.

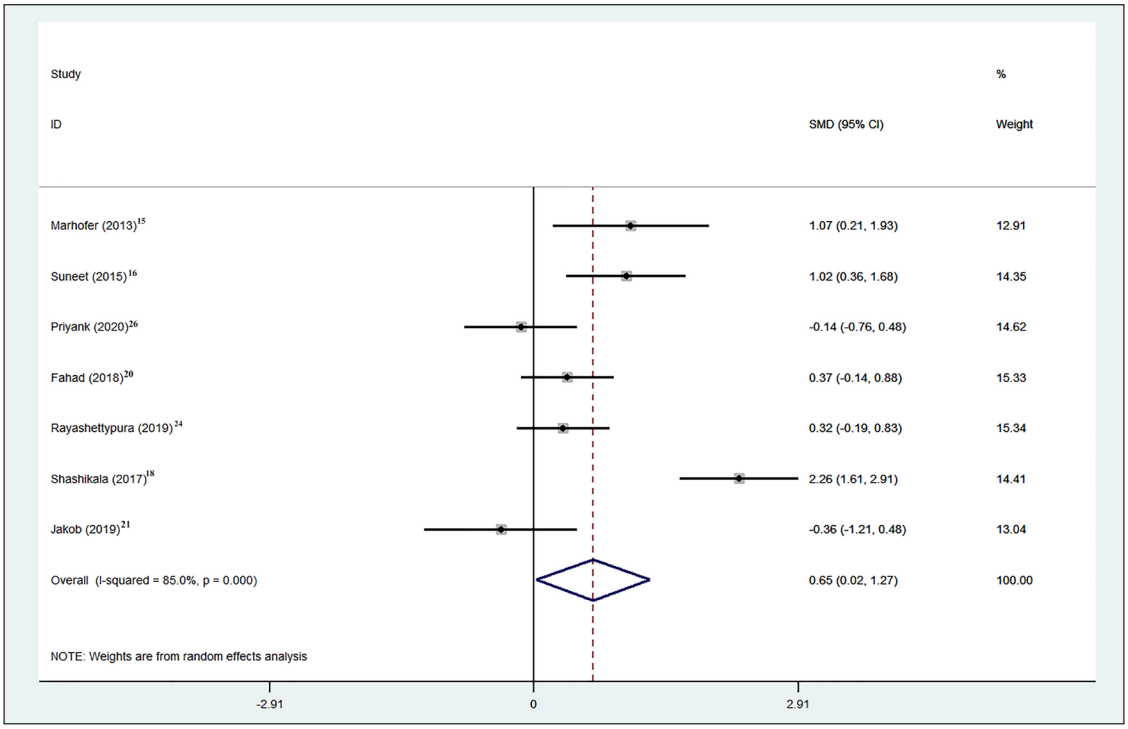

Figure 7. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the onset time of motor block. CI indicates confidence interval.

still lower than that in intravenous group [SMD: 0.43, 95% CI, (0.06, 0.80) p=0.022, I^2=58.7%].

Patients of RSS>3

Patients of RSS>3 were reported in three studies[16,19,24]. The results (**Supplementary Figure 2**) reported that the incidence of patients of RSS>3 was higher in the intravenous group [Relative risk (RR): 3.03, 95% CI, (1.49, 6.17) p=0.002, I^2=6.4%], compared with the perineural group.

Hypotension and Bradycardia

Four studies[16-18,24] described the incidence of hypotension. The results (**Supplementary Figure 3**) showed that there was no significant difference between the two groups in the incidence of hypotension [RR: 1.54, 95% CI, (0.97, 2.46) p=0.069, I^2=6.3%]. Five studies[16-18,24,26] described the incidence of bradycardia. The results (**Supplementary Figure 4**) showed that the incidence of bradycardia was higher in the intravenous group [RR: 3.71, 95% CI, (1.27, 10.86) p=0.025, I^2=0%], when compared with the perineural group.

Postoperative Neurologic Symptoms

Three studies[17,23,28] recorded postoperative neurologic symptoms, such as dizziness and weakness. The results showed the incidence of postoperative neurologic symptoms between the intravenous and perineural group was not statistically different [RR: 1.90, 95% CI, (0.79, 4.61) p=0.154, I^2=0%].

Side Effects

Three studies[17,24,28] reported the side effects. The side effects included nausea, vomiting, and respiratory depression. The result of the incidence of the side effects between the intravenous and perineural group was not statistically different [RR: 1.55, 95% CI, (0.19, 12.86) p=0.927, I^2=69%].

Publication Bias

Begg's test (p=0.047) and Egger's test (p=0.008) were carried to explore the possible presence of publication bias. The result showed that publication bias existed in the analysis of duration of analgesia.

Quality of Evidence

GRADE system grades of evidence are low quality for duration of analgesia, onset time of sensory and motor block, duration of sensory and motor block, moderate quality for analgesic consumption and incidence of the side effects, high quality for incidence of patients of RSS>3, hypotension, bradycardia, and postoperative neurologic symptoms (Table III).

Table III. Quality assessment. GRADE quality of evidence is reported only when an outcome is reported by at least three studies. RSS: ramsay sedation score. ⊕ ⊕ ⊕ ⊕, high quality evidence; ⊕ ⊕ ⊕ ⊖, moderate quality evidence; ⊕ ⊕ ⊖ ⊖, low quality evidence, ⊕ ⊖ ⊖ ⊖, very low-quality evidence.

Outcome	Limitation	Inconsistency	Indirectness	Imprecision	Publication bias	Summary in finding				Quality of evidence (GRADE)
						No. participants in PN group	No. participants in IV group	SMD (95% CI) /RR (95% CI)	*p*-value for the overall effect	
Duration of analgesia	None	High inconsistency	None	None	Yes	331	330	SMD: -1.8, 95% CI, [-2.75, -0.86]	*<0.0001*	⊕ ⊕ ⊖ ⊖ Low quality
Duration of sensory block	None	High inconsistency	None	None	Not suggestive	193	193	SMD: -4.11, 95% CI, [-6.04, -2.19]	*<0.0001*	⊕ ⊕ ⊖ ⊖ Low quality
Duration of motor block	None	High inconsistency	None	None	Not suggestive	186	187	SMD: -1.65, 95% CI, [-2.87, -0.44]	*0.007*	⊕ ⊕ ⊖ ⊖ Low quality
Onset time of sensory block	Concealment not clear in most studies	High inconsistency	None	None	Not suggestive	182	182	SMD: 1.57, 95% CI, [0.17, 2.97]	*0.028*	⊕ ⊕ ⊖ ⊖ Low quality
Onset time of motor block	None	High inconsistency	None	None	Not suggestive	153	153	SMD: 0.65, 95% CI, [0.02, 1.27]	*0.043*	⊕ ⊕ ⊖ ⊖ Low quality
Analgesic consumption	None	Moderate inconsistency	None	None	Not suggestive	178	177	SMD: 0.37, 95% CI, [0.05, 0.69]	*0.023*	⊕ ⊕ ⊕ ⊖ Moderate quality
Incidence of patients of RSS>3	None	Low inconsistency	None	None	Not suggestive	90	88	RR: 3.03, 95% CI, [1.49, 6.17]	0.002	⊕ ⊕ ⊕ ⊕ High quality
Incidence of hypotension	None	Low inconsistency	None	None	Not suggestive	113	114	RR: 1.54, 95% CI, [0.97, 2.46]	*0.069*	⊕ ⊕ ⊕ ⊕ High quality
Incidence of bradycardia	None	Low inconsistency	None	None	Not suggestive	133	134	RR: 3.71, 95% CI, [1.27, 10.86]	*0.025*	⊕ ⊕ ⊕ ⊕ High quality
Incidence of postoperative neurologic symptoms	None	Low inconsistency	None	None	Not suggestive	93	94	RR: 1.9, 95% CI, [0.79, 4.61]	*0.154*	⊕ ⊕ ⊕ ⊕ High quality
Incidence of the side effects	None	Moderate inconsistency	None	None	Not suggestive	103	104	RR: 1.55, 95% CI, [0.19, 12.26]	*0.927*	⊕ ⊕ ⊕ ⊖ Moderate quality

RR: Relative risk; CI: Confidence interval. GRADE: Grading of recommendations assessment,de velopment, and evaluation system. PN: Perineural(ly). IV: Intravenous(ly).

Discussion

Intravenous dexmedetomidine is frequently used for sedation and analgesia as an adjuvant drug in non-intubated or intubated patients for surgical and other procedures, such as mechanically ventilated patients in intensive care unit[29]. The described mechanism underlying the intravenous injection of dexmedetomidine is that it can act on the a_2-receptor in the nucleus ceruleus of the brainstem to produce its sedative-hypnotic and antianxiety effects and relieve the patient's stress[30]. Furthermore, at the level of peripheral nerves, the possible mechanisms of dexmedetomidine as an analgesic adjuvant may be as follows: first, dexmedetomidine suppresses the production of action potentials by C and A_δ fibers, enhances the inhibition of Na^+ channels by local anesthetics, and blocks the conduction of excitation[31]; second, both the activation of inwardly rectifying G1-protein-gated potassium channels and the regulation of entry of calcium through N-type voltage-gated calcium channels are independent of cyclic adenosine monophosphate (cAMP) and protein phosphorylation. Additionally, the progress is mediated by G0 proteins. Leading to membrane hyperpolarization and decreasing the firing rate of excitable cells in the central nervous system (CNS) are considered to be a crucial mechanism of the inhibitory neuronal action of dexmedetomidine[20]; third, dexmedetomidine strengthens activity-dependent hyperpolarization by inhibiting the I_h current. The I_h current exerts cell excitability, especially the firing frequency, both in the CNS and peripheral nervous systems[32,33].

Our meta-analysis showed that perineural dexmedetomidine as a local anesthetic adjuvant significantly prolonged the duration of analgesia and reduced the analgesic consumption, compared with the intravenous dexmedetomidine group. Sensitivity analysis showed that prolonged duration of analgesia effect in the perineural group was reliable and stable. Moreover, both meta-analysis and sensitivity analysis showed that duration of sensory block was longer and onset time of motor block was shorter in the perineural group compared to the intravenous group. The administration of perineural dexmedetomidine demonstrated the superior effects in duration of analgesia and sensory block, which may be attributed to the fact that dexmedetomidine in the perineural level acts on the α_2-receptors in peripheral vascular smooth muscle cells to constrict the peripheral blood vessels. Finally, it reduces the absorption of local anesthetics and prolongs the block duration[27].

Our meta-analysis also found that perineural dexmedetomidine had a shorter onset time of motor block than the intravenous approach. This might be explained by the fact that ultrasound guidance or nerve stimulator was used in the included studies[15,16,18,20,21,24,26], which shortened the onset time of peripheral nerve blocks[15] in comparison with intravenous administration of dexmedetomidine. A faster local action was completed for the presence of a_2-acceptors in the brachial plexus[16]. However, sensitivity analysis showed that there was no significant difference in duration of motor block and onset time of sensory block between the two groups. Two studies[18,21] might be the source of clinical heterogeneity and affect the results for the ambiguous definitions of primary and secondary outcomes[18] and the distinct dosage of local anesthetic used in the study[21], respectively.

The effects of intravenous dexmedetomidine on the cardiovascular system are shown as decreased heart rate and hypotension, related to the dose and infusion speed of dexmedetomidine[34] for its inhibition of sympathetic nervous systerm[35]. In our analysis, perineural dexmedetomidine had a lower incidence of bradycardia than the intravenous approach. In agreement with that, Wang et al[36] also found that bradycardia was not observed in patients undergoing knee arthroplasty anesthetized with adductor canal block and dexmedetomidine for perineural injection.

Limitations

Our review has several limitations. There was a high level of heterogeneity in the primary and secondary outcomes. The meta-regression also did not show a significant association of dosage of dexmedetomidine, level of PNB, type of surgery and country with the primary outcome. The possible explanations could be as follows: first, different local anesthetics and the doses were used among the fourteen studies[15-28]; second, the method of operating nerve block was not unified, including ultrasound-guided or nerve stimulator; third, the level of PNBs among these studies[15,16,19,21-23,25,27,28] were different. Both Rettig et al[37] and Stundner et al[38] reported that the systemic uptake and neuraxial spread might affect the magnitude of dexmedetomidine effects on the various PNBs; forth, the different definition and assessment of outcomes might be the main reasons for the methodological shortcomings; fifth, the intensity and duration of noxious stimulation varied with the type and duration of surgeries[39]; sixth, the results of Begg's test and Egger's test suggested that publication bias was present in our study.

In contrast, our review has several points of strength. The literature review we conducted was exhaustive and included all relevant databases without language restrictions. We carefully checked the data reported in journal publications and www.chictr.org.cn. for consistency. Furthermore, the primary outcome maintained their robustness despite our attempt to explore statistical heterogeneity by sensitivity analysis. However, the strength of evidence remains limited due to clinical heterogeneity, risk of bias and the small number of studies. More high-quality studies are needed to confirm our results.

Conclusions

Our meta-analysis currently generates the evidence that perineural dexmedetomidine administration offers advantages not only in prolonging the duration of analgesia and sensory block, but also in shortening the onset time of motor block, when compared with the intravenous administration.

Authors' Contributions

Yan Feng: helped conduct, analyze, write and revise the study. Xiao-Bo Chen: helped design, conduct, analyze, write and revise the study.

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Conflicts of Interest

None of the authors has potential conflict of interest to be disclosed.

Ethics Approval

No patients or members of the public were involved in the present study. Ethical approval was not required.

Informed Consent

No patient consent was required.

Availability of Data and Materials

Data are available from the corresponding author on a reasonable request.

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