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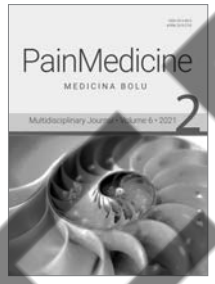

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Intravenous versus perineural dexmedetomidine in prolongation of analgesia with regional anesthesia: a meta-analysis and systematic review

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Abstract

Background and Objective. *It is unclear whether perineural administration offers advantages when compared to intravenous dexmedetomidine in local anesthesia. To compare the efficacy of perineural versus intravenous dexmedetomidine as local anesthetic adjuvant, we conducted the meta analysis and systematic review.*

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 versus perineural dexmedetomidine as local anesthetic adjuvant without any language restrictions.*

Results. *We identified 14 randomized controlled trials (801 patients). The results revealed that the duration of analgesia (SMD: -1.76, 95%CI, [-2.7, -0.83] P = 0.000, I^2 = 96%), the duration of sensory block (SMD:- 3.99, 95% CI, [-5.88, -2.0], P = 0.000, I^2 = 97.6%), the duration of motor block (SMD: -1.6, 95%CI, [-2.78, -0.41] P = 0.008, I^2 = 95.5%) were significantly longer in the perineural group, when compared to systematic dexmedetomidine. The onset time of sensory block (SMD: 1.55, 95%CI, [0.16, 2.94] P = 0.028, I^2 = 96.7%) and the onset time of motor block (SMD: 0.84, 95%CI, [0.17, 1.5] P = 0.013, I^2 = 88.3%) were shorter in perineural group compared to intrave-*

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nous dexmedetomidine. Meanwhile, analgesic consumption in 24 hours (SMD: 0.37, 95% CI, [0.05, 0.69] P = 0.023, I^2 = 55.6%) and the incidence of patients of Ramsay Sedation Scale >3(RR: 3.8, 95% CI, [1.45, 9.97] P = 0.000, I^2 = 26.9%), hypotension (RR: 1.74, 95% CI, [1.15, 2.65] P= 0.009, I^2 = 32.7%) and bradycardia (RR: 3.71, 95% CI, [1.27, 10.86] P = 0.017, I^2 = 0%) were lower in perineural dexmedetomidine compared to the intravenous group.

Conclusions. *Our meta-analysis generates the evidence that perineural dexmedetomidine is a superior adminstration for prolonging the duration of analgesia. Perineural dexmedetomidine also shows the advantages in duration of sensory block and the onset time of sensory and motor block, when compared to the intravenous administration. Simultaneously, dexmedetomidine as a local anesthetic adjuvant for perineural injection may be much safer than intravenous application because of the lower incidence of patients of Ramsay Sedation Scale > 3 and lower incidence of hypotension and bradycardia.*

Key words*: local anesthesia; dexmedetomidine; adjunct drug; perineural; intravenous; analgesia; nerve block; adverse event.*

Introduction

Postoperative pain, playing an important part in unpleasant experience, negatively affects postoperative recovery, not only increases hospitalization costs, but also the risk of postoperative adverse events and the development of chronic pain [1]. There are numerous researches to improve the prolongation of analgesia after surgery. Especially, several available options are applied to prolong the duration of analgesia of peripheral nerve blocks (PNBs) under regional anesthesia. Such as using perineural catheters to continuous infusion of local anesthetics and using liposomal preparations of local anesthetics [2]. However, both options are not desirable. Combination of local anesthetics with different several adjuvants can prolong the duration of analgesia associated with PNBs [3]. The popular adjuvants, epinephrine and clonidine, reportedly increase the duration of analgesia, but are sometimes with limited success for the neurotoxicity and cardiovascular side effects [4, 5].

Dexmedetomidine, a highly selective α_2-adrenergic receptor agonist, is widely used in clinical anesthesia due to its properties of sedation, anxiolysis, analgesia [6, 7]. Some studies [8–10] demonstrated that either perineural or intravenous injection of dexmedetomidine to PNBs with local anesthetics, is effective in prolonging the duration of analgesia. However, it remains controversial whether the perineural or systematic route of dexmedetomidine is superior. Faraj et al. [17] reported that both perineural and intravenous dexmedetomidine could equally effectively prolong the PNB analgesic duration. On the other hand, Andersen et al. [21] showed that the efficacy of perineural and intravenous dexmedetomidine were not comparable. Therfore, with the present meta-analysis and systematic review, we attempted to integrate all the data assessing primary outcome: duration of analgesia and secondary outcomes between perineural and intravenous administration of dexmedetomidine in patients undergoing surgery with regional anesthesia.

Methods

Our meta-analysis was registered with PROSPERO, the international prospective 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 and Wanfang from inception to September 1st, 2020 in order to identify randomized controlled trials comparing perineural with intravenous dexmedetomidine in prolonging duration of analgesia after receiving regional anesthesia without any language restrictions. The search strategies for the different databases are in **Appendix A**.

The program endnote X9 was employed to manage the studies identifified by the search. After removing duplicate articles, two authors (Y.F., P.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) had to have the following characteristics:

- patients: adults under regional anesthesia alone or combined with a general anesthesia for selective surgeries;
- intervention: addition of dexmedetomidine to PNB at single level with local anesthetics for perioperative analgesia (perineural dexmedetomidine group);
- comparison: addition of dexmedetomidine intravenously to PNB at 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 Scale (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-year.

Assessment of risks of bias

We used the Cochrane Risk of Bias tool [12] to analyse the methodological quality of the studies by Review Manager 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014); this analysis was completed by two authors independently (Y.F., P.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); In case of disagreement between the two authors (Y.F., P.C.), we planned to consult a third author (X.B.C.) to resolve the disagreement. These results are divided into three categories: low risk of bias, unclear risk of bias, or high risk of bias. We considered a trial to be at low risk of bias if there was adequate in random sequence generation, allocation concealment and blinding of outcome assessment.

Data extraction

Two reviewers (Yan Feng and Pan Chang) 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 anaesthesia, dose of perineural and intravenous dexmedetomidine, block characteristics, outcomes. We also extracted the data of means, standard deviations, standard mean difference, 95% confidence intervals (CIs), number of events, relative risk. 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.

Statistical analysis

We decided to conduct meta-analysis when at least three studies performed directly comparison of perineural and intravenous dexmedetomidine [13]. We used Stata/SE 12.1 (Statacorp LP 4905 Lakeway Drive College Station, TX77845 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 (eg: $\geq 1\mu$g/kg or $< 1\ \mu$g/kg), level of PNBs and country. The I^2 coefficient was used to evaluate heterogeneity with predetermined thresholds for low (25%–49%), moderate (50%–74%), and high (> 75%) levels. A random-effects model was applied when I^2 coefficient was more than 50%; otherwise, a fixed-effects model was used [14]. A P-value of less than 0.05 was considered as statistical significance.

Results

Study selection

Figure 1 shows the flow chart of our study selection. Of the 1 278 studies retrieved, A total of 14 randomized controlled trials involving 801 patients were identified (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 1 contained the details of the included studies and the primary and secondary outcomes. **Table 2** summarized the definitions used by the authors of the studies.

Risk of bias within studies

The methodological quality of the studies were given in **Figure 2**. 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 for no disagreements between the authors existed.

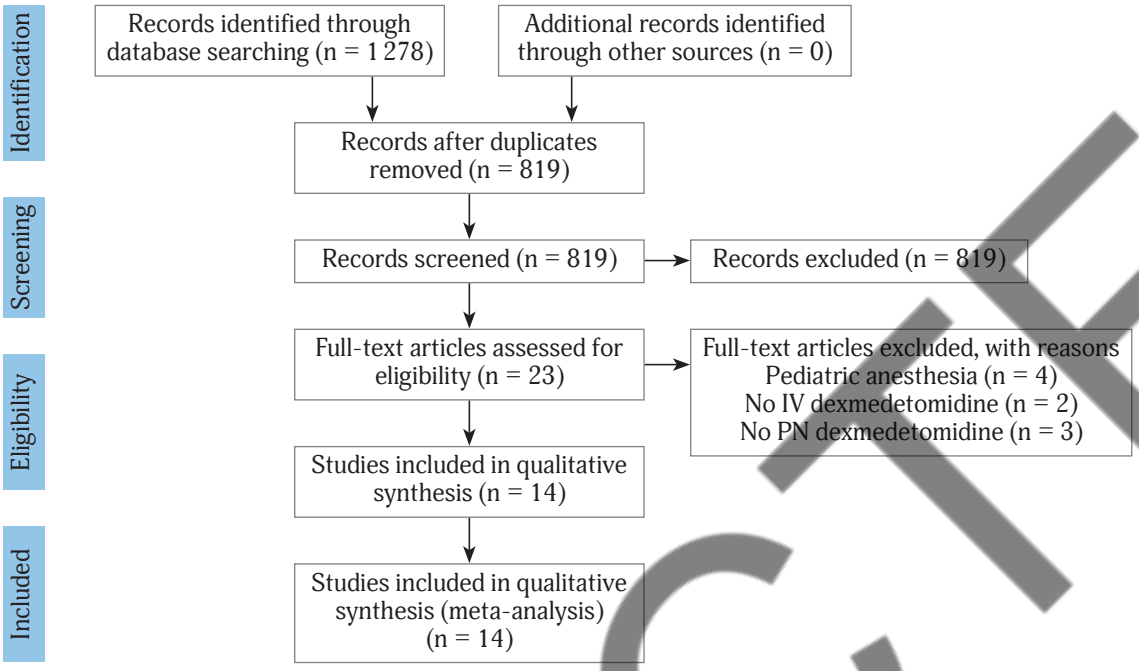

Figure 1. PRISMA flow diagram showing literature search results. 14 randomized controlled trials were included in the analysis. IV: intravenous; PN: perineural; n: number of studies

Synthesis of results

Primary outcome: duration of analgesia

Figure 3A showed the meta-analysis for the duration of analgesia including twelve trials that had data for this outcome [15–19, 21–27]. When compared to systematic dexmedetomidine, the duration of analgesia was significantly longer in the perineural group (SMD: -1.76, 95 % CI, [-2.7,-0.83] *P=0.000*, I^2=96 %) using a random-effect model. In meta-regression analysis, dosage of dexmedetomidine (*P=0.529*), level of PNBs (*P=0.467*) and country *P=0.953*) did not correlate with the duration of analgesia.

Sensitivity analysis: three studies [18, 21, 27] may have led to heterogeneity among studies. After removing the studies, the heterogeneity of the remaining studies was reduced (I^2=84.8 %). Using a random-effect model, the results of meta-analysis (**Figure 3B**) showed that the duration of analgesia was still statistically significantly longer in the perineural group (SMD: -0.54, 95 % CI, [-1.03,-0.05] *P=0.032*, I^2=84.8 %).

Secondary outcomes

Duration of sensory block: eight studies reported this variable [15, 16, 18, 20, 21, 24, 26, 28]. In **Figure 4**, the meta-analysis was shown. When comparing perineural with intravenous dexmedetomidine, the duration of sensory block was longer in the perineural group (SMD: -3.99, 95 % CI, [-5.88,-2.0], *P=0.000,* I^2=97.6 %).

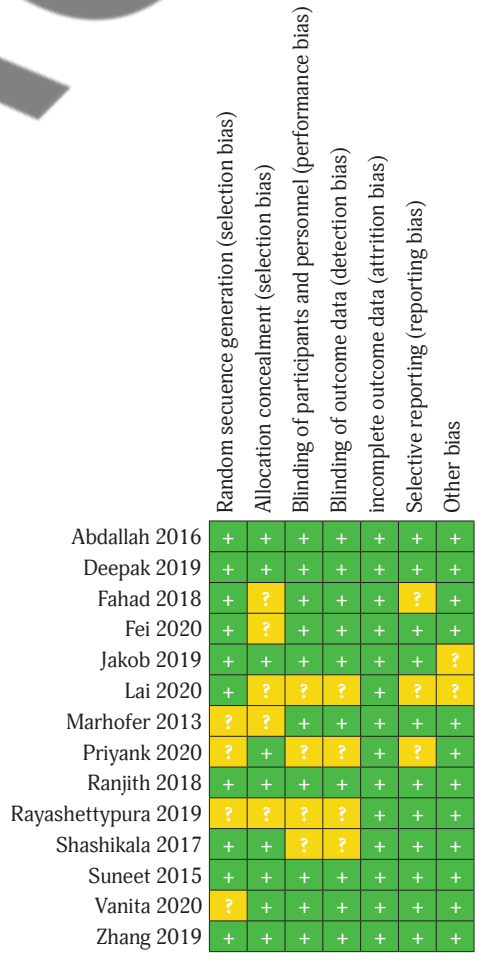

Figure 2.

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Table 1. 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 outcome	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		
Suneet et al. [16]	20	20	Elective upper limb surgery	Ultrasound-guided supraclavicular 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 h postoperatively; adverse events: respiratory depression,bradycardia, hypotension,skin rash, nausea, vomiting		Injection diclofenac sodium 75 mg intramuscular was administered 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	Premication: 1000 mg oral acetaminophen and 400 mg celecoxib, all patients received 1 to 4 mg IV midazolam and/or 25 μg IV fentanyl for anxiolysis and analgesia before block, GA: 1 to 3 μg/kg IV fentanyl, 2 to 4 mg/kg IV propofol, and 0.6 mg/kg IV rocuronium	VAS ≥ 4 : 25 to 50 μg IV fentanyl every 5min followed by 2 to 4 mg IV morphine
Shashikala et al. [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 intravenously midazolam 0.02 mg/kg before block	
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 h; total consumption of morphine in 24 h; number of used PCA boluses of morphine; VAS; adverse events: nausea, vomiting	Premication: orally diazepam 5 mg,100 μg/kg morphine intravenously before the-block,GA: 5 mg/kg sodium thiopentone and 0.5 mg/kg atracurium intravenously (IV)	PCA morphine, Intravenous paracetamol of 1 g to ensure NRS below 4 at movement

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 outcome	Other anesthesia techniques	Postoperative analgesia
	IV	PN								
Fahad et al. [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		
Jakob et al. [21]	11	11	Volunteer study	Ultrasound–guided ulnar nerve block with 4 ml ropivaca line 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	On the subsequent treatment day 1 ml of normal saline plus 4 ml of ropivacaine at either 7.5 mg/ml (HiRopi) or 5 mg/ml (NoDex)	
Deepak 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	24hours' total morphine consumption,	VAS; RSS; hemodynamic parameters: mean systolic blood pressure and heart rate	At the completion of surgery, all subjects received paracetamol 1 g IV prior to shifting into PACU.	PCA (morphine and paracetamol 1 g in the postoperative period. Rescue analgesia was 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 h, VAS, RSS,Adverse events: bradycardia, hypotension, respiratoryrate 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
Rayashettypura 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 Scale; 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
Vanita 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 perioperative	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 patients 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

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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 outcome	Other anesthesia techniques	Postoperative analgesia
	IV	PN								
Priyank et al. [26]	20	20	Upper extremity orthopaedic surgery	Nerve stimulator-guided supraclavicular block with 40 ml solution containing 5 mg/kg lignocaine (2%) with adrenaline (1:200,000) and 2 mg/kg of bupivacaine (0.5%)	1 mcg/kg	1 mcg/kg	The duration of analgesia	Onset and duration of sensory and motor block,haemodynamic parameters		Rescue analgesia was provided in the form of diclofenac 75 mg intravenously when VAS was > 4
Fei 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	Untensioned repair of inguinal hernia	Ultrasound-guided iliohypogastric 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		

Table 2.

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	
Suneet 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 24 h period postoperatively was noted

Author	Duration of analgesia	Duration of sensory block	Duration of motor block	Onset time of sensory block	Onset time of motor block	Analgesic consumption
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 et al. [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	
Ranjith et al. [19]	Time taken for the first analgesic requirement in the post-operative period					Total consumption of morphine in 24 h was calculated
Jakob 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		
Zhang et al. [23]	Time elapsed from the end of the block till the first report of postoperative pain at the surgical site					Total consumption of fentanyl in PCIA
Rayashettypura 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
Vanita et al. [25]	Time to the first tramadol PCA					The cumulative postoperative tramadol consumption at 4, 6, 12, 18, 24, 30, 36, and 42 hours following surgery

Author	Duration of analgesia	Duration of sensory block	Duration of motor block	Onset time of sensory block	Onset time of motor block	Analgesic consumption
Priyank 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	
Fei 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		

Duration of motor block: this outcome was reported in seven studies [15–18, 20, 21, 24, 26]. When compared to systematic dexmedetomidine, the duration of motor block was longer in the perineural group (SMD: -1.6, 95 % CI, [-2.78, -0.41] *P=0.008*, I^2=95.5 %) in **Figure 5**.

Onset time of sensory block: this outcome was reported in seven studies [15, 16, 18, 20, 24, 26, 28] and a meta-analysis was shown in **Figure 6**. Compared to intravenous dexmedetomidine, the onset time of sensory block was shorter in perineural group (SMD: 1.55, 95 % CI, [0.16, 2.94] *P=0.028*, I^2=96.7 %). **Onset time of motor block (min)**: This outcome was reported in seven studies [15, 16, 18, 20, 21, 24, 26] and shown in **Figure 7**. Compared to intravenous dexmedetomidine, the onset time of motor block was shorter in perineural group (SMD: 0.84, 95 % CI, [0.17, 1.5] *P=0.013*, I^2=88.3 %).

Analgesic consumption: analgesic consumption in 24 hours was reported in six studies [16, 17, 19, 22, 23, 25] in **Figure 8**, the cumulative analgesic consumption in 24 hours in perineural group was lower than that in perineural group (SMD: 0.37, 95 % CI, [0.05, 0.69] *P=0.023*, I^2=55.6 %).

Patients of RSS > 3: patients of RSS > 3 were reported in three studies [16, 19, 24]. The results (**Figure 9**) reported that the incidence of patients of RSS > 3 was higher in intravenous group (RR: 3.8, 95 % CI, [1.45, 9.97] *P=0.000*, I^2=26.9 %), compared to the perineural group.

Hypotension and bradycardia: four studies described the incidence of hypotension [16–18, 24]. The results (**Figure10**) showed the incidence of hypotension was higher in intravenous group (RR: 1.74, 95 % CI, [1.15, 2.65] P=0.009, I^2=32.7 %). Five studies described the incidence of bradycardia [16–18, 24, 26]. The results (**Figure 11**) showed that incidence of bradycardia was higher in intravenous group (RR: 3.71, 95 % CI, [1.27, 10.86] P=*0.017*, I^2=0 %), when compared to the perineural group.

Postoperative neurologic symptoms: three studies recorded postoperative neurologic symptoms [17, 23, 28], such as dizziness and weakness. The results (**Figure 12**) showed that incidence of postoperative neurologic symptoms between intravenous and perineural group was not statistically significant different (RR: 2.04, 95 % CI, [0.85, 4.87] *P=0.11*, I^2=0 %).

The side effects: Three studies recorded the side effects [17, 24, 28]. The side effects included nausea, vomiting, and respiratory depression. The meta-analysis result (**Figure 13**) of the incidence of the side effects between intravenous and perineural group was not statistically significant different (RR: 1.55, 95 % CI, [0.19, 12.86] *P=0.685*, I^2=69 %).

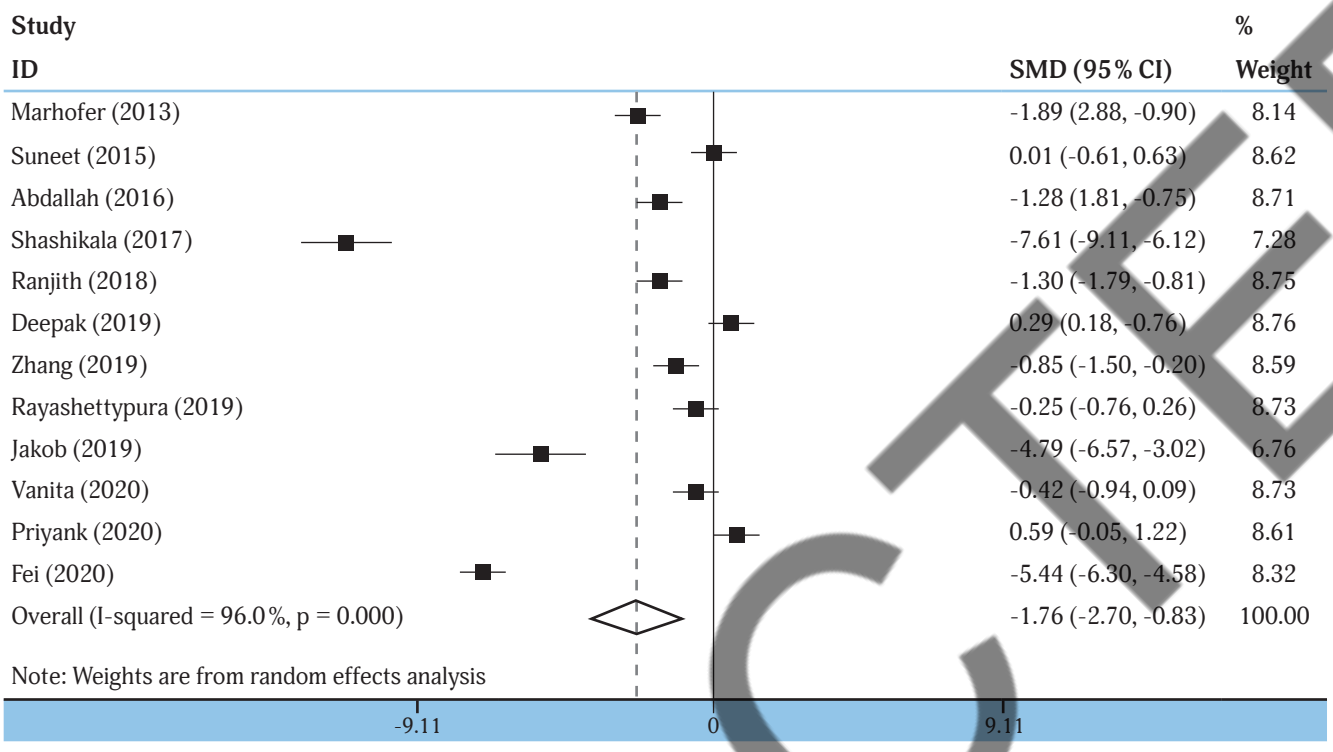

Figure 3A. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of analgesia. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

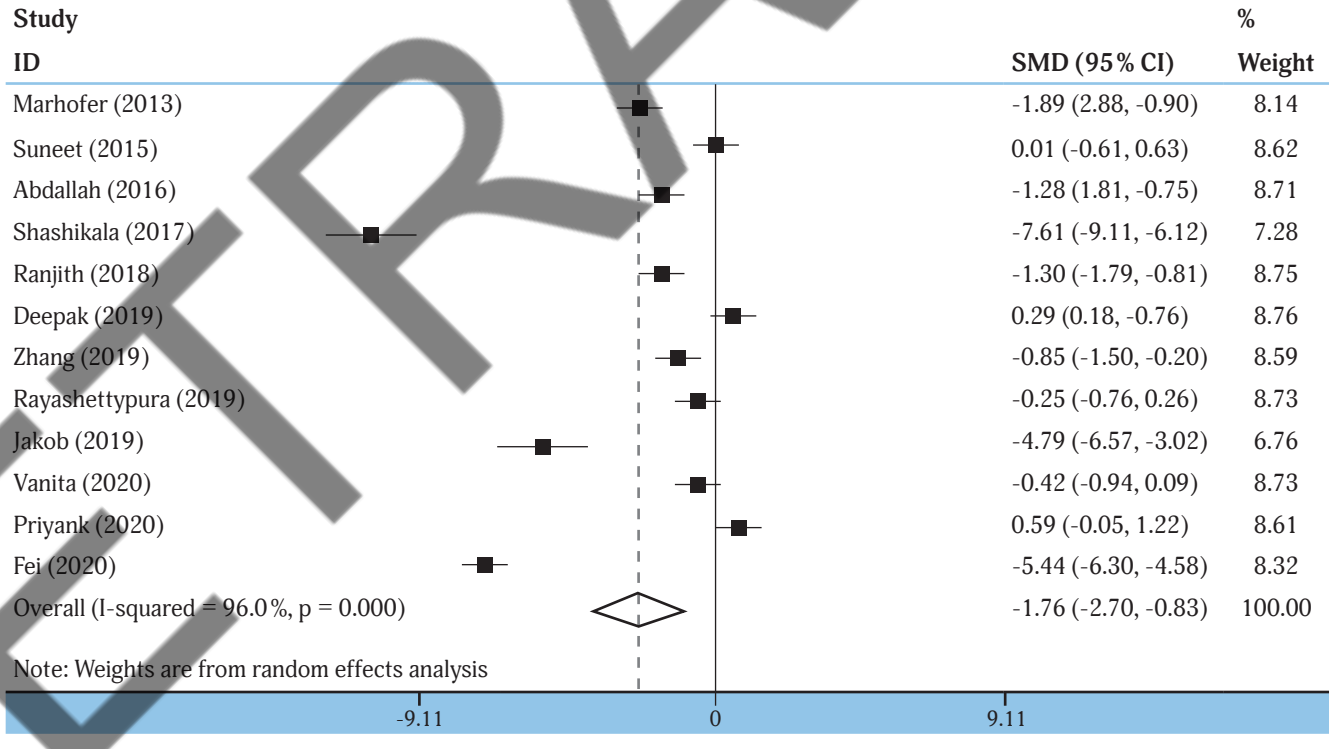

Figure 3B. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of analgesia. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

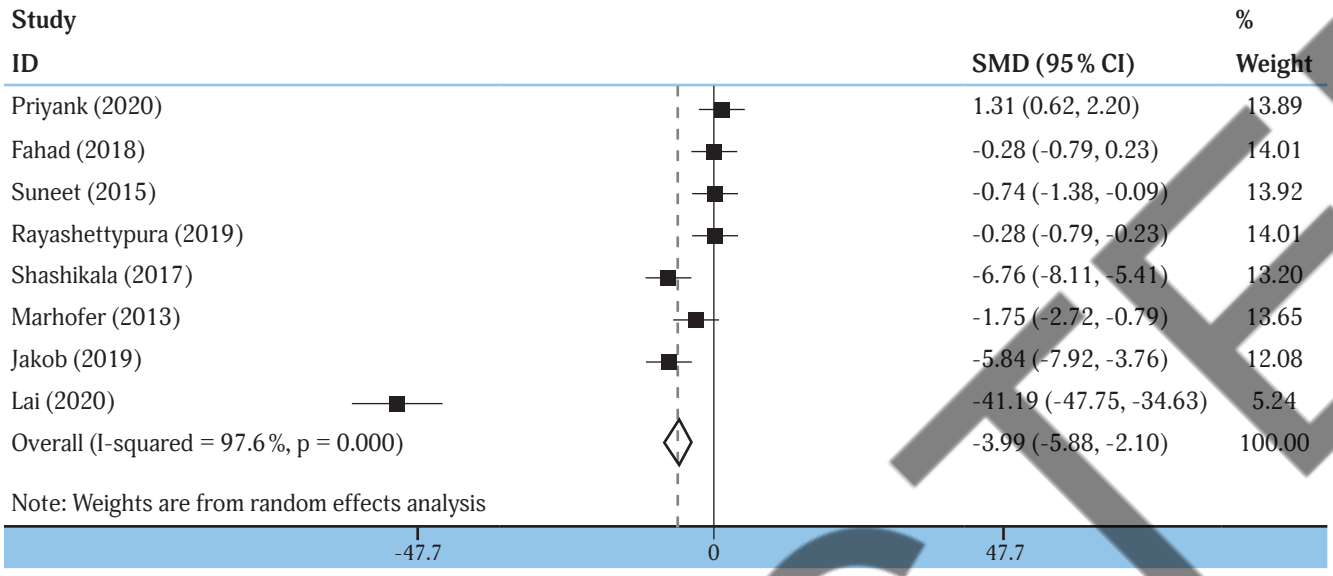

Figure 4. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of sensory block. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

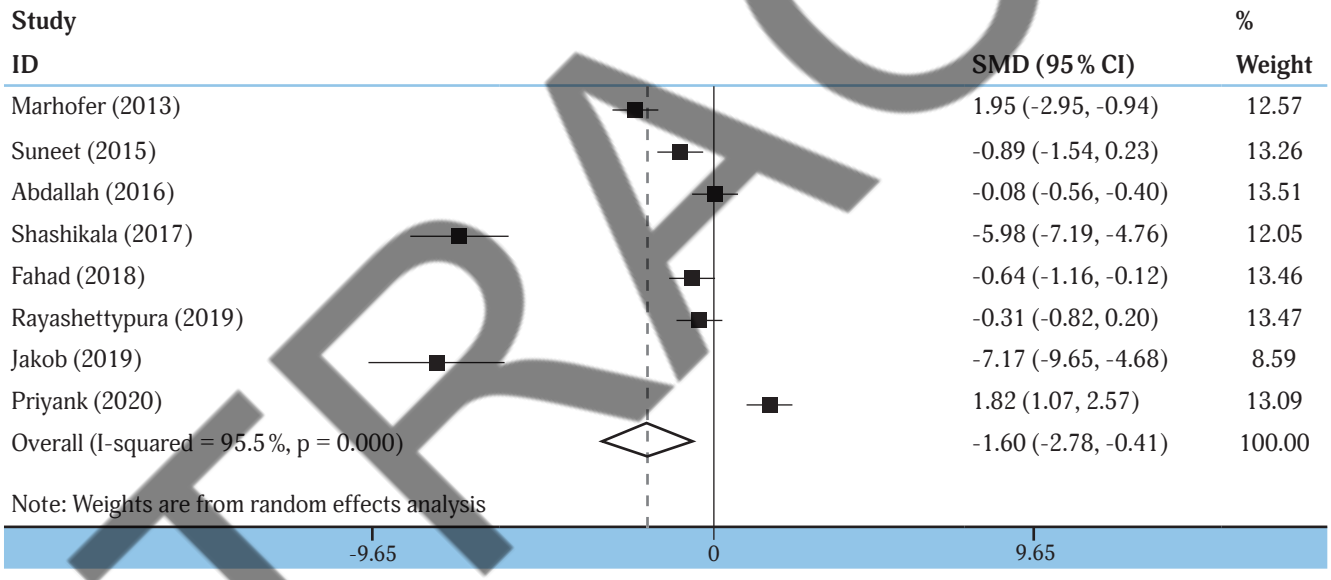

Figure 5. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the duration of motor block. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

Disscussion

Intravenous dexmedetomidine is applied for sedation and analgesia as an adjuvant drug in nonintubated patients for surgical and other procedures and intubated and mechanically ventilated patients in the intensive care unit [29]. The described mechanism of action for intravenous dexmedetomidine is that it can act on the α_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, the activation of inwardly rectifying G1-protein-gated potassium channels and regulation of entry of calcium through N-type voltagegated calcium channels, which is independent of cAMP and protein phosphorylation and is

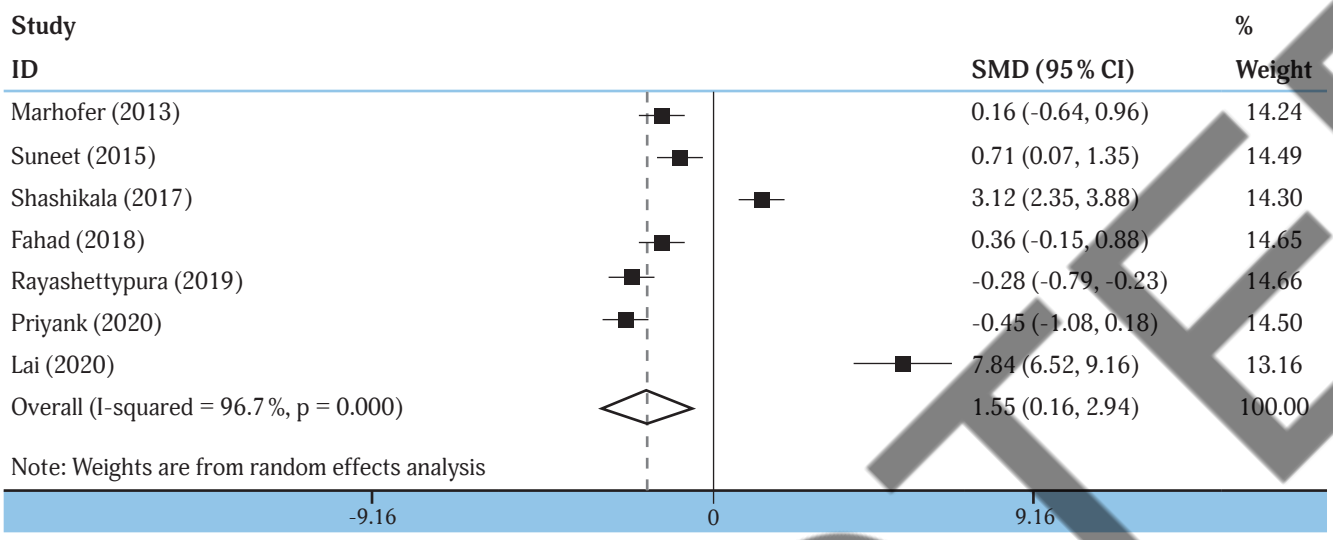

Figure 6. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the onset time of sensory block. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

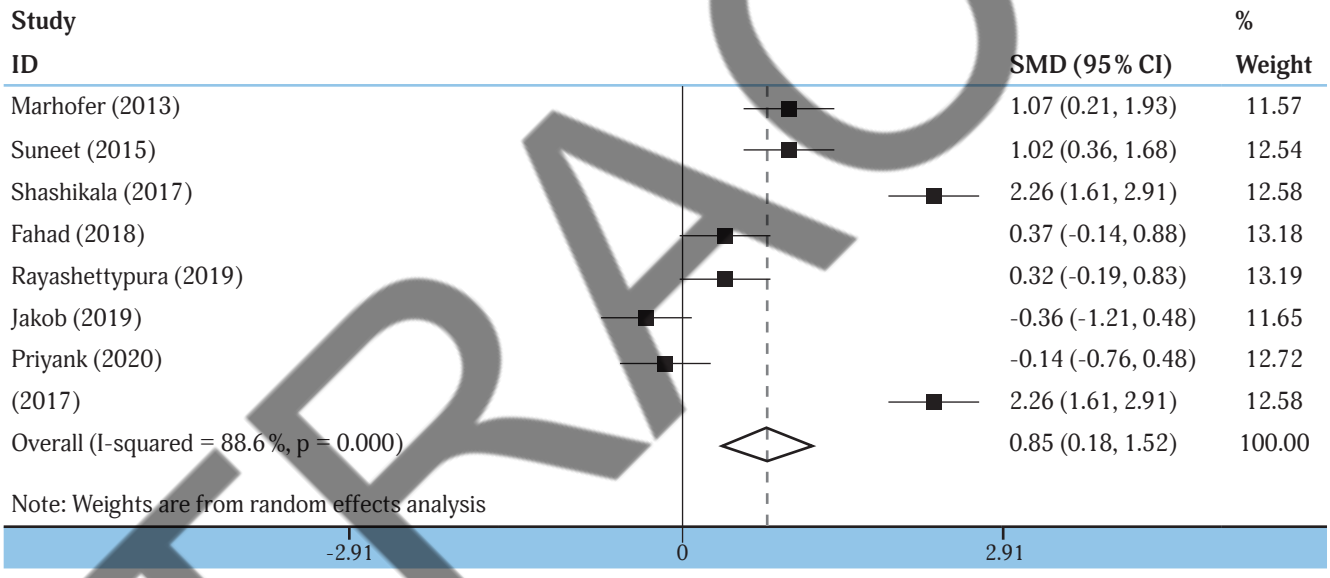

Figure 7. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the onset time of motor block. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

mediated by G0 proteins, leading to membrane hyperpolarization and decreasing the firing rate of excitable cells in the central nervous system (CNS) is considered to be a crucial mechanism of the inhibitory neuronal action of dexmedetomidine [20]; third, dexmedetomidine strengthenes activity-dependent hyperpolarization by inhibiting the I_h current. The I_h current exerts cell excitability, especially the firing frequency, in both the central and peripheral nervous systems [32, 33].

Based on 12 randomized controlled trials inclusive of 661 patients, our meta-analysis showed that perineural dexmedetomidine as local anesthetic adjuvant significantly prolonged the duration of analgesia and reduced the analgesic consumption, compared to intravenous dexmedetomidine group. Moreover, the duration of sensory and motor block were longer in perineural group than that in systematic group, which may be attributed to that dexmedetomidine in 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]. However, prolonged duration of motor block may limit the ability to ambulate and be associated with a increased risk of vein thrombosis and

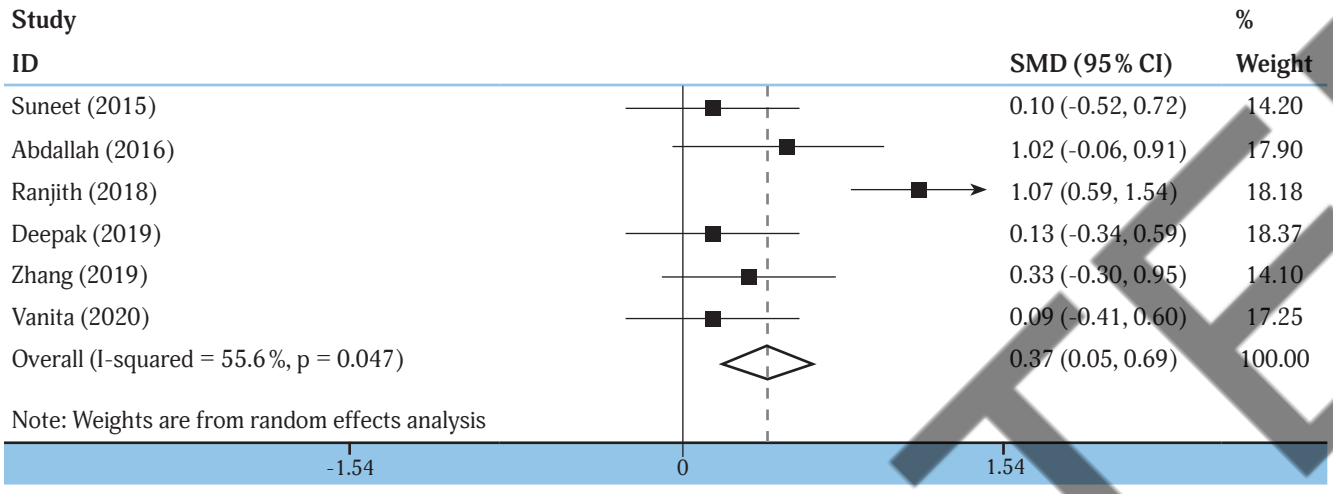

Figure 8. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the analgesic consumption in 24 hours. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval.

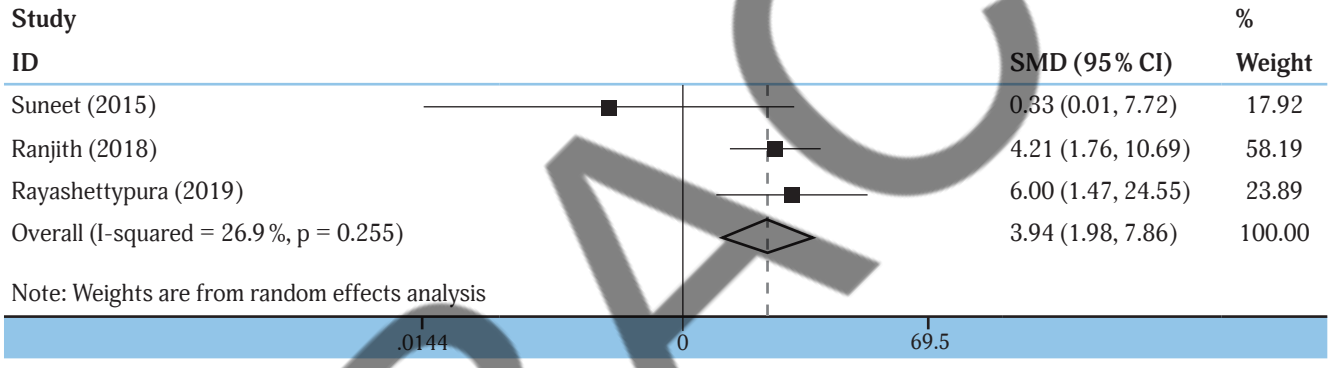

Figure 9. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the incidence of patients of Ramsay Sedation Scale > 3. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

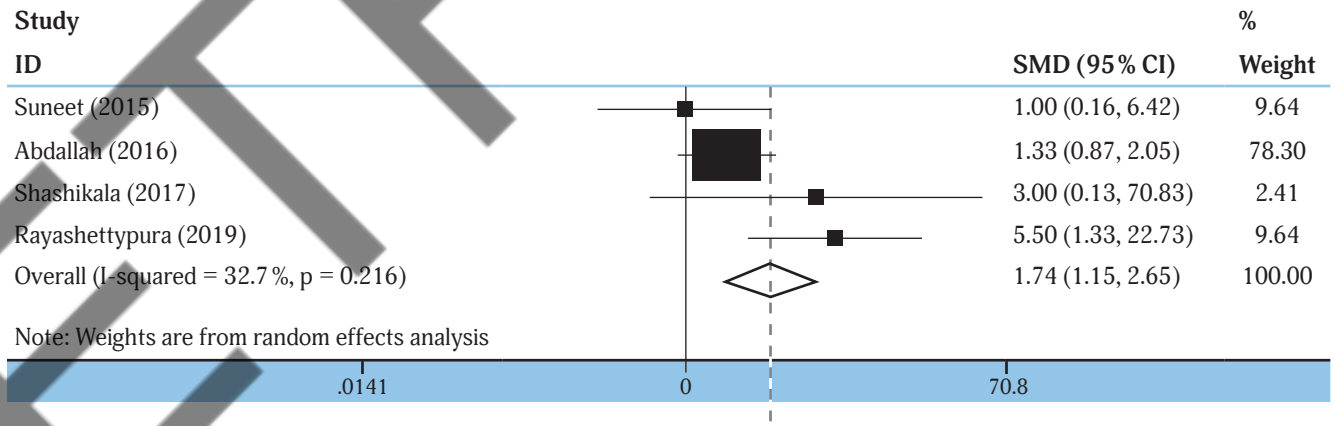

Figure 10. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the incidence of hypotension. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval.

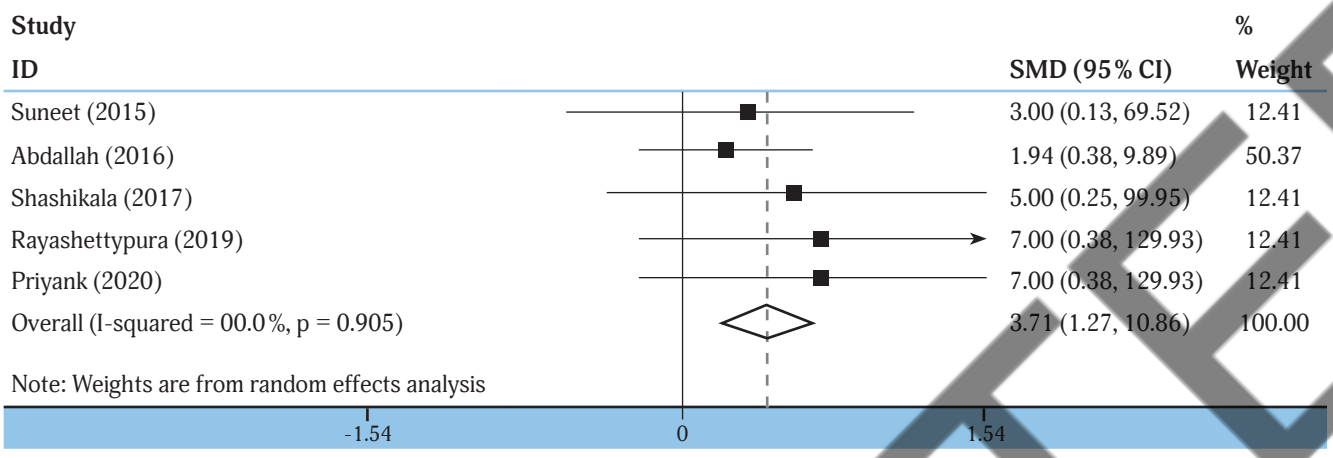

Figure 11. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the incidence of bradycardia. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

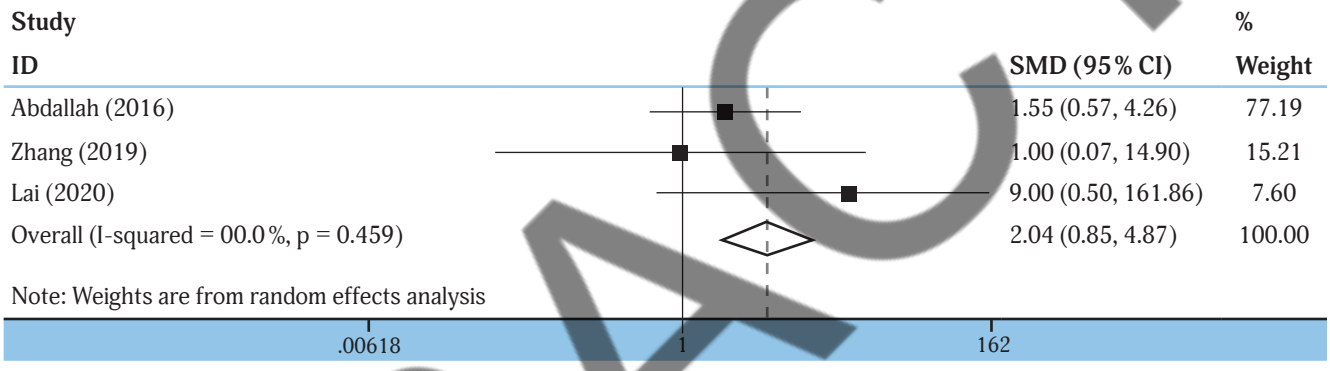

Figure 12. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the incidence of postoperative neurologic symptoms. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval.

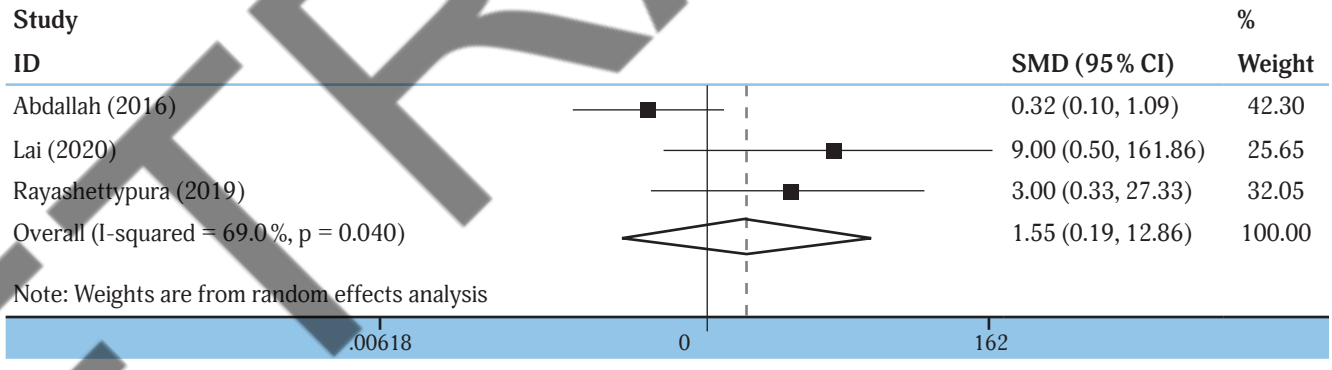

Figure 13. Forest plot depicting the effect of perineural dexmedetomidine and intravenous dexmedetomidine on the incidence of the side effects. The pooled estimates of the standard mean difference are shown. CI indicates confidence interval

delayed postoperative recovery for patients undergoing lower extremity surgery [34].

In our meta-analysis, we also found that perineural dexmedetomidine had a shorter onset time of sensory and motor block, compared to the intravenous group. This might be explained by the fact that ultrasound guidance or nerve stimulator was used in included included, which shortened the onset time of peripheral nerve blocks [15] in comparison with intravenous administration of dexmedetomidine because of the presence of α_2-ARs in brachial plexus and hence a faster local action [16].

The effects of intravenously dexmedetomidine on the cardiovascular system are shown as the lowered heart rate and hypotension, which is related to the dose and infusion speed of dexmedetomidine [35]. In our analysis, perineural dexmedetomidine had a lower incidence of hypotension and bradycardia compared to the intravenous group. Wang and his colleagues [36] aslo found the similar result, bradycardia and hypotension were 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 high level of heterogeneity in the primary and secondary outcomes and the meta-regression also did not show significant association of dosage of dexmedetomidine, level of PNB and country with the primary outcome. The possible explanations could be the following aspects. First, different local anesthetics and the dose were used among the fourteen studies; 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 H. C. et al. [37] and Stundner O. et al. [38] reported that the systemic uptake and neuraxial spread may 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 type and duration of surgeries were different. In contrast, our review has several points of strength. The literature review we conducted was exhaustive and included all relevant databases without any language restrictions. In particular, we carefully checked the data reported in journal publications and www.chictr.org.cn. for consistency. Furthermore, the primary outcome result 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 conclusions.

Conclusion

Our meta-analysis generates the evidence that perineural dexmedetomidine is a superior adminstration for prolonging the duration of analgesia. Perineural dexmedetomidine also shows the advantages in duration of sensory block and the onset time of sensory and motor block, when compared to the intravenous administration. Simultaneously, dexmedetomidine as a local anesthetic adjuvant for perineural injection may be much safer than intravenous application because of the lower incidence of patients of Ramsay Sedation Scale > 3 and lower incidence of hypotension and bradycardia.

Authors' contributions

Yan Feng: This author helped design, conduct, analyze, write and revise the study. Pan Chang: This author helped conduct, analyze, and revise the study. Xiao-Bo Chen: This author helped analyze, write and revise the study. Xiao-Lin Yang: This author helped conduct, analyze, revise the study. Yu-Jun Zhang: This author helped analyze and revise the study. Wen-Sheng Zhang: This author helped design, conduct, analyze, write and revise the study.

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Conflicts of interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary data

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('intravenous anesthesia'/de OR 'intravenous drug administration'/de OR (intraven* OR systemic* OR ((IV) NEAR/3 (administrat* OR inject*)):ab,ti) AND ('local anesthesia'/exp OR'regional anesthesia'/de OR'nerve block'/exp OR (((local* OR region* OR nerve* OR plexus OR abdomin* OR TAP OR perineural* OR axillar* OR interscalen* OR femoral* OR poplitea* OR) NEAR/3 (anesthes* OR anaesthes* OR block*))):ab,ti) AND ('alpha2-agonists'/exp OR'Dexmedetomidine'OR 'Medetomidine'):ab,ti)

MEDLINE PubMed (Ovid)

("Anesthetics, intravenous"/OR exp "Administration, Intraven ous"/OR (intraven* OR systemic* OR ((IV) ADJ3 (administrat* OR inject*))).ab,ti.) AND ("Local Anesthesia"/OR "Anesthesia, Conduction"/OR exp "Nerve Block" OR (((local* OR region* OR nerve* OR plexus OR abdomin* OR TAP OR perineural* OR axillar* OR interscalen* OR femoral* OR poplitea*) ADJ3 (anesthes* OR anaesthes* OR block*))).ab,ti.) AND ("Dexmedetomidine" OR"Medetomidine"OR "alpha2-agonists."). ab,ti.)

Cochrane Central

((intraven* OR systemic* OR ((IV) NEAR/3 (administrat* OR inject*))):ab,ti) AND ((((local* OR region* OR nerve* OR plexus OR abdomin* OR TAP OR perineural* OR axillar* OR interscalen* OR femoral* OR poplitea*) NEAR/3 (anesthes* OR anaesthes* OR block*))):ab,ti) AND ((Dexmedetomidine OR Medetomidine OR alpha2-agonists):ab,ti)

Web of Science

(((intraven* OR systemic* OR ((IV) NEAR/2 (administrat* OR inject*))))) AND ((((local* OR region* OR nerve* OR plexus OR abdomin* OR TAP OR perineural* OR axillar* OR interscalen* OR femoral* OR poplitea*) NEAR/2 (anesthes* OR anaesthes* OR block*)))) AND ((Dexmedetomidine OR Medetomidine OR alpha2-agonists))

Wanfang database

(intravenous OR systemic OR IV administration OR injection) AND (local OR regional OR nerve OR plexus OR anesthesia block) AND (dexmedetomidine OR Medetomidine OR alpha2-agonists)

Порівняння внутрішньовенного та периневрального дексмедетомідину при пролонгації аналгезії за допомогою регіональної анестезії: метааналіз та систематичний огляд

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 # Ці автори зробили однаковий внесок у цю роботу: Співавтори.

Анотація

Передумови та мета: *Незрозуміло, чи має периневральне введення дексмедетомідину переваги порівняно з внутрішньовенним під місцевою анестезією. Для порівняння ефективності периневрального проти внутрішньовенного дексмедетомідину як ад'юванта місцевого анестетика ми провели метааналіз та систематичний огляд.*

Матеріали та методи: *Два дослідники шукали дані MEDLINE, OVID, PubMed, Embase, Cochrane Central, Web of Science та Wanfang для рандомізованих контрольованих досліджень, які порівнювали ефект внутрішньовенного та периневрального введення дексмедетомідину як місцевого анестетика без будь-яких мовних обмежень.*

Результати: *Ми визначили 14 рандомізованих контрольованих досліджень (801 пацієнт). Результати показали, що тривалість аналгезії (SMD: -1,76, 95% CI, [-2,7, -0,83] P = 0,000, I^2 = 96%), тривалість сенсорного блоку (SMD: -3,99, 95% ДІ, [-5,88, -2,0], P = 0,000, I^2 = 97,6%), тривалість мотоблоку (SMD: -1,6, 95% CI, [-2,78, -0,41] P = 0,008, I^2 = 95,5%) значно довше в периневральній групі порівняно з систематичним дексмедетомідином. Час початку сенсорного блоку (SMD: 1,55, 95% CI, [0,16, 2,94] P = 0,028, I^2 = 96,7%) і час початку моторного блоку (SMD: 0,84, 95% CI, [0,17, 1,5] P = 0,013, I^2 = 88,3%) був коротшим у периневральній групі порівняно з внутрішньовенним дексмедетомідином. Тимчасом споживання анальгетиків протягом 24 годин (SMD: 0,37, 95% CI, [0,05, 0,69] P = 0,023, I^2 = 55,6%) та частота пацієнтів з показником седації за Рамсі >3 (RR: 3,8, 95% CI, [1,45, 9,97] P = 0,000, I^2 = 26,9%), гіпотензія (RR: 1,74, 95% CI, [1,15, 2,65] P = 0,009, I^2 = 32,7%) та брадикардія (RR: 3,71, 95% CI, [1,27, 10,86] P = 0,017, I^2 = 0%) були нижчими для периневрального дексмедетомідину порівняно з внутрішньовенною групою.*

Висновки: *Наш метааналіз надає докази того, що периневральний дексмедетомідин є найкращим засобом для продовження тривалості аналгезії. Периневральний дексмедетомідин також показує переваги щодо тривалості сенсорної блокади та часу настання сенсорної і моторної блокади порівняно з внутрішньовенним уведенням. Водночас дексмедетомідин як ад'ювант місцевого анестетика для периневральної ін'єкції може бути набагато безпечнішим, ніж внутрішньовенне введення, через меншу частоту пацієнтів з показником седації за Рамсі > 3 та меншу частоту гіпотензії та брадикардії.*

Ключові слова: *місцева анестезія; дексмедетомідин; ад'ювантний препарат; периневрально; внутрішньовенно; аналгезія; нервовий блок; несприятлива подія.*

Сравнение внутривенного и периневрального дексмедетомидина при пролонгации анальгезии при помощи регионарной анестезии: метаанализ и систематический обзор

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 # Эти авторы внесли равный вклад в эту работу: Соавторы.

Резюме

Предпосылки и цель: *Неясно, дает ли перинервальное введение преимущества по сравнению с внутривенным введением дексмедетомидина при местной анестезии. Чтобы сравнить эффективность перинервального и внутривенного дексмедетомидина в качестве адъюванта местного анестетика, мы провели метаанализ и систематический обзор.*

Материалы и методы: *Два исследователя провели поиск в данных MEDLINE, OVID, PubMed, Embase, Cochrane Central, Web of Science и Wanfang в поисках рандомизированных контролируемых испытаний, сравнивающих действие дексмедетомидина внутривенного и перинервального в качестве адъюванта местного анестетика без каких-либо языковых ограничений.*

Результаты: *Мы нашли 14 рандомизированных контролируемых испытаний (801 пациент). Результаты показали, что продолжительность анальгезии (SMD: -1,76, 95% CI, [-2,7, -0,83] P = 0,000, I^2 = 96%), продолжительность сенсорного блока (SMD: -3,99, 95% CI, [-5,88, -2,0], P = 0,000, I^2 = 97,6%), продолжительность моторного блока (SMD: -1,6, 95% CI, [-2,78, -0,41] P = 0,008, I^2 = 95,5%) была значительно выше в группе перинервального введения по сравнению с систематическим дексмедетомидином. Время начала сенсорного блока (SMD: 1,55, 95% CI, [0,16, 2,94] P = 0,028, I^2 = 96,7%) и время начала моторного блока (SMD: 0,84, 95% CI, [0,17, 1,5] P = 0,013, I^2 = 88,3%) были короче в группе перинервального введения по сравнению с дексмедетомидином внутривенно. Между тем, потребление анальгетиков в течение 24 часов (SMD: 0,37, 95% CI, [0,05, 0,69] P = 0,023, I^2 = 55,6%) и частота пациентов с показателем седации по Рамси > 3 (RR: 3,8, 95%ДИ, [1,45, 9,97] P = 0,000, I^2 = 26,9%), гипотония (RR: 1,74, 95% CI, [1,15, 2,65] P = 0,009, I^2 = 32,7%) и брадикардия (RR: 3,71, 95% CI, [1,27, 10,86] P = 0,017, I^2 = 0%) были ниже в группе перинервального введения дексмедетомидина по сравнению с группой внутривенного введения.*

Выводы: *Наш метаанализ дает доказательства того, что перинервальное введение дексмедетомидина является лучшим средством для увеличения продолжительности анальгезии. Перинервальный дексмедетомидин также показывает преимущества в продолжительности сенсорного блока и времени начала сенсорного и моторного блока по сравнению с внутривенным введением. В то же время дексмедетомидин в качестве адъюванта местного анестетика для перинервальной инъекции может быть намного безопаснее, чем внутривенное введение, из-за более низкой частоты у пациентов с показателем седативного эффекта по Рамси > 3 и более низкой частоты гипотонии и брадикардии.*

Ключевые слова: *местная анестезия; дексмедетомидин; адъювант лекарственный; перинервально; внутривенно; анальгезия; блокада нерва; неблагоприятное событие.*