Systematic Review

Perineural Versus Intravenous Dexamethasone for Brachial Plexus Block: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Perineural (PN) dexamethasone (DEX) administration can prolong the analgesic time of a brachial plexus block. However, its efficacy and safety are controversial due to its off-label use and different routes of administration.

Objectives: This meta-analysis aimed to assess the safety and efficacy of PN versus intravenous (IV) dexamethasone.

Study Design: Systematic review and meta-analysis of randomized controlled trials (RCTs).

Setting: Relevant studies were found through a comprehensive literature search of PubMed, Web of Science, Ovid, EMBASE, and the Cochrane Library (from the inception until January 2020).

Methods: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this meta-analysis was conducted to identify RCTs comparing PN and IV dexamethasone in brachial plexus block. A randomized effect model was used in the meta-analysis and the subgroup analysis was performed with adrenaline stratification. The quality of evidence and the strength of recommendations were graded by GradePro version 3.6.1.

Results: Twelve RCTs with a total of 1,345 subjects were included. We found that PN dexamethasone could prolong the duration of analgesia (mean difference [MD]: 131.82 minutes, 95% confidence interval [CI] [38.96, 224.68], $I^2 = 82\%$, $P = 0.005$), motor block (MD: 218.85 minutes, 95% CI [113.65,324.05], $I^2 = 72\%$, $P < 0.0001$) and sensory block (MD: 209.57 minutes, 95% CI [72.64, 346.50], $I^2 = 87\%$, $P = 0.003$) in the main analysis with significant difference. In the absence of epinephrine, there were no significant differences between PN dexamethasone and IV dexamethasone. Except for adverse-effects, no significant differences were observed in secondary outcomes. PN dexamethasone had slightly higher adverse-effects; however, these could be altered if a sensitivity analysis was conducted.

Limitations: There was high heterogeneity among included studies.

Conclusions: PN dexamethasone can prolong the duration of analgesia, sensory block, and motor block, when compared with IV dexamethasone. In a subgroup analysis without epinephrine, the 2 routes of administration were equivalent to topical anesthesia. There were no differences in secondary outcomes, except for adverse effects, which could be altered if a sensitivity analysis was conducted. Therefore, despite the advantages of PN dexamethasone, caution is needed due to its off-label character. While the results of this study are promising, additional large and well-designed RCTs are needed to validate these initial findings and their implications.

Key words: Analgesia, brachial plexus block, dexamethasone, intravenous, meta-analysis, perineural, randomized controlled trial

Pain Physician 2021: 24:E693-E707

Postoperative pain is very common in upper limb surgeries below the shoulder joint. It effects both patients and surgeons (1), and is not conducive to rehabilitation. The brachial plexus block has gained popularity for its reliable analgesia and has been widely used for postoperative pain control (2,3); however, its use is limited by its brief duration of action (3). In recent years, fast-track surgery has been increasingly advocated to promote functional recuperation, as well as to reduce the required period of hospitalization, postoperative fatigue, and complications (i.e., deep venous thrombosis, muscle atrophy, stiffness, etc.) (4). Optimal postoperative pain control is a prerequisite for fast-track surgery; furthermore, the duration of analgesia is also critical, as postoperative pain prevents patients from resuming their normal activities. Thus, prolonging the duration of the block is essential for successful fast-track surgery.

A continuous perineural (PN) catheter with an infusion pump can significantly prolong the duration of a brachial plexus block; however, catheter-related infection, migration, anesthetic extravasation, catheter obstruction, and pump dysfunction may complicate this method (5). The use of catheter for infusion is more invasive than a single shot and may be accompanied by adverse effects, such as respiratory distress, dyspnea, and nerve injury (6). Therefore, it is desirable to identify a method for prolonging the duration of analgesia provided by a brachial block via a single-shot injection. While some adjuvant drugs(e.g., epinephrine, clonidine, opioids, adenosine, and tramadol) have been admixed with brachial plexus anesthetic (3), these combinations have failed to achieve the desired effect.

Recently, dexamethasone (DEX), a steroidal anti-inflammatory drug, has been suggested as an adjunct to prolong the duration of regional anesthetic blocks (7,8). DEX inhibits cyclooxygenase-2 and prostaglandin production, suppressing the inflammatory nerve responses (9,10). It can be administered via either a PN (11) or an IV route (12). However, there are still controversial views on the optimal method for DEX administration. In a multicenter randomized controlled trial (RCT), PN DEX prolonged postoperative analgesia, sensory block, and motor block compared to IV DEX (13); however, other studies have reported that PN and IV DEX provide equivalent durations of analgesia (14,15). Therefore, a meta-analysis on RCTs was performed to compare the efficacy and safety of PN versus IV DEX administration for the brachial plexus block. We hypothesized that the PN administration of DEX would have longer action du-ration and lower incidence of adverse effects compared to IV administration .

Methods

This systematic review and meta-analysis was conducted based o PRISMA guidelines and the recommendation of the Cochrane Collaboration Group (16,17).

Eligibility Criteria

Types of Studies

Only RCTs comparing PN DEX with IV DEX were included in the meta-analysis. Two authors (authors 3 and 4) independently reviewed and screened the abstracts. After screening the relevant full-text articles, further analysis was conducted on the studies meeting the inclusion criteria.

Patients

Adults (age > 18 years) who received a brachial plexus block prior to orthopedic surgeries were involved in this meta-analysis.

Types of Intervention

In this meta-analysis, the intervention was PN DEX, while the control was IV DEX.

Outcome Measurement

Primary outcomes: Duration of analgesia, duration of motor block, duration of sensory block.

Secondary outcomes: Performance time, onset time, pain score at 24 hours, postoperative nausea and vomiting (PONV) at 24 hours, and adverse-effects (eg, paresthesia, paralysis, dysesthesia, muscle weakness, pain in any area, Horner's syndrome, or hoarseness).

Exclusion Criteria

Studies that compared PN DEX versus PN saline or IV saline, or studies using other peripheral nerve blocks were excluded from this meta-analysis.

Literature Search

A comprehensive literature search was carried out in the following databases: PubMed, Web of Science, Ovid, EMBASE and the Cochrane library. The searches included articles indexed from the inception of each database to January 2020. Languages and regions were not restricted in the retrieval. We also manually retrieved the reference lists of the relevant articles, so as not to miss studies which met our inclusion criteria.

Search Strategy

We formulated a search strategy according to the recommendation of the database. The search strategies are presented in the Appendix. Two authors (Qiulin Huang and Jiaheng Wu) independently screened the searched results and excluded duplicate and irrelevant abstracts and studies. Discrepancies were settled by consultation with another author (Jinmin Zhao).

Data Extraction

The data extracted from the eligible studies by Qiulin Huang and Jiaheng Wu independently, and an Excel database was completed. Relevant variables in this meta-analysis included the following: first author, publication year, age, sample size, anesthesia approach, type of anesthetic agent employed, ultrasound guidance (US) or nerve stimulation (NS), DEX dose, and primary outcomes.

Methodological Quality Assessment

The methodological quality of the studies was appraised by Tao Bei and Junting Liu independently and any conflicts were resolved by the corresponding author. The Cochrane Collaboration's risks of bias tool was used to assess the quality of the included studies. Six items including random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases were included in the tool.

Assessment of Quality of Outcomes

The quality of each result was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system (18).

Statistical Analysis

We used Review Manager 5.3 to conduct this meta-analysis. For dichotomous outcomes, Relative Risk (RR) was calculated effect size. For continuous outcomes, mean difference (MD) was calculated when the same measurement was used; otherwise, a standardized mean difference (SMD) was calculated. Both calculations involved the determination of 95% confidence interval (CIs). If the 95% CI for the MD or SMD contained 0, or the 95% CI for RR contained one, 0 difference was indicated. The heterogeneity index (I^2) of the included studies was determined with a chi-square test, with the level of statistical significance set at $\alpha = 0.10$. If I^2 was < 50%, the fixed-effects model was used to pool effect size; if I^2 was > 50%, the random-effects model was used to pool effect size. The mean and standard deviation (SD) were estimated, according to the method recommended by Hozo et al (19), in instances where studies only reported the following values: median and range; mean and 95% CI; or median and interquartile range (IQR). For a given median and IQR , the mean and SD were estimated according to the method recommend by Wan, et al. (20). If the mean and 95% CI were reported, the SD was calculated utilizing the following criteria: if sample size n ≥ 100, SD = √n × [upper – lower] / 3.92; if n < 60, then SD = (√n × [upper – lower] / 2)*t; and if 60 ≤ n < 100, then either of the formulas could be utilized. If data values were only presented within graphs, we extracted the data by using the software GetData Graph Digitizer version 2.26. A funnel plot was used to assess the publication bias. Subgroup analysis was performed based on the usage of epinephrine as an adjuvant.

Sensitivity Analysis

The stability of the meta-analysis results was detected by sensitivity analysis which was carried out by successively eliminating a single study. Robustness was verified by the fact there was no substantial change in the results.
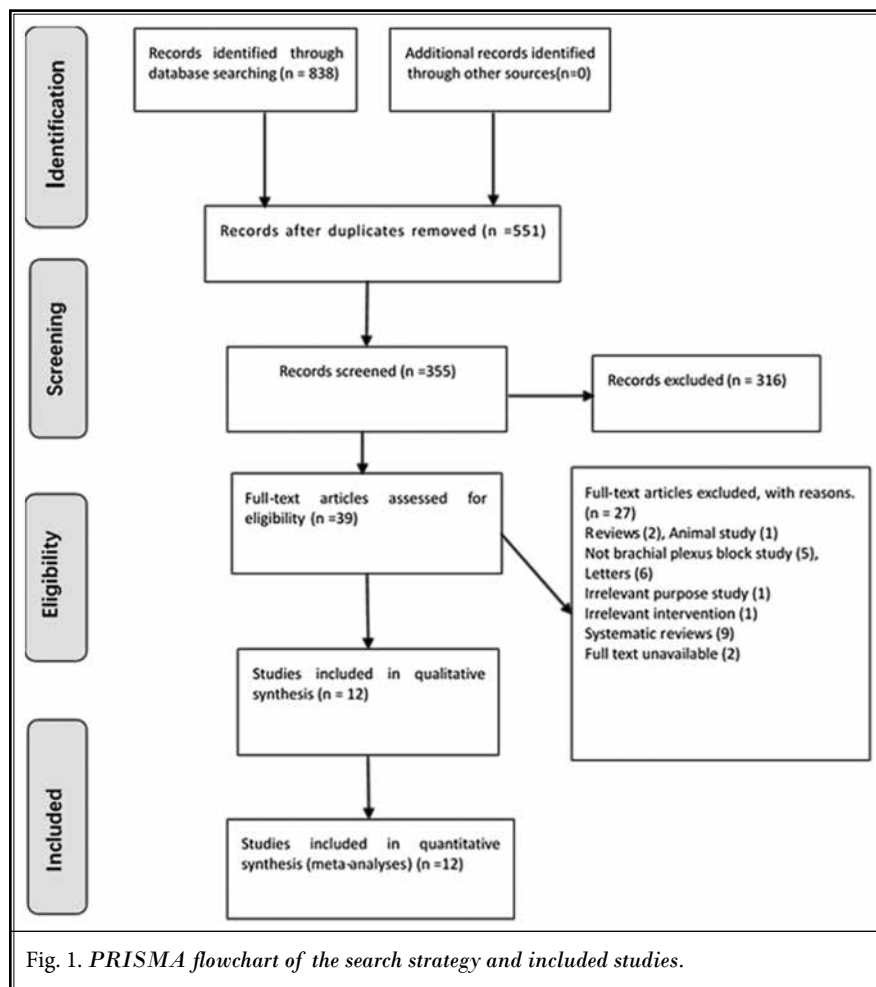
RESULTS

Literature Search Results

A total of 838 articles were initially identified from the aforementioned databases, and 12 articles were finally included in the meta-analysis based on the inclusion criteria (13,15,21-30). The flow diagram of the study selection procedure is shown in Fig.1.

Characters of Included Studies

All the included studies were reviewed and were found to be published in English. The interscalene brachial plexus block (ISB) was performed in 8 studies (15,23,25-30). Supraclavicular block (SB) was used in 2 studies (21,24). Aliste et al (22) used axillary block (AXB), and Leurcharusmee et al (13) used infraclavicular brachial plexus blocks (ICB) for the brachial plexus block. The US technique was used in 9 trials (13,22,23,25-30). Nerve stimulator (NS) was used in 2 trials (15,24). The combination of NS and US was used in one trial (21). Holland et al (25) compared PN and IV DEX in 4 groups according DEX dose (4 mg and 8 mg); therefore, the results of the study were divided accordingly. One study published an erratum (21), and we used the corrected results in the final meta-analysis. The characteristics of the included studies are shown in Table 1. The risk of bias of the included studies is presented in Fig. 2.

Fig. 1. *PRISMA flowchart of the search strategy and included studies.*

Primary Outcomes

Duration of Analgesia

A total of 11 studies reported results pertaining to analgesia duration (13,15,21-29). Chun et al (23) used the median analgesic time to assess analgesic duration, which was not in accordance with other studies; therefore, their study was withdrawn in the final analysis. Finally, 10 studies and 11 comparisons were involved in the final meta-analysis. PN DEX was significantly more effective than IV DEX in prolonging analgesia in the main analysis (MD: 131.82 minutes, 95% CI [38.96, 224.68], I^2 = 82%, *P* = 0.005) as revealed by a random-effects model. In subgroup analysis with the usage of epinephrine, PN DEX prolonged the duration of analgesia by 275.95 minutes (95% CI [200.95, 350.96], I^2 = 49%, *P* < 0.00001) compared with IV DEX. Without epinephrine usage, no significant difference was observed in analgesic duration among the groups (MD: 71.92 minutes, 95% CI [-19.84, 163.67], I^2 = 62%, *P* = 0.12) (Fig. 3).

Duration of Sensory Block

No significant difference was observed in the duration of sensory block as revealed by random-effects model when PN DEX was compared with IV DEX (MD: 209.57 minutes, 95% CI [72.64, 346.50], I^2 = 87%, *P* = 0.003). In subgroup analysis with the usage of epinephrine, PN DEX prolonged the duration of analgesia by 250.46 minutes (95% CI [161.71, 339.21], I^2 = 72%, *P* < 0.00001) when compared with IV DEX. However, there was no significant difference between PN DEX and IV DEX when epinephrine was not used (MD: 278.67 minutes, 95% CI [-425.32, 982.66], I^2 = 87%, *P* = 0.44) (Fig. 4).

Duration of Motor Block

In the main analysis, PN DEX significantly prolonged the duration of motor block by 218.85 minutes, when compared to IV DEX (95% CI [113.65, 324.05], I^2 = 72%, *P* < 0.001) as revealed by random-effects model. In a subgroup analysis stratified by the usage of epinephrine, PN DEX prolonged the duration of the motor block by 271.52 minutes (95% CI [184.99, 358.02], I^2 = 70%, *P* < 0.00001) when compared with IV DEX. However, there was no significant difference between PN DEX and IV DEX without epinephrine (MD: 12.88 minutes, 95% CI [-337.43, 324.05], I^2 = 69%, *P* = 0.94) (Fig. 5).

Secondary Outcomes

Performance Time

Three trials reported performance time. The fixed-effects model indicated the lack of a significant difference between PN and IV DEX (MD 0.32 minutes, 95% CI [–0.31, 0.95], I^2 = 0%, *P* = 0.32). (Fig. 6A)

Table 1. *Characteristics of included studies*

Author	Age		Sample size		Type of Anesthesia	Anesthetics	US or NS	Dose of Dex		Primary Outcomes
	PN	IV	PN	IV				PN	IV	
Aliste et al 2017 (22)	42 ± 17	45 ± 17	75	75	AXB	1.0% lidocaine-0.25% bupivacaine +epinephrine 5 ug/mL	US	8 mg	8 mg	Duration of analgesia, Duration of motor block, Duration of sensory block
Abdallah et al 2015 (21)	51.8 ± 15.3	46.1 ± 15.9	25	25	SB	30 mL bupivacaine 0.5%	US + NS	8 mg	8 mg	Duration of analgesia, Duration of motor block
Chun et al 2016 (23)	50.8 ± 17.5	53.0 ± 14.2	50	50	ISB	60 mg ropivacaine	US	5 mg	5 mg	Duration of anesthesia
Desmet et al 2013 (15)	53.0 ± 13.9	51.6 ± 14.0	50	50	ISB	30 mL ropivacaine 0.5%	NS	10 mg	10 mg	Duration of analgesia
Godbole et al 2019 (24)	38.5 ± 11.9	37.2 ± 11.7	28	29	SB	lignocaine with adrenaline 2% 10 mL+ bupivacaine 0.5% 20 mL+5 mL normal saline	NS	0.05 mg/ kg	0.05 mg/ kg	Duration of analgesia, Duration of motor block, Duration of sensory block
Holland et al 2018 (4 mg) (25)	54 ± 12	53 ± 14	70	70	ISB	30 mL preservative-free 0.5% bupivacaine	US	4 mg	4 mg	Duration of analgesia
Holland et al 2018 (8 mg) (25)	51 ± 14	50 ± 15	70	70	ISB	30 mL preservative-free 0.5% bupivacaine	US	8 mg	8 mg	Duration of analgesia
Kahn et al 2018 (26)	50 ± 14	47 ± 15	64	64	ISB	30 mL bupivacaine 0.5%	US	2 mg	1 mg	Duration of analgesia
Kawanishi et al 2014 (27)	55.6 ± 12.8	59.2 ± 15.3	12	10	ISB	20 mL ropivacaine 0.75%	US	4 mg	4 mg	Duration of anesthesia
Leurcharusmee et al 2016 (13)	45.7 ± 15.1	42.5 ± 15.5	75	75	ICB	35 mL 1.0% lidocaine-bupivacaine 0.25% + epinephrine 5 µg/mL	US	5 mg	5 mg	Duration of analgesia, Duration of motor block, Duration of sensory block
McHardy et al 2019 (28)	51.6 (18 - 73)	52.8 (22 - 76)	92	90	ISB	3 mL ropivacaine 1% +0.9%, saline (2 mL)	US	4 mg	4 mg	Duration of sensory block, Duration of motor block
Rosenfeld et al 2016 (29)	67.5 ± 12.7	68.4 ± 7.7	44	42	ISB	28 mL ropivacaine 0.5%	US	8 mg	8 mg	Duration of analgesia
Sakae et al 2016 (30)	53.2 ± 9.8	52.1 ± 12.3	20	20	ISB	20 mL of 0.75% ropivacaine	US	4 mg	4 mg	Duration of motor block, Duration of sensory block

Onset time

Four trials reported onset time. No significant difference was observed in onset time between the PN and IV DEX groups, as revealed by the random-effects model (MD: -0.35 minutes, 95%CI [-1.92, 1.23], I^2 = 57%, *P* = 0.67) (Fig. 6B).

Fig. 2. *Risk of bias assessments for included studies. Green - low risk of bias; red - high risk of bias; yellow - unclear risk of bias.*
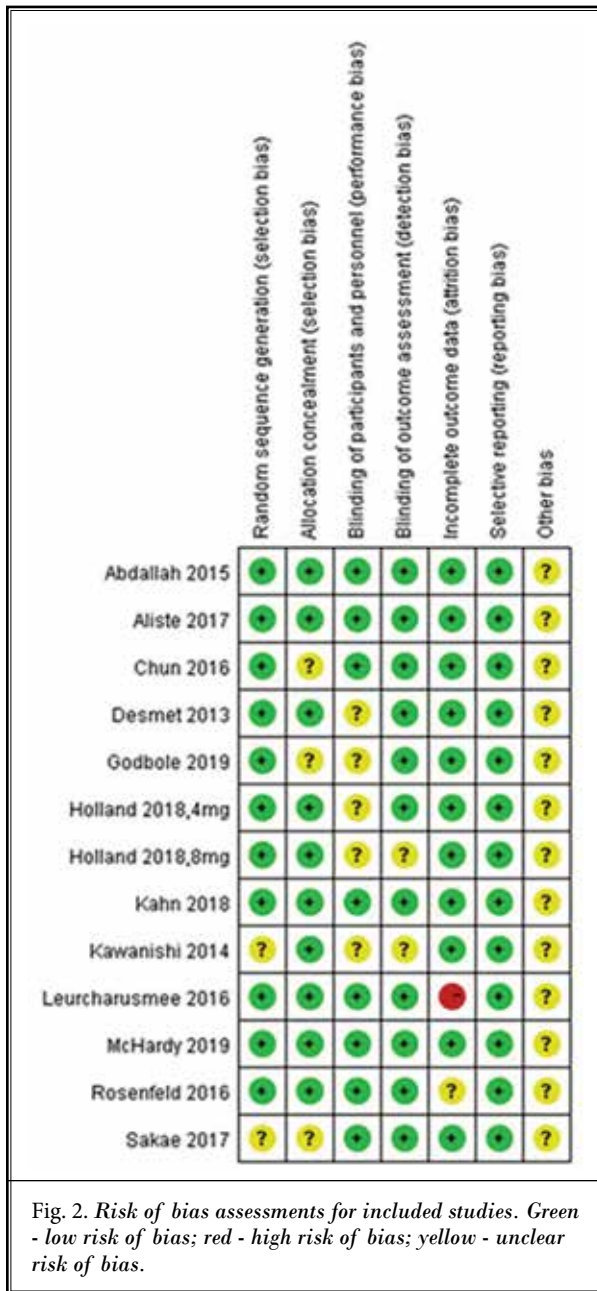
Pain Score at Postoperative 24 hours

Seven trials reported on pain score at 24 hours. Three (21,29,30) and 4 studies (23,26-28) assessed postoperative pain at 24 hours via the visual analog and numeric rating scales, respectively. The random-effects model suggested no significant difference was found between PN and IV DEX groups (SMD: -0.01, 95% CI [-0.17, 0.15], $I^2 = 50\%$, $P = 0.90$) (Fig. 7).

PONV

Seven studies reported the incidence of PONV. The results of the fixed-effects model suggested no significant difference was observed between the PN and IV DEX groups (RR 0.78, 95% CI [0.55, 1.11], $I^2 = 0$, $P = 0.16$) (Fig. 8).

Adverse Effects

Seven studies (8 comparisons) reported adverse effects. The fixed-effects model indicated a significantly higher ratio of adverse effects for PN DEX (RR 1.32, 95% CI [1.06, 1.63], $I^2 = 0$, $P = 0.01$) (Fig. 9A). However, a significant difference was not maintained, if the study by Holland et al (25) was withdrawn from analysis (RR 1.14, 95% CI [0.88, 1.47], $I^2 = 0$, $P = 0.33$) (Fig. 9B).

Sensitivity Analysis

Sensitivity analysis results suggested that all results were not materially changed, with the exception of adverse effects (Fig. 9B).

Publication Bias

A funnel plot was constructed for the duration of analgesia to detect publication bias. The funnel plot was found to be symmetric, indicating the absence of publication biases (Fig. 10).

Evidence of GRADE Quality

The GRADE quality of evidence assessments is summarized in Table 2.

Discussion

The results of the meta-analysis indicated that the use of PN DEX in the brachial plexus block significantly prolonged the duration of analgesia (131.82 minutes longer), sensory block (209.57 minutes longer), and motor block (218.85 minutes longer) in comparison to IV DEX. In a subgroup analysis accounting for the use of epinephrine, PN DEX provided a significantly longer duration of anesthesia (275.95 minutes longer), sensory block (250.44 minutes longer), and motor block (271.52 minutes longer) in comparison to IV DEX. No significant differences were found in these parameters between PN DEX and IV DEX when epinephrine was not used. The postoperative pain score at 24 hours, onset time, and performance time were equivocal between the 2 groups. Although PN DEX was associated with a slightly higher rate of complications, this effect was altered when the study by Holland et al (25) was withdrawn from the analysis, indicating an unstable result.
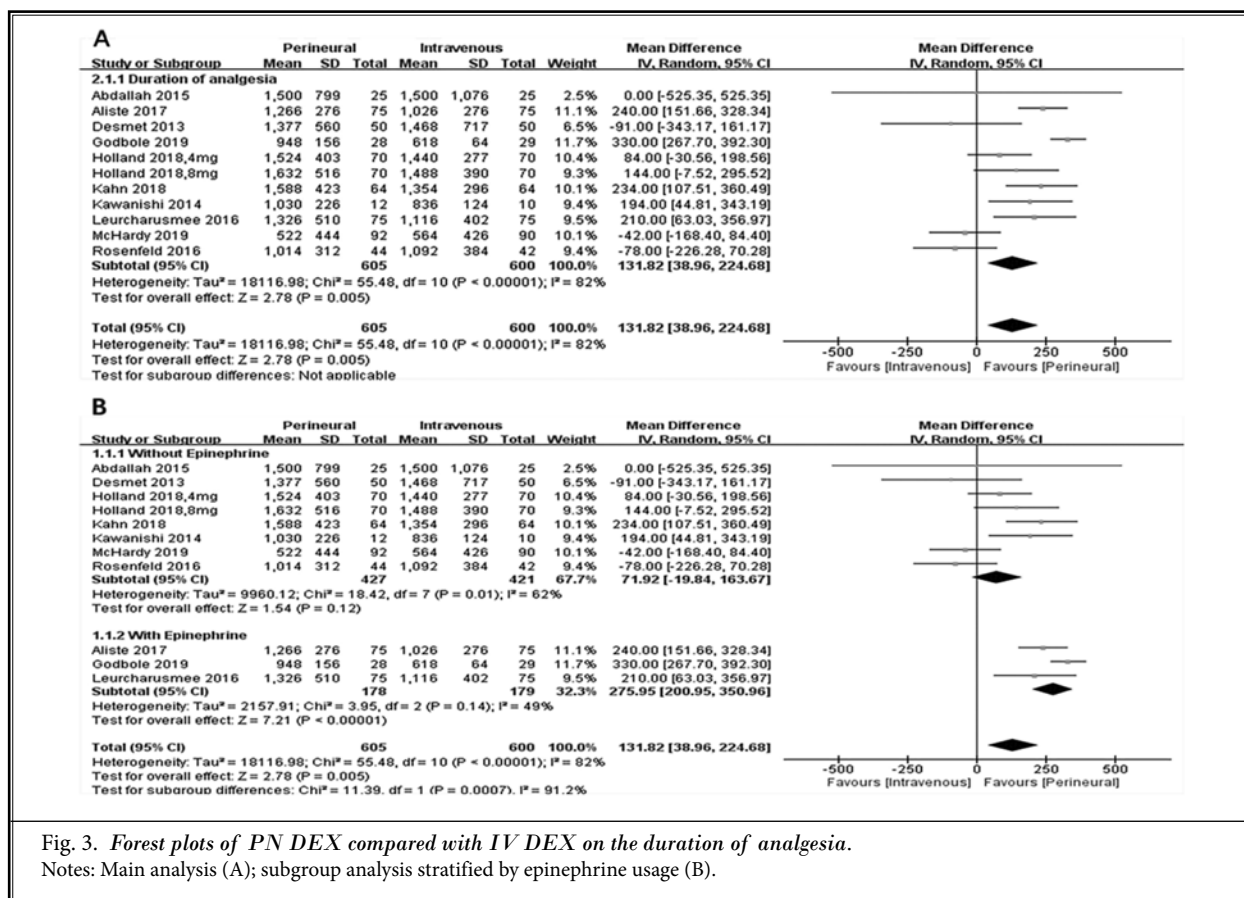
Fig. 3. *Forest plots of PN DEX compared with IV DEX on the duration of analgesia.*
Notes: Main analysis (A); subgroup analysis stratified by epinephrine usage (B).

The brachial plexus block has been traditionally advocated for upper limb surgery due to its effectiveness in providing postoperative analgesia, especially in fast-track surgeries; however, the short duration of analgesia is the main limitation of the brachial plexus block. It remains controversial as to whether a single-shot injection or a continuous indwelling catheter is the more advantageous method for administrating anesthetic agents (31). Catheter use has inherent pitfalls, such as infection, dislodgement, requiring further workup, and increased financial burden; thus, it is desirable to find an ideal adjunct to prolong the analgesic time of a single-shot brachial plexus block. Some adjuncts, such as DEX, epinephrine, clonidine, opioids, and tramadol (3), have been co-administered with local anesthetics to prolong the duration of single-shot brachial plexus block. Among them, dexamethasone is the most commonly used in clinical practice. DEX is a member of the glucocorticoid family and has been used for over 50 years to alleviate rheumatoid and osteoarthritis pain (32), as well as postoperative pain after orthopedic surgery (33).

Intravenous DEX administration is routinely performed for the alleviation of postoperative pain (34); however, the PN administration of DEX is prescribed as an "off-label use" owing to its potential toxicity to the nerve root (35). Thus, there is still a dispute regarding the suitability of PN DEX administration for brachial plexus blocks. However, the results of several meta-analyses suggest that administering PN DEX as an adjuvant to local anesthetics can prolong the duration of anesthesia, without associated adverse events (36-38). The analgesic mechanism of DEX is still not fully understood. It is postulated that DEX could suppress the local inflammation response, excitability of nociceptive C fibers, ectopic neural discharge, and neuropeptide immune response to injury (39).

Several meta-analyses have suggested that PN DEX can prolong the duration of anesthesia when compared to IV DEX. Heesen et al (40) found that PN DEX could prolong the duration of anesthesia by 241 minutes Baeriswyl et al (41) reported that the duration of anesthesia was 180 minutes longer with PN DEX compared to IV DEX. In a meta-analysis of 10 RCTs,
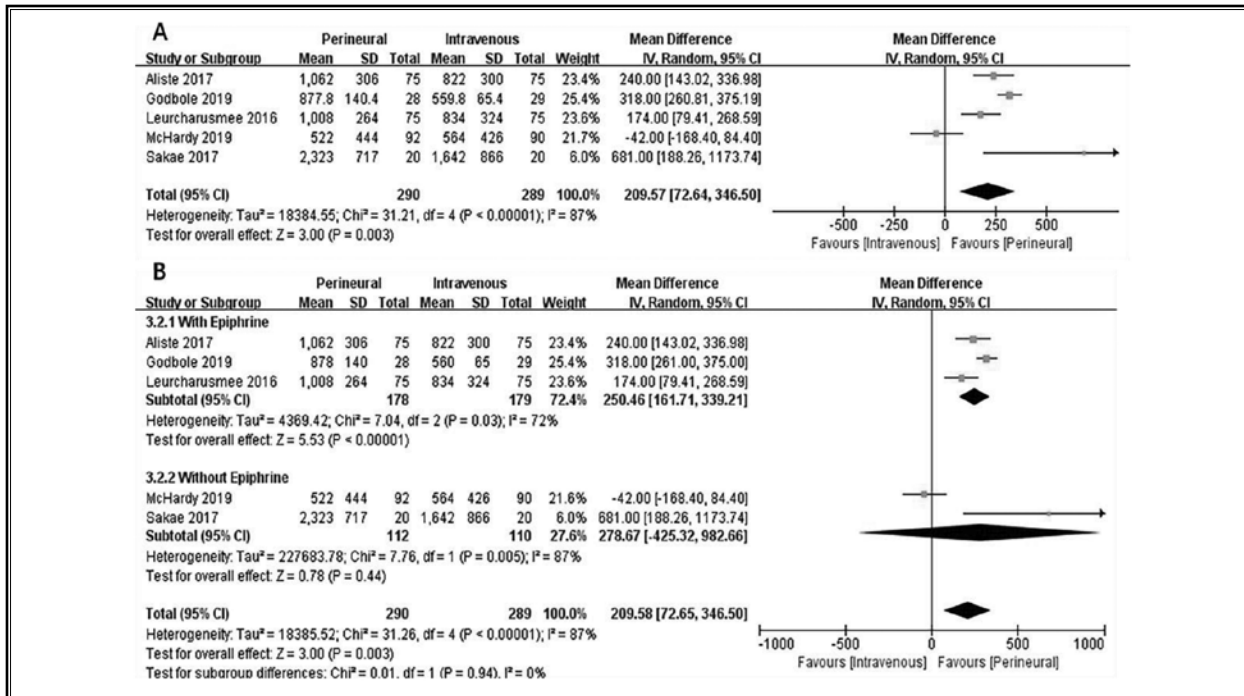
Fig. 4. *Forest plots of PN DEX compared with IV DEX on duration of sensory block.*
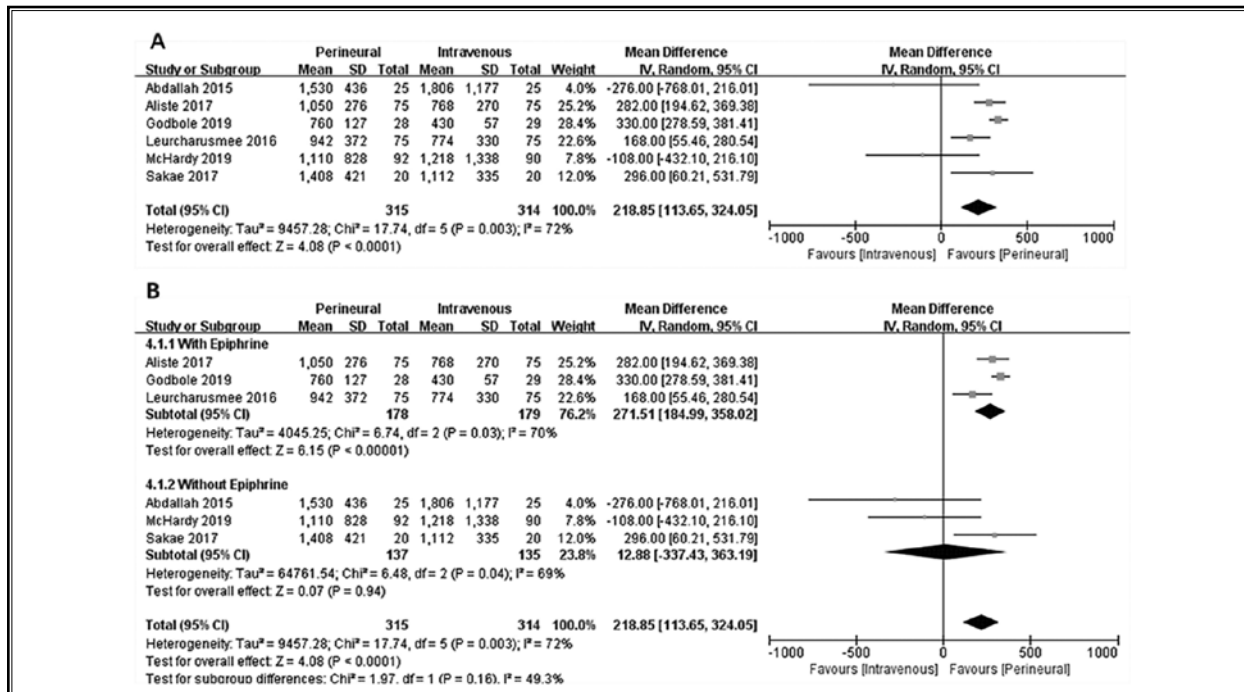Notes: Main analysis (A); subgroup analysis stratified by epinephrine usage (B).

Fig. 5. *Forest plots of PN DEX compared with IV DEX on duration of motor block.*
Notes: Main analysis (A); subgroup analysis stratified by epinephrine usage (B).
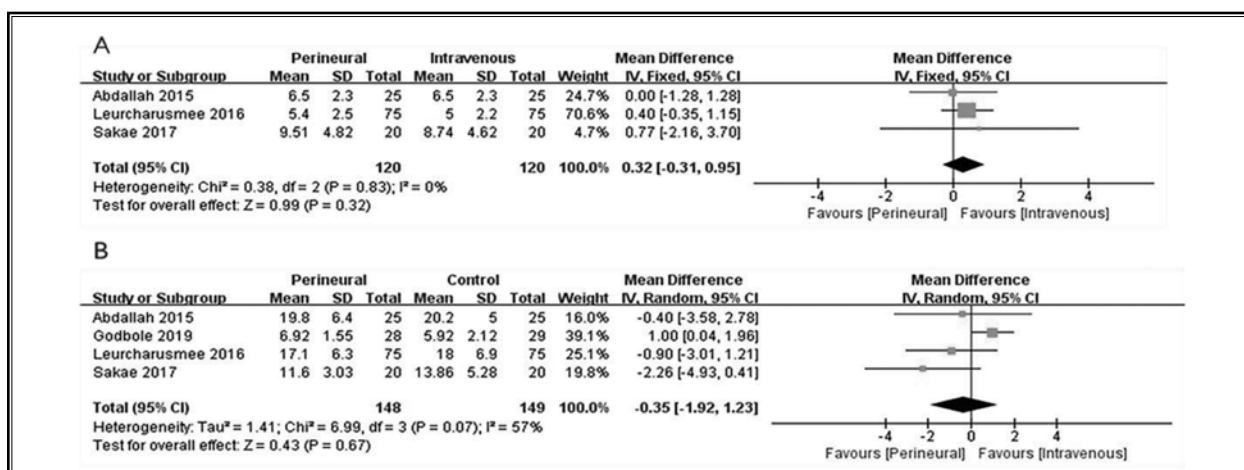
Fig. 6. *Forest plots of PN DEX compared with IV DEX on performance time (A) and onset time (B).*
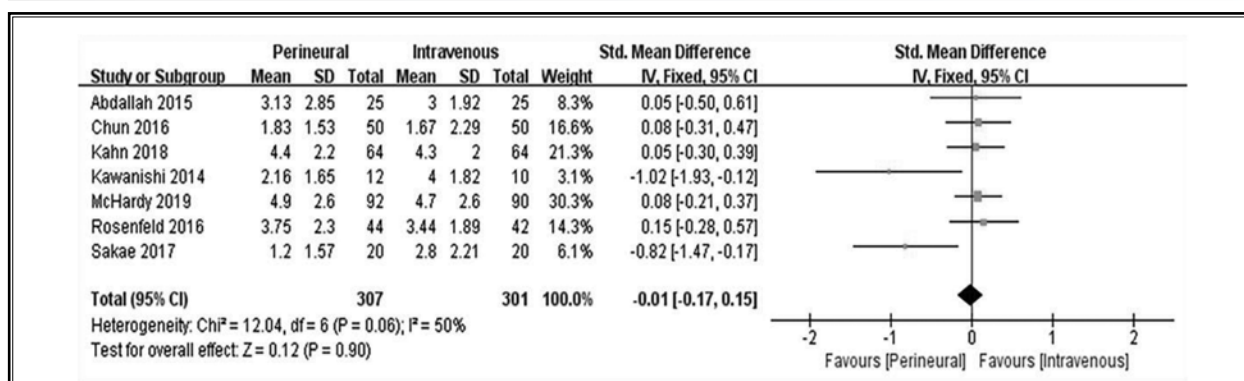

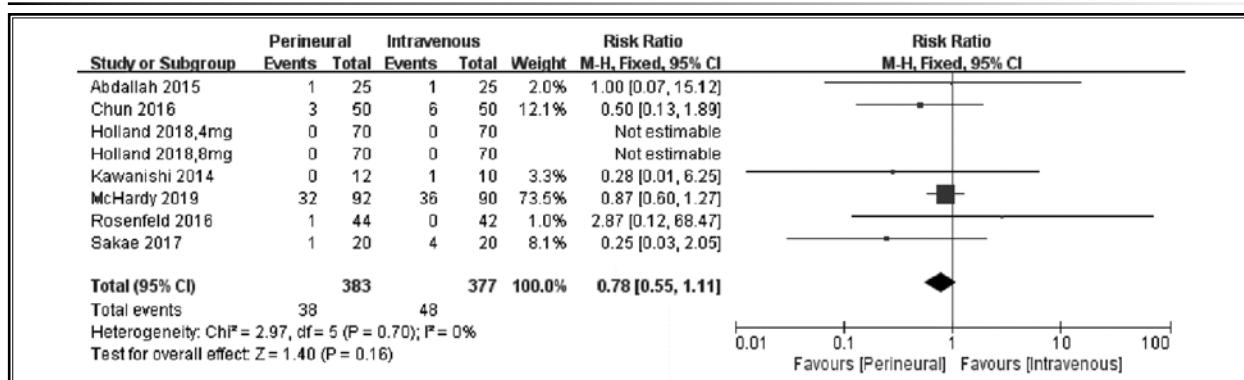Fig. 7. *Forest plots of PN DEX compared with IV DEX on the postoperative pain score at 24 hours.*

Fig. 8. *Forest plots of incidence of PONV at 24 hours (A).*
PONV, postoperative nausea and vomiting

Zhao et al (42) reported that PN DEX could increase analgesia duration by 3.96 and 0.3 hours with and without epinephrine, respectively. Zorrilla-Vaca et al (43) conducted a meta-analysis comprised of 13 RCTs and concluded that PN DEX could more effectively prolong analgesia as compared to IV DEX (SMD 0.48 hours, 95% CI 0.18-0.79). Chong et al (44) conducted a meta-analysis of 11 RCTs and reported that PN DEX
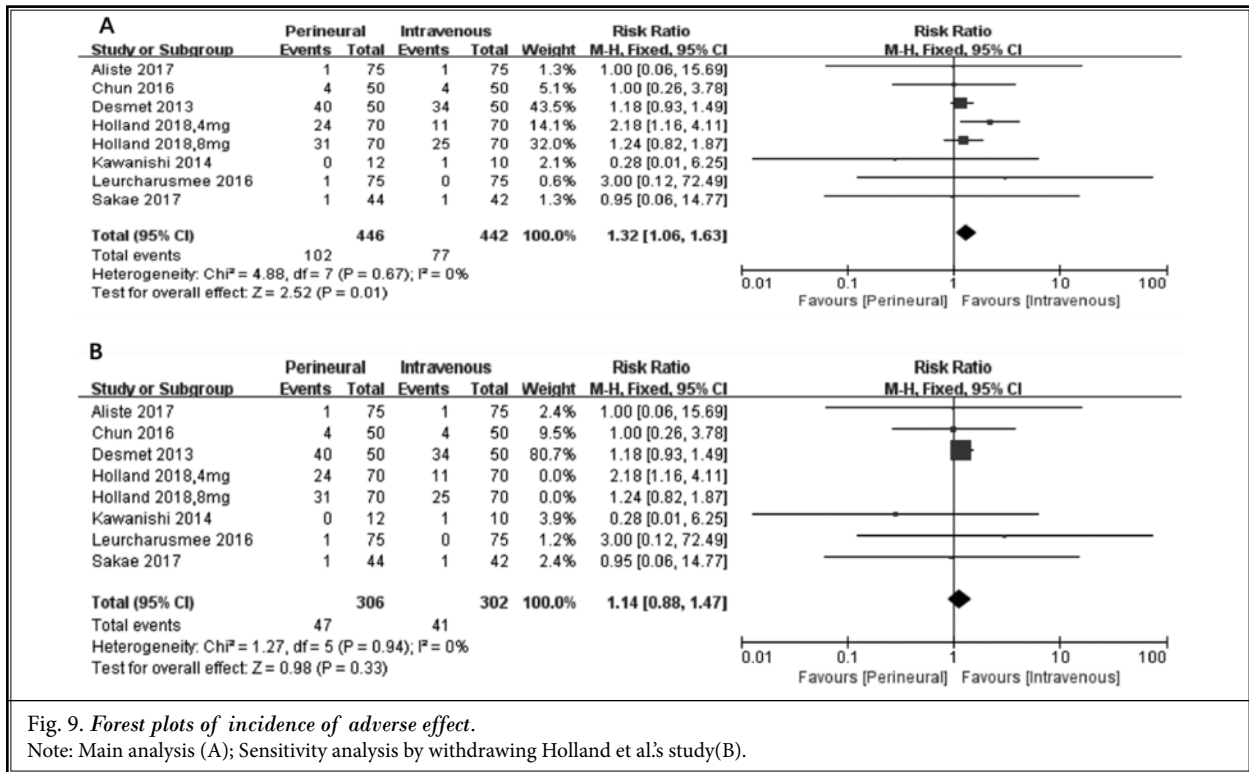
Fig. 9. *Forest plots of incidence of adverse effect.*
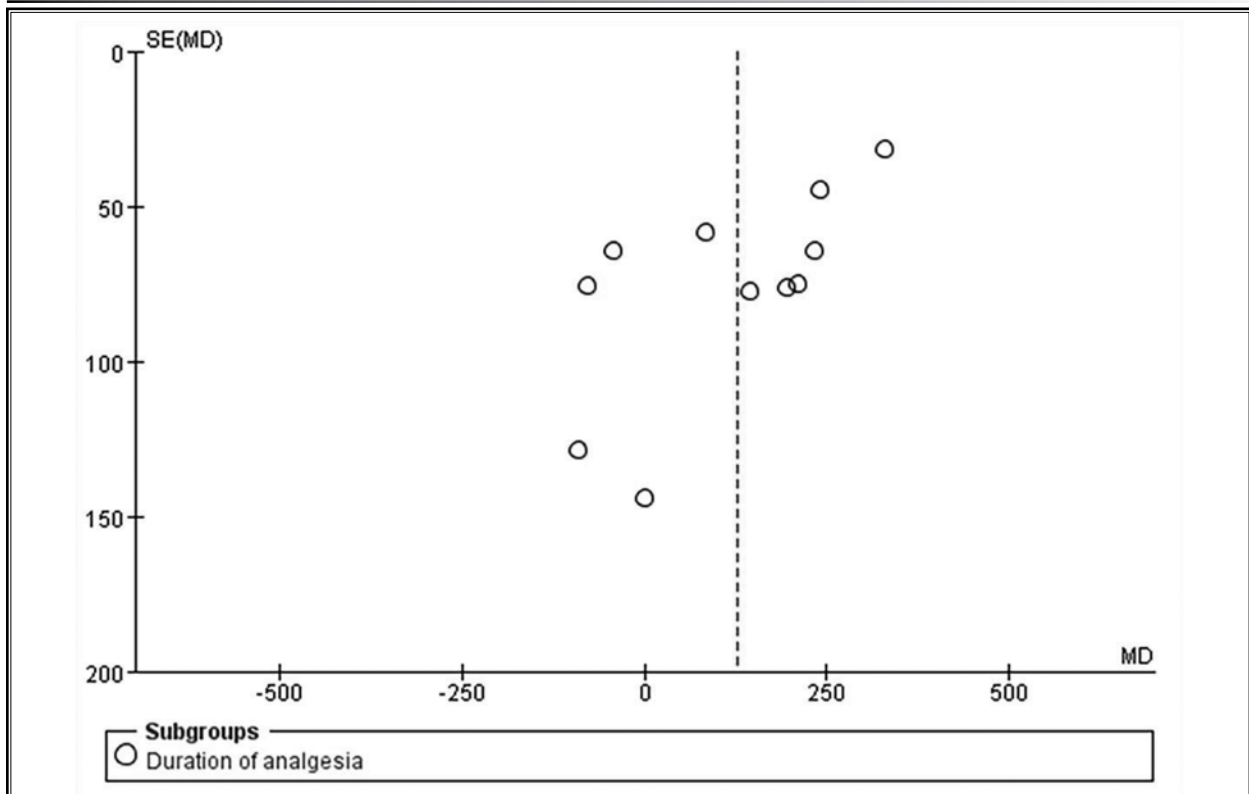Note: Main analysis (A); Sensitivity analysis by withdrawing Holland et al.'s study(B).

Fig. 10. *-Funnel plot for the duration of analgesia.*
MD, mean difference; SE, standard error

Table 2. *Summary of findings*

Outcomes		Number of patients		Quality assessment						Quality of evidence (grade)
		PN	IV	Study design	Incon-sistency	Indirect-ness	Imprecision	Publication bias		
Duration of analgesia: main analysis (11 studies)		605	600	RCT	no serious	serious[1]	no serious	no serious	none	⊕⊕⊕- MODERATE
Duration of analgesia: subgroup analysis	with epinephrine (3 studies)	178	179	RCT	serious[2]	no serious	no serious	no serious	none	⊕⊕⊕- MODERATE
	without epinephrine (8 studies)	427	421	RCT	no serious	serious[3]	no serious	no serious	none	⊕⊕⊕- MODERATE
Duration of sensory block: main analysis (5 studies)		290	289	RCT	no serious	serious[4]	no serious	no serious	none	⊕⊕⊕- MODERATE
Duration of sensory block: subgroup analysis	with epinephrine (3 studies)	178	179	RCT	serious[5]	no serious	no serious	no serious	none	⊕⊕⊕- MODERATE
	without epinephrine (2 studies)	112	110	RCT	no serious	very serious[6]	no serious	serious[7]	none	- - - VERY LOW
Duration of motor block main analysis (6 studies)		315	314	RCT	no serious	very serious[8]	no serious	serious[9]	none	- - - VERY LOW
Duration of motor block: subgroup analysis	with epinephrine (3 studies)	178	179	RCT	serious[10]	serious[11]	no serious	no serious	none	⊕⊕- - LOW
	without epinephrine (3 studies)	137	135	RCT	no serious	very serious[12]	no serious	no serious	none	⊕- - - VERY LOW
Performance time (3 studies)		120	120	RCT	no serious	no serious	no serious	very serious[13]	none	⊕⊕- - LOW
Onset time (4 studies)		148	148	RCT	no serious	no serious	no serious	no serious	none	⊕⊕⊕⊕ HIGH
Pain score (7 studies)		307	301	RCT	no serious	serious[14]	no serious	no serious	none	⊕⊕⊕- MODERATE
PONV (8 studies)		383	377	RCT	no serious	no serious	no serious	very serious[15]	none	⊕⊕- - LOW
Complications (8 studies)		446	442	RCT	no serious	no serious	no serious	very serious[16]	none	⊕- - LOW

[1]CIs do not overlap; [2]Low-quality study design in one study; [3]CIs do not overlap, $P < 0.05$, $I^2 = 62\%$; [4]CIs do not overlap, $I^2 = 87\%$; [5]Low quality study; [6]CIs do not overlap, $P < 0.05$ for heterogeneity, I^2 is 87%; [7]Too wide CIs around the estimated effect, [8]CIs do not overlap, $P < 0.05$ for heterogeneity, I^2 is 94%. Two studies favor experimental, and another 4 favor control; [9]CIs was too wide around zero effect; [10]Low-quality study design in 1 study; [11]CIs do not overlap; [12]CIs do not overlap, $P < 0.05$ for heterogeneity, I^2 is 94%. One study favors control, and another 2 favor experimental; [13]Results had too wide CIs around estimated effect; [14]CIs of 2 studies do not overlap with others; [15,16]Too wide CIs around estimated effect.

prolonged the duration of analgesia by 3.77 hours, compared to IV DEX. PN DEX has also been observed to prolong motor and sensory duration, as well as reduce oral opioid consumption.

The evaluation of PN DEX administration in the aforementioned meta-analysis included brachial plexus block, sciatic nerve block, lumbar plexus block, femoral block, tibial and peroneal nerve block, and infracla-

vicular ulnar block. However, to minimize heterogeneity, our meta-analysis only included studies comparing PN DEX and IV DEX use in the brachial plexus block. Our results were consistent with previously published meta-analyses, indicating that PN DEX could effectively prolong the analgesia duration, regardless of the type of PN block. The mechanism by which DEX prolongs the duration of anesthesia is unclear. One possibility is that DEX constricts the PN blood vessels, thus slowing the absorption of local anesthetics (45). Another possible mechanism is that DEX effects neural conduction, as previously reported in an experimental study (46). However, the results of our subgroup analysis suggests that the effects of DEX on the duration of anesthesia, sensory block, and motor block were dependent on epinephrine use. Epinephrine can induce vasoconstriction, resulting in a slower absorption of local anesthetics and longer duration of anesthesia (47). Thus, the use of epinephrine as an adjuvant may have masked the true effects of DEX on the duration of anesthesia and sensory block; as such, these results should be interpreted with caution.

PN DEX is prescribed for "off-label use" owing to its potential neurological toxicity (48). In an in vivo animal study, Wang et al (46) reported that topical application of DEX on the sciatic nerve could adversely affect neural conduction in a dose-dependent manner. Another animal study conducted by Zuloaga et al (49) reported that DEX could induce neuronal apoptosis in the central nervous system (49). However, an in vivo animal study which assessed the co-administration of DEX with a PN block demonstrated a prolonged sensory block duration without increased neural toxicity (50). Another study concluded that PN DEX could prolong sensory and motor block duration, and had a protective effect on local anesthetic-induced reversible neurotoxicity in an in vivo animal study (51). These.studies suggest that the effect of topical DEX on the PN nerve system are complex and yet to be known. Co-administration of DEX with local anesthetics could lead to crystallization and potential toxicity to the nerve, when topical or systematic application is performed (42). In our meta-analysis, the rate of PONV was similar between PN DEX and IV DEX. Although there were a higher rate of complications in the PN DEX group, this result was altered in the sensitivity analysis, indicating that the results of the main analysis were weak and not clinically significant. Furthermore, the complications could not be directly attributed to the use of PN DEX.

We observed significant heterogeneity in the duration of analgesia, sensory block, motor block, performance time, onset time, and postoperative pain score. All of these outcomes were subjective outcomes, and may have been effected for various reasons. Differences in the definition of outcomes between the included studies may have been a source of heterogeneity. For example, 2 studies defined the duration of analgesia as the time from complete injection of the anesthetic solution to the point at which the patient first experienced shoulder pain after surgery (25,29). In contrast, other studies defined the duration of analgesia as the time from the achievement of a successful block (i.e., a minimal composite score of 14 points at 30 minutes) to the first experience of pain at the surgical site (13,22) The homogeneity of the included studies may also have been affected by inter-subject variability. For example, some patients may have been more inherently insensitive to touch and pain, leading to a greater prolonged duration of analgesia, and vice versa. The visual analog scale and numeric rating scale were frequently used to assess postoperative pain, which required pooling of the outcomes by determining the SMD. However, this method postulates that the difference in SDs among studies only reflects differences in measurement scales, rather than actual differences in variability among study populations. This is problematic, if a real difference is to be expected in variability between patients among different studies. Since the use of SMDs involves units of SD, as opposed to the units of a given measurement scale, caution is required for the interpretation of these results.

Limitations

There are some limitations of our meta-analysis. First, the data we pooled from some studies may have had a skewed, nonnormal distribution. We converted median and IQR into mean and SD via the method recommended by Hozo et al and Wan et al (19,20). Therefore, there is some uncertainty in the pooled results, as the data used in a meta-analysis should ideally be normally distributed. Second, the endpoint outcomes varied between studies; this may have contributed to the heterogeneity of the pooled outcomes. Although we combined the outcomes for the duration of analgesia, sensory block, motor block, and postoperative pain score, these outcomes were not equivalent. Ideally, in a meta-analysis, the outcomes should be comparable before deciding to combine them. Third, the methods used for the brachial plexus blocks (e.g., block ap-

proach, NS, US-guided, with or without epinephrine) varied among the included studies, which have been a substantial source of heterogeneity. Fourth, the level of blood glucose was not assessed in our meta-analysis. While 2 of the included studies reported no significant differences in perioperative blood glucose (15,23), both PN and IV DEX were found to increase mean postoperative blood glucose concentrations. McHardy et al (13) reported a significantly higher blood glucose level in the PN DEX group (MD 0.34; 95% CI, 0.03 - 0.07; *P* = 0.02); however, this was not considered to be clinically relevant. Fifth, we did not analyze postoperative opioid consumption in the included studies. Six studies reported postoperative opioid consumption (21,25,26,28-30). Four studies assessed opioid consumption by morphine-equivalent administration (21,26,28,29) and concluded that no significant difference was observed in postoperative opioid consumption between PN and IV DEX administration groups. Two additional studies assessed opioid consumption using a binary evaluation (25,30), and also did not find a significant difference in postoperative opioid consumption; however, the differing patterns of opioid prescriptions may have been a confounding variable, so we did not analyze postoperative opioid consumption. Sixth, while seven of the included studies were registered at www.clinicaltrials.gov, it was unclear as to whether the other five trials were registered or not. Thus, there may have been publication bias, despite the approximately symmetrical funnel plot that we obtained. Some ongoing trials are registered at clinicaltrials.gov or International Clinical Trial Registry Platform (NCT03512223, NCT02190760, CTRI/2018/12/016524, NCT01495624), and we are waiting for their completion to incorporate their results into our meta-analysis. Seven, the local anesthetics used in the present meta-analysis included both bupivacaine and ropivacaine, which might have been an additional source of heterogeneity. Baeriswyl, et al (41), conducted a subgroup analysis in the light of the type of anesthetics used and concluded that PN DEX co-administration of bupivacaine significantly increased the duration of analgesia, but ropivacaine failed. However, 2 of the included studies in the bupivacaine subgroup used epinephrine as an adjuvant, which may have modified the overall effect, due to the ability of epinephrine to prolong the duration of local anesthetics. While ropivacaine may be potentially superior to bupivacaine for brachial plexus block due to its low cardiotoxicity (52), no significant differences were observed between these 2 anesthetic agents in a clinical and pharmacokinetic study conducted by Vainionpaa et al (53); therefore, we did not evaluate the effect of specific local anesthetics in our meta-analysis.

Conclusions

Our meta-analysis demonstrated that PN DEX is superior to IV DEX for prolonging the postoperative analgesic time, sensory block, and motor block. Nevertheless, a high level of statistical heterogeneity was observed and a subgroup analysis indicated that the effects of PN DEX may have been masked by epinephrine usage. No significant differences were found in secondary outcomes between PN DEX and IV DEX, except for adverse effects. Although there were slightly more adverse-effects in the PN DEX group, this difference was nullified in the sensitivity analysis, thus indicating a lack of clinical significance.

There are still disputes concerning DEX administration. The topical administration of PN DEX may avoid the side effects associated with systemic administration. For the off-label use of PN DEX, considering the low quality of evidence, high heterogeneity of results and unclear mechanism of action, the PN route of DEX administration should be exercised with caution in clinical practice. Further animal and human studies focusing on the pharmacology and toxicology of PN DEX are required to confirm its superior safety and effectiveness.

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