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REVIEW

Perineural versus intravenous dexamethasone as an adjuvant in regional anesthesia: a systematic review and meta-analysis

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Background: Dexamethasone is a common adjuvant for local anesthetics in regional anesthesia, but the optimal route of administration is controversial. Therefore, we did a systematic review and meta-analysis of randomized controlled trials to assess the effect of perineural versus intravenous dexamethasone on local anesthetic regional nerve-blockade outcomes.

Materials and methods: Medline (through PubMed), Embase, Cochrane, Web of Science, and Biosis Previews databases were systematically searched (published from inception of each database to January 1, 2017) to identify randomized controlled trials. The data of the selected trials were statistically analyzed to find any significant differences between the two modalities. The primary outcome was the duration of analgesia. Secondary outcomes included duration of motor block, postoperative nausea and vomiting, and postoperative analgesic dose at 24 hours. We conducted a planned subgroup analysis to compare the effects between adding epinephrine or not.

Results: Ten randomized controlled trials met the inclusion criteria of our analysis, with a total of 749 patients. Without the addition of epinephrine, the effects of perineural and intravenous dexamethasone were equivalent concerning the duration of analgesia (mean difference 0.03 hours, 95% CI –0.17 to 0.24). However, with the addition of epinephrine, the analgesic duration of perineural dexamethasone versus intravenous dexamethasone was prolonged (mean difference 3.96 hours, 95% CI 2.66–5.27). Likewise, the impact of epinephrine was the same on the duration of motor block. The two routes of administration did not show any significant differences in the incidence of postoperative nausea and vomiting, nor on postoperative analgesic consumption at 24 hours.

Conclusion: Our results show that perineural dexamethasone can prolong the effects of analgesic duration when compared to the intravenous route, only when epinephrine is coadministered. Without epinephrine, the two modalities show equivalent effect as adjuvants on regional anesthesia.

Keywords: anesthesia adjuvants, dexamethasone, regional anesthesia

Introduction

Uncontrolled pain after surgery may produce a range of detrimental acute and chronic effects.[1] In some surgical procedures under regional anesthesia, commonly used local anesthetics cannot provide analgesia for a sufficiently prolonged time. Therefore, local anesthetic–opioid combinations or continuous catheterization are chosen to prolong analgesic duration. However, unintentional opioid-associated side effects and several problems associated with carrying a catheter, especially for day-care patients, make these treatment options unsatisfactory. Since 1982, anesthesiologists have been using a variety of adjuvants added to local anesthetics to enhance regional anesthesia.[2] Dexamethasone is one of these additives.[3]

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Dexamethasone has been proved to be an effective adjuvant for extending the duration of sensory and motor block for peripheral nerve block when given perineurally.[4–6] Intravenous injection can also be used for alleviating postoperative pain.[7] However, there are conflicting reports about which of the two routes of administration is the best or if both exert an equivalent effect.[8–12]

To solve this query, a series of randomized controlled trials (RCTs) were conducted to compare the effect of prolongation of analgesia between perineural and intravenously administered dexamethasone. We carried out a systematic review and meta-analysis to assemble all the associated individual clinical trials to assess the two modalities on the main outcomes: prolonging sensory-block duration, decreasing postoperative nausea and vomiting, and sparing analgesic consumption at 24 hours after surgery.

Materials and methods

This systematic review and the meta-analysis results were reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy

Two authors (WLZ and XFO) independently searched the following databases: Medline (through PubMed), Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Biosis Previews, from inception of each database to January 1, 2017. There were no language restrictions. The full literature-search strategies for PubMed and Embase are presented in Table S1. In brief, we used MeSH terminology for dexamethasone, regional anesthesia, and their synonyms to search the five databases to obtain relevant literature. Then, all the titles and abstracts were screened and full texts of eligible RCTs retrieved. The references of key English reviews and eligible studies were also manually searched.

Selection criteria

When the titles and abstracts were screened, four selection criteria were applied: 1) population – adult patients (aged ≤19 years) under surgery who received regional anesthesia; 2) intervention – dexamethasone given perineurally as an adjuvant to local anesthetics; 3) control – same-dose dexamethasone given intravenously; and 4) design – RCTs. Studies that satisfied these criteria were retrieved for full texts to be assessed. Meeting abstracts were eliminated due to their incomplete information.

Data extraction

Two authors (WLZ and XFO) independently extracted the following raw data from the selected studies: main authors, year of publication, country, number of patients, type of nerve block, ultraguided localization technique, type and dose of local anesthetics (including dexamethasone and other adjuvants), and main outcomes. Then, concrete data of the following outcomes were extracted: duration of analgesia or sensory block, duration of motor block, incidence of postoperative nausea and vomiting, and postoperative analgesic use (morphine equivalents) at 24 hours. For the continuous type of data, we emailed the corresponding author to obtain the raw data when the variables in full text were not reported as means and SD. If authors did not respond, we used a method of data conversion. For calculation of given means, 95% CIs, SD ($(\sqrt{n} \times [\text{upper} - \text{lower}]/2t$), given medians, and interquartile ranges, the method reported by Hozo et al was used.[13] Each of the two aforementioned authors checked these data at least three times. Any disagreements on the results were resolved independently by a third experienced author (JL).

Assessment for risk of bias in included studies

Risks of included studies were assessed by the Cochrane risk-of-bias tool. We classified risk of bias as low, unclear, or high for each of random-sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (such as missing participant data). To grade the qualities of evidence and the strength of recommendations, we used GradePro version 3.6.1 for our four outcomes.

Statistical analysis

Continuous variables, analgesic duration, duration of motor block, and postoperative analgesic use at 24 hours were reported as mean differences (MDs) with 95% CIs. We analyzed postoperative nausea and vomiting as the categorical variable and expressed relative risk with 95% CIs. Heterogeneity of the four outcomes was evaluated by using the χ^2 and I^2 tests. A fixed-effect model was used when χ^2 P-value was >0.1 and I^2<50%. When P<0.1 and I^2>50%, we chose a random-effect model, and the planned subgroup analysis was performed to compare adding epinephrine or not to the local anesthetic mixture. Potential publication biases were assessed by funnel-plot analysis. All analyses were performed with RevMan (version 5.3; Cochrane Library, Oxford, UK).

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Results

Study selection and characteristics

A flowchart of the study-selection procedure is shown in Figure 1. In order to avoid any missing studies, we did not restrict the design of RCTs in searching Web of Science and Biosis Previews or define the route of administration. A total of 2,939 studies were identified during our first search: 638 articles were removed due to duplication, and 2,301 titles and abstracts were eliminated after screening. Finally, ten studies were included in our ultimateanalysis.[14–23] One study was eliminated due to its high standard deviation, which was even larger than the mean value, possibly due to the small-study effect.[24,25] The basic information of the ten studies is presented in Table 1. Patients of seven studies received brachial nerve block, one study used a nerve simulator to localize the nerve, and the rest were ultrasound-guided. The remaining studies were on perianal block, sciatic nerve block, and ankle block. Two of the studies were multicenter clinical trials, which were conducted in Canada and Thailand. The dose of dexamethasone ranged from 4 to 10 mg. Three trials added epinephrine with local anesthetics and dexamethasone, and hence they constituted the planned subgroup analysis in this study.

The risks of bias for the ten studies included here were discussed by all the authors; the risks discussed are summarized in Figure S1. One study[16] did not present the process they used to generate random sequences for group allocation. They also unveiled the allocation results to the anesthesiologists who participated in that trial, and did not refer to any blinding of the outcome assessment, as with another one.[14] For one of the ten studies,[22] the methods section did not clearly show the approach used for blinding the participants.

Duration of analgesia

The duration of sensory block or analgesia was reported by nine trials. One[19] was eliminated due to its definition of median analgesia time, namely time to first analgesic request in >50% of patients, which was far different to other studies' definitions (Table S2). In a random-effect model, a pooled analysis of nine trials showed that the MD between perineural and intravenous dexamethasone was 1.62 hours (95% CI –0.05 to 3.29, I^2=80%; P=0.06; Figure 2A), which indicated that dexamethasone given perineurally or intravenously had a similar effect on the duration of sensory block or analgesia. Due to the high heterogeneity, we conducted a subgroup analysis comparing the addition or exclusion of epinephrine. When epinephrine was used, perineural dexamethasone prolonged analgesic duration by 3.96 hours (95% CI 2.66–5.27, P<0.00001)

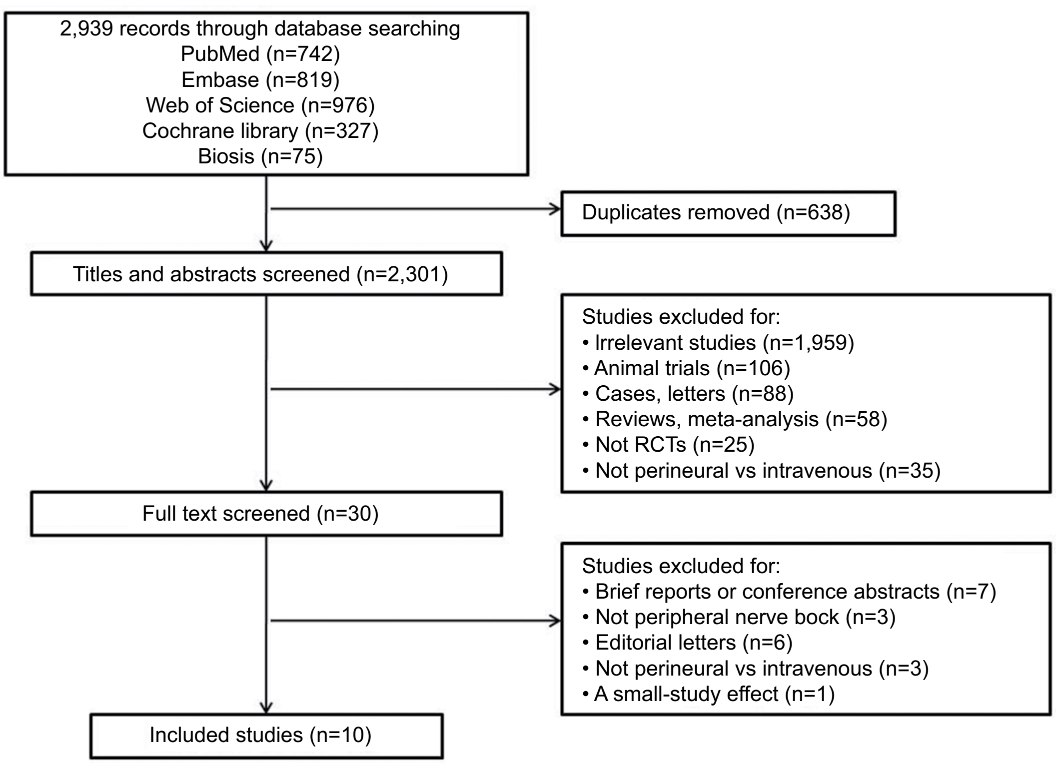

Figure 1 Flowchart of the search strategy.
Abbreviation: RCTs, randomized controlled trials.

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Table 1 Characteristics of included studies

Study	Country	n	Nerve block	Ultrasound-guided	Local anesthetics (n)	Outcomes
Abdelmonem and Rizk[14]	Egypt	56	Perianal block	No	Bupivacaine 100 mg + perineural dexamethasone 8 mg (18), bupivacaine 100 mg + intravenous dexamethasone 8 mg (19), bupivacaine 100 mg + intravenous normal saline (19)	Onset of sensory blockade, onset of motor blockade, duration of analgesia, VAS at 6 hours after rescue analgesic, postoperative nausea and vomiting
Desmet et al[15]	Belgium	144	Interscalene brachial plexus block	No (nerve stimulator)	Ropivacaine 150 mg + perineural dexamethasone 10 mg (49), ropivacaine 150 mg + intravenous dexamethasone 10 mg (49), ropivacaine 150 mg + intravenous normal saline (46)	Duration of analgesia, pain scores, motor-block scores, analgesic need, sleep disturbance, overall satisfaction, postoperative blood glucose concentrations
Kawanishi et al[16]	Japan	34	Interscalene brachial plexus block	Yes	Ropivacaine 150 mg + perineural dexamethasone 4 mg (12), ropivacaine 150 mg + intravenous dexamethasone 4 mg (10), ropivacaine 150 mg (12)	Duration of anesthesia, NRS the morning after surgery, analgesic need, sleep disturbance, overall-satisfaction score, postoperative nausea and vomiting, incidence of dyspnea
Rahangdale et al[17]	USA	76	Sciatic nerve block	Yes	Bupivacaine 0.5% 0.45 mL/kg, epinephrine 1:300,000 + perineural dexamethasone 8 mg (27); bupivacaine 0.5% 0.45 mL/kg, epinephrine 1:300,000 + intravenous dexamethasone 8 mg (23); bupivacaine 0.5% 0.45 mL/kg, epinephrine 1:300,000 + intravenous normal saline (26)	Quality of recovery (QoR-40), pain (NRS 0–11), time to first toe movement, analgesia duration, postoperative opioid consumption, patient satisfaction, recommend technique to family or relative, postoperative neurologic symptoms
Abdallah et al[18]	Canada	75	Supraclavicular brachial plexus block	Yes	Bupivacaine 150 mg + perineural dexamethasone 8 mg (25), bupivacaine 150 mg + intravenous dexamethasone 8 mg (25), bupivacaine 150 mg + intravenous normal saline (25)	Duration of analgesia, duration of motor function, VAS pain scores, cumulative intraoperative opioid consumption, cumulative postoperative opioid consumption, postoperative nausea and vomiting, patient satisfaction, occurrence of any block-related complications
Rosenfeld et al[22]	USA	120	Interscalene brachial plexus block	Yes	Ropivacaine 140 mg + perineural dexamethasone 8 mg (42), ropivacaine 140 mg + intravenous dexamethasone 8 mg (37), ropivacaine 140 mg + intravenous normal saline (41)	Block duration, opioid consumption, VAS, administration of "rescue" antiemetic medication, adverse events
Chun et al[19]	South Korea	99	Interscalene brachial plexus block	Yes	Ropivacaine 60 mg + perineural dexamethasone 5 mg (50), ropivacaine 60 mg + intravenous dexamethasone 5 mg (49)	Median analgesia time, patient-satisfaction scores, side effects, neurological symptoms, incidence of motor block, analgesic administration, blood glucose values
Aliste et al[23]	Canada, Thailand	131	Axillary brachial plexus block	Yes	Lidocaine 300 mg, bupivacaine 75 mg, epinephrine 150 μg + perineural dexamethasone 8 mg (64), bupivacaine 300 mg, bupivacaine 75 mg, epinephrine 150 μg + intravenous dexamethasone 8 mg (67)	Duration of motor block, duration of sensory block, duration of postoperative analgesia
Dawson et al[20]	Australia	90	Ankle block	Yes	Bupivacaine 150 mg + perineural dexamethasone 8 mg (30), bupivacaine 150 mg + intravenous dexamethasone 8 mg (30), bupivacaine 150 mg + intravenous normal saline (30)	Time to return of some sensation or movement, time to return of neurology, pain scores, total postoperative analgesic use
Leurcharusmee et al[21]	Thailand, Canada	123	Infraclavicular brachial plexus block	Yes	Lidocaine 350 mg, bupivacaine 87.5 mg, epinephrine 175 μg + perineural dexamethasone 5 mg (61); lidocaine 350 mg, bupivacaine 87.5 mg, epinephrine 175 μg + intravenous dexamethasone 5 mg (62)	Duration of motor block, duration of sensory block, duration of postoperative analgesia

Abbreviations: NRS, numeric rating scale; VAS, visual analog scale.

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A

Study or Subgroup	Perineural Mean	Perineural SD	Perineural Total	Intravenous Mean	Intravenous SD	Intravenous Total	Weight	Mean difference IV, random 95% CI
Abdallah et al[18] 2015	25	9.57	25	25	7.27	25	7.3%	0.00 [–4.71, 4.71]
Abdelmonem and Rizk[14] 2011	4.8	0.35	18	4.77	0.28	19	17.4%	0.03 [–0.17, 0.23]
Aliste et al[23] 2017	21.1	4.6	64	17.1	4.6	67	15.1%	4.00 [2.42, 5.58]
Dawson et al[20] 2016	24.1	7.41	30	20.9	7.04	30	9.5%	3.20 [–0.46, 6.86]
Desmet et al[15] 2013	23.42	8.58	49	21.25	11.61	49	8.6%	2.17 [–1.87, 6.21]
Kawanishi et al[16] 2014	14.5	5.04	12	15.5	2.45	10	10.5%	–1.00 [–4.23, 2.23]
Leurcharusmee et al[21] 2016	22.1	8.5	61	18.6	6.7	62	11.9%	3.50 [0.79, 6.21]
Rahangdale et al[17] 2014	35.5	7.7	27	30.5	8.9	23	7.4%	5.00 [0.35, 9.65]
Rosenfeld et al[22] 2016	16.9	5.2	42	18.2	6.4	37	12.3%	–1.30 [–3.89, 1.29]
Total (95% CI)			328			322	100.0%	1.62 [–0.05, 3.29]

Heterogeneity: τ^2=4.17; χ^2=39.56, *df*=8 (*P*<0.00001); I^2=80%
Test for overall effect: *Z*=1.90 (*P*=0.06)

B

Study or Subgroup	Perineural Mean	Perineural SD	Perineural Total	Intravenous Mean	Intravenous SD	Intravenous Total	Weight	Mean difference IV, random 95% CI
Epinephrine								
Aliste et al[23] 2017	21.1	4.6	64	17.1	4.6	67	1.6%	4.00 [2.42, 5.58]
Leurcharusmee et al[21] 2016	22.1	8.5	61	18.6	6.7	62	0.5%	3.50 [0.79, 6.21]
Rahangdale et al[17] 2014	35.5	7.7	27	30.5	8.9	23	0.2%	5.00 [0.35, 9.65]
Subtotal (95% CI)			152			152	2.4%	3.96 [2.66, 5.27]
Heterogeneity: χ^2=0.31, *df*=2 (*P*<0.86); I^2=0% Test for overall effect: *Z*=5.94 (*P*<0.00001)								
Not epinephrine								
Abdallah et al[18] 2015	25	9.57	25	25	7.27	25	0.2%	0.00 [–4.71, 4.71]
Abdelmonem and Rizk[14] 2011	4.8	0.35	18	4.77	0.28	19	95.9%	0.03 [–0.17, 0.23]
Dawson et al[20] 2016	24.1	7.41	30	20.9	7.04	30	0.3%	3.20 [–0.46, 6.86]
Desmet et al[15] 2013	23.42	8.58	49	21.25	11.61	49	0.2%	2.17 [–1.87, 6.21]
Kawanishi et al[16] 2014	14.5	5.04	12	15.5	2.45	10	0.4%	–1.00 [–4.23, 2.23]
Rosenfeld et al[22] 2016	16.9	5.2	42	18.2	6.4	37	0.6%	–1.30 [–3.89, 1.29]
Subtotal (95% CI)			176			170	97.6%	0.03 [–0.17, 0.24]
Heterogeneity: χ^2=0.31, *df*=2 (*P*<0.86); I^2=0% Test for overall effect: *Z*=5.94 (*P*<0.00001)								
Total (95% CI)			328			322	100.0%	0.13 [–0.08, 0.33]

Heterogeneity: χ^2=39.56, *df*=8 (*P*<0.00001); I^2=80%
Test for overall effect: *Z*=1.23 (*P*=0.22)
Test for subgroup differences: χ^2=33.90, *df*=1 (*P*<0.00001); I^2=97.0%

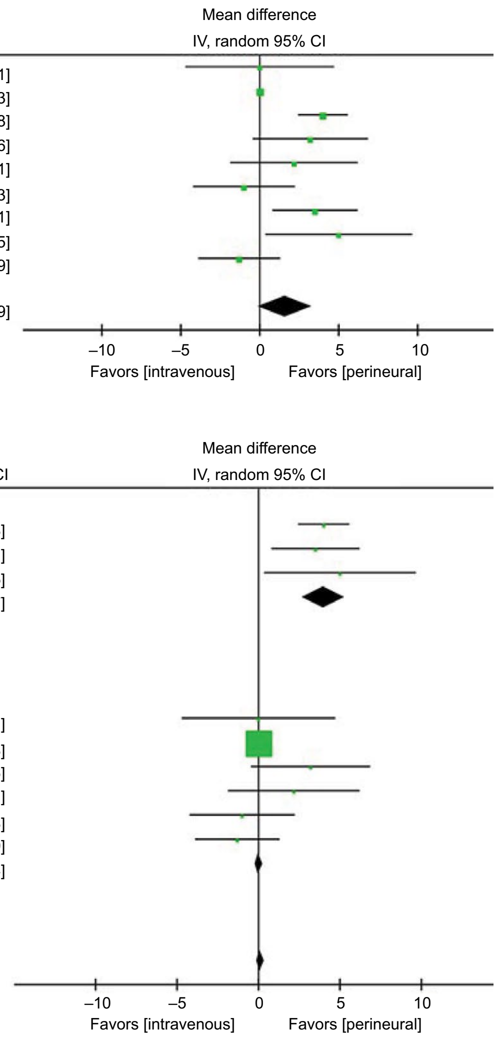

Figure 2 Forest plots showing the duration of analgesia.
Notes: Analysis of all data in the associated studies (**A**); subgroup analysis by differentiating addition or not of epinephrine (**B**).

in comparison to the intravenous dexamethasone group, with no heterogeneity (I^2=0). In the absence of epinephrine, both groups had equal analgesic duration (MD 0.03 hours, I^2=7%, 95% CI –0.17 to 0.24; *P*=0.75; Figure 2B). There were no observations of publication biases when constructing the funnel plots (Figure S2).

Duration of motor block

Four trials reported on duration of motor block. The effects on prolonging duration of motor block between the two modalities was statistically insignificant (MD 1.67 hours, I^2=94%, 95% CI –2.88 to 6.22; *P*=0.47; Figure 3A) as revealed by the random-effect model. However, subgroup analysis showed that in the presence of epinephrine, the perineural dexamethasone group had duration prolonged by 4 hours (95% CI 2.82–5.20, I^2=3%; *P*<0.00001; Figure 3B) when compared to the intravenous dexamethasone group.

Postoperative nausea and vomiting

Six studies assessed the incidence of postoperative nausea and vomiting. The pooled analysis demonstrated that there was no difference between the perineural and intravenous dexamethasone groups (risk ratio 0.87, 95% CI 0.35–2.11; *P*=0.75; Figure 4A), without heterogeneity (I^2=0) or publication bias (Figure S3).

Postoperative analgesic use at 24 hours

Postoperative opioid consumption (morphine equivalents) at 24 hours was evaluated by three trials. In this analysis, analgesic use was the same between the two groups (MD –3.66 mg, I^2=0, 95% CI –8.67 to 1.34; *P*=0.15; Figure 4B).

Grade quality

GradePro evaluation of the confidence of evidence is shown in Table 2.

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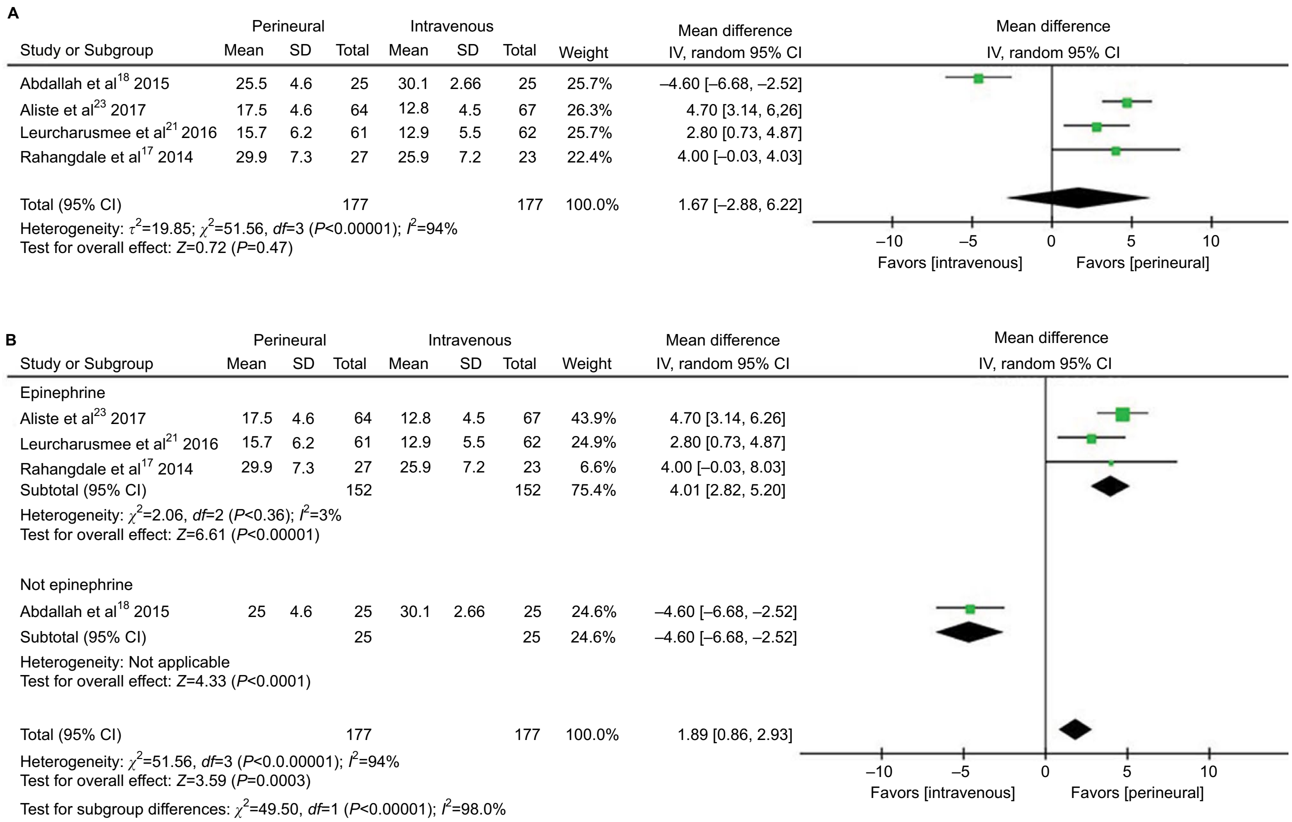

Figure 3 Forest plots showing the duration of motor block.
Notes: Analysis of four studies (**A**) and subgroup analysis by differentiating addition or not of epinephrine (**B**).

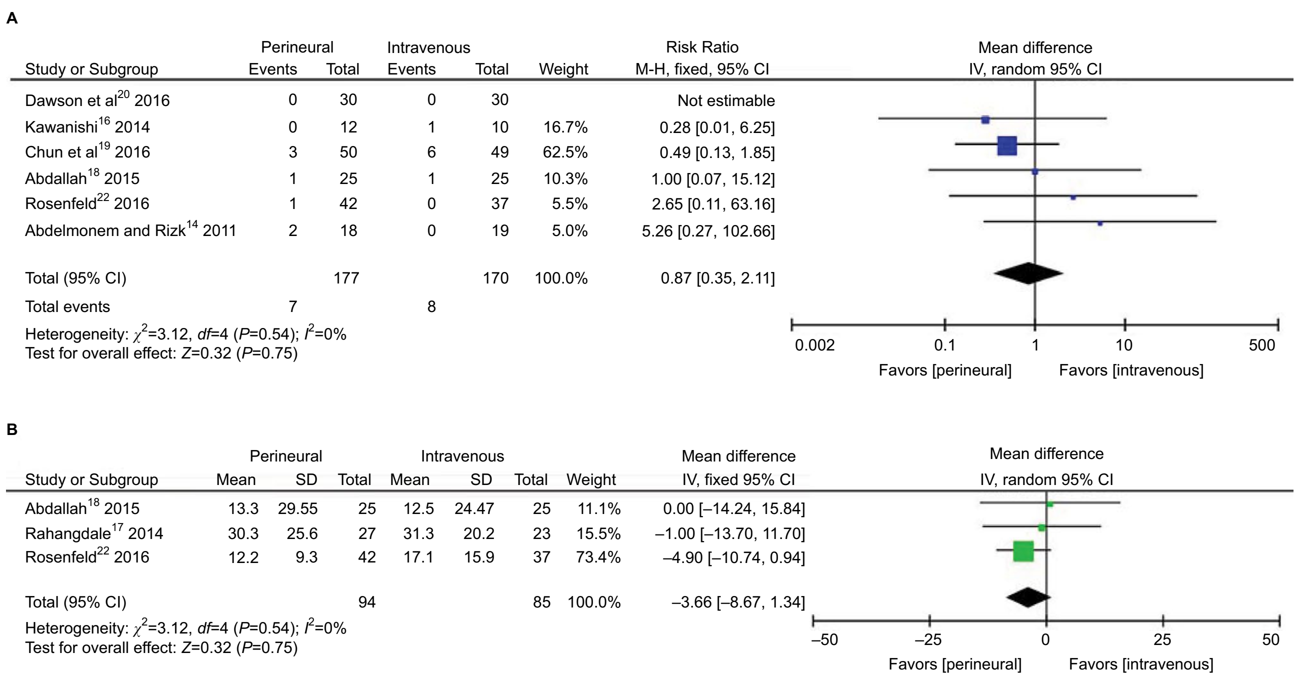

Figure 4 Forest plots comparing perineural and intravenous groups at 24 hours.
Notes: Incidence of postoperative nausea and vomiting (**A**); postoperative analgesic consumption (**B**).

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Table 2 Summary of findings

Outcomes	Number of participants		Quality assessment						Quality of evidence (grade)
	Perineural	Intravenous	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
Duration of analgesia: epinephrine (three studies)[17,18,22]	152	152	RCT	Not serious	Not serious	Not serious	Serious[a]	Not serious	⊕⊕⊕⊖ Moderate
Duration of analgesia: not epinephrine (six studies)[14,16,18,19,20,22]	176	170	RCT	Not serious	Not serious	Not serious	Serious[b]	Not serious	⊕⊕⊕⊖ Moderate
Duration of motor block: epinephrine (three studies)[17,18,22]	152	152	RCT	Not serious	Not serious	Not serious	Serious[a]	Not serious	⊕⊕⊕⊖ Moderate
Postoperative nausea and vomiting (six studies)[14,16,18,19,20,22]	177	170	RCT	Not serious	Not serious	Not serious	Serious[b]	Not serious	⊕⊕⊕⊖ Moderate
Postoperative opioid use at 24 hours (three studies)[17,18,22]	94	85	RCT	Not serious	Not serious	Not serious	Serious[a,b]	Not serious	⊕⊕⊕⊖ Moderate

Notes: [a]Number of RCTs not sufficient; [b]results had wide CIs around the estimated effect. High quality: further research very unlikely to change our confidence in the estimate of effect. Moderate quality: further research likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.
Abbreviation: RCT, randomized controlled trial.

Discussion

The results of our review and meta-analysis show that the two modalities of perineural and intravenous dexamethasone as local anesthetic additives can produce a similar effect on the duration of analgesia or sensory block. From the subgroup analysis, we found that the high heterogeneity in the data analysis stemmed from adding epinephrine or not, a well-known adjuvant in local anesthetics to prolong block duration.[26,27] With epinephrine, prolongation of duration of analgesia and motor block were observed in the perineural dexamethasone group when compared to the intravenous dexamethasone method. Without epinephrine, both groups showed an equivalent effect on analgesia duration. In addition, the incidence of postoperative nausea and vomiting and postoperative analgesic consumption at 24 hours exhibited no statistical significant differences when comparing the two routes of administration.

Such adjuvants as midazolam,[28] ketamine,[29] clonidine,[30] dexmedetomidine,[31] epinephrine, or dexamethasone are coadministered with local anesthetics in order to enhance the effect of single-shot peripheral nerve block. Although several meta-analyses[4–6] have demonstrated that dexamethasone given perineurally can extend the analgesic duration of common local anesthetics for brachial plexus block, the effectiveness of intravenous dexamethasone has been controversial.[12] Actually, in a meta-analysis of 38 studies, systemic dexamethasone (>0.1 mg·kg^{-1}) reduced postoperative pain and analgesic consumption.[7] As such, the current paramount issue is to demonstrate that perineural dexamethasone has an extra effect on the duration of analgesia through a direct mechanism on nerve blocking.[32] In this meta-analysis, the pooled results from ten RCTs revealed that dexamethasone (4–10 mg) can produce similar duration of sensory or motor block when administered perineurally or intravenously without epinephrine. In other words, the viewpoint that dexamethasone has a direct inhibition of peripheral nerves needs to be considered carefully and examined again. However, limited evidence in our review and meta-analysis elucidates that there may be a synergistic effect between dexamethasone and epinephrine when given locally.

On the one hand, whether or not dexamethasone has a direct effect on nerve conduction has been disputed. In isolated rat sciatic nerves, neither dexamethasone nor buprenorphine can inhibit the compound action potentials from A and C fibers.[33] In vivo, an animal study demonstrated that bupivacaine plus 67 μg dexamethasone did not increase block duration more than bupivacaine alone.[34] In contrast, in a mouse sciatic nerve-blockade model, high-dose (0.5

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mg·kg^{-1}) perineural dexamethasone added to bupivacaine prolonged the duration of sensory and motor block, while low-dose (0.14 mg·kg^{-1}) dexamethasone did not. However, these results should be considered with skepticism, because of the unblinded procedure in that study.[35] Despite the fact that sciatic nerves are commonly used to evaluate the effect of local anesthetic, we cannot directly extrapolate the results from rodents to humans. In addition, the period of block conduction can differ due to the neurobiology of acute postoperative pain in clinical patients. Acute postoperative pain includes not the conduction of nociception, but direct nerve damage and inflammatory mediator release, which activate peripheral nociceptors to deliver information to the central nervous system.[1] Dexamethasone, a long-effective glucocorticoid, has the appropriate anti-inflammatory property by increasing the production of anti-inflammatory substances and decreasing the release of inflammatory mediators.[36] This characteristic may be responsible for its systematic mechanism in prolonging block duration. Overall, further studies are needed to find and prove the precise indirect mechanism of dexamethasone and also its interaction with epinephrine perineurally.

On the other hand, dexamethasone is prescribed "off-label" for perineural administration. Neurotoxicity is a serious problem for local anesthetics and additives that we have to consider. Dexamethasone 133 μg·mL^{-1} combined with ropivacaine increased neurotoxicity for isolated sensory neurons. As such, the author advised that much attention be paid to the time- and concentration-dependent toxicity when dexamethasone is combined with ropivacaine.[37] In agreement with previous results,[38,39] in a preliminary animal experiment, we found that solutions of commonly used local anesthetics (bupivacaine, ropivacaine) in combination with nonparticulate dexamethasone sodium phosphate could crystallize, even in physiological pH (unpublished data). Therefore, the patient's safety might be compromised when crystalliferous solution is unintentionally injected into the subarachnoid space or into the blood vessels.

Considering potential neurotoxicity or hazards from crystallization, the unknown mechanism of action, and the fact that both methods have a similar effect on block duration, controlling nausea and vomiting, and sparing opioid consumption, we conclude that intravenous dexamethasone is preferable to perineural dexamethasone, as it carries fewer risks to the patient. Moreover, a recent published meta-analysis[40] proved that a combination of intravenous dexamethasone with other antiemetics showed more efficacy than a single antiemetic in preventing nausea and vomiting after laparoscopic cholecystectomy.

There are some limitations of this analysis. Firstly, postoperative blood glucose levels and long-term neurological sequelae were not analyzed. Only two of the ten trials[15,19] chosen here reported blood glucose concentrations after surgery. In these two studies, data demonstrated that there were no significant differences in blood glucose levels between the two routes of administration. Also, no serious relevant neurologic symptoms were found in these clinical trials. Secondly, although heterogeneity was low or inexistent among the four outcomes, there was a risk of bias in some of the studies. Thirdly, this review did not evaluate the interaction between the dosage of dexamethasone and block duration. However, Albrecht et al[41] elucidated that no inconclusive evidence was found between different concentrations of dexamethasone (4–10 mg) and analgesic duration by subgroup analysis.

Knowledge on many aspects of the two modalities is not clear, and further clinical studies are required to explore and determine their mechanism of action. A large-scale, multicenter, prospective, double-blinded RCT is needed to be performed to prove which is the most effective adjuvant, the best method of delivery (local anesthetic, perineural, or intravenous dexamethasone), and whether dexamethasone has a synergistic or additive effect with epinephrine when administered locally. If the most efficient route of administration proves to be additive, then the optimal dose of dexamethasone has to be determined. Finally, prospective studies should investigate the safety of dexamethasone at higher doses (>133 μg·mL^{-1}), when administered perineurally with local anesthetics.

Conclusion

Our systematic review and meta-analysis suggests that local epinephrine and dexamethasone have a synergistic effect. However, without epinephrine, intravenous dexamethasone and perineural dexamethasone share similar effects on block duration, postoperative nausea and vomiting, and postoperative analgesic consumption at 24 hours. At present, and considering the potential risk of the off-label use of dexamethasone perineurally and its as yet unknown mechanism of action, the route of intravenous administration is thus preferable. Further animal and human studies are needed to explore the definite relationship and the potential synergistic mechanism between local dexamethasone and epinephrine and to select the most effective route of administration required to guide clinical practice.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Search strategy

#	PubMed
1	Search ((((((((((((((((((((dexamethasone[MeSH Terms]) OR dexamethasone[Text Word]) OR Methylfluorprednisolone[Text Word]) OR Hexadecadrol[Text Word]) OR Decameth[Text Word]) OR Foy Brand of Dexamethasone[Text Word]) OR Decaspray[Text Word]) OR Merck Brand of Dexamethasone[Text Word]) OR Dexasone[Text Word]) OR ICN Brand of Dexamethasone[Text Word]) OR Dexpak[Text Word]) OR ECR Brand of Dexamethasone[Text Word]) OR Maxidex[Text Word]) OR Alcon Brand of Dexamethasone[Text Word]) OR Millicorten[Text Word]) OR Oradexon[Text Word]) OR Decaject[Text Word]) OR Merz Brand 1 of Dexamethasone[Text Word]) OR Decaject-L.A.[Text Word]) OR Decaject L.A.[Text Word]) OR Merz Brand 2 of Dexamethasone[Text Word]) OR Hexadrol[Text Word]
2	Search ((((Anesthesia, Conduction[MeSH Terms]) OR Anesthesia, Conduction[Text Word]) OR Conduction Anesthesia[Text Word]) OR Anesthesia, Regional[Text Word]) OR Regional Anesthesia[Text Word]
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5	Search ((((((Anesthesia, Local[MeSH Terms]) OR Anesthesia, Local[Text Word]) OR Local Anesthesia[Text Word]) OR Anesthesia, Infiltration[Text Word]) OR Infiltration Anesthesia[Text Word]) OR Neural Therapy of Huneke[Text Word]) OR Huneke Neural Therapy[Text Word]
6	Search ((((Anesthesia, Spinal[MeSH Terms]) OR Anesthesia, Spinal[Text Word]) OR Anesthesias, Spinal[Text Word]) OR Spinal Anesthesia[Text Word]) OR Spinal Anesthesias[Text Word]
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10	Search ((clinical[tiab] AND trial[tiab]) OR "clinical trials as topic"[mesh] OR "clinical trial"[pt] OR random*[tiab] OR "random allocation"[mesh] OR "therapeutic use"[sh])
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12	1 and 11 and 10

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3	exp regional anesthesia
4	(Anesthesia, Conduction or Conduction Anesthesia or Anesthesia, Regional or Regional Anesthesia).tw.
5	exp epidural anesthesia
6	(Anesthesia, Epidural or Anesthesia, Peridural or Anesthesias, Peridural or Peridural Anesthesia or Peridural Anesthesias or Anesthesia, Extradural or Anesthesias, Extradural or Extradural Anesthesia or Extradural Anesthesias or Epidural Anesthesia or Anesthesias, Epidural or Epidural Anesthesias).tw.
7	exp caudal anesthesia
8	(Anesthesia, Caudal or Caudal Anesthesia or Anesthesia, Sacral Epidural or Epidural Anesthesia, Sacral or Sacral Epidural Anesthesia).tw.
9	exp local anesthesia
10	(Anesthesia, Local or Local Anesthesia or Anesthesia, Infiltration or Infiltration Anesthesia or Neural Therapy of Huneke or Huneke Neural Therapy).tw.
11	exp spinal anesthesia
12	(Anesthesia, Spinal or Anesthesias, Spinal or Spinal Anesthesia or Spinal Anesthesias).tw.
13	exp nerve block
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15	exp local anesthetic agent
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Table S2 Definitions

Study	Duration of analgesia	Duration of motor block
Abdelmonem and Rizk[1]	Duration of analgesia was measured after the onset of sensory blockade till the patient's first request of analgesia (VAS >3).	None
Desmet et al[2]	Duration of analgesia was defined as the time between the performance of the block and the first administration of analgesia.	None
Kawanishi et al[3]	Duration of analgesia was defined as the time between the performance of the sensory block and the first administration of analgesia	None
Rahangdale et al[4]	Duration of analgesia was defined as the time to first reported pain	Duration of motor block was defined as the time to first toe movement
Abdallah et al[5]	Duration of analgesia was defined as the time in hours to the first report of postoperative pain at the surgical site.	Duration of motor block, defined as the time (in hours) to return to normal
Rosenfeld et al[6]	Duration of analgesia was defined as the time from injection until the patient detected complete resolution of sensory blockade	None
Chun et al[7]	The definition of "median analgesia time" was the time to first analgesic request in >50% of patients.	None
Aliste et al[8]	For duration of postoperative analgesia, patients were instructed to record the exact time they first experienced pain at the surgical site.	Duration of motor block, defined as the exact time they first regained movement of their fingers
Dawson et al[9]	Durations of blockade was defined as the time until ankle and foot sensation or movement started to return.	None
Leurcharusmee et al[10]	For duration of postoperative analgesia, patients were instructed to record the exact time they first experienced pain at the surgical site.	Duration of motor block, defined as the exact time they first regained movement of the fingers

Abbreviation: VAS, visual analog scale.

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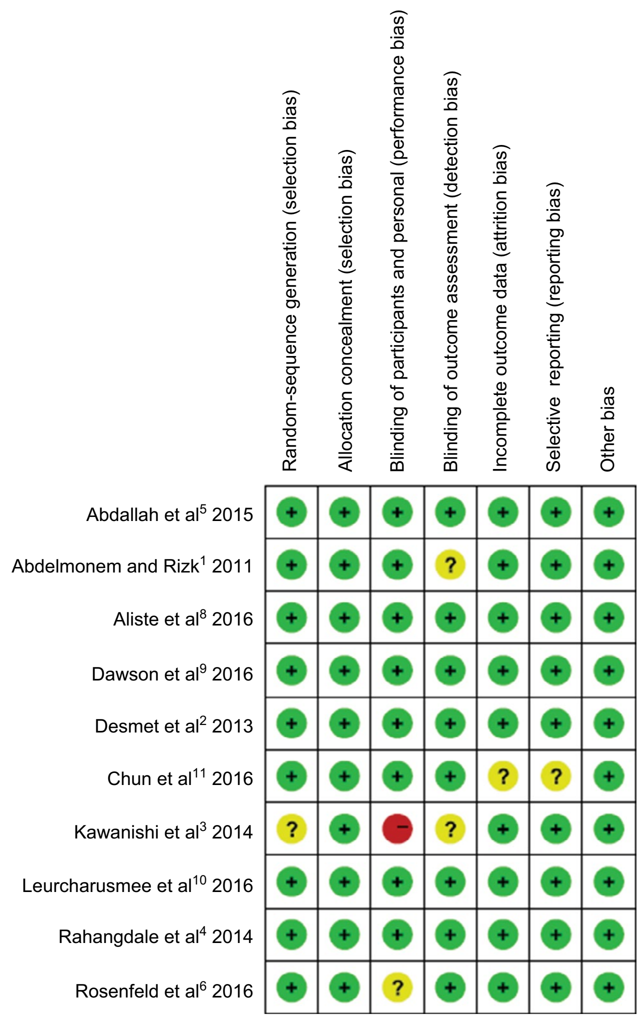

Figure S1 Risks of bias for the ten included studies by all authors' judgment.
Notes: Red, high risk of bias; yellow, unclear risk of bias; green, low risk of bias.

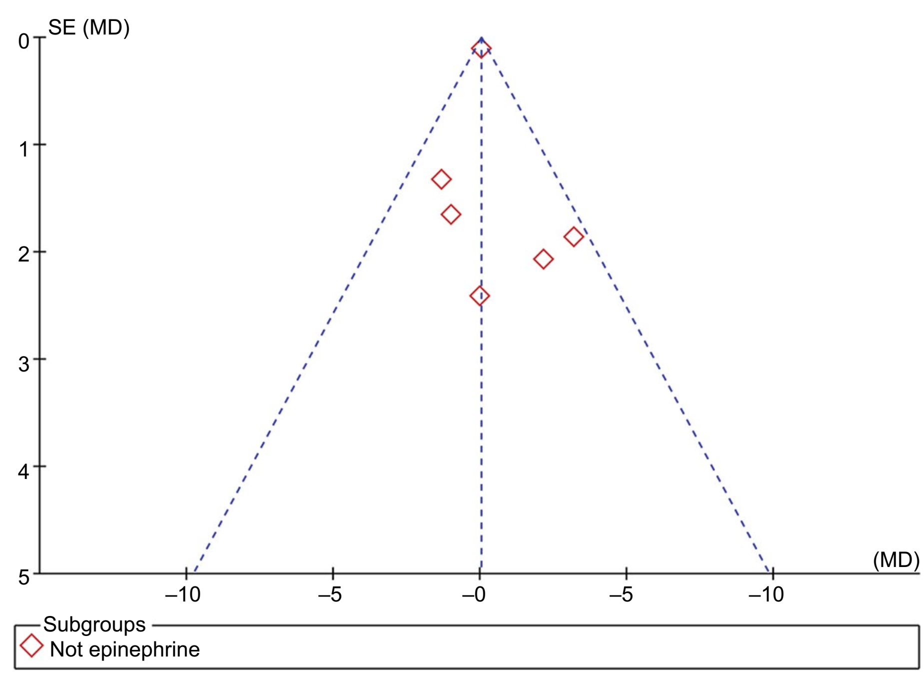

Figure S2 Funnel plots of duration of analgesia: adding epinephrine (left) and not adding epinephrine (right).

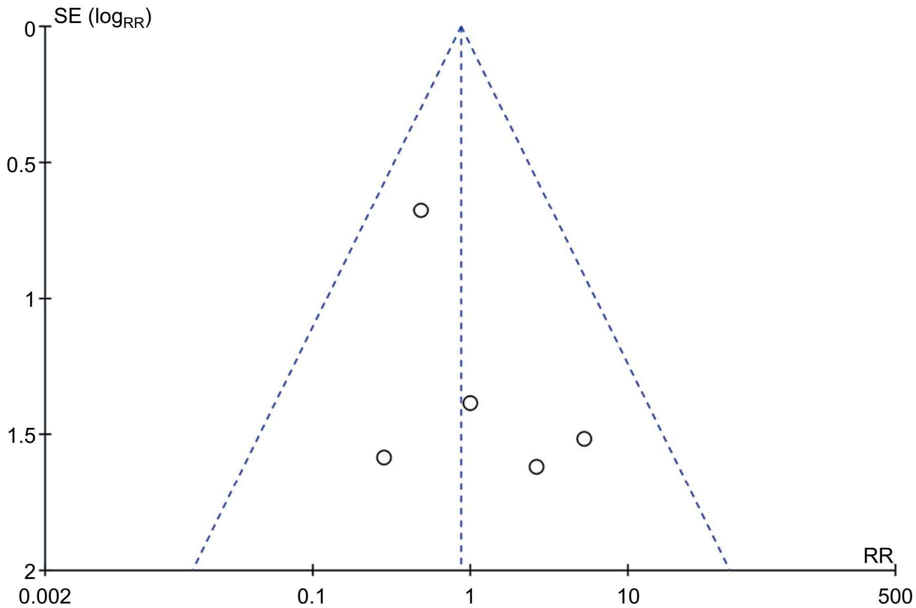

Figure S3 Funnel plot of postoperative nausea and vomiting.

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