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META-ANALYSIS

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Fetal and Maternal Responses to Dexmedetomidine Intrathecal Application During Cesarean Section: A Meta-Analysis

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Manuscript Preparation E
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Background: Intrathecal dexmedetomidine (DEX) can improve the blockade of spinal anesthesia, but there is no clear conclusion on whether it has an effect on the fetus during cesarean section. Our meta-analysis evaluated the safety and efficacy of intrathecal DEX in cesarean delivery.

Material/Methods: We searched Cochrane, Embase, PubMed, and CBM for eligible studies, and used the Revised Cochrane Risk of Bias Tool (RoB 2.0) to assess the risk of bias of each study. RevMan was used for statistical analyses. We have registered this meta-analysis on PROSPERO (CRD42019120995).

Results: The meta-analysis included 10 RCTs, but only 5 were prospectively registered. The results of preregistration studies, including the 1- or 5-min Apgar score (mean difference [MD], –0.03; 95% confidence intervals [CI], –0.16 to 0.10; *P*=0.64 or MD, 0.00; 95% CI, –0.09 to 0.09; *P*=1), the umbilical arterial oxygen or carbon dioxide partial pressure (MD, 0.90; 95% CI, –4.92 to 6.72; *P*=0.76 or MD, 1.20; 95% CI, –2.06 to 4.46; *P*=0.47), and the cord blood pH (MD, –0.01; 95% CI, –0.05 to 0.03; *P*=0.72), showed that intrathecal DEX had no significant difference in neonatal outcomes compared with placebo. In maternal outcomes, intrathecal DEX significantly prolonged postoperative pain-free period and reduced the incidence of postoperative shivering, which did not increase spinal anesthesia-associated adverse effects.

Conclusions: Intrathecal DEX is safe for the fetus during cesarean section and can improve the blockade effects of spinal anesthesia on puerperae.

MeSH Keywords: **Adjuvants, Anesthesia • Anesthesia, Spinal • Dexmedetomidine • Fetus • Meta-Analysis • Randomized Controlled Trial**

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Background

Cesarean section is an effective means of solving dystocia and certain obstetric complications to save maternal and perinatal life [1]. Spinal anesthesia has always been the preferred anesthesia for cesarean section because it can avoid the risk of general anesthesia such as tracheal intubation failure, aspiration, high medical expenses, and lung infection, and can provide excellent postoperative analgesia [2–4]. In addition, spinal anesthesia can ensure that the mother is awake during cesarean section and fully experience the birth process of the fetus, thus promoting early breastfeeding and contact between mother and infant. More importantly, spinal anesthesia can better prevent direct effects of general anesthetics (e.g., opioids) on the fetus through placental transfer compared with general anesthesia [5]. General anesthesia has been shown to reduce neonatal Apgar scores as early as the 1970s [6]. With the advancement of anesthesia techniques and the development of anesthetics, recent studies have shown that general anesthesia has little effect on cord blood gas parameters and neonatal Apgar scores [7]. However, more high-quality clinical studies are needed to confirm whether general anesthesia can replace spinal anesthesia as the preferred anesthesia for cesarean section in the future.

In clinical practice, spinal anesthesia with small doses of local anesthetics is not sufficient to inhibit visceral pain and often causes maternal pain and discomfort intraoperatively and insufficient postoperative analgesia, while high-dose local anesthetics are prone to cause maternal hypotension and neonatal acidosis [8,9]. Prolonging postoperative analgesia without affecting early activity is the common goal of most puerperae. To overcome these limitations and further improve spinal anesthesia, the application of local anesthetics combined with adjuvants has gradually become a focus of anesthesiologists [10]. Recent research shows that many drugs can be used intrathecally in combination with local anesthetics to improve spinal anesthesia, of which dexmedetomidine (DEX) is a good choice [11,12].

DEX has sedative, analgesic, and anti-sympathetic effects, and has no significant effect on respiration [13]. Use of DEX in cesarean section anesthesia has received more and more attention. Studies have shown that DEX can be used as an auxiliary for general anesthesia and intrathecal anesthesia in cesarean section; it can enhance the anesthetic effects, prevent and reduce adverse reactions of anesthetics, and reduce the amount of anesthetic drugs used [14–16]. However, when DEX is used in cesarean section to improve anesthesia, there are concerns about whether DEX will adversely affect the fetus. Our present meta-analysis was based on the intrathecal application of DEX, and the use of large sample sizes to confirm the safety of intrathecal DEX to the fetus. In addition, few high-quality studies have evaluated the effect of intrathecal DEX on spinal anesthesia during cesarean section, and some of the results are still controversial. The secondary aim of our meta-analysis was to evaluate whether intrathecal DEX has an improved effect for spinal anesthesia and adverse effects on puerpera during cesarean section. Due to the lack of studies on the long-term physiological effects of intrathecal DEX on neonates, this meta-analysis only focused on short-term neonatal outcomes, such as neonatal Apgar score, umbilical blood carbon dioxide partial pressure, umbilical blood oxygen partial pressure, and umbilical blood pH.

Material and Methods

This meta-analysis was registered with PROSPERO (*https://www.crd.york.ac.uk/PROSPERO*), and the registration code is CRD42019120995. The preparation of our manuscript is based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [17].

Searching strategy

The electronic databases Cochrane Library, Embase, PubMed, and CBM were searched by 2 researchers to find available randomized controlled trials (RCTs). The search strategy used of Medical Subject Headings (MeSH) terms and corresponding free words. The phrases for MeSH search included: "DEX", "Anesthesia, Spinal", "Injections, Spinal", "Bupivacaine", "Ropivacaine", "Cesarean Section", and "Randomized controlled trial". The last search was performed on December 18, 2018. In addition, the searchers read the references to find other eligible articles.

Study inclusion criteria

Our meta-analysis included RCTs in which adult full-term pregnant women who underwent selective cesarean section under spinal anesthesia were randomly divided into groups, including an intrathecal DEX group and a blank control group without any adjuvant. We excluded studies in which there were premature delivery (<37 weeks of pregnancy), multiple pregnancies, cardiovascular disease (e.g., pre-eclampsia and hypertension), drug addiction, allergy to DEX or local anesthetics, and patients who cannot undergo spinal anesthesia.

Data extraction

A pre-designed data table was used to collect data from the included studies, including: the first author's name, published time, countries, registration number, the included studies application, sample size, local anesthetics, and total volume (Table 1). The 2 reviewers completed data extraction independently, and

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Table 1. Characteristics of included studies in the meta-analysis.

Author	Years	Country	Registration number	Application (ug)	Sample size	Local anesthetics (mg)	Total volume (ml)
Bi et al. [10]	2017	China	ChiCTR-IIR-16008497	NS/D3/D5	20/20/20	Bup 10	2
Fawzy et al. [21]*	2016	Egypt	–	NS/D5	30/30	Bup 12.5	2.5
He et al. [22]	2017	China	ChiCTR-IIR-15007548	NS/D2.5/D5	30/30/30	Bup 12.5	3
Kamali et al. [23]*	2018	Iran	–	T25/D25/NS	36/36/36	Lid 100	2
Li et al. [24]*	2015	China	–	NS/F15/C75/D10	21/21/21/21	Bup 10	-
Nasseri et al. [25]	2017	Iran	IRCT201511301766N7	D5/NS	25/25	Bup 12.5	3
Qi et al. [26]	2016	China	ChiCTR-TRC-14005227	D5/M100/NS	40/40/40	Bup 10	2
Sun et al. [27]*	2015	China	–	NS/F25/D10	30/30/30	Bup 10	3
Teymourian et al. [28]*	2018	Iran	–	D10/NS	76/76	Bup 15	3
Xia et al. [29]	2018	China	ChiCTR-IPR-16009699	D5/NS	45/45	Bup 8.4/12.1	3

* Studies are unregistered studies. NS – saline; D – dexmedetomidine; T – tramadol; F – fentanyl; C – clonidine; M – morphine; Bup – bupivacaine; Lid – lidocaine.

disagreements between reviewers were resolved through discussions with third parties.

Assessment of risk of bias

The methodological quality of each of the studies we included was independently assessed by 2 reviewers using the Revised Cochrane Risk of Bias Tool (RoB 2.0) [18]. The tool considers 5 different areas, each of which was classified as low risk of bias, some concerns, or high risk of bias. If all 5 of the areas are low risk, the overall risk of bias is low; if the assessment results in any of the areas are high risk, or the assessment results in multiple areas are some concerns, the overall risk of bias is high; otherwise, the overall risk of bias is some concerns. Any disagreement on method quality assessment can be resolved through group consensus and discussion.

Statistical analysis

The statistical analyses were performed using RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK), and Stata 12.0 (StataCorp, College Station, TX, USA) was used for Begg's test. For dichotomous data, the Mantel-Haenszel method was used to calculate the risk ratio (RR) with 95% confidence interval (95% CI). For continuous data, if the measurement methods or units of the indicators among included studies were the same, the inverse variance method was used to calculate the mean difference (MD) with 95% CI; otherwise, the standardized mean difference (SMD) with 95% CI was calculated. The Z test was used to assess the overall effect of the indicator, and the difference was considered statistically significant when 95% CI did not include 1 for RR and 0 for MD or SMD. Testing for heterogeneity of the pooled results was performed using the I-square (I^2) test. A random-effects model was used when a large heterogeneity was presented (I^2>50%); otherwise, a fixed-effect model was used in meta-analysis. In addition, when heterogeneity was significant, we performed subgroup analysis or sensitivity analysis to find sources of heterogeneity and minimize heterogeneity. The publication bias of primary outcomes (neonatal outcomes with more than 3 studies) was quantitatively assessed using Begg's test. Some indicators of included studies, such as Apgar score and VAS score, expressed clinical efficacy by median and its range. To analyze variables, mean and standard deviation (SD) of the indicators were obtained by using the online calculator (*http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html*) based on the sample size, median, and range, and the indicators mean was estimated using the method of Luo et al. [19] while the SD was estimated using the method of Wan et al. [20].

Results

Characteristics of eligible studies and risk of bias

The meta-analysis ultimately included 10 RCTs (Figure 1) with a total of 706 patients, of which 9 studies [10,21,22,24–29] used bupivacaine and 1 study [23] used lidocaine for spinal anesthesia. In these studies, 6 compared DEX with saline, and the remaining 4 studies compared DEX with tramadol and saline,

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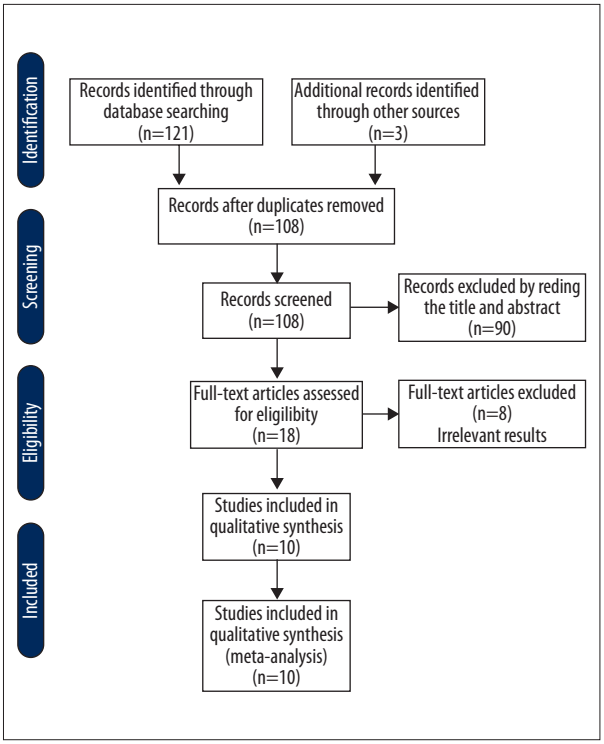

Figure 1. Flow chart for articles selection.

clonidine with DEX and saline and fentanyl, DEX with morphine and saline, and DEX with saline and fentanyl, respectively. The main objective of this meta-analysis was to assess the effect of intrathecal DEX on neonates during cesarean section, so only DEX versus placebo (saline) was compared, and we ignored the data on clonidine, tramadol, fentanyl, and morphine. However, 5 [21,23–24,27,28] of these studies were not registered prospectively.

The 2 reviewers were completely consistent in the assessment results on the potential risk bias of included studies, which showed that 3 of the included studies were low risk and the remaining 7 were some concerns, as shown in Figure 2.

Neonatal outcomes

Seven RCTs [10,21,22,24,26–28] reported Apgar scores of newborns at 1 and 5 min, 3 RCTs [10,24,27] reported umbilical carbon dioxide partial pressure and oxygen partial pressure, and 4 RCTs [10,24,27,29] reported pH values of cord blood. These indicators – the 1-min Apgar score (MD, 0.14; 95% CI, –0.19 to 0.47; P=0.4; I^2=93%), the 5-min Apgar score (MD, 0.00; 95% CI, –0.06 to 0.06; P=1; I^2=0), the umbilical arterial oxygen partial pressure (MD, 0.09; 95% CI, –2.46 to 2.64; P=0.95; I^2=0) and umbilical carbon dioxide partial pressure (MD, 0.85; 95% CI, –1.56 to 3.26; P=0.49; I^2=0), and the cord blood pH values (MD, –0.00; 95% CI, –0.04 to 0.04; P=0.96; I^2=63%) – showed there was no significant difference in neonatal outcome between the 2 groups (Figure 3).

There was a significant heterogeneity in the indicator of neonatal 1-min Apgar score (I^2=93%; P<0.001). We observed that 1 [21] of the 7 studies had significantly lower Apgar scores than the others. After removal of the study, the heterogeneity of this indicator was significantly reduced among other studies (I^2=0; P=0.56) using a fixed-effects model for pooling, and the results showed that the difference was still not statistically significant (MD, 0.02; 95% CI, –0.09 to 0.12; P=0.77; I^2=0, Figure 4A). Removal of the study also showed that there was no statistically significant difference in neonatal Apgar score at 1 min between intrathecal DEX and placebo groups.

Study	Randomization	Interventions	Missing outcom data	Outcome measueement	Reported results	Overall
Bi et al 2017	+	?	?	+	+	?
Fawzy et al 2016	+	+	+	+	+	+
He et al 2017	?	+	?	+	+	?
Kamali et al 2018	?	+	?	+	+	?
Li et al 2015	?	+	+	+	+	?
Nasseri et al 2017	?	+	+	+	+	?
Qi et al 2016	+	+	+	+	+	+
Sun et al 2015	+	+	?	+	+	?
Teymourian et al 2018	?	?	+	+	+	?
Xia et al 2018	+	+	+	+	+	+

Figure 2. Risk-of-bias graph of the included studies. + low risk; ? some concerns; + high risk.

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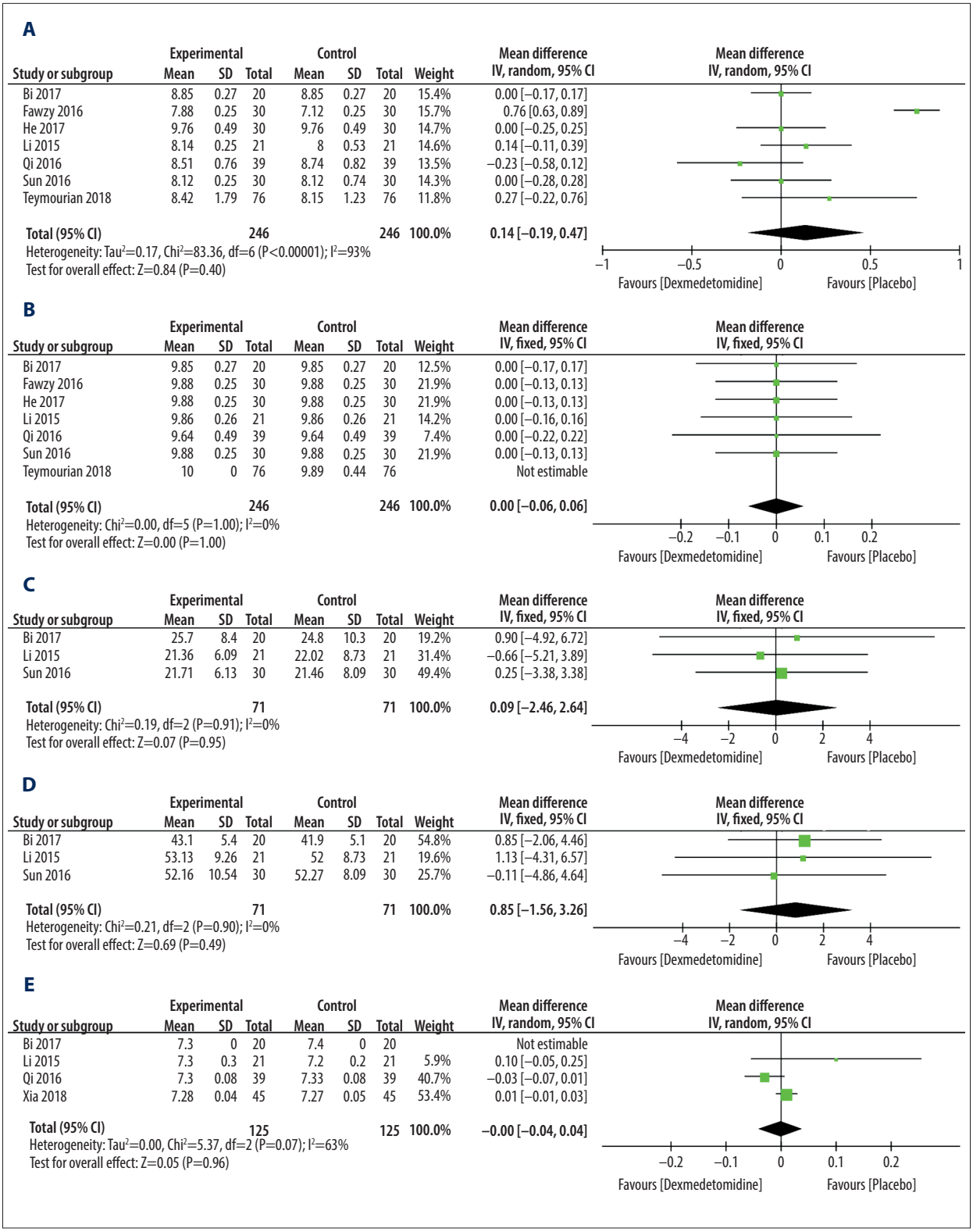

Figure 3. Forest plot for neonatal outcomes. (**A**) Apgar score at 1 min; (**B**) Apgar score at 5 min; (**C**) Cord blood oxygen partial pressure data; (**D**) Cord blood carbon dioxide partial pressure data; (**E**) Data on pH.

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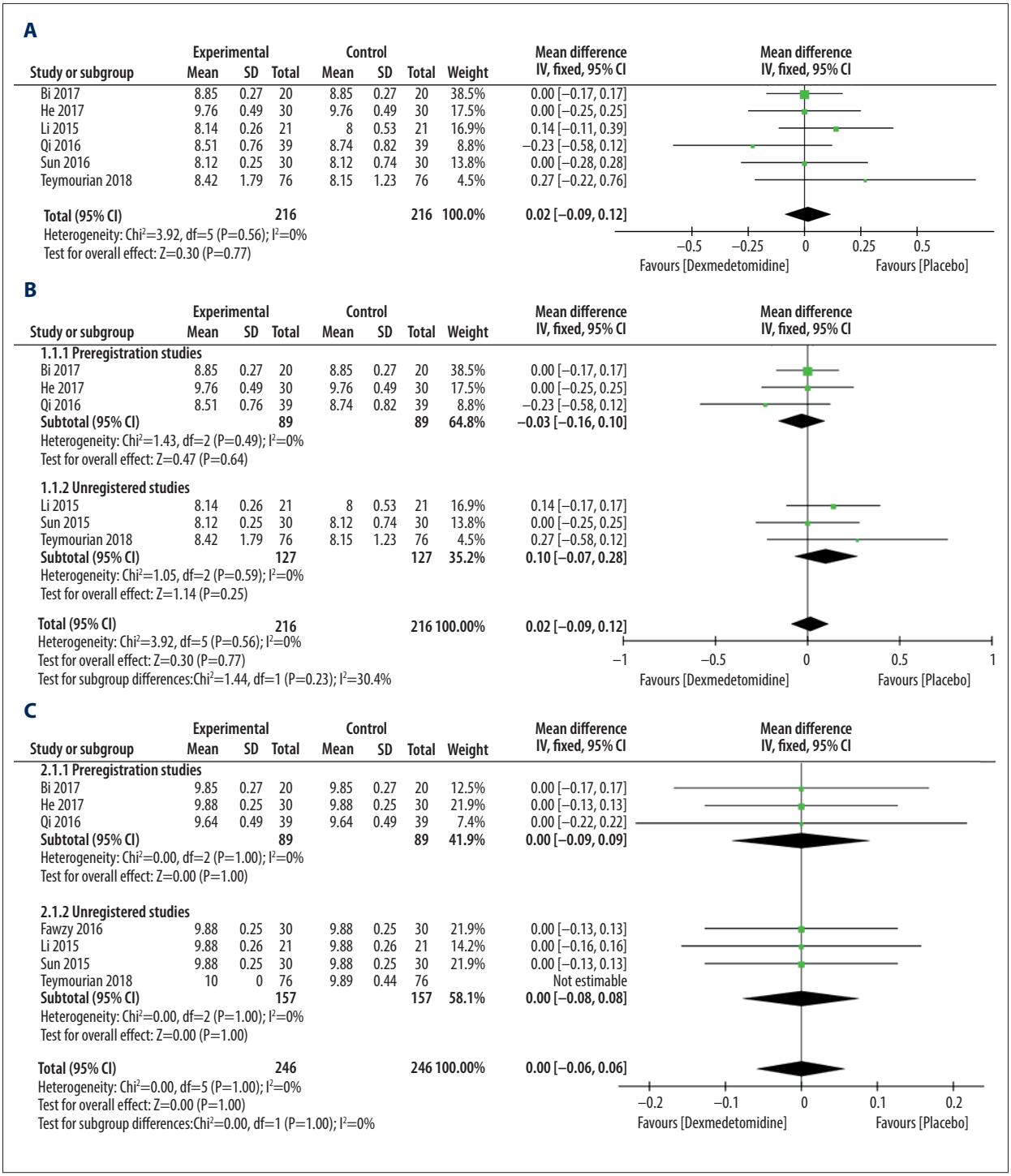
Subgroup analysis: 5 [10,22,25,26,29] of the included 10 RCTs were prospectively registered. We performed a subgroup analysis of the neonatal outcomes based on whether the included studies were registered prospectively. The results of studies with prospective registration, including 1- or 5-min Apgar score (MD, –0.03; 95% CI, –0.16 to 0.10; *P*=0.64 or MD, 0.00; 95% CI, –0.09 to 0.09; *P*=1), umbilical arterial oxygen or carbon dioxide partial pressure (MD, 0.90; 95% CI, –4.92 to 6.72; *P*=0.76 or MD, 1.20; 95% CI, –2.06 to 4.46; *P*=0.47), and cord blood PH values (MD, –0.01; 95% CI, –0.05 to 0.03; *P*=0.72), were consistent with unregistered studies, which showed intrathecal DEX had no significant effect on the short-term neonatal outcomes compared with placebo (Figure 4B–4F). The 1-min Apgar score of one study [21] was significantly lower



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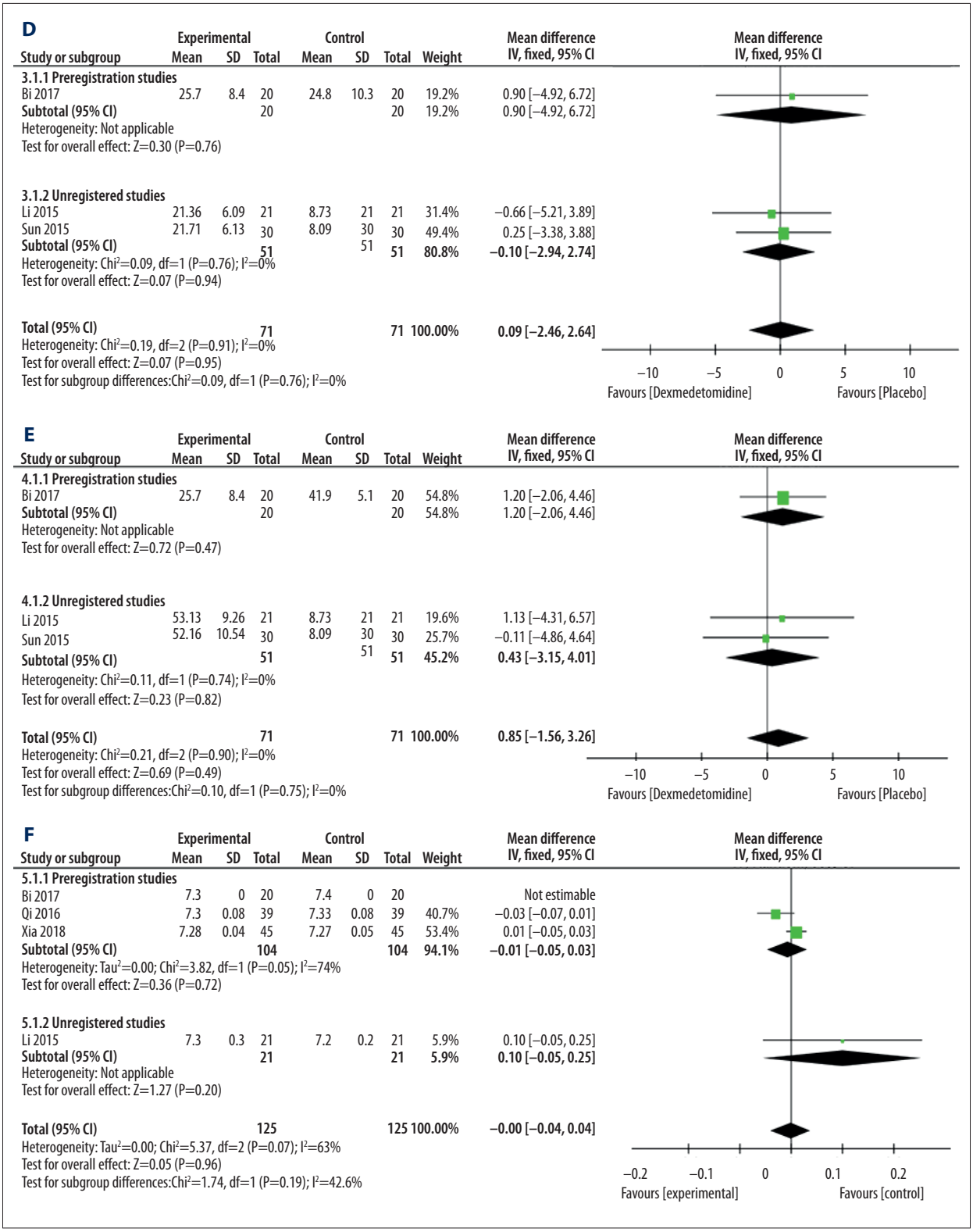

Figure 4. Forest plot for sensitivity analysis and subgroup analysis of neonatal outcomes. (**A**) The sensitivity analysis of Apgar score at 1 min; (**B**) The subgroup analysis of Apgar score at 1 min; (**C**) The subgroup analysis of Apgar score at 5 min; (**D**) The subgroup analysis of umbilical oxygen partial pressure; (**E**) The subgroup analysis of umbilical dioxide partial pressure; (**F**) The subgroup analysis of umbilical blood PH.

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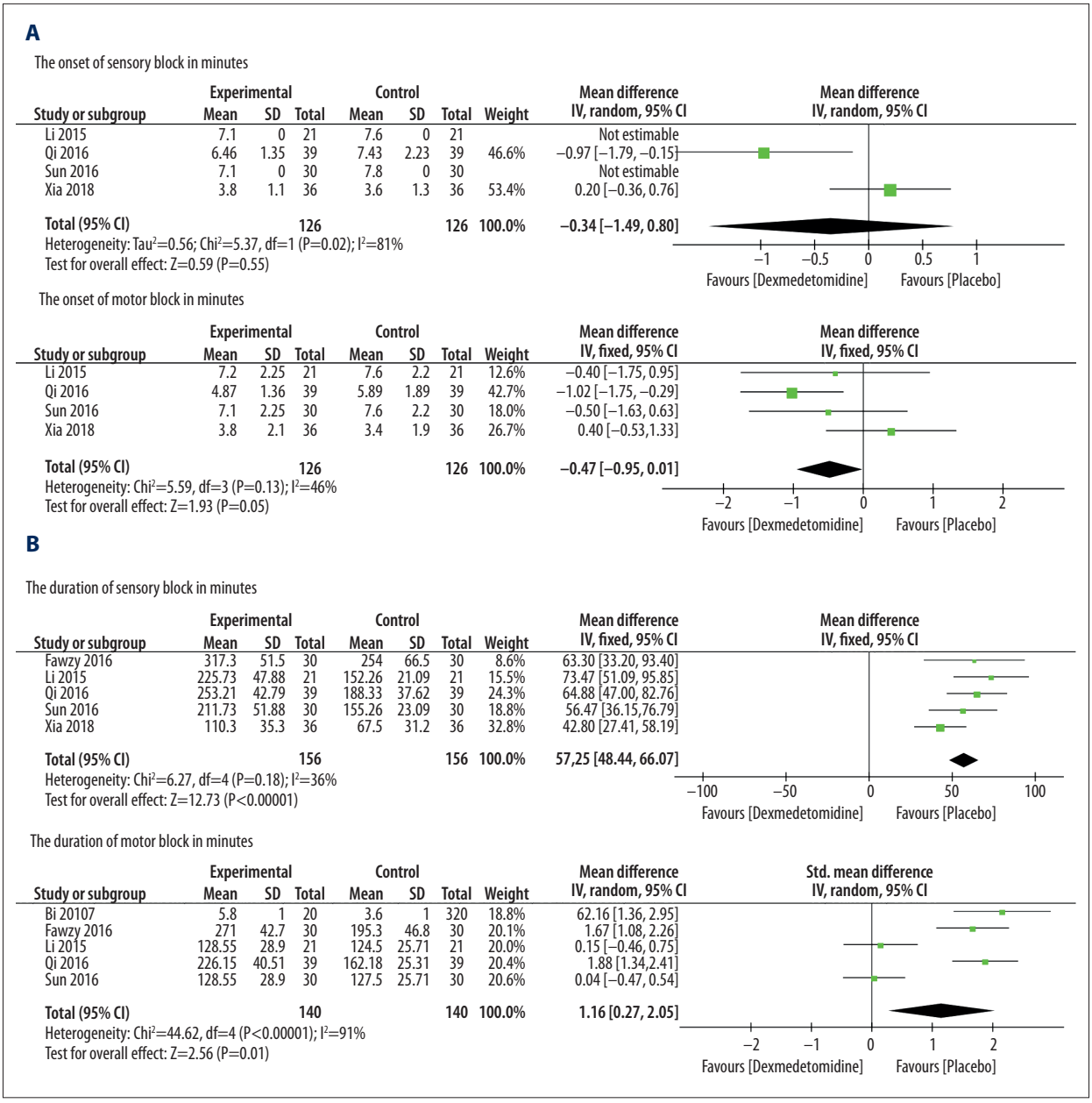

Figure 5. (**A**) Forest plot comparing the onset of sensory and motor block between DEX and placebo groups; (**B**) Forest plot comparing the duration of sensory and motor block between DEX and placebo groups.

than others, and it was excluded from the subgroup analysis of Apgar score at 1 min because it caused greater heterogeneity in the pooled results (Figure 4B).

Pregnant woman outcomes

The block onset and duration

Four studies [24,26,27,29] compared the effect of DEX as the intrathecal local anesthetics adjuvant on the onset of blockade, and 6 studies [10,19,21,24,26,27] reported the duration of blockade. As part of spinal anesthesia, intrathecal DEX accelerates the onset of motor block (MD, –0.47; 95% CI, –0.95 to 0.01; *P*=0.05; I^2=46%), while it has no obvious improvement effect on the onset of sensory block (MD, –0.34; 95% CI, –1.49 to 0.80; *P*=0.55; I^2=81%, Figure 5A), and DEX can significantly prolong the blockade time, as shown in Figure 5B, whether it is sensory block (MD, 57.25; 95% CI, 48.44 to 66.07; *P*<0.001, I^2=36%) or motor block (SMD, 1.16; 95% CI, 0.27 to 2.05; *P*=0.01; I^2=91%).

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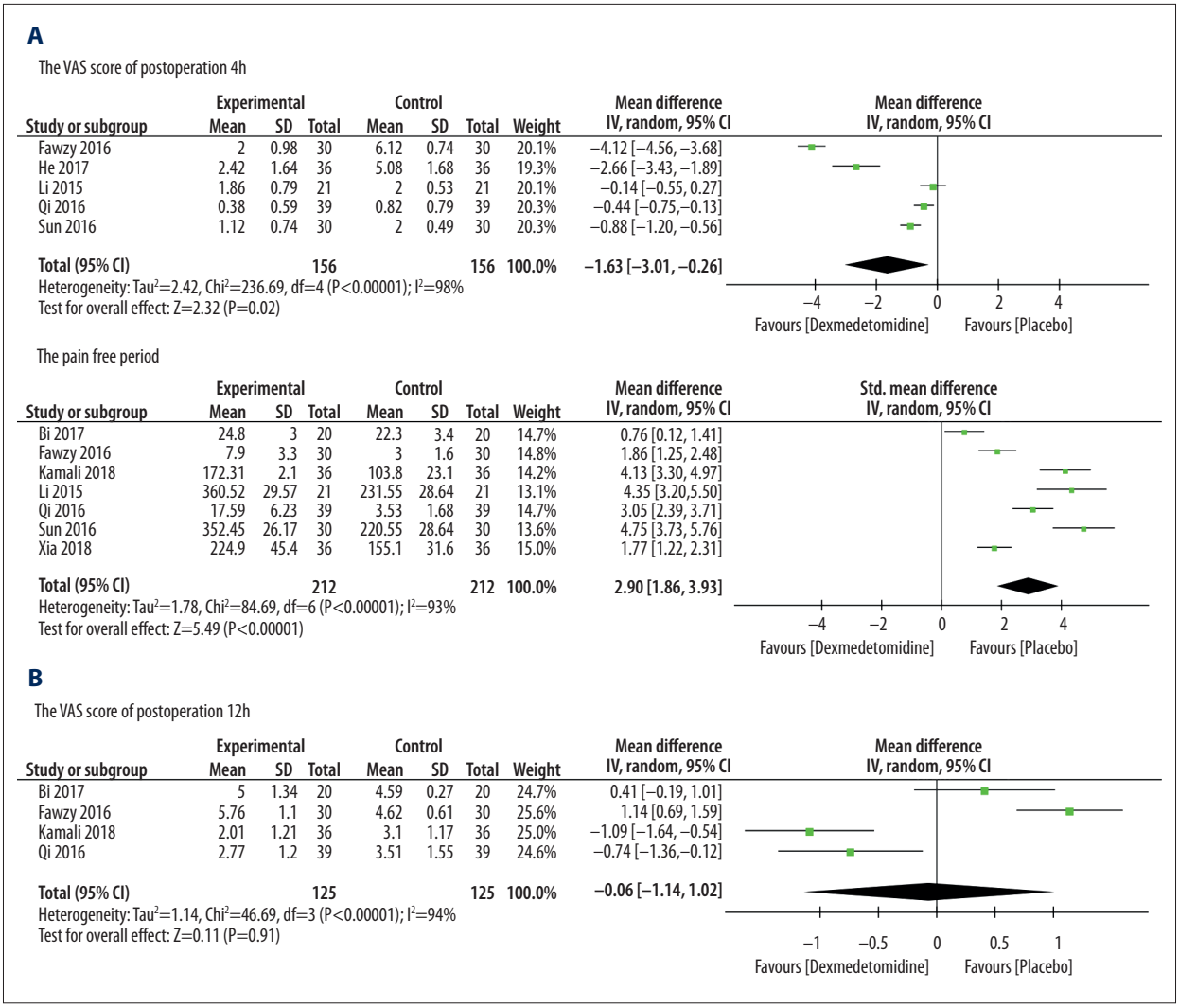

Figure 6. (**A**) Forest plot for the VAS score of postoperation 4 h and the pain-free period; (**B**) Forest plot for the VAS score of postoperation 12 h.

DEX improved the analgesic effect

Under spinal anesthesia, DEX as a local anesthetics adjuvant significantly reduced the analgesia score 4 hours after cesarean section (MD, –1.63; 95% CI, –3.01 to –0.26; *P*=0.02, I^2=98%) and significantly prolonged postoperative analgesia (SMD, 2.90; 95% CI, 1.86 to 3.93; *P*<0.001, I^2=93%), as shown in Figure 6A. However, the effect of intrathecal DEX on improving maternal analgesia was limited. We found no significant difference between the 2 groups in VAS scores at 12 h after cesarean section (MD, –0.06; 95% CI, –1.14 to 1.02; *P*=0.91; I^2=94%, Figure 6B). The heterogeneity among the pooled studies was very significant, which may be related to differences in ethnicity, indicator units, local anesthetic types, and the definition of pain-free period in different studies. Although we performed subgroup analysis and sensitivity analysis based on local anesthetic types, indicator units, prospective registration, and ethnicity, it did not significantly reduce the heterogeneity among studies, and the results of subgroup analysis and sensitivity analysis were consistent with previous results.

Effect of DEX on maternal postoperative shivering

There were 8 studies [10,21–23,25–27,29] reporting the incidence of postoperative shivering. Our meta-analysis showed that the incidence of maternal postoperative shivering was significantly reduced by intrathecal DEX relative to placebo (RR, 0.45; 95% CI, 0.32 to 0.63; *P*<0.001; I^2=37%, Figure 7A).

The adverse effects

Data from 7 studies [21,22,24–27,29] found that intrathecal DEX did not increase the risk of maternal hypotension (RR, 0.88; 95% CI, 0.71 to 1.08; *P*=0.22; I^2=22%) and bradycardia

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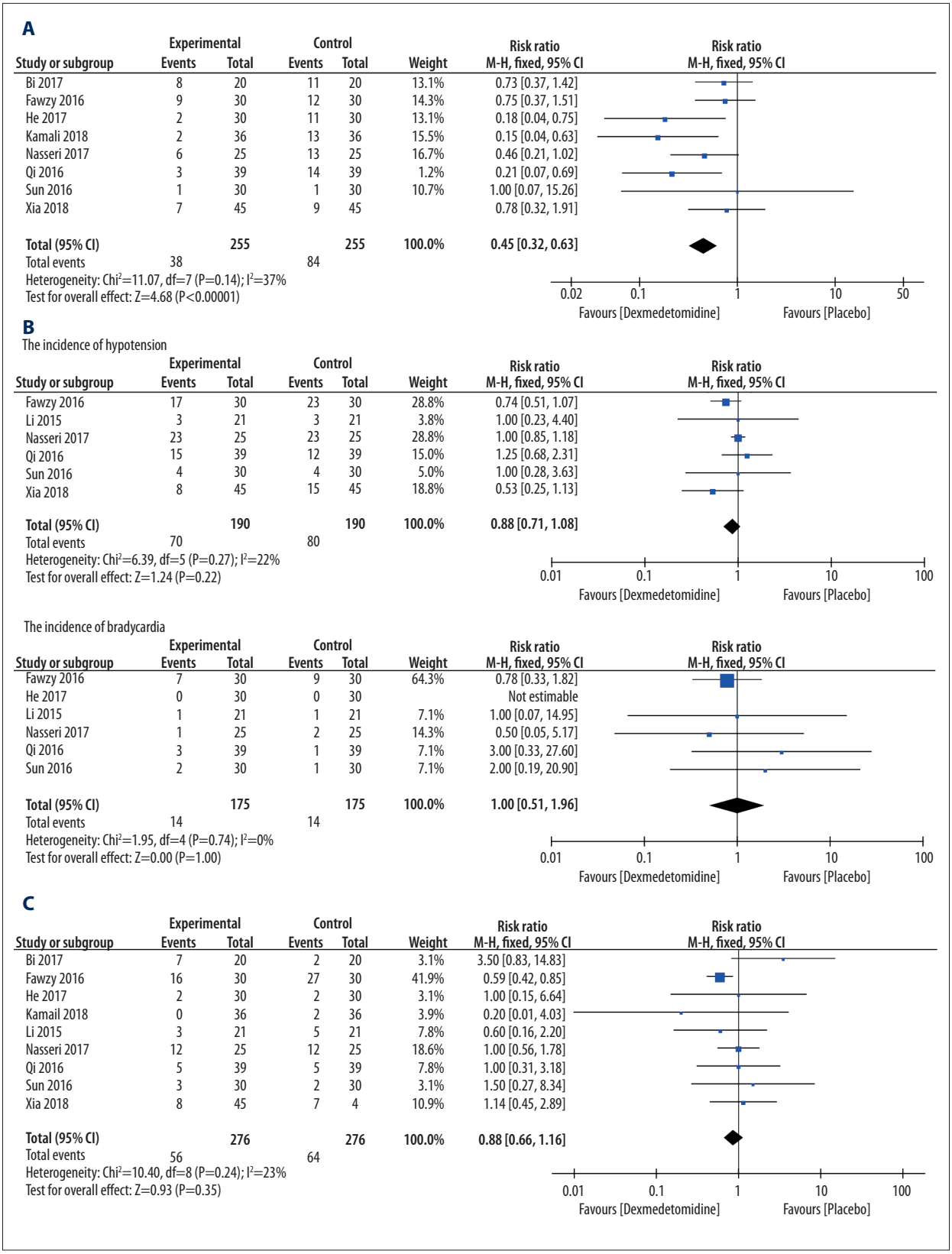

Figure 7. (**A**) Forest plot for postoperative shivering; (**B**) Forest plot for hypotension and bradycardia; (**C**) Forest plot for other adverse effects.

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(RR, 1.00; 95% CI, 0.51 to 1.96; P=1.00; I^2=0) compared with placebo (Figure 7B). In addition to hypotension and bradycardia, we also observed other spinal anesthesia-related complications, such as itching, nausea, and vomiting. The results also showed that intrathecal application of DEX did not increase other maternal adverse events associated with spinal anesthesia (RR, 0.88; 95% CI, 0.66 to 1.16; P=0.35; I^2=23%), as shown in Figure 7C.

Publication bias

We used Stata software to assess the publication bias of the main results. The P values of Begg's test on the 1-min Apgar score, 5-min Apgar score, and umbilical blood PH were 0.176, 1, and 1, respectively. Therefore, we believe that the risk of publication bias is low in this meta-analysis.

Discussion

In clinical practice, spinal anesthesia is a good anesthesia program for cesarean section, which can avoid the adverse reactions in the fetus, such as potential respiratory depression caused by general anesthesia drugs through the placenta, while reducing the amount of local anesthetics to reduce the potential risk of local anesthetics poisoning and significantly shortening the onset time of anesthesia compared with epidural anesthesia. However, single spinal anesthesia often has limited time for postoperative analgesia. Increasing the amount of local anesthetic drugs to prolong the analgesic time can cause serious inhibition of circulation and adverse effects such as central nervous system problems and cardiotoxicity [30]. Therefore, the addition of appropriate adjuvants to local anesthetics during spinal anesthesia with the synergistic analgesic effect of adjuvants to prolong postoperative analgesia while avoiding the use of large doses of local anesthetics has gradually become a new choice for anesthesiologists [12].

Several studies have confirmed that DEX is a more promising local anesthetics adjuvant than other drugs (e.g., fentanyl, morphine, and clonidine) for intrathecal application, and can better improve the blockade quality of spinal anesthesia, prolong the pain-free period of patients, and no cause significant adverse effects [12,26,31–33]. However, as DEX is applied intrathecally during cesarean section, we are most worried about whether DEX affects the fetus, such as neonatal respiratory depression, lower Apgar score, and acidosis, because if the neonatal 5-min Apgar score is <7 or pH is <7.20, the newborn needs to stay in the neonatal intensive care unit (NICU) for treatment, or even requires establishing an artificial airway, which will undoubtedly lead to an increase in neonatal mortality [5,34,35]. DEX was first approved as a sedative for use in the ICU. Therefore, a comprehensive and effective evaluation of whether intrathecal DEX has an effect on the fetus is important during cesarean section, although it had been previously reported that, due to the fat-soluble characteristics of DEX, it is not easily transferred through the placenta [36,37].

Our meta-analysis based on 10 RCTs indicates that intrathecal use of DEX as the local anesthetics adjuvant did not increase neonatal adverse reactions during cesarean section. Compared with the placebo, there were no significant differences in neonatal 1- and 5-min Apgar scores or cord blood gas parameters. In addition, 1 [10] of the studies also reported no statistically significant differences in umbilical glucose and lactate of newborns between the 2 groups. Since only 1 study reported the parameter, this meta-analysis did not incorporate this indicator. Our results demonstrate the safety of intrathecal use of DEX in cesarean section. In addition, we found that intrathecal application of DEX can significantly increase maternal sensory and motor block time, and the incidence of postoperative shivering was significantly reduced, which was mainly due to DEX inhibiting central thermoregulation and attenuating the stress response in the perioperative period [38], and it did not increase the incidence of adverse reactions such as maternal bradycardia and hypotension. More importantly, the use of intrathecal DEX for spinal anesthesia can significantly prolong the analgesic time and improve the analgesic effect after cesarean section. This is mainly related to inhibition of C-fiber transmitter and substance P release, as well as α_2 receptor agonist-related post-synaptic horn neuron hyperpolarization and upregulation of adrenergic receptor subtypes in the dorsal root ganglia [39,40]. However, unlike a previous meta-analysis [5], there was no obvious improvement effect on the onset of sensory block of spinal anesthesia.

Our meta-analysis has some limitations. First, although we tried to find all the studies that met the inclusion criteria, it is still possible that some relevant studies were omitted. Second, some indicators related to puerpera have significant heterogeneity affecting the stability of the results, and this may be related to the small sample size of the included studies, the difference in local anesthetics (bupivacaine, lidocaine), different drug doses, and different ethnicity. Third, our results were based on intrathecal application of low-dose DEX (≤25 ug), and it is unknown whether a larger dose of DEX will affect the fetus. Fourth, the included studies in this meta-analysis were mainly from China and Iran, and 1 was from Egypt, which resulted in geographical limitations of this study. In addition, 5 of the included studies [21,23,24,27,28] lacked prospective registration. Finally, we only focused on the short-term effects, so whether intrathecal DEX during cesarean section has a long-term effect on the fetus is not clear. These shortcomings need to be addressed in future research.

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Conclusions

Intrathecal DEX appears to be safe for the fetus during cesarean section, and can significantly prolong postoperative analgesia and reduce the incidence of postoperative shivering of puerperae. However, the adjuvants are not necessary during spinal anesthesia and the adjuvant itself may cause unnecessary adverse reactions (e.g., intrathecal application of opioids often causes itching, and DEX can induce bradycardia). In addition, the most worrying adverse reaction from intrathecal DEX during spinal anesthesia is its neurotoxicity, although some animal studies have confirmed that a very large dose of DEX is required to cause demyelination of the white matter [41], and there have been no reports of DEX neurotoxicity in clinical practice. However, the possibility of long-term neurotoxicity still needs to be assessed.

References:

1. Karlström A: Women's self-reported experience of unplanned caesarean section: Results of a Swedish study. Midwifery, 2017; 50: 253–58
2. Practice Guidelines for Obstetric Anesthesia: An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for Obstetric Anesthesia and Perinatology. Anesthesiology, 2016; 124: 270–300
3. Campbell JP, Stocks GM: Management of hypotension with vasopressors at caesarean section under spinal anaesthesia-have we found the Holy Grail of obstetric anaesthesia? Anaesthesia, 2018; 73: 3–6
4. Butwick AJ, Blumenfeld YJ, Brookfield KF et al: Racial and ethnic disparities in mode of anesthesia for cesarean delivery. Anesth Analg, 2016; 122: 472–79
5. Zhang J, Zhou H, Sheng K et al: Foetal responses to dexmedetomidine in parturients undergoing caesarean section: A systematic review and meta-analysis. J Int Med Res, 2017; 45: 1613–25
6. James FM, Crawford JS, Hopkinson R et al: A comparison of general anesthesia and lumbar epidural analgesia for elective cesarean section. Anesth Analg, 1977; 56: 228–35
7. Chen Y, Liu W, Gong X, Cheng Q: Comparison of effects of general anesthesia and combined spinal/epidural anesthesia for cesarean delivery on umbilical cord blood gas values: A double-blind, randomized, controlled study. Med Sci Monit, 2019; 25: 5272–79
8. Bremerich DH, Fetsch N, Zwissler BC et al: Comparison of intrathecal bupivacaine and levobupivacaine combined with opioids for caesarean section. Curr Med Res Opin, 2007; 23: 3047–54
9. Reynolds F, Seed PT: Anaesthesia for caesarean section and neonatal acid-base status: A meta-analysis. Anaesthesia, 2005; 60: 636–53
10. Bi YH, Cui XG, Zhang RQ et al: Low dose of dexmedetomidine as an adjuvant to bupivacaine in cesarean surgery provides better intraoperative somato-visceral sensory block characteristics and postoperative analgesia. Oncotarget, 2017; 8: 63587–95
11. Swain A, Nag DS, Sahu S, Samaddar DP: Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases, 2017; 5: 307–23
12. Sun S, Wang J, Bao N et al: Comparison of dexmedetomidine and fentanyl as local anesthetic adjuvants in spinal anesthesia: A systematic review and meta-analysis of randomized controlled trials. Drug Des Devel Ther, 2017; 11: 3413–24
13. Conti G, Ranieri VM, Costa R et al: Effects of dexmedetomidine and propofol on patient-ventilator interaction in difficult-to-wean, mechanically ventilated patients: A prospective, open-label, randomised, multicentre study. Crit Care, 2016; 20: 206
14. Bao Z, Zhou C, Wang X, Zhu Y: Intravenous dexmedetomidine during spinal anaesthesia for caesarean section: A meta-analysis of randomized trials. J Int Med Res, 2017; 45: 924–32
15. Yu M, Han C, Jiang X et al: Effect and placental transfer of dexmedetomidine during caesarean section under general anaesthesia. Basic Clin Pharmacol Toxicol, 2015; 117: 204–8
16. Liu L, Qian J, Shen B et al: Intrathecal dexmedetomidine can decrease the 95% effective dose of bupivacaine in spinal anesthesia for cesarean section: A prospective, double-blinded, randomized study. Medicine (Baltimore), 2019; 98: e14666
17. Moher D: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med, 2009; 6: e1000097
18. Higgins JPT, Sterne JAC, Savovic J et al: A revised tool for assessing risk of bias in randomized trials. Cochrane Db Syst Rev, 2016; 10: 29–31
19. Luo D, Wan X, Liu J, Tong T: Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res, 2018; 27: 1785–805
20. Wan X, Wang W, Liu J, Tong T: Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol, 2014; 14: 135
21. Fawzy M, Elzaiat N, Refaie A, Bakr H: Dexmedetomidine added to bupivacaine versus bupivacaine alone in spinal anesthesia for cesarean section. Cairo Univ, 2016; 84: 831–41
22. He L, Xu JM, Liu SM et al: Intrathecal dexmedetomidine alleviates shivering during cesarean delivery under spinal anesthesia. Biol Pharm Bull, 2017; 40: 169–73
23. Kamali A, Shokrpour M, Radmehr A, Pazuki S: Comparing the effect of adding dexmedetomidine and tramadol to lidocaine 5% in elongating the period of post operative analgesia in spinal anesthesia. Biomed Res, 2018; 29: 454–59
24. Li Z, Tian M, Zhang CY et al: A randomised controlled trial to evaluate the effectiveness of intrathecal bupivacaine combined with different adjuvants (fentanyl, clonidine and dexmedetomidine) in caesarean section. Drug Res (Stuttg), 2015; 65: 581–86
25. Nasseri K, Ghadami N, Nouri B: Effects of intrathecal dexmedetomidine on shivering after spinal anesthesia for cesarean section: A double-blind randomized clinical trial. Drug Des Devel Ther, 2017; 11: 1107–13
26. Qi X, Chen D, Li G et al: Comparison of intrathecal dexmedetomidine with morphine as adjuvants in cesarean sections. Biol Pharm Bull, 2016; 39: 1455–60
27. Sun Y, Xu Y, Wang GN: Comparative evaluation of intrathecal bupivacaine alone, bupivacaine-fentanyl, and bupivacaine-dexmedetomidine in caesarean section. Drug Res (Stuttg), 2015; 65: 468–72
28. Teymourian H, Khorasanizadeh S, Ansar P et al: Comparison of the effect of bupivacaine in combination with dexmedetomidine with bupivacaine plus placebo on neonatal apgar score, bispectral index, and sedation level of parturient women. Anesth Pain Med, 2018; 8: e81947
29. Xia F, Chang X, Zhang Y et al: The effect of intrathecal dexmedetomidine on the dose requirement of hyperbaric bupivacaine in spinal anaesthesia for caesarean section: A prospective, double-blinded, randomized study. BMC Anesthesiol, 2018; 18: 74
30. Marri SR: Adjuvant agents in regional anaesthesia. Anaesthesia and Intensive Care Medicine, 2012; 13: 559–62
31. Qi X, Li Y, Rahe-Meyer N et al: Intrathecal dexmedetomidine as adjuvant to ropivacaine in hysteroscopic surgery: A prospective, randomized control study. Int J Clin Pharmacol Ther, 2016; 54: 185–92
32. Mahendru V, Tewari A, Katyal S et al: A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind controlled study. J Anaesthesiol Clin Pharmacol, 2013; 29: 496–502
33. Suresh G, Prasad CG: A comparative study of intrathecal 0.5% hyperbaric bupivacaine with dexmedetomidine and 0.5% hyperbaric bupivacaine with fentanyl for lower abdominal surgeries. Sri Lankan Journal of Anaesthesiology, 2016; 24: 22–27
34. Victory R, Penava D, Da Silva O et al: Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. Am J Obstet Gynecol, 2004; 191: 2021–28
35. Malin GL, Morris RK, Khan KS: Strength of association between umbilical cord pH and perinatal and long term outcomes: Systematic review and meta-analysis. BMJ, 2010; 340: c1471

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36. Neumann MM, Davio MB, Macknet MR, Applegate RL 2nd: Dexmedetomidine for awake fiberoptic intubation in a parturient with spinal muscular atrophy type III for cesarean delivery. Int J Obstet Anesth, 2009; 18: 403–7
37. Palanisamy A, Klickovich RJ, Ramsay M et al: Intravenous dexmedetomidine as an adjunct for labor analgesia and cesarean delivery anesthesia in a parturient with a tethered spinal cord. Int J Obstet Anesth, 2009; 18: 258–61
38. Talke P, Tayefeh F, Sessler DI et al: Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. Anesthesiology, 1997; 87: 835–41
39. Kim JE, Kim NY, Lee HS, Kil HK: Effects of intrathecal dexmedetomidine on low-dose bupivacaine spinal anesthesia in elderly patients undergoing transurethral prostatectomy. Biol Pharm Bull, 2013; 36: 959–65
40. Tamagaki S, Suzuki T, Hagihira S et al: Systemic daily morphine enhances the analgesic effect of intrathecal dexmedetomidine via up-regulation of alpha 2 adrenergic receptor subtypes A, B and C in dorsal root ganglion and dorsal horn. J Pharm Pharmacol, 2010; 62: 1760–67
41. Konakci S, Adanir T, Yilmaz G, Rezanko T: The efficacy and neurotoxicity of dexmedetomidine administered via the epidural route. Eur J Anaesthesiol, 2008; 25: 403–9

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