e-ISSN 1643-3750 © Med Sci Monit. 2020: 26: e918523 DOI: 10.12659/MSM.918523

**META-ANALYSIS** 



Received: 2019.07.05 Accepted: 2019.10.17 Published: 2020.01.29

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

Autho D Stati Data anuscri Lite Fui	rs' Contribution: Study Design A lata Collection B stical Analysis C Interpretation D pt Preparation E erature Search F nds Collection G	ADE 1 BC 2 B 1 C 1 AB 1 A 1	ShuJun Sun JiaMei Wang JingXu Wang FuQuan Wang HaiFa Xia ShangLong Yao	<ol> <li>Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China</li> <li>College of Life and Health Sciences, Northeastern University, Shenyang, Liaoning, P.R. China</li> </ol>							
	Corresponding Source o	g Authors: f support:	HaiFa Xia, e-mail: haifaxia@163.com, ShangLong Yao, e-mail: y Departmental sources	/sltian@163.com							
Background: Material/Methods: Results: Conclusions:			Intrathecal dexmedetomidine (DEX) can improve the clusion on whether it has an effect on the fetus during ty and efficacy of intrathecal DEX in cesarean deliver. We searched Cochrane, Embase, PubMed, and CBM for Bias Tool (RoB 2.0) to assess the risk of bias of each seregistered this meta-analysis on PROSPERO (CRD420) The meta-analysis included 10 RCTs, but only 5 were studies, including the 1- or 5-min Apgar score (mea –0.16 to 0.10; $P$ =0.64 or MD, 0.00; 95% Cl, –0.09 to ide partial pressure (MD, 0.90; 95% Cl, –4.92 to 6.72; the cord blood pH (MD, –0.01; 95% Cl, –0.05 to 0.03; difference in neonatal outcomes compared with place prolonged postoperative pain-free period and reduce increase spinal anesthesia-associated adverse effects	blockade of spinal anesthesia, but there is no clear con- g cesarean section. Our meta-analysis evaluated the safe- y. or eligible studies, and used the Revised Cochrane Risk of study. RevMan was used for statistical analyses. We have 19120995). e prospectively registered. The results of preregistration n difference [MD], $-0.03$ ; 95% confidence intervals [CI], 0.09; $P=1$ ), the umbilical arterial oxygen or carbon diox- P=0.76 or MD, 1.20; 95% CI, $-2.06$ to 4.46; $P=0.47$ ), and P=0.72), showed that intrathecal DEX had no significant tebo. In maternal outcomes, intrathecal DEX significantly d the incidence of postoperative shivering, which did not							
			Intrathecal DEX is safe for the fetus during cesarean section and can improve the blockade effects of spinal an- esthesia on puerperae.								
	MeSH Ke	ywords:	Adjuvants, Anesthesia • Anesthesia, Spinal • Dexmedetomidine • Fetus • Meta-Analysis • Randomized Controlled Trial								
	Full-1	text PDF:	https://www.medscimonit.com/abstract/index/idArt	/918523							
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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

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

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

\* 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% Cl). 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% Cl; otherwise, the standardized mean difference (SMD) with 95% Cl 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 ( $l^2$ >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,



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;  $l^2$ =93%), the 5-min Apgar score (MD, 0.00; 95% CI, –0.06 to 0.06; P=1;  $l^2$ =0), the umbilical arterial oxygen partial pressure (MD, 0.09; 95% CI, –2.46 to 2.64; P=0.95;  $l^2$ =0) and umbilical carbon dioxide partial pressure (MD, 0.85; 95% CI, –1.56 to 3.26; P=0.49;  $l^2$ =0), and the cord blood pH values (MD, –0.00; 95% CI, –0.04 to 0.04; P=0.96;  $l^2$ =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 ( $l^2$ =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 ( $l^2$ =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;  $l^2$ =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	Ð			Ð	Ð	?
Fawzy et al 2016	Ð	Ð	Ð	<b>•</b>	Ð	Ð
He et al 2017	?	Ð	?	Ð	Ð	?
Kamali et al 2018	?	Ð	?	<b>•</b>	Ð	?
Li et al 2015	?	Ð	•	Ð	Ð	?
Nasseri et al 2017	?	Ð	Ð	Đ	•	?
Qi et al 2016	Ð	Ð	Ð	Ð	Ð	Ð
Sun et al 2015	Ð	Ð	?	Ð	Ð	?
Teymourian et al 2018	?	?	Ð	Ð	Ð	?
Xia et al 2018	Đ	Ð	Ð	Đ	Ð	Ð



Study or subgroup         Experimental Mean         Stol Stol Stal         Control Mean         Stol Stol Stol Stal         Control Mean         Mean difference N, random, 95% Cl         Mean difference N, random, 95% Cl         Mean difference N, random, 95% Cl           B2017         8.85         0.27         20         15.4%         0.001(-0.17, 0.01)
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% CI         IV, random, 95% CI           Bi 2017         8.85         0.27         20         8.85         0.27         20         15.4%         0.00 [-0.17, 0.17]         0.00 [-0.17, 0.17]           Favry 2016         8.15         0.25         30         9.76         0.49         30         14.7%         0.00 [-0.25, 0.25]           Guido 16         8.12         2.07         8.8         0.82         21         14.6%         0.00 [-0.25, 0.25]         0.01 [-0.25, 0.25]           Sun 2016         8.12         0.27         11.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.20]         14.4%         0.001 [-0.26, 0.26]         14.4%         0.001 [-0.26, 0.26]         14.4%         0.001 [-0.20, 0.20]         14.4%         0.000 [-0.13, 0.13]         14.4%         0.
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-1       -0.5       0       0.5         Fast for overall effect: Z=0.84 (P=0.40)         Image: Study or subgroup       Mean SD Total       Mean difference       Notal difference       Notal difference       Notal difference       Nean diff
B         Experimental         Control         Mean         SD         Total         Weight         IV, fixed, 95% Cl         IV, fixed, 95% Cl         IV, fixed, 95% Cl           Bi 2017         9.85         0.27         20         9.85         0.27         20         12.5%         0.00 [0.17, 0.17]           Fawry 2016         9.88         0.25         30         21.9%         0.00 [0.17, 0.17]           Fawry 2016         9.88         0.25         30         21.9%         0.00 [0.17, 0.17]           Favours [Placebr         9.86         0.26         21         14.2%         0.00 [0.17, 0.17]           Gi 2016         9.46         0.49         39         9.64         0.49         39         7.4%         0.00 [0.13, 0.13]           Ui 2016         9.46         0.49         39         9.44         76         Not estimable           Total (95% Cl)         246         246         100.0%         0.00 [-0.13, 0.13]         -0.2         -0.1         0         1         0.2           Test for overall effect: Z=0.00 (P=1.00); P=0%         Z46         100.3         20         19.2%         0.09 (-4.92, 6.72]         -0.2         -0.1         0.2         Favours [Placebr           Sun 2016
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Experimental         Control         Mean difference IV, fixed, 95% CI         Mean difference IV, fixed, 95% CI         Mean difference IV, fixed, 95% CI           Bi 2017         25.7         8.4         20         24.8         10.3         20         19.2%         0.90 [-4.92, 6.72]         IV, fixed, 95% CI         IV, fixed, 95% CI           Bi 2017         25.7         8.4         20         24.8         10.3         20         19.2%         0.90 [-4.92, 6.72]         IV, fixed, 95% CI
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, fixed, 95% Cl         IV, fixed, 95% Cl           Bi 2017         25.7         8.4         20         24.8         10.3         20         19.2%         0.90 [-4.92, 6.72]         IV, fixed, 95% Cl
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D         Experimental         Control         Mean difference         Mean difference         Mean difference           Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, fixed, 95% Cl         IV, fixed, 95% Cl         IV, fixed, 95% Cl         IV           Bi 2017         43.1         5.4         20         41.9         5.1         20         54.8%         0.85 [-2.06, 4.46]         IV
Experimental         Control         Mean difference         Mean difference           Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, fixed, 95% CI         IV, fixed, 95% CI           Bi 2017         43.1         5.4         20         41.9         5.1         20         54.8%         0.85 [-2.06, 4.46]         IV           Li 2015         53.13         9.26         21         52         8.73         21         19.6%         1.13 [-4.31.6.57]         Image: Control of the second seco
Study or subgroup         Mean         SD         Total         Weight         IV, fixed, 95% Cl         IV, fixed, 95% Cl           Bi 2017         43.1         5.4         20         41.9         5.1         20         54.8%         0.85 [-2.06, 4.46]         IV, fixed, 95% Cl           Li 2015         53.13         9.26         21         52         8.73         21         19.6%         1.13 [-4.31.6 57]
Study or subgroup         Mean         SU         Iotal         Weight         IV, Incel, 2570 CI         IV, Incel, 9570 CI           Bi 2017         43.1         5.4         20         41.9         5.1         20         54.8%         0.85 [-2.06, 4.46]
bi 2017 43.1 5.4 20 41.9 5.1 20 54.8% 0.85 [-2.06, 4.46]
Sun 2016 52.16 10.54 30 52.27 8.09 30 25.7% -0.11 [-4.86, 4.64]
Total (95% Cl) 71 71 100.0% 0.85 [-1.56, 3.26]
Heterogeneity: Chi <sup>2</sup> =0.21, df=2 (P=0.90); l <sup>2</sup> =0%
Test for overall effect: Z=0.69 (P=0.49)
Favours [Dexmedetomidine] Favours [Placebo
Experimental Control Mean difference Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95% Cl IV, random, 95% Cl
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable         IV
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable           Li 2015         7.3         0.3         21         7.2         0.2         21         5.9%         0.10 [-0.05, 0.25]
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable           Li 2015         7.3         0.3         21         7.2         0.2         21         5.9%         0.10 [-0.05, 0.25]           Qi 2016         7.3         0.08         39         40.7%         -0.03 [-0.07, 0.01]
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable           Li 2015         7.3         0.3         21         7.2         0.2         21         5.9%         0.10 [-0.05, 0.25]           Qi 2016         7.3         0.08         39         7.33         0.08         39         40.7%         -0.03 [-0.07, 0.01]           Xia 2018         7.28         0.04         45         7.27         0.05         45         53.4%         0.01 [-0.01, 0.03]
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable           Li 2015         7.3         0.3         21         7.2         0.2         21         5.9%         0.10 [-0.05, 0.25]           Qi 2016         7.3         0.08         39         7.33         0.08         39         40.7%         -0.03 [-0.07, 0.01]           Xia 2018         7.28         0.04         45         7.27         0.05         45         53.4%         0.01 [-0.01, 0.03]
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable           Li 2015         7.3         0.3         21         7.2         0.2         21         5.9%         0.10 [-0.05, 0.25]           Qi 2016         7.3         0.08         39         7.33         0.08         39         40.7%         -0.03 [-0.07, 0.01]           Xia 2018         7.28         0.04         45         7.27         0.05         45         53.4%         0.01 [-0.01, 0.03]           Total (95% Cl)         125         125         100.0%         -0.00 [-0.04, 0.04]
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% Cl         IV, random, 95% Cl           Bi 2017         7.3         0         20         7.4         0         20         Not estimable           Li 2015         7.3         0.3         21         7.2         0.2         21         5.9%         0.10 [-0.05, 0.25]           Qi 2016         7.3         0.08         39         7.33         0.08         39         40.7%         -0.03 [-0.07, 0.01]           Xia 2018         7.28         0.04         45         7.27         0.05         45         53.4%         0.01 [-0.01, 0.03]           Total (95% Cl)         125         125         100.0%         -0.00 [-0.04, 0.04]         -0.2         -0.1         0         0.1         0.2
Study or subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV, random, 95% CI         IV, random, 95% CI           Bi 2017         7.3         0         20         7.4         0         20         Not estimable           Li 2015         7.3         0.3         21         7.2         0.2         21         5.9%         0.10 [-0.05, 0.25]           Qi 2016         7.3         0.08         39         7.33         0.08         39         40.7%         -0.03 [-0.07, 0.01]           Xia 2018         7.28         0.04         45         7.27         0.05         45         53.4%         0.01 [-0.04, 0.04]           Heterogeneity: Tau <sup>2</sup> =0.00, Chi <sup>2</sup> =5.37, df=2 (P=0.07); l <sup>2</sup> =63%         125         100.0%         -0.00 [-0.04, 0.04]         -0.2         -0.1         0         0.1         0.2           Test for overall effect: Z=0.05 (P=0.96)           -0.2         -0.1         0         0.1         0.2

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.

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

Α								
	Experi	mental	Сог	ntrol			Mean difference	Mean difference
Study or subgroup	Mean	SD Total	Mean	SD	Total	Weight	IV, fixed, 95% CI	IV, fixed, 95% Cl
Bi 2017 He 2017 Li 2015 Qi 2016 Sun 2016 Teymourian 2018	8.85 9.76 8.14 8.51 8.12 8.42	0.27 20 0.49 30 0.26 21 0.76 39 0.25 30 1.79 76	8.85 9.76 8 8.74 8.12 8.15	0.27 0.49 0.53 0.82 0.74 1.23	20 30 21 39 30 76 216	38.5% 17.5% 16.9% 8.8% 13.8% 4.5%	0.00 [-0.17, 0.17] 0.00 [-0.25, 0.25] 0.14 [-0.11, 0.39] -0.23 [-0.58, 0.12] 0.00 [-0.28, 0.28] 0.27 [-0.22, 0.76]	
Heterogeneity: Chi <sup>2</sup> =3.92 Test for overall effect: Z=	2, df=5 (P= 0.30 (P=0	=0.56); l <sup>2</sup> =0%			210	100.070	0.02 [-0.07, 0.12]	-0.5 -0.25 0 0.25 0.5 Favours [Dexmedetomidine] Favours [Placebo]
В								
	Experi	mental	Сог	ntrol			Mean difference	Mean difference
Study or subgroup	Mean	SD Total	Mean	SD	Total	Weight	IV, fixed, 95% CI	IV, fixed, 95% Cl
1.1.1 Preregistration stu Bi 2017 He 2017 Qi 2016 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> =1.43 Test for overall effect: Z=(	1dies 8.85 9.76 8.51 , df=2 (P= 0.47 (P=0.	0.27 20 0.49 30 0.76 39 <b>89</b> =0.49); l <sup>2</sup> =0% 64)	8.85 9.76 8.74	0.27 0.49 0.82	20 30 39 <b>89</b>	38.5% 17.5% 8.8% <b>64.8</b> %	0.00 [-0.17, 0.17] 0.00 [-0.25, 0.25] -0.23 [-0.58, 0.12] -0.03 [-0.16, 0.10]	
1.1.2 Unregistered studi Li 2015 Sun 2015 Teymourian 2018 Subtotal (95% Cl) Heterogeneity: Chi <sup>2</sup> =1.05 Test for overall effect: Z= <sup>-1</sup>	es 8.14 8.12 8.42 , df=2 (P= 1.14 (P=0.	0.26 21 0.25 30 1.79 76 <b>127</b> =0.59);   <sup>2</sup> =0% 25)	8 8.12 8.15	0.53 0.74 1.23	21 30 76 <b>127</b>	16.9% 13.8% 4.5% <b>35.2%</b>	0.14 [-0.17, 0.17] 0.00 [-0.25, 0.25] 0.27 [-0.58, 0.12] <b>0.10 [-0.07, 0.28</b> ]	
<b>Total (95% CI)</b> Heterogeneity: Chi <sup>2</sup> =3.92 Test for overall effect: Z=0 Test for subgroup differen	df=5 (P= .30 (P=0.) res:Chi <sup>2</sup> =1	<b>216</b> =0.56); I <sup>2</sup> =0% 77) 44 df=1 (P=	0 23)· I <sup>2</sup> =3	30.4%	216 1	00.00%	0.02 [−0.09, 0.12] ⊢ −1	-0.5 0 0.5 1 Favours [Dexmedetomidine] Favours [Placeho]
		, u (.	0120771					
Study or subgroup	Experi Mean	mental SD Total	Cor Mean	ntrol SD	Total	Weight	Mean difference IV, fixed, 95% Cl	Mean difference IV, fixed, 95% Cl
Bi 2017 Qi 2017 Qi 2016 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> =0.00 Test for overall effect: Z=0	9.85 9.88 9.64 , df=2 (P= ).00 (P=1.	0.27 20 0.25 30 0.49 39 <b>89</b> =1.00); l <sup>2</sup> =0% .00)	9.85 9.88 9.64	0.27 0.25 0.49	20 30 39 <b>89</b>	12.5% 21.9% 7.4% <b>41.9%</b>	0.00 [-0.17, 0.17] 0.00 [-0.13, 0.13] 0.00 [-0.22, 0.22] 0.00 [-0.09, 0.09]	
2.1.2 Unregistered studi Fawzy 2016 Li 2015 Sun 2015 Teymourian 2018 Subtotal (95% Cl) Heterogeneity: Chi <sup>2</sup> =0.00 Test for overall effect: Z=6	es 9.88 9.88 9.88 10 , df=2 (P= ).00 (P=1.	0.25 30 0.26 21 0.25 30 0 76 157 =1.00); l <sup>2</sup> =0% .00)	9.88 9.88 9.88 9.89	0.25 0.26 0.25 0.44	30 21 30 76 <b>157</b>	21.9% 14.2% 21.9% 58.1%	0.00 [-0.13, 0.13] 0.00 [-0.16, 0.16] 0.00 [-0.13, 0.13] Not estimable 0.00 [-0.08, 0.08]	
<b>Total (95% CI)</b> Heterogeneity: Chi <sup>2</sup> =0.00, Test for overall effect: Z=0 Test for subgroup difference	df=5 (P= .00 (P=1.0 ces:Chi <sup>2</sup> =0	246 =1.00); l <sup>2</sup> =0% 00) 0.00, df=1 (P=	1.00); l²=0	0%	246 1	00.00%	0.00 [-0.06, 0.06] —	-0.2 -0.1 0 0.1 0.2 Favours [Dexmedetomidine] Favours [Placebo]

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D Study or subgroup	Experimental	Control	Total	Woight	Mean difference IV. fixed, 95% Cl	Mean difference IV. fixed, 95% (1
3.1.1 Preregistration stud Bi 2017 Subtotal (95% CI) Heterogeneity: Not applicat Test for overall effect: Z=0.3	ies 25.7 8.4 20 20 20 20 20 20 20 20 20	24.8 10.3	20 20	19.2% 19.2%	0.90 [-4.92, 6.72] 0.90 [-4.92, 6.72]	
<b>3.1.2 Unregistered studie:</b> Li 2015 Sun 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Chi <sup>2</sup> =0.09, c Test for overall effect: Z=0.0	$\begin{array}{ccccc} s & & \\ 21.36 & 6.09 & 21 \\ 21.71 & 6.13 & 30 \\ tf = 1 (P = 0.76); P = 0\% \\ 07 (P = 0.94) \end{array}$	8.73 21 8.09 30 51	21 30 <b>51</b>	31.4% 49.4% <b>80.8%</b>	-0.66 [-5.21, 3.89] 0.25 [-3.38, 3.88] - <b>0.10 [-2.94, 2.74]</b>	
<b>Total (95% Cl)</b> Heterogeneity: Chi <sup>2</sup> =0.19, c Test for overall effect: Z=0.0 Test for subgroup difference	71 ff=2 (P=0.91); I <sup>2</sup> =0% 17 (P=0.95) ss:Chi <sup>2</sup> =0.09, df=1 (P=0.	76); l²=0%	71 1	00.00%	0.09 [-2.46, 2.64]	-10 -5 0 5 10 Favours [Dexmedetomidine] Favours [Placebo]
E Study or subgroup	Experimental Mean SD Total	Control Mean SD	Total	Weight	Mean difference IV, fixed, 95% Cl	Mean difference IV, fixed, 95% Cl
4.1.1 Preregistration stud Bi 2017 Subtotal (95% CI) Heterogeneity: Not applicat Test for overall effect: Z=0.7	ies 25.7 8.4 20 20 Dle 72 (P=0.47)	41.9 5.1	20 20	54.8% 54.8%	1.20 [-2.06, 4.46] 1.20 [-2.06, 4.46]	
<b>4.1.2 Unregistered studies</b> Li 2015 Sun 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Chi <sup>2</sup> =0.11, o Test for overall effect: Z=0.2	s 53.13 52.16 10.54 30 51 ff=1 (P=0.74); P=0% 23 (P=0.82)	8.73 21 8.09 30 51	21 30 <b>51</b>	19.6% 25.7% <b>45.2%</b>	1.13 [-4.31, 6.57] -0.11 [-4.86, 4.64] <b>0.43 [-3.15, 4.01</b> ]	
<b>Total (95% CI)</b> Heterogeneity: Chi <sup>2</sup> =0.21, c Test for overall effect: Z=0.c Test for subgroup difference	71 ff=2 (P=0.90); I <sup>2</sup> =0% 59 (P=0.49) ss:Chi <sup>2</sup> =0.10, df=1 (P=0.	75); l²=0%	71 1	00.00%	0.85 [–1.56, 3.26] —	-10 -5 0 5 10 Favours [Dexmedetomidine] Favours [Placebo]
<b>F</b> Study or subgroup	Experimental Mean SD Total	Control Mean SD	Total	Weight	Mean difference IV, fixed, 95% Cl	Mean difference IV, fixed, 95% Cl
5.1.1 Preregistration stud Bi 2017 Qi 2016 Xia 2018 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> =0.00; Test for overall effect: Z=0.3	ies 7.3 0 20 7.3 0.08 39 7.28 0.04 45 104 Chi <sup>2</sup> =3.82, df=1 (P=0.05 36 (P=0.72)	7.4 0 7.33 0.08 7.27 0.05 ); l <sup>2</sup> =74%	20 39 45 <b>104</b>	40.7% 53.4% <b>94.1%</b>	Not estimable -0.03 [-0.07, 0.01] 0.01 [-0.05, 0.03] -0.01 [-0.05, 0.03]	*
<b>5.1.2 Unregistered studie</b> : Li 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Not applical Test for overall effect: Z=1.2	s 7.3 0.3 21 21 Dle 27 (P=0.20)	7.2 0.2	21 <b>21</b>	5.9% <b>5.9%</b>	0.10 [-0.05, 0.25] 0.10 [-0.05, 0.25]	
<b>Total (95% Cl)</b> Heterogeneity: Tau <sup>2</sup> =0.00; / Test for overall effect: Z=0.0 Test for subgroup difference	<b>125</b> Chi <sup>2</sup> =5.37, df=2 (P=0.07 J5 (P=0.96) ss:Chi <sup>2</sup> =1.74, df=1 (P=0.	); I²=63% 19); I²=42.6%	125 1	00.00%	-0.00 [-0.04, 0.04]	-0.2 -0.1 0 0.1 0.2 Favours [experimental] Favours [control]

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.

Α The onset of sensory block in minutes Experimental Control Mean difference Mean difference IV, random, 95% CI IV, random, 95% CI Study or subgroup Mean SD Total Mean SD Total Weight Not estimable Li 2015 7.1 0 21 7.6 0 21 Qi 2016 6.46 1.35 39 2.23 39 46.6% [-1.79, -0.15] 7.43 -0 97 Sun 2016 7.1 0 30 7.8 0 30 Not estimable Xia 2018 3.8 1.1 36 1.3 53.4% 0.20 [-0.36, 0.76] 3.6 36 Total (95% CI) 126 126 100.0% -0.34 [-1.49, 0.80] Heterogeneity: Tau<sup>2</sup>=0.56; Chi<sup>2</sup>=5.37, df=1 (P=0.02); I<sup>2</sup>=81% -0.5 0.5 Test for overall effect: Z=0.59 (P=0.55) Favours [Dexmedetomidine] Favours [Placebo] The onset of motor block in minutes Experimental Control Mean difference Mean difference IV, fixed, 95% CI IV, fixed, 95% CI Weight Study or subgroup Mean SD Total Mean SD Total -0.40 [-1.75, 0.95] Li 2015 7 2 2.25 21 7.6 2.2 21 12.6% 0i 2016 4 87 1 36 39 5 89 1 89 39 42 7% -1 02 [-1 75 -0 29] Sun 2016 71 2 2 5 30 7.6 22 30 18.0% -0.50 [-1.63, 0.63] Xia 2018 3.8 2.1 36 3.4 1.9 36 26.7% 0.40 [-0.53,1.33] Total (95% CI) 126 126 100.0% -0.47 [-0.95, 0.01] Heterogeneity: Chi<sup>2</sup>=5.59, df=3 (P=0.13); I<sup>2</sup>=46% Test for overall effect: Z=1.93 (P=0.05) \_7 Favours [Dexmedetomidine] Favours [Placebo] B The duration of sensory block in minutes Mean difference Mean difference Experimental Control IV, fixed, 95% CI IV, fixed, 95% CI Study or subgroup Mean SD SD Weight Total Mean Total Fawzy 2016 51.5 63.30 [33.20, 93.40] 317.3 30 254 66.5 30 8.6% 225.73 253.21 47.88 42.79 152.26 188.33 21.09 37.62 21 39 73.47 51.09, 95.85 li 2015 21 39 15.5% 24.3% 0i 2016 211.73 51.88 30 155.26 23.09 30 18.8% 56.47 [36.15,76.79 Sun 2016 Xia 2018 110.3 35.3 36 67.5 31.2 36 32.8% 42.80 [27.41, 58.19] Total (95% CI) 156 156 100.0% 57,25 [48.44, 66.07] Heterogeneity: Chi<sup>2</sup>=6.27, df=4 (P=0.18); l<sup>2</sup>=36% 100 -100-<u>5</u>0 Ó 50 Test for overall effect: Z=12.73 (P<0.00001) Favours [Dexmedetomidine] Favours [Placebo] The duration of motor block in minutes Experimental Control Mean difference Std. mean difference IV, random, 95% CI IV, random, 95% CI SD Weight Study or subgroup Mean Total Mean SD Total 5.8 320 18.8% 62.16 [1.36, 2.95 Bi 20107 20 3.6 Fawzy 2016 Li 2015 42 7 195.3 124.5 30 21 1.67 [1.08, 2.26] 0.15 [-0.46, 0.75] 271 30 21 46.8 20.1% 28.9 20.0% 128.55 25.71 40.51 25.31 226.15 30 162.18 39 20.4% Qi 2016 1.88 [1.34.2.4] Sun 2016 128.55 28.9 30 127.5 25.71 30 20.6% 0.04 [-0.47, 0.54] Total (95% CI) 140 140 100.0% 1.16 [0.27, 2.05] Heterogeneity: Chi<sup>2</sup>=44.62, df=4 (P<0.00001); l<sup>2</sup>=91% -2 -1 0 Test for overall effect: Z=2.56 (P=0.01) Favours [Placebo] Favours [Dexmedetomidine]

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% Cl, -0.95 to 0.01; P=0.05;  $l^2=46\%$ ), while it has no obvious improvement effect on the onset of sensory block (MD, -0.34; 95% Cl, -1.49 to 0.80; P=0.55;  $l^2=81\%$ , Figure 5A), and DEX can significantly prolong the blockade time, as shown in Figure 5B, whether it is sensory block (MD, 57.25; 95% Cl, 48.44 to 66.07; P<0.001,  $l^2=36\%$ ) or motor block (SMD, 1.16; 95% Cl, 0.27 to 2.05; P=0.01;  $l^2=91\%$ ).

## Α

The VAS score of postoperation 4h

	Evnori	imontal	(	ntrol			Moon difforence	Maan difference
Study or subaroun	Морп		al Moan		Total	Weight	IV. random, 95% Cl	IV. random, 95% Cl
Fawzy 2016	2	0.98 30	) 6.12	0.74	30	20.1%	-4 12 [-4 56 -3 68]	
He 2017	2.42	1.64 30	5.08	1.68	36	19.3%	-2.66 [-3.43, -1.89]	
Li 2015	1.86	0.79 2	2	0.53	21	20.1%	-0.14[-0.55, 0.27]	
Qi 2016	0.38	0.59 3	0.82	0.79	39	20.3%	-0.44 [-0.75,-0.13]	
Sun 2016	1.12	0.74 3	) 2	0.49	30	20.3%	-0.88 [-1.20, -0.56]	
Total (95% CI)		15	6		156	100.0%	-1.63 [-3.01, -0.26]	
Heterogeneity: Tau <sup>2</sup> =2.4	12, Chi²=23	6.69, df=4	P<0.00001)	; l <sup>2</sup> =989	6			
Test for overall effect: Z=	=2.32 (P=0	.02)		,				-4 -2 0 2 4
	, i i							Favours [Dexmedetomidine] Favours [Placebo]
The pain free period								
	Experi	imental	Co	ontrol			Mean difference	Std. mean difference
Study or subgroup	Mean	SD Tot	al Mean	SD	Total	Weight	IV, random, 95% Cl	IV, random, 95% Cl
Bi 2017	24.8	3 2	22.3	3.4	20	14.7%	0.76 [0.12, 1.41]	
Fawzy 2016	7.9	3.3 30	) 3	1.6	30	14.8%	1.86 [1.25, 2.48]	
Kamali 2018	1/2.31	2.1 3	103.8	23.1	36	14.2%	4.13 [3.30, 4.97]	
LI 2015	360.52	29.57 2	231.55	28.64	21	13.1%	4.35 [3.20,5.50]	
QI 2016	17.59	0.23 3	3.53	1.68	39	14.7%	3.05 [2.39, 3.71]	
SUII 2010 Via 2019	352.45	20.1/ 3	J 220.55	28.04	30	15.0%	4./5[5./5, 5./6]	
XId 2018	224.9	45.4 30	155.1	31.0	30	15.0%	1.//[1.22, 2.31]	
Total (95% CI)		21	2		212	100.0%	2.90 [1.86, 3.93]	•
Heterogeneity: Tau <sup>2</sup> =1.7	78, Chi²=84	.69, df=6 (l	2<0.00001);	l <sup>2</sup> =93%			-	
Test for overall effect: Z=	=5.49 (P<0	.00001)						-4 -2 0 2 4
								Favours [Dexmedetomidine] Favours [Placebo]
В								
The VAS score of postope	ration 12h							
	Experi	imental	Co	ontrol			Mean difference	Mean difference
Study or subgroup	Mean	SD Tot	al Mean	SD	Total	Weight	IV, random, 95% Cl	IV, random, 95% Cl
Bi 2017	5	1.34 20	4.59	0.27	20	24.7%	0.41 [-0.19, 1.01]	
Fawzy 2016	5.76	1.1 30	4.62	0.61	30	25.6%	1.14 [0.69, 1.59]	
Kamali 2018	2.01	1.21 3	5 3.1	1.17	36	25.0%	-1.09 [-1.64, -0.54]	
Qi 2016	2.77	1.2 3	3.51	1.55	39	24.6%	-0.74 [-1.36,-0.12]	
Total (95% CI)		17	5		125	100 0%	-0.06 [-1.14, 1.02]	
Heterogeneity: Tau <sup>2</sup> =1.1	14. Chi <sup>2</sup> =46	.69. df=3 (	_ ?<0.00001):	l <sup>2</sup> =94%	125	/0		
Test for overall effect: Z=	=0.11 (P=0	.91)						1 05 0 05 1
								Favours [Dexmedetomidine] Favours [Placebo]

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,  $l^2=98\%$ ) and significantly prolonged postoperative analgesia (SMD, 2.90; 95% CI, 1.86 to 3.93; P<0.001,  $l^2=93\%$ ), 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;  $l^2=94\%$ , 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*<sup>2</sup>=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<sup>2</sup>=22%) and bradycardia

Α	Fxperim	ental	Con	trol		Dickratio	Dick ratio	
Study or subaroun	Experim	Total	Events	Total	Weight	M-H fixed 95% (1	M-H fixed 95% (1	
Ri 2017	2	20	11	20	12 1%	0.73 [0.37 1.42]		
Fawzy 2016	9	30	12	30	14 3%	0.75 [0.37, 1.42]		
He 2017	2	30	11	30	13.1%	0.18 [0.04, 0.75] -		
Kamali 2018	2	36	13	36	15.5%	0.15 [0.04, 0.63] —		
Nasseri 2017	6	25	13	25	16.7%	0.46 [0.21, 1.02]		
0i 2016	3	39	14	39	1.2%	0.21 [0.07, 0.69]		
Sun 2016	1	30	1	30	10.7%	1.00 [0.07, 15.26]		
Xia 2018	7	45	9	45		0.78 [0.32, 1.91]		
<b>Total (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> =11	38 .07. df=7 (P=	<b>255</b>	84 7%	255	100.0%	0.45 [0.32, 0.63]	•	L
Test for overall effect: Z	=4.68 (P<0.0	0001)				0.02	0.1 1 10 5	0
B						Favour	s [Dexmedetomidine] Favours [Placebo]	
The incidence of hypoter	nsion							
Ctudu or cubaroun	Experim	ental	Con	trol	Woight	Risk ratio	Risk ratio	
Study of Subgroup	17	20	Evenus	20	20 00/	M-n, lixeu, 95% Cl		
FdWZy 2010	1/	3U 21	23	3U 21	20.0%	0.74 [0.51, 1.07] 1.00 [0.52, 7.70]		
LI ZU I J Naccori 2017	د رر	21	د ۲۲	21 25	2.0% 28.8%	1.00 [0.25, 4.40] 1.00 [0.25, 1.19]		
NdSSEIT 2017 0; 2016	15	20	12	20	15.0%	1.00 [0.00, 1.10]		
QI 2010 Sun 2016	4	30	4	30	5.0%	1.00 [0.28, 3, 63]		
Xia 2018	8	45	15	45	18.8%	0.53 [0.25, 1.13]	<b>_</b>	
<b>Total (95% CI)</b> Total events	70	190	80	190	100.0%	0.88 [0.71, 1.08]	•	
Heterogeneity: Chi <sup>2</sup> =6.3	39, df=5 (P=0	0.27); l <sup>2</sup> =22	%			L		
Test for overall effect: Z=	=1.24 (P=0.2	2)				0.01	0.1 İ İO	100
		,				Favour	s [Dexmedetomidine] Favours [Placebo]	
The incidence of bradyca	ardia Evnerim	ontal	Con	trol		Pick ratio	Dick ratio	
Study or subaroup	Experim	Total	Events	Total	Weight	M-H, fixed, 95% Cl	M-H, fixed, 95% Cl	
Fawzy 2016	7	30	9	30	64.3%	0.78 [0.33, 1.82]		
He 2017	0	30	0	30		Not estimable	—	
Li 2015	1	21	1	21	7.1%	1.00 [0.07, 14.95]		
Nasseri 2017	1	25	2	25	14.3%	0.50 [0.05, 5.17]		
Qi 2016	3	39	1	39	7.1%	3.00 [0.33, 27.60]		
Sun 2016	2	30	1	30	7.1%	2.00 [0.19, 20.90]		
<b>Total (95% CI)</b> Total events	14	175	14	175	100.0%	1.00 [0.51, 1.96]	•	
Heterogeneity: Chi <sup>2</sup> =1.9	95, df=4 (P=0	0.74); l <sup>2</sup> =0%	Ď			L	<u> </u>	
lest for overall effect: Z=	=0.00 (P=1.0	0)				0.01		100
_						Favour	s [Dexmedetomidine] Favours [Placebo]	
C								
	Experim	ental	Con	trol		Risk ratio	Risk ratio	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% Cl	M-H, fixed, 95% Cl	
Bi 2017	/	20	2	20	3.1%	3.50 [0.83, 14.83]		
Fawzy 2016	16	30	2/	30	41.9%	0.59 [0.42, 0.85]		
He ZUT/ Kemeil 2010	2	30	2	30	3.1%	1.00 [0.15, 0.04]		
Kdffidil 2018	0	30 21	2	30 21	3.9%	0.20 [0.01, 4.03]		
LI ZU I S Naccori 2017	3 12	21	) 10	21	7.8%	0.00 [0.10, 2.20]		
NdSSel1 2017	12	20	12	20	10.0%	1.00 [0.30, 1.76]		
QI 2016	5	39	5	39	7.8%	1.00 [0.31, 3.18]		
SUN 2016	3	30	2	30	3.1%	1.50 [0.27, 8.34]		
	0		/	4	10.9%	1.14 [0.45, 2.89]		
Ald 2010	8	45	,					
Total (95% CI) Total events	56	45 276	64	276	100.0%	0.88 [0.66, 1.16]	•	
<b>Total (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> =10	56 0.40, df=8 (P=	45 <b>276</b> =0.24); l <sup>2</sup> =2:	64 3%	276	100.0%	0.88 [0.66, 1.16]	•	
<b>Total (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> =10 Test for overall effect: Z=	8 56 0.40, df=8 (P= =0.93 (P=0.3	45 276 =0.24); l <sup>2</sup> =2: 5)	64 3%	276	100.0%	0.88 [0.66, 1.16] .001 Favour	0.1 1 10 10 s [Dexmedetomidine] Favours [Placebo]	0

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

(RR, 1.00; 95% CI, 0.51 to 1.96; P=1.00;  $l^2=0$ ) 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;  $l^2=23\%$ ), 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 **META-ANALYSIS** 

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  $\alpha_{2}$  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 metaanalysis [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 ( $\leq 25$  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 longterm effect on the fetus is not clear. These shortcomings need to be addressed in future research.

## 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

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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.

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