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Foetal responses to dexmedetomidine in parturients undergoing caesarean section: a systematic review and meta-analysis

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Abstract

Objective: This current meta-analysis was conducted to evaluate effects of dexmedetomidine on neonatal maternal factors.

Methods: The electronic databases of PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched. The primary outcomes were neonatal parameters, including umbilical blood gases and Apgar scores. The secondary outcomes were maternal parameters.

Results: We identified six randomized controlled trials (RCTs). No differences in neonatal umbilical blood gases, and Apgar scores at 1 min (WMD: −0.09; 95% CI: −0.21 to 0.04; $I^2 = 0\%$) and 5 min (weighted mean difference (WMD): 0.03; 95% CI: −0.05 to 0.11; $I^2 = 37\%$) were observed with dexmedetomidine. For maternal parameters, characteristics of motor and sensory block and postoperative analgesia (standard mean difference (SMD): 3.99; 95% CI: 2.85 to 5.12; $I^2 = 78\%$) were significantly improved after dexmedetomidine treatment. Adverse events, including nausea/vomiting and shivering (risk ratio (RR): 0.26; 95% CI: 0.11 to 0.60; $I^2 = 0\%$), were lower after dexmedetomidine treatment.

Conclusion: This meta-analysis shows that dexmedetomidine is safe for neonates who are delivered by caesarean section. Moreover, dexmedetomidine used in neuraxial anaesthesia can improve the characteristics of motor and sensory block and prolong the maternal pain-free period. Dexmedetomidine can also reduce the maternal incidence of postoperative adverse effects.

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Introduction

Anaesthesia in caesarean section is a challenge for anaesthesiologists. In this situation, the anaesthesiologist needs to take into account the safety of two lives. The rate of caesarean sections is increasing yearly.[1,2] Therefore, effectiveness and safety of anaesthesia are important for ensuring success of the operation.[3] Neuraxial anaesthesia and general anaesthesia can be performed in caesarean section.[4,5] However, in clinical practice, some anaesthetics (e.g., opioids) have a potential for respiratory depression of neonates,[6] which leads to a decrease in Apgar scores and pH values. If the neonatal Apgar score is < 7 at 5 min or pH is < 7.20, newborns are admitted to the neonatal intensive care unit. In this situation, assisted ventilation is required,[7] and morbidity and mortality[8] are increased.

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist that binds to transmembrane G protein-binding receptor. Dexmedetomidine induces sedation, analgesia, amnesia, and perioperative sympatholytic, anaesthetic-sparing, and hemodynamic-stabilizing properties without depressing respiratory function.[9–14] Dexmedetomidine can also act by different administration routes. Intravenous and intrathecal dexmedetomidine can improve characteristics of block in spinal anaesthesia, including prolonging the duration of sensory block and motor block.[15] Additionally, the placental transfer rate of dexmedetomidine is much lower than that of clonidine and that of remifentanil.[16] Clinical researchers have already studied administration of dexmedetomidine in parturients undergoing caesarean section, but the clinical safety and effects of dexmedetomidine on the foetus are still controversial. However, quantitative analysis of these data has not been performed. Therefore, we conducted the present meta-analysis to assess foetal responses to dexmedetomidine in parturients undergoing caesarean section.

Methods

This systematic review and meta-analysis was registered in PROSPERO (www.crd.york.ac.uk/PROSPERO) with the unique identification number CRD42016040045. Our analysis included randomized, controlled trials (RCTs) that compared the neonatal efficacy of dexmedetomidine with placebo in parturients undergoing caesarean section. We reported the study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[17,18]

Systematic search and strategy

The electronic databases PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to June 2016, without language limitations. We also searched the reference lists of included studies and grey literature using the System for Information on Grey Literature in Europe (SIGLE) database to identify potential RCTs. The final update of this literature search was performed on the 14 December 2016.

The search strategy consisted of a combination of free text words and medical subject headings (MeSH) terms as follows: ''dexmedetomidine'', ''drug therapy'', ''caesarean section'', ''abdominal delivery'', ''C-Section'', ''randomized controlled trial'', ''controlled clinical trial'', ''randomized'',

"randomly", and "trial". Details of our search strategy are provided in the Appendix.

Eligibility criteria

Studies were included in the systematic review if they satisfied all of the following pre-established criteria: (1) RCT; (2) participants were adults (18 years or older) with American Society of Anesthesiologists (ASA) physical status (classified by conditions of patients and risks of surgery) I–II and term or near-term singleton pregnancies, scheduled for caesarean delivery; (3) perioperative administration of dexmedetomidine compared with placebo; (4) dexmedetomidine administrated by intravenous, intrathecal, or epidural injection before delivery, regardless of the type of anaesthesia; and (5) outcomes included umbilical blood gas parameters and Apgar scores.

We excluded studies if they were duplicate publications, reviews, abstracts from conferences, letters to the editor, animal studies, and labour analgesic trials. We also excluded patients with ASA III–IV, prematurity, multiple gestations, preeclampsia, a history of allergy to dexmedetomidine, alcohol or drug abuse, foetal distress, and known foetal abnormalities. We did not include studies that did not report the specific results of neonatal parameters.

Data extraction and risk of bias assessment

Two reviewers (J.Z. and H.B.Z.) independently worked and assessed the studies for compliance with the eligibility criteria. Any discrepancies were resolved by consultation with a third reviewer (A.S.W.). The PRISMA flow diagram was used to summarize the processes of study selection.

Extracted data included the following: name of the first author; publication year; age of participants and their ASA physical status; gestational age; interventions; patients; type of anaesthesia; length of operation; and dose and timing of target drug administration. All graphical data were converted into numerical data. Extraction of all of the data mentioned above was performed by two reviewers (J.Z. and H.B.Z.) and another reviewer (K.H.S.) checked the extracted data.

Two authors (J.Z. and T.T.) evaluated the overall risk of bias in individual studies. This was performed according to the guideline recommended by the Cochrane Collaboration, with regard to the adequacy of randomization, concealment of allocation, blinding (of patients, healthcare providers, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. Each parameter was classified as low, high, or unclear.

Statistical analysis

For binary variables, the pooled risk ratio (RR) and 95% confidence interval (95% CI) were calculated. Continuous data were assessed by the pooled weighted mean difference (WMD) or pooled standard mean difference (SMD). The overall effect was assessed by the Z test and statistical significance was determined when the 95% CIs did not include the value of 1.0 for the RR or 0 for the WMD or SMD. Methods as the measure of treatment effect were reported by an accompanying range in some studies. To calculate variables, the standard deviation (SD) was estimated from the range and the mean from the median as follows: SD = range/4 and mean = median.[19,20] The I^2 test was used to measure heterogeneity. An I^2 score of $\geq$40% indicated more than moderate heterogeneity when a random effects model was used, otherwise a fixed effects model was used.

Sensitivity analysis was performed by changing the effects model of the statistical method (fixed effect vs. random effect model). Potential publication bias was

evaluated by Egger's regression test with Stata (Version 13.0.; Stata Corp., TX, USA). Statistical analyses were performed using Review Manager (Version 5.3.; The Cochrane Collaboration, Oxford, UK).

Results

Study selection

A systematic search of PubMed, Embase, CENTRAL, SIGLE, and reference lists generated 58 articles. Of these, 27 duplicated records that were identified by the title, authors, journal citation, and date published were removed. After retrieval and review of the articles' abstracts, 19 studies were excluded depending on the title and abstract because of reviews (n = 12), an abstract from a conference (n = 1), case reports (n = 5), and labour analgesic trials (n = 1). The remaining 12 studies were examined in detail. A further six studies were then excluded because of a lack of intended intervention and outcomes of interest. Finally, six studies[21–26] including 458 parturients with singleton pregnancies fulfilled the criteria for the systematic review and meta-analysis. The study selection processes are shown in Figure 1.

Study characteristics

All of the included studies[21–26] investigated the efficacy of dexmedetomidine on neonates compared with placebo. Neuraxial anaesthesia was performed in four studies[22–25] and general anaesthesia was used in the other two trials.[21,26] Dexmedetomidine was administered during induction of anaesthesia in all of the studies.[21–26] Four studies[22–25] showed characteristics of block in neuraxial anaesthesia, including onset of sensory block,[22,24] onset of motor block,[23–25] duration of sensory block,[22–25] duration of motor block,[23–25] and the time for the first postoperative analgesic.[23–25] Five studies[21–25] reported adverse events, including nausea/vomiting,[21–25] shivering,[22,24,25] pruritus,[23–25] hypotension,[21,23–25] and bradycardia.[21,23–25] Table 1 shows the characteristics of all included studies.

Risk of bias within studies

The overall risk of bias within studies was low in four studies,[21,24–26] while one study[23] did not describe detailed information on random sequence generation. One trial[22] did not describe the methods of allocation concealment (Figure 2).

Meta-analyses of primary results

Neonatal outcomes. No differences in umbilical blood gas parameters were observed between the two groups, including arterial partial pressure of oxygen (WMD: −0.93 mmHg; 95% CI: −1.97 to 0.11; $I^2 = 0\%$), arterial partial pressure of carbon dioxide (WMD: −1.11 mmHg; 95% CI: −2.26 to 0.04; $I^2 = 33\%$), pH values (WMD: −0.01; 95% CI: −0.03 to 0.01; $I^2 = 22\%$), and base excess data (WMD: −0.14 mmol/l; 95% CI: −0.38 to 0.11; $I^2 = 0\%$). Apgar scores at 1 (WMD: −0.09; 95% CI: −0.21 to 0.04; $I^2 = 0\%$) and 5 min (WMD: 0.03; 95% CI: −0.05 to 0.11; $I^2 = 37\%$) were also not different between the groups. Neonatal outcomes were shown in Figure 3.

Meta-analyses of secondary results

Maternal outcomes. When dexmedetomidine was administrated by intravertebral injection in neuraxial anaesthesia, the time of onset to motor block (WMD: −0.79 min; 95% CI: −1.34 to −0.23; $I^2 = 0\%$) was significantly shorter in the dexmedetomidine group compared with the placebo group. The duration of sensory block (WMD: 74.75 min; 95% CI: 52.65 to 96.85; $I^2 = 70\%$) and the first postoperative

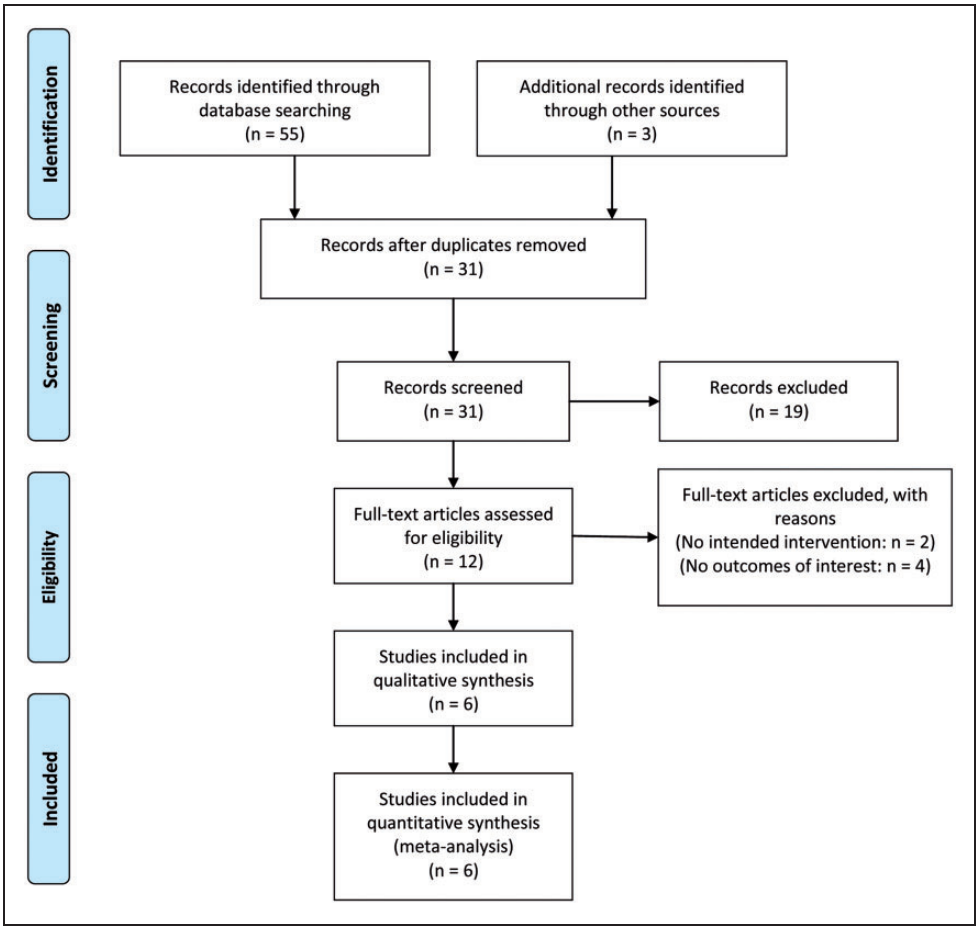

Figure 1. Search flow diagram for studies that were included in the meta-analysis.

analgesic (SMD: 3.99; 95% CI: 2.85 to 5.12; $I^2 = 78\%$) were significantly longer in the dexmedetomidine group compared with the placebo group.

Adverse events, including nausea/vomiting (RR: 0.61; 95% CI: 0.32 to 1.18; $I^2 = 1\%$) and shivering (RR: 0.26; 95% CI: 0.11 to 0.60; $I^2 = 0\%$), were lower in the dexmedetomidine group than in the placebo group, but this was not quite significant for nausea/vomiting. Meta-analysis showed no differences in the rates of common adverse effects, such as pruritus, hypotension, and bradycardia, between the dexmedetomidine and placebo groups. Maternal outcomes were shown in Figure 4.

Publication bias and sensitivity analysis

None of the primary and secondary results of the Egger regression asymmetry tests achieved statistical significance (primary results: $P = 0.106$, $P = 0.458$, $P = 0.369$, $P = 0.473$, $P = 0.982$, $P = 0.247$; secondary results: $P = 0.717$, $P = 0.848$, $P = 0.376$, $P = 0.261$, $P = 0.235$).

Table 1. Characteristics of studies included in the present systematic review and meta-analysis.

Authors	Year	Patients	ASA	Type of anaesthesia	Trail	Dosage regimen	Comparisons	Total	Gestational age (mean ± SD, wk)
El-Tahan[22]	2012	Singleton pregnancy of at least 36 weeks term, elective caesarean section	I–II	GA	I	C	Dexmedetomidine IV 0.2 μg/kg/h	17	37.1 ± 1.1
							Dexmedetomidine IV 0.4 μg/kg/h	17	37.5 ± 1.0
							Dexmedetomidine IV 0.6 μg/kg/h	17	36.8 ± 0.8
							Placebo IV	17	37.0 ± 0.9
Han[26]	2014	Singleton term pregnancy, elective caesarean section	I–II	EA	I	S	Dexmedetomidine EA 1 μg/kg	20	38.4 ± 1.5
							Fentanyl EA 1 μg/kg	20	39.2 ± 0.9
							Placebo EA	20	38.6 ± 1.1
Li[21]	2015	Singleton pregnancy of 36–40 weeks term, elective caesarean section	I–II	SA	I	S	Dexmedetomidine SA 10 μg	21	38.27 ± 0.61
							Fentanyl SA 15 μg	21	38.38 ± 0.59
							Clonidine SA 75 μg	21	38.41 ± 0.58
							Placebo SA	21	38.55 ± 0.77
Qi[24]	2016	Singleton full-term pregnancy, elective caesarean section	I–II	SA	I	S	Dexmedetomidine SA 5 μg	39	38.98 ± 0.86
							Morphine SA 100 μg	40	39.06 ± 0.90
							Placebo SA	39	38.88 ± 0.84
Sun[25]	2014	Singleton pregnancy of 36–40 weeks term, elective caesarean section	I–II	SA	I	S	Dexmedetomidine SA 10 μg	30	38.27 ± 0.61
							Fentanyl SA 25 μg	30	38.38 ± 0.59
							Placebo SA	30	38.55 ± 0.77
Yu[23]	2015	Singleton term pregnancy, elective caesarean section	I–II	GA	I	L	Dexmedetomidine 0.6 μg/kg, followed by 0.4 μg/kg/h IV	19	38.9 ± 1.5
							Placebo IV	19	39.2 ± 0.9

GA: general anaesthesia, SA: spinal anaesthesia, EA: epidural anaesthesia, IV: intravenous, I: induction of anaesthesia, S: single dose, L: loading dose followed by continuous infusion, C: continuous infusion.

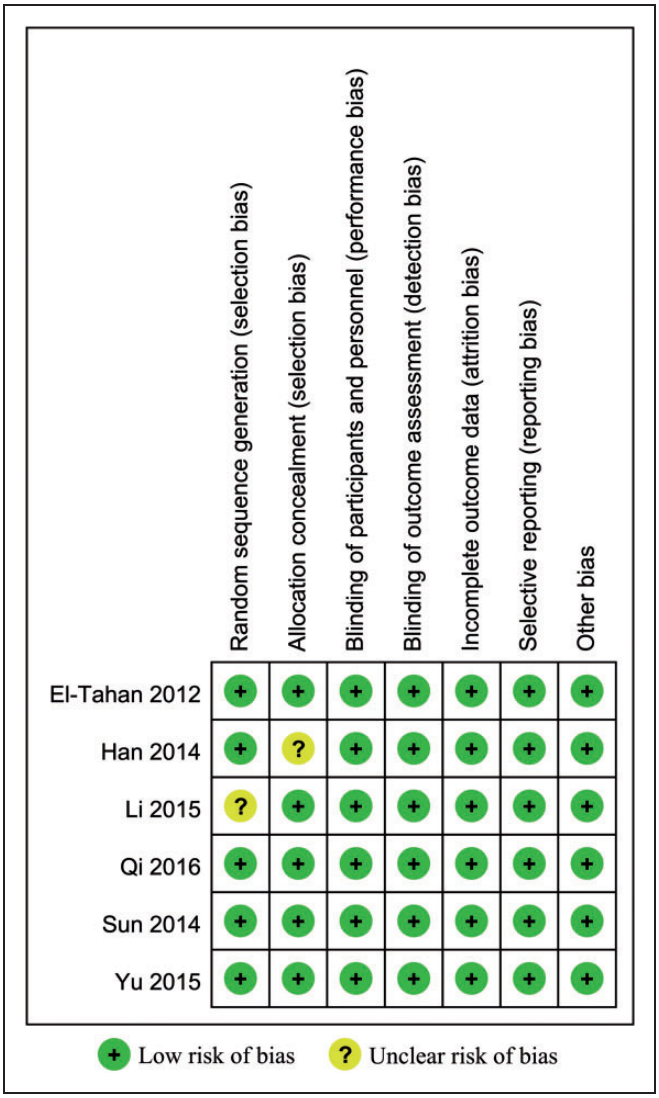

Figure 2. Risk of bias summary: review authors' judgments regarding each risk of bias item presented as percentages across all included studies.

Sensitivity analysis by changing the effects model of the statistical method did not alter the primary and secondary results.

Discussion

The present meta-analysis of six RCTs evaluated the efficacy and safety of dexmedetomidine for foetal and maternal responses in parturients undergoing caesarean section. We found that dexmedetomidine was safe for neonates, with no significant differences in Apgar scores at 1 and 5 min, and umbilical blood gas parameters compared with the placebo group. Dexmedetomidine used in neuraxial anaesthesia could improve characteristics of block by shortening the onset time of motor block,

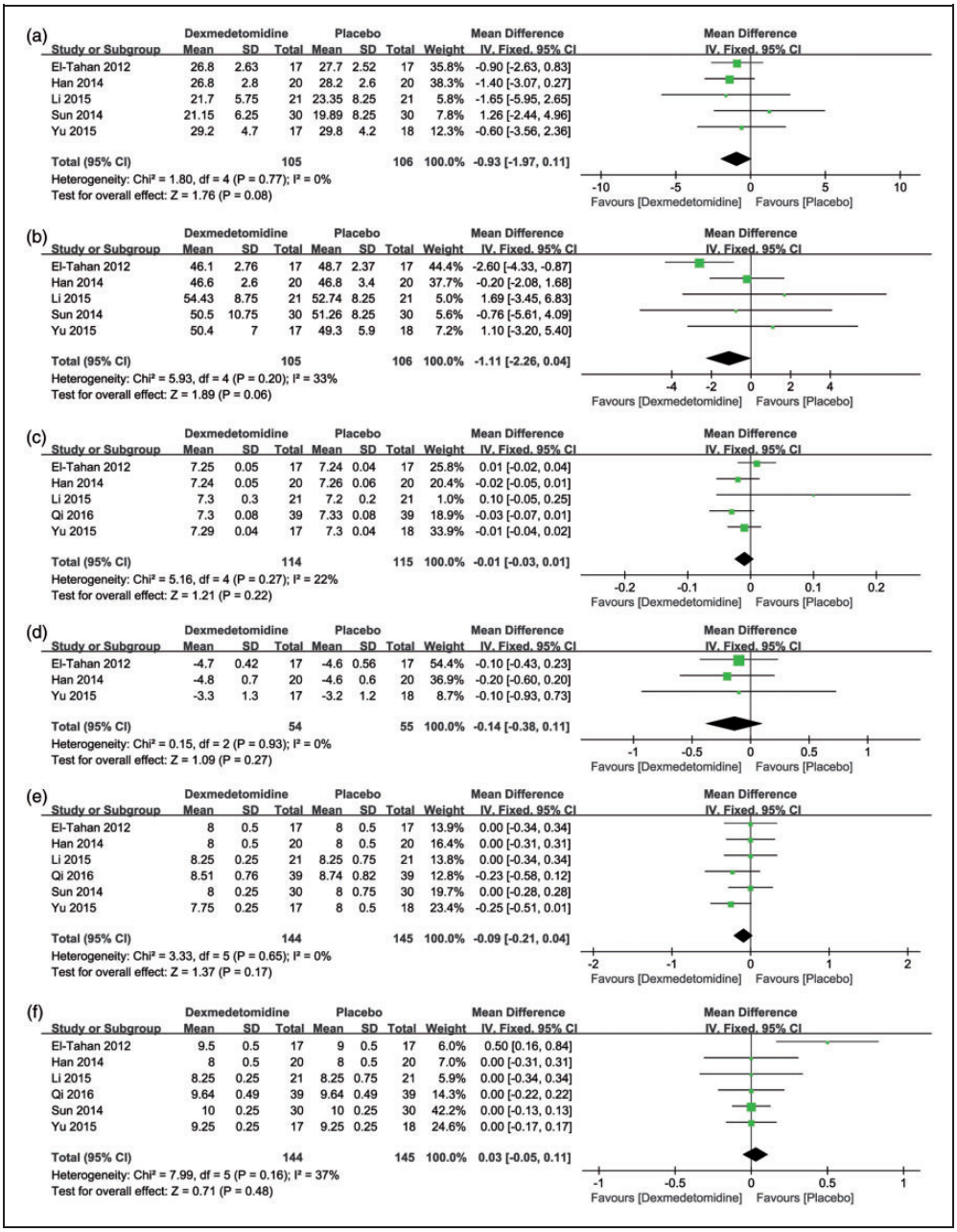

Figure 3. Neonatal outcomes

(a) Data of partial pressure of oxygen. (b) Data of partial pressure of carbon dioxide. (c) Data of pH. (d) Data of base excess. (e) Apgar values at 1 min. (f) Apgar values at 5 min. WMD, weighted mean difference; CI, confidence interval; SD, standard deviation; IV, inverse variance.

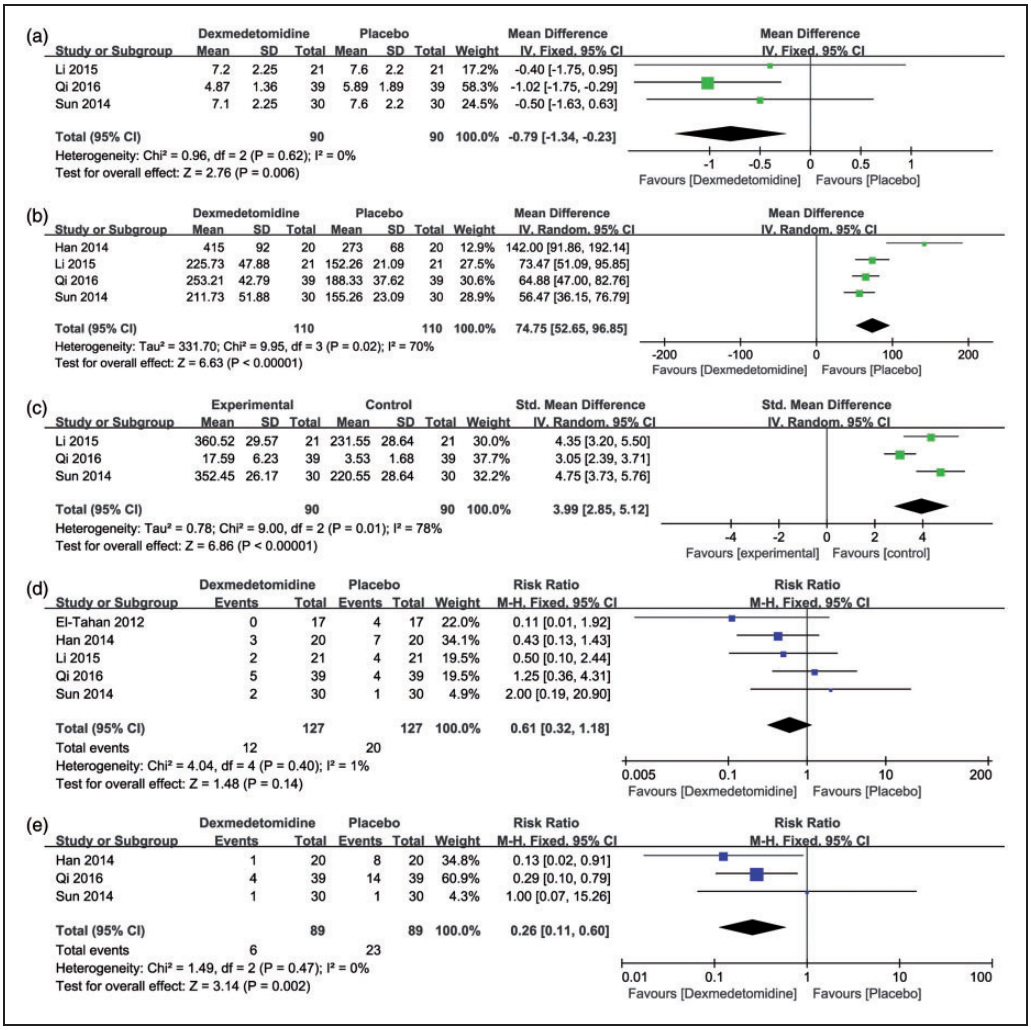

Figure 4. Maternal outcomes
(a) Time of onset to motor block. (b) Duration of sensory block. (c) First postoperative analgesic. (d) Nausea/vomiting. (e) Shivering. WMD, weighted mean difference; SMD, standard mean difference; RR, risk ratio; CI, confidence interval; SD, standard deviation; IV, inverse variance.

prolonging the duration of sensory block, and allowing a pain-free period. The incidence of adverse effects, including nausea/vomiting and shivering, was lower with dexmedetomidine than with placebo.

The mechanism of action for the sedative and analgesic effects of dexmedetomidine can be explained by its highly selective α_2 adrenoceptor (α_2-AR) agonist.[27] The α_2-ARs are widely expressed in the brain and spinal cord[28] and dexmedetomidine can pass the blood–brain barrier rapidly because of its high lipophilicity.[29] Therefore, dexmedetomidine may act via different administration routes, including intravenous injection and intravertebral injection. This beneficial,

safe effect for the neonate can also be explained by conscious sedation properties related to its highly selective α_2-AR agonist. By reducing release of norepinephrine and excitability of the postsynaptic membrane, dexmedetomidine inhibits the cortical arousal response, which is controlled by dorsal norepinephrine fibres from the nucleus coeruleus. However, function of the wake-up system still exists and sedative–hypnotic effects can be stopped by language stimulation.[30,31] Therefore, a physiological stimulus could cause the neonate to cry naturally after delivery. Additionally, because dexmedetomidine has a high placental retention for its fat-soluble characteristic,[16,32] a decrease in the placental transfer rate could explain the safe effect of dexmedetomidine, as indicated by previous reports.[33,34] As a result, dexmedetomidine has the potential for conscious sedation properties without neonatal respiratory depression. This can decrease the need for assisted ventilation, and subsequently reduce the incidence of neonatal morbidity and mortality.

Postoperative adverse effects are undesired outcomes after sedation or anaesthesia, and can result in unplanned admission or a delay in discharge from hospital. Dexmedetomidine may also have other advantages for postoperative adverse effects.[35] Numerous studies[36,37] have shown that infusion of dexmedetomidine commonly prevents postoperative shivering. The anti-shivering mechanism of dexmedetomidine is related to decreasing vasoconstriction, thresholds of shivering, or inhibiting central thermoregulation.[38] A previous meta-analysis by Wu et al.[39] reported that dexmedetomidine used in neuraxial anaesthesia could improve the characteristics of block and prolong postoperative analgesia, which is consistent with our findings. The mechanisms of this improvement are related to hyperpolarization of post-synaptic dorsal horn neurons,[40] α_2-AR agonists to motor neurons in the dorsal horn,[41] and upregulation of adrenergic receptor subtypes on the dorsal horn and the lumbar dorsal root ganglia.[42]

To the best of our knowledge, this is the first study to examine the safety of dexmedetomidine in caesarean section in neonates by using a meta-analysis of RCTs. The included studies were well designed and assessed as low risk or unclear. Sensitivity analysis was performed by changing the effects model of the statistical method. Therefore, these processes improved the accuracy of outcomes.

Our study has several limitations. The number of RCTs included in our meta-analysis and the sample size were small. Therefore, our conclusions are still based on a relatively small amount of studies. Furthermore, elective caesarean delivery was performed in parturients with normal pregnancy who underwent different types anaesthesia, and patients with pregnancy-induced complications were excluded. Finally, the different methods that were used for reporting outcomes in the six included studies may be considered as a source of heterogeneity. Therefore, further well-designed trials with a larger number of parturients are warranted to clarify the safety of dexmedetomidine before it can be recommended for routine clinical use.

In conclusion, the current meta-analysis suggests that dexmedetomidine is safe and effective for neonates who are delivered by caesarean section. Additionally, administration of dexmedetomidine via intravertebral injection could improve the characteristics of motor and sensory block and prolong the pain-free period. Dexmedetomidine can also reduce the incidence of postoperative adverse effects, such as nausea/vomiting and shivering. Our study suggests extension of the clinical value of dexmedetomidine.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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