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Dexmedetomidine as an adjuvant for single spinal anesthesia in patients undergoing cesarean section: a system review and meta-analysis

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Abstract

Objective: Previous studies reported the effect of dexmedetomidine on intrathecal anesthesia. In this review, we explored the impact of dexmedetomidine as an adjunct for lumbar anesthesia in patients undergoing cesarean section.

Methods: Two authors searched eligible random controlled trials in electronic databases, including PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, the Chinese BioMedical database, Chinese Scientific Journal Database, and the Wanfang database.

Results: Ten trials comprising 970 patients were included in this review. Intrathecal dexmedetomidine significantly reduced the onset time of sensory block (standardized mean difference (SMD), −1.50, 95% confidence interval (CI) −2.15, −0.85, $I^2 = 92\%$) and motor block (SMD −0.77, 95% CI −1.50, −0.49, $I^2 = 60\%$) and prolonged the block duration time (sensory block: SMD 2.02, 95% CI 1.29, 2.74, $I^2 = 93\%$; motor block: SMD 1.90, 95% CI 1.07, 2.74, $I^2 = 94\%$). Patients who received dexmedetomidine showed a lower incidence of shivering. No significant difference was reported for the neonatal Apgar score and other complications.

Conclusion: The use of intrathecal dexmedetomidine during cesarean section can shorten the onset time of spinal anesthesia and enhance the effect of local anesthetic. It has no significant impact on neonates and there were no other adverse events.

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Keywords
Dexmedetomidine, spinal anesthesia, cesarean section, meta-analysis, local anesthetic, neonate, adverse events

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Background

Among pregnant women who undergo cesarean section, subarachnoid block has been a common and safe anesthesia method.[1–3] To decrease maternal discomfort, sensory block has been required up to the level of T4.[4] However, this level for single spinal anesthesia requires a high dose of local anesthetics such as bupivacaine, which might be closely related to hypotension, shivering, pruritus, nausea, and vomiting.[5] Various studies demonstrated that different drugs could enhance the effect of local anesthetics,[6–8] but no definitive conclusion has been reached. Therefore, it is necessary to find an auxiliary drug that enhances anesthesia and has fewer side effects.

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that produces sedative and analgesic effects[9], and it has been widely used in different types of nerve blockade.[10–12] Previous studies confirmed that dexmedetomidine might play a role in improving the effectiveness of spinal anesthesia while administered as an adjunct.[13,14] A meta-analysis indicated that dexmedetomidine could shorten the spinal anesthesia onset time in cesarean section.[15] However, the inclusion criteria are flawed, and neonate safety was not assessed. Thus, we performed this meta-analysis to explore the function of dexmedetomidine as an adjunct for spinal anesthesia in cesarean section.

Materials and methods

Reporting for this systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] All data in this study were from published studies and did not involve patients directly. Therefore, ethics committee approval and informed consent were not required.

Systematic literature search

Two independent investigators (Lu and Yuan) searched PubMed, the Cochrane library, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), the Chinese BioMedical database (CBM), Chinese Scientific Journal Database (VIP), and the Wanfang database from database establishment to 30 September 2019, to find available randomized controlled trials (RCTs) without language restrictions. The search strategy for PubMed was as follows: ((“caesarean section”[All Fields] OR “cesarean section” [MeSH Terms] OR (“cesarean”[All Fields] AND “section”[All Fields]) OR “cesarean section”[All Fields]) OR (“cesarean section”[MeSH Terms] OR (“cesarean” [All Fields] AND “section”[All Fields]) OR “cesarean section”[All Fields] OR “c section”[All Fields])) OR (“cesarean section”[MeSH Terms] OR (“cesarean” [All Fields] AND “section”[All Fields]) OR “cesarean section”[All Fields] OR (“abdominal”[All Fields] AND “deliveries” [All Fields]) OR “abdominal deliveries”[All Fields])) AND ((((“dexmedetomidine” [MeSH Terms] OR “dexmedetomidine” [All Fields] OR “mpv 1440”[All Fields]) OR (“dexmedetomidine”[MeSH Terms]

OR "dexmedetomidine"[All Fields] OR "precedex"[All Fields])) OR ("dexmedetomidine" [MeSH Terms] OR "dexmedetomidine"[All Fields] OR ("dexmedetomidine"[All Fields] AND "hydrochloride"[All Fields]) OR "dexmedetomidine hydrochloride" [All Fields])) OR ("dexmedetomidine" [MeSH Terms] OR "dexmedetomidine" [All Fields])). We also manually retrieved relevant studies and references from the included studies.

Selection criteria and data extraction

The inclusion criteria were as follows: (1) Patients (P): patients undergoing caesarean section under lumbar anesthesia; (2) Interventions (I): dexmedetomidine administered as an adjunct in spinal anesthesia; (3) Comparisons (C): local anesthetic plus dexmedetomidine vs. local anesthetic plus placebo; (4) Outcomes (O): the effect on the mother and neonate is provided; and (5) Study design (S): an RCT. The exclusion criteria included the following: (1) other types of anesthesia and surgery; (2) intravenous injection of dexmedetomidine; and (3) duplicate publications.

Two reviewers (Li and Yuan) independently extracted the following items: author, year of publication, sample size, anesthetic techniques, and outcomes. A conflict of opinion was resolved by a third reviewer (Zhou).

Quality and risk assessment

The risk of bias for the included studies was assessed based on the Cochrane guidelines (RevMan version 5.3, Copenhagen: The Nordic Cochrane Centre, 2014). The criteria were as follows: random sequence generation, allocation concealment, double-blinding, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each trial was classified into a high risk, unclear, or low risk category. The assessment was reviewed independently by two team members (Lu and Yuan), and disagreement was resolved by a third reviewer (Zhou).

The quality of evidence was evaluated using Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[17] for the outcomes based on the following criteria: study design, risk of bias (for the included study), rating inconsistency in results (for the heterogeneity, $I^2 \geq 50\%$ without satisfactory explanation was considered suspect), rating indirectness of evidence (for the data converted from figures or different scales), and others. Each outcome was evaluated as high, moderate, low, or very low levels.

Statistical analysis

We performed this review using RevMan 5.3 (RevMan, version 5.3, Copenhagen). For dichotomous outcomes, we calculated a pooled risk ratio (RR) and 95% confidence intervals (CIs). For continuous data that were described as the median (range) in the studies, we converted it to the mean and standard deviation, based on the protocol.[18,19] The mean difference (MD) and 95% CI were calculated for continuous data with the same measure-evaluation methods and units. Otherwise, the standardized mean difference (SMD) was applied. A P-value of less than 0.05 was considered to be statistically significant. The heterogeneity of trials was assessed using I^2. High heterogeneity most likely existed because of the clinical and methodological factors, so the random effect model was applied in this meta-analysis even if I^2 was small. Funnel plots were performed to examine the publication bias.

Our primary outcomes were onset time and duration of sensory and motor block. Apgar score, occurrence of hypotension, bradycardia, shivering, nausea, and vomiting were secondary outcomes.

Results

Search results

Initially, 782 relevant trials were identified after the database search. We excluded 288 duplicate studies, and another 474 trials were excluded based on their irrelevant titles and abstracts. Then, we carefully evaluated the full-text of 20 studies. Five trials were excluded because of epidural–spinal combined anesthesia.[13,14,20–22] Two articles were excluded because they were not RCTs,[23,24] two articles were excluded because of the type of surgery,[25,26] and one trial was excluded because the control was not placebo.[27] Finally, ten RCTs were included in our meta-analysis.[4,28–36] The literature screening process is shown in Figure 1.

Assessment of bias

Seven studies[4,28–33] explicitly reported the method of random sequence generation and two trials[29,31] described allocation concealment. Double-blinding was used in seven trials.[4,28–33] Six studies[28,30,31,33,34,36] mentioned that the assessors were blinded, and they evaluated attrition bias. No selective reporting was reported. Five trials[28–30,32,33] did not have sample size calculations before interventions. The summary of the risk of bias is shown in Figure 2.

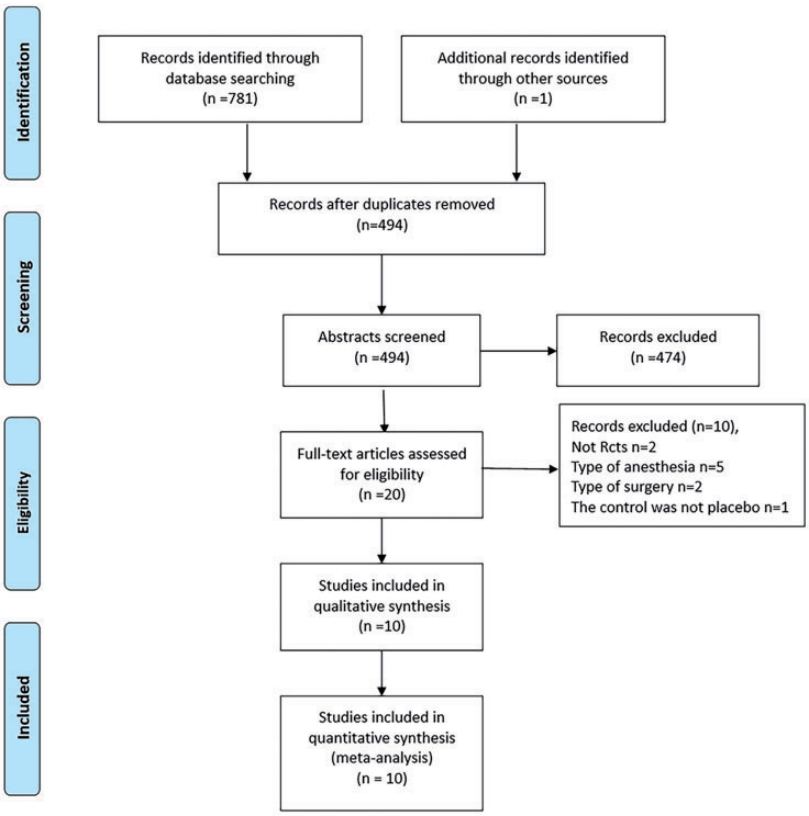

Figure 1. Flow chart of study retrieval.

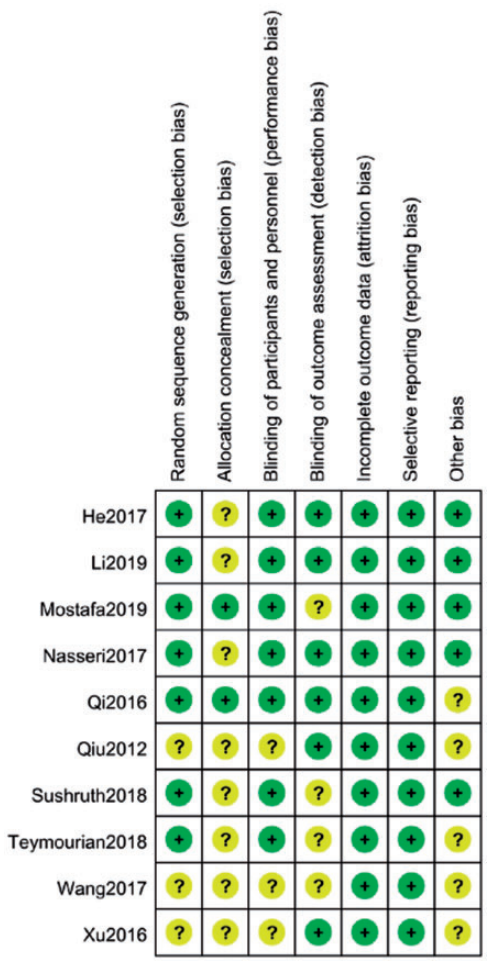

Figure 2. Risk bias in the included studies.

Study characteristics

Table 1 shows detailed information about the included studies. Dexmedetomidine was administrated as an adjunct for spinal anesthesia in all trials. The American Society of Anesthesiology (ASA) physical status ranged from I–III. The publication years were 2016 to 2019.

Synthesized results

Primary outcomes. Compared with placebo, patients in the dexmedetomidine group showed shorter sensory block onset time (SMD −1.50, 95% CI −2.15, −0.85, $P < 0.05$, $I^2 = 92\%$, Figure 3) and motor block onset time (SMD −0.77, 95% CI −1.50, −0.49, $P < 0.05$, $I^2 = 60\%$, Figure 4). Forest plots revealed that dexmedetomidine significantly prolonged the sensory block duration (SMD 2.02, 95% CI 1.29, 2.74, $P < 0.05$, $I^2 = 93\%$, Figure 5) and motor block duration (SMD 1.90, 95% CI 1.07, 2.74, $P < 0.05$, $I^2 = 94\%$, Figure 6).

Second outcomes. The Apgar score for the neonate was evaluated in five studies.[4,28,29,31,35] Forest plots show no difference for the Apgar scores (1-minute: MD 0.03, 95% CI −0.09, 0.15, $P > 0.05$, $I^2 = 7\%$; 5-minute: MD −0.01, 95% CI −0.08, 0.07, $P < 0.05$, $I^2 = 0\%$, Figure 7). Patients who administrated dexmedetomidine had a lower incidence of shivering (RR 0.32, 95% CI 0.21, 0.48, $P < 0.05$, $I^2 = 0\%$, Figure 8), while no significant differences were reported for other complications (Figures 9–11).

GRADE evaluation. The GRADE levels of evidence for onset time of sensory and motor block and the duration of sensory and motor block were moderate, while the other results (Apgar scores at 1 and 5 minutes, shivering, hypotension, bradycardia, and nausea and vomiting) had high GRADE levels (Table 2). The overall results are shown in Table 2.

Publication bias. We performed funnel plots for the onset time of sensory and motor block. The funnel plots showed a symmetric distribution, which indicates that there was no obvious publication bias.

Discussion

The current meta-analysis was performed to investigate the impact of dexmedetomidine as an adjuvant for single spinal

Table 1. Detailed information about the included studies.

Study	Sample size	ASA Grade	Anesthesia position	Local anesthetic	Intervention	Comparison	Outcome
Teymourian 2018[4]	152	I–II	Sitting	Bupivacaine	7.5 μg DEX	DEX vs. placebo	(5)
Sushruth 2018[32]	60	II	Right lateral	Bupivacaine	5 μg DEX	DEX vs. placebo	(1) (2) (3) (4) (6) (7) (9)
Qi 2016[31]	80	I–II	Lateral decubitus	Bupivacaine	5 μg DEX	DEX vs. placebo	(1) (2) (3) (4) (5) (6) (7) (8) (9)
Nasseri 2017[30]	50	I–II	Sitting	Bupivacaine	5 μg DEX	DEX vs. placebo	(6) (7) (8) (9)
Mostafa 2019[29]	60	I–II	Sitting	Bupivacaine	5 μg DEX	DEX vs. placebo	(1) (3) (5)
He 2017[28]	90	I–II	Left lateral	Bupivacaine	Group 1: 2.5 μg DEX Group 2: 5 μg DEX	DEX vs. placebo	(5) (7) (8)
Li 2019[33]	100	I–II	Left lateral	Bupivacaine	5 μg DEX	DEX vs. placebo	(1) (2) (3) (4) (6) (8) (9)
Qiu 2012[34]	80	II–III	Left lateral	Bupivacaine	5 μg DEX	DEX vs. placebo	(1) (2) (3) (4) (6) (9)
Wang 2017[35]	100	II–III	Left lateral	Bupivacaine	5 μg DEX	DEX vs. placebo	(1) (2) (3) (4) (5) (6) (8) (9)
Xu 2016[36]	120	I–II	Left lateral	Bupivacaine	6 μg DEX	DEX vs. placebo	(1) (2) (3) (4) (6) (9)

Abbreviations: ASA, American Society of Anesthesiology; DEX, dexmedetomidine.

anesthesia. The synthesized results showed that dexmedetomidine shortened the onset time of local anesthetic, prolonged the duration of sensory and motor block, and reduced the occurrence of shivering, while having no impact on the neonate. The drug-related side effects also did not increase.

Recently, dexmedetomidine has been commonly applied as an assistant drug for a subarachnoid block during the perioperative period.[37–39] A previous meta-analysis by Liu et al.[15] considered that the addition of dexmedetomidine could significantly reduce the onset time of spinal anesthesia. However, two trials[14,20] in that meta-analysis did not meet the inclusion criteria because of the combined spinal and epidural anesthesia. In addition, only studies published in English were included and neonate safety was not demonstrated. Furthermore, the effect of dexmedetomidine on the duration of local anesthetic has not been evaluated. Thus, it was necessary for us to conduct this review.

We found that dexmedetomidine can enhance the effect of local anesthetic and prolong the duration of analgesia. Several studies had a similar result.[40,41] Gautam et al.[42] suggested that dexmedetomidine is better than fentanyl as an intrathecal adjuvant to reduce visceral pain and in prolonged post-operative analgesia. Some studies considered that dexmedetomidine induces vasoconstriction by acting on the α2-adrenergic receptor to help prolong the period of analgesia,[43,44] while Yoshitomi et al.[45] suggested that dexmedetomidine directly affects its ability via the α2-adrenergic receptor.

Perioperative shivering is a common complication after spinal anesthesia. In our study, dexmedetomidine prevented the occurrence of shivering. The mechanism is complex. Several studies have demonstrated that dexmedetomidine alleviated shivering effects via α2-adrenergic receptors, which are widely distributed in the hypothalamus

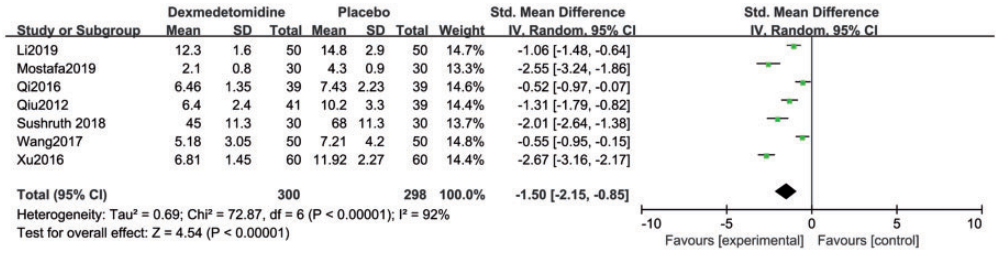

Figure 3. Forest plot of the pooled analysis showing the onset time of sensory block.

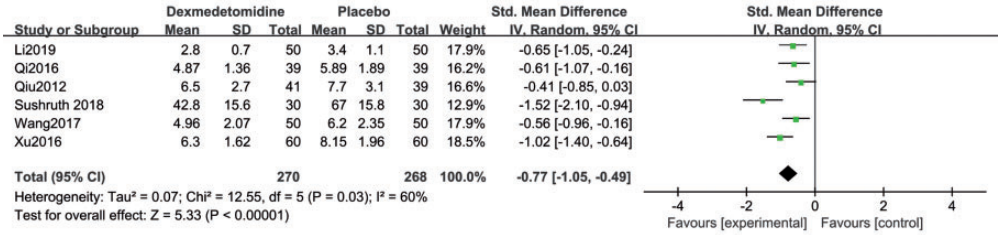

Figure 4. Forest plot of the pooled analysis showing the onset time of motor block.

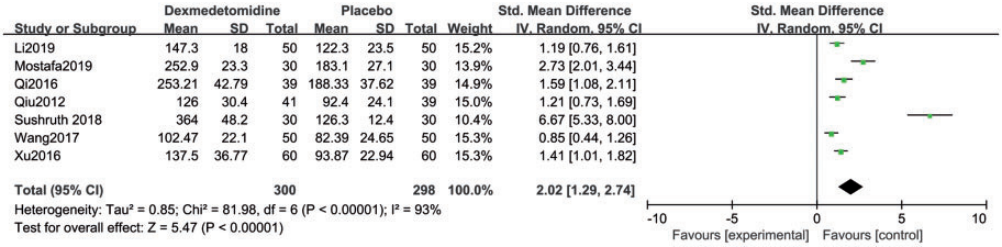

Figure 5. Forest plot of the pooled analysis showing the duration of sensory block.

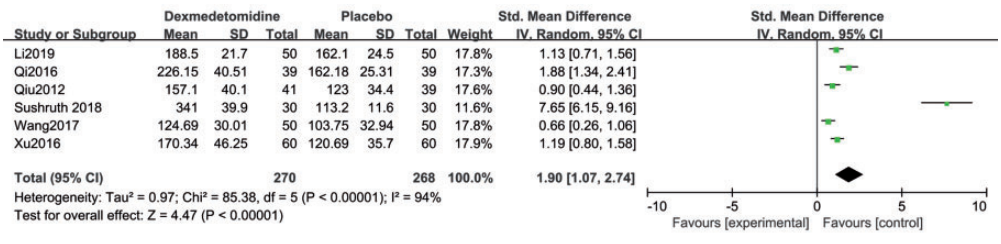

Figure 6. Forest plot of the pooled analysis showing the duration of motor block.

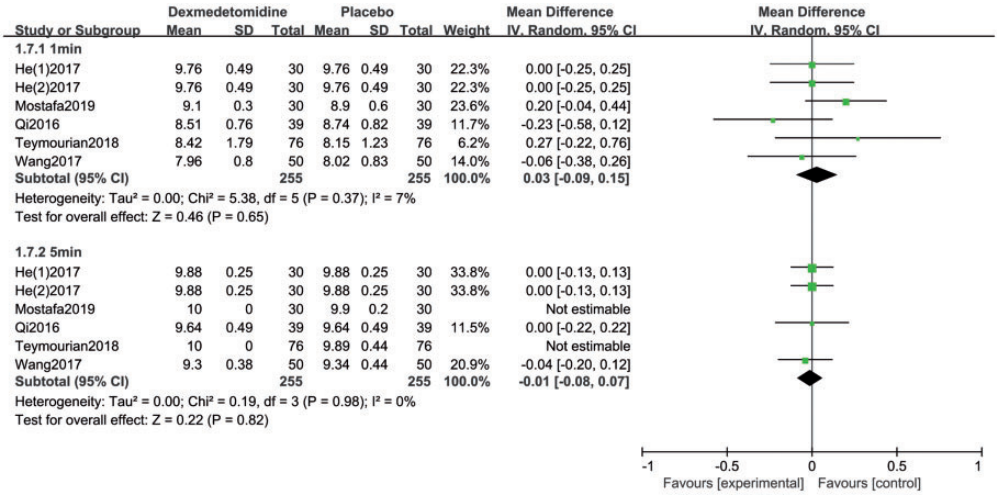

Figure 7. Forest plot of the pooled analysis showing the Apgar scores.

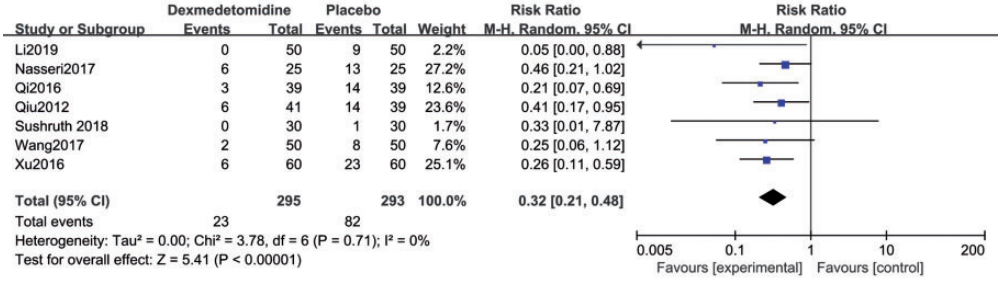

Figure 8. Forest plot of the pooled analysis showing the incidence of shivering.

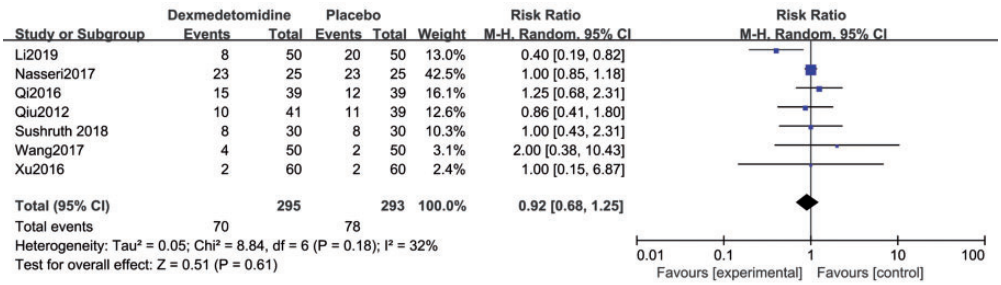

Figure 9. Forest plot of the pooled analysis showing the incidence of hypotension.

to mediate thermoregulatory inhibition.[46] Other studies confirmed that dexmedetomidine directly increased the temperature range without affecting thermoregulatory defenses, thereby decreasing the occurrence of shivering.[47,48]

The Apgar score is widely used for evaluating neonates.[49] In our study, 1- and

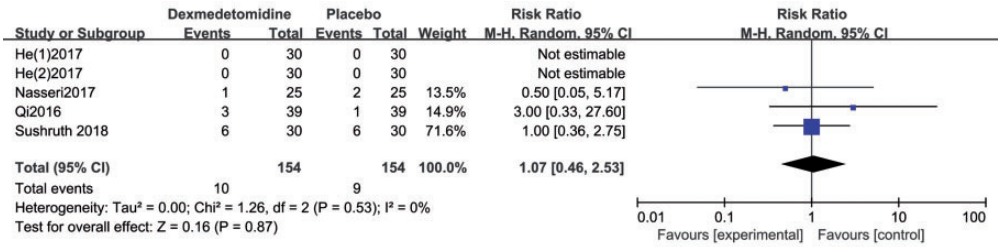

Figure 10. Forest plot of the pooled analysis showing the incidence of bradycardia.

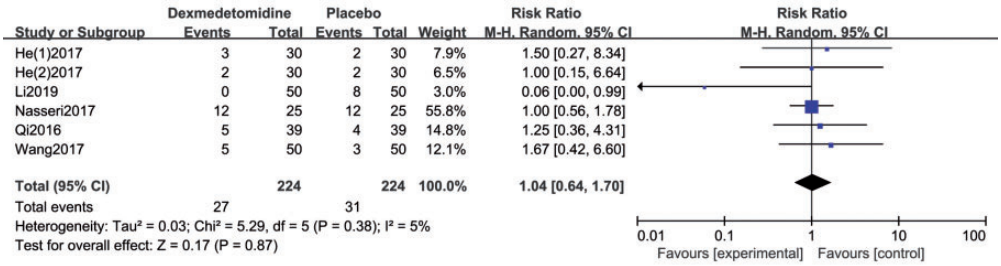

Figure 11. Forest plot of the pooled analysis showing the incidence of nausea and vomiting.

Table 2. Summary of the results.

Outcomes	RR/SMD/MD (95%CI)	P	I^2	GRADE
Onset time of sensory block	−1.50 (−2.15, −0.85)	<0.05	92%	⊕⊕⊕◯ MODERATE
Onset time of motor block	−0.77 (−1.05, −0.49)	<0.05	60%	⊕⊕⊕◯ MODERATE
Duration of sensory block	2.02 (1.29, 2.74)	<0.05	93%	⊕⊕⊕◯ MODERATE
Duration of motor block	1.90 (1.07, 2.74)	<0.05	94%	⊕⊕⊕◯ MODERATE
Apgar scores at 1 minute	0.03 (−0.19, 0.15)	N.S.	7%	⊕⊕⊕⊕ HIGH
Apgar scores at 5 minute	−0.01 (−0.08, 0.07)	N.S.	0%	⊕⊕⊕⊕ HIGH
Shivering	0.32 (0.21, 0.48)	<0.05	0%	⊕⊕⊕⊕ HIGH
Hypotension	0.92 (0.68, 1.25)	N.S.	32%	⊕⊕⊕⊕ HIGH
Bradycardia	1.07 (0.46, 2.52)	N.S.	0%	⊕⊕⊕⊕ HIGH
Nausea and vomiting	1.04 (0.64, 1.70)	N.S.	5%	⊕⊕⊕⊕ HIGH

Outcome: (1) sensory block duration; (2) motor block duration; (3) sensory block onset time; (4) motor block onset time; (5) Apgar score; (6) hypotension; (7) bradycardia; (8) nausea and vomiting; (9) shivering
N.S., not significant, CI, confidence interval; RR, relative risk; MD, mean difference; SMD, standardized mean difference.

5-minute Apgar scores and the umbilical blood pH were not significantly different between the two groups. Therefore, we considered that intrathecal dexmedetomidine was safe for neonates. Other complications, including hypotension, bradycardia, pruritus, nausea and vomiting, showed an occurrence rate that was not significantly different between the groups. In addition, no spinal anesthesia-related neurological complications were reported in the included studies. However, the dexmedetomidine dose in our study was small, ranging from 2.5 to 7.5 μg. More high-quality studies are required to ensure the dose safety of dexmedetomidine.

Heterogeneity was high in most of the outcomes, which likely has several explanations. First, most of the outcomes were continuous data, and there was high heterogeneity. Second, the units were inconsistent in the included studies. Third, there might be high clinical heterogeneity.

There were some limitations in this meta-analysis. There was a very small number of eligible RCTs and patients, which may be subject to a small-study effect bias. Various dosages of dexmedetomidine, different anesthesia techniques, and the surgeon's experience all lead to high clinical heterogeneity. Therefore, a random effects model was used in this meta-analysis. This meta-analysis does not have a registered protocol, which might cause some bias.

Conclusion

Intrathecal dexmedetomidine was shown to be safe for the mother and neonate. In addition, it can shorten the onset time of local anesthesia, prolong the block duration time, and decrease the occurrence of shivering without increasing the drug-related side effects. However, this result should be interpreted with caution because of the high heterogeneity. Further well-designed studies with a larger sample size are required to verify the efficacy and safety.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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