Efficacy of dexmedetomidine as a neuraxial adjuvant for elective cesarean sections: a meta-analysis of randomized trials

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Abstract: Objective: To evaluate the efficacy and safety of dexmedetomidine as a neuraxial adjuvant for elective cesarean section. Methods: We searched the randomized controlled trials (RCTs) assessing the effect of dexmedetomidine as a neuraxial adjuvant in elective cesarean section in PubMed, EMBase, Web of Science, EBSCO, and Cochrane library databases. Results: 11 RCTs were included. Overall, compared with control intervention in patients with elective cesarean section, dexmedetomidine intervention could significantly improve the characteristics of the block, including onset of sensory block (MD: -1.31 minutes; 95% CI: -2.68 to -0.06; P < 0.1), onset of motor block (MD: -0.79 minutes; 95% CI: -1.13 to -0.46; P < 0.05), duration of the sensory block (MD: 64.30 minutes; 95% CI: 21.67 to 106.93; P < 0.05) and duration of the motor block (MD: 24.69 minutes; 95% CI: 8.67 to 44.31; P < 0.05). Additionally, when compared with control group dexmedetomidine could prolong time to rescue analgesia (SMD: 3.81; 95% CI: 2.92 to 4.70; P < 0.05) and reduce the fentanyl consumption (RR=0.20, 95% CI: 0.10-0.38, P < 0.05). The incidence of shivering in the dexmedetomidine group was significantly lower than that in the control group (RR=0.41, 95% CI: 0.29-0.58, P < 0.05). The incidences of nausea and vomiting, bradycardia, hypotension and pruritus were not different between the two groups. Conclusion: Dexmedetomidine as a neuraxial adjuvant can improve the characteristics of the block, prolong time to rescue analgesia, reduce fentanyl consumption, and decrease the incidence of shivering during elective cesarean section.

Keywords: Dexmedetomidine, neuraxial anesthesia, cesarean section, meta-analysis

Introduction

Neuraxial anesthesia is widely used and preferred method for elective cesarean section since it has a number of benefits including lower incidence of adverse neonatal outcomes, higher cost-effectiveness while the patient remaining conscious throughout the procedure, shorter hospital stays following cesarean section when compared with general anesthesia [1-3]. However, neuraxial anesthesia has several disadvantages, such as inadequate pain relief, intraoperative shivering, lack of long lasting postoperative analgesia and so on. To improve neuraxial anesthesia and analgesia quality during both intra and post operation, aid early recovery from motor block, reduce the incidence of associated side effects, combined local anesthetics with adjuvant drugs such as opioids was well accepted currently to be used in clinical neuraxial anesthesia practice [4-6]. The adjuvants most commonly used in combination are opioids and clonidine.

Dexmedetomidine is a new and highly selective α₂-A receptor with sedative, anxiolytic, analgesic, anti-hypertensive and sympatholytic properties [7-9]. Pre-clinic evidence showed that dexmedetomidine, used as an adjuvants to local anesthetic for neuraxial anesthesia, can shorten the onset time of the block [10], decrease postoperative pain intensity [11], prolong the duration of the block [12], reduce the requirement of the analgesics [13] and lower the incidence of adverse effect [14]. Hence, we here conducted a meta-analysis to investigate the effects of dexmedetomidine as a neuraxial adjuvant on characteristics of the anesthesia, analgesia and adverse effects during elective cesarean section.
Methods

Systematic search and strategy

This systematic review was performed in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [15] and the Cochrane Handbook for Systematic Reviews of Interventions [16]. All data were collected from previous published studies, and thus, no ethical approval and patient consent were required.

PubMed, EMBASE, Web of science, EBSCO, and the Cochrane library were systematically searched up to November 10, 2017, no limitation was enhanced. We also searched the reference lists of the retrieved studies and relevant reviews to include additional eligible studies. The search strategy consisted of a combination of free text words and Medical Subject Headings (MeSH) terms. The search equation for PubMed was adapted for each database.

Inclusion criteria

The inclusion criteria were as follows: (1) original and independent studies; (2) RCTs; (3) neuraxial dexmedetomidine was delivered via any intravertebral routes, such as epidural, intrathecal, and caudal route in women undergoing elective cesarean sections.

Exclusion criteria

Any study with one of the following conditions was excluded: (1) non-RCTs; (2) abstracts from conferences, letters to the editor, or animal studies; (3) systematic reviews.

Assessment of study quality

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [17]. Two reviewers separately assessed the quality of the studies. Any disagreement was resolved by negotiation with a third reviewer. The main categories consisted of the following 4 items: (1) whether the study was described as randomized; (2) whether allocation concealment was used and whether the method was correct; (3) whether the study was described as double-blind; and (4) whether there were withdrawals or dropouts.

Statistical analysis

We performed a meta-analysis using Review Manager (Version 5.3.; The Cochrane Collaboration, Oxford, UK) and examined heterogeneity by conducting the chi-square test. Continuous data were assessed by pooled weighted mean difference (MD) or pooled standard mean difference (SMD) with 95% confidence intervals (CIs). SMD was calculated for the time to rescue analgesia because of different units. Dichotomous outcomes were assessed by risk ratios (RRs) with 95% CIs. If $P$ was < 50%, there was homogeneity, and the fixed-effects model was used to conduct the meta-analysis. If $P$ was > 50% and heterogeneity between the groups needed to be combined, the random-effects model was selected for performing the meta-analysis.
# Table 1. Characteristics and Jadad scores of the included studies in the meta-analysis

<table>
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<tr>
<th>No.</th>
<th>Ref.</th>
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<th>Number</th>
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<th>Surgery duration (min)</th>
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<td></td>
<td></td>
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<td>/</td>
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<td>/</td>
<td>48±8.5</td>
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<td>32.64±5.24</td>
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<td>51.04±19.39</td>
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<td></td>
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<td>Dexmedetomidine 3 μg</td>
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<td>39</td>
<td>47.3±11.5</td>
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<td>Control</td>
<td>20</td>
<td>29.5±3.9</td>
<td>38.5</td>
<td>48.0±8.8</td>
<td>Intrathecal 10 mg bupivacaine</td>
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</table>
Results

Literature screening

In accordance with the search strategy, 221 articles were included in the initial search. Of these, 125 articles were duplications and were excluded. Then, 16 articles were selected after excluding non-relevant literature and nonoriginal studies by reading titles and abstracts. A further 5 studies were then excluded because of a lack of intended intervention and conference abstracts. Finally, 11 studies [18-28] fulfilled the criteria for systematic review and meta-analysis. The study selection processes are shown in Figure 1.

Data extraction and evaluation of quality

The basic information of the 11 eligible RCTs in the meta-analysis is shown in Table 1. The doses and methods of dexmedetomidine were different in each RCT. They were epidural 15 mL 0.75% ropivacaine plus dexmedetomidine 1 μg/kg versus epidural 15 mL 0.75% ropivacaine [18]; intrathecal 10 mg bupivacaine plus 10 μg dexmedetomidine versus intrathecal 10 mg bupivacaine [20, 26], intrathecal 10 mg bupivacaine plus 5 μg dexmedetomidine versus intrathecal 10 mg bupivacaine [22, 27], intrathecal 12.5 mg bupivacaine plus 10 μg dexmedetomidine versus intrathecal 12.5 mg bupivacaine [23], intrathecal 10 mg bupivacaine with epidural 10 mL 0.25% bupivacaine plus mixture of fentanyl 100 μg and dexmedetomidine 1 μg/kg in 10 mL 0.9% sodium chloride versus intrathecal 10 mg bupivacaine with epidural 10 mL 0.25% bupivacaine plus fentanyl 100 μg in 10 mL 0.9% sodium chloride [24], epidural 10 mL 0.25% bupivacaine plus fentanyl 50 μg and dexmedetomidine 0.5 μg/kg versus epidural 10 mL 0.25% bupivacaine plus fentanyl 50 μg [25], intrathecal 10 mg bupivacaine plus 5 μg (or 3 μg) dexmedetom-

dine versus intrathecal 10 mg bupivacaine [28], intrathecal 10 mg bupivacaine plus 10 μg dexmedetomidine versus intrathecal 15 mg bupivacaine [21], intrathecal 10 mg bupivacaine plus 5 μg (or 2.5 μg) dexmedetomidine versus intrathecal 10 mg bupivacaine [19]. Two researchers independently evaluated the quality using the Jadad scale. The quality of the original literature is shown in Table 1.

Meta-analysis results

Characteristics of the block

The characteristics of spinal blockade are summarized in Table 2. When compared to control group, the dexmedetomidine group showed shorter time of onset to block, including onset of sensory block (MD: -1.31 minutes; 95% CI: -2.68 to -0.06; P < 0.1) and onset of motor block (MD: -0.79 minutes; 95% CI: -1.13 to -0.46; P < 0.05). The duration of the block were significantly longer in the dexmedetomidine group compared with the control group, the duration of the sensory block (MD: 64.30 minutes; 95% CI: 21.67 to 106.93; P < 0.05), the duration of the motor block (MD: 24.69 minutes; 95% CI: 8.67 to 44.31; P < 0.05). Additionally, Dexmedetomidine could prolong time to rescue analgesia (SMD: 3.81; 95% CI: 2.92 to 4.70; P < 0.05) and, which was also statistically significant as compared with control group (Table 2).

Fentanyl consumption

As for the fentanyl consumption, 2 studies were included. The heterogeneity test both intraoperatively and postoperatively showed that I²=0%, and thus the fixed-effects model was used for the meta-analysis. Compared with control intervention, dexmedetomidine intervention lower the fentanyl usage both intraop-
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Adverse effects

Effect of dexmedetomidine on nausea and vomiting: 11 studies were included. The heterogeneity test showed that $I^2=0\%$, and thus the fixed-effects model was used for the meta-analysis. Compared with control intervention, dexmedetomidine intervention showed similar incidence of nausea and vomiting (RR=1.15, 95% CI: 0.48-2.72, $P=0.76$; Figure 4).

Effect of dexmedetomidine on pruritus: 9 studies were included. The heterogeneity test showed that $I^2=0\%$, and thus the fixed-effects model was used for the meta-analysis. Compared with control intervention, dexmedetomidine intervention showed similar incidence of pruritus (RR=1.15, 95% CI: 0.71-1.56, $P=0.79$; Figure 3).

Effect of dexmedetomidine on bradycardia: 8 studies were included. The heterogeneity test showed that $I^2=0\%$, and thus the fixed-effects model was used for the meta-analysis. Compared with control intervention, dexmedetomidine intervention showed similar incidence of bradycardia (RR=1.44, 95% CI: 0.75-2.79, $P=0.27$; Figure 5).
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Effect of dexmedetomidine on hypotension: 7 studies were included. The heterogeneity test showed that $I^2=10\%$, and thus the fixed-effects model was used for the meta-analysis. Compared with control intervention, dexmedetomidine intervention showed similar incidence of hypotension (RR=1.05, 95% CI: 0.81-1.36, $P=0.70$; Figure 6).

Effect of dexmedetomidine on shivering: 9 studies were included. The heterogeneity test showed that $I^2=26\%$, and thus the fixed-effects model was used for the meta-analysis. Compared with control intervention, dexmedetomidine intervention showed significantly reduced incidence of shivering (RR=0.41, 95% CI: 0.29-0.58, $P<0.05$; Figure 7).

Discussion

Our meta-analysis clearly suggested that dexmedetomidine as a neuraxial adjuvant could improve the characteristics of the block, such as shortening the onset time of the block, prolonging the duration of the block, prolonging rescue analgesia time, increasing dose of fentanyl consumption, decreasing the incidence of shivering, but had no effect on nausea and vomiting, bradycardia, hypotension and pruritus.

The anesthesia blockade characteristics shown in Table 2 were improved and fentanyl consumption was lowered in the dexmedetomidine intervention group as compared with control.
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Figure 6. Forest plot for the meta-analysis of hypotension.

Figure 7. Forest plot for the meta-analysis of shivering.

group. These findings were similar to previous numerous studies [29-31]. The mechanisms were complicated and may be related to the suppression of C-fiber transmitter release and the hyperpolarization of post-synaptic dorsal horn neurons, $\alpha_2$-adrenoceptor agonists to motor neurons in the dorsal horn, and upregulation of the adrenergic receptor subtypes on the dorsal horn and the lumbar dorsal root ganglia [32-35].

Shivering is a common complication during caesarean section. The incidence of shivering ranges from 5% to 65% in patients undergoing caesarean section under neuraxial anesthesia. Some factors including aging, sensory-block levels, temperatures of the intrathecal local anesthetics, intravenous fluids, and operation room had been considered relating the shivering [36, 37]. For parturients, severe shivering can lead to increased consumption of oxygen, a rise in production of CO$_2$ and blood sugar, acceleration of heart rate, and in severe cases, severe hypoxaemia and acidosis. Dexmedetomidine, a highly selective and a novel $\alpha_2$-adrenergic receptor agonist, demonstrates almost 8-10 times higher affinity to $\alpha_2$-ARs than clonidine. When administered as a neuraxial adjuvant, dexmedetomidine can quickly bind to dorsal horn of the spinal cord $\alpha_2$-ARs, subsequently to inhibit the spontaneous firing rate of neurons and sympathetic tone [38, 39].
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The anti-shivering mechanism of dexmedetomidine can be explained by inhibiting central thermoregulation and attenuation of hyperadrenergic response to perioperative stress [39, 40].

The exact aetiology of perioperative nausea and vomiting remains unclear. A variety of factors including cerebral ischemia, blocking of sympathetic nerves and hypotension are likely to cause nausea and vomiting [41]. In our meta-analysis, dexmedetomidine has little effect on nausea/vomiting during caesarean section. Bradycardia and hypotension are the most significant side effects reported for the use of α₂-adrenoreceptor agonists as a neuraxial adjuvant, but in the present study, the incidence of bradycardia and hypotension were not significant. The incidence of pruritus was also not significant.

Several limitations of this meta-analysis should be taken into account. First, the number of included RCTs was too small. Second, the doses and methods of dexmedetomidine in the included studies were different, and might have some impact on the pooled results. Furthermore, we only included published literature, the search strategy and publication bias also could have affected the results of this study.

Dexmedetomidine as a neuraxial adjuvant can improve the characteristics of the block, prolong the time to rescue analgesia and reduce the fentanyl consumption, and decrease the incidence of shivering in patients undergoing elective caesarean section. Dexmedetomidine was recommended to be administrated for elective caesarean section, but more studies should investigate its optimal dose and method.

Acknowledgements

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Disclosure of conflict of interest

None.

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