Review Article
The effect of different doses of intrathecal dexmedetomidine on spinal anesthesia: a meta analysis

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Abstract: Background: Some studies indicated dexmedetomidine had synergistic effect on spinal anesthesia when using intrathecally. Several studies also compared the effect of different doses of dexmedetomidine on spinal anesthesia. However, the results were inconsistent. We performed this meta-analysis to investigate the safety and efficacy of different doses of dexmedetomidine on spinal anesthesia. Methods: Pubmed, Embase and Cochrane library were searched. All randomized controlled trials that compared the effect of different doses of dexmedetomidine on spinal anesthesia were included. Sensory and motor block onset times, block durations, duration of analgesia, postoperative anesthetic consumption, and side effects were analyzed. Sensory block duration was our primary outcome. Meta-analysis was performed using a random effects model. Results: Nine randomized controlled trials were included in our meta-analysis. Compared with low-dose dexmedetomidine group, high-dose dexmedetomidine group prolonged sensory block duration by 36.06 min [95% CI: 33.90, 38.22, P<0.00001], decreased sensory and motor block onset times by 0.69 min [95% CI: 0.25, 1.13, P=0.002] and 0.62 min [95% CI: 0.22, 1.02, P=0.002], respectively, and prolonged motor block duration by 54.27 min [95% CI: 23.18, 85.36, P=0.0006]. High-dose dexmedetomidine also prolonged the duration of analgesia by 108.13 min [95% CI: 52.77, 163.50, P=0.0001], and decreased postoperative anesthetic consumption was decreased by 60.1 mg [95% CI: 7.83, 112.36, P<0.00001]. However, the risk of bradycardia was increased [OR, 1.91, 95% CI: 1.06, 3.43; P=0.03] in high-dose intrathecal dexmedetomidine group. Conclusion: Increasing the dose of intrathecal dexmedetomidine may prolong the action of spinal anesthesia. However, the risk of bradycardia was increased at the same time.

Keywords: Different dose, dexmedetomidine, spinal anesthesia, meta-analysis

Introduction

Spinal anesthesia provides solid analgesic effect by inhibiting nociceptive transmission from peripheral to central nerves system [1, 2]. It blunts the “stress response” to surgery and decreases intraoperative blood loss and the risk of postoperative thromboembolic events [3]. It is still the first choice in lower abdominal and lower limb surgeries. However, due to the relatively short action duration of currently available local anesthetics, these advantages can be limited [4-6]. A variety of adjuvants including dexmedetomidine (Dex) have been used to prolong the action duration of spinal anesthesia [7-17]. Dex, a highly selective α₂-adrenergic receptors (α₂ AR) agonist, have sedative and analgesic properties. It exerts its analgesic actions both at the spinal and supraspinal levels [18]. Some studies indicated intrathecal Dex can prolong the action duration of spinal anesthesia and reduce postoperative anesthetic consumption compared with normal saline [14, 15]. Some studies also compared the effect of different doses of intrathecal Dex on spinal anesthesia and the dose of intrathecal Dex ranged from 2 ug to 15 ug [16, 17, 19, 20]. However, the results were unclear and inconsistent. As a result, we performed this meta-analysis to compare the efficacy and safety of different doses of intrathecal Dex on spinal anesthesia.

Methods

This meta-analysis was conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [21].
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Literature search and study identification

The PubMed, Embase, and Cochrane Library databases were searched for studies evaluated the effects of different doses of intrathecal Dex on spinal anesthesia. The following search strategy was used: (dexmedetomidine OR precedex) AND (intrathecal OR subarachnoid). In addition, a hand search in reference sections of included trials, relevant review articles, and published meta-analyses was performed to identify potentially eligible studies. There was no publication language restriction. Two reviewers (YZ & ZS) independently screened the database search for titles and abstracts. If either reviewer felt a title and abstract met study eligibility criteria, the full text of the study was retrieved.

All available randomized controlled trials (RCTs) that meet the following inclusion criteria were included: (i) population: patients that received single-injected spinal anesthesia without general anesthesia; (ii) intervention: single dose of intrathecal dexmedetomidine; (iii) comparison: different doses of intrathecal dexmedetomidine; (iv) outcome parameters: sensory and motor block onset times, sensory and motor block durations, duration of analgesia, postoperative anesthetic consumption (PAC) and side effects (bradycardia and hypotension).

Data abstraction and quality assessment

Two reviewers (YZ & ZS) independently abstracted relevant information from each eligible study using a standardized form. The following information was extracted from each included study: first author, year of publication, surgery type, number of patients enrolled, and Dex doses. Following outcomes information was extracted if reported: sensory block onset and duration, motor block onset and duration, duration of analgesia, PAC and side effects (bradycardia and hypotension). Sensory block duration and was our primary outcome. The Jadad scale was used to assess the methodological quality of RCTs [22]. Disagreements between the investigators were resolved by discussion. When necessary, a third investigator (LK) helped to reach a consensus with all investigators.

Statistical analysis

The meta-analysis was performed using the Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Mean differences (MD) and odds ratios (OR) were calculated to compare continuous and dichotomous variables, respectively. All results were reported with 95% confidence intervals (CIs). Continuous variables that presented as median and range values, mean and standard deviations were calculated using the technique described by Hozo et al. [23]. The $\chi^2$ test was used for the heterogeneity test. Heterogeneity was quantified using the $I^2$
## Table 1. Main character of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Jadad score</th>
<th>Surgery</th>
<th>Space</th>
<th>Local anesthetic</th>
<th>Intervention (Dex)</th>
<th>Control group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh et al. [25]</td>
<td>2015</td>
<td>5</td>
<td>Lower abdominal</td>
<td>L3-L4/L4-L5</td>
<td>IsoRop 15 mg</td>
<td>10 ug (30) 5 ug (30)</td>
<td>NS (30)</td>
</tr>
<tr>
<td>Das A et al. [26]</td>
<td>2015</td>
<td>3</td>
<td>Abdominal hysterectomy</td>
<td>L3-L4</td>
<td>HyperBup 15 mg</td>
<td>10 ug (50) 5 ug (50)</td>
<td></td>
</tr>
<tr>
<td>Naithani et al. [24]</td>
<td>2016</td>
<td>4</td>
<td>Abdominal hysterectomy</td>
<td>L2-L3</td>
<td>IsoRop 15 mg</td>
<td>5 ug (36) 3 ug (35)</td>
<td></td>
</tr>
<tr>
<td>Halder et al. [27]</td>
<td>2014</td>
<td>5</td>
<td>Traumatized lower limb orthopaedic</td>
<td>L3-L4</td>
<td>HyperBup 15 mg</td>
<td>10 ug (40) 5 ug (40)</td>
<td></td>
</tr>
<tr>
<td>Yektaş A et al. [20]</td>
<td>2014</td>
<td>3</td>
<td>Inguinal</td>
<td>L4-L5</td>
<td>HyperBup 15 mg</td>
<td>4 ug (20) 2 ug (20)</td>
<td>NS (20)</td>
</tr>
<tr>
<td>Gupta M et al. [19]</td>
<td>2016</td>
<td>4</td>
<td>Lower abdominal/limb</td>
<td>L3-L4</td>
<td>HyperBup 15 mg</td>
<td>10 ug (30) 5 ug (30) 2.5 ug (30)#</td>
<td></td>
</tr>
<tr>
<td>Al-Mustafa et al. [16]</td>
<td>2009</td>
<td>5</td>
<td>Urological</td>
<td>L3-L4</td>
<td>IsoBup 12.5 mg</td>
<td>10 ug (21) 5 ug (21)</td>
<td>NS (22)</td>
</tr>
<tr>
<td>Eid et al. [17]</td>
<td>2011</td>
<td>4</td>
<td>Anterior cruciate ligament reconstruction</td>
<td>L3-L4/L4-L5</td>
<td>HyperBup 15 mg</td>
<td>15 ug (16) 10 ug (15)</td>
<td>NS (16)</td>
</tr>
<tr>
<td>Shaikh et al. [28]</td>
<td>2016</td>
<td>4</td>
<td>Urological/gynecological/orthopaedic</td>
<td>L3-L4</td>
<td>HyperBup 15 mg</td>
<td>10 ug (30) 5 ug (30)</td>
<td>NS (30)</td>
</tr>
</tbody>
</table>

Note: Dex = Dexmedetomidine; HyperBup = Hyperbaric Bupivacaine; IsoBup = Isobaric Bupivacaine; NS = Normal saline. IsoRop = Isobaric Ropivacaine. # = The trial had three dexmedetomidine group without control group.
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statistic. When $I^2$ was 50% or lower, a low heterogeneity was rated, otherwise a high heterogeneity was rated. Subgroup analysis was performed according to different definition of outcomes. Funnel plot was used to assess the publication bias. Meta-analysis was performed using a random effects model. Statistical significance was set at a $P$ value $\leq$ 0.05.

Results

Literature search and study selection

In total, 633 studies were identified through the initial search. Of the 633 studies, 631 studies were identified through database search, including 143 in PubMed, 430 in Embase and 58 in Cochrane Library and 2 studies were identified through relevant articles reference list. Of the 633 citations, 191 were duplicates and 433 were removed through titles and abstracts. Full-text of the remaining 9 eligible studies were screened. All 9 studies were included in the final meta-analysis. The flow diagram of search strategy and study selection was presented in Figure 1.

Characteristics of the included studies

All of the 9 studies were published from 2009 to 2016 and designed as RCT. The dose of intrathecal Dex ranged from 2 ug to 15 ug. One trial had three different doses of intrathecal Dex, the doses were 2.5 ug, 5 ug, and 10 ug. The remaining 8 trials all had two different doses of Dex. Five trials performed spinal tap at L3-L4 intervertebral space, two trials at L3-L4 or L4-L5 intervertebral space, one trial at L2-L3, and one trial at L4-L5. Four trials designed without normal saline control group and 5 trials designed with normal saline control group. Six trials used hyperbaric bupivacaine, two trials used isobaric ropivacaine and one trial used isobaric bupivacaine. The main characteristics of the included studies were presented in Table 1.

Quality assessment of included studies

The Jadad score of each included study was presented in Table 1. Two studies had a score of 3, four studies had a score of 4 and three studies had a score of 5. The median quality score was 4 (range from 3 to 5).

Primary outcome

Sensory block duration: Sensory block duration was reported in all 9 trials, and the definition varied from trial to trial. High-dose Dex group increased sensory block duration by 36.06 min [95% CI: 33.90, 38.22, $P<0.00001$]. The het-
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erogeneity was significant ($I^2=99\%$). Subgroup analysis was performed according to different definition of sensory block duration. High-dose dexmedetomidine group increased time for sensory block regression to S1 by 82.74 min [95% CI: 56.14, 109.34, $P<0.00001$], regression to S2 by 64.54 min [95% CI: 25.31, 103.77, $P=0.001$] and increased time for two dermatomal regression by 29.90 min [95% CI: 0.02, 59.83, $P=0.05$]. The heterogeneity was still significant in subgroup analysis. The results were presented in Figure 2. A funnel plot of studies included in primary outcome of sensory block duration was created to explore publication bias. Figure 3 showed a symmetric distribution around the effect estimate, indicating there may be minimal publication bias in the included studies.

Secondary outcomes

All the results of secondary outcomes were presented in Table 2.

Sensory block onset time: Onset time of sensory block was reported in 7 trials, and the definition was time for sensory block reach T10 dermatomal. Sensory block onset time was decreased by 0.69 min [95% CI: 0.25, 1.13, $P=0.002$] with high dose intrathecal DEX. The value of $I^2$ (89%) indicating a significant heterogeneity.

Motor block onset time: Motor block onset time was reported in 7 trials, and the definition was time for motor block reach Bromage score (BS) 3 [19] or Modified Bromage score 3 [16, 24-28]. High-dose Dex group decrease motor block onset time by 0.62 min [95% CI: 0.22, 1.02, $P=0.002$]. The heterogeneity was significant ($I^2=75\%$).

Motor block duration: Motor block duration was reported in 8 trials. The definition was time to regression to BS 0. High-dose intrathecal Dex increased motor block duration by 54.27 min [95% CI: 23.18, 85.36, $P=0.0006$]. The heterogeneity was high ($I^2=99\%$).

Duration of analgesia: Duration of analgesia was reported in 6 trials, and the definition was time to first postoperative anesthetic requirement. High-dose Dex group increased the duration of analgesia by 108.13 min [95% CI: 52.77, 163.50, $P=0.0001$]. The value of $I^2$ was 99%.

Postoperative anesthetic consumption: Postoperative anesthetic consumption was reported in 3 trials. Two trials used diclofenac sodium and one trial used tramadol. Compared with low-dose group, high-dose group decrease postoperative anesthetic consumption by 60.1 mg [95% CI: 7.83, 112.36, $P<0.00001$]. The value of $I^2$ was 95%.

Dex-related side effects: Bradycardia was reported in 7 trials. High-dose Dex group increase the risk of bradycardia (OR, 1.91; 95% CI: 1.06, 3.43; $P=0.03$). The value of $I^2$ was 0%. Hypotension was reported in 7 trials. High-dose Dex group increase the risk of hypotension (OR, 1.44; 95% CI: 0.82, 2.52; $P=0.20$). The value of $I^2$ was 0%. The result was not statistically significant.

Discussion

Nine trials were included in our meta-analysis. The results of our meta-analysis of the literature suggested that increase the dose of intrathecal Dex can decrease sensory and motor block onset times. However, a decrease of approximate 0.69 min for sensory block onset and 0.62 min for motor block onset were considered as no clinical significance. High dose...
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intrathecal DEX can prolong the duration of both sensory and motor block, which may cause delaying rehabilitation compared with low dose intrathecal DEX. Besides, more attention needed to paid to patients to avoid accidental falls in early postoperative stage. The results of our meta-analysis showed that increase the dose of intrathecal DEX can also prolong the duration of analgesia and decrease postoperative anesthetic consumption, which may reduce the incidence rate of postoperative opioid-related side effects such as respiratory depression. It is noteworthy that increase the dose of intrathecal DEX may lead to increasing risk of transient and reversible bradycardia.

Previous meta-analysis focused on the comparison of Dex group and normal saline control group. The study of the effect of different doses of intrathecal DEX on spinal anesthesia was lacking. A meta-analysis found, compared with normal saline, intrathecal DEX can prolong the duration of sensory and motor block, time to first analgesic request, and decrease sensory block onset time [29]. Another meta-analysis found that intrathecal DEX can prolong the duration of sensory and motor block, time to first analgesic requirement and increase the risk of bradycardia, decrease sensory block onset time and the number of postoperative analgesic requirements [30]. Put the results of previous meta-analysis and our meta-analysis together we can draw a conclusion that there may be a dose-dependent relationship between the dose of intrathecal Dex and the action duration of spinal anesthesia. The results of previous meta-analysis and our meta-analysis, and the possible conclusion drawn from the two studies were showed in Table 3.

The safety of patient should be always considered seriously, especially when the use of intrathecal Dex is still not approved by the U.S. Food and Drug Administration (FDA) [31]. Most trials focused on transient, reversible side effects such as bradycardia and hypotension. The data of long term outcomes of patients and neurotoxicity of intrathecal Dex are lacking. A study showed that Dex may have a harmful effect on the myelin sheath when administrated via the epidural route in rabbits [32]. More attention should be paid to investigate the neurological effects of Dex. A recent study indicated intravenous and perineural DEX similarly prolong the duration of analgesia after interscalene brachial plexus block [33]. This reminded us intravenous and intrathecal Dex may have similarly effect on spinal anesthesia. More trials designed strict and consistent are needed to compare the efficacy and safety of intra-

<table>
<thead>
<tr>
<th>Table 2. Secondary outcomes</th>
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<tbody>
<tr>
<td>Outcome</td>
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<tr>
<td>Sensory block onset (min)</td>
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<tr>
<td>Motor block onset (min)</td>
</tr>
<tr>
<td>Motor block duration (min)</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
</tr>
<tr>
<td>PAC (mg)</td>
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<tr>
<td>Incidence of bradycardia (n/N)</td>
</tr>
<tr>
<td>Incidence of hypotension (n/N)</td>
</tr>
</tbody>
</table>

Note: * = Statistical significant; PAC = Postoperative anesthetic consumption.

<table>
<thead>
<tr>
<th>Table 3. Dexmedetomidine dose-dependent effect on spinal anesthesia</th>
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<tbody>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Abdallah FW (29)</td>
</tr>
<tr>
<td>Sensory block onset</td>
</tr>
<tr>
<td>Motor block onset</td>
</tr>
<tr>
<td>Sensory block duration</td>
</tr>
<tr>
<td>Motor block duration</td>
</tr>
<tr>
<td>Duration of analgesia</td>
</tr>
<tr>
<td>PAC</td>
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<tr>
<td>Bradycardia</td>
</tr>
</tbody>
</table>

Note: + = Statistical significant; - = Not statistical significant; N = Not mentioned; M = Maybe; MN = Maybe not; U = Unclear.
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However, several limitations should be taken into account when interpreting the results. First, the qualities of most trials included in our meta-analysis were generally low. Second, the primary outcome of our meta-analysis was pooled with significant heterogeneity. Although we performed subgroup analysis to identify the source of heterogeneity, there was still high heterogeneity. Besides, sensory block onset, motor block onset, duration of analgesia and PAC were all pooled with significant heterogeneity. Local anesthetics used in the trials (Bupivacaine or Ropivacaine), dose of intrathecal Dex (range from 2 to 15 ug), and different measurement criteria may lead to the significant heterogeneity together. As a result, the generalizability of the result of our study was limited. Third, most trials included in our study investigated two different doses of intrathecal Dex. More different doses of intrathecal Dex are needed to evaluated in further research.

Conclusion

Increasing the dose of intrathecal dexmedetomidine may prolong the action of spinal anesthesia. However, the risk of bradycardia is increased at the same time. More studies are needed in the future to testify the safety of intrathecal dexmedetomidine.

Disclosure of conflict of interest

None.

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