

**Dexmedetomidine as an Intrathecal Adjuvant for Subarachnoid Block for Women**

**Undergoing Elective Cesarean Section: An Integrative Review**

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## **Abstract**

**Aims and Objectives:** This integrative review aims to evaluate the safety and effectiveness of intrathecal dexmedetomidine as an adjunct to hyperbaric bupivacaine for elective cesarean sections using subarachnoid block (SAB).

**Methods:** A review of the literature was performed on the following databases: PubMed, CINAHL Complete, Google Scholar, and Cochrane Collection. Relevant research articles were critically evaluated and added to a literature matrix for synthesis.

**Results:** Intrathecal dexmedetomidine-5 mcg enhances the efficacy of intrathecal bupivacaine 0.75% by 24% in women undergoing elective cesarian sections using SAB. Intrathecal bupivacaine administered with 5 mcg dexmedetomidine produced a similar analgesic effect as intrathecal morphine 100 mcg, with less pruritus and shivering. Dexmedetomidine also provides similar SAB characteristics compared to opioids. Dexmedetomidine increases block onset time, duration of the block, and time to first pain medication post-operatively.

**Conclusion:** Dexmedetomidine is a safe and effective local anesthetic (LA) adjuvant for SAB for elective Cesarian sections. It has not been shown to increase adverse patient outcomes such as nausea/vomiting, bradycardia, decreased APGAR score, and hypotension compared to other LA adjuvants. Using intrathecal dexmedetomidine instead of opioids decreases the incidence of shivering and pruritus.

**Keywords:** intrathecal dexmedetomidine, subarachnoid blockade (SAB), Cesarean Section (c-section), intrathecal opioids, local anesthetic adjuvants

## **Introduction**

In the United States, roughly 1.2-1.3 million women undergo a cesarean section (c-section) every year.<sup>1</sup> In 2018 the CDC reported that the cesarean delivery rate in the United States was roughly 31.7% or 1,186,397 births, and since 1996 the rate of c-section has increase by % 20 for all births.<sup>2</sup> C-sections are now the most commonly done operating room procedure in the United States. C-sections account for approximately 0.004% of all inpatient hospital stays in the United States, making c-sections the most common OR procedure requiring hospitalization.<sup>3</sup>

Subarachnoid blockade (SAB) is the preferred method of anesthesia used for cesarian section. The local anesthetic widely utilized is bupivacaine 0.50% or 0.75% with a typical dose range of 7.5-15 mg to reach a T4 level blockage required for a c-sections. Intrathecal adjuvants are commonly used with LA to prolong the duration of the neuraxial blockade, increase onset on the blockade, improve the analgesic effect while reducing the amount of LA.<sup>3,4</sup> Morphine and fentanyl are the most widely used SAB adjuvants, but there is not a general consensus on the appropriate intrathecal dosage for parturients.<sup>5</sup> Providers commonly use fentanyl 10-25 mcg and or morphine 100-250 mcg as an adjuvant to bupivacaine 10-15 mg for c-sections. Neuraxial opioids improve analgesia and anesthesia for labor and surgical delivery but are associated with side effects (pruritus, respiratory depression, urinary retention, nausea/vomiting).<sup>6,7</sup> The incidence of pruritus is roughly 50- 80% in postpartum women after neuraxial opioids administration.<sup>8</sup>

Dexmedetomidine (DEX) is a highly selective alpha-2 agonist possessing analgesic, sedative, sympatholytic properties without late respiratory depression.<sup>9</sup> Dexmedetomidine has primarily been used as an intravenous agent for surgical and intensive care unit sedation and

recently has been assessed in central and peripheral nerve blocks. Multiple studies have suggested that the addition of intrathecal DEX to bupivacaine provides adequate anesthesia and postoperative pain relief compared to neuraxial opioids without causing any significant increase of adverse effect.<sup>7,10</sup>

The purpose of this integrative review is to evaluate the safety and effectiveness of intrathecal DEX as an adjunct to hyperbaric bupivacaine for elective c-sections using SAB. The questions that guided this integrative review were as follows:

- Does intrathecal DEX affect SAB characteristics with bupivacaine for c-sections?
- What maternal/fetal side effects are associated with intrathecal DEX?
- Is there a greater incidence of side effects associated with intrathecal DEX when compared to intrathecal opioids for c-sections?

## **Methods**

A review of the literature was performed on the following electronic databases: PubMed, CINAHL Complete, Google Scholar, and Cochrane Collection. Relevant research articles were critically evaluated and added to a literature matrix for synthesis. Keyword search alone and in combination included: intrathecal dexmedetomidine, subarachnoid blockade (SAB), cesarean section (c-section), intrathecal opioids, local anesthetic adjuvants, Precedex, neuraxial anesthesia, intrathecal Bupivacaine, and spinal. Initial electronic database resulted in 21 research articles. Articles were then evaluated for their reliability, validity, and rigor. Articles were selected based on study designs and methods that answered the guided research questions. Failure to meet these objectives resulted in the research article being omitted from this integrative review. Twelve relevant research articles (9-Randomized control trial and 3-meta-analysis) were then synthesized into an evidence matrix for data extraction. Web Based searches

included: Centers for Disease Control and Prevention (CDC), Department of Health and Human service (DHHS), and Healthcare Cost and Utilization Project of the DHHS. The search was limited to the English language and took place from February 2021 thru October 2021.

## **Results**

### ***Intrathecal dexmedetomidine mechanism of action***

DEX has been primary used for ICU and procedural sedation since FDA approval in 1999. DEX is a highly selective alpha 2- adrenergic agonist possessing analgesic, sedative, hypnotic, sympatholytic properties without late respiratory depression.<sup>9</sup> DEX binds to central nervous system pre/postsynaptic alpha-2 receptors resulting in a decreased norepinephrine level, causing sedation and analgesic effects. DEX has shown efficacy in decreasing the need for opioids, benzodiazepines, propofol, and other sedative medications. Short-term sedation has been shown to be safe in studies, although hypotension and bradycardia are the most significant side effects.<sup>9</sup> Recently, DEX has been gaining popularity as a LA adjuvant for central and peripheral nerve block. DEX is associated with sedative and analgesic effects in supraspinal and spinal sites and has an antinociceptive impact on both visceral and somatic pain. More importantly, this drug does not cross the placenta significantly, which is beneficial in cesarean delivery.<sup>11</sup>

### ***Dexmedetomidine effects on SAB characteristics***

Liu et al. (2019)<sup>3</sup> demonstrated that intrathecal DEX decreases the ED-95 for bupivacaine in SAB required for T6 for c-section. The sensory level was tested via 17 g blunt needle and the motor block was assessed with Bromage Score (0=No Block, 1= able to bend knees/ankles, 3= cannot bend knees/ankles). 5 mcg of DEX increases bupivacaine's efficacy by 24% in patients undergoing elective c-section via SAB. It required 11 mg of bupivacaine plus normal saline (NS)

to achieve a T6 level block compared to only 7.4 mg of bupivacaine with 5 mcg of DEX.<sup>1</sup> Using 5 mcg of DEX as a SAB adjuvant decreases the ED-95 of bupivacaine by 3.6 mg.<sup>3</sup>

Onset time of motor/sensory block was statistically significant but not clinically significant when comparing bupivacaine to bupivacaine plus DEX.<sup>4,7,12</sup> Motor onset time with bupivacaine 10 mg plus DEX 5 mcg was 4.87 min compared to 7.43 min with bupivacaine 10 mg as the sole agent.<sup>3</sup> Sensory onset time decreases with bupivacaine plus DEX compared to bupivacaine only (6.46 minutes vs. 7.43 minutes).<sup>3</sup> Intrathecal opioids (fentanyl or morphine), clonidine, and DEX appear to have similar motor/sensory block onset times. However, neither is clinically relevant when compared to bupivacaine as the sole agent for SAB.<sup>4,10</sup>

Sensory and motor blockade appears to be prolonged with DEX compared morphine, and bupivacaine with NS.<sup>4,7</sup> 120 ASA I-II were divided into groups receiving either 10 mg of 0.5% Bupivacaine, 10mg of 0.5% bupivacaine plus 5 mcg DEX, or 10 mg of 0.5% bupivacaine plus 100 mcg morphine.<sup>4</sup> They measured every 15 minutes until sensory and motor blockade regressed to S1 level and a Bromage scale of 0. The addition of 5 mcg of DEX prolonged sensory regression by approximately 60 mins compared to morphine and bupivacaine-only groups.<sup>4</sup> Motor regression to Bromage Scale of 0 was prolonged with the addition of DEX in a similar manner, approximately 65 mins.<sup>2</sup> Multiple studies also found a statistically significant and clinically significant increase in motor and sensory block duration when using DEX along with LA for SAB.<sup>3,10,11</sup>

### ***Duration of analgesia***

Intrathecal morphine is commonly used to extend the duration of analgesia for SAB in c-sections. There is evidence that intrathecal morphine produces a clinically relevant reduction in postoperative pain and analgesic consumption; however, there is only evidence for a small effect

for other opioids such as fentanyl and sufentanil.<sup>5</sup> Qi et al. (2016)<sup>4</sup> found similar duration of analgesia between intrathecal DEX 5 mcg and morphine 100 mcg as adjuvants to bupivacaine 10 mg of 0.5% for post-operative c-section patients. Time to first analgesic was 17.6 hours for the DEX group, 16.7 hours for the morphine group and 3.5 hours for the bupivacaine only group. The addition of DEX 5 mcg to bupivacaine produced a similar analgesic profile (pain scores, time to first requested pain medication) compared to morphine 100 mcg, with less pruritus and shivering.<sup>4</sup>

#### ***Side effect of intrathecal dexmedetomidine on neonate***

Sun. et al. (2020)<sup>13</sup> meta-analysis investigated the effects of intrathecal DEX on the fetus after SAB for c-sections. They looked at 10 RCTs that included 706 ASA I-II parturients undergoing elective c-section using SAB as the primary mode of anesthesia. They compared DEX 2.5-10 mcg to intrathecal tramadol 25 mcg, fentanyl 15-25 mcg, clonidine 100 mcg, morphine 100 mcg, and NS as adjuvants to bupivacaine for SAB. They examined the effect on the fetus by measuring APGAR at 1 min and 5 min, umbilical blood gases, umbilical glucose, and lactate. Intrathecal DEX used as LA adjuvant did not increase neonatal adverse reactions during c-sections. There is no significant difference in neonatal 1 min and 5 min APGAR scores, umbilical blood gas, umbilical glucose, and lactate amongst LA adjuvant tested.<sup>13</sup> The LA adjuvant DEX appears to be safe for fetus/neonate during c-section and postoperative period.<sup>14</sup> DEX can significantly prolong postoperative analgesia and reduce the incidence of postoperative shivering.<sup>13</sup>

There are no studies currently that investigate the rate of placental transfer of intrathecal DEX in women undergoing c-section via SAB block. DEX's rate of placental transfer has been studied for c-section under general anesthesia and for c-section under epidural anesthesia.

Intravenous DEX maintained hemodynamic stability in parturient during c-section under general anesthesia without any adverse neonatal effect.<sup>15</sup> Epidural DEX and has not been shown to cause an increased incidence of adverse effects on newborns.<sup>16</sup>

### ***Maternal side effect of intrathecal dexmedetomidine***

The primary concern with the administration of intrathecal DEX for elective c-section is the lack of information on the risk of side effects in parturients. DEX has been shown to cause hypotension and bradycardia with intravenous infusion in some patient populations. This integrative review focused on the common side effects associated with SAB for c-sections, which are hemodynamic instability (hypotension, bradycardia), nausea and vomiting, shivering, and pruritus. Potential side effects not investigated by this integrative review due to lack on information are urinary retention, respiratory depression, and rate of post-dural puncture headache (PDPH).

### ***Intrathecal dexmedetomidine effect on maternal hemodynamics***

Injection of intrathecal LA blocks nociceptive pain fibers and produces vasodilation by sympathectomy-like effect. As a result of the temporary sympathetic block; blood pressure fluctuates and can result in hypotension.<sup>17</sup> Other factors also influence intra-operative hypotension during c-section, such as bleeding, volume status, and patient position. This integrative review focused on DEX and other LA adjuvants effect on the incidence of hypotension during elective c-section.

Sun et al. (2020)<sup>13</sup> conducted a meta-analysis that included 10 RCTs with a total of 706 parturients undergoing SAB for elective c-sections, and they investigated the incidence of hypotension and bradycardia in this population. They compared intrathecal DEX 2.5-10 mcg to other LA adjuvants (tramadol, fentanyl clonidine, morphine) and bupivacaine as the sole



medication for SAB. The meta-analysis concluded that intrathecal DEX did not increase the incidence of bradycardia and hypotension for women undergoing SAB for c-sections.<sup>13</sup>

Wang et. al (2019)<sup>18</sup> conducted a meta-analysis comparing 0.5% bupivacaine plus NS to 0.5% bupivacaine plus DEX 5 mcg and found similar results with the incidence of bradycardia and hypotension. This study included 278 ASA I/II patients from four RCTs. There was no significant difference in intraoperative hypotension or bradycardia between the DEX and placebo groups. They concluded that intrathecal DEX does not affect hemodynamics during a c-section.<sup>18</sup> A meta-analysis of 970 ASA I-III patients from 10 RCTs investigated the addition of DEX to bupivacaine and found no increased incidence of bradycardia or hypotension compared to bupivacaine as a sole agent.<sup>14</sup> The rate of hypotension and bradycardia was not clinically or statistically significant with intrathecal DEX compared to placebo.<sup>14</sup>

Of the 9 RCTs included in this integrative review, only two showed an increased incidence of hypotension, and none showed an increased incidence of bradycardia with the addition of DEX. These RCTs compared LA adjuvants in obstetric patient populations and used the max dose of intrathecal bupivacaine 15mg for SAB. Gautam et al. (2018)<sup>19</sup> studied 58 ASA I-II females undergoing SAB for abdominal hysterectomies. They compared DEX 10 mcg and fentanyl 25 mcg added to 0.75% bupivacaine 15 mg. They reported a 31% increased rate of hypotension between the groups (fentanyl 6/29, DEX 15/29).<sup>19</sup> Kurhekar et al. (2016)<sup>7</sup> RCT found an increased rate of hypotension with the addition of DEX 2.5 mcg when compared to morphine 250mcg to 0.5% bupivacaine 15mg for 50 ASA I-II females undergoing gynecological surgeries using SAB as the primary mode of anesthesia. The incidence of hypotension was increased by 32% with the addition of DEX when compared to morphine.<sup>7</sup> Both of the RCT's

that showed an increased incidence of hypotension had a relatively small sample size (50, 58 patients), and also used the max dose of bupivacaine 15mg.

### ***Intrathecal dexmedetomidine effect on shivering***

Neuraxial anesthesia is associated with a significant increase in shivering; approximately 40-60% of all patients receiving neuraxial anesthesia suffer from shivering.<sup>20</sup> One of the most significant benefits of using intrathecal DEX as a LA adjuvant for c-section is the decrease incidence in maternal shivering. The exact mechanism for DEX anti-shivering properties is not well understood. It is believed that the DEX alleviates the shivering effect via alpha two adrenergic receptors, which are located in the hypothalamus.<sup>14</sup> DEX decreases the vasoconstriction and shivering threshold; such that a higher degree of hypothermia is required to elicit the shivering response.<sup>21</sup>

Nasseri et al. (2017)<sup>21</sup> investigated the effect of intrathecal DEX on shivering after SAB for c-section. This RCT compared 50 ASA I-II parturients receiving 0.5% bupivacaine 12.5 mg plus 0.5ml of NS or 0.5% bupivacaine 12.5 mg plus DEX 5 mcg. The incidence of shivering in the bupivacaine plus NSL group was 52% (13/25) compared to the bupivacaine plus DEX group was 24% (6/25). Also, it was noted that the DEX group had a decreased intensity of shivering when compared to the NSL group. Adding 5 mcg to heavy bupivacaine in SAB can decrease the intensity and incidence of shivering without any significant adverse effect.<sup>21</sup>

Three meta-analysis studies (total-1,954 ASA I-III parturients undergoing SAB for elective c-sections) included in this review found that intrathecal DEX decreases the incidence of shivering during the c-section perioperative period.<sup>13,14,18</sup> Qi et al. (2017)<sup>4</sup> an RCT of 120 ASA I-II investigated LA adjuvants in parturients undergoing elective c-section with SAB. They found the addition DEX 5 mcg to bupivacaine decreases the incidence of shivering by 22% when

compared morphine 100 mcg. DEX's anti-shivering effect for parturients is well established and has shown to be clinically relevant.<sup>21</sup>

### ***Intrathecal dexmedetomidine and pruritus***

It has been well established that intrathecal opioids cause pruritus. Pruritus can begin shortly after analgesia is achieved, but the duration, onset, and severity depend on the opioid used and dose. It is estimated the 60-100% of all parturients experience pruritus after neuraxial opioid administration, and approximately 29% of those patients report the pruritus as severe.<sup>6</sup> Dahl et al. (1999)<sup>5</sup> found the incidence of pruritus to be very high (50-84%) with intrathecal opioids such as morphine, fentanyl, and sufentanil. Intrathecal DEX has not been shown to cause pruritus when used for SAB for parturients undergoing elective c-section with SAB. Supplementation of intrathecal bupivacaine with DEX 5 mcg produces a similar analgesic effect as morphine 100 mcg with any incidence of pruritus.<sup>4</sup>

### ***Intrathecal dexmedetomidine and nausea and emesis***

Nausea and vomiting is a common side for parturients undergoing SAB for elective c-sections. Nausea and vomiting come from two separate locations in the medulla, the chemoreceptor trigger zone, and the vomiting center. Currently, the literature estimates the incidence of intraoperative nausea and vomiting during SAB for c-sections around 80%.<sup>22</sup> The underlying mechanism for intraoperative nausea and vomiting and PONV during c-section is hypotension due to the sympathectomy during neuraxial anesthesia, Unopposed vagal tone resulting in bradycardia, and the noxious visceral stimulation from the surgical incision.<sup>17</sup> Intrathecal DEX does not increase the incidence of nausea and vomiting for women undergoing c-section when compared to other LA adjuvants used for SAB.<sup>10,12,13,18,23</sup>

## **Conclusion**

In conclusion, intrathecal DEX appears to be a safe and effective alternative to intrathecal opioids for SAB for elective c-sections. DEX does not increase adverse patient outcomes such as nausea/vomiting, bradycardia, hypotension, and lower APGAR scores when compared to other LA adjuvants. The addition of DEX to SAB for c-sections decreases the incidence of shivering and pruritus. The addition of DEX 5 mcg produced a similar analgesic effect as intrathecal morphine 100 mcg, with less pruritus and shivering, and prolonged sensory and motor blockade.<sup>2</sup> With current practice shifting towards opioid limiting anesthesia, intrathecal DEX is a promising LA adjuvant for SAB for elective c-section. The majority of current research on intrathecal DEX for c-sections is based out of China and India. Further research is recommended to support the widespread use of intrathecal DEX for SAB for c-section.

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