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Is intrathecal bupivacaine plus dexmedetomidine superior to bupivacaine in spinal anesthesia for a cesarean section? A systematic review and meta-analysis

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ABSTRACT. – OBJECTIVE: **This study aimed to investigate whether the administration of intrathecal dexmedetomidine as a bupivacaine adjuvant for caesarean section can prolong the duration of analgesia compared with bupivacaine alone. Secondary outcomes included postoperative pain, the time interval to the first analgesic request, the level of sedation, the incidence of adverse effects, and the fetal outcomes.**

MATERIALS AND METHODS: **A systematic review and meta-analysis were conducted. The study compared the intrathecal administration of bupivacaine plus dexmedetomidine (group BD) to the intrathecal administration of bupivacaine alone (group B) for cesarean sections.**

RESULTS: **Fourteen publications were included. Among patients who underwent spinal anesthesia for a cesarean section, 514 patients received intrathecal bupivacaine alone, and 533 patients received intrathecal bupivacaine plus dexmedetomidine. The onset of sensory and motor block was essentially the same in both groups; the time for sensory and motor block regression was significantly longer in the BD group. Postoperative Visual Analogue Scale (VAS) values were similar in group BD when compared to group B. Postoperative VAS scores remained consistently low in Group BD compared to Group B, starting from 1 hour after surgery. The level of sedation measured at the end of the cesarean section in both groups was almost similar. No difference in terms of safety, adverse events, and neonatal outcomes was found between the two groups.**

CONCLUSIONS: **Use of intrathecal dexmedetomidine for spinal anesthesia in cesarean section significantly prolongs sensory and motor block compared to using bupivacaine alone as an adjuvant. It also improves analgesia after 1 hour with no difference in the incidence of maternal and neonatal adverse effects compared to bupivacaine alone. The optimal dose of dexmedetomidine to use remains to be ingested.**

Key Words:

Cesarean section, Dexmedetomidine, Bupivacaine, Spinal anesthesia, Intrathecal administration, Sensory block, Motor block, Adjuvant.

Introduction

According to the World Health Organization (WHO)[1], cesarean section (CS) is one of the most prevalent surgical procedures worldwide, accounting for more than 1 in 5 (21%) of all childbirths. According to research, this number is set to continue increasing over the next decade, with 29% of all births likely to occur by cesarean section by 2030[2].

Elective CS is usually performed under neuraxial anesthesia[3]. The overall prevalence of requirement for supplemental analgesia or anesthesia is 14.6%[4].

The typical neuraxial technique for CS is the single-shot spinal technique[5]. The duration of a single shot spinal is variable and depends on the agents used, but normally provides adequate surgical anesthesia for more than 90 minutes. Bupivacaine is frequently used for CS spinal anesthesia with doses between 10 and 15 mg[5].

The advantages of neuraxial anesthesia over general anesthesia for CS are widely demonstrated, especially in terms of fetal and maternal outcomes[6]. However, these initial benefits may be short-lived due to the relatively brief duration of action of local anesthetics. To prolong the dura-

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tion of sensory block and reduce the local anesthetic dose, various adjuvants such as fentanyl[7], sufentanil[8], morphine[9], and clonidine[10] are used in combination with local anesthetics.

Dexmedetomidine (DEX) is an alpha-adrenergic agonist that is approximately 8 times more selective for the alpha-2 receptor than clonidine. According to the Food and Drug Administration (FDA)[11] and the European Medicine Agency (EMA)[12], DEX is indicated for: 1) "sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting"; 2) "sedation of non-intubated patients prior to and/or during surgical and other procedures". All the other uses are off-label. In 1991, Fisher et al[13] demonstrated that intrathecal administration of DEX into the rat lumbar subarachnoid space produced dose-dependent prolonged antinociception. Alpha-2 adrenergic receptors are present in the central and peripheral nervous system, especially in the pontine locus coeruleus, spinal cord tracts, rostral ventrolateral medulla, and dorsal horn of the spinal cord. DEX causes neuromodulation in these centers, leading to sedation and analgesia with few adverse effects on the cardiovascular and respiratory systems[14]. Previous studies[15] have confirmed that DEX could play a role in improving the efficacy of spinal block when used as an adjuvant.

The primary objective of this systemic review is to determine whether the administration of intrathecal DEX as a bupivacaine adjuvant for CS can prolong the duration of analgesia compared with bupivacaine alone. The secondary objective was to compare the effects of DEX on maternal and fetal outcomes for CS. The maternal outcome variables were postoperative pain, the time interval to the first analgesic request, the level of sedation, and the incidence of adverse effects. The fetal outcomes variables were 1st and 5th minute APGAR scores and umbilical arterial blood pH.

Materials and Methods

Protocol and Registration

We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[16]. The protocol of this study is available upon request.

Literature Search Strategy

The main electronic databases (PubMed, Embase, Scopus, Google Scholar, and Cochrane Library) were screened to identify randomized controlled trials (RCTs) comparing intrathecal bupivacaine plus DEX to bupivacaine alone in spinal anesthesia for CS. Other relevant RCTs were identified from the references list. We used a combination of keywords (MeSH terms), including "dexmedetomidine", "bupivacaine", "spinal anesthesia" and "cesarean section".

Two authors (L.G.G. and F.C.) screened all the titles and the abstracts to identify the keywords; the selected articles were read in full by the reviewers, and a third reviewer (P.S.) was consulted in case of disagreement. The risk of biases was assessed by two authors (L.G.G. and P.S.) for all the included studies using the bias domain described in the Cochrane Handbook for Systematic Review of Interventions version 5.3.5.[16]. As shown in Figure 1, all included studies were assigned a judgment of "high," "low," or "unclear" risk of bias across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.

The initial search was performed on March 8, 2023. All articles were included from inception up until the end of February 2023. No language restrictions were applied.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) the study was a randomized controlled trial (RCT); 2) the full study was published; 3) the study described the intrathecal administration of bupivacaine plus DEX in spinal anesthesia for cesarean section (CS); 4) the comparator was the intrathecal administration of bupivacaine alone in spinal anesthesia for CS; 5) the study reported the maternal and fetal outcomes following intrathecal administration of bupivacaine plus DEX in spinal anesthesia for CS.

The exclusion criteria were as follows: 1) study designs other than an RCT; 2) DEX was administered intravenously or no spinal blocks were performed; 3) the study did not report clinical outcomes; 4) the study contained duplicate data with others (in these cases, only the largest study was included); 5) the study presented aggregated data that did not allow for the extrapolation of useful information.

Data Extraction and Management

The data extracted included the following:

- Number of patients enrolled and completing the study.

- Demographic (age, weight, height, BMI) and baseline clinical (hemodynamics characteristics such as heart rate and arterial pressure) characteristics.
- Characteristics of spinal anesthesia. Intervertebral space and local anesthetic volume were recorded.
- Characteristics of sensory and motor block. The sensory block was evaluated considering the T7 level of sensory block (which is midway between the level of the xiphoid process and the level of the umbilicus) as the standard to achieve for surgery. The motor block was assessed according to the modified Bromage scale (MBS): MBS 0, the patient is able to move the hip, knee, and ankle; MBS 1, the patient is unable to move the hip but is able to move the knee and ankle; MBS 2, the patient is unable to move the hip and knee but able to move the ankle; MBS 3, the patient is unable to move the hip, knee and ankle.
- Pain intensity and postoperative analgesia. Visual analogue pain score (VAS) between 0 ("no pain") and 10 ("most severe pain") was record-

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Azemati S et al[17], 2022	+	+	+	+	+	+	?
Bi YH et al[18], 2017	+	+	+	+	+	+	?
Elgebaly SE et al[19], 2018	+	+	+	+	+	+	?
Farooq S et al[20], 2022	+	+	-	+	+	+	?
He L et al[21], 2017	+	+	+	+	+	+	?
Li X et al[22], 2020	+	+	+	+	+	+	?
Li Z et al[23], 2015	+	+	+	+	+	+	?
Magdy H et al[24], 2015	+	+	+	+	+	+	?
Mahdy WR et al[25], 2011	+	+	+	+	+	+	?
Mostafa MF et al[26], 2020	+	+	+	+	+	+	?
Qi X et al[27], 2016	+	+	+	+	+	+	?
Sun Y et al[28], 2015	+	+	+	+	+	+	?
Sushruth MR et al[29], 2018	+	+	+	+	+	+	?
Xia F et al[30], 2018	+	+	+	+	+	+	?

Figure 1. Risk of bias of the included studies (green: low risk of bias; red: high risk of bias; yellow: unclear).

Table I. Studies characteristics.

	No. of patients	Anesthesia	Intervertebral space	Local anaesthetic	Dexmetomidine	Total volume	Comparator
Azemati et al[17]	90	S	L4/L5	Bupivacaine 0.5% - 10 mg	5 μg	2 ml	Saline (30) - Meperidine 10 mg (30)
Bi et al[18]	60	CSE	L2/L3 – L3/L4	Bupivacaine 0.5% - 10 mg	3 μg - 5 μg	2 ml	Saline
Elgebaly et al[19]	90	CSE	L4/L5	Bupivacaine 0.5% - 10 mg	5 μg	3 ml	Saline (30) - Dexmetomidine IV (30)
Farooq et al[20]	105	S	L4/L5	Bupivacaine 0.75% - 12 mg	10 μg	2 ml	Saline (35) - Fentanyl 25 μg (35)
He et al[21]	90	S	L3/L4	Bupivacaine 0.5% - 12.5 mg	2.5 μg (30) - 5 μg (30)	3 ml	Saline (30)
Li et al[22]	300	S	L3/L4	Bupivacaine 0.75% - 9 mg	5 μg (100)	2.2 ml	Saline (100) - Fentanyl 20 μg (100)
Li et al[23]	84	CSE	L2/L3 – L3/L4	Bupivacaine 0.5% - 10 mg	10 μg (21)	4 ml	Saline (21) - Fentanyl 15 μg (21) - Clonidine 75 μg (21)
Magdy et al[24]	100	S	L3/L4 – L4/L5	Bupivacaine 0.5% - 10 mg	5 μg (33)	2.5 ml	Saline (34) - Dexmetomidine IV (33)
Mahdy et al[25]	90	S	L4/L5	Bupivacaine 0.5% - 10 mg	5 μg (30)	2.5 ml	Saline (30) - Fentanyl 25 μg (30)
Mostafa et al[26]	90	S	L4/L5	Bupivacaine 0.5% - 12.5 mg	5 μg	3 ml	Saline (30) - $MgSO_4$ 50 mg (30)
Qi et al[27]	120	S	L3/L4	Bupivacaine 0.5% - 10 mg	5 μg	2 ml	Saline (40) - Morphine 100 μg (40)
Sun et al[28]	90	CSE	L2/L3 – L3/L4	Bupivacaine 0.5% - 10 mg	10 μg	3 ml	Saline (30) - Fentanyl 25 μg (30)
Sushruth et al[29]	60	S	L3/L4	Bupivacaine 0.5% - 9 mg	5 μg	2 ml	Saline
Xia et al[30]	90	CSE	L3/L4	Bupivacaine 0.75% - 5 mg	5 μg	3 ml	Saline

S, spinal anesthesia; CSE, combined spinal-epidural anesthesia.

ed for all the measured time points (baseline and after 1, 6, 12 and 24 hours). The time to the first post-operative analgesic dose was also recorded.

- Level of sedation. Sedation was recorded using the Ramsay sedation score (RSS). This score, from 1 to 6, describes a patient as follows: RSS1, agitated or restless, or both; RSS2, cooperative, oriented, and calm; RSS3, awake but responsive to commands only; RSS4, brisk response to light or loud auditory stimulus; RSS5, sluggish response to light or loud auditory stimulus; RSS6, unresponsive.
  Adverse events (AEs). The severity and incidence of AEs like nausea, vomiting, shivering, pruritus, bradycardia, and hypotension were recorded.
- Fetal outcomes. The neonatal outcome for all neonates was assessed by Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores at 1st and 5th min and umbilical artery samples for pH.

Statistical Analysis

Data were analyzed using a standard computer program (Excel, 2016). Results are reported as mean±standard deviation (SD). We tested the consistency of our data using the Chi-square test and a 95% confidence level. Comparisons were performed using a Student *t*-test, and the level of statistical significance was $p < 0.05$. We used R software (version 4.3.1; Beagle Scouts, Vienna, Austria) to perform a meta-analysis of the extracted data.

Results

The flow diagram (Figure 2) shows the results from the literature search and the study selection process. Fourteen publications[17-30] met the eligibility criteria. Table I displays the fourteen papers included in this review.

Two authors (L.G.G. and F.C.) independently evaluated the quality of the RCTs. None of the 14 studies had a high risk of bias (Table I). All stud-

ies had a low risk of bias, and several elements had an unclear risk of bias.

In the included publications, 1,459 patients underwent spinal anesthesia for cesarean section: 514 patients received intrathecal bupivacaine alone, and 533 patients received intrathecal bupivacaine plus dexmedetomidine. The remaining patients received other adjuvants as comparators together with intrathecal bupivacaine; these were included in our review.

Demographic and Baseline Clinical Characteristics of the Patients

Demographic and surgical characteristics are reported in Table II. All patients were American Society of Anesthesiologists (ASA) physical status I and II and with uncomplicated term pregnancy of a singleton fetus. The demographic profiles of the patients in groups B and BD were comparable in terms of age, body mass index (BMI), baseline heart rate (HR), and mean blood pressure. There was no significant difference in terms of duration of surgery between the two groups ($p > 0.05$).

Spinal Block Characteristics

Spinal anesthesia or combined spinal-epidural (CSE) anesthesia was performed at the level of L2-L3, L3-L4 or L4-L5. The two groups were scheduled to receive drugs as follows: bupivacaine (group B) or bupivacaine + dexmedetomidine (group BD). Each group received 5-12.5 mg of bupivacaine 0.5%-0.75%, then 2.5-10 μg of dexmedetomidine was added to the bupivacaine in group BD. In most of the studies (11 out of 14), dexmetomidine 5 μg was administered (Table III).

The onset of sensory and motor block (min) was essentially the same in both groups. The onset of sensory block was shorter in group BD (4.59±1.92) than in the control group (5.46±1.79) but did not record a statistically significant onset ($p = 0.14$). Similarly, the onset of motor block was earlier in group BD (5.3±1.41) than in group B (6.23±1.66).

The time for sensory and motor block regression to Bromage 0 was significantly longer in the BD group. Sensory regression at the T8 level occurred after 209.45±73.44 minutes in group

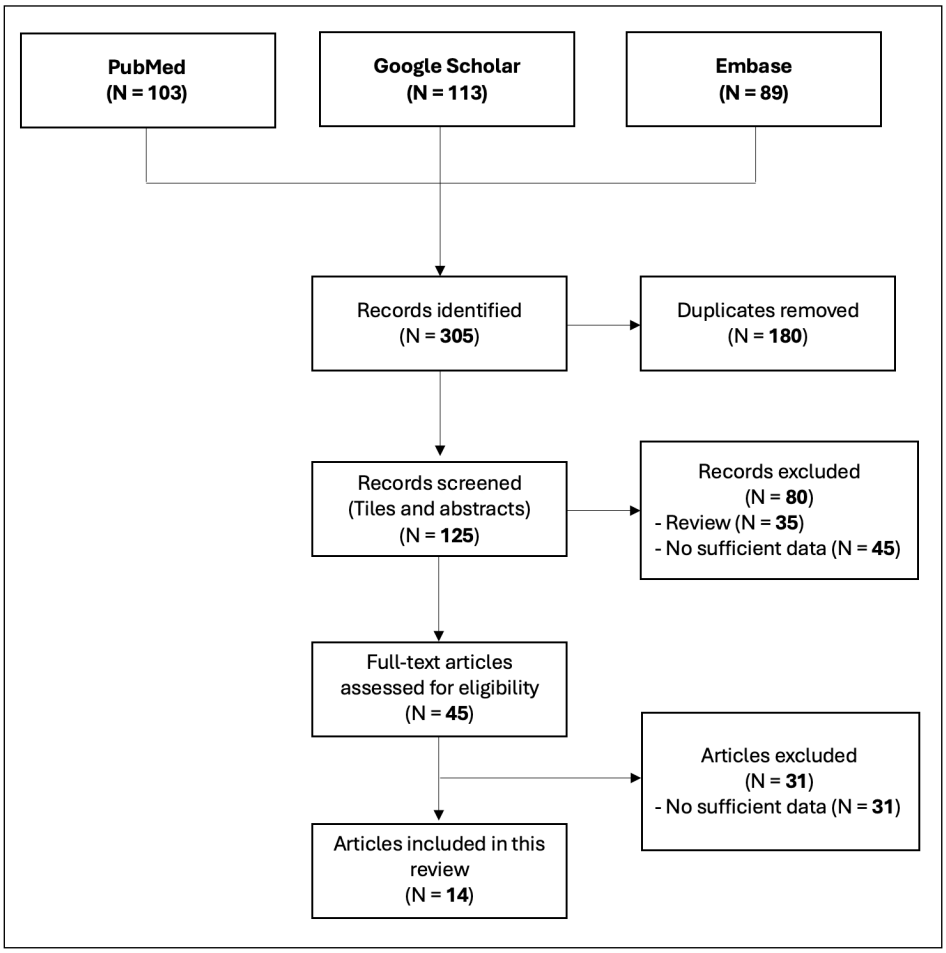

Figure 2. Flow diagram study selection process.

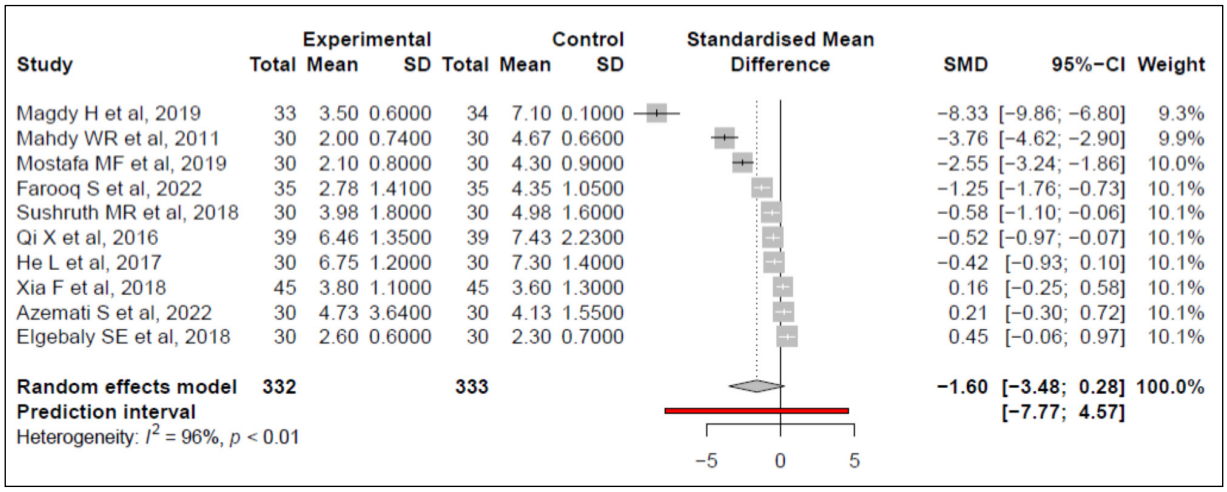

Figure 3. Forest plot of the effect of dexmedetomidine on sensory block onset.

BD compared to 136.27±44.55 minutes in group B, with a statistically significant difference ($p < 0.05$). Achievement of a Bromage 0 occurred after 216.78±69.96 minutes in group BD *vs.* 142.34±32.27 minutes in group B, with a statistically significant difference ($p < 0.05$).

Forest plots of the effect of dexmedetomidine on block onset and regression are shown in Figures 3, 4, 5, and 6.

Analgesia Characteristics

Postoperative VAS data are illustrated in Table IV. Lower VAS values were recorded in group BD when compared to group B, with no statistically significant difference between the two groups regarding VAS values at different times. Only after 1 hour, postoperative VAS score was consistently low in Group BD compared to Group B (0.43±0.47 *vs.* 2.59±1.23, $p < 0.05$).

Time to the first request of postoperative analgesia was significantly longer in group BD than in group B (669.3 *vs.* 372.22 min), but no statistically significant difference was reported.

Level of Sedation

The Ramsay sedation score (RSS) measured at the end of the cesarean section in both groups was almost similar (Table V).

Safety and Adverse Events (AEs)

Both groups were observed for the occurrence of possible adverse effects like nausea, vomiting, shivering, pruritus, bradycardia, respiratory depression, and hypotension. The incidence of these adverse effects was low and not significant (see Table VI). Nausea and vomiting were more frequent in group BD than in group B, with no significant difference ($p > 0.05$). The incidence of shivering in the group B was 37.6%, while 30.7% of patients in the group BD. In relation to pruritus, this adverse event occurred in 7 (4.3%) of patients in group B and 9 (5.5%) of those in group BD. Hypotension

Table II. Demographic and surgical characteristics.

	B	BD	*p*-value
Age (years)	28.76±2.37	29.02±2.65	0.394131
Weight (kg)	71.35±7.24	71.49±6.69	0.479759
Height (cm)	160.41±5.91	160.41±5.78	0.499834
BMI (kg/m²)	27.85±3.84	27.80±3.80	0.487628
Baseline HR (bpm)	89.65±5.21	87.90±4.83	0.262692
Baseline MAP (mmHg)	86.54±6.71	87.22±6.34	0.424419
Duration of surgery (min)	45.51±5.07	46.25±5.05	0.390597

B, bupivacaine; BD, bupivacaine + dexmetomidine; BMI, body mass index; HR, heart rate; MAP, mean arterial pressure. Red, not statistically significant.

and bradycardia were noted as two of the hemodynamic adverse events. Hypotension occurred in 55 (33.3%) of patients in group B and 47 (28.8%) of those in group BD. The occurrence of bradycardia was similar in the two groups; 13 (7.9%) women in group B and 12 (8.8%) women in group BD had mild hypotension. Respiratory depression affected only 1.2% of patients in both groups.

Neonatal Outcomes

As shown in Table VII, there were no significant differences regarding different parameters of neonatal assessments: APGAR scores at 1 and 5 min, as well as umbilical artery pH, were comparable between group B and group BD.

Discussion

Spinal anesthesia has become the preferred anesthesia type for cesarean section. In clinical practice, spinal anesthesia is often not enough to inhibit visceral pain, causing maternal discomfort during surgery and affecting the quality of recovery in the postoperative period[31]. Increasing the doses of local anesthetics to prolong analgesic duration could lead to adverse effects such as central nervous system problems and cardiotoxicity. In recent years, many adjuvants have been used to prolong intraoperative and postoperative analgesia after spinal block[7-10]. DEX is a highly selective α2-adrenergic receptor agonist and can provide good sedation, high-quality analgesia, and stable hemodynamic conditions with minimal adverse effects. Studies[32-34] have reported that the use of intrathecal DEX as an adjuvant to hyperbaric bupivacaine is associated with a longer duration of analgesia and faster times to onset.

Our analysis of 14 studies, comprising 1,047 patients undergoing spinal anesthesia for cesarean section, showed that intrathecal DEX significantly increased the duration of spinal block when

Table III. Characteristics of sensory and motor block.

	Sensory block				Motor block			
	Onset (min)		Regression (T8, min)		Onset (min)		Regression (B0, min)	
	B	BD	B	BD	B	BD	B	BD
Azemati et al[17]	4.13	4.73	79.86	127.73	5.53	5.47	111	158.86
Bi et al[18]	–	–	–	–	–	–	216	348 - 306
Elgebaly et al[19]	2.3	2.6	200.23	230.4	5.5	5.7	170.5	190.6
Farooq et al[20]	4.35	2.78	115.2	171.88	5.82	5.42	132.25	212.05
He et al[21]	7.3	6.8 - 6.7	–	–	–	–	–	–
Li et al[22]	–	–	108.4	148.2	3.4	2.9	147.5	190.3
Li et al[23]	7.6	7.1	107.35	155.9	7.6	7.2	124.5	128.55
Magdy et al[24]	7.1	3.5	183.1	253.2	7.6	7.3	160	187
Mahdy et al[25]	4.67	2.0	173.7	292.8	8.5	4.7	88.4	176.2
Mostafa et al[26]	4.3	2.1	183.1	252.9	–	–	–	–
Qi et al[27]	7.43	6.46	188.33	253.21	5.89	4.87	162.18	226.15
Sun et al[28]	7.8	7.1	102.2	152.9	7.6	7.1	127.5	128.55
Sushruth et al[29]	4.98	3.98	126.3	364	7.7	3.8	113.2	341
Xia et al[30]	3.6	3.8	67.5	110.3	3.4	3.8	155.1	224.9
Mean±SD	**5.46±1.79**	**4.59±1.92**	**136.27±44.55**	**209.45±73.44**	**6.23±1.66**	**5.3±1.41**	**142.34±32.27**	**216.78±69.96**
***p*-value**	0.135616		0.004924		0.094859		0.001842	

B, bupivacaine; BD, bupivacaine + dexmetomidine; SD, standard deviation. Red, not statistically significant; blue, statistically significant.

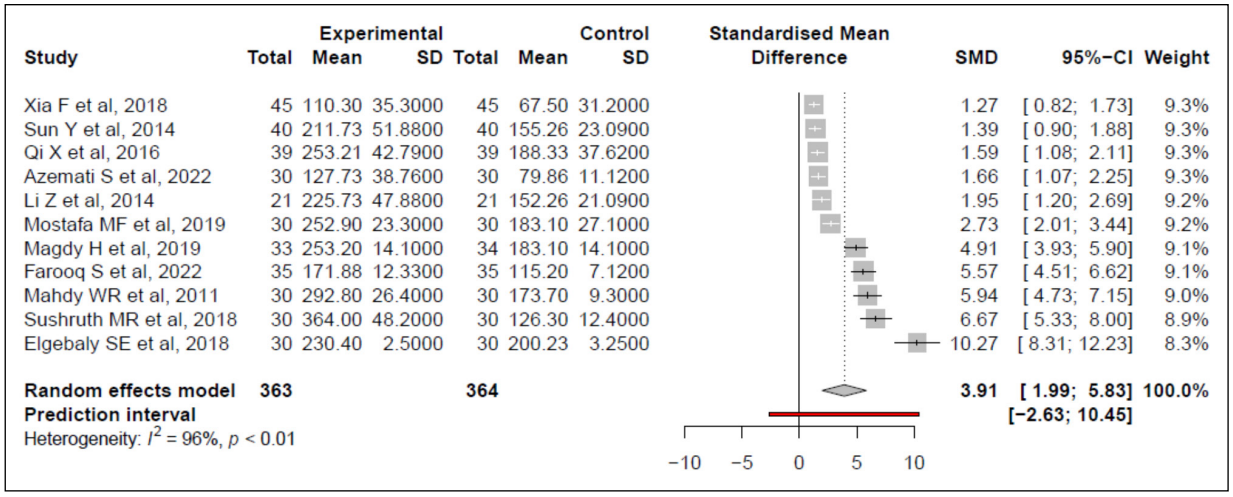

Figure 4. Forest plot of the effect of dexmedetomidine on sensory block regression.

compared to a placebo. While the extension of the sensory block may be desirable, the extension of the motor block could be disadvantageous for the patient undergoing surgery as it could delay normal activities[35]. In our study, intrathecal DEX also shortened the onset of both sensory and motor block but without reaching statistical significance. The mechanism of DEX for increasing the duration of the block may be attributable to the depression of the release of neurotransmitters by presynaptic C-fibres and the hyperpolarization of postsynaptic dorsal horn neurons[36].

With regards to postoperative pain, we chose to examine pain scores at 1, 6, 12, and 24 postoperative hours. There was a significant reduction in pain scores during the 24 postoperative hours, but only after 1 hour was it statistically significant.

In our review, different DEX doses were used. Studies using a combination of intrathecal DEX and local anesthetics are lacking. Animal studies[37-39] have used intrathecal DEX at a dose range of 2.5-100 µg; no neurological deficits in the studied animals were reported. Different studies[40] in humans found that 5 µg of DEX administered intrathecally could prolong the duration of sensory and motor block and the time to the first analgesic request. The use of intrathecal clonidine (15 to 150 µg) has a well-established synergistic effect with local anaesthetics[41,42]. A 1:10 dose ratio between intrathecal DEX and clonidine produces similar effects[43].

Although our analysis failed to detect any differences in postoperative sedation between groups, patients receiving DEX had a Ramsay

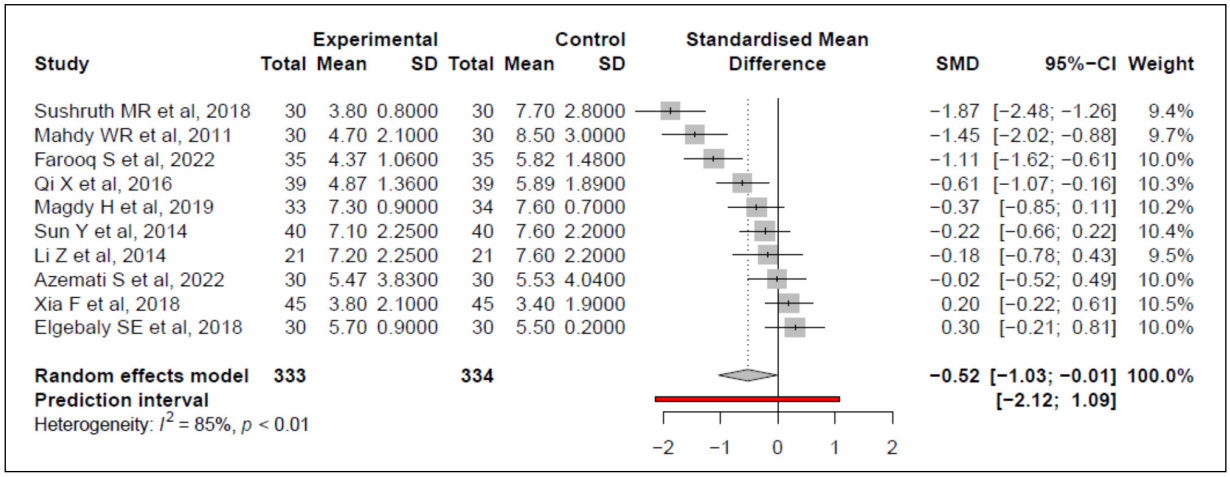

Figure 5. Forest plot of the effect of dexmedetomidine on motor block onset.

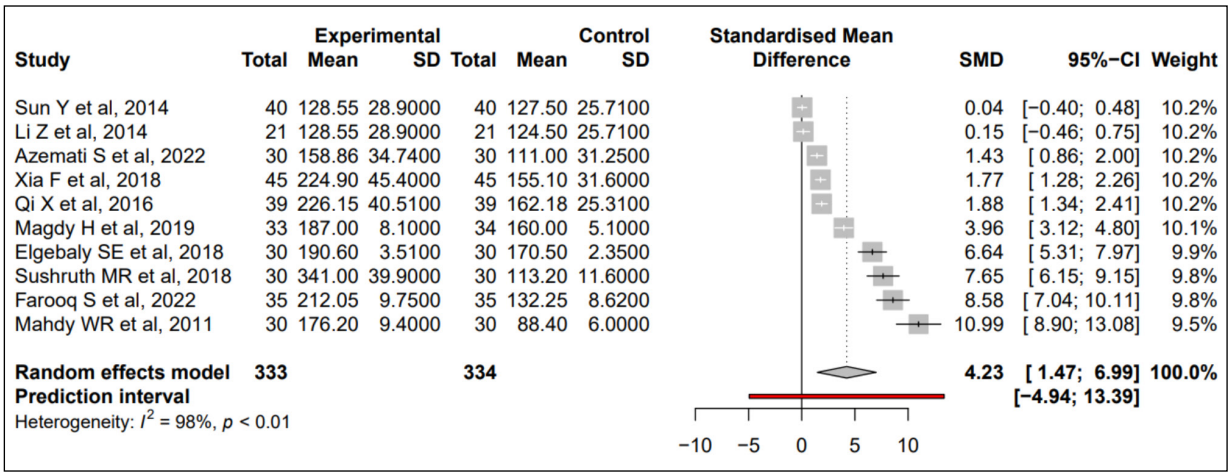

Figure 6. Forest plot of the effect of dexmedetomidine on motor block regression.

sedation score of 2.5±0.95 with no respiratory depression and were easily arousable. DEX, like other α2-agonists, has a dose-dependent sedative effect when intrathecally administered[44]. The doses of DEX used in the studies of our review were quite low. This explains the lack of sedative effects between groups B and BD, as demonstrated by the low sedation scores in the postoperative period.

The most significant reported adverse events associated with the use of intrathecal DEX are bradycardia and hypotension, according to previous studies[45]. Post-synaptic activation of α2-adrenoceptors by DEX in the central nervous system inhibits sympathetic activity and may result in hypotension and bradycardia. However, the difference in the incidence of these side effects using DEX as an adjuvant to local anesthetics is undetectable. The cardiovascular effects of intrathecal α2-adrenergic agonists are dose-related, so the addition of a small amount of DEX to intrathecal anesthetic will have minimal to no effects on hemodynamics[46]. It has also been found to decrease the risk of shivering in most studies[47,48]. Our data confirm these previous results. Shivering is a common complication occurring in 40-60% of patients who undergo spinal anesthesia. DEX reduces shivering by inhibiting central thermoregulatory control by limiting neuronal conductance and suppressing vasoconstriction and shivering thresholds[49]. Perioperative nausea and vomiting are common adverse events for patients. The exact etiology of perioperative nausea and vomiting is unclear. In our review, more than 25% of patients who received intrathecal DEX experienced nausea and vomiting. This is in contrast to previous studies[50-52], in which the potential mechanisms by which DEX reduces nausea and vomiting were as follows: (1) reduction of pain and therefore opioid consumption, with fewer adverse events opioid-related including nausea and vomiting[53]; (2) DEX decreases noradrenergic activity by binding to α2-adrenoceptors in the locus coeruleus with an antiemetic effect[54]; (3) the overall reduction in sympathetic outflow and catecholamine release caused by DEX[55]. As also demonstrated previ-

Table IV. VAS and time to first request of analgesics.

	T0		T1		T6		T12		T24		Time to 1st dose (min)	
	B	BD	B	BD	B	BD	B	BD	B	BD	B	BD
VAS	0.94±0.50	0.35±0.39	2.59±1.23	0.43±0.47	2.16±1.60	1.52±0.93	3.54±0.34	2.62±0.95	3.77±0.64	3.14±0.90	372.22	669.3
p-value	0.079793		0.005536		0.254703		0.053099		0.2307		0.155466	

B, bupivacaine; BD, bupivacaine + dexmetomidine; VAS, visual analogue scale. Red, not statistically significant; blue, statistically significant.

Table V. Ramsay sedation scale (RSS).

	B	BD	*p*-value
Ramsay sedation scale	1.73±0.68	2.5±0.95	0.085745

B, bupivacaine; BD, bupivacaine + dexmetomidine. Red, not statistically significant.

Table VI. Adverse events (AEs), n (%).

	B	BD	*p*-value
Nausea/Vomiting	26 (15.8)	43 (26.4)	0.054494
Shivering	62 (37.6)	50 (30.7)	0.356065
Pruritus	7 (4.3)	9 (5.5)	0.374505
Bradycardia	13 (7.9)	12 (8.8)	0.451425
Respiratory depression	2 (1.2)	2 (1.2)	0.5
Hypotension	55 (33.3)	47 (28.8)	0.332376
Total	**165**	**163**	

B, bupivacaine; BD, bupivacaine + dexmetomidine. Red, not statistically significant.

Table VII. Neonatal outcomes.

	B	BD	*p*-value
pH	7.29±0.06	7.29±0.04	0.468042
APGAR			
– 1'	8.63±0.62	8.55±0.62	0.388288
– 5'	9.61±0.53	9.69±0.42	0.351814

APGAR, Appearance, Pulse, Grimace, Activity, Respiration; B, bupivacaine; BD, bupivacaine + dexmetomidine. Red, not statistically significant.

ously[56], DEX had little effect on pruritus during cesarean section.

When used intravenously, DEX can easily pass through the placental barrier like other anesthetic drugs. In *in vitro* studies[57], the rate of placental transfer of DEX was 0.77; in *in vivo* studies[58], it was 0.76. This is similar to that of propofol[59], but much lower than that of clonidine (0.85) and that of remifentanil (0.88)[60]. No adverse neonatal effects were reported[57]. After spinal or epidural anesthesia, the sympathetic blockade decreases venous return and blood pressure, leading to a reduction in blood flow across the placenta. Therefore, the rate of placental transfer of DEX through the placenta during neuraxial anesthesia is lower, which is safer for newborns[61]. Our data confirm the safety profile of intrathecal DEX for newborns.

Limitations

The results of our review are subject to several limitations. First, the sample size of all the included studies is small. Second, different doses of bupivacaine (5-12.5 mg) and DEX (2.5-10 µg) were used in the studies included in our review. In addition to this, spinal anesthesia effects cannot be precisely compared because the injection volume and site are different. Fourth, the different types of surgical techniques undertaken and the variable duration of surgery (weight mean duration range 38.4-53.37 min) are other important limitations. Finally, there are different outcome measures.

DEX is currently only approved for intravenous sedation, and the lack of FDA and EMA approval for intrathecal DEX may have prevented the approval of further RCTs. The general concern with intrathecal DEX is its possible neurotoxic poten-

tial, and there is currently a lack of data on long-term neurological outcomes in patients who have had intrathecal DEX.

Conclusions

In conclusion, this review demonstrated that intrathecal DEX, used for spinal anesthesia during cesarean section, significantly prolonged the duration of sensory and motor blocks compared to a placebo. DEX also reduced pain scores at 1 hour. There was no increase in adverse effects when compared with bupivacaine alone. No adverse neonatal effects were reported. Intrathecal DEX can be considered for patients undergoing cesarean section. However, the optimal dose of intrathecal DEX, as well as its long-term neurological effects, warrants further studies.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval and Informed Consent

Not applicable due to the design of the study.

Authors' Contributions

L.G.G. and P.S. helped to design and conduct the study, analyze the data, and write the manuscript; F.C. helped to design and conduct the study, and analyze the data; M.B.P., M.C.P., and V.P. helped to design the study and analyze the data. All authors have read and agreed to the published version of the manuscript.

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Availability of Data and Materials

Datasets are sourced from public resources and can be obtained upon request. For any inquiry, please contact Luca Gregorio Giaccari at lucagregorio.giaccari@gmail.com.

AI Disclosure

Artificial intelligence or assisted technologies were not used in the production of the study.

References

1) WHO. Caesarean section rates continue to rise, amid growing inequalities in access. Available at: https://www.who.int/news/item/16-06-2021-caesarean-section-rates-continue-to-rise-amid-growing-inequalities-in-access (Accessed on April 4, 2023).
2) Betran AP, Ye J, Moller AB, Souza JP, Zhang J. Trends and projections of caesarean section rates: global and regional estimates. BMJ Glob Health 2021; 6: e005671.
3) Roofthooft E, Joshi GP, Rawal N, Van de Velde M; PROSPECT Working Group of the European Society of Regional Anaesthesia and Pain Therapy. PROSPECT guideline for elective caesarean section: an update. Anaesthesia 2023; 78: 1170-1171.
4) Patel R, Kua J, Sharawi N, Bauer ME, Blake L, Moonesinghe SR, Sultan P. Inadequate neuraxial anaesthesia in patients undergoing elective caesarean section: a systematic review. Anaesthesia 2022; 77: 598-604.
5) Rollins M, Lucero J. Overview of anesthetic considerations for Cesarean delivery. Br Med Bull 2012; 101: 105-125.
6) Watson SE, Richardson AL, Lucas DN. Neuraxial and general anaesthesia for caesarean section. Best Pract Res Clin Anaesthesiol 2022; 36: 53-68.
7) Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, Hertwig LM, Ostheimer GW. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiology 1989; 71: 535-540.
8) Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for caesarean section. Anesth Analg 1997; 85: 1288-1293.
9) Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivacaine for cesarean section. Anesth Analg 1988; 67: 370-374.
10) Benhamou D, Thorin D, Brichant JF, Dailland P, Milon D, Schneider M. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anesth Analg 1998; 87: 609-613.
11) Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021038s021lbl.pdf. (Accessed on April 4, 2023).
12) European Medicine Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/dexdor-epar-product-information_en.pdf. (Accessed on April 4, 2023).
13) Fisher B, Zornow MH, Yaksh TL, Peterson BM. Antinociceptive properties of intrathecal dexmedetomidine in rats. Eur J Pharmacol 1991; 192: 221-225.
14) Nguyen V, Tiemann D, Park E, Salehi A. Alpha-2 Agonists. Anesthesiol Clin 2017; 35: 233-245.
15) Shen QH, Li HF, Zhou XY, Yuan XZ, Lu YP. Dexmedetomidine as an adjuvant for single spinal anesthesia in patients undergoing cesarean section: a system review and meta-analysis. J Int Med Res 2020; 48: 300060520913423.
16) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J,

Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.

17) Azemati S, Zarghami A, Jouybar R, Naderi-Boldaji V. Analgesic Characteristics of Bupivacaine Alone and in Combination with Dexmedetomidine or Meperidine in Spinal Anesthesia during Cesarean Section: A Double-Blind Randomized Clinical Trial Study. Pain Res Manag 2022; 2022: 5111214.

18) Bi YH, Cui XG, Zhang RQ, Song CY, Zhang YZ. Low dose of dexmedetomidine as an adjuvant to bupivacaine in cesarean surgery provides better intraoperative somato-visceral sensory block characteristics and postoperative analgesia. Oncotarget 2017; 8: 63587-63595.

19) Elgebaly AS. Evaluation the Effects of Intravenous vs. Spinal Dexmedetomidine during Anesthesia for Cesarean Sections with Severe Pre-Eclampsia. J Anesth Clin Res 2018; 9: 801.

20) Farooq S, Rizvi MFA, Yousuf SMA, Dilshad R, Bashir G, Dilshad A. Comparing intrathecal dexmedetomidine and fentanyl as adjuvants to hyperbaric bupivacaine in elective casarian section, a study. Professional Med J 2022; 29: 218- 226.

21) He L, Xu JM, Liu SM, Chen ZJ, Li X, Zhu R. Intrathecal Dexmedetomidine Alleviates Shivering during Cesarean Delivery under Spinal Anesthesia. Biol Pharm Bull 2017; 40: 169-173.

22) Li XX, Li YM, Lv XL, Wang XH, Liu S. The efficacy and safety of intrathecal dexmedetomidine for parturients undergoing cesarean section: a double-blind randomized controlled trial. BMC Anesthesiol 2020; 20: 190.

23) Li Z, Tian M, Zhang CY, Li AZ, Huang AJ, Shi CX, Xin DQ, Qi J, Li KZ. A Randomised Controlled Trial to Evaluate the Effectiveness of Intrathecal Bupivacaine Combined with Different Adjuvants (Fentanyl, Clonidine and Dexmedetomidine) in Caesarean Section. Drug Res (Stuttg) 2015; 65: 581-586.

24) Magdy H, Mohsen M, Saleh MA. The effect of intrathecal compared with intravenous dexmedetomidine as an adjuvant to spinal bupivacaine anesthesia for cesarean section. Ain-Ain Shams J Anesthesiol 2015; 8: 93-99. Available at: https://api.semanticscholar.org/CorpusID:73232421. (Accessed on April 4, 2023).

25) Mahdy W, Abdallah S. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics and neonatal outcome in uncomplicated cesarean delivery: a randomized double blind placebo controlled study. Menoufia Med J 2011; 24: 221-232.

26) Mostafa MF, Herdan R, Fathy GM, Hassan ZEAZ, Galal H, Talaat A, Ibrahim AK. Intrathecal dexmedetomidine versus magnesium sulphate for postoperative analgesia and stress response after caesarean delivery; randomized controlled double-blind study. Eur J Pain 2020; 24: 182-191.

27) Qi X, Chen D, Li G, Huang X, Li Y, Wang X, Li Y. Comparison of Intrathecal Dexmedetomidine with Morphine as Adjuvants in Cesarean Sections. Biol Pharm Bull 2016; 39: 1455-1460.

28) Sun Y, Xu Y, Wang GN. Comparative Evaluation of Intrathecal Bupivacaine Alone, Bupivacaine-fentanyl, and Bupivacaine-dexmedetomidine in Caesarean Section. Drug Res (Stuttg) 2015; 65: 468-472.

29) Sushruth MR, Rao DG. Effect of adding intrathecal dexmedetomidine as an adjuvant to hyperbaric bupivacaine for elective cesarean section. APIC 2018; 22: 348-354.

30) Xia F, Chang X, Zhang Y, Wang L, Xiao F. The effect of intrathecal dexmedetomidine on the dose requirement of hyperbaric bupivacaine in spinal anaesthesia for caesarean section: a prospective, double-blinded, randomized study. BMC Anesthesiol 2018; 18: 74.

31) Catro-Alves LJ, De Azevedo VL, De Freitas Braga TF, Goncalves AC, De Oliveira GS Jr. The effect of neuraxial versus general anesthesia techniques on postoperative quality of recovery and analgesia after abdominal hysterectomy: a prospective, randomized, controlled trial. Anesth Analg 2011; 113: 1480-1486.

32) Kumar R, Suhail F, Neha, Sethi C, Sahi P. Comparative evaluation of intrathecal dexmedetomidine and fentanyl as adjuvant to bupivacaine for lower abdominal surgery. Int J Sci Study 2016; 4: 126e129.

33) Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, Al-Edwan GM, Ramsay MA. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. Saudi Med J 2009; 30: 365-370.

34) Gautam B, Niroula S, Sharma M, Lama SM. Effects of intrathecal dexmedetomidine as an adjuvant to hyperbaric bupivacaine for spinal anaesthesia in adults undergoing elective infraumbilical surgery. J Nepal Med Assoc 2017; 56: 379e387.

35) Paramasivan A, Lopez-Olivo MA, Foong TW, Tan YW, Yap APA. Intrathecal dexmedetomidine and postoperative pain: A systematic review and meta-analysis of randomized controlled trials. Eur J Pain 2020; 24: 1215-1227.

36) Kroin JS, Buvanendran A, Beck DR, Topic JE, Watts DE, Tuman KJ. Clonidine prolongation of lidocaine analgesia after sciatic nerve block in rats Is mediated via the hyperpolarization-activated cation current, not by alpha-adrenoreceptors. Anesthesiology 2004; 101: 488-494.

37) Takano Y, Yaksh TL. Characterization of the pharmacology of intrathecally administered alpha 2-agonists and antagonists in rats. J Pharmacol Exp Ther 1992; 261: 764-772.

38) Eisenach JC, Shafer SL, Bucklin BA, Jackson C, Kallio A. Pharmacokinetics and pharmacodynamics of intraspinal dexmedetomidine in sheep. Anesthesiology 1994; 80: 1349-1359.

39) Lo WC, Harris J, Clarke RW. Endogenous opioids support the spinal inhibitory action of an alpha

2-adrenoceptor agonist in the decerebrated, spinalised rabbit. Neurosci Lett 2003; 340: 95-98.

40) Liu S, Zhao P, Cui Y, Lu C, Ji M, Liu W, Jiang W, Zhu Z, Sun Q. Effect of 5-μg Dose of Dexmedetomidine in Combination With Intrathecal Bupivacaine on Spinal Anesthesia: A Systematic Review and Meta-analysis. Clin Ther 2020; 42: 676-690.e5.

41) Strebel S, Gurzeler J, Schneider M, Aeschbach A, Kindler C. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: a dose–response-study. Anesth Analg 2004; 99: 1231-1238.

42) Dobrydnjov I, Axelsson K, Thörn SE, Matthiesen P, Klockhoff H, Holmström B, Gupta A. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. Anesth Analg 2003; 96: 1496-1503.

43) Kalso E, Poyhia R, Rosenberg P. Spinal antinociception by dexmedetomidine, a highly selective α2-adrenergic agonist. Pharmacol Toxicol 1991; 68: 140-143.

44) D'Angelo R, Evans E, Dean LA, Gaver R, Eisenach JC. Spinal clonidine prolongs labor analgesia from spinal sufentanil and bupivacaine. Anesth Analg 1999; 88: 573-576.

45) Zhang C, Li C, Pirrone M, Sun L, Mi W. Comparison of Dexmedetomidine and Clonidine as Adjuvants to Local Anesthetics for Intrathecal Anesthesia: A Meta-Analysis of Randomized Controlled Trials. J Clin Pharmacol 2016; 56: 827-834.

46) Asano T, Dohi S, Ohta S, Shimonaka H, Iida H. Antinociception by epidural and systemic α2-adrenoceptor agonists and their binding affinity in rat spinal cord and brain. Anesth Analg 2000; 90: 400-407.

47) Omar H, Aboella WA, Hassan MM, Hassan A, Hassan P, Elshall A, Khaled D, Mostafa M, Tawadros PZ, Hossam Eldin M, Wedad M, Abdelhamid BM. Comparative study between intrathecal dexmedetomidine and intrathecal magnesium sulfate for the prevention of post-spinal anaesthesia shivering in uroscopic surgery; (RCT). BMC Anesthesiol 2019; 19: 190.

48) Nasseri K, Ghadami N, Nouri B. Effects of intrathecal dexmedetomidine on shivering after spinal anesthesia for cesarean section: a double-blind randomized clinical trial. Drug Des Devel Ther 2017; 11: 1107-1113.

49) Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. Anesthesiology 1997; 87: 835-841.

50) Zhang W, Wang R, Li B, Zhao Y, Liu X, Yuan J. The Effect of Dexmedetomidine on Postoperative Nausea and Vomiting in Patients Undergoing Thoracic Surgery-A Meta-Analysis of a Randomized Controlled Trial. Front Surg 2022; 9: 863249.

51) Jin S, Liang DD, Chen C, Zhang M, Wang J. Dexmedetomidine prevent postoperative nausea and vomiting on patients during general anesthesia: A PRISMA-compliant meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017; 96: e5770.

52) Zhong WG, Ge XY, Zhu H, Liang X, Gong HX, Zhong M, Xiao X. Dexmedetomidine for antiemesis in gynecologic surgery: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2015; 8: 14566-14576.

53) Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth 2006; 53: 646-652.

54) Whittington RA, Virág L. Dexmedetomidine-induced decreases in accumbal dopamine in the rat are partly mediated via the locus coeruleus. Anesth Analg 2006; 102: 448-455.

55) Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992; 77: 162-184.

56) Bao Z, Zhou C, Wang X, Zhu Y. Intravenous dexmedetomidine during spinal anaesthesia for caesarean section: A meta-analysis of randomized trials. J Int Med Res 2017; 45: 924-932.

57) Ala-Kokko TI, Pienimäki P, Lampela E, Hollmén AI, Pelkonen O, Vähäkangas K. Transfer of clonidine and dexmedetomidine across the isolated perfused human placenta. Acta Anaesthesiol Scand 1997; 41: 313-319.

58) Yu M, Han C, Jiang X, Wu X, Yu L, Ding Z. Effect and Placental Transfer of Dexmedetomidine During Caesarean Section Under General Anaesthesia. Basic Clin Pharmacol Toxicol 2015; 117: 204-208.

59) Dailland P, Cockshott ID, Lirzin JD, Jacquinot P, Jorrot JC, Devery J, Harmey JL, Conseiller C. Intravenous propofol during cesarean section: placental transfer, concentrations in breast milk, and neonatal effects. A preliminary study. Anesthesiology 1989; 71: 827-834.

60) Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP. Intravenous remifentanil: placental transfer, maternal and neonatal effects. Anesthesiology 1998; 88: 1467-1474.

61) Wang C, Liu S, Han C, Yu M, Hu Y, Liu C. Effect and placental transfer of dexmedetomidine during caesarean section under epidural anaesthesia. J Int Med Res 2017; 45: 964-972.