

Effect of intrathecal dexmedetomidine on cesarean section during spinal anesthesia: a meta-analysis of randomized trials

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Yun-Qi Wang^{1,2}
Xian-Jie Zhang¹
Ying Wang¹

¹Department of Anesthesiology, People's Hospital of Deyang City, Sichuan, People's Republic of China; ²Department of Anesthesiology, The Sixth People's Hospital of Deyang City, Sichuan, People's Republic of China

Objective: Intrathecal dexmedetomidine has been used in spinal anesthesia during cesarean sections. The purpose of this meta-analysis was to investigate the effect of intrathecal dexmedetomidine on the adverse reactions of spinal anesthesia during cesarean section.

Methods: We searched for relevant studies using PubMed, Web of Science, and the Cochrane library. After screening studies and extracting data, we performed a meta-analysis on the effect of intrathecal dexmedetomidine during cesarean section.

Results: A total of 278 patients from 4 studies were included in this meta-analysis. The incidence of shivering in the dexmedetomidine groups was significantly lower than that in the placebo groups during cesarean section (RR=0.40, 95% CI [0.25, 0.65], $P=0.0002$). Intrathecal dexmedetomidine had no effect on nausea and vomiting (RR=1.08, 95% CI [0.68, 1.71], $P=0.74$), bradycardia (RR=1.33, 95% CI [0.31, 5.76], $P=0.70$), and hypotension during cesarean section (RR=0.78, 95% CI [0.59, 1.03], $P=0.08$).

Conclusion: Intrathecal dexmedetomidine can effectively reduce the occurrence of shivering during cesarean section, but it does not affect the occurrence of nausea and vomiting, bradycardia or hypotension.

Keywords: dexmedetomidine, cesarean section, spinal anesthesia, adverse reactions

Introduction

Spinal anesthesia has become the most commonly used anesthesia in cesarean sections because it is easy to operate, has little impact on the body's physiological functions, allows patients to stay awake during surgery and avoids the risks of general anesthesia.¹⁻³ Although spinal anesthesia during cesarean section is safer than general anesthesia, the adverse reactions of spinal anesthesia still seriously threaten the safety of maternal and fetal life.⁴⁻⁶ These adverse reactions mainly include shivering, nausea and vomiting, hypotension, and bradycardia. Shivering can affect maternal metabolic activity and cause increased oxygen consumption, which may lead to an increased risk of cardiovascular and cerebrovascular diseases due to hypoxia. In addition, increased peripheral vascular resistance, carbon dioxide retention and metabolic acidosis can also occur.^{6,7} If nausea and vomiting occur during the operation, the contents of the stomach may be inhaled into the lungs by mistake, leading to life-threatening pneumonia.⁴ Maternal hypotension may occur due to the sympathetic nerve transmission block caused by spinal anesthesia. Maternal hypotension may cause a decrease in blood supply to the placenta,

Correspondence: Ying Wang
Department of Anesthesiology, People's Hospital of Deyang City, No. 173, Section 1, Taishan North Road, Deyang City, Sichuan Province, People's Republic of China
Email 459088699@qq.com

which ultimately leads to hypoxia and acidosis in the fetus.^{8,9} To improve the safety of spinal anesthesia during cesarean section, several adjuvants are widely used during anesthesia, including a new type of α -2 adrenergic agonist: dexmedetomidine.^{3,10,11} Dexmedetomidine can be administered intravenously or intrathecally during spinal anesthesia, but there is some controversy about which method should be used during anesthesia for pregnant women. The use of dexmedetomidine by the intravenous route has been reported to result in hemodynamic instability.¹² Therefore, we aimed to investigate the effect of intrathecal dexmedetomidine on the adverse effects of spinal anesthesia during cesarean section.

Methods

Search strategy

Two authors (Yun-Qi Wang and Xian-Jie Zhang) searched the PubMed, Web of Science, and Cochrane library databases using the keywords “cesarean section”, “dexmedetomidine” and “spinal anesthesia” without language restrictions until January 23, 2019. To ensure that all available evidence was included, we also identified any potential related articles by manually searching the references of the original articles.

Inclusion criteria

Randomized controlled trials (RCTs) that adopted a blinding method were included in this analysis. The criteria for inclusion in these trials were as follows:

Patients: female patients undergoing cesarean section with spinal anesthesia.

Interventions: any trials on the administration of dexmedetomidine via the intrathecal route.

Comparisons: patients who received placebo treatment.

Outcomes: the trials must contain at least one of the following adverse reactions: (1) shivering; (2) nausea and vomiting; (3) hypotension; and (4) bradycardia.

Exclusion criteria

Trials that met any of the following conditions were excluded: (1) nonrandomized controlled trials (non-RCTs); (2) retrospective studies; (3) systematic reviews; (4) case reports; (5) non-intrathecal administration; and (6) no intraoperative adverse reactions were reported.

Study quality assessment criteria

Each of the studies included was independently assessed by two authors (Xian-Jie Zhang and Ying Wang) according to

the Cochrane risk of bias tool,¹³ in the case of a disagreement, a third author (Yun-Qi Wang) participated in the discussion until an agreement was reached. The following items were assessed: (1) generation of random sequences; (2) concealment of allocation; (3) blinding of participants and implementers; (4) blinding of analysis results to personnel; (5) incomplete outcome data; (6) selective reporting; and (7) other bias (including the authenticity of clinical trials and whether the data are authentic and reliable; whether the baseline characteristics are the same between the experimental groups and the control groups; and whether the evaluation results are appropriate). These items are divided into three categories: low risk of bias, unclear of bias, or high risk of bias.

Data extraction

Two authors (Xian-Jie Zhang and Ying Wang) independently extracted the data from the included studies based on standard data tables. For any differences, a third author (Yun-Qi Wang) was brought in for discussion to resolve the differences. The following data was extracted from each of the included studies: the first author, the author's nationality, the publication date, the number of patients in the experimental group and control group, the intervention, and the relevant data of intraoperative adverse reactions (including shivering, nausea and vomiting, hypotension, and bradycardia).

Statistical analyses

We used Review Manager (version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, 2014) to perform a meta-analysis of the extracted data. The I^2 statistic was used to assess heterogeneity. The criteria and solutions for heterogeneity in the trials included in this meta-analysis are as follows. (1) $I^2 < 50\%$ indicates the existence of homogeneity, so we used the fixed-effect model for the meta-analysis. (2) $I^2 \geq 50\%$ indicates the presence of heterogeneity, so we used the random-effects model for the meta-analysis. If heterogeneity exists, we performed sensitivity analysis and subgroup analysis for the factors that may cause heterogeneity. The results of the dichotomous outcomes are described by the risk ratio (RR) and 95% confidence interval (CI).

Results

Study screening

Through the above search strategy, we initially found a total of 144 studies. After removing duplicated studies, we read the titles and abstracts of the remaining studies and

excluded 6 reviews, 20 meta-analyses, and 16 studies on postoperative analgesia. We then evaluated the full-text of the remaining 10 studies. Following the strict exclusion and inclusion criteria for screening, another 6 studies did not meet the requirements for the following reasons: dexmedetomidine was administered via the intravenous route (n=4); and the result was postoperative adverse reactions (n=2). Finally, we included only 4 studies after several rounds of screening.¹⁴⁻¹⁷ Figure 1 shows the process of study inclusion.

Characteristics and quality of the included studies

Table 1 summarizes the basic characteristics of the 4 studies included in the meta-analysis. All studies used

bupivacaine for spinal anesthesia. In the experimental groups, 5 μ g of dexmedetomidine were injected intrathecally. Two authors independently assessed all studies that were eventually included by using the Cochrane risk of bias tool.¹³ The specific quality assessment rules are shown in Figure 2.

(Other bias including: the authenticity of clinical trials and whether the data are authentic and reliable; whether the baseline characteristics are the same between the experimental groups and the control groups; and whether the evaluation results are appropriate)

Results of the meta-analysis

The effect on shivering: All of the studies reported the occurrence of intraoperative shivering. The incidence of shivering was compared between the dexmedetomidine

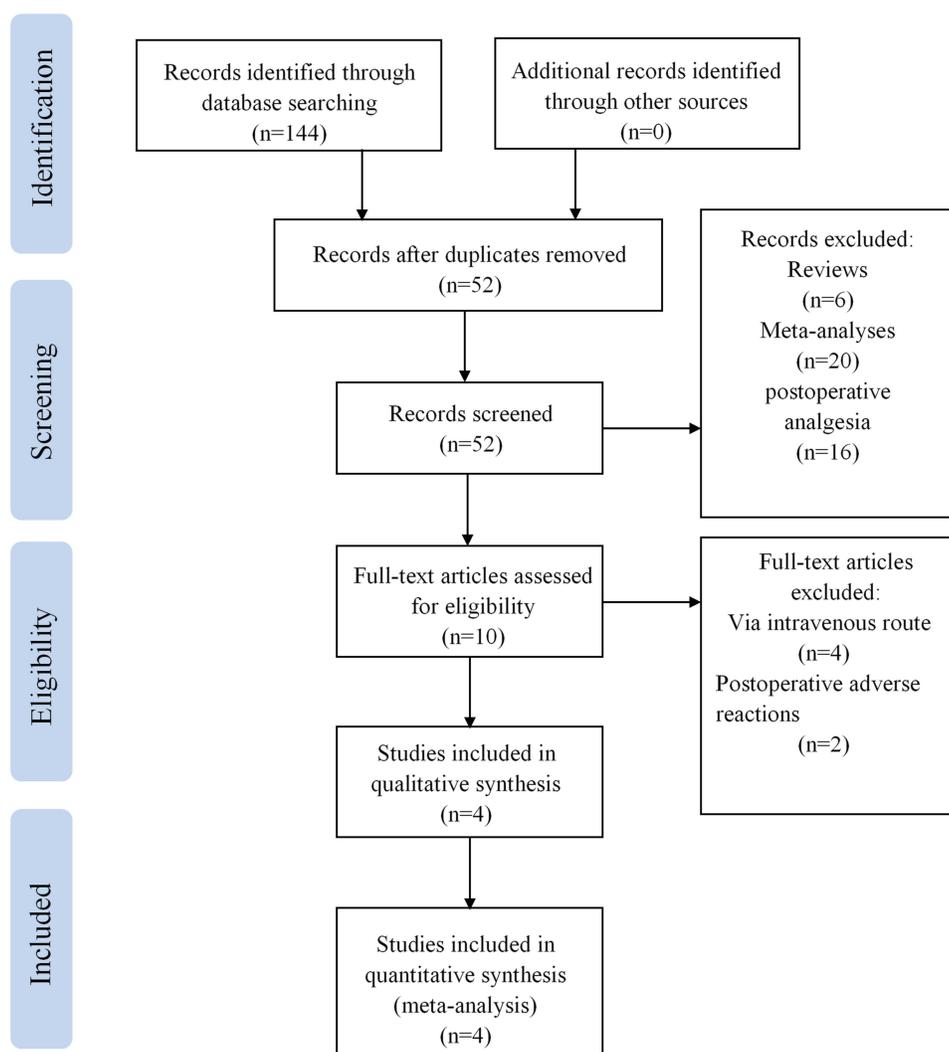


Figure 1 PRISMA flowchart of the included studies.

Abbreviation: PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Table 1 Characteristics of all the studies included in the meta-analysis

Authors	Country	Number of patients		Intervention	
		Dexmedetomidine	Placebo	Dexmedetomidine group	Placebo group
He ¹⁴ 2016	China	30	30	Bupivacaine 0.5% 2.5 mL + Dexmedetomidine 5 µg	Bupivacaine 0.5% 2.5 mL + Normal saline 0.5 ml
Nasseri ¹⁵ 2017	Iran	25	25	Bupivacaine 0.5% 12.5 mg + Dexmedetomidine 5 µg	Bupivacaine 0.5% 12.5 mg + Normal saline 0.5 ml
Qi ¹⁶ 2016	China	39	39	Bupivacaine 0.5% 2 mL + Dexmedetomidine 5 µg	Bupivacaine 0.5% 2 mL
Xia ¹⁷ 2018	China	45	45	Bupivacaine 8.4 mg + Dexmedetomidine 5 µg	Bupivacaine 12.1 mg

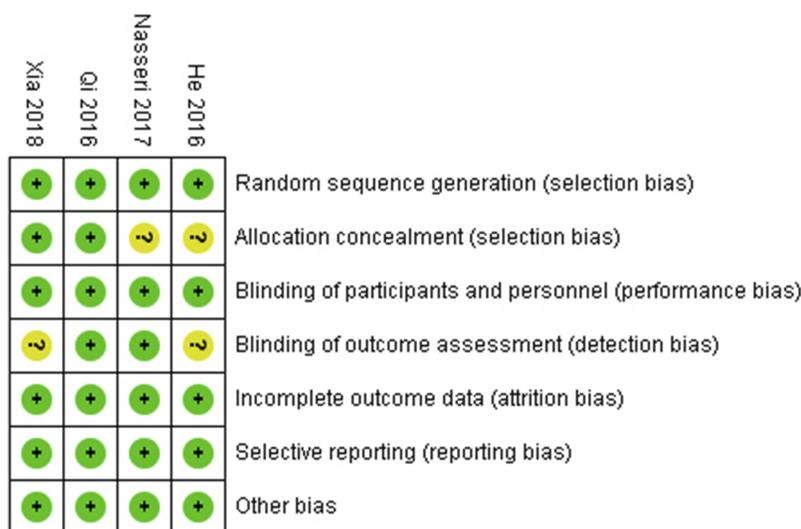


Figure 2 The risk of bias of all the included trials.

groups and the placebo groups, and the heterogeneity test showed that $I^2=19\%$, so a fixed-effects model was used for the meta-analysis. Compared with the placebo, dexmedetomidine was effective in reducing the incidence of shivering during cesarean section (RR=0.40, 95% CI [0.25, 0.65], $P=0.0002$; **Figure 3**).

The effect on nausea and vomiting: Four studies reported the occurrence of intraoperative nausea and vomiting. The incidence of nausea and vomiting was compared between the dexmedetomidine groups and the placebo groups, and the heterogeneity test showed that $I^2=0\%$, so a fixed-effects model was used for the meta-analysis. Using dexmedetomidine did not reduce the risk of intraoperative nausea and vomiting (RR=1.08, 95% CI [0.68, 1.71], $P=0.74$; **Figure 4**).

The effect on bradycardia: Only three studies¹⁴⁻¹⁶ reported the occurrence of intraoperative bradycardia.

The incidence of bradycardia was compared between the dexmedetomidine groups and the placebo groups, and the heterogeneity test showed that $I^2=16\%$, so a fixed-effects model was used for the meta-analysis. The dexmedetomidine groups did not have an increased risk of bradycardia compared with the placebo groups (RR=1.33, 95% CI [0.31, 5.76], $P=0.70$; **Figure 5**).

The effect on hypotension: Three studies¹⁵⁻¹⁷ reported the occurrence of intraoperative hypotension. The incidence of hypotension was compared between the dexmedetomidine groups and the placebo groups, and the heterogeneity test showed that $I^2=46\%$; since $I^2=46\%$ is considered median heterogeneity, we used a fixed-effects model and a random-effects model for the meta-analysis. There was no significant difference in intraoperative hypotension between the dexmedetomidine groups and the placebo groups (fixed-effects model: RR=0.78,

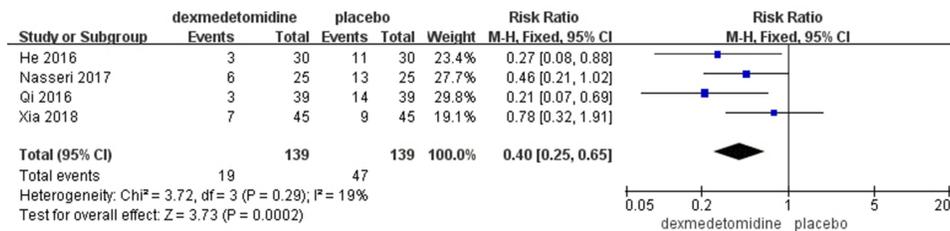


Figure 3 Forest plot of the effect of dexmedetomidine on shivering. **Abbreviations:** CI, confidence interval; M-H, Mantel-Haenszel.

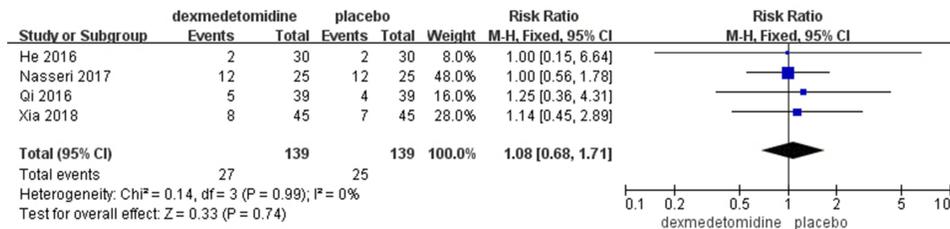


Figure 4 Forest plot of the effect of dexmedetomidine on nausea and vomiting. **Abbreviations:** CI, confidence interval; M-H, Mantel-Haenszel.

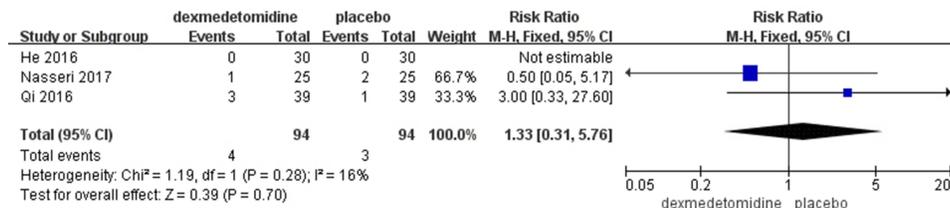


Figure 5 Forest plot of the effect of dexmedetomidine on bradycardia. **Abbreviations:** CI, confidence interval; M-H, Mantel-Haenszel.

95% CI [0.59, 1.03], $P=0.08$; **Figure 6**; random-effects model: RR=0.78, 95% CI [0.52, 1.17], $P=0.23$).

Discussion

We conducted a meta-analysis of 4 RCTs and found that intrathecal dexmedetomidine significantly reduced the occurrence of shivering during cesarean section. Moreover, dexmedetomidine did not increase the incidence of nausea and

vomiting during the operation, nor did it significantly cause hypotension or bradycardia. Dexmedetomidine is a novel, highly selective α -2 adrenergic agonist that has become a commonly used adjuvant in anesthesia because it can enhance sedative and analgesic effects and reduce the adverse reactions of anesthesia.^{18–20}

In the case of spinal anesthesia, the possibility of shivering during cesarean section is 55%.³ Intraoperative shivering

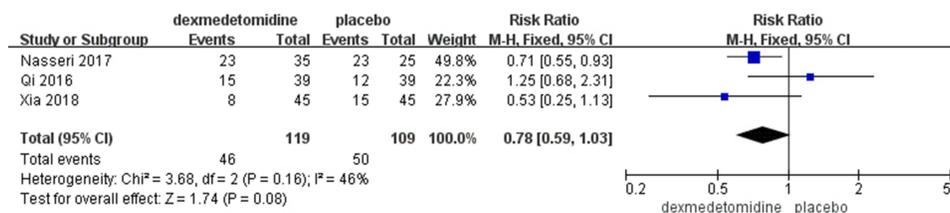


Figure 6 Forest plot of the effect of dexmedetomidine on hypotension (fixed-effects model). **Abbreviations:** CI, confidence interval; M-H, Mantel-Haenszel.

leads to increased oxygen consumption and carbon dioxide production, which has a certain impact on maternal physiological functions.²¹ The cause of shivering during cesarean section under spinal anesthesia is still unknown, but the occurrence of shivering may be related to the loss of heat, the suppression of the body's thermoregulatory mechanism, and the redistribution of heat in the body. Dexmedetomidine may play an antishivering role by regulating the shivering threshold of the central thermoregulatory system and reducing the contraction of vessels.^{12,22} Although intravenous dexmedetomidine can reduce the incidence of shivering, it has an inhibitory effect on the respiratory rate.²³ Intrathecal dexmedetomidine inhibits the body's thermoregulatory center by inhibiting the transmission of body temperature information at the level of the spinal cord, ultimately reducing the incidence of shivering during cesarean section.² Our meta-analysis found that intrathecal dexmedetomidine significantly reduces the incidence of shivering during cesarean section.

Although intrathecal opioids can enhance the effects of anesthesia, they cause a significant increase in the incidence of nausea and vomiting during cesarean section.¹¹ Interestingly, through this meta-analysis, we found that dexmedetomidine does not increase the probability of intraoperative nausea and vomiting. The cause of nausea and vomiting during spinal anesthesia is not well understood, and nausea and vomiting are common side effects of cesarean section under spinal anesthesia. Sympathetic blockade during anesthesia, hypotension, and vagal reflex caused by visceral traction during cesarean section are the leading causes of nausea and vomiting, and hypotension is probably the most important cause,² which explains why intrathecal dexmedetomidine does not increase the incidence of nausea and vomiting during cesarean section. Yousef et al²⁰ found that intrathecal dexmedetomidine does not increase the incidence of hypotension, and this meta-analysis also confirmed that finding. Li et al¹⁸ confirmed that dexmedetomidine can effectively reduce the use of opioids during cesarean section, indicating that with the use of dexmedetomidine, the probability of nausea and vomiting during cesarean section will decrease as the dose of opioids decreases. However, when no opioids were used, dexmedetomidine did not appear to significantly reduce the incidence of nausea and vomiting during cesarean section. Therefore, intrathecal dexmedetomidine neither increases nor decreases the incidence of nausea and vomiting during cesarean section.

The use of dexmedetomidine via venous access has been found to result in hypotension during cesarean section.^{24,25} The reason for the hypotension induced by intravenous

dexmedetomidine is that the action of the α -2 adrenergic agonist is manifested as sympatholysis, which is the ability to block the sympathetic arm of the autonomic nervous system.²⁶ Therefore, intravenous dexmedetomidine should be used with caution if maternal circulatory dysfunction exists.²⁴ The decrease in blood pressure caused by spinal anesthesia is due to the intrathecal injection of local anesthetics that causes sympathetic blockade. In general, this sympathetic block is very close to the maximum during spinal anesthesia. In this situation, adding low doses of an α -2 adrenergic agonist (for example, dexmedetomidine) to a high dose of local anesthetic does not further affect the nearly maximal sympatholysis.²⁷ Therefore, intrathecal dexmedetomidine does not increase the risk of hypotension during cesarean section.

The intravenous administration of dexmedetomidine can cause bradycardia, and these heart rate changes are usually caused by baroreflex-mediated changes.^{2,23,28} However, we found in this meta-analysis that intrathecal dexmedetomidine did not increase the incidence of bradycardia in cesarean section. The reason for this may be that intrathecal dexmedetomidine has little effect on the baroreflex-mediated changes.

There are several shortcomings in our meta-analysis. First, the number of RCTs that were included was small, and the number of samples was small, which led to our conclusions being based on small samples. Second, regarding the quality of the included RCTs, not all included studies had a low risk of bias. Third, only published RCTs were included in our study, and the search strategy also influenced the results of our study. Fourth, all 4 RCTs included in the study used 5 μ g of dexmedetomidine and lacked an evaluation of the effect of other intrathecal doses of dexmedetomidine on cesarean section.

Conclusion

Intrathecal dexmedetomidine can effectively reduce the occurrence of shivering during cesarean section under spinal anesthesia, and it has no significant effect on the occurrence of nausea and vomiting during cesarean section. Moreover, the occurrence of bradycardia and hypotension did not increase, indicating that intrathecal dexmedetomidine does not affect hemodynamics during cesarean section.

Acknowledgment

No funding was received for this research.

Disclosure

The authors report no conflicts of interest in this study.

References

- Carrie LE. Extradural, spinal or combined block for obstetric surgical anaesthesia. *Br J Anaesth*. 1990;65(2):225–233. doi:10.1093/bja/65.2.225
- 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(3):924–932. doi:10.1177/0300060517708945
- 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(38):63587–63595. doi:10.18632/oncotarget.18864
- Lussos SA, Bader AM, Thornhill ML, Datta S. The antiemetic efficacy and safety of prophylactic metoclopramide for elective cesarean delivery during spinal anesthesia. *Reg Anesth*. 1992;17(3):126–130.
- Klohr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. *Acta Anaesthesiol Scand*. 2010;54(8):909–921. doi:10.1111/j.1399-6576.2010.02239.x
- Botros JM, Mahmoud AMS, Ragab SG, et al. Comparative study between dexmedetomidine and ondansetron for prevention of post spinal shivering. A randomized controlled trial. *BMC Anesthesiol*. 2018;18(1):179. doi:10.1186/s12871-018-0540-6
- 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(9):468–472. doi:10.1055/s-0034-1387740
- Corke BC, Datta S, Ostheimer GW, Weiss JB, Alper MH. Spinal anaesthesia for caesarean section. The influence of hypotension on neonatal outcome. *Anaesthesia*. 1982;37(6):658–662. doi:10.1111/j.1365-2044.1982.tb01278.x
- Doherty A, Ohashi Y, Downey K, Carvalho JC. Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes. *Anesth Analg*. 2012;115(6):1343–1350. doi:10.1213/ANE.0b013e31826ac3db
- Hanoura S, Hassanin R, Singh R. Intraoperative conditions and quality of postoperative analgesia after adding dexmedetomidine to epidural bupivacaine and fentanyl in elective cesarean section using combined spinal-epidural anesthesia. *Anesthesia*. 2013;7(2):168.
- Dyer RA, Joubert IA. Low-dose spinal anaesthesia for caesarean section. *Curr Opin Anaesthesiol*. 2004;17(4):301–308. doi:10.1097/01.aco.0000137088.29861.64
- Yu G, Jin S, Chen J, Yao W, Song X. The effects of novel -adrenoreceptor agonist dexmedetomidine on shivering in patients underwent caesarean section. *Biosci Rep*. 2019;39(2):BSR20181847. doi:10.1042/BSR20181847
- Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. 2011;343(182):d5928–d5928. doi:10.1136/bmj.d5928
- 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(2):169–173. doi:10.1248/bpb.b16-00651
- 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. doi:10.2147/DDDT.S131866
- Qi X, Chen D, Li G, et al. Comparison of intrathecal dexmedetomidine with morphine as adjuvants in cesarean sections. *Biol Pharm Bull*. 2016;39(9):1455–1460. doi:10.1248/bpb.b16-00145
- 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(1):74. doi:10.1186/s12871-018-0540-6
- Li Z, Tian M, Zhang CY, et al. 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(11):581–586. doi:10.1055/s-0034-1395614
- Wang J, Han Z, Zhou H, Wang N, Ma H. Effective loading dose of dexmedetomidine to induce adequate sedation in parturients undergoing caesarean section under spinal anaesthesia. *Turk J Anaesthesiol Reanim*. 2017;45(5):260–263. doi:10.5152/TJAR.2017.04578
- Yousef AA, Salem HA, Moustafa MZ. Effect of mini-dose epidural dexmedetomidine in elective cesarean section using combined spinal-epidural anesthesia: a randomized double-blinded controlled study. *J Anesth*. 2015;29(5):708–714. doi:10.1007/s00540-015-2027-7
- Park SM, Mangat HS, Berger K, Rosengart AJ. Efficacy spectrum of antishivering medications: meta-analysis of randomized controlled trials. *Crit Care Med*. 2012;40(11):3070–3082. doi:10.1097/CCM.0b013e31825b931e
- Doufas AG, Lin CM, Suleman MI, et al. Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. *Stroke*. 2003;34(5):1218–1223. doi:10.1161/01.STR.0000068787.76670.A4
- Hogue CW Jr., Talke P, Stein PK, Richardson C, Domitrovich PP, Sessler DI. Autonomic nervous system responses during sedative infusions of dexmedetomidine. *Anesthesiology*. 2002;97(3):592–598. doi:10.1097/0000542-200209000-00012
- Jiang W, Wang Q, Xu M, et al. Assessment of different loading doses of dexmedetomidine hydrochloride in preventing adverse reaction after combined spinal-epidural anesthesia. *Exp Ther Med*. 2017;13(6):2946–2950. doi:10.3892/etm.2017.4335
- Niu XY, Ding XB, Guo T, Chen MH, Fu SK, Li Q. Effects of intravenous and intrathecal dexmedetomidine in spinal anesthesia: a meta-analysis. *CNS Neurosci Ther*. 2013;19(11):897–904. doi:10.1111/cns.12172
- Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. *Anesthesiology*. 2000;93(5):1345–1349. doi:10.1097/0000542-200011000-00030
- Kanazi GE, Aouad MT, Jabbour-Khoury SI, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand*. 2006;50(2):222–227. doi:10.1111/j.1399-6576.2006.00919.x
- Memis D, Turan A, Karamanlioglu B, Pamukcu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. *Anesth Analg*. 2004;98(3):835–840, table of contents. doi:10.1213/01.ane.0000100680.77978.66

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also

been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>

Dovepress