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REPORTS OF ORIGINAL INVESTIGATIONS

Intravenous dexmedetomidine for the treatment of shivering during Cesarean delivery under neuraxial anesthesia: a randomized-controlled trial

Administration de dexmédétomidine intraveineuse pour le traitement des frissons pendant un accouchement par césarienne sous anesthésie neuraxiale : une étude randomisée contrôlée

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Abstract

Purpose *About 55% of patients undergoing a Cesarean delivery under spinal or epidural anesthesia will experience shivering, which may interfere with the monitoring of vital signs. Recent studies have shown that dexmedetomidine could potentially help to alleviate shivering associated with anesthesia. We investigated whether dexmedetomidine, an alpha 2-adrenergic agonist, reduces the duration of shivering associated with neuraxial anesthesia during Cesarean delivery.*

Methods *Eighty parturients undergoing Cesarean delivery under neuraxial anesthesia and experiencing shivering were enlisted in this prospective, randomized, double-blind trial. After childbirth, the intervention group (n = 40) received a single intravenous bolus of dexmedetomidine (30 μg) while the control group (n = 40) received saline. Randomization and allocation were based on a computer-generated list. The primary outcome measure was the time required for an observable decrease in shivering after the intervention.*

Results *One hundred fifty-five patients were recruited, 80 of whom presented with shivering and were randomized. Our study showed that dexmedetomidine reduced the mean (standard deviation) duration of shivering after a single intravenous bolus to 2.6 (2.1) min after dexmedetomidine from 17.9 (12.6) min after saline (difference in means, -15.3 min; 95% confidence interval [CI], -11.2 to -19.4). The effect of dexmedetomidine persisted 15 min after the bolus was administered, as shivering had completely stopped in 90% of the patients in the intervention group vs 22.5% in the control group (relative risk, 4.0; 95% CI, 2.2 to 7.2). No adverse effects, including bradycardia, were observed.*

Conclusion *A single intravenous bolus of dexmedetomidine decreased the duration of shivering for up to 15 min during Cesarean delivery under neuraxial anesthesia.*

Trial registration *www.clinicaltrials.gov (NCT02384343); registered 10 March, 2015.*

Résumé

Objectif *Environ 55 % des patientes subissant un accouchement par césarienne sous anesthésie rachidienne ou épidurale vont manifester des frissons, lesquels peuvent interférer avec la mesure des signes vitaux. Des études récentes ont démontré que la dexmédétomidine a le potentiel de réduire les frissons associés à l'anesthésie. Nous avons cherché à démontrer si la dexmédétomidine, un agoniste des récepteurs alpha-2-adrénergiques, peut réduire la durée des frissons associés*

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à l'anesthésie neuraxiale lors d'un accouchement par césarienne.

Méthode *Quatre-vingts parturientes subissant un accouchement par césarienne sous anesthésie neuraxiale et manifestant des frissons ont été recrutées pour cette étude prospective, randomisée et à double insu. Après la naissance, le groupe intervention (n = 40) a reçu un bolus intraveineux unique de dexmédétomidine (30 µg) alors que le groupe témoin (n = 40) a reçu une solution saline. La randomisation et l'attribution ont suivi une liste générée par ordinateur. Le critère d'évaluation principal était le temps nécessaire avant d'observer une réduction des frissons après l'intervention.*

Résultats *Cent cinquante-cinq patientes ont été recrutées, dont 80 ont présenté des frissons et ont été randomisées. Notre étude a montré que la dexmédétomidine réduisait la durée moyenne (écart type) des frissons après un bolus intraveineux unique à 2,6 (2,1) min après l'administration de dexmédétomidine par rapport à une durée moyenne de 17,9 (12,6) min après la solution saline (différence de moyennes, -15,3 min; intervalle de confiance [IC] 95 %, -11,2 à -19,4). L'effet de la dexmédétomidine persistait 15 min après l'administration du bolus, où les frissons avaient complètement cessé chez 90 % des patientes du groupe intervention vs 22,5 % du groupe témoin (risque relatif, 4,0; IC 95 %, 2,2 à 7,2). Aucun effet secondaire néfaste, y compris la bradycardie, n'a été observé.*

Conclusion *Un bolus intraveineux unique de dexmédétomidine réduit la durée des frissons jusqu'à 15 min lors d'un accouchement par césarienne sous anesthésie neuraxiale.*

Enregistrement de l'étude *www.clinicaltrials.gov (NCT02384343); enregistrée le 10 mars 2015.*

Neuraxial anesthesia is the technique of choice in Cesarean delivery; it is selected because it allows mothers to remain conscious and avoids risks associated with general anesthesia.[1] Nevertheless, in obstetrical populations, neuraxial anesthesia is associated with shivering in approximately 53% of patients.[1] Shivering causes physiological stress, interferes with the monitoring of vital signs, and adversely affects patient comfort and satisfaction.[1] Several classes of pharmacological agents, including opioids, 5-HT_3 receptor antagonists, α_2 receptor agonists, and possibly N-methyl-D-aspartate receptor antagonists, appear to modulate central thermoregulatory control mechanisms.[2] Most of these agents, proven to reduce the incidence of shivering, have analgesic and sedative properties. Currently, the most common drug used to treat shivering is meperidine, a synthetic opioid.[3] Nevertheless, meperidine is no longer recommended as a first-line agent for pain management and is in increasingly scarce supply at North American health centres; an effective alternative agent is increasingly sought after.[4,5]

Dexmedetomidine, a highly selective α_2 adrenergic agonist, is an alternative treatment for shivering. Dexmedetomidine was initially approved by the United States Food and Drug Administration in 1999 for use as a sedative in intensive care units. It acts at the level of the locus ceruleus to sedate, and at the level of the spinal cord to potentiate analgesia.[6] It also leads to sympatholysis via central and peripheral pathways, reducing both vasoconstriction and shivering thresholds.[7] Dexmedetomidine is currently widely used off label as an intraoperative adjuvant, and to mitigate postoperative complications such as emergence delirium; the rationale behind its use, as opposed to meperidine, is that it is able to alleviate shivering while avoiding side effects associated with opiates. Indeed, the safety profile of dexmedetomidine has increasingly been characterized in a number of studies conducted in vulnerable populations, including critically ill,[8] pediatric,[9,10] and obstetrical patient populations.[11-13]

This study tested whether a single bolus of 30 µg *iv* of dexmedetomidine, administered five minutes after childbirth, reduces the duration of shivering during Cesarean delivery under neuraxial anesthesia. The fixed dose selected was based on clinical experience at CHU St. Justine, where shivering following Cesarean delivery has been treated with dexmedetomidine for more than five years.

Methods

Trial design

This study was a single centre, randomized, double-blind, placebo-controlled, parallel-group study conducted at CHU Sainte-Justine, located in Montréal, QC, Canada. The use of dexmedetomidine in the context of this study was approved by Health Canada (i.e., a *No Objection Letter* was provided) and the Sainte-Justine University Hospital Research Ethics Board. The trial was registered at ClinicalTrials.gov, number: NCT02384343.

Eighty parturients were randomly assigned, in a 1:1 ratio, to receive either dexmedetomidine or a normal saline placebo. The monitoring committee reviewed unblinded data with the accrual of each 20 patients to ensure that the use of dexmedetomidine was safe in the context of the ongoing study. The monitoring committee was composed of three doctors independent of the study. For each randomized patient, the committee evaluated the

incidence of significant bradycardia (< 50 beats·min^{-1}) and/or hypotension (> 20% drop from the baseline mean blood pressure). In reviewing said unblinded data, at no point did the monitoring committee discover any adverse complications, and as such determined that the study, as conducted, raised no patient safety concerns.

Participants

Eligible participants were adults aged 18 and over who presented to the birthing unit at CHU Sainte-Justine for Cesarean delivery. Exclusion criteria were: emergency Cesarean delivery, weight below 60 kg or over 120 kg, known hypersensitivity to dexmedetomidine, heart, renal or hepatic disease requiring follow-up or medication, pre-eclampsia, general anesthesia, combined spinal-epidural anesthesia (where medication had been administered in both the spinal and epidural spaces at the time of Cesarean delivery), administration of blood products during surgery, or the incidence of major surgical complications.

Recruitment took place form June 2015 to April 2016 at the CHU Sainte-Justine birthing unit. All eligible patients who presented when one of the five anesthesiologists involved in the study was available, were approached. Informed written consent was obtained by a member of the study, immediately after the preoperative anesthesia evaluation was performed.

Interventions

Medication was distributed each day by a research pharmacist in an opaque box containing six vials of dexmedetomidine 100 μg·mL^{-1} 2 mL, six vials of normal saline 10 mL, and 12 1-mL syringes. The box also contained a computer-generated randomization list, and sheets on which to record the date and time of administration, recipient patient identification number, vial serial number, and the identity of the person who prepared the medication. The box was stored in a room adjacent to the operating room where surgery was performed. One vial was dispensed per participant. The syringes were identified by a numbered label. The appearance of each syringe was identical. The pharmacist was responsible for the disposal and replacement of used vials.

Upon arrival to the operating room, patients were placed on standard monitoring. This involved continuous electrocardiogram, continuous pulse oximetry, and non-invasive blood pressure (measured once per minute). Antibiotic prophylaxis of 2 g cefazolin *iv* (Hospira, Saint-Laurent, QC, Canada) was administered. Patient temperature was measured using an oral thermometer (SureTemp plus 690, Welch Allyn, Mississauga, ON, Canada). A 10 mg *iv* dose of metoclopramide (Sandoz, Boucherville, Quebec, Canada) and 4 mg *iv* dose of ondansetron (Sandoz, Boucherville, QC, Canada) were administered to prevent nausea and vomiting. The initial shivering grade and sedation score were then recorded.

Shivering was graded using a five-point scale as outlined by Crossley and Mahajan[14]:

- Grade 0: no shivering;
- Grade 1: one or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis, but without visible muscle activity;
- Grade 2: visible muscle activity confined to one muscle group;
- Grade 3: visible muscle activity in more than one muscle group;
- Grade 4: gross muscle activity involving the whole body.

The degree of sedation was graded on a four-point scale described by Filos *et al.*[15]:

- Grade 1: awake and alert;
- Grade 2: drowsy, responsive to verbal stimuli;
- Grade 3: drowsy, arousable to physical stimuli;
- Grade 4: unarousable.

Spinal anesthesia was administered to patients who did not already have epidural catheters in place. Spinal anesthesia consisted of 12 mg hyperbaric bupivacaine 0.75% (Hospira, Saint-Laurent, QC, Canada), 150 μg morphine (Sandoz, Boucherville, QC, Canada), and 15 μg fentanyl (Sandoz, Boucherville, QC, Canada). Spinal anesthesia was performed in the sitting position at the L3-L4 interspace with a midline approach using a 25 or 27G Whitacre needle (B. Braun Medical Inc., Bethlehem, PA, USA). An infusion of phenylephrine 0.1 mg.mL^{-1} *iv* was systematically started at a dose of 30 μg·min^{-1} after spinal anesthesia and then titrated to maintain a mean arterial blood pressure within 20% of baseline.

Epidural anesthesia was administered in patients who already had an epidural catheter in place. Epidural anesthesia consisted of 2% lidocaine (Alveda Pharmaceuticals Inc., Toronto, ON, Canada) with 1:200,000 epinephrine and 100 μg of fentanyl, totaling 15-20 mL. A single dose of 2.5 mg morphine (Sandoz, Boucherville, Quebec, Canada) was administered to the epidural space at the end of surgery.

After neuraxial anesthesia, parturients were placed supine with left uterine displacement. Patients were covered with one standard cotton sheet, but were not actively warmed. A bolus of 15 mL·kg^{-1} of room temperature Ringer's Lactate solution was administered as a co-load concomitant with neuraxial anesthesia. Sensory anesthesia was assessed via pinprick and noted ten minutes after neuraxial injection. The decision to administer supplemental fluid and/or

intraoperative analgesia (intravenous fentanyl or remifentanil) was left to the discretion of the anesthesiologist responsible for the case.

Immediately after cord clamping, a bolus of 100 μg carbetocin *iv* (Jubilant HollisterStier, Kirkland, QC, Canada) was administered. Skin-to-skin contact between the newborn and mother was always offered where possible, and whether or not this contact was made was noted.

At the moment of childbirth, patients were assessed for shivering. Where significant shivering (grade 3 or 4 on the shivering scale) was observed, an anesthesia assistant independent of the study was asked to access the study box and prepare a 1 mL syringe of either 0.3 mL of 100 $\mu g.mL^{-1}$ (30 μg) dexmedetomidine (Hospira, Boucherville, QC, Canada) or 0.3 mL of normal saline according to the pre-established randomization sequence. Five minutes following childbirth, where a patient continued to show significant shivering (grade 3 or 4 on the shivering scale), the content of the syringe was injected intravenously by the study anesthesiologist. At the time of injection, a timer was started, and the patient was observed continuously until the end of surgery. The time at which a significant reduction in shivering was noticed was recorded. Where no reduction was detected, the time of the end of surgery was recorded. The intensity of shivering was also noted at five, ten, and 15 min after the bolus injection to best evaluate the evolution of shivering over time. Patients that were not significantly shivering were not randomized.

Adverse effects such as hypotension (> 20% drop from the baseline mean arterial blood pressure) and bradycardia (< 50 beats·min^{-1}) were noted as they occurred from the time of administration of the bolus until the end of the surgery. The sedation score was recorded five minutes after the administration of the bolus. Where hypotension arose, it was treated with a bolus of 100-200 μg of phenylephrine *iv* and/or 5-10 mg *iv* ephedrine as needed.

Study follow-up ended with the transfer of the patient to the recovery room, where the duration of surgery, volume of crystalloid and colloid solution administered, blood loss, and doses of phenylephrine, ephedrine, fentanyl and remifentanil administered were recorded. Furthermore, patients' oral temperature (SureTemp plus 690, Welch Allyn) was measured a second time.

Outcome

The primary endpoint was the time elapsed for significant reduction in shivering (from grade 3 or 4 to grade 0 or 1 as per the Crossley and Mahajan scale[14] discussed above). Additional analyses evaluated the incidence of adverse effects including bradycardia, hypotension, and sedation scores as described by Filos *et al.*[15]

Randomization

A permuted blocked randomization method was used to allocate eligible subjects. The randomization process consisted of computer-generated random lists of treatment allocations in variable permuted blocks of 6 and 8. Randomization lists were generated by the Data Coordinating Centre statistician and the study staff were blinded to the allocated treatment. No stratified randomization of the type of anesthesia (epidural or spinal) was employed. A research pharmacist assigned a consecutively numbered vial of either dexmedetomidine or normal saline to each participant per the randomization list.

Blinding

Participants, care givers, and those assessing the outcomes were blinded to group assignment. The medication was prepared out of the operating room, before each administration, by an anesthesia assistant per the randomization list. The content of each of the numbered syringes was unknown to the participant, the study members, the anesthesiologist in charge of the case and the statistician.

Statistical methods

A non-parametric test was used to assess time to significant decrease in shivering after bolus administration. A chi-square test was used to evaluate the proportion of patients with decreased shivering after bolus administration in each group. A $P < 0.05$ considered statistically significant.

Sample size

Based on a study conducted by Mittal *et al.*, using intravenous dexmedetomidine after spinal anesthesia in a non-obstetrical context, the mean time for a cessation of shivering was 180 sec with a standard deviation (SD) of 240 sec.[16] Using a power of 90%, and a two-sided alpha error of 0.05 (Pass 12 software), 39 participants per group were needed to detect a mean difference of 180 sec between dexmedetomidine and placebo. Considering a dropout of approximately 2%, 40 participants were needed in each group.

Results

Participant flow

One hundred fifty-five patients undergoing a Cesarean delivery under neuraxial anesthesia met the inclusion criteria and were

recruited, of whom 80 (52%) were shivering and thus randomized into two groups of 40 each. Of the 80 patients that were randomized, 24 were administered epidural anesthesia, and 56 were administered spinal anesthesia. As this was an intraoperative study, no patients were lost to follow-up (Figure).

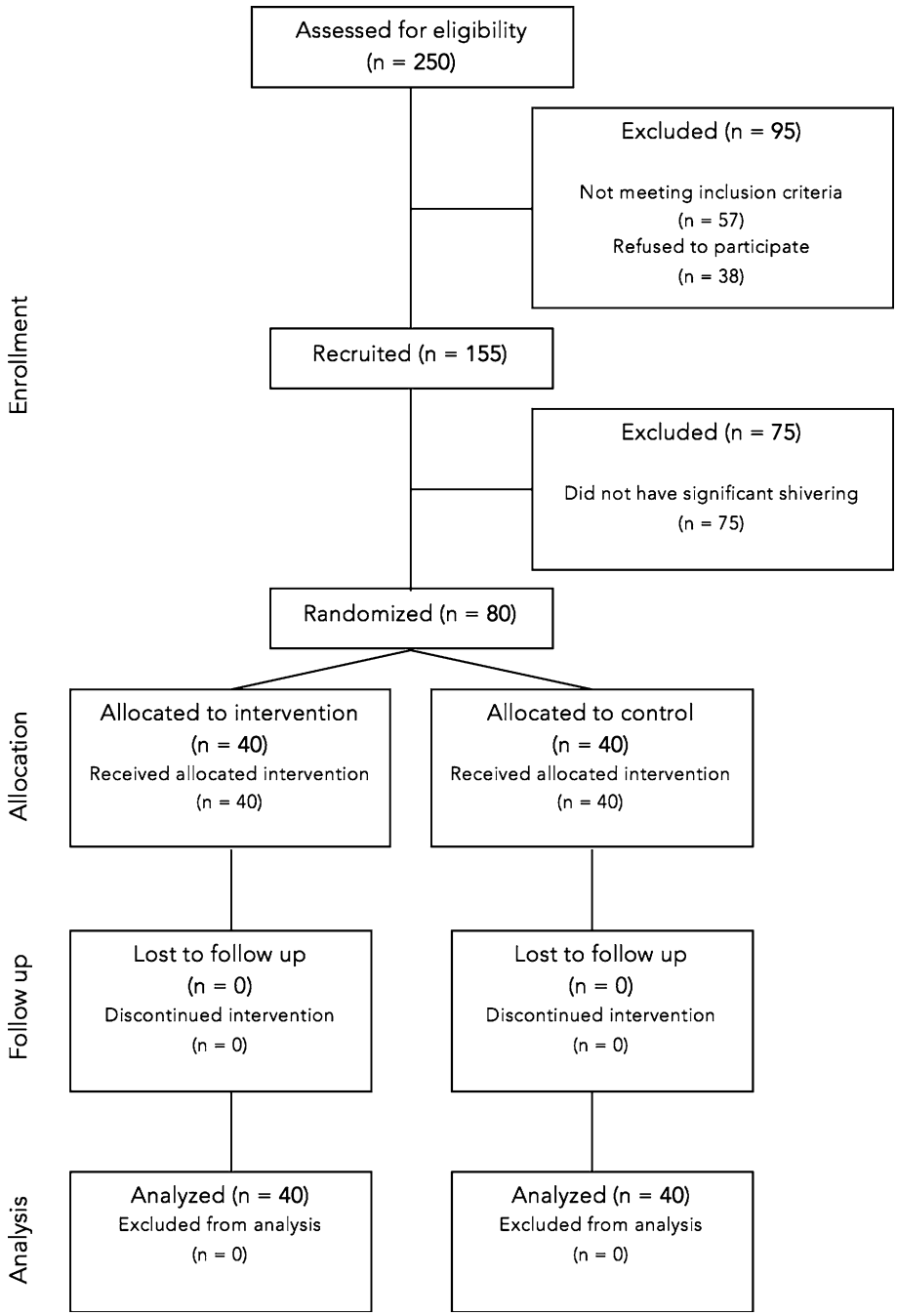
Recruitment

Participants were recruited between June 2015 and April 2016.

Baseline data

Both groups were comparable with respect to age, weight, height, gestational age, and active labour. The number of patients undergoing an elective procedure was equally distributed in both groups as well as the number of patients that received epidural anesthesia *vs* spinal anesthesia. Nine patients shivered significantly before the initiation of neuraxial anesthesia in the intervention group *vs* five patients in the control group. The level of sensory block, skin-to-skin contact or lack of between the newborn and

Figure Flow diagram



the mother, the total volume of crystalloid administered, the number of patients who received intravenous colloids and opioids and their respective amounts, the duration of the surgery, and the estimated blood loss per patient were similar in both groups. The differences in oral temperature at the beginning *vs* at the end of the procedure were also comparable in both groups (Table 1a, 1b).

Number analyzed

The primary analysis involved all patients who were randomly assigned.

Outcomes

The difference in the time interval between the administration of the bolus and the decrease of shivering (from a grade 3 or 4 to a grade 0 or 1) was significantly shorter in the dexmedetomidine group compared with the placebo group. The mean (SD) time to decrease shivering after a single bolus of 30 μg *iv* dexmedetomidine was 2.6 (2.1) min *vs* 17.9 (12.6) min after a bolus of saline (difference in means -15.3 min; 95% CI, -11.2 to -19.4). The effect of dexmedetomidine persisted for ten and 15 min after its administration, with shivering completely arrested (grade 0) in 90% of the patients in the intervention group *vs* 22.5% in the control group after 15 min (relative risk, 4.0; 95% CI, 2.2 to 7.2) (Table 2).

Hypotension (> 20% drop from the baseline mean arterial pressure) was observed in both groups, with only one event occurring following administration of dexmedetomidine as opposed to two events following administration of placebo. The mean doses of intravenous phenylephrine and ephedrine administered were similar in both groups. No significant bradycardia (< 50 beats·min^{-1}) occurred in any of the study participants, although a slowing of heart rate was observed in the dexmedetomidine group. No participants showed significant sedation (grades 3 or 4) at five minutes after the administration of the bolus (Table 3).

Table 1a Characteristics of the patients at baseline

Characteristic	DEX $n = 40$	Control $n = 40$
Age (yr), mean (SD)	31.8 (4.3)	33.1 (4.8)
Weight (kg), mean (SD)	83.1 (16.8)	78.1 (12.6)
Height (cm), mean (SD)	163.1 (5.8)	163.2 (5.5)
Gestational age (weeks), mean (SD)	38.5 (1.6)	38.6 (1.4)
Patients in active labour (%)	12 (30)	13 (32.5)
Elective Cesarean delivery (%)	26 (65)	26 (65)
Epidural anesthesia (%)	12 (30)	12 (30)
Spinal anesthesia (%)	28 (70)	28 (70)
Significant shivering before anesthesia (Crossley and Mahajan[14] grade 3-4) (%)	9 (22.5)	5 (12.5)
Anesthesia sensitive level, mean (SD)	T4 (3)	T4 (1)
Skin-to-skin contact (%)	19 (47.5)	23 (57.5)

SD = standard deviation

Table 1b Characteristics of the patients post-randomization

Characteristic	DEX $n = 40$	Control $n = 40$	*P* value
Duration of surgery (min), mean (SD)	37 (10.5)	42 (12.8)	0.09
Volume of crystalloids (mL), mean (SD)	1528 (461)	1548 (400)	0.84
Number of patients who received colloids (%)	1 (2.5)	3 (7.5)	0.62
Number of patients who received intravenous fentanyl (%)	2 (5)	4 (10)	0.68
Number of patients who received intravenous remifentanil (%)	3 (7.5)	3 (7.5)	1.00
Blood loss (mL), mean (SD)	601 (284)	619 (302)	0.78
Difference in oral temperature between the beginning and the end of the procedure, mean (SD)	0.28 (0.28)	0.23 (0.29)	0.44

SD = standard deviation

Table 2 Parameters for shivering

Outcome	DEX $n = 40$	Control $n = 40$	P value	Effect size Difference in means (95% CI)
Time to decrease shivering after bolus administration (minutes), mean (SD)	2.6 (2.07)	17.9 (12.62)	< 0.001	-15.3 (-11.2 to -19.4)
				Relative risks (95% CI)
Number of patients without significant shivering at 5 min (%)	29 (72.5)	7 (17.5)	< 0.001	4.1 (2.1 to 8.3)
Number of patients without significant shivering at 10 min (%)	36 (90.0)	9 (22.5)	< 0.001	4.0 (2.2 to 7.2)
Number of patients without significant shivering at 15 min (%)	36 (90.0)	9 (22.5)	< 0.001	4.0 (2.2 to 7.2)

CI = confidence interval; SD = standard deviation. Relative risks are for the DEX group compared with the control group

Table 3 Adverse effects

	DEX $n = 40$	Control $n = 40$	P value
Patient with hypotension (> 20% drop from baseline mean arterial pressure) (%)	1 (2.5)	2 (5)	1.00
Patient with bradycardia (< 50 beats·min^{-1}) (%)	0 (0)	0 (0)	1.00
Patient with sedation (score 3 or 4 Filos *et al*. scale)[15] (%)	0 (0)	0 (0)	1.00
Mean dose of phenylephrine (μg), mean (SD)	737 (763)	754 (907)	
Mean dose of ephedrine (mg), mean (SD)	0 (0)	1 (3.6)	

SD = standard deviation

Discussion

Shivering during Cesarean delivery under neuraxial anesthesia occurs frequently and can be very distressing.[17] Its origin is both thermogenic and non-thermogenic. Internal redistribution of core temperature, loss of thermoregulatory vasoconstriction below the level of blockade, and a decrease of the vasoconstriction threshold are possible explanations for shivering under neuraxial anesthesia.[18] Nevertheless, the association between perioperative hypothermia and shivering in the setting of Cesarean delivery under neuraxial anesthesia is complex and remains poorly understood.[19] Active warming methods, such as forced air blankets, are an intuitive and attractive solution to such a problem; nevertheless, studies regarding their effectiveness in the context of parturients undergoing Cesarean delivery have been conflicting and do not address the complex pathophysiology of shivering.[20,21]

Through its action on the a_{2b}-drenoceptor in the hypothalamus, dexmedetomidine suppresses the spontaneous firing rate of neurons, decreases central thermosensitivity, and reduces vasoconstriction and shivering thresholds.[22] The present study showed that a single intravenous 30 μg bolus of dexmedetomidine effectively reduced the duration of shivering following Cesarean delivery under neuraxial anesthesia, without significant hemodynamic or sedative effects.

The incidence of shivering following neuraxial anesthesia in obstetrical populations has been reported at approximately 53%, according to a review article by Crowley *and al*.[1] The present study was largely consistent with said findings, recording a 52% incidence of shivering among participants. Both spinal and epidural techniques, as well as labouring and non-labouring women, were included in the study with hopes to best represent obstetric populations at large. Since the causative factors of shivering may be different depending on the type of anesthesia and presence of labour, it may be of interest to study the efficacy of dexmedetomidine among different obstetrical subgroups in the future.

The efficacy of dexmedetomidine for the treatment of shivering associated with anesthesia has been shown in a growing body of literature concerning both pediatric and non-obstetric adult populations.[23-25] In a study comparing the use of dexmedetomidine (0.5 μg·kg^{-1} *iv*) with tramadol to treat shivering following spinal anesthesia, Mittal *et al*. reported a mean (SD) time to cessation of shivering of 2.5 (0.44) min and a response rate of 100% at 15 min following the administration of dexmedetomidine.[16] These results are consistent with those observed in the present study. There exists, however, scant research concerning the use of dexmedetomidine in obstetric applications. Recently, dexmedetomidine has been shown to reduce shivering during Cesarean delivery when administered intrathecally,[26,27] yet no study has considered its use intravenously. The present study evaluates the intravenous administration of dexmedetomidine to treat shivering for the first time in the obstetrical context; therefore there is no

data to compare our results with. One hopes that future studies applying this novel approach will further validate its efficacy and safety.

While dexmedetomidine causes hypotension, bradycardia, and sedation, the doses needed to suppress shivering were too small to cause these adverse side effects. Through its action on α-2 adrenergic receptors in the brain and spinal cord, dexmedetomidine inhibits sympathetic tone, reducing patients' shivering threshold.[28,29] This sympatholytic action causes sedation without respiratory depression, but reduces the heart rate and blood pressure.[30] A study by Kundra *et al.* determined that the minimum doses of dexmedetomidine required to treat grade 3 and grade 4 shivering associated with spinal anesthesia were 0.26 $\mu g \cdot kg^{-1}$ and 0.3 $\mu g \cdot kg^{-1}$, respectively. The aforementioned study observed that at such doses, none of the patients developed bradycardia, hypotension, or significant sedation.[31] Furthermore, Abdel-Ghaffar *et al.*[32] studied three intravenous doses of dexmedetomidine for the treatment of shivering following spinal anesthesia (0.5 $\mu g \cdot kg^{-1}$, 0.3 $\mu g \cdot kg^{-1}$, and 0.2 $\mu g \cdot kg^{-1}$) and found that 0.3 $\mu g \cdot kg^{-1}$ was the dose that most effectively treated shivering with the fewest adverse effects. On the basis of those studies, and to be internally consistent the current practice at CHU Sainte-Justine, a fixed dose of 30 μg was selected. By including only participants weighing between 60 and 120 kg, the administration of a final dose of 0.25 to 0.5 $\mu g \cdot kg^{-1}$ was ensured.

In this study, out of 40 patients treated with dexmedetomidine, only one instance of hypotension was observed as opposed to two instances with placebo. Furthermore, the dose of vasopressors given after bolus administration in the dexmedetomidine group was not higher than in the placebo group. No events of bradycardia were observed and this can likely be explained by the fact that dexmedetomidine was administered at a period where the parturient was relatively tachycardic. An increase in heart rate is often seen in the immediate post-partum period because of physiological changes associated with delivery and the administration of carbetocin.[14] In fact, a brief decrease in heart rate was observed shortly after the administration of dexmedetomidine but never reached levels below 50 $beats \cdot min^{-1}$ and thus never required any intervention. Thus, as shown in this study, a 30-μg dose reduced or stopped shivering and occasioned only one instance of hypotension, which was less than in the control group.

No grade 3 or 4 sedation (as per Filos *et al.*)[15] was observed after dexmedetomidine administration among participants. This is probably because only low doses were needed to stop shivering. It is worth mentioning that after childbirth, particularly after prolonged labour, it was not uncommon that patients relaxed and closed their eyes. Nevertheless, these patients were easily arousable with a verbal stimulus.

Some studies have suggested that that dexmedetomidine is not only safe for the parturient but also the newborn. A study focusing on the concentration of dexmedetomidine in the colostrum noted that administration of 0.6 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ *iv* following cord clamping did not produce any significant adverse effects in the mother, and led to negligible amounts of dexmedetomidine in breastmilk.[33]

Limitations

A limitation of our study is the subjective appreciation of shivering and sedation, which is subject to inter-observer variability. Although the majority of the data were recorded by only two members of the study team, and this risk was minimized, it remains a methodological shortcoming of this study. The fact that patients were knowingly observed for shivering may have influenced participants' rates of shivering. Furthermore, the fact that observers specifically recorded episodes of shivering according to a strict definition may have led to the inclusion of cases ignored in practice, as shivering may be treated as a secondary concern perioperatively. It is our contention that the incidence of shivering is higher than commonly believed. Another limitation is that the grading of shivering was stopped 15 min following bolus administration, therefore ignoring any shivering that occurred later. Furthermore, the dose administered (30 μg) is likely inappropriate in patients with extreme weight (< 60 kg or > 120 kg). A more accurate methodology would have to treat each patient with $\mu g \cdot kg^{-1}$ dosing of dexmedetomidine.

Generalizability

This study included patients in active labour with epidural analgesia, and patients not in active labour receiving a planned surgery under spinal anesthesia; therefore, this study covered a broad spectrum of the obstetrical population, so is likely generalizable. The findings of this study highly suggest that the majority of healthy patients presenting with significant shivering following Cesarean delivery under neuraxial anesthesia would benefit from administration of a single bolus of dexmedetomidine for effective treatment of shivering. As patients affected by cardiovascular, renal, or hepatic disease were excluded from the study, such findings cannot be extended to those obstetrical populations; such questions are ripe for the focus of future studies. Lastly, as intravenous dexmedetomidine is not commonly used in parturients, its safety must continue to be evaluated.

Conclusion

A single intravenous bolus of 30 μg of dexmedetomidine significantly decreased the duration of shivering during Cesarean delivery under neuraxial anesthesia. This effect was noticeable up to 15 min after administration of the medication. No significant sedation was observed five minutes after the administration of dexmedetomidine and no significant bradycardia or hypotension were recorded until the transfer to the recovery room. Moreover, there was no difference in the incidence of hypotension or mean doses of intravenous phenylephrine or ephedrine administered between the two groups.

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