Intravenous Dexmedetomidine For The Management Of Shivering Post Sub Arachnoid Blockade For Conduction Of Caesarean Delivery: A Randomised Controlled Trial

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Abstract: Background: About 52% of patients who undergo 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 mitigate shivering associated with anesthesia. In accordance with them we decided to investigate the capability of dexmedetomidine, an alpha 2-adrenergic agonist, in reducing the duration of shivering associated with spinal anesthesia during Cesarean delivery. Material And Methods: Forty parturient going through Cesarean delivery under spinal anesthesia and experiencing shivering were included in this randomized, double-blind, prospective trial. After delivery, the intervention group (n = 20) was administered a single intravenous bolus of dexmedetomidine (20 microgram) while the control group (n =20) was given normal saline. Randomization and allocation were based on a computer-generated list. The primary outcome parameter was the time required for an observable reduction in shivering after the intervention. Result: Eighty patients were recruited, 40 of whom presented with shivering and underwent randomization. Our study recorded that dexmedetomidine alleviated the mean duration of shivering after a single intravenous bolus to 2.2 (2.07) min after dexmedetomidine from 18.9 (12.72) min after saline (95% confidence interval [CI],). The effect of dexmedetomidine was sustained 15 min after the bolus was administered, and shivering had completely stopped in 90% of the patients in the intervention group vs. 22.6% in the control group. No adverse effects were recorded. Conclusion: Our study found that a single intravenous bolus of dexmedetomidine reduced the duration of shivering for up to 15 min during Cesarean delivery under spinal anesthesia when compared against a placebo. [M Tanya Natl J Integr Res Med, 2021; 12(6): 1-8]

Key Words: Dexmedetomidine, Post Subarachnoid Block, Shivering, Caesarean, Parturient

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Introduction: Neuraxial blockade is the technique of choice in Cesarean delivery as it allows mother to remain conscious, awake and thus avoiding risks associated with general anesthesia[1]. Although it is associated with shivering in approximately 55% obstetrical patients[1] which causes physiological stress, interferes with the monitoring of vital signs, and adversely affects patient satisfaction and comfort[1].

Several classes of pharmacological drugs, including opioids, 5-HT3 receptor antagonists, alpha 2 receptor agonists, and possibly N-methyl-D-aspartate receptor antagonists, appear to modulate central thermoregulatory control mechanisms[2]. Most of these agents who are 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]. Now-a-days, meperidine is no longer recommended as a first-line drug for pain management and so an alternative agent is increasingly sought after[4,5] Dexmedetomidine, a highly selective a2 adrenergic agonist, could be an alternative treatment for shivering.

Dexmedetomidine was initially approved by the United States Food and Drug Administration in 1999 for use as a sedative agent in intensive care units. It acts at the level of the locus ceruleus (CNS) to sedate, and at the level of the spinal cord to potentiate analgesia[6]. It acts as a sympatholytic via central and peripheral pathways, reducing both vasoconstriction and shivering thresholds[7]. Dexmedetomidine is currently being widely used off label as an intraoperative adjuvant, and to lessen postoperative complications such as emergence delirium. The rationale behind its use, in contrast

to meperidine, is that it is able to mitigate shivering while avoiding side effects associated with opiates. Indeed, the safety profile of dexmedetomidine has increasingly been advocated in a number of studies conducted in vulnerable populations, including critically ill[8], pediatric[9,10], and obstetrics[11-13]. This study was designed to test whether a single bolus of 20 microgram iv of dexmedetomidine, administered five minutes after childbirth, lessens the duration of shivering during Cesarean delivery under spinal anesthesia or has no such effect. The fixed dose selected was based on a study conducted by Lamontagne et al published in 2019 in Canadian Journal of Anaesthesiology.

Material & Methods: Trial Design: This study was a single centre, randomized, placebo-controlled, double blind, parallel-group study conducted at the hospital attached with Dutta Meghe institute of Medical Sciences, Sawangi, Maharashtra. The use of dexmedetomidine in the context of this study was approved by the institutional ethical committee. 80 parturients were randomly assigned, in a 1:1 ratio, to receive either dexmedetomidine or a normal saline placebo.

Participants: Inclusion criteria were: pregnant females aged 18 years and above who presented to the out-patient department of the hospital for Cesarean delivery. Exclusion criteria were: emergency Cesarean delivery, weight below 60 kg or over 120 kg, known hypersensitivity or allergy to dexmedetomidine, cardiac, kidney or liver disease requiring follow-up or medication, preeclampsia/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 intra-operatively, or any incidence of major surgical complications.

Recruitment took place form September 2020 to November 2020 at hospital attached to Datta Meghe institute of medical sciences. Informed written consent was obtained by a member of the study, immediately after the preoperative anesthesia check up (PAC).

Interventions: Medicine was distributed each day by a research pharmacist in an opaque box containing six ampoule of dexmedetomidine (100 microgram per mL) 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 medicine 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 surgeries were performed. One vial was dispensed per participant. The syringes were identified by a numbered label. Upon arrival to the operating room, patients were attached standard monitoring which involved continuous electrocardiogram, continuous pulse oximetry, and noninvasive blood pressure (measured once per minute).

Patient temperature was measured using an oral thermometer (Hicks Thermometer). A 10 mg iv dose of metoclopramide, 50 mg iv dose of Ranitidine and 4 mg iv dose of ondansetron were administered to prevent nausea and vomiting.

The initial shivering grade and sedation scores were then recorded. Shivering was graded using a 5-point scale as outlined by Crossley and Mahajan[14]:

- Grade 0: no shivering;
- Grade 1: one or more of the following: pilo-erection, 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 4-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 which consisted of 10 mg hyperbaric bupivacaine 0.50%, performed in the sitting position at the L3-L4 inter-space with a midline approach using a 25 G Whitacre needle (B. Braun). After Spinal anesthesia, parturients were placed supine with left uterine displacement. Patients were covered

with one standard cotton drape, but were not actively warmed. A bolus of 15 mL per Kg of room temperature Ringer's Lactate solution was administered as a co-load concomitant with spinal anesthesia.

Sensory anesthesia was assessed via pinprick and noted ten minutes after spinall injection. The decision to administer supplemental fluid was left to the discretion of the anesthesiologist responsible for the case.

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 bring the study box and prepare a 1 mL syringe of either 0.2 mL of 100 microgram per mL (20 microgram) dexmedetomidine or 0.2 mL of normal saline according to the pre-established randomization sequence.

Five minutes following childbirth, if 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 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 5, 10, and 15 min after the bolus injection to assess the evolution of shivering over time. Patients that were not significantly shivering were not included for randomization.

Adverse effects such as hypotension (20% drop from the baseline mean arterial blood pressure) and Bradycardia (less than 50 beats per min) were noted if 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 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, doses of ephedrine and blood loss was noted and patients' oral temperature was measured a second time.

Outcome: The primary endpoint was the time lapsed 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). Secondary analyses evaluated the incidence of adverse effects viz bradycardia, hypotension, and sedation scores as described by Filos et al.[15]

Blinding: Participants, care givers, and statistician were blinded to group assignment. The medication was prepared outside the operating room, before each administration, by an anesthesia assistant as per the randomization list.

Each of the participant, the study members, the anesthesiologist in charge of the case and the statistician were blinded to the content of each numbered syringe.

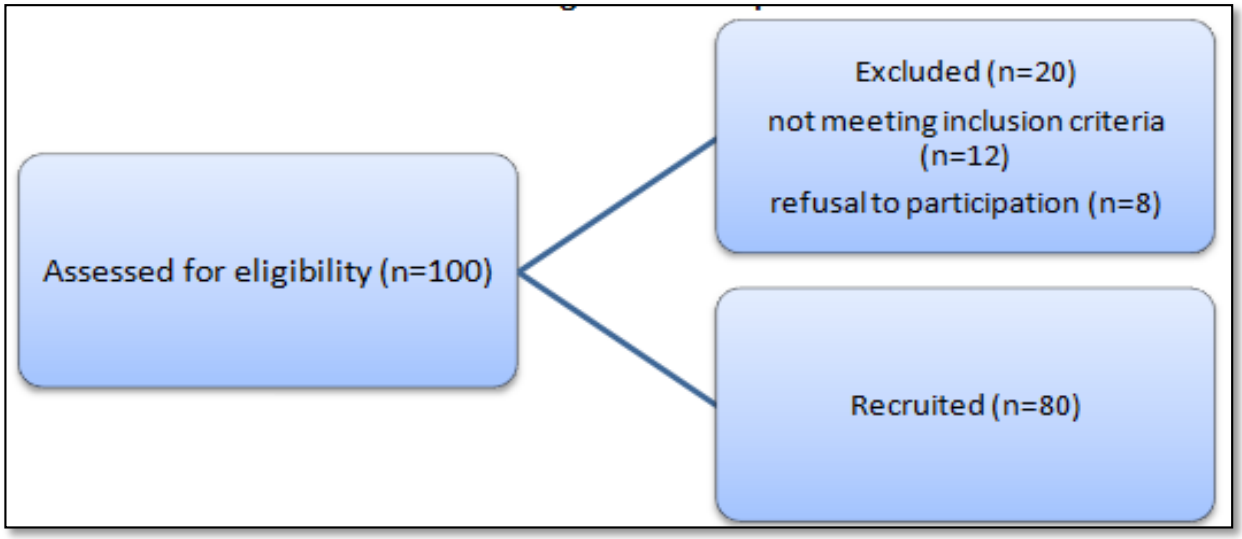
Statistical Methods: A non-parametric test was used to evaluate time to significant decrease in shivering after bolus administration. A chi-square test was used to assess the proportion of patients with decreased shivering after bolus administration in each group. A P-value of less than 0.05 was taken as statistically significant.

Sample Size: Based on a study conducted by Mittal et al., using intravenous dexmedetomidine after spinal anesthesia in a non-obstetrical context, in which the mean time for cessation of shivering was 180 sec with a standard deviation (SD) of 240 sec[16], and using a power of 80%, and a two-sided alpha error of 0.05, 16 participants per group were needed to detect a mean difference of 180 sec between dexmedetomidine and placebo. Considering a dropout of approximately 4%, 20 patients were needed in each group.

Results: Participant Flow: Eighty parturients undergoing a Cesarean section under spinal anesthesia met the inclusion criteria and were recruited, of whom 40 (50%) were shivering and thus randomized into two groups of 20 each.

As it was an intra-operative study, there were no losses to follow up.

Figure 1: Participant Flow



Baseline Data: Both groups were comparable in terms of age, weight, height, gestational age, and stage of labour. The number of patients undergoing an elective procedure was equally distributed in both the groups. Three patients shivered significantly before the initiation of spinal anesthesia in the intervention group vs one patient in the control group. The level of sensory block, skin-to-skin contact or lack of between the mother and the child, the total volume of crystalloid administered, the number of patients who received intravenous colloids and the amounts, the duration of the surgery, and the estimated blood loss per patient were comparable in both groups. The difference in oral temperature at the beginning and at the end of the procedure was also comparable in both groups (Table 1a, 1b).

Analysis: The primary analysis involved all the patients who were randomly assigned.

Outcomes: The difference in the time interval between the administration of the bolus and the reduction of shivering (from a grade 3 or 4 to a grade 0 or 1) was significantly low in the dexmedetomidine group when compared with the placebo group. The mean (SD) time to decrease shivering after a single bolus of 20 microgram iv dexmedetomidine was 2.6 (2.1) min vs 17.9 (12.6) min after a bolus of saline.

The effect of dexmedetomidine sustained for 10 and 15 min after its administration, with shivering completely arrested (grade 0) in 90% of the patients in the intervention group v/s 22.5% in the control group after 15 min (95% CI) (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 normal saline. The mean doses of IV ephedrine administered were similar in both groups. No significant bradycardia (less than 50 beats per min) occurred in any of the participants, although a slowing of heart rate was observed in the dexmedetomidine group. No participants showed significant sedation (grades 3 or 4) at 5 minutes after the administration of the bolus (Table 3).

Table 1a: Features Of The Patients At Baseline

Characteristic	Dexmedetomidine (N=20)	Control (N=20)
Age (Yr), Mean (SD)	30.8 (4.3)	32.1(4.8)
Weight (Kg), Mean (SD)	81.1 (16.8)	75.1 (12.6)
Height (Cm), Mean (SD)	153.1 (5.8)	153.2 (5.5)
Gestational Age (Weeks), Mean (SD)	38.4 (1.6)	38.5 (1.4)
Patients In Active Labour (%)	6 (30)	7 (32.5)
Significant Shivering Before Anesthesia (Crossley And Mahajan14 Grade 3-4) (%)	3	1
Skin-To-Skin Contact (%)	9 (47.5)	11 (58.5)
Anesthesia Sensory Level, Mean (SD)	T4 (3)	T4 (1)

SD= Standard Deviation

Table 1b: Features Of The Patients Post-Randomization

Characteristic	Dexmed (N=20)	Control (N=20)	P-Value
Duration Of Surgery (Min), Mean (SD)	36 (10.5)	41 (12.8)	0.09
Volume Of Crystalloids (Ml), Mean (SD)	1518 (461)	1538 (400)	0.84
Number Of Patients Who Received Colloids (%)	1 (2.5)	3 (7.5)	0.62
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	Dexmed (N=20)	Control (N=20)	P-Value
Time To Decrease Shivering After Bolus Administration (Minutes), Mean (SD)	2.2 (2.07)	18.9 (12.72)	<0.001
Number Of Patients Without Significant Shivering At 5 Min (%)	14 (72.5)	4 (18.5)	<0.001
Number Of Patients Without Significant Shivering At 10 Min (%)	16 (90.0)	5 (22.6)	<0.001
Number Of Patients Without Significant Shivering At 15 Min (%)	17 (90.2)	5 (22.6)	<0.001

SD= Standard Deviation

Table 3: Adverse Effects

	Dexmed (N=20)	Control (N=20)	P-Value
Patient With Hypotension (>20% Drop From Baseline Mean Arterial Pressure) (%)	1 (2.5)	2 (5)	1.00
Patient With Bradycardia (<50 Beats Per Min) (%)	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 Ephedrine (Mg), Mean (SD)	0 (0)	1 (3.2)	

SD= Standard Deviation

Discussion: Shivering during Cesarean delivery under neuraxial anesthesia is seen quite frequently in clinical scenario and can be very problematic[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]. Yet, the association between peri-operative hypothermia and shivering in the setting of Cesarean delivery under neuraxial anesthesia is complex and vaguely understood[19].

Active warming methods are an intuitive and attractive solution to such a problem although studies regarding their effectiveness in the context of parturients undergoing Cesarean section have been contradicting thus not addressing the complicated patho-physiology of shivering[20,21]. Through its action on the alpha 2 b-adrenoceptor in the hypothalamus, dexmedetomidine suppresses the spontaneous discharge rate of neurons, decreases central thermal sensitivity, and reduces vasoconstriction and shivering thresholds[22]. The present study showed that a single intravenous 20 microgram bolus of dexmedetomidine effectively reduced the duration of shivering following Cesarean delivery under spinal anesthesia, without significant hemodynamic or sedative effects.

The incidence of shivering following neuraxial anesthesia in obstetrical populations has been reported to approximately 53%, according to a review article by Crowley and al.[1] The present study was largely consistent with its findings, recording a 52% incidence of shivering among participants. 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 further study the efficacy of dexmedetomidine amongst different obstetrical subgroups in the future.

The efficacy of dexmedetomidine for the management of shivering associated with

anesthesia has been shown in a lot of research literature relevant to both pediatric and non-obstetric adult populations[23-25]. In a study comparing the use of dexmedetomidine (0.5 microgram per kg 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 very much in line with those observed in the present study.

There exists, however, scarce research concerning the use of dexmedetomidine in obstetric population. Recently, dexmedetomidine has been shown to reduce shivering during Cesarean delivery when administered intrathecally[26,27], yet only one study i.e. Lamontagne et al 2019 has considered its use intravenously. The current study evaluates the intravenous administration of dexmedetomidine to treat shivering but there is not much data to compare our results with. Hoping that more and more studies applying this novel approach in future will further validate its efficacy and safety.

While dexmedetomidine causes hypotension, bradycardia, and sedation, the doses required to suppress shivering were too low to cause these adverse side effects. Through its action on a-2 adrenergic receptors in the brain and spinal cord, dexmedetomidine inhibits sympathetic tone thus 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 microgram per kg and 0.3 microgram per kg, respectively.

This 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 microgram per kg, 0.3 microgram per kg, and 0.2 microgram per kg) and found that 0.3 microgram per kg was the dose that most effectively countered shivering with the fewest adverse effects. Making a base of those studies, and to evaluate further the efficacy of a lower dose, a fixed dose of 20 microgram was selected. By including only participants weighing between 60 and 120 kg, the administration of a final dose of 0.25 to 0.5 microgram per kg was ensured. In this study, out of 20 patients treated with dexmedetomidine, only one incidence of hypotension was observed as opposed to two with placebo. Moreover, the dosage of vasopressor given after bolus administration in the dexmedetomidine group was not higher than the placebo group.

No finding of Bradycardia were observed and this can likely be explained by the fact that dexmedetomidine was administered at a period where the parturient was already experiencing a relative tachycardia (increase in heart rate is often seen in the immediate post-partum period because of physiological changes associated with delivery and the administration of oxytocin)[14].

In fact, a transient decrease in heart rate was noted shortly after the administration of dexmedetomidine but never reached levels below 50 beats per min and thus nor required any intervention. Thus, as shown in this study, a 20 microgram dose reduced or stopped shivering with only one case of hypotension. No grade 3 or 4 sedation (as per Filos et al.)[15] was observed after dexmedetomidine administration among participants probably because only low doses were needed to stop shivering. It is worth to mention that after childbirth, particularly after prolonged labour, it was common that patients relaxed and closed their eyes but these patients were easily arousable with a verbal stimulus. So sedation cannot be claimed.

Limitations: A limitation of our study is the subjective appreciation of shivering and sedation, which is bound to have inter-observer variability. Although the majority of the data were recorded by only two members of the study team, thus minimizing this risk, 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 peri-operatively.

It is our proposal that the incidence of shivering is much higher than what is commonly believed.

Another limitation is that the assessment of shivering was stopped 15 min after bolus administration, therefore ignoring any episode occurring later. Furthermore, the dose administered (20 microgram) is likely inappropriate in patients with extreme weight (<60 kg or >120 kg).

Generalization: This study included patients who were not in active labour and received a planned surgery under spinal anesthesia; therefore, this study did not cover a broad spectrum of the obstetrical population, so the findings cannot be applied to other subgroups. The findings of this study highly suggest that the majority of healthy patients presenting with significant shivering following Cesarean delivery under spinal 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 populations remain an area of focus for future studies. Lastly, as intravenous dexmedetomidine is not commonly used in parturients, its safety needs to be evaluated further on a more larger scale.

Conclusion: A single intravenous bolus of 20 microgram of dexmedetomidine significantly decreased the duration of shivering during Cesarean delivery under spinal anesthesia which was noticeable up to 15 min after administration of the medication. No major adverse effects (Bradycardia, hypotension, sedation) were recorded until the transfer to the recovery room.

More so, there was no difference in the incidence of hypotension or mean dose of intravenous ephedrine required to manage that between the two groups.

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