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RESEARCH ARTICLE

Efficacy of low dose intravenous dexmedetomidine versus clonidine in treatment of shivering during caesarean section under spinal anaesthesia: a double blind randomized controlled trial

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ABSTRACT

Objectives: Dexmedetomidine and clonidine have been used to prevent and treat shivering after spinal anaesthesia. A double blind randomized controlled trial was conducted to compare the efficacy and safety of low dose intravenous dexmedetomidine and clonidine in controlling post-spinal anaesthesia shivering during caesarean section. **Methods:** 260 pregnant women of American Society of Anesthesiologists physical status I and II, aged between 18 - 40 years posted for caesarean section who developed grade 3 or 4 shivering after spinal anaesthesia were randomly divided into two groups, Group D (n = 130) received intravenous dexmedetomidine 0.5 µg/kg and Group C (n = 130) received clonidine 0.5 µg/kg. Time required to control shivering, response rate, recurrence rate, and adverse effects were observed. **Results:** The time taken to cease the shivering was short (2.20 ± 0.35 min) with no recurrence in dexmedetomidine in comparison with clonidine group (5.51 ± 0.48 min). There was 27.69% recurrence with clonidine. Response rate was 100% in dexmedetomidine against 82.3% of clonidine group. The sedation level was adequate with dexmedetomidine without respiratory depression. The haemodynamic parameters and other side effects were comparable and no adverse neonatal outcome was observed in both the groups. **Conclusion:** Intravenous dexmedetomidine 0.5 µg/kg has early onset of effect, higher response rate without recurrence with added advantage of good sedation and stable cardiorespiratory function and neonatal outcome than clonidine 0.5 µg/kg in controlling post-spinal anaesthesia shivering during caesarean section.

Keywords: Shivering, spinal anaesthesia, caesarean section, α2 agonist, dexmedetomidine, clonidine.

Shivering is an involuntary, rhythmic skeletal muscular movement of varying frequency in response to reduction of body temperature which is a natural protective mechanism of our body in an attempt to increase metabolic heat generation in order to restore homeostasis [1]. The causes of shivering in patients undergoing surgery lie mainly on intraoperative heat loss, pain, increased sympathetic tone, and systemic release of pyrogens [1]. Human core temperatures are generally maintained within a narrow range of 36.5 - 37.5 degrees celsius, which is known as the inter-threshold range or thermo neutral zone. When core temperature falls below the usual range, thermoregulatory reactions such as vasoconstriction and shivering are triggered [2]. The neurological mechanism of shivering is mediated by the spinal α - motor neurons and their axons with their center in preoptic nucleus of anterior hypothalamus [3].

Shivering is one of the most common complications occurring after spinal anaesthesia. In a review of 21 research studies, the average incidence of shivering associated to regional anaesthesia was found to be 55% [4]. In a recent

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cross-sectional study they found that the overall incidence of shivering during cesarean section under spinal anesthesia was 51.8% [5]. Spinal anaesthesia is a well accepted anaesthesia technique considered for cesarean section, as it has many advantages over general anaesthesia like rapid onset, high success rate, less adverse maternal and neonatal outcome with optimal surgical condition [6]. Spinal anesthesia impairs the thermoregulation mechanism by inhibiting the tonic vasoconstriction which plays significant role in temperature regulation [8]. Due to vasodilatations spinal anesthesia also causes redistribution of core body heat from the trunk to the peripheral tissues. These two effects predispose patients to hypothermia and shivering [9, 10]. In a parturient hormonal factors, anxiety, sleep deprivation are likely to influence thermoregulatory responses [11, 12]. Cold intravenous fluid infusion, cold operating room environment are other factors which predispose to shivering during surgery under spinal anaesthesia.

Shivering potentially increases oxygen consumption up to 300-400%. It also increases lactic acid and carbon dioxide production and patient discomfort [13, 14]. These effects may cause adverse neonatal outcome while inside the parturient womb. It also interferes with blood pressure, electrocardiogram, and oxygen saturation monitoring. It also increases the morbidity or mortality of patients with cardiovascular disease as it raises cardiac output and metabolic heat production up to 600% [15]. Shivering during caesarean section under spinal anaesthesia has been prevented or treated by various pharmacological and non-pharmacological ways with varying degrees of success. Intrathecal opioids like fentanyl, sufentanil, pethidine and intravenous tramadol, magnesium sulphate, ketamine etc. have been tried [6,16,17]. Intravenous dexmedetomidine compared with placebo[18,19] and clonidine compared with placebo or other drugs [20,21] also have been tried with good success rates. Non-pharmacological options include warm fluid therapy, radiant warm heater and covering with blanket [22,23]. Dexmedetomidine and clonidine both α_2 agonists having good anti-shivering property are never compared between two for post spinal anaesthesia shivering in caesarean section operation. Hence the study was conducted to compare efficacy and side effects between low doses of intravenous dexmedetomidine and clonidine in treatment of shivering during caesarean section under spinal anaesthesia.

Methods

This hospital based prospective double blind randomized controlled trial was conducted in the department of anaesthesia in caesarean section (CS) operation theatre (OT) of Tezpur Medical College and Hospital, a tertiary care teaching hospital situated in North-East India, from August 2021 to January 2022 after obtaining ethical clearance from the institutional ethics committee.

A total of 260 pregnant women of American Society of Anesthesiologists (ASA) physical status I and II, [24] aged between 18 - 35 years undergoing elective or emergency CS who developed grade 3 or 4 shivering after spinal anaesthesia (SA) were enrolled. Pregnant ladies who refused to participate or having cardiovascular, renal, respiratory, hepatic, neurological, thyroid, psychiatric disorders, pre-eclampsia, eclampsia, gestational diabetes, drugs or alcohol abuse and on vasodilator treatments were excluded. Patients with body temperature <36º C and >38º C, known hypersensitivity to dexmedetomidine and clonidine were also excluded from the trial.

The eligible pregnant women were briefed about the nature of the study and written informed consents were obtained. Clinical details of the patients and relevant documents were retrieved. An independent anesthetist made the random allocation cards for 260 selected patients using computer-generated random numbers and divided them into two equal groups of 130 each. The groups were named as Group-D (Dexmedetomidine group) and Group-C (Clonidine group). He kept the original random allocation sequences in an inaccessible third place and worked with a copy. Since the executers could get confused with the original coding of D and C later, the allocator recorded exactly what these codes meant to avoid further confusion. Another independent anesthetist had put these cards in sequentially numbered, opaque envelops according to the randomization order of the patients and sealed and stapled them (SNOSE method) [25] to conceal the allocation sequence from the researcher enrolling and assessing participants. The envelopes were opened sequentially just before the injection by an independent nurse, who, maintaining all aseptic and antiseptic measures, prepared the injection as mentioned in the card inside for that particular patient and would hand over the syringe containing the injectate to the investigator performing the procedure. This method blinded the participant and the investigator performing the intervention and prevented selection bias. Input date, time, patient ID, results after the procedure, etc. were recorded by the investigator on the envelope or another sheet inside the envelope. The envelopes were sealed and preserved in a secured place for analysis by principal investigator and for future references.

Before administering spinal anaesthesia, standard monitoring of pulse rate, oxygen saturation (SPO2), non-

invasive blood pressure (BP) and electrocardiogram (ECG) were recorded continuously and axillary body temperature was recorded before starting the surgery. Oxygen supplementation was done to all the patients @4 litres/min through face mask and the patients were covered in single drape without active warming. The ambient temperature was maintained at 24 - 26º C. Neither premedication nor pre-loading was done to avoid their influence on the shivering mechanism.

Under all aseptic and antiseptic precautions spinal anaesthesia was given at L_3-L_4/L_4-L_5 intervertebral space with 25 G Quincke type spinal needle with 2.3 ml of 0.5% bupivacaine heavy with 0.2 ml of buprenorphine. Block up to T_4-T_6 dermatome was targeted. The parturient who developed grade 3 or 4 shivering after spinal anaesthesia were included in the study. Grading of shivering was done as per shivering score (Sing et al) [26-28]. Grade 0: no shivering. Grade 1: one or more of piloerection, peripheral vasoconstriction, peripheral cyanosis with, 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. Once the shivering was observed Group D patients received Dexmedetomidine 0.5 mcg/kg and Group C patients received Clonidine 0.5 mcg/kg slow intravenous bolus injection.

Both primary and secondary outcome measurements were measured after spinal anaesthesia by attending anaesthetist who was not involved in the study. Time of onset of shivering, severity of the shivering (shivering grade), time of disappearance of shivering (in min) and response rate (shivering ceased after treatment in 15 minutes) were recorded. Durations of surgery were noted. If shivering did not subside by 15 minutes, the treatment was considered to be not effective. Recurrence of shivering was also noticed until the patient left the operation theatre. Patients who did not respond or in whom recurrence of shivering occurred were treated with additional dose of dexmedetomidine (0.5 mcg/kg IV) or clonidine (0.5 mcg/kg IV) in the respective groups.

Secondary outcome measurements, like blood pressure (BP) and heart rate (HR) were monitored just before administration of intrathecal anaesthetic, at 3 minutes interval for first 20 minutes and then at 5 minutes interval until the operations were completed and the patients were shifted to the recovery room. A lowering of systolic BP ≥ 20% from baseline or recording of <100 mm Hg at any point after spinal anaesthesia, was regarded as hypotension and treated with titrated dose of intravenous mephentermine. HR <50 bpm (beat per minute) was regarded as bradycardia and was treated with appropriate dose of intravenous atropine (if simultaneous systolic BP was <100 mm Hg or decreases by ≥ 20% from baseline). Nausea, vomiting, dry mouth and headache were recorded and treated accordingly. Sedation was assessed by a four point sedation scale (Filos et al) [29]. 1 = awake and alert. 2 = awake but drowsy, responding to verbal stimulus. 3 = drowsy but rousable, responding to physical stimulus. 4 = unrousable, not responding to physical stimulus. Neonatal outcome was assessed by Apgar score at 1st and 5th mins after delivery [30].

Statistical methods -

Sample size determination was done based on the previous studies. They found an average incidence of shivering of the order of 51.8% in CS after SA [5]. We anticipated an incidence of 50% of shivering. As per records, on average 3000 caesarean sections per year are done in this hospital which comes 1500 in every six months. Considering that post spinal anaesthesia shivering occurs in 50% of the cases, 750 patients become the total population of our study. A total 254 patients were required to have a confidence level of 95%, type I error (α) of 0.05 and 80% of power of our study (Krejcie Morgan table) [31]. Hence, considering some probable dropouts, we selected 260 patients in total dividing into two groups of 130 each. The results are shown as mean (±SD), exact numbers or proportions are expressed as a percentage. Statistical comparison of patient demographic profiles and time to stop shivering between groups were performed using the Z-test. Nominal or categorical data, including overall frequency and grade of shivering, response rate, recurrence, and adverse effects between groups, were analyzed and compared using the chi-square test at 5% level of significance ($p < 0.05$).

Results

The demographic characteristic of the patients in both groups was comparable with regards to age, body weight, baseline temperature and ASA physical status (table 1). The duration of caesarean section operation was comparable in both the groups. It was 31±4.62 min and 32.53±4.25 min (mean ± SD) for dexmedetomidine and clonidine groups respectively which is statistically not significant. In dexmedetomidine group 105 patients had grade III and 25 patients had grade IV shivering. In clonidine group 100 patients had grade III and 30 patients had grade IV shivering which were also comparable in both the groups (table 2).

Table 1: Patient characteristics and duration of surgery

Variables	Group D (n=130)	Group C (n=130)	P - value
Age (in years)	24.22 ± 3.51	25.25 ± 3.41	>0.05
Body weight (kg)	59.61 ± 4.41	58.71 ± 4.60	>0.05
Baseline temperature (ºC)	37.06 ± 0.21	37.03 ± 0.18	>0.05
ASA (I/II)	105/25	108/22	>0.05
Duration of surgery (min)	31 ± 4.62	32.53 ± 4.25	>0.05

Table 2: Grades of shivering and response to treatment

Parameters	Group D (n=130)	Group C (n=130)	P - value
Shivering grade (III/IV)	105/25	100/30	> 0.05
Time taken to cease shivering (min)* (mean ± SD)	2.20 ± 0.35	5.51 ± 0.48	< 0.05
Response rate# (%)	130 (100)	107 (82.30)	< 0.05
Recurrence rate† (%)	0	36 (27.69)	< 0.05

*Time from drug injection to complete cessation of shivering. #Cessation of shivering within 15 min. †Recurrence before completion of surgery. SD = Standard deviation.

Table 3: Adverse effects

Parameters		Group D (n=130)	Group C (n=130)	P – value
Bradycardia		5 (4%)	8 (6%)	>0.05
Hypotension		5 (4%)	8 (6%)	>0.05
Nausea		13 (10%)	17 (13%)	>0.05
Vomiting		8 (6%)	13 (10%)	>0.05
Respiratory depression		0	0	-
Apgar score	1st min	8.10 ± 0.76	8.00 ± 0.68	>0.05
	5th min	9.21 ± 0.78	9.11 ± 0.89	

Time taken to cease shivering was significantly lower in Group D (2.20 ± 0.35 min) when compared to Group C (5.51 ± 0.48 min) which is statistically significant (p <0.05). All 130 patients got relieved from agonizing feel of shivering in Group D. Whereas in Group C only 107 patients got relieved of shivering. Hence the response rate (cessation of shivering within 15 min) in Group D was significantly excellent statistically (100% vs. 82.3%) when compared to Group C (p<0.05) (Table 2). There was no recurrence of shivering in Group D, whereas in Group C, 36 patients (27.69%) had recurrence of shivering during surgical period which is highly significant (p<0.05). Incidence of bradycardia (heart rate falling below 50 bpm) and hypotension (systolic BP <100 mmHg or a decrease of >20% of the pre-anesthetic baseline) were similar in both the groups and statistically non-significant. The frequency of nausea and vomiting were also similar in both groups (table 3). There was no incidence of respiratory depression in both the groups. Apgar scoring was done at 1st and 5th min post-delivery for babies in parturients who developed shivering before delivery of babies and required administration of study drug either dexmedetomidine or clonidine. The Apgar score was high in both the groups and was comparable and statistically not significant (table 3).

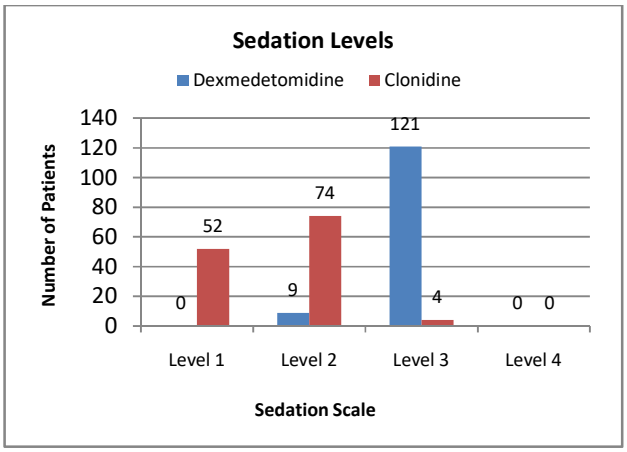

Figure 1: Bar diagram for sedation levels

The sedation level was higher in Group D when compared to Group C (figure 1). 9 patients were drowsy but responding to verbal stimulus (level 2) and 121 patients were drowsy but rousable to physical stimulus in Group D (level 3). Whereas, in Group C, 52 patients were awake and alert (level 1), 74 patients were drowsy but responding to verbal stimulus (level 2) and only 4 patients were at sedation level 3. Sedation was better in Group D which was statistically highly significant (p <0.05). Neither of the groups had any patients with profound sedation or sedation level >3 or having respiratory depression.

Discussion

The neurotransmitter pathways involved in the initiation of shivering includes opioids, α2 adrenergic agonists, anticholinergic and serotenergic receptors [1]. Hence, the drugs acting on these pathways (fentanyl, meperidine, tramadol, ondansetron, dexmedetomidine, clonidine etc.) have been used in the treatment of shivering [6, 16-21]. However, their side effects such a hypotension, hypertension, sedation, nausea, vomiting, and respiratory depression limit their use in the treatment of shivering. Patient warming with warm blanket and warm fluids have been tried with varying success [22,23].

Studies have demonstrated that α2 agonists can effectively reduce the shivering by binding to α2 receptors that mediates vasoconstriction and exert antishivering effects [32]. The drugs dexmedetomidine and clonidine are the α2 agonists that have sedative, analgesic, and antishivering properties [20,21,32,33]. They act by acting on presynaptic α2 receptors thereby inhibiting noradrenaline release and

enhancing the activity of descending inhibitory gamma aminobutyric acid (GABA) neurons in the ventrolateral pre-optic nucleus of hypothalamus [33]. Clonidine is an α2 agonist with α1: α2 affinity of 1: 220. It is basically used as antihypertensive. It is also used as an adjunct to general anaesthesia, neuraxial anaesthesia and nerve blocks. Dexmedetomidine is a highly potent α2 agonist with α1 : α2 affinity of 1 : 1620. It is originally used for intensive care unit (ICU) sedation. Procedural sedation, adjunct to general anaesthesia and neuraxial blocks and antishivering are other uses of the dexmedetomidine [18,19,32,34].

Our study was designed to compare a small dose of 0.5 μg/kg dexmedetomidine with 0.5 μg/kg of clonidine for control of shivering during caesarean section under spinal anaesthesia. In caesarean deliveries the anti-shivering effects of these two drugs has not been compared. So, we conducted this trial to compare the efficacy of these α2 agonists in controlling shivering, their side effects and maternal and neonatal outcomes during caesarean section under spinal anaesthesia. Low doses were chosen because studies have shown that incidence of cardiac arrest increases with the indiscriminate use of dexmedetomidine [35] and adverse foetal outcome was seen with higher doses of clonidine [36].

The results of our study showed that the time taken to cease the shivering was short (2.20 ± 0.35 min) with no recurrence in dexmedetomidine group in comparison with clonidine group (5.51 ± 0.48 min). There was 27.69% recurrence with clonidine. Response rate or cessation of shivering within 15 min was 100% in dexmedetomidine against 82.3% of clonidine group. The sedation level was better with dexmedetomidine without respiratory depression. This is due to the properties of α2 agonists with sedation without respiratory depression. The hemodynamic parameters were stable and manageable in both the groups which were beneficial for patients and the anesthetist. No effect on neonatal outcome was observed in both the groups as assessed by Apgar score at 1st and 5th min post delivery.

Reddy et al [21] compared IV clonidine (1 μg/kg) and IV tramadol (1 mg/kg) in controlling the shivering in patients undergoing cesarean section. They concluded that clonidine had a lower response rate and a longer time to control shivering. The response rate of clonidine in their study was 86.6% compared to our study, which was 82.3%. The time required to stop shivering with clonidine was 3.17 ± 0.03 mins, compared to 5.51 ± 0.48 mins in our study. The lower response rate and longer time required to control shivering in clonidine group may be due to lower dose (0.5 μg/kg) taken in our study. Usta et al [37] also found that IV infusion of injection dexmedetomidine 1 μg/kg reduced the shivering during perioperative period. Mittal et al [38] compared injection dexmedetomidine 0.5 μg/kg with injection tramadol 0.5 mg/kg. They found that injection dexmedetomidine controlled the shivering with lesser time (2.52 ± 0.44 compared to 2.20 ± 0.35 mins in our study) and with lesser side effects. The response rate of injection dexmedetomidine was 100% which is comparable to our study. Panneer et al [39] compared 0.5 μg/kg IV dexmedetomidine versus 1 μg/kg IV clonidine for the treatment of shivering following spinal blockade in patients undergoing lower limb orthopedic surgeries. They found that time taken to control shivering was 2.23 ± 0.43 mins and 5.54 ± 0.58 mins in dexmedetomidine and clonidine groups respectively. In our study we found 2.20 ± 0.35 mins in dexmedetomidine and 5.51 ± 0.48 mins in clonidine group which corroborates with their findings. The response rate, level of sedation and side effects of both the groups were similar in our study. Wang et al [40] in their meta-analysis on six randomized controlled trials on IV dexmedetomidine versus IV clonidine for post-spinal anesthesia shivering found that dexmedetomidine had higher effective rate of shivering treatment, shorter time to cease shivering, lower recurrence rate of shivering and higher incidence of sedation compared to clonidine which is corroborated with our finding.

The results of our study provide added strength and evidence to the studies which showed low dose IV dexmedetomidine significantly reduce the time it took to cease shivering without recurrence. The full response rate of dexmedetomidine with good sedation without adverse maternal and neonatal outcome is a better choice for the control of post-spinal anaesthesia shivering in patients undergoing caesarean section. Research studies on various doses of dexmedetomidine and its comparisons with established drugs such as meperidine should be performed in the future for postspinal anesthesia shivering in cesarean section. In addition, newer drugs such as granisetron and palonosetron need to be evaluated for their anti-tremor effects in order to solve this perioperative problem.

The limitations of our study include (1) short surgical period, (2) study on analgesia and its effects on shivering was not done, (3) postoperative follow up was not undertaken for monitoring of shivering.

Conclusion

Both low doses of intravenous dexmedetomidine and clonidine are effective in controlling post-spinal anaesthesia shivering during caesarean section. But dexmedetomidine

has got faster onset of action, excellent response rate, no recurrence with good sedation without respiratory depression and adverse maternal and neonatal outcome in comparison to clonidine. We recommend that low dose of intravenous dexmedetomidine may safely be used for control of shivering during caesarean section under spinal anaesthesia.

Conflict of interest: None. **Disclaimer:** Nil.

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