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ORIGINAL RESEARCH **OBSTETRIC ANESTHESIA**

Efficacy and safety of dexmedetomidine to prevent shivering in cesarean delivery under spinal anesthesia: a double-blind, randomized controlled trial

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ABSTRACT

Background & objective: Postoperative shivering is a source of much discomfort to the patients following spinal anesthesia (SA), especially in patients undergoing cesarean delivery. The anesthetists have employed various medications and a variety of measures to prevent shivering in their patients. The objective of this study was to investigate the efficacy and safety of intravenous (IV) dexmedetomidine in preventing shivering in patients undergoing cesarean delivery under SA.

Methodology: This prospective, double-blind, randomized trial involved 62 parturients undergoing cesarean delivery under SA. They were randomly divided into two groups; patients in dexmedetomidine group (Group D, n = 31) received dexmedetomidine 0.5 µg/kg IV over 10 min followed by infusion of 0.4 µg/kg/h until the end of surgery; whilst patients in the control group (Group C, n = 31) received equivalent loading and infusion volume of 0.9% saline. Both groups were operated upon by a standardized spinal anesthesia technique. The occurrence of shivering, sedation score and hemodynamic parameters were recorded intraoperatively. The recording anesthetist was blinded regarding the study or the control groups.

Results: The occurrence of shivering was significantly reduced in Group D as compared to Group C (3.2% vs 64.5%, $P < 0.001$). Patients in Group D were more sedated as compared to Group C (51.6% vs 0%, $P < 0.001$). There was no statistically significant difference in systolic and diastolic blood pressure readings between both of the groups. Heart rates in Group D were significantly lower than the Group C but still were within normal physiological range.

Conclusion: IV dexmedetomidine was effective in reducing the occurrence of shivering but with significant sedative effect and lowering of heart rate than the placebo. Although the heart rates remained within normal range in both groups.

Key words: Anesthesia, Spinal; Cesarean; Dexmedetomidine; Shivering

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1. INTRODUCTION

Shivering is a common complication following anesthesia, described as repetitive, non-voluntary movement. The incidence of shivering following general or regional anesthesia has been reported as high as 70%.[1] It has also been regarded as one of the most discomforting experience to patients undergoing anesthesia, alongside pain and post-operative nausea/vomiting (PONV).[2] Shivering often comes with increased oxygen consumption and carbon dioxide production, pain aggravation and interference with intra-operative standard monitoring.[2,3]

Various pharmacological interventions have been studied for the use in prevention of perioperative shivering. Dexmedetomidine is among the most popular drugs being studied recently due to its better side effects profile compared to other drugs such as tramadol and pethidine.[4-8]

Cesarean delivery is commonly undertaken under spinal anesthesia (SA) and the presence of shivering intraoperatively would be highly uncomfortable for an awake patient. It is ideal if shivering can be prevented in the first place. There has been lack of trials on the use of intravenous (IV) dexmedetomidine in cesarean delivery, especially for shivering prophylaxis.

We investigated the efficacy of IV dexmedetomidine in prevention of shivering and its safety in terms of sedation and hemodynamic response in patients undergoing cesarean delivery under SA.

2. METHODOLOGY

Ethical approval was obtained from Human Research Ethics Committee USM (HREC) with protocol code USM/JePEM/ 17060303 and written consent was taken prior to commencement of this study.

This prospective, double-blind, placebo-controlled, randomized study, took place in Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan.

Eligible participants were all parturients aged 18 to 45 y old, undergoing elective Lower Segment Cesarean Section (LSCS) under SA with ASA classification of II and stable hemodynamics. Exclusion criteria were height less than 1.5 m, morbid obesity with BMI > 40 kg/m^2, known allergy to dexmedetomidine or pethidine, use of epidural catheter, presence of significant cardiac, liver or renal problem, pre-existing hypo- or hyperthermia (< 36°C or >38°C) before operation and presence of shivering prior to fetal delivery. Withdrawal criteria for this study were conversion to general anesthesia intraoperatively, blood loss of more than 1 L, administration of blood products and duration of surgery of more than 2 h.

Patients were randomized according to block randomization technique. For every block of 10 patients, 5 would be allocated to each arm. The order of interventions within each block varied randomly, as determined by computer random number generator. This technique was chosen to ensure similar numbers of patients in each group at any point during trial. The allocation sequence was enclosed in opaque envelopes and revealed once patient was already inside the operating room.

In this study, blinding was applied to the patients and the attending anesthesiologist who was responsible for administration of the study drug as well as assessing the outcome of the study.

Study drugs were prepared in an equivalent 20 ml syringe which contained similar colorless solution for either group. The preparation was done by the principal investigator who was not blinded.

In the operating room, patient was attached to standard monitoring and initial parameters were taken, including non-invasive blood pressure (NIBP), oxygen saturation (SpO_2), respiratory rate (RR) and heart rate (HR). All patients were preloaded with 10 ml/kg of crystalloid fluids before the administration of SA.

SA was administered using the standard dose of heavy 0.5% bupivacaine 2.0 ml and fentanyl 15 µg with total volume of 2.3 ml, at the level of L3/L4 or L2/L3 under aseptic technique. Patient was asked to lie supine following SA administration with slight left lateral tilt. Supplementary oxygen was given via face mask with oxygen flow rate of 5L/min.

Surgery was started after level of spinal blockade was adequate for the surgery. Level of blockade was assessed by using Bromage score and testing for light touch using cotton wool. Intraoperatively, patients' vital signs were regularly monitored every 5 min. After delivery of baby, IV pitocin 5 units slow bolus was given followed by 40 units infused over next 8 h.

The study drug infusion was then started after 5 min of the delivery of baby. Group D (dexmedetomidine group) received loading dose of dexmedetomidine 0.5 µg/kg IV over 10 min, and subsequently followed by dexmedetomidine infusion at the rate of 0.4 µg/kg/h. Dexmedetomidine solution was diluted at 4 µg/ml. Group C (control group) received normal saline loading volume and infusion rate to the intervention group based on the patient's weight. In both of the groups, infusions were continued until the operation completed.

All fluids given were preheated to 37°C in a fluid warmer. Operating room temperature was maintained at 20-24°C. Patient warming methods were standardized and restricted to the use of air warming blanket.

The temperature of the patient was recorded preoperatively and intraoperatively every 30 min by using an infra-red tympanic membrane thermometer.

Presence of shivering was observed from the time after the study drug was given until patient was discharged. Similar observations were made with regards to sedation score and hemodynamic parameters.

Patients who developed grade 4 shivering for more than 10 min after the infusion of study drugs were administered pethidine 0.2-0.4 mg/kg IV as rescue therapy.

The event of bradycardia and hypotension requiring treatment were documented. Bradycardia was treated with atropine 0.6 mg IV and hypotension was treated with ephedrine 6 mg IV, with additional repeated doses if necessary.

Box 1: Grades of shivering[8]

Grade	Description
0	No shivering
1	Piloerection or peripheral vasoconstriction but no visible shivering
2	Muscular activity in only one muscle group
3	Muscular activity in more than one muscle group, but not generalized shivering
4	Shivering involving the whole body

Shivering was graded based on its severity (Box 1), using grading system validated in an earlier study.[8] Shivering was considered absent for grade 0 or 1, and considered present if the grade was 2, 3 or 4.

Box 2: Modified Wilson Sedation Scale

Grade	Sedation state
1	Oriented; eyes may be closed but can respond to “Can you tell ne your name?” “Can you tell me you are fine now?”
2	Drowsy; eyes may be closed, rousable only to command: “(name), please open your eyes”.
3	Rousable to mild physical stimulation (earlobe tug)
4	Unarousable to mild physical stimulation

Sedation status was based on Modified Wilson sedation scale which ranges from 1 to 4 (Figure 2). This was assessed by the attending anesthesiologist or the medical officer in-charge. The assessment was performed every 10 min from the administration time of study drug for total of 1 hour. The modified Wilson sedation scale provides a simple and reliable method of monitoring for sedation during regional anesthesia, with inter-rater agreement of 84%.[9] Sedation was considered present if the score is 2 or more.

Hemodynamic parameters were recorded every 10 min from the administration time of the study drug until the end of the infusion. Measurements were performed by using standard monitoring device in operating room. Bradycardia was defined as HR of less than 50 beats per min. Hypotension was defined as MAP reduction > 20% from the baseline value.

For statistical analysis, hemodynamic parameters were analyzed at three different times; at the start of infusion (T0), after loading dose which was 10 min after starting infusion (T1) and at the end of infusion (T2).

Statistical analysis

Sample size was calculated based on the aim to detect a reduction of heart rate by 5 bpm, systolic BP by 10 mmHg and diastolic BP by 5 mmHg. Based on standard deviation in a previous study by Venkatraman et al.[12], with a two-sided 5% significance level and a power of 80%, a sample size of 16, 12 and 26 patients per group were necessary for each change. Given an anticipated dropout rate of 10%, we concluded that 31 patients per group was needed for this study.

The incidence of shivering and sedation were analyzed using Pearson Chi-square test. The hemodynamic response was analyzed using Repeated Measure Analysis of Variance (RM ANOVA). $P < 0.005$ was considered statistically significant.

3. RESULTS

A total of 62 participants were recruited in this study; 31 were randomized into Group C and another 31 into Group D. There were no significant differences in baseline characteristics of patients between these two groups, as shown in Table 1.

There was a statistically significant association between groups and shivering status. The percentage of shivering was significantly lower in Group D than Group C (3.2% vs 96.8%, $P < 0.001$). There was a statistically significant association between the group and sedation. The sedation in Group D was significantly higher than Group C (51.6% vs 0%, $P < 0.001$).

There was a statistically significant interaction between the two groups and time on systolic blood pressure ($P = 0.011$). Further analysis showed no significant

differences between the groups at each measurement time of T0, T1 and T2 (Table 3). Subsequent analysis on the effect of time showed \no significant difference of systolic blood pressure in Group D or in Group C (no significant difference after Bonferroni correction by adjustment of alpha value to 0.01667) (Table 4).

Table 1: Comparison of patient characteristics between groups

Parameter		Group D (n = 31)	Group C (n = 31)	P value
Age (y)		30.6 ± 6.9	30.1 ± 5.5	0.792
Weight (kg)		69.9 ± 11.2	73.2 ± 11.6	0.261
Height (cm)		155.8 ± 4.6	157.3 ± 5.2	0.203
BMI		28.8 ± 4.3	29.6 ± 4.7	0.475
Gravida		3.0 ± 2.2	2.9 ± 1.9	0.852
Para		1.7 ± 1.9	1.7 ± 1.6	0.774
Baseline temperature (°C)		36.76 ± 0.37	36.91 ± 0.25	0.070
Duration of operation (min)		49.1 ± 12.6	48.1 ± 16.0	0.799
Duration of drug infusion (min)		34.0 ± 10.1	33.0 ± 12.0	0.707
Baseline SBP (mmHg)		115.6 ± 13.8	111.1 ± 13.3	0.198
Baseline DBP (mmHg)		61.5 ± 8.7	60.2 ± 9.2	0.572
Baseline HR (/min)		90.1 ± 14.0	89.2 ± 13.0	0.794
ASA, n (%)	• I • II • III	12 (38.7) 17 (54.8) 2 (6.6)	16 (51.6) 14 (45.2) 1 (3.2)	0.550**

*Mean ± SD (P value based on independent-samples t-test); **Pearson chi square*

Table 2: Comparison of mean systolic blood pressure between two groups

Time	Group D	Group C	P value [a]
Adjusted mean (95% CI)			
T0	115.06 (110.41-119.72)	111.06 (106.40-115.72)	0.011[a]
T1	110.90 (105.89-115.92)	111.35 (106.34-116.37)	
T2	108.74 (104.09-113.39)	114.39 (109.74-119.04)	
Mean score ± SD			
T0	115.06 ± 12.63	111.06 ± 13.30	0.229 [b]
T1	110.90 ± 11.82	111.35 ± 15.82	0.899 [b]
T2	108.74 ± 12.38	114.39 ± 13.47	0.091 [b]

a Repeated Measure ANOVA; b Independent-samples t-test

There was no statistically significant interaction between the two groups and time on diastolic blood pressure (P = 0.840) as displayed in (Table 5).

For HR analysis, there were a statistically significant interaction between the two groups and time on HR (P < 0.001). Further analysis showed significant differences between the two groups at T1 (P = 0.005) and T2 (P = 0.002) (Table 6). Subsequent analysis on the effect of time showed significantly lower HR in Group D at T1 (P < 0.001) and T2 (P < 0.001) as compared to T0 (significant difference after Bonferroni correction by adjustment of alpha value to 0.01667) (Table 7).

Episodes of hypotension during study period was treated with vasopressor (ephedrine 6 mg IV). There was no significant difference between the groups regarding the use of vasopressor; e.g., 4 (12.9%) vs. 8 (25.8%) in Group D and C respectively (P = 0.199). There were no episodes of bradycardia in both groups throughout our study which would require the use of atropine as rescue therapy.

Table 3: The mean systolic blood pressure differences of time within each group

Comparisons	Group D		Group C	
	Mean score difference (95% CI)	P value[a]	Mean score difference (95% CI)	P value[a]
T0 – T1	4.16 (0.11-8.21)	0.044	–0.29 (–4.94-4.36)	0.899
T0 – T2	6.32 (0.89-11.75)	0.024[b]	–3.32 (–7.76-1.12)	0.137
T1 – T2	2.16 (–1.46-5.78)	0.054	–3.03 (–7.83-1.76)	0.206

[a] *Multiple paired t test;* [b] *No significant difference after Bonferroni correction*

4. DISCUSSION

In this study, we observed a significant reduction in the occurrence of shivering in Group D compared to Group C. Patients in Group D were significantly associated with more sedation than the control group. There were no significant differences in blood pressure readings (either systolic or diastolic BP) between both groups in this study. However, there were significant difference in terms of HR measurement, either between the two groups (lower HR in Group D) and within Group D itself (lower HR over time). However, all HR measurements were still within normal physiological range.

Table 4: Comparison of mean and 95% confidence interval of diastolic blood pressure between groups

Time	Adjusted mean (95% CI)		F statisticsa (df)	P value[a]
	Group D	Group C		
T0	61.45 (58.24-64.67)	60.16 (56.95-63.38)	0.174 (2-120)	0.840
T1	61.16 (58.12-64.20)	59.61 (56.58-62.65)		
T2	60.42 (57.58-63.26)	60.03 (57.19-62.87)		

[a] *Repeated Measure ANOVA*

Table 5: Comparison of mean and 95% confidence interval of heart rate (beats/min)

Time	Group D	Group C	P value
Adjusted mean (95% CI)			
T0	90.10 (85.42-94.77)	88.71 (84.03-93.39)	< 0.001[a]
T1	81.16 (76.69-85.64)	90.35 (85.88-94.83)	
T2	81.00 (76.93-85.07)	90.52 (86.44-94.59)	
Mean score ± SD			
T0	90.10 ± 14.04	88.71 ± 11.90	0.676[b]
T1	81.16 ± 12.74	90.35 ± 12.16	0.005[b]
T2	81.00 ± 12.06	90.52 ± 10.57	0.002[b]

[a] *Repeated Measure ANOVA;* [b] *Independent t-test*

Shivering occurring perioperatively is mainly as a response to hypothermia, although the exact mechanism is poorly understood,[13] which may include cessation of central thermoregulation, internal body heat redistribution and environmental heat loss.[14] Dexmedetomidine (an α-2 adrenergic agonist) acts mainly on presynaptic receptors in the brainstem leading to minimized sympathetic activity with decreased central regulation of vasoconstriction.[13] Reduced vasoconstriction together with an increased level of shivering thresholds lead to reduced incidence of shivering in dexmedetomidine group.[15]

This study found that the occurrence of shivering was significantly reduced in Group D as compared to Group C. This finding is similar to several previous studies on prevention of shivering by dexmedetomidine, in which the occurrence of shivering in dexmedetomidine group ranged from 5-12% as compared to control group which ranged from 42.5-64.3%.[5,15-19] All these studies were using intravenous dexmedetomidine except one study which used intramuscular route.[18] Two other variations of intravenous doses were dexmedetomidine 0.5 µg/kg,[16] as well as 1 µg/kg followed by infusion at 0.4 µg/kg/h during surgery.[5, 15]

Another interesting study published recently investigated the minimum dose of dexmedetomidine required to stop shivering during SA.[20] The authors found out that the dose of less than 0.3 µg/kg was adequate to treat shivering.[20]

There was one previous study in patients undergoing cesarean delivery under SA but the chosen route for dexmedetomidine administration was through intrathecal.[21] In this study, intrathecal dexmedetomidine

Table 6: The mean heart rate differences of time within each group

Comparisons	Group D		Group C	
	Mean score difference (95% CI)	P value[a]	Mean score difference (95% CI)	P value[a]
T0 – T1	8.94 (5.67-12.20)	< 0.001[b]	–1.65 (–4.2-0.95)	0.206
T0 – T2	9.10 (5.46-12.73)	< 0.001[b]	–1.81 (–4.59-0.98)	0.195
T1 – T2	0.16 (–2.57-2.89)	0.905	–0.16 (–2.95-2.63)	0.907

[a] *Multiple paired t test;* [b] *Significant difference after Bonferroni correction*

of 5 µg managed to reduce the incidence of shivering by 30% as compared to control group.

Our study observed a statistically significantly higher sedation effect between patients in Group D than Group C based on Modified Wilson Sedation Scale. This is important as deeply sedated patient is undesirable especially in the parturients with high risk of aspiration. Another perspective of this would be the use of dexmedetomidine as conscious sedation in cesarean delivery to provide added comfort for the patient, without additional risk of deep sedation.

Previous studies using dexmedetomidine for anesthetic shivering resulted in mixed results. Two studies which utilized the dose of 1 µg/kg loading dexmedetomidine followed by 0.4 µg/kg/h infusion reported high incidence of sedation score, where majority patients (60-100%) had a sedation score of 2 and above.[5, 15] This is close to our findings where 51.6% of our patient had sedation score of 2, but none of our patient had higher sedation score. Two studies had similar findings with 60-70% of their patients with sedation score of 2 when they were using dexmedetomidine 0.5 µg/kg slow bolus.[12, 22]

The findings in our study showed that there were no significant differences for systolic and diastolic BP within or between group comparisons. Heart rate measurements were found to be lower in Group D. The use of vasopressor, although being used more in Group C, was not significantly different between the two groups. There were no incidence of bradycardia requiring atropine.

Effect of dexmedetomidine on hemodynamics profile from other studies were also variable. There were studies which 0.5 µg/kg he reported similar findings of lower BP and HR in dexmedetomidine group.[11, 12, 15] Usta et al. found that use of atropine and ephedrine were not significantly different from the control group, whilst Hatem et al. did not require any treatment for hypotension or bradycardia for their patients.[11,15] Other studies using 0.5 µg/kg of dexmedetomidine reported the incidence of bradycardia and hypotension ranging between 12-20% and 2-12% respectively.[5, 11, 22] There is one study by Mittal et al. which reported no incidence of hypotension or bradycardia.[6]

There were no significant differences in terms of estimated blood loss (P = 0.328), the volume of colloids (P = 0.214) and of crystalloids (P = 0.154) administrated between the Group D and Group C in our study.

5. LIMITATIONS

There are several limitations in our study. Firstly, the sample size was calculated to achieve 5% significance level with power of 80%. It can be further increased to achieve more power and improve sensitivity of this study. Temperature measurement used during this study was using tympanic membrane infrared thermometer. This is not reflective of the true core temperature for the patient; however, it is impractical to replace with more invasive thermometer in patients undergoing cesarean delivery. We did not ascertain exact block height for each patient, as operation was started once the level was assessed to be adequate.

6. CONCLUSION

Based on our study, we can safely use dexmedetomidine infusion to prevent shivering in patients undergoing Cesarean delivery under SA. This might be applied to patients who have experienced shivering during previous operation or in selected patients in which increased oxygen consumption would be very detrimental. Dexmedetomidine was effective in reducing the occurrence of shivering but with significant sedative effect and lowering of heart rate than the placebo.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

We gratefully thank Faculty of School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

WAAWMA: Concept, conduction of the study work

WMNWH: Concept, Interpretation of data for the work

PS, SCO: Drafting the work and revising it critically for important intellectual content; Manuscript editing

NANM: Acquisition, analysis, or interpretation of data for the work; Manuscript editing

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