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Effect of Intravenous Dexmedetomidine on Shivering in Cesarean Section under Intrathecal Anesthesia: Randomized Clinical Trial

Sholeh Nesioonpour [1], Soraya Bayat [1,*], Ali Ghomeishi [1], Kaveh Behaeen [1], Mohsen Savaie [1] and Azar Ahmadzadeh [2]

[1]Department of Anesthesiology, Pain Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Department of Gynecology, School of Medicine, Ahvaz Jundishapur Univercity of Medical Science, Ahvaz, Iran

[*]*Corresponding author*: Department of Anesthesiology, Pain Research Center, Ahvaz Jundishapur Univercity of Medical Sciences, Ahvaz, Iran. Email: bayat.s@ajums.ac.ir

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Abstract

Background: Shivering is one of the most common side effects after cesarean section (C-section) under spinal or epidural anesthesia. However, it is often not treated.
Objectives: The aim of this study was to evaluate the effectiveness of intravenous dexmedetomidine (DEX) in the prevention of shivering after intrathecal anesthesia in women undergoing C-sections.
Methods: This double-blind, placebo-controlled clinical trial was conducted on 80 women candidates for elective C-sections under intrathecal anesthesia who were referred to Imam Khomeini Governmental Hospital in Ahvaz, Iran, during 2020 - 2021. Patients were randomly divided into two groups of intravenous DEX (group D; 0.5 μg/kg) and normal saline (control, group C) and received the medications after umbilical cord clamping. All patients were evaluated during and after surgery for hemodynamic changes, the incidence and severity of shivering based on Chu and Tsai, side effects (e.g., nausea, vomiting), and sedation level based on the Ramsey scale.
Results: The incidence of shivering in group C was significantly higher than in group D ($P = 0.003$). Moreover, the severity of shivering on minutes 20, 30, and 45 in group C was significantly higher than in group D ($P < 0.05$). The mean sedation score during minutes 10 - 30 in group D was significantly higher than in group C ($P < 0.05$). Heart rate was not significantly different between the two groups ($P < 0.05$). Systolic and diastolic blood pressure were higher in group D than in group C ($P < 0.05$).
Conclusions: The administration of intravenous DEX effectively reduces the incidence and severity of shivering and provides appropriate sedation in patients undergoing C-sections, and it does not cause remarkable side effects.

Keywords: Cesarean Section, Dexmedetomidine, Intrathecal Anesthesia, Shivering, Temperature

1. Background

Shivering is an adverse event after anesthesia, with a reported incidence of 5%-65% after general anesthesia and 33% after regional anesthesia. The prevalence of shivering during cesarean section (C-section) under neuraxial anesthesia is 55% (1-3). Shivering is a recurrent involuntary skeletal muscle activity that increases oxygen consumption, CO_2 production, lactic acid accumulation, cardiac output, heart rate, blood pressure, intraocular pressure, and catecholamine release. It also interferes with monitoring blood pressure, oxygen saturation, and electrocardiography. Shivering may predispose patients with intrapulmonary shunt, limited respiratory reserve, or fixed cardiac output to various problems (4).

Diverse mechanisms have been suggested for shivering, including perioperative hypothermia, intraoperative heat loss, increased sympathetic tone, pain, and systemic release of pyrogens (5-7). The main causes of intraoperative hypothermia are the inhibition of body temperature regulation by anesthetic medicines, reduction of body metabolism, contact with cold air in the operating room, and opening of body cavities (8). Hypothermia inhibits platelet function and coagulation factors, leading to exacerbated postoperative bleeding. In addition, it inhibits drug metabolism, prolongs muscle block, delays the patient's awakening, and prolongs hospital stay (9). In intrathecal anesthesia, the body temperature regulation mechanism is inhibited, which results in perioperative hypothermia and shivering as a temperature-regulating response to hypothermia (10).

Various methods have been used to prevent and treat shivering. The non-pharmacological methods include

warming the body surface by forced air warmers, blankets, and the infusion of warm fluids. The pharmacological methods entail opioids (e.g., meperidine and tramadol), ondansetron, and clonidine. Side effects of meperidine, the most common treatment, are nausea, vomiting, pruritus, and respiratory depression, especially at high doses (11, 12). Furthermore, tramadol may trigger a seizure (13), and clonidine causes hypotension, anxiety, bradycardia, hyperglycemia, nausea, and vomiting (14).

Dexmedetomidine (DEX) is a potent, selective α2-adrenoceptor agonist eight times stronger than clonidine and promotes sedation, anxiety reduction, and analgesia without causing respiratory depression. The antishivering effects of DEX are induced by binding to the α2 receptor, which causes vasoconstriction. In addition, it has a thermoregulatory impact on the hypothalamus (15-17). It seems that DEX could be useful in controlling shivering with fewer side effects than common medications. The exact mechanism of DEX for shiver control is unclear and complex. DEX reduces shivering by inhibiting central thermoregulatory control, inhibiting neuronal conductance, suppressing vasoconstriction, and reducing shivering thresholds (18). However, limited studies have assessed the efficacy of DEX and, in particular, its efficacy on perioperative shivering at C-section.

2. Objectives

This study aimed to evaluate the effect of DEX on shivering in patients undergoing C-sections after intrathecal anesthesia.

3. Methods

This double-blind placebo-controlled clinical trial was performed on women candidates for elective C-sections at Imam Khomeini Governmental Hospital in Ahvaz, Iran, during 2020 - 2021. This study was carried out after approval by the Research Ethics Committee of the Research Department of Ahvaz Jundishapur University of Medical Sciences (ethics code IR.AJUMS.REC.1399.305) and received the IRCT code from the Iranian Clinical Trials System (IRCT20200107046042N1). Informed written consent was received from all individuals to participate in the study. Moreover, in all stages of the study, Helsinki's Code of Ethics in Research and the principles of confidentiality of patient information were observed.

The inclusion criteria entailed being 18 - 35 years, first or second pregnancy, ASA class I and II. The exclusion criteria were a history of seizures, allergies to our study medicines, febrile illness, coagulation disorders, any contraindication for intrathecal anesthesia, and severe cardiac, respiratory, hepatic, renal, and muscular diseases. Patients' demographic information was recorded in a data collection questionnaire. Standard monitoring was performed, including electrocardiography, pulse oximetry, and non-invasive blood pressure. Heart rate, blood pressure, body temperature, shivering, and sedation were recorded before anesthesia, and 10 cc/kg of Ringer's serum was infused. Room temperature was maintained at 24°C - 26°C.

Spinal anesthesia was performed at the L3 - L4 or L4 - L5 space with an injection of 10 mg of bupivacaine 0.5% (cenex' France for AstraZeneca) by a Quincke needle (25G Dr Japan Co. Ltd.) in a sitting position. Blocking was confirmed by pinprick test and foot movement. Patients were randomly divided into groups D and C. Randomization was undertaken using a random number table. Group D received 0.5 μg/kg of DEX (Exir Pharmaceutical Company, Iran) diluted with normal saline to a volume of 20 cc. Group C (control group) received 20 cc of normal saline. DEX or normal saline infusion was performed by pumping over 10 min after umbilical cord clamping at a rate of 120 cc/h. The syringes containing DEX and normal saline were prepared in advance and kept at room temperature. Intervention (receiving DEX or normal saline) and patient evaluation were completed blindly by an anesthesiologist. In addition, the patients, data collector, and the analyzer of the results were unaware of patient grouping.

Duration and severity of shivering, hemodynamic changes (heart rate and blood pressure), changes in body temperature, sedation rate, and side effects (nausea and vomiting) were evaluated and recorded before and after spinal anesthesia, during umbilical cord clamping, and then every 5 min until 45 min after drug administration. The duration of spinal anesthesia and surgery were also recorded. The end of spinal anesthesia was when patients could move their legs.

Patients' body temperature was measured by a thermometer (Micro Life, Medisa Novin Payesh Company, Taiwan). In the case of hypotension of more than 20% of baseline or blood pressure less than 90 mmHg, 5 mg ephedrine was injected intravenously. Furthermore, a decrease in heart rate (HR < 60 beats/min) was treated with 0.5 mg intravenous atropine. The incidence of nausea and vomiting was also recorded and managed under the supervision of an anesthesiologist.

The level of shivering was measured based on the Chu and Tsai score in four grades as follows: (1) grade 0: no shivering; (2) grade 1: piloerection and peripheral vasoconstriction without obvious shivering; (3) grade 2: muscle activity (frequent contractions) in only one muscle group; (4)

grade 3: muscle activity in more than one muscle group but not generalized; (5) grade 4: shivering all over the body. If the patient had $\geq$ grade 3 continuous shivering for 15 min, 0.5 mg/kg meperidine was used to control the shivering. Sedation score was evaluated and recorded in 5 levels based on: (1) the Ramsey sedation scale: 1; (2) fully awake and alert: 2; (3) sleepy: 3; (4) the patient closes her eyes and wakes up with a command: 4; (5) the eyes are closed, and the patient wakes up with physical stimulation: 5. The eyes are closed, and the patient does not wake up with physical stimulation.

3.1. Statistical Analysis

The sample size was determined to be 40 subjects in each group based on the previous research by Yu et al. (15), with a mean difference of 0.4 for shivering score between the two groups, 95% confidence interval, and 15% sample dropout using the following formula:

$$n_1 = n_2 = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(S_1^2 + S_2^2\right)}{\left(\bar{x}_1 - \bar{x}_2\right)^2}$$

The SPSS software version 22 was used for statistical analysis. Obtained data were analyzed by descriptive statistics, including mean, standard deviation, frequency, and percentage. The normality of variables was assessed using the Kolmogorov Smirnov test. Moreover, the Mann-Whitney and Chi-square tests (or Fisher's exact test) were used to investigate the differences between the two groups and compare the quantitative and qualitative variables, respectively. Paired t-test was utilized to compare the mean differences between the pairs. P-value < 0.05 was considered significant.

4. Results

A total of 80 women with a mean age of 26.61 $\pm$ 5.7 years (18 - 35 years) participated in the study. The results related to the basic characteristics of patients and the duration of spinal anesthesia and surgery are presented in Table 1. As could be observed, the two groups were not significantly different in terms of age, height, weight, body mass index, duration of spinal anesthesia, duration of surgery, and spinal interval to the start of surgery ($P < 0.05$).

The hemodynamic changes at different times in groups D and C are presented in Table 2. As observed, heart rate was not significantly different between the two groups in none of the studied times ($P < 0.05$). Mean systolic blood pressure on minutes 5, 10, 15, 20, and 30 was significantly different between the two groups so that at the mentioned times, it was higher in group D than in group C. However, no significant difference was observed between the two groups at other times. Furthermore, diastolic blood pressure was significantly higher in group D on minutes 5 and 10 than in group C, but there was no significant difference between the two groups at other times.

The changes in body temperature and shivering score at different times are presented in Table 3. As shown in Table 3, body temperature at the time of umbilical cord clamping showed a significant difference between the two groups ($P = 0.035$). No significant difference was observed between the two groups at other times ($P < 0.05$). In addition, the mean score of shivering on minutes 20, 30, and 45 in group D was significantly lower than group C ($P = 0.022$, $P = 0.029$, and $P < 0.0001$, respectively). No significant difference was found between the two groups at other times ($P < 0.05$). In group D, the shivering score did not significantly differ between different times ($P < 0.05$).

The results of sedation scores at different times before and after spinal anesthesia in two groups are presented in Table 4. According to Table 4, the mean sedation score on minutes 10, 15, 20, and 30 in group D was significantly higher than in group C ($P < 0.05$). Sedation scores at other times did not show a significant difference between the two groups ($P > 0.05$). In group D, sedation score was significantly different between the time of umbilical cord clamping and minute 5 ($P = 0.025$), minutes 5 and 10 ($P = 0.001$), minutes 20 and 30 ($P = 0.014$), and minutes 30 and 45 ($P = 0.001$). In group C, there was a significant difference in sedation scores between minutes 15 and 20 ($P = 0.046$). No significant difference was observed in the sedation score ($P > 0.05$) at other times. There was no significant difference in the incidence of nausea and vomiting side effects between the two groups.

5. Discussion

The results of this study demonstrated a statistically significant higher incidence of shivering in group C compared to group D. Shivering (score 3) was only observed in one patient of group D and 11 patients of group C 15 min after cord clamping. Shivering of the patient of group D occurred on minute 30 and disappeared on minute 45. There was no significant difference between the two groups regarding shivering scores prior to and immediately after spinal anesthesia in this study. Mean shivering score on minutes 20, 30, and 45 was significantly lower in group D. In this study, body temperature was not significantly different between the two groups except at umbilical cord clamping. Yu et al. in women undergoing C-sections with spinal anesthesia-related shivering reported that all patients responded to 0.5 μg/kg DEX within 15 min (15).

Table 1. Basic Characteristics of Subjects in Two Groups of DEX and Control [a]

Variables	DEX (n = 40)	Control (n = 40)	P-Value [b]
Age (y)	26.4 ± 5	26.83 ± 6.38	0.769
Height (cm)	160.28 ± 6.03	161.33 ± 4	0.153
Weight (kg)	74.4 ± 10.37	71.6 ± 10.33	0.291
BMI (kg/m^2)	28.96 ± 3.72	27.49 ± 3.83	0.065
Spinal anesthesia duration (min)	99.47 ± 21.46	109.57 ± 29.85	0.17
Duration of surgery (min)	49.33 ± 16.67	48.23 ± 10.64	0.757
Spinal to the start of surgery time (min)	5.2 ± 1.93	5.73 ± 2.24	0.319
Start of surgery to cord clamping time (min)	6.45 ± 2.73	5.2 ± 1.94	0.036

Abbreviations: DEX, dexmedetomidine; BMI, body mass index.
[a] Values are expressed as mean ± SD.
[b] Mann-Whitney test, P < 0.05 is significant.

The results of the study by Lamontagne et al. showed that intravenous administration of DEX (30 μg) reduced the duration of shivering in women undergoing C-section under spinal and epidural anesthesia compared to placebo (2.6 min vs. 17.9 min). The shivering stopped in 90% of patients in the DEX group versus 22.5% in the control group after 15 min of drug administration (19). Evaluation of the effect of DEX (5 μg intrathecal) in women undergoing C-sections under spinal anesthesia by Nasseri et al. revealed that body temperature (core body and forehead) during and after surgery was not significantly different between the two groups of DEX and normal saline. However, the incidence of shivering in the normal saline group was significantly higher than in the DEX group (52% vs. 24%). Moreover, the severity of shivering based on Chu and Tsai was significantly higher in the control group than in the DEX group (20). In another study, He et al. showed that 5 μg intrathecal DEX reduced the incidence and severity of shivering compared to the control group (36.5% vs. 6.7%, P = 0.005). In comparison, 2.5 μg DEX did not reduce shivering in women under C-section with spinal anesthesia compared to the control group. However, the severity of shivering in both DEX groups decreased compared to group control (21). Botros et al. demonstrated that the prophylactic administration of DEX (1 μg/kg) effectively reduced the incidence and severity of shivering after spinal anesthesia compared to placebo (7).

Concerns with DEX are hemodynamic instability and excessive sedation, which can occur following bolus injection (< 2 min). However, these changes are reversible over time (15, 22, 23). Therefore, in the present study, DEX was injected as a continuous infusion for 10 min. We found that DEX infusion at umbilical cord clamping during C-section was associated with less hemodynamic instability than placebo. Both groups showed decreasing systolic blood pressure after spinal anesthesia but rose rapidly at the time of umbilical cord clamping in group D. In addition, diastolic blood pressure was significantly higher in group D than in group C on minutes 5 and 10. There was no significant difference between the two groups at other times.

In another study by Yu et al., the continuous infusion of 0.5 μg/kg DEX in 10 min after the clamping of the umbilical cord was associated with more stable blood pressure, tympanic temperature regulation, and a high level of sedation (15). The results of a clinical trial by He et al. showed that mean arterial pressure and heart rate at different times after C-section under spinal anesthesia were not significantly different between the two groups (21). Prabhakaran et al. reported that the incidence of bradycardia and hypotension was not significantly different between DEX and normal saline groups after spinal anesthesia (24).

The results of the present study showed that the mean sedation score on minutes 10, 15, 20, and 30 in the DEX group was significantly higher than in the control group. The results of Nasseri et al. (20) indicated that the sedation level in the DEX group was significantly higher than in the control group. In another study, Botros et al. showed that the prophylactic administration of DEX (1 μg/kg) following spinal anesthesia in patients undergoing lower-body surgery resulted in marked sedation compared to placebo (7). DEX is a selective α2-adrenoceptor agonist with centrally mediated sympatholytic, sedative, and analgesic effects (23, 25, 26).

In the current investigation, there was no significant difference in the incidence of side effects (nausea and vomiting) between groups D and C (11 vs. 13). In the studies by Nasseri et al. (20) and He et al. (21), the incidence of side effects, including nausea, vomiting, and bradycardia following the administration of DEX in women undergo-

Table 2. Comparison of Hemodynamic Parameters at Different Times Between the Two Groups [a]

Time and Groups	HR	P-Value [b]	SBP	P-Value [b]	DBP	P-Value [b]
Before spinal anesthesia		0.066		0.513		0.104
DEX	101.4 ± 12.99		122.83 ± 14.52		79.08 ± 9.87	
Control	96.28 ± 15.08		120.95 ± 16.12		75.87 ± 14.12	
After spinal anesthesia		0.949		0.501		0.949
DEX	103.95 ± 15.99		110.93 ± 17.63		68 ± 10.89	
Control	105.08 ± 14.81		114.88 ± 19.72		71.6 ± 16.86	
Cord clamping		0.444		0.065		0.366
DEX	109.28 ± 18.68		119.93 ± 17.3		70.05 ± 11.64	
Control	103.65 ± 17.05		113.53 ± 15.42		69.13 ± 13.39	
Minute 5		0.773		< 0.0001		0.012
DEX	106.08 ± 19.48		122.1 ± 15.45		70.65 ± 11.71	
Control	106.43 ± 15.99		106.85 ± 18.42		64.53 ± 13.71	
Minute 10		0.144		< 0.0001		0.013
DEX	98.63 ± 17.83		122.85 ± 13.07		70.3 ± 9.5	
Control	103.53 ± 15		111.28 ± 14.8		65.63 ± 11.18	
Minute 15		0.133		0.03		0.207
DEX	99.48 ± 17.5		119.4 ± 19.61		67.68 ± 12.76	
Control	103.25 ± 13.75		111.18 ± 14.82		65.2 ± 11.02	
Minute 20		0.35		0.012		0.181
DEX	98.93 ± 15.12		116.83 ± 13.07		66.18 ± 9.58	
Control	101.93 ± 13.73		110.88 ± 15.42		63.73 ± 11.75	
Minute 30		0.229		0.004		0.27
DEX	94.23 ± 15.41		115.53 ± 11.51		67.5 ± 9.91	4
Control	98.72 ± 14.4		109.54 ± 16.7		64.95 ± 11.2	
Minute 45		0.102		0.157		0.933
DEX	91.58 ± 13.43		113.98 ± 12.02		66.9 ± 9.93	
Control	96.95 ± 11.49		111.26 ± 15.21		66.67 ± 10.48	

Abbreviations: DEX, dexmedetomidine; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a] Values are expressed as mean ± SD.
[b] Mann-Whitney test, P < 0.05 is significant.

ing C-section under spinal anesthesia did not have a significant difference with the placebo. Some discrepancies between our study and previous research could be due to variations in the characteristics of the study subjects and different methodology. The present study had limitations, such as the small sample size and not evaluating the core body temperature. Therefore, further multicenter studies with a larger sample size are recommended for more accurate results.

5.1. Conclusion

The results of the present study suggested that the intravenous administration of DEX could effectively reduce the incidence and severity of shivering in patients undergoing C-sections, creating a higher sedation level and more hemodynamic stability without significant complications. Consequently, intravenous DEX could be used as an effective and safe medicine in preventing shivering and reducing patient discomfort in women undergoing C-sections.

5.2. Recommendations

- Evaluating the effects of other doses of DEX on shivering and hemodynamic changes.
- Measuring the core body temperature.
- Evaluating the DEX effects on neonates.

Table 3. Comparison of Mean Body Temperature and Shiver Intensity Score at Different Times Between Two Groups [a]

Time	Body Temperature			Shivering Intensity Score		P-Value [b]
	DEX	Control	P-Value [b]	DEX	Control	
Before spinal anesthesia	36.94 ± 0.61	37.1 ± 0.37	0.179	0.08 ± 0.26	0.05 ± 0.22	0.649
After spinal anesthesia	36.83 ± 0.72	37.07 ± 0.32	0.055	0.05 ± 0.22	0.18 ± 054	0.365
Cord clamping	36.64 ± 1.09	37.05 ± 0.49	0.035	0 ± 0	0.05 ± 0.22	0.155
Minute 5	36.6 ± 1.29	36.95 ± 0.44	0.103	0 ± 0	0.05 ± 0.22	0.155
Minute 10	36.52 ± 1.27	36.79 ± 1.22	0.332	0 ± 0	0.05 ± 0.22	0.155
Minute 15	36.46 ± 1.47	36.74 ± 1.15	0.345	0 ± 0	0.08 ± 0.26	0.079
Minute 20	36.48 ± 1.31	36.73 ± 0.78	0.299	0 ± 0	0.33 ± 0.91	0.022
Minute 30	36.38 ± 1.19	36.7 ± 1	0.198	0.08 ± 0.47	0.38 ± 0.92	0.029
Minute 45	36.4 ± 1.25	36.71 ± 0.83	0.191	0 ± 0	0.58 ± 1.05	< 0.0001

Abbreviation: DEX: dexmedetomidine.
[a] Values are expressed as mean ± SD.
[b] Mann-Whitney test, P < 0.05 is significant.

Table 4. Comparison of Sedation Scores at Different Times in Two Groups [a]

Time	DEX	Control	P-Value [b]
Before spinal anesthesia	1 ± 0	1 ± 0	1
After spinal anesthesia	1 ± 0	1 ± 0	1
Cord clamping	1 ± 0	1.05 ± 0.22	0.155
Minute 5	1.13 ± 0.33	1.1 ± 0.3	0.725
Minute 10	1.43 ± 0.5	1.13 ± 01.33	0.003
Minute 15	1.55 ± 0.59	1.15 ± 0.36	0.001
Minute 20	1.73 ± 0.78	1.05 ± 0.22	< 0.0001
Minute 30	1.5 ± 0.67	1.05 ± 0.22	< 0.0001
Minute 45	1.05 ± 0.22	1 ± 0	0.155

Abbreviation: DEX: Dexmedetomidine
[a] Values are expressed as mean ± SD.
[b] Mann-Whitney test, P < 0.05 is significant.

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Footnotes

Authors' Contribution: Study concept and design, Sholeh Nesioonpoor and Soraya Bayat; Data collecting, Soraya Bayat; Analysis and interpretation of data, Sholeh Nesioonpoor and Soraya Bayat; Manuscript preparation, Ali Ghomeishi, Kaveh Behaeen, Mohsen Savaie, and Azar Ahmadzadeh; Critical revision, Sholeh Nesioonpoor and Soraya Bayat.

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Conflict of Interests: The authors declare no conflicts of interest.

Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

Ethical Approval: This study was carried out after approval by the Research Ethics Committee of the Re-

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