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Comparing the Effects of Low Dose of Ketamine, Tramadol, and Ondansetron in Prevention of Post Spinal Anesthesia Shivering in Cesarean Section

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Abstract

Background: Shivering frequently occurs in cesarean section (CS) under spinal anesthesia (SA), resulting in several complications. To date, pethidine has been considered as the gold standard for post-SA shivering control, but it is contraindicated in breastfeeding women.

Methods: This randomized, double-blind study was conducted at Alzahra hospital in Guilan, Iran, From January 2019 to November 2020. A total of 508 eligible term parturient women were enrolled and randomly divided into four groups of low dose ketamine (K), tramadol (T), ondansetron (O), and placebo (P). The incidence and severity of shivering and patients' complications were recorded and compared among the groups.

Results: The patients were homogenous in terms of demographic variables. Shivering was witnessed in 68 (53.5%), 26 (20.5%), 75 (59.1%), and 82 (64.6%) patients in K, T, O, and P groups, respectively (P = 0.0001). Regarding shivering severity, there was a significant difference among the four groups (P = 0.0001). In addition, a significant difference was seen regarding Apgar scores at the first minute, but not at the fifth minute (P = 0.168).

Conclusions: Considering the high incidence of shivering in placebo group, prophylactic intervention in CS under SA seems to be necessary. Among the studied drugs, tramadol was the most effective one, followed by a low dose of ketamine and ondansetron.

Keywords: Cesarean Section, Ketamine, Ondansetron, Tramadol, Shivering, Spinal Anesthesia

1. Background

Spinal anesthesia (SA) is preferred for cesarean section (CS) compared with general anesthesia (GA) because of several advantages, including prevention of the potential risk of GA-related neurotoxicity (1), its early-onset and easy to perform nature, and post-operation pain reduction (2-4).

However, shivering is a frequent and undesirable side effect of the procedure among a parturient woman undergoing CS under SA. It may be a natural thermoregulatory response to central hypothermia, or it may be the result of cytokine release during surgery (5). Shivering induces several complications such as interfering with standard monitoring, lactic acidosis, increased carbon dioxide production, and oxygen consumption (6-8). To date, a variety of pharmacologic agents including magnesium sulfate, opioids, α_2-agonists, N-methyl D-aspartate receptor antagonists, serotonin 5-HT3 receptor antagonist (9-11), and non-pharmacological interventions such as blankets, radiant heat, and forced air warmers have been used to suppress perioperative shivering (12).

However, the problem still exists, and investigation for novel approaches with enough safety and efficacy is strongly recommended. In this regard, in spite of considering pethidine as the gold standard of post-SA shivering reduction agent (13), it is contraindicated in breastfeeding women, which is both legally and ethically challenging. Therefore, pregnant women should particularly be considered for this issue (14). Indeed, the purpose of this survey was to replace pethidine with a safe and effective anti-shivering agent in CS.

2. Objectives

In this study, we aimed to investigate and compare the efficacy and safety of tramadol, low dose of ketamine, and ondansetron with normal saline on post-SA shivering in CS.

3. Methods

This randomized, double-blind clinical trial was conducted at Alzahra hospital, which is a referral center affiliated to Guilan University of Medical Sciences (GUMS), Iran, from January of 2019 to November 2020. After obtaining informed consent from all patients, we collected their information, including demographic data, medical records, and medications.

3.1. Inclusion Criteria

In this study, we included term parturient women aged between 18 - 40 years who were candidates for CS under SA according to the American Society of Anesthesiologists (ASA) II classification.

3.2. Exclusion Criteria

The exclusion criteria were as follows: (1) parturient women with any contraindication or hypersensitivity to the study drugs; (2) any history of cardiovascular diseases, psychosis, hypertension, fetal distress, cord prolapse initial; (3) temperature more than 38°C or less than 36°C; history of opioids, alcohol, or any substance abuse; the need of a transfusion or any unusual intraoperative and postoperative bleeding; receiving other drugs with the property of altering thermoregulation; failed SA; and change to GA.

Anesthesia management and intervention firstly, an 18 gauge intravenous cannula was inserted, and 10 mL/kg of ringer lactate was infused for 15 minutes. All the patients underwent the standard monitoring, including electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (BP), and oxygen saturation (SPO_2). SA was performed in sitting position at L_3 - L_4 or L_4 - L_5 levels by using a 25 gauge Quincke spinal needle and 12.5 mg isobar bupivacaine. In order to assess the quality of SA block, Bromage scale and Pinprick test were used. The desired sensory block was T_4 - T_6 and regarding motor block and Bromage scale, 3 was acceptable. In supine position, the patients received 4L/minute oxygen via a face mask. The patients were randomly divided into four groups of tramadol 0.5 mg/kg (T), low dose of ketamine 0.2 mg/kg (K), ondansetron 4 mg (O), and placebo with normal saline (P). The patients did not receive any drugs as premedication, and they were not actively warmed. The anesthesiologist, who was not engaged in the study process, prepared the study drugs in 5 mL coded syringes and a responsible anesthesiologist administrated the drugs as an intravenous (IV) bolus just after SA was confirmed. Shivering severity was recorded every 5 minutes during surgery and until 45 minutes in recovery. Apgar scores were evaluated at the first and 5th minutes. The severity of shivering was graded as grade 0: lack of shivering, grade I: slight shivering (inconsiderable yet apparent peripheral vasoconstriction), grade II: medium level shivering (muscular activity in one muscle group only), and grade III: severe shivering (muscular activity in more than one muscle group). In resistant shivering, pethidine 25 mg IV was injected after clamping the umbilical cord. Atropine 0.5 mg IV was administrated when HR was lower than 50 bpm, ephedrine 5 mg IV was administrated if blood pressure dropped below 20% from baseline or systolic blood pressure was less than 100 mmHg, and metoclopramide 10 mg IV was administrated if the patient complained of nausea and vomiting. Hemodynamic parameters and any adverse drug reaction (ADR) were also documented during the study period.

3.3. Statistical Analysis

The data were analyzed by SPSS software version 21. One-way analysis of variance (ANOVA) was used to analyze continuous variables with normal distribution. Repeated-measures ANOVA was used to analyze temperature values. Nonparametric data regarding shivering severity were compared among groups by the Mann-Whitney U test, and the chi-square test was also used. Statistically, a P-value < 0.05 was considered significant.

4. Results

Socio-demographic data were compared among the groups (Table 1). No significant difference was observed among the four groups concerning the baseline data. The overall incidence of shivering was 64.6%. Moreover, shivering was witnessed in 68 (53.5%), 26 (20.5%), 75 (59.1%), and 82 (64.6%) of patients in K, T, O, and P groups, respectively (P = 0.0001). Regarding shivering severity, there was also a significant difference among the four groups (P = 0.0001) (Table 2). In addition, a significant difference was shown regarding Apgar scores at the first minute (P = 0.0001), but not at the fifth minute (P = 0.168) (Table 3). Shivering in grade 4 was recorded only in 6 (4.7%) cases of the placebo group and none of the therapeutic groups. Grade 3 was reported in 9 (7%), 4 (3.1%), and 19 (14.9%) patients in the K, T, and O groups, respectively. The occurrence of ADR has been presented in Table 4.

Table 1. Demographic Characteristics of Patients [a]

Variables	Low-Dose Ketamine Recipient (N = 127)	Tramadol Recipient (N = 127)	Ondansetron Recipient (N = 127)	Placebo Recipient (N = 127)	P Value
ASA class					0.965
I	92 (72.4)	94 (74)	92 (74.4)	95 (74.8)	
II	35 (27.6)	33 (26)	35 (27.6)	32 (25.2)	
Age (y)	28.69 ± 4.65	28.25 ± 5.27	28.99 ± 5.36	28.92 ± 5.56	0.677
Temperature (°C)	37 ± 0.25	37.03 ± 0.22	37.01 ± 0.18	37.05 ± 0.23	0.391
Operating room temperature (°C)	22.19 ± 0.83	22.41 ± 0.82	22.4 ± 0.97	22.4 ± 1.07	0.167
Duration of surgery (min)	53.74 ± 8.11	53.61 ± 5.96	52.17 ± 7.13	52.42 ± 9.56	0.256
BMI (kg/m^2)	28.94 ± 4.42	28.54 ± 2.7	29.32 ± 4.43	29.4 ± 3.1	0.238
Block sensory level					0.969
2	24 (18.9)	26 (20.5)	23 (18.1)	25 (19.7)	
3	103 (81.8)	101 (79.5)	104 (81.9)	102 (80.3)	
Total	127 (100)	127 (100)	127 (100)	127 (100)	

[a] Values are expressed as mean ± SD or No. (%).

Table 2. Comparison of the First and Fifth Apgar Scores Among the Study Groups [a]

Variables	Low-dose Ketamine Recipient (N = 127)	Tramadol Recipient (N = 127)	Ondansetron Recipient (N = 127)	Placebo Recipient (N = 127)	P Value
Apgar minute one					0.0001
5	0 (0)	1 (0.8)	1 (0.8)	0 (0)	
6	1 (0.8)	7 (5.5)	1 (0.8)	2 (1.6)	
7	21 (16.5)	53 (48.8)	24 (18.9)	11 (8.7)	
8	105 (82.7)	57 (44.9)	101 (79.5)	114 (89.7)	
Apgar minute five					0.168
8	4 (3.1)	8 (6.3)	3 (2.4)	2 (1.6)	
9	123 (96.9)	119 (93.7)	124 (97.6)	125 (98.4)	
Apgar minute one	7.81 ± 0.4	7.37 ± 0.62	7.77 ± 0.49	7.88 ± 0.36	0.0001
Apgar minute five	8.96 ± 0.17	8.93 ± 0.24	8.97 ± 0.15	8.98 ± 0.12	0.169

[a] Values are expressed as mean ± SD or No. (%).

5. Discussion

In this study, the incidence of shivering was 64.5%, which was higher than some previous studies (15); this could be explained by different operating room conditions and patients characteristics. The study drugs have been reported to control post-SA shivering by different mechanisms and degrees. Tramadol, a centrally acting analgesic agent, is structurally similar to codeine and morphine, with the effects on μ-opioid receptors. The anti-shivering properties of tramadol include inhibiting noradrenaline and serotonin uptake in the spinal cord and triggering the secretion of hydroxyl-tryptamine, which modulates the human temperature regulation center (16-18). Comparing the study drugs, IV tramadol showed superior effects; however, the mean Apgar score was significantly lower in this group, which casts doubt to introduce tramadol as the first option.

It should be noted that in our study, most of the surgeries were performed by obstetric residents under the supervision of attendings. Hence, the mean surgery duration was also significantly longer in our study (53.61 ± 5.96) compared to some other studies, such as the survey by Gemal (45.5 ± 7.2) (19). Thus, it is expected that more drugs could pass through the placenta to the fetus circulation.

Table 3. Comparison of the Incidence and Severity of Shivering Among the Study Groups [a]

Parameters	Low-Dose Ketamine Recipient (N = 127)	Tramadol Recipient (N = 127)	Ondansetron Recipient (N = 127)	Placebo Recipient (N = 127)	P Value
Shivering (%)					0.0001
No	59 (46.5)	101 (79.5)	52 (40.9)	45 (35.4)	
Yes	68 (53.5)	26 (20.5)	75 (59.1)	82 (64.6)	
Severity of shivering (%)					0.0001
Grade I	38 (29.9)	15 (11.8)	20 (15.7)	16 (12.6)	
Grade II	21 (16.5)	7 (5.5)	36 (28.3)	31 (24.4)	
Grade III	9 (7)	4 (3.1)	19 (14.9)	29 (22.8)	
Grade IV	0 (0)	0 (0)	0 (0)	6 (4.7)	

[a] Values are expressed as No. (%).

Table 4. The Frequency of Side Effects in Four Study Groups [a]

Side Effects	Ketamine	Tramadol	Ondansetron	Normal Saline	P Value
Nausea &vomiting	25 (19.7)	63 (49.6)	15 (11.8)	51 (40.2)	0.0001
Hypotension	7 (5.51)	28 (22.04)	15 (11.81)	17 (13.38)	0.001
Bradycardia	0 (0)	14 (11)	8 (6.3)	7 (5.5)	0.002
Hallucination	9 (7.1)	0 (0)	0 (0)	0 (0)	0.0001
Nystagmus	13 (10.2)	0 (0)	0 (0)	0 (0)	0.0001
Headache	5 (3.9)	10 (7.9)	2 (1.6)	3 (2.4)	0.048

[a] Values are expressed as No. (%).

Similar to our results, in the study by Gemal, 23% of the cases in the tramadol group complained of shivering; this rate was 25% in our study. They also used a higher dosage of 1 mg/kg of tramadol with no adverse effect on Apgar scores, which confirms the effect of length of surgery on neonate Apgar score. In order to prove the effects of surgery duration on the results, the survey should enroll private hospitals, where in contrast to academic wards, only obstetrics are involved in the surgery process. In line with our findings, Ejiro et al. reported that the prophylaxic effect of IV tramadol 0.5 mg/kg on post-SA shivering in CS was significantly superior to 4 mg IV ondansetron. Only 7.16% of their cases in tramadol group experienced shivering, while none of them developed severe grades (16). The same promising results were observed in two studies conducted by Talakoub and Noori Meshkati (20) and Seyam (21). However, Ilyas et al. reported different results, supporting the superiority of low-dose ketamine compared to IV tramadol (22). In this study, we found that 0.02 mg/kg IV ketamine significantly reduced both the incidence and the intensity of shivering compared to placebo. Ketamine, the antagonist of N-methyl-D-aspartate, resets the thermoregulation system via many receptors affecting serotoninergic and noradrenergic neurons. IV ketamine, in addition to anti-shivering effects, provides more advantages such as hemodynamic stability and reduction of post-operation pain (23, 24).

In our study, 53.5% of cases in ketamin group developed shivering, which was different from the studies by Honarmand and Safavi (23.3%) (25), Sagir et al. (0%) (26), and Jaafarpour et al. (17.4%) (27). In a different study, Lema et al. found that ketamine 0.2 mg/kg was significantly superior to tramadol 0.5 mg/kg as an anti-shivering agent in CS under SA (9). In the study by Kumar et al., the incidence of shivering was 33% in ketamine group, which was significantly lower compared to this study. This might be attributed to the higher drug dosage (0.5 mg/kg vs. 0.2 mg/kg) used in this study (28). The other study drug was ondansetron, which is a 5HT3 receptor agent with anti-shivering effects through influencing both heat loss and heat production pathways (16).

Inconsistent with our study, Browning et al. demonstrated that ondansetron 8 mg IV had no efficacy on post-SA shivering in CS compared to the placebo group. They reported these findings despite administrating a larger dosage of ondansetron (8 mg) compared to our study (4 mg) (29).

In a supportive study, Nallam et al. reported that on-

dansetron 8 mg IV could effectively prevent post-SA shivering in CS with an incidence of 10% compared with 59.1% in our study, with no adverse effects (30). Overall, it should be kept in mind that the incidence of high grades of shivering is much more important than its overall incidence among the patients, which should be noticed and discussed. In our study, for example, in the tramadol group, the incidence of shivering was 20.5%, while only 3.1% were affected by grade 3 of shivering, or in ketamine group, the overall incidence of shivering was 53.5%, while in 7% of the cases grade 3 of shivering was reported. Therefore, the results of studies with no analysis regarding the degrees of shivering might not be comparable. Furthermore, when interpreting the anti-shivering properties of a drug, an important and determinative item would be the incidence of shivering in the placebo group. Because baseline characteristics regarding both individuals and environmental factors are not the same. Therefore, the results of studies with no placebo group might not be reliable. Overall, searching the literature, a marked discrepancy is observed among the findings of different studies (26), which could be justified by the following reasons: the differences in methodologies, studied population, operating room conditions, genetics, preheating of fluids, room temperature of drugs, and the level of sensory block. Besides, in different studies, patients have not been assessed by equal accuracy, especially lower grades of shivering (0 and 1) might not be detected. Furthermore, it has been shown that level of preoperative anxiety in pregnant women is strongly correlated with the severity of shivering (31). In this study, the incidence of perioperative DAR like, nausea, vomiting, hallucination, nystagmus, and sedation showed a significant difference among the four study groups. We witnessed that the study drugs were significantly superior to placebo. On the other hand, the high incidence of shivering showed the need for effective intervention. Therefore, a proper prophylaxic drug according to the patients' conditions, such as medical history, is strongly recommended.

5.1. Limitations

Despite providing valuable information regarding the prevention of shivering in CS under SA, a few limitations of this study should be noted. First, it was a single-center study, and private sectors were not included. Second, room and fluid temperature could not be tightly controlled.

5.2. Conclusion

According to our results, the incidence of shivering was 64.5% in this study, indicating the need for practical interventions. We recommend tramadol IV or low-dose ketamine as prophylaxis for post-SA shivering in CS. Although IV tramadol had superior effects, the other study drugs could be effective according to the patients' conditions.

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Footnotes

Authors' Contribution: GB and HSH, wrote the first draft of the manuscript; AMJ, edited and critically reviewed manuscript; MMG and ZRS, collaborated in the collection of data and quality control; AS and VI, collaborated in data processing, interpreted the results; TZN, conceptualized and designed the study, performed statistical analysis. All authors reviewed and approved the final draft of the manuscript.

Clinical Trial Registration Code: The study protocol was registered in the Iranian registry of clinical trials (IRCT20110425006281N2).

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

Ethical Approval: The study protocol was approved by the Research Ethics Committee of the Guilan University (ethical code: IR.GUMS.REC.1397.208).

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