RESEARCH ARTICLE

A Comparative Study on the Effect of Intravenous Hydrocortisone and Ketamine on Reducing Shivering after Spinal Anesthesia in Cesarean Section: A Double-blind Randomized Controlled Trial

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Background: Shivering is rhythmic vibratory motions in one or more group of muscle that caused after general or local anesthesia. Prevention and early treatment of Shivering lead to not conflict with patient monitoring and also reduce cardio-respiratory and metabolic side effects in patients. The aim of this study is comparing effect of ketamine and hydrocortisone on reducing post spinal shivering.

Methods: In this prospective study, 150 pregnant women randomly were divided into three groups after Spinal anesthesia. Patients received 3cc hydrocortisone (2 mg/kg, A group), 3cc ketamine (0.5 mg/kg, B group) and 3cc normal saline (%0.9, C group) intravenously in 10-15 S duration after umbilical cord clamping. In all patients systolic and diastolic pressure, mean arterial pressure, heart rate, oxygen saturation level and body temperature were recorded before anesthesia and then every minute for 5 minutes, every 5 minutes for 15 minutes, every 10 minutes until the end of surgery. Also sedation score, hallucination, nausea and vomiting, intensity of shivering and using amount of pethidine and ephedrine were recorded in questionnaire.

Results: All three groups were similar in basic blood pressure, sensory and motor level. The rate of shivering in hydrocortisone group was significantly lower than control group (P=0.000). The rate of shivering in ketamine group was significantly lower than control group (P=0.00). Also the rate of shivering in hydrocortisone group was significantly higher than ketamine group (P=0.004).

Conclusion: Intravenous Hydrocortisone and ketamine are effective in reducing shivering occurring after spinal anesthesia in the cesarean surgery, however ketamine is significantly more effective than hydrocortisone in shivering control.

Keywords: spinal anesthesia; cesarean section; ketamine; Shivering; hydrocortisone

Shivering is one of the unpleasant complications of cesarean section (C-section) in the operating room and has great impact on patient health. Shivering is a rhythmic movement, happening in the arms, legs, neck, and jaw. This is a common complication occurring after general and local anesthesia. The frequency of shivering in general and regional anesthesia is about 40-65% and 45-85% in the C-section, respectively. Shivering is very unpleasant for the patients and can even occasionally increase oxygen consumption rate up to 100-600%. In addition to the creation of discomfort and dissatisfaction in the patients, shivering can increase the recovery time, pain level, as well as intraocular and intracranial pressures [1].

This movement is usually due to a reduction in body temperature, decreased sympathetic tone and release of cytokines during surgery, as well as increased central and peripheral temperature gradient [2]. The decline in body temperature happens as a result of the direct inhibition of thermoregulation caused by anesthesia, loose peripheral vasculature (vasodilation), open body cavities, and cool operating room [3].

C-section is a term used to describe giving birth to a baby through an incision on the abdominal and uterine walls [4]. In the recent years, the use of C-section has become intensely worldwide in many developing and developed countries. Moreover, due to inability to intubate the pregnant women and subsequesnt high risk of aspiration in geneal anesthesia, spinal anesthesia is selected as the method of choice in C-section [5]. The management of patients after C-section is a critical issue due to patient condition, and the shivering caused by this surgery should be managed by using different medications. For this purpose, multiple drugs, including opioids and non-opioids such as tramadol, pethidine, clonidine, ketamine, hydrocortisone, etc., have been used [6-7].

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Ketamine is an intravenous hypnotic drug and antagonist of N-methyl-d-aspartate receptors causing direct stimulation of the sympathetic central nervous system and inhibition of the release of norepinephrine by sympathetic post-ganglionic terminals. Ketamine can cause tachycardia, hypertension, and increased cardiac output; while it seems that ketamine due to aforementioned mechanism, reduce distribution of central heat to peripherals and lead to reduced prevalence of post-spinal anesthesia shivering [8]. On the other hand, hydrocortisone is one of the glucocorticoids that can be useful in the prevention of postoperative shivering, acting through the fat, carbohydrate, protein, and purine metabolism [9].

Furthermore, this complication can cause disturbance in the monitoring function of electrocardiography, blood pressure, as well as arterial oxygen saturation and delay the effective mother-child contact. Therefore, it is important to choose an appropriate drug for the prevention of shivering during spinal anesthesia with minimal side effects on mother and child [7,10].

Shivering is highly prevalent and has unpleasant side effects on the patients. Regarding this and considering its recovery condition, the present study aimed to determine and compare the effects of intravenous hydrocortisone and ketamine on the reduction of shivering occurring after spinal anesthesia in C-section.

Methods

This prospective, double blind, randomized, controlled trial was conducted on 150 patients within the age range of 18-40 years with American Society of Anesthesiology (ASA) [11] grades I and II physical status, who undertook C-section. The patients with following conditions were excluded: High risk pregnancy, multiple-pregnancy, emergency cesarean section, preeclampsia and eclampsia, cardiovascular diseases, pulmonary diseases, history of psychiatric disorders, thyroid disease, type I and II diabetes, history of corticosteroid therapy, hypertension, peptic ulcer, need to transfusion, fever more than 38 degrees centigrade, and contraindication for spinal anesthesia.

Prior to the spinal anesthesia, all patients were supplied with oxygen (6 L/min) through a facemask. Fluid therapy was administered with Ringer's solution (10-15 mL/kg/hr). The spinal anesthesia was performed using disposable Quincke spinal needle (25G) at L3-L4 and L4-L5 intervertebral spaces. The temperature of the operating room was kept at 23°C. The maternal weight was measured and recorded before the surgery.

The patients were randomly divided into three groups based on the type of shivering drugs. Groups A and B received 2 m/kg hydrocortisone and 0.5 mg/kg ketamine, respectively. On the other hand, group C (control) was intravenously supplied with normal saline (0.9%) with the same volume of 3 ml after clamping the umbilical cord within 10-15 sec. In all patients, such parameters as

systolic and diastolic blood pressure, mean arterial pressure, heart rate, arterial blood oxygen saturation, and temperature were determined. These parameters were recorded prior to and after the induction of anesthesia every 1-5 and 5/15 min, respectively; in addition, they were documented every 10 min thereafter.

The level of sedation, hallucination, nausea, vomiting, shivering intensity, and the amount of analgesic consumption were recorded as well. Shivering (as a primary outcome) was classified by a blinded observer during the intraoperative and postoperative periods using the scale validated by Crossley and Mahajan [12]. This scale is rated on a 4-point Likert scale (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). In case the obtained score was higher than two, the patients were intravenously managed with 0.25-0.5 mg/kg pethidine. In addition, for the treatment of nausea and vomiting, 10 mg metoclopramide IV was considered.

Statistical analysis

The statistical analysis was performed using the SPSS (version 16.0; SPSS Inc, Chicago, IL). According to the type of data, they were presented as mean and standard deviation or frequency and percentage. The study groups were compared using the Chi-square test. P-value less than 0.05 was considered statistically significant.

Ethical consideration

The ethica issue of this study was considered and approved by the Ethics Committee of "Hamadan" University of Medical Sciences (ethical code: IR.UMSHA.REC.1394.462). This study was a clinical trial and so registered and approved by Iran regional committee of clinical trials (IRCT2016073110841N6).

Results

A total of 150 patients with the ASA grades I and II candidates for C-section were randomly selected. There was no statistical difference between the study groups regarding the demographic data, including age, gravidity, sensory block level, which was indicative of the proper distribution of the patients and the similarity between the groups in this regard (Table 1).

The independent t-test was applied to compare these parameters between the study groups. According to Table 2, the systolic blood pressure had a higher reduction in the hydrocortisone group, compared to that in the control group. Nevertheless, this reduction was not statistically significant (P=0.113). On the other hand, this value had a higher elevation in the ketamine group as compared to that in the control group; however, this increase was not significant (P=0.197). Nonetheless, there was a significant difference between the hydrocortisone and ketamine groups in terms of the systolic blood pressure (P=0.020).

The diastolic blood pressure was much lower in the hydrocortisone group than that in the normal saline group; however, this difference was not significant (P=0.936). Furthermore, this value was higher in the ketamine group, compared to those in the control and hydrocortisone groups (P=0.048, P=0.028, respectively). In addition, the heart rate was higher in the hydrocortisone group than that in the control group; nonetheless, this difference was not statistically significant (P=0.308). On the contrary, this value was lower in the ketamine group, compared to that in the control group, and this difference was statistically significant (P=0.008).

There was no significant difference between the hydrocortisone and ketamine groups in terms of the heart rate (P=0.159). The mean arterial pressure was lower in the hydrocortisone group than that in the control group;

however, this difference was not significant (P=0.665). The other data and significant differences are displayed in (Table 2).

The Chi-square test was employed to compare the side effects between groups. As shown in Table 3, the incidence of hallucination in the hydrocortisone and ketamine groups was similar to that in the control group (Odds ratio [OR]=1.000, P=1.00). Therefore, the two drugs, namely hydrocortisone and ketamine, had no role in causing hallucination. The incidence of nausea in the hydrocortisone (OR=0.207, P=0.001) and ketamine (OR=0.141, P=0.000) groups was statistically significant in comparison to that in the control group.

According to the odds ratio, the incidence of nausea was lower in the ketamine group than that in the hydrocortisone group; however, this difference was not significant (P=0.538). Both hydrocortisone and ketamine were effective in reducing nausea, and ketamine caused less nausea than hydrocortisone. No difference was observed between the hydrocortisone and ketamine groups in the incidence of nystagmus (P=1.000). Furthermore, the two drugs had no role in the onset of nystagmus.

The intensity of shivering in the hydrocortisone and ketamine groups was significantly lower than that in the control group (P=0.000). In addition, this value was lower in the ketamine group than that in the hydrocortisone group, which as statistically significant (P=0.007). The intensity of shivering between the three groups was compared through the independent sample t-test (Table 3).

Chi-square test was applied to compare the prevalence of these drugs. The rate of ephedrine consumption in the hydrocortisone group was .768 (Odd Ratio=.768) compared to the control group (p=0.548). The ratio of 0.291 was measured between the ketamine group compared to controls (Odd Ratio=0.291) and also significant difference in the administration of ephedrine were observed between ketamine and control groups (P=0.004).

These results indicated that ketamine has a significant effect on the reduction of ephedrine use, but this effect was not detectable in hydrocortisone group. The ratio of consumption of pethidine in the hydrocortisone group compared to the control group was 0.208 (odd ratio=0.298) and there was a significant difference in use of pethidine between the hydrocortisone and control groups (p<0.001). The ratio of pethidine administration in the ketamine group was zero compared to the control group (Odd Ratio=0). Also, there was a significant difference in pethidine consumption between ketamine and control groups (p<0.001). These results indicated that both ketamine and hydrocortisone have a significant role in reducing the use of pethidine. But, regarding the odd ratio value, ketamine was more effective than hydrocortisone in preventing pethidine administration, but there was no significant difference in the rate of administration of the two drugs (p=0.495) (Table 4).

Table 1- Demographic and clinical characteristics of the patients undergoing C-section

Parameters	Ketamine	Hydrocortisone	Normal saline	P-value (one-way ANOVA test)
Age (years)	30.62±5.04	29.46±5.38	29.28±6.82	0.458
Gravidity	2.42±1.01	1.98±0.79	2.12±0.98	0.059
Sensory block (seconds)	4.54±0.73	4.42±0.70	4.24±0.62	0.094
Motor block (seconds)	6.54±0.73	6.46±0.73	6.24±0.62	0.089

Table 2- Comparison of systolic and diastolic blood pressure, heart rate, mean arterial pressure, arterial oxygen saturation, temperature, and sedation points in the three groups under study

	Hydrocortisone group			Ketamine group			Normal saline group (control)		
	Surgery	Recovery	Total mean	Surgery	Recovery	Total mean	Surgery	Recovery	Total mean
Systolic blood pressure (mmHg) (mean±SD)	109.57±7.61	106.18±9.52	107.88±7.13	115.43±10.64	108.65±11.93	112.04±10.07	109.50±11.62	109.33±10.15	109.41±10.06
Diastolic blood pressure (mmHg) (mean±SD)	59.31±7.85	59.51±10.13	59.41±7.49	63.38±9.61	62.53±9.47	62.96±8.43	59.52±9.64	59.01±11.21	59.26±9.91
Heart rate (b/min) (mean±SD)	98.110±13.40	90.53±12.59	94.32±12.07	95.20±9.20	87.42±10.47	91.31±8.97	98.50±12.47	94.82±11.12	96.66±10.67
Mean arterial pressure (mmHg) (mean±SD)	74.70±7.52	73.01±10.26	73.85±7.33	79.76±9.81	76.07±10.50	77.91±9.10	75.02±10.19	74.17±10.18	74.59±9.50
Arterial blood oxygen saturation (%) (mean±SD)	97.27±1.66	97.02±1.74	97.15±1.48	97.68±1.42	97.13±1.58	97.41±1.27	98.06±1.47	97.68±1.86	97.87±1.48
Patient's body temperature (◦C) (mean±SD)	36.60±0.34	36.60±0.36	36.60±0.35	36.55±0.37	36.55±0.36	36.55±0.37	36.53±0.32	36.55±0.30	36.54±0.30
Sedation point (mean±SD)	1.95±0.29	1.90±0.35	1.92±0.29	2.58±0.40	2.25±0.35	2.42±0.31	2.01±0.11	1.99±0.07	2.00±0.07

Table 3- Comparison of the shivering intensity during surgery and recovery in the three study groups

	Hydrocortisone			Ketamine			Normal saline (control)		
	Section	Recovery	Total	Section	Recovery	Total	Section	Recovery	Total
Shivering intensity	0.20	0.26	0.23	0.00	0.04	0.02	2.14	1.70	1.92

Table 4- Comparison of efedrin and petidine in three study groups

Groups		Hydrocortison group	Ketamin	Saline
Variables				
Efedrin	Yes	23	12	26
	No	27	38	24
Petidine	Yes	2	0	12
	No	48	50	38

Discussion

Shivering is an involuntary movement of muscles that can lead to increased production of heat and metabolites [13]. Shivering is a common complication occurring after general or regional anesthesia with an incidence of 5-65% or 40%, respectively [14-15]. This problem not only leads to adverse effects on the patients, but also can be associated with serious complications. These adverse effects include up to 600% increase in oxygen consumption and increased catecholamine release, cardiac output, carbon dioxide emissions, as well as intraocular and intracranial pressure [14].

In addition, shivering raises the metabolic rate, and in severe cases can cause lactic acidosis. This complication can also affect the patient's postoperative monitoring, electrocardiography, and blood pressure. Given the high prevalence of shivering and its unpleasant side effects, this condition should be also given sufficient attention like the other post-operative complications to be prevented [14].

In the present study, a significant difference was observed between the ketamine and control groups regarding the incidence and intensity of shivering. This finding indicates the effectiveness of ketamine in the prevention of shivering and reduction of its intensity. Similarly, in a survey conducted by Dal et al., following the spinal anesthesia, the shivering was significantly lower in the ketamine group, compared to that in the control group (placebo) [13].

They concluded that ketamine was effective in preventing and reducing the severity of shivering after spinal anesthesia [13]. In line with the results of the present study, in a study carried out by by Abdelrahman et al., the shivering during spinal anesthesia in the ketamine group was significantly lower than that in the other groups [16]. Nevertheless, Elmawgood et al. reported the reduction of the shivering intensity in the hydrocortisone and ketamine groups. They demonstrated that hydrocortisone was a better alternative to pethidine, compared to ketamine [17].

In a double blind randomized clinical trial, Manouchehrian and colleagues, they studied 70 obstetric patients with ASA class I or II who reported shivering after spinal anesthesia with bupivacaine. These patients were of two groups receiving tramadol, or meperidine. They reported that shivering ceased after 2.57±2.26 and 6.24±4.76 minutes in group tramadol and meperidine groups, respectively. Moreover, they demonstrated significant different pre- and post-injection heart rate, respiratory rate and arterial oxygen saturation [18].

In a study conducted by Pazoki et al., the shivering rates of C-section in ketamine (0.5 mg per kg) and pethidine (3.0 mg per kg) groups were 81.77% and 58.7%, respectively. In the mentioned study, the pethidine group had lower shivering incidence and severity, compared to the ketamine group. They revealed the better efficacy of pethidine, compared to ketamine; however, they pointed out the limited use of pethidine due to its effect on the central nervous system, respiratory depression, as well as exacerbation of nausea and vomiting [19].

In the current study, the hydrocortisone and ketamine groups were comparable regarding the incidence of hallucination. The frequency of nystagmus was zero in the hydrocortisone and control groups and 2% in the ketamine group. The ketamine and hydrocortisone groups had a significant difference with the control group in terms of the nausea occurrence. Therefore, it can be concluded that these two drugs reduced the incidence of nausea.

Likewise, the incidence risk of nausea in the hydrocortisone group was one to 46 times as much as that in the ketamine group. On the other hand, age, gravidity, sensory and motor block levels, blood pressure, heart rate, arterial blood pressure, and blood oxygen saturation of arterial blood were compared between the three groups. However, there was no significant difference between the groups regarding these variables.

Conclusion

In the present study, we investigated the value of intravenous hydrocortisone and ketamine in reducing shivering occurring after spinal anesthesia in the cesarean surgery. As the results of this study indicated, there was a significant difference between the effects of hydrocortisone, ketamine, and normal saline on reducing the incidence and intensity of shivering.

Ketamine was more effective and safer than hydrocortisone in preventing and controlling shivering post-spinal anesthesia. To obtain more accurate results, it is recommended to conduct the same study with larger sample size. Future studies can also compare the different medications, such as pethidine, used in the treatment post-operation shivering or investigate the concurrent use of medications with fewer side effects in this regard.

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