ORIGINAL ARTICLE

The evaluation of effects two different doses of hydrocortisone on the intensity of perioperative shivering in elective surgery under spinal anesthesia: A double-blind randomized controlled trial study

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Background: Post- and intra-operative shivering is one of the most complications of spinal anesthesia so recommend a suitable drug with at least complications for prevention and control of postoperative shivering. This current study aimed to compare the preventive effect of hydrocortisone on intra- and post-operative shivering in patients undergoing surgery with spinal anesthesia. **Materials and Methods:** In a clinical trial study, ninety patients who candidate for surgery with spinal anesthesia were selected and randomly divided into three groups. The first and second groups were received 1 mg/kg and 2 mg/kg hydrocortisone, respectively, and the third group was received normal saline, and postoperative shivering was compared between the three groups. **Results:** The investigation of the incidence of inter- and post-operative shivering in patients in the three groups revealed that within the study period, 31 patients suffered from shivering among which 9, 5, and 17 cases were in 1 mg/kg hydrocortisone group, 2 mg/kg hydrocortisone group, and placebo group, respectively, and according to the Chi-square test, the difference among the three groups was significant ($P = 0.004$). **Conclusion:** According to the obtained results, the overall conclusion of the study is that using hydrocortisone at least with the dose of 1 mg/kg as a preventive drug reduced the incidence of intra- and post-operative shivering with spinal anesthesia.

Key words: Hydrocortisone, postoperative shivering, spinal anesthesia

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INTRODUCTION

The reactions of the immune system to temperature loss include activities of skin vasomotor, thermogenesis, sweating, and shivering, which is indeed the last immune mechanism, is produced in associated with muscular activities with a frequency of 4–8 Hz, and reinforces the temperature metabolism to 600% compared to the base level.[1-6] Some processes can lead to central hypothermia. General and regional anesthesia are the same and in both the distribution of heat is from the center to the initial process environment that in spinal and epidural, the process does not reach to the balance because the environmental vasoconstriction is lost and shivering and low temperature are produced by a small volume of muscles above the block level.[7,8] Shivering occurs in 50% of patients with the core temperature of 35.5°C and in 90% of cases with the core temperature of 34.5°C.[9] Postoperative shivering is a common complication of spinal anesthesia which has different incidence in various studies and has been expressed up to 40–56.7% depending on the type and consumed drug.[10,11] To treatment and prevent postoperative shivering, different drugs can be used that among from opioid drugs, pethidine, fentanyl, and tramadol and out of nonopioid drugs, dexamethasone, ondansetron, clonidine, pentazocine, ketamine, and magnesium sulfate can be mentioned.[7] Hydrocortisone is corticosteroids similar to the natural hormone produced by the adrenal gland that causes to remove inflammation (sweating, heat, redness, and pain)

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and its intravenous injection controls postoperative shivering with general anesthesia. The mechanism of hydrocortisone effect is applied through anti-inflammatory mechanism, core temperature gradient, and skin.[11] Since it is tried to recommend a suitable drug with at least side complications for the prevention and control of postoperative shivering, most conducted studies emphasize on the treatment of shivering, and prophylaxis has been studied less; on the other hand, until now, such study has not been conducted on people with spinal anesthesia and given the prevalence and increase of surgeries with spinal anesthesia, the current study aimed to compare the preventive effect of hydrocortisone on the incidence and intensity of shivering in patients undergoing surgery with spinal anesthesia.

MATERIALS AND METHODS

This is a randomized, double-blind clinical trial study conducted in an educational hospital (Kashani Hospital) of Isfahan University of Medical Sciences in Isfahan, Iran on 2013–2014. Patients were selected from those who were referred for elective orthopedic operation. Inclusion criteria were the age range of 18–60-year-old, patients undergoing lower extremity orthopedic operation with spinal anesthesia (knee arthroplasty, hip arthroplasty, femoral fracture…) American Society of Anesthesiologists physical status I–II,[2] no having hypothyroidism, hyperthyroidism, cardiopulmonary diseases, psychological disorders, no alcohol and drugs, lack of using vasodilator or drugs affecting the body's temperature settings, and patient's consent to participate in the study. It was also decided that patients requiring blood transfusions during operation, with the base temperature more than 38°C and <36°C or change in the techniques of anesthesia were excluded from the study.

We assumed the incidence of shivering in the case and control group 10% and 40%, respectively, due to previous studies[5,6] with respect to α =0.05 and β =0.2. We calculated 29 patients in each group as the sample size.

The method was in a way that after the approval of proposal and adoption of consent of Medical Ethics Committee, ninety patients with inclusion criteria were selected and divided into three 30-case equal groups by using random allocation software. Exactly, 1 mg/kg hydrocortisone + 2 cc normal saline, 2 mg/kg hydrocortisone + 2 cc normal saline, and the same normal saline (2 cc) were injected to patients in M, P, and C (control) groups, respectively. The volume of each syringe was maximally 2 cc. The syringe was similar with respect to the shape and color. The study drugs were administered 10 min before spinal anesthesia. Fluid therapy and anesthesia method were the same in all three groups. All patients were NPO for 8 h and during this time, the fluid therapy was done according to 4-2-1 formula of serum (4 ml/kg/h for the first 10 kg of body weight, 2 ml/kg/h for the second 10 kg of body weight, and 1 ml/kg/h for the third 10 kg of body weight) and then intravenous midazolam 0.05 mg/kg was injected to all patients 5 min before the onset of anesthesia. Before the onset of anesthesia, 10 cc/kg of Ringer Lactate was injected to all patients within 30 min, and patients were routinely monitored including pulse oximetry, automatic control blood pressure, central and peripheral temperature, and 3-lead electrocardiogram. Oxygen was given to the patients via a face mask as 5 l/min until the end of the operation. Spinal anesthesia was performed at L4–L5 or L3–L4 of the spinal needle of 24-gauge, midline, and at sitting position. After leaving transparent and cerebrospinal fluid, 2.5 cc bupivacaine of 0.5% was injected within 10 s for the anesthesia. Then, the patient was immediately placed at supine position and the patient's head was put 15–20°C above the horizon and no analgesic drug was injected into the patient. The level of sensory block was determined using bilateral pin-prick test in midclavicular line. When the level of block reached to the desired level, the lower limb operation was started. The temperature of the operating room had been maintained at 21–22° and nonoperative parts were covered by a layer of cloth. After the operation, the whole parts of the body were covered by a layer of cotton blanket and then, the patients were transferred to the recovery room. The temperature of recovery room was similar for all patients, and no heating device was individually used for patients. The baseline level of the central and peripheral temperatures was measured. Moreover, immediately before anesthesia (on operating table), immediately after the anesthesia, 5 min after anesthesia, before and after drug injection, every 10 min during the operation, at the onset of entrance to the recovery room, and after recovery at 10, 20, 30, 40, 50, and 60 min, central and peripheral temperatures were measured by tympanic thermometer (OMRON Medizintechnik GmbH, Mannheim, Germany) and an axillary thermometer (BMEcenter.ir, Iran). If the peripheral temperature was below 36°C, hypothermia would be considered. In hypothermic patients, if they had shivering with grade = 4. Meperidine 0.4 mg/kg was administered. To ensure that the study was double-blinded (both patients and physician who recorded the data), drugs were encoded by an operating room staff. All patients received postoperative routine nursing care and in all cases, basic rate of parameters including blood pressure, respiratory rate, heart rate, shivering score (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; and 4, shivering involving the whole body), pain score, drowsiness score, and vomiting was recorded. The incidence and intensity of shivering was evaluated during intra- and post-operative periods. Hypotension (low systolic

pressure below 100 mmHg or 25% reduction in systolic blood pressure compared to patients' baseline pressure) was treated by intravenous Ringer lactate serum and 5 mg intravenous ephedrine. If the heart rate drops below 55 rates, the patients would receive 0.01 mg intravenous atropine per kg of body weight and if necessary, it would be repeated up to a maximum dose of 0.04 mg per kg of body weight. You should declare that as the ephedrine and atropine could alter the body temperature these nausea and vomiting were treated by 10 mg intravenous metoclopramide. All the received drugs, the number of frequency, and their dose were recorded. If patients had shivering Grade 4, meperidine 0.4 mg/kg was administered. The degree of sedation was evaluated as 1, fully awake and oriented; 2, drowsy; 3, eyes closed but rousable to command; 4, eyes closed but rousable to mild physical stimulation; and 5, eyes closed but unrousable to mild physical stimulation. The study data were entered into the computer after collecting and were analyzed using SPSS software version 20. Chi-square test (for comparison of qualitative data between groups), one-way analysis of variance (ANOVA) (for comparison of quantitative date between groups), and repeated measure ANOVA (for comparison of trend of quantities date between groups) with repeated observations, and median test were run to analyze the data.

RESULTS

In this study, ninety patients undergoing surgery with spinal anesthesia were investigated and assessed that during the study, no patient excluded from the study due to the incidence of unwanted complications such as hemodynamic and in the anesthesia method and all ninety patients were present in the study until the end of the study. In Table 1, the distribution of demographic and general variables of patients in the three groups has been shown.

The investigation of the incidence of shivering in patients in the three groups revealed that within the study period, 31 patients suffered from shivering among which 9, 5, and 17 cases were in the 1 mg/kg hydrocortisone group, 2 mg/kg hydrocortisone group, and placebo group, respectively, and according to the Chi-square test, the difference among the three groups was significant ($P = 0.004$). Moreover, the intensity of shivering had no significant difference among the three groups ($P = 0.046$). The distribution of the frequency of the incidence and intensity of shivering in the three groups are given in Table 2. Comparing the incidence and intensity of shivering in binary groups indicated that the two groups of hydrocortisone of 1 mg/kg and 2 mg/kg had no significant difference in terms of the incidence and intensity of shivering ($P = 0.23$ and $P = 0.2$, respectively), while the incidence and intensity of shivering had a significant difference between the two groups of hydrocortisone of 1 mg/kg and placebo group ($P = 0.039$ and $P = 0.018$, respectively). Moreover, the incidence and intensity of shivering had a significant difference between the two groups of hydrocortisone of 2 mg/kg and placebo group ($P = 0.0001$ and $P = 0.001$, respectively). The score of sedation in patients in the three groups had no significant difference from the onset of the induction of anesthesia to 60 min of recovery in none of the studied periods. Within the study period, no patient suffered from drug allergy, whereas out of hydrocortisone group 2 mg/kg, one patient suffered from bradycardia and one patient suffered from hypotension. One of the

Table 1: Distribution of demographic and general variables in three study groups

Variables	Groups			*P**
	1 mg/kg hydrocortisone	2 mg/kg hydrocortisone	Control	
Age	39.8±10.3	40.8±13.4	41.5±13.5	0.87
Sex				
Male	24 (80)	25 (83.3)	23 (76.7)	0.81
Female	6 (20)	5 (16.7)	7 (23.3)	
ASA				
I	22 (73.3)	25 (83.3)	23 (76.7)	0.64
II	8 (26.7)	5 (16.7)	7 (23.3)	
Weight (kg)	70.7±3.14	72.2±8.1	73.5±4.4	0.16
Height (cm)	165.5±8.9	166.6±9	168.5±8.5	0.43
Surgical time (min)	106.9±21.7	108.6±23.9	105.3±23.4	0.16
Recovery time (min)	58.6±7.5	57.4±8	57.8±7.7	0.84
Maximum block				
T5	3 (10)	2 (6.7)	2 (6.7)	0.99**
T6	6 (20)	10 (33.3)	8 (26.7)	
T7	6 (20)	5 (16.7)	6 (20)	
T8	6 (20)	5 (16.7)	6 (20)	
T9	6 (20)	6 (20)	5 (16.7)	
T10	3 (10)	2 (6.7)	3 (10)	

*Based on one-way ANOVA, **Based on Chi-square test. Data are presented as mean±SD, or *n* (%) where applicable. ASA = American Society of Anesthesiologists; SD = Standard deviation; ANOVA = Analysis of variance

Table 2: Distribution of the frequency of the incidence and intensity of shivering in the three groups

Variables	Groups			*P*
	1 mg/kg hydrocortisone	2 mg/kg hydrocortisone	Control	
Incidence of shivering				
No	21 (70)	25 (83.3)	17 (56.7)	0.004*
Yes	9 (30)	5 (16.7)	13 (43.3)	
Intensity of shivering				
Grade 0	21 (70)	25 (83.3)	13 (43.3)	0.046*
Grade 1	4 (13.3)	3 (10.0)	4 (13.3)	
Grade 2	5 (16.7)	2 (6.7)	10 (33.3)	
Grade 3	0 (0)	0 (0)	2 (6.7)	
Grade 4	0 (0)	0 (0)	1 (3.3)	

*Based on Chi-square test. Data are presented as *n* (%)

hydrocortisone 1 mg/kg group and 1 case of hydrocortisone 2 mg/kg group suffered from postoperative nausea and vomiting, while no significant difference was observed among the three groups ($P = 0.6$).

Figures 1 and 2 shown the mean central and peripheral temperatures in the three studied groups from the onset of the operation until 60 min of recovery. According to the one-way ANOVA test, the mean central and peripheral temperatures had no significant difference between the three groups in any of the study periods. Furthermore, repeated measure ANOVA indicated that the process of changes in the central and peripheral temperatures had no significant difference among the three groups ($P = 0.64$ and $P = 0.31$, respectively). The lowest core and peripheral temperatures were 35.75°C and 35.70°C, respectively, which occurred 90 min after spinal anesthesia. Figures 3 and 4 shown the Mean blood pressure from 0 to 60 min recovery in the three groups ($P = 0.82$) and Mean heart rate from 0 to 60 min recovery in the three groups ($P = 0.77$). Repeated measure ANOVA indicated that had no significant difference among the three groups ($P = 0.82$ and $P = 0.77$).

DISCUSSION

Shivering is the involuntary movements of one or several muscle groups and generally occurs in the initial phase of recovery after anesthesia. The incidence of this condition varies between 6.3% and 66% depending on the type and duration of operation, anesthesia technique, and patient's age and gender[1-10] and has minimum incidence to 40% in patients operation with spinal anesthesia.[10,11] With regard to the incidence and clinical significance, shivering has been known as the sixth major problem among from 33 clinical cases with the low rate of morbidity in clinical anesthesiology.[12] Of postoperative complications, the increase in oxygen consumption at the rate of 200–500%, production of CO_2, heart rate and stroke volume, and blood pressure can be pointed out that their suppression reduces the metabolic need and myocardial function.[13-18] Other complications include the increase of intraocular pressure and intracranial pressure, creation of problem in monitoring the patient, and interference with the surgical cares, especially in cases requiring immobilization, for example, secular or nerve anastomosis.[14-16] According to the results of our study, three studied groups had no significant difference in terms of demographic variables and operation features such as duration of operation and anesthesia and sensory block level and no confounding effect of the above-mentioned factors was observed on the incidence and intensity of shivering and therefore it may pertain to the fact that the difference in the incidence of postoperative shivering is related to the type and rate of preventive consuming drug. According to the results of our study, the incidence of shivering in the group receiving hydrocortisone including a dose of 1 mg/kg or 2 mg/kg was considerably and significantly less

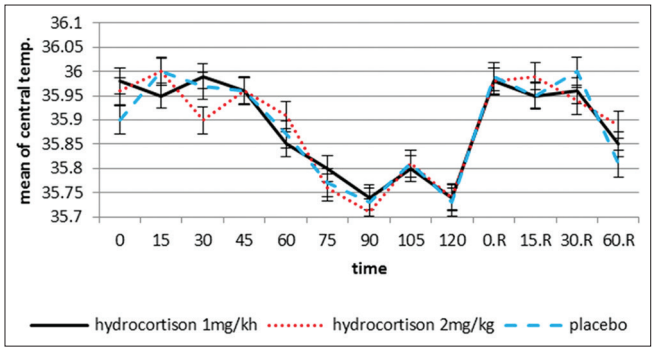

Figure 1: Mean central temperature from 0 to 60 min recovery in the three groups ($P = 0.64$)

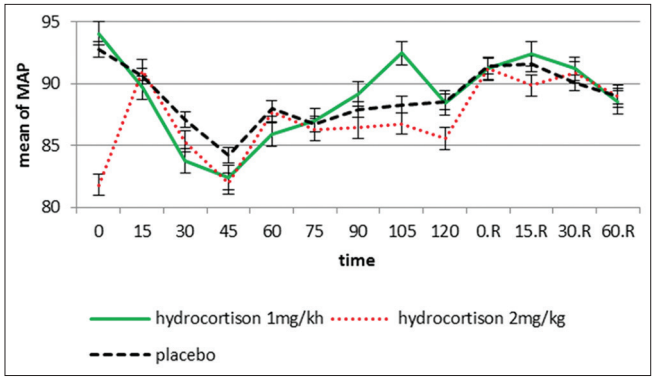

Figure 3: Mean blood pressure from 0 to 60 min recovery in the three groups ($P = 0.82$)

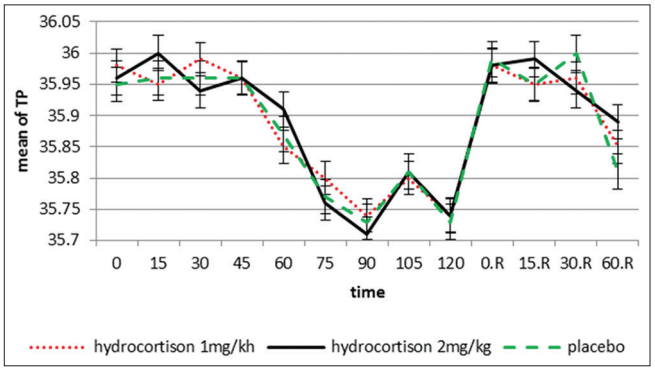

Figure 2: Mean peripheral temperature from 0 to 60 min recovery in the three groups ($P = 0.31$)

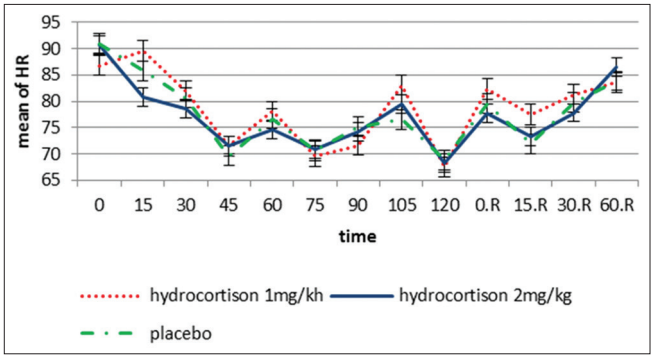

Figure 4: Mean heart rate from 0 to 60 min recovery in the three groups ($P = 0.77$)

than the control group. On the other hand, patients receiving hydrocortisone had lower shivering; however, no significant difference was observed between the two doses of the drug. A number of pharmaceutical interventions for the treatment and prophylaxis of shivering including clonidine, ketamine, doxapram, tramadol, pethidine, and other opioids have so far been examined (14, 17, and 18). In the study by Pawar *et al.*, in 2011, the effectiveness of hydrocortisone for the prevention of shivering was approved so that the incidence of shivering was 32% in patients receiving hydrocortisone and 82% in the control group.[18] In their study, Yousef and Johnson showed that using hydrocortisone as a preventive drug reduced the incidence of hypothermia; consequently, it reduced the incidence of shivering in patients undergoing an operation.[19] Therefore, according to the obtained results, the overall conclusion of the study is that using hydrocortisone at least with the dose of 1 mg/kg as a preventive drug reduced the incidence of shivering with spinal anesthesia. However, because limitations of our study such as small sample size, to highly ensure the effect of dose-response of the drug, further studies are recommended.

CONCLUSION

According to this study using hydrocortisone at least with the dose of 1 mg/kg as a preventive drug reduced the incidence of intra- and post-operative shivering with spinal anesthesia.

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Conflicts of interest

The authors have no conflicts of interest.

AUTHORS' CONTRIBUTION

MRS has planned the study and finalized it; FK, AH, MN, HS, and MRS did the statistical analysis and prepared the first version of the manuscript for publish. All authors read and approved the final manuscript.

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