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Comparative Randomized Controlled Blind Study of the Anti-Shivering Effect of Hydrocortisone, Granisetron and Meperidine in Post-Spinal Anesthesia in Patients Undergoing Cesarean Section

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ABSTRACT

Background: it was observed that a considerable proportion of patients undergoing surgery experience intraoperative and postoperative hypothermia and it was found that misregulation of body temperature due to anesthesia as well as the cold temperature of the operation room were the main cause.

Purpose: to compare the anti-shivering effect of meperidine, hydrocortisone and granisetron after spinal anesthesia during elective cesarean section. **Patients and Methods:** this study presents a placebo-controlled prospective randomized blind study. Included patients were randomly (using computer generated randomization table) allocated into four equal groups each group consists of 28 patients. **Results:** in our study, age, sex, and ASA grade distribution of patients were nearly identical in the four groups. Furthermore, the duration of surgery and amount of irrigation fluid used in the four different groups were also similar. We did not observe a change in temperature gradient between the four groups. A study with a more prolonged duration of postoperative temperature monitoring is needed to note if core-periphery temperature changes occur with passage of time. **Conclusion:** the results indicate that IV granisetron 40 µg/kg was effective as IV meperidine 0.4 mg/kg and both are slightly effective than IV hydrocortisone 2 mg/kg in reducing the incidence and intensity of shivering during spinal anesthesia compared to control group.

Keywords: Anti-shivering - Hydrocortisone - Granisetron – Meperidine - Cesarean Section - Post-spinal Anesthesia

INTRODUCTION

Shivering is a common problem encountered by an anesthesiologist during intraoperative as well as in postoperative period. Shivering occurs during both general anesthesia and regional anesthesia. Incidence of shivering is up to 33% in the patients undergoing surgery under regional anesthesia and up to 56–66% under general anesthesia. A number of factors including age, duration of surgery, temperature of the operating room, type of regional anesthesia (spinal or epidural), and infusion solution are risk factors for hypothermia and shivering [(1)].

Perioperative shivering causes patient discomfort because of severe muscle movements, it also induces elevated blood pressure and tachycardia, aggravates wound pain by stretching incision, increase intra ocular pressure and increase intracranial pressure. Shivering may also increase tissue oxygen demand by as much as 150% and accompanied by increase in minute ventilation and cardiac output to maintain aerobic metabolism this eventually leads to increased oxygen consumption, increased carbon dioxide synthesis that results in an increased pulmonary ventilation capacity and cardiac workload, and an increase in the metabolic rate by up to 400%. Shivering may also interfere with the monitoring of patients by causing artifacts of electrocardiography, blood pressure and pulse oximetry [(2)]. Neuraxial anesthetic techniques are the most commonly indicated for cesarean section due to lower rates of maternal morbidity and mortality and less neonatal depression compared with general anesthesia. The combination of lipophilic opioids with hyperbaric bupivacaine during spinal anesthesia for cesarean section provides reduced latency, longer duration, and better quality of anesthesia without increasing the incidence of neonatal depression. Another known effect of opioids is the prevention and treatment of postoperative shivering [(3)].

Various methods have been used to prevent and treat shivering in patients who receive spinal anesthesia, one of these, meperidine appears to be the most effective treatment agent for perioperative shivering, although meperidine is the best studied drug in the treatment of post anesthetic shivering, other drugs like tramadol, hydrochloride, ketamine and magnesium sulfate infusion were used [(4)].

AIM OF THE WORK

Compare the anti-shivering effect of meperidine, hydrocortisone and granisetron after spinal anesthesia during elective cesarean section.

PATIENTS AND METHODS

After approval of Ethics Committee and obtaining written informed consent from eligible parturients, the study was conducted on 112 full term pregnant patients classified according to American Society of Anaesthesiologist (ASA)

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classification as (ASA) I and II, scheduled for elective cesarean section.

The exclusion criteria was emergency cases, multiple pregnancies, preterm pregnancies, patients with uncontrolled diabetes mellitus and/or hypertension including preeclampsia and eclampsia, cases with obstetric complications such as antepartum hemorrhage and cases contraindicated for regional anesthesia or refusing a regional technique.

This study presents a placebo-controlled prospective randomized blind study. Included patients were randomly (using computer generated randomization table) allocated into four equal groups each group consists of 28 patients:

- **Group S,** control group, received placebo of 3 ml of normal saline.
- **Group H** received 2 mg/kg IV hydrocortisone.
- **Group G** received 40 mcg/kg IV granisetron.
- **Group P** received 0.4 mg/kg IV meperidine.

All these drugs were given after delivery of the fetus in the operating room.

Preoperative evaluation

All patients in this study were subjected to full history taking, clinical examination and routine laboratory investigations, including complete blood count (CBC), random blood glucose (RBG), liver function tests (LFT), kidney function tests (KFT), prothrombin time (PT) and partial thromboplastin time (PTT). Presence of any of exclusion criteria will be determined.

Maternal measurements

Automatic readings of heart rate, mean arterial blood pressure, respiratory rate, and saturation using pulse oximetry were obtained. Recording of obtained measures were done at baseline and every 15 minutes, starting half an hour before induction of regional anesthesia extending to 3 hours postoperatively.

Shivering was graded using a 5-item scale. The possible side effects of the study drug (i.e., nausea, vomiting, hypotension, tachycardia, dry mouth, and dizziness) were recorded. In the recovery room also all patients were monitored, received oxygen through facemask and were covered with woolen blanket. Patient with nausea and vomiting were treated with metoclopramide 10 mg. Tramadol 1 mg/kg was kept as rescue medication to treat the shivering more than Grade II on 5-item scale as shown in table below:

Table (1): Grades of Shivering [5]

5-item scale of assessing shivering	
Grade 0	No shivering
Grade 1	Piloerection, peripheral vasoconstriction or peripheral cyanosis without other cause
Grade 2	Visible muscular activity confined to one muscle group
Grade 3	Visible muscular activity in more than one muscle group
Grade 4	Gross muscular activity involving the entire body

RESULTS

In our study, age, sex, and ASA grade distribution of patients were nearly identical in the four groups. Furthermore, the duration of surgery and amount of irrigation fluid used in the four different groups were also similar. We did not observe a change in temperature gradient between the four groups. A study with a more prolonged duration of postoperative temperature monitoring is needed to note if core-periphery temperature changes occur with passage of time. In our study, there was no statistically significant difference found between the studied groups regarding age while there was statistically significant difference between them regarding height, weight and BMI. In our study, incidence of hypotension was more noted in Group G and Group H compared to the Group P and nausea and vomiting was more in Group P compared to the Group G and the Group H.

Table (2): Comparison between the studied groups regarding demographic data of the studied patients

Demographic data		**S group**	**H group**	**G group**	**P group**	**Test value•**	**P-value**
		No. = 28	**No. = 28**	**No. = 28**	**No. = 28**		
Age (years)	Mean ± SD	27.54 ± 6.00	26.64 ± 5.81	25.32 ± 5.07	25.50 ± 5.20	0.985	0.403
Height (cm)	Mean ± SD	158.96 ± 5.29	158.21 ± 4.35	160.25 ± 4.97	163.29 ± 4.21	6.264	0.001
Weight (kg)	Mean ± SD	73.61 ± 6.51	77.32 ± 4.87	78.25 ± 5.03	76.79 ± 4.97	3.919	0.011
BMI (kg/m2)	Mean ± SD	29.10 ± 1.82	30.87 ± 1.21	30.49 ± 1.80	28.78 ± 1.19	12.454	0.001

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: One Way ANOVA test

The previous table shows that there was no statistically significant difference found between the studied groups regarding age while the table also shows that there was statistically significant difference between them regarding height, weight and BMI.

Table (3): Comparison between the studied groups regarding hemodynamic data of the studied patients

Hemodynamic		S group No. = 28	H group No. = 28	G group No. = 28	P group No. = 28	est lue	-value
Systolic BP (mmHg)	Mean ± SD	113.57 ± 9.99	113.57 ± 8.99	113.03 ± 9.99	112.85 ± 9.99	036	0.991
Diastolic BP (mmHg)	Mean ± SD	67.50 ± 7.14	69.28 ± 7.29	68.21 ± 6.8	68.21 ± 7.35	296	0.828
HR (beat/m)	Mean ± SD	73.14 ± 7.01	73.46 ± 6.71	73.42 ± 6.67	73.78 ± 6.29	044	0.988
RR (breath/m)	Mean ± SD	15.50 ± 2.52	15.64 ± 2.54	15.39 ± 2.51	15.71 ± 2.46	092	0.964
SpO_2	Mean ± SD	97.64 ± 1.13	97.64 ± 1.13	97.64 ± 1.13	97.64 ± 1.13	000	1.000

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant,•: One Way ANOVA test

The previous table shows that there was no statistically significant difference found between the studied groups regarding hemodynamic data.

Table (4): Comparison between the studied groups regarding grades of shivering by time

Grades of shivering by time (minutes)		**S group**		**H group**		**G group**		**P group**		**Test value***	**P-value**
		No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
Baseline	Grade 0	28	100.0%	28	100.0%	28	100.0%	28	100.0%	NA	NA
15 min	Grade 0	28	100.0%	28	100.0%	28	100.0%	28	100.0%	NA	NA
30 min	Grade 0	11	39.3%	21	75.0%	22	78.6%	22	78.6%	24.526	0.017
	Grade 1	3	10.7%	3	10.7%	3	10.7%	3	10.7%		
	Grade 2	3	10.7%	2	7.1%	2	7.1%	2	7.1%		
	Grade 3	6	21.4%	1	3.6%	1	3.6%	1	3.6%		
	Grade 4	5	17.9%	1	3.6%	0	0.0%	0	0.0%		
45 min	Grade 0	11	39.3%	21	75.0%	22	78.6%	22	78.6%	24.526	0.017
	Grade 1	3	10.7%	3	10.7%	3	10.7%	3	10.7%		
	Grade 2	3	10.7%	2	7.1%	2	7.1%	2	7.1%		
	Grade 3	6	21.4%	1	3.6%	1	3.6%	1	3.6%		
	Grade 4	5	17.9%	1	3.6%	0	0.0%	0	0.0%		
60 min	Grade 0	11	39.3%	21	75.0%	22	78.6%	22	78.6%	24.526	0.017
	Grade 1	3	10.7%	3	10.7%	3	10.7%	3	10.7%		
	Grade 2	3	10.7%	2	7.1%	2	7.1%	2	7.1%		
	Grade 3	6	21.4%	1	3.6%	1	3.6%	1	3.6%		
	Grade 4	5	17.9%	1	3.6%	0	0.0%	0	0.0%		
75 min	Grade 0	15	53.6%	22	78.6%	22	78.6%	24	85.7%	18.253	0.108
	Grade 1	3	10.7%	3	10.7%	3	10.7%	3	10.7%		
	Grade 2	3	10.7%	2	7.1%	2	7.1%	1	3.6%		
	Grade 3	4	14.3%	1	3.6%	1	3.6%	0	0.0%		
	Grade 4	3	10.7%	0	0.0%	0	0.0%	0	0.0%		
90 min	Grade 0	24	85.7%	27	96.4%	23	82.1%	25	89.3%	8.242	0.510
	Grade 1	2	7.1%	1	3.6%	3	10.7%	3	10.7%		
	Grade 2	1	3.6%	0	0.0%	2	7.1%	0	0.0%		
	Grade 3	1	3.6%	0	0.0%	0	0.0%	0	0.0%		
105 min	Grade 0	28	100.0%	28	100.0%	28	100.0%	27	96.4%	3.027	0.387
	Grade 1	0	0.0%	0	0.0%	0	0.0%	1	3.6%		
120 min	Grade 0	28	100.0%	28	100.0%	28	100.0%	28	100.0%	NA	NA
135 min	Grade 0	28	100.0%	28	100.0%	28	100.0%	28	100.0%	NA	NA
150 min	Grade 0	28	100.0%	28	100.0%	28	100.0%	28	100.0%	NA	NA
165 min	Grade 0	28	100.0%	28	100.0%	28	100.0%	28	100.0%	NA	NA
180 min	Grade 0	28	100.0%	28	100.0%	28	100.0%	28	100.0%	NA	NA

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test

The previous table shows that there was statistically significant difference found between S group and the other three studied groups regarding shivering at 30, 45 and 60 min while there was no statistically significant difference between the studied groups at the other times of measurement.

The previous table shows that the S group was experienced high grades of shivering than the other three studied groups at 30, 45 and 60 min while there was no statistically significant difference between the studied groups at the other times of measurement.

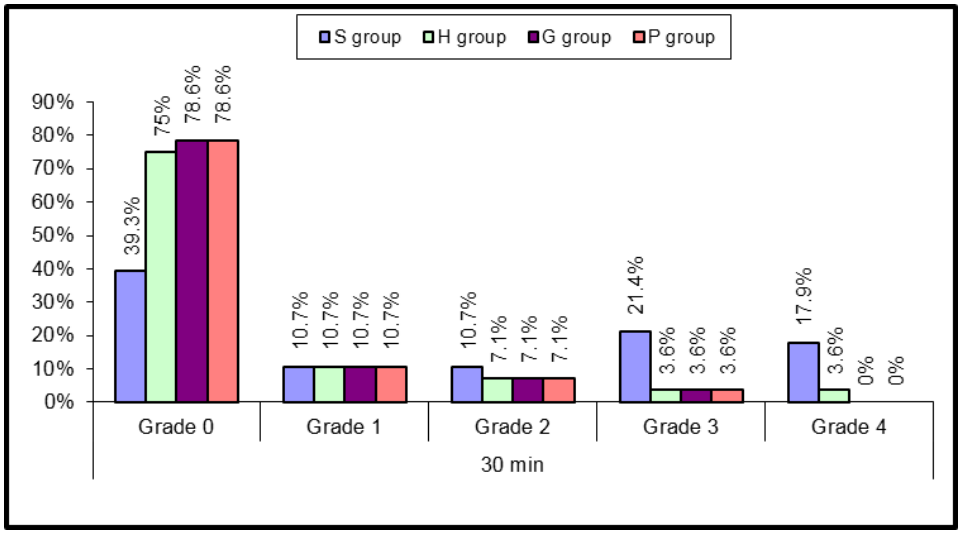

Figure (1): Comparison between the studied groups regarding grades of shivering by 30 min.

Table (5): Comparison between the studied groups regarding complications

Complications		S group		H group		G group		P group		Test value*	P-value
		No.	%	No.	%	No.	%	No.	%		
Nausea	No	12	42.9%	17	60.7%	22	78.6%	15	53.6%	7.821	0.050
	Yes	16	57.1%	11	39.3%	6	21.4%	13	46.4%		
Vomiting	No	13	46.4%	19	67.9%	25	89.3%	8	28.6%	23.866	0.001
	Yes	15	53.6%	9	32.1%	3	10.7%	20	71.4%		
Hypotension	No	9	32.1%	10	35.7%	10	35.7%	15	53.6%	3.294	0.348
	Yes	19	67.9%	18	64.3%	18	64.3%	13	46.4%		
Tachycardia	No	15	53.6%	16	57.1%	16	57.1%	16	57.1%	0.109	0.991
	Yes	13	46.4%	12	42.9%	12	42.9%	12	42.9%		
Dry mouth	No	21	75.0%	21	75.0%	21	75.0%	21	75.0%	0.000	1.000
	Yes	7	25.0%	7	25.0%	7	25.0%	7	25.0%		
Dizziness	No	27	96.4%	27	96.4%	27	96.4%	27	96.4%	0.000	1.000
	Yes	1	3.6%	1	3.6%	1	3.6%	1	3.6%		

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test

Table (5) shows that there was statistically significant difference between the studied groups regarding incidence of nausea, which was higher in S group than the other studied groups while no statistically significant difference found between the studied groups regarding other complications.

Table (5) also shows that there was highly statistically significant difference between the studied groups regarding incidence of vomiting which was higher in P group than the other studied groups while no statistically significant difference found between the studied groups regarding other complications.

DISCUSSION

Shivering is not only distressing to patients, but can lead to physiological changes such as increased tissue oxygen consumption and carbon dioxide production, resulting in raised minute ventilation and cardiac output. It also interferes with patient monitoring and with the mother's ability to hold her baby in an obstetric setting [(1)].

There are three reasons for developing hypothermia under spinal anesthesia. First, spinal anesthesia leads to an internal redistribution of heat from the core to the peripheral compartment. Redistribution of core temperature during regional

anesthesia is typically restricted to the lower extremity. Second, with loss of thermoregulatory vasoconstriction below the level of the spinal blockade, there is increased heat loss from body surfaces of the patient. Last, there is altered thermoregulation under spinal anesthesia characterized by a 0.5°C decrease in vasoconstriction and shivering thresholds and a slight increase in the sweating threshold [6].

In our study, our results indicate that IV granisetron 40 µg/kg was effective as i.v. meperidine 0.4 mg/kg and both are slightly effective than i.v. hydrocortisone 2 mg/kg in reducing the incidence and intensity of shivering during spinal anaesthesia compared to control group.

In our study, the incidence of shivering in hydrocortisone group was 25% compared to 60.7% in control group. Our results are in agreement with the studies done by **Pawar *et al.*** [4] who reported that hydrocortisone (1–2 mg/kg i.v.) was effective in prevention of postoperative shivering after knee arthroscopy under general anesthesia where the incidence of shivering was 20% and 32% with hydrocortisone 2 mg/kg and 1 mg/kg respectively compared to 60% in control group.

The same was recorded in the findings of ***Mohamed et al.*** [7] who showed that incidence of shivering were significantly reduced in ketamine and Hydrocortisone groups being 20% and 23.3% respectively compared to S group ($p < 0.05$). Patients received meperidine to control shivering were significantly low in Groups K and H compared to group S ($p < 0.05$), with no difference between Groups K and H. This study was done on female patients undergoing posterior vaginal repair surgeries under spinal anesthesia. The hypothermia during spinal anesthesia can be explained by heat redistribution from core to periphery, vasodilatation with heat loss and inhibition of thermoregulation. The decrease in temperature was less significant in ketamine group than hydrocortisone and saline groups; this may be due to vasoconstrictive effect of ketamine.

Our study was similar to the study of ***Mohamed et al.*** [7] being spinal anesthesia used in both studies in female patients ASA I–II, but was different being showed mild significant efficacy of ketamine than hydrocortisone.

In our study, the incidence of shivering in pethidine group was 21.4% compared to 60.7% in control group. This is in consistence with many studies that reported the effectiveness of pethidine in prevention of postoperative shivering, ***Dal et al.*** [6] found that pethidine 20 mg was effective like low dose ketamine in prevention of the postoperative shivering after general anesthesia and ***Kose et al.*** [8] found that meperidine 25 mg was effective as i.v. ketamine 0.5 and 0.75 mg/kg for the treatment of postoperative shivering.

Similarly, ***Eydi et al.*** [9] study showed that the use of pethidine 0.5mg/kg as opposed as to the ketamine 0.2 mg/kg are both equally effective in the reduction of postoperative shivering. In this study, 60 patients who underwent ENT surgery with general anesthesia and had shivering during recovery were randomly divided into two groups of 30 patients each receiving ketamine (0.2 mg/kg IV) and pethidine (0.5 mg/kg). There was no statistically significant difference between the shivering intensity in both groups. Only regarding the shivering in the first minute after entering the recovery room, there was an obvious difference between ketamine and pethidine groups which was again not statistically significant (P = 0.07).

Despite using general anesthesia in this study, our results are similar to the results of this study indicating highly efficacy of pethidine in prevention of post-anaesthetic shivering.

Our study is similar to the study of ***Kabade et al.*** [10] being spinal anesthesia used in both studies which done in patients young aged ASA I–II, but different that our studywas performed in pregnant females but this study done in both sexes undergoing lower abdominal surgeries. This is most probably indicates that pethidine has higher efficacy in prevention of post spinal shivering.

The same was recorded in the findings of ***Kranke et al.*** [11] who found that efficacy with meperidine 25 mg, clonidine 150µg, ketanserin 10 mg, and doxapram 100mg was reported in at least three trials, all were significantly more effective than control in treatment of postoperative shivering.

Our study is different from the study carried out by ***Sajedi and colleagues*** [2] in choice of anesthesia. This study was performed under general anesthesia in patients undergoing orthopedic surgery while our study was done under spinal anesthesia in pregnant females undergoing cesarean section. Our results are similar to the results of this study. This is most probably indicates highly significant efficacy of pethidine despite choice of anaesthesia.

Our results were discrepant from those found by ***Sayed and Ezzat*** [12]**.** In their study, they investigated the ability of prophylactic intravenous granisetron, a selective 5-HT3 receptor antagonist, to prevent or decrease shivering in parturients scheduled for elective cesarean section. They found that 3 mg prophylactic intravenous granisetron did not prevent (P = 0.138) or decrease (P = 0.462) the incidence of shivering significantly in comparison with the placebo group in an obstetric setting.

There are a few possible explanations as to why this study did not benefit from granisetron in preventing shivering. First, these study patients included only relatively young pregnant women, who are special segments of the population. Another factor is that evidence shows that shivering during pregnancy differs in many ways to that in the nonpregnant population, which is mainly thermoregulatory in nature.

In addition, an immunological response to fetomaternal transfusion is postulated by some researchers to be partly the cause of peripartum shivering. It is also possible that, because of the physiological changes in this group of patients, such as increased blood volume and cardiac output in the third trimester, 3 mg granisetron used in this study may have been less effective and a higher dose is needed to establish the desired effect.

The incidence of side effects such as nausea and vomiting was little with granisetron but was seen with pethidine, and the results of our study are in consistent with the above-mentioned other studies. Nausea in pethidine group was treated with IV metoclopramide 10 mg.

Limitations of our study that we considered one segment of populations with special characteristics only young pregnant women done cesarean section under spinal anesthesia, and thus further studies are needed to evaluate the effects of these drugs on different segments of populations.

CONCLUSION

Our results indicate that IV granisetron 40 µg/kg was effective as i.v. meperidine 0.4 mg/kg and both are slightly effective than i.v. hydrocortisone 2 mg/kg in reducing the incidence and intensity of shivering during spinal anaesthesia compared to control group.

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