Original Article • นิพนธ์ต้นฉบับ

Efficacy of Intravenous Paracetamol for Prevention of Shivering in Cesarean Section Under Spinal Anesthesia: a Randomized Controlled Trial

Warangkura Ularangkura, Natsupa chokchalermwong, Teeratat Sukonpatip
Department of Anesthesiology, Faculty of Medicine, Thammasat University, Pathumthani 12120, Thailand

Abstract

Introduction: Shivering is an important complication during and after caesarean section under spinal anesthesia cause discomfort to the parturient. Several pharmaceutical agents were used to reduce shivering. The aim of the study is to evaluate the efficacy of intravenous paracetamol for prevention of shivering in pregnancy during and after caesarean section under spinal anesthesia.

Methods: A prospective randomized double-blind controlled clinical trial, 93 pregnant women, who scheduled for elective caesarean section under spinal anesthesia were randomly divided into two groups. One group received 100 ml of normal saline (group NS, n=46), and the other received 1000 mg of paracetamol intravenously (group P, n=47), after the delivery. The anesthetic technique was similar in both groups. Axillary temperature was measured before anesthesia, 30 min after anesthesia, end of the operation, immediately at PACU, every 30 min in PACU, and end of PACU. Intraoperative and postoperative shivering was graded on a scale of 0-4.

Results: There were no significant differences in demographics, surgical characteristics and body temperature between the two groups. Shivering was observed in 2 patients (4.0%) in group NS and 3 patients (6.0%) in group P during surgery and was noted in 7 patients (15.0%) in group NS and 7 patients (15.0%) in group P at PACU. There was no significant shivering score between the two groups. There was no significant in the incidence of hypotension, nausea, and vomiting during surgery.

Conclusion: Administration of intravenous paracetamol does not prevent the shivering in pregnant patients during and after cesarean section undergoing spinal anesthesia.

Keywords: cesarean section, paracetamol, shivering, spinal anesthesia

Correspondence to: Warangkura Ularangkura, E-mail: warang99@yahoo.com
Received September 29, 2022, Revised July 24, 2023, Accepted July 24, 2023

Introduction

Spinal anesthesia is method in cesarean section due to low maternal mortality and morbidity rate and low neonatal depression. After spinal anesthesia, autonomic regulation of temperature is impaired and resulted to vasodilation, heat loss and reduced core temperature. This consequence stimulate hypothalamus to increase core temperature by many mechanisms. One response is a shivering-like tremor with unclear etiology.[1] Shivering is an important complication during and after caesarean section under spinal anesthesia, the incidence is about 20-60%.[2,3] Shivering and vasoconstriction are thermoregulatory mechanisms that are required to increase core body temperature in patients with core hypothermia. During regional anesthesia, the autonomic regulation is impaired and results in reduced central temperature, vasodilation, and shivering threshold. Shivering can also increase patient's oxygen consumption, CO_2 production, increase blood pressure. Moreover, shivering can increase the risk of cardiovascular complications, interfere with vital sign monitoring, and a sense of discomfort, and increase the length of PACU stay.[1]

Several methods and drugs were used for the prevention and treatment of shivering. Nonpharmacologic techniques such as controlling the operating room temperature and cutaneous warming at the skin surface[2], and warmed intravenous fluid[1,4] were very low adverse effects and were easy to use. The other methods for prevention of shivering were not a too long duration of operation and not a too high anesthetic block level.[1] Pharmacological methods used during shivering management require adequate attention to the degrees of sedation and the hemodynamic effects.[5] Several drugs including tramadol[1,6], ondansetron[7], intrathecal fentanyl[8], intravenous pethidine[1,9] and low dose ketamine[6] could reduce the shivering. Pethidine is one of the frequent drugs used to reduce intraoperative shivering. However, the important complications of pethidine are respiratory depression, sedation, nausea, and vomiting. In addition, ketamine has many side effects such as increased blood pressure and heart rate, as well as nausea and vomiting. The concern about medications used for prevention and treatment of shivering during cesarean section should be considered as their side effects.

Postoperative shivering can be explained as a heat-production reaction to the postoperative decrease in the core body temperature and should be resolved when the body temperature reaches the elevated body temperature set point.[10] Paracetamol is an effective, safe synthetic non-opioid analgesic and antipyretic agent. It acts by inhibiting cyclooxygenase-mediated prostaglandin synthesis to decrease the hypothalamic temperature set point.[5] A previous study showed that warmed intravenous fluid 37°C could prevent intraoperative hypothermia in cesarean section by general anesthesia.[4] Furthermore, several studies demonstrated that intravenous paracetamol could prevent the shivering.[3,11] However, there were limited information about the efficacy of paracetamol in prevention of shivering in the cesarean section patients. Therefore, this study aimed to evaluate the efficacy of intravenous paracetamol for prevent of shivering in termed pregnant patients during and after cesarean section under spinal anesthesia in Thammasat Hospital.

Materials and methods

This double-blind randomized controlled trial was approved by The Human Research Ethics Committee (COA 162/2020), Thammasat University. The data was collected between September 2020 and March 2021. The patients

were visited preoperatively by the anesthesiologist one day before surgery, and all patients provided written informed consent before enrollment in the study. The inclusion criteria were aged 18-45 years, ASA status I or II, and underwent an elective cesarean section. The exclusion criteria included contraindications for spinal anesthesia, underlying disease (chronic kidney disease, liver failure, psychosis, and asthma), allergy to the drug used, pregnancy with complications (preterm, premature rupture of membrane, placenta previa totalis, and massive blood transfusion), and body temperature greater than 37.8°C or less than 36.0°C.

The sample size required for the study was determined based on a previous study.[3] Reference to the mean shivering score, the effect size in OR group was 0.46 and in PACU group was 0.75. With a power of 0.8, the sample size was set at 50 cases in each group. All 100 subjects were selected through randomization using a computer-generated method. However, seven pregnant women were excluded from the study. From 93 pregnant patients, there were 46 patients in the normal saline (NS) group and 47 patients were in the paracetamol (P) group.

Researchers of this study prepared paracetamol and normal saline by filling them into an infusion bag of 100 ml and covering it with an opaque coated bag in the morning before starting the operation. The patients randomly received 100 ml of normal saline in group NS and 15 mg/kg or 1000 mg of paracetamol if their body weight >50 kg in group P. The anesthesiologist and the nurse anesthetist who administered the investigated agent were blinded. Heart rate, blood pressure, and oxygen saturation were monitored before the procedure. Skin temperature was measured by a Terumo digital thermometer C205 at the axilla before spinal block, 30 min after spinal block, and at the end of the operation. The OR temperature was maintained at 22.0 to 24.0°C, and an upper body forced-air warming blanket was used at 37°C. Intravenous fluids were prewarmed at 37.0°C. Before anesthesia, a 10-20 ml/kg of Ringer lactate or Ringer acetate was infused. Spinal anesthesia was performed by an anesthesiologist who did not involve in the study at L2-3, L3-4, or L4-5 intervertebral spaces with a Quincke needle of 27 gauge and 10-12.5 mg of 0.5% bupivacaine with 0.2 mg of morphine. Immediately after delivery of the infant, an infusion of normal saline or paracetamol was infused. During surgery, blood pressure was measured every 2 min until delivery and every 5 min until the end of surgery. When blood pressure declined more than 20% from baseline, a 6 mg of ephedrine intravenous was injected and repeated until stable. The severity of the shivering was graded.

To determine the incidence of shivering, the scale proposed by Crossley and Mahajan[12] was used: 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, and 4 = shivering involving the whole body. After spinal block, if patients had a shivering score greater than 2 before delivery, to avoid respiratory depression in the infant, a 0.5 mg/kg of tramadol was administered. After delivery, if the shivering score is more than 2, an anesthesiologist could administer a 0.5 mg/kg of tramadol. The vital signs and side effects such as hypotension, nausea/vomiting, and respiratory depression were observed. All the above data were recorded by a nurse anesthetist in the operating room who was blinded to the patient group. At PACU, with a full body forced-air warming blanket at 37°C, the skin temperature was measured immediately after admission, 30 min after admission, and before discharge from PACU. During observation in PACU, the

severity of shivering was graded, and if the score was more than 2, a 25 mg of pethidine was administered by the PACU nurse. The vital signs and side effects such as hypotension, nausea, vomiting, and respiratory depression were observed by a PACU nurse who was blinded to the patient groups.

Data analyses were performed using SPSS version [21]. The data were expressed as mean±SD for normal distribution data and median (min, max) for non-normally distributed data. An unpaired t-test or Mann-Whitney U test was used for comparison of continuous data and body temperature between the groups. The block level was used for Fisher's exact test. Fisher's exact test determined the grades of shivering and the incidence of adverse effects between the two groups. A *P*-value of less than 0.05 was considered to be statistically significant. Primary outcomes were the incidences and scores of shivering in the intra- and post-operative periods. Secondary outcomes were body temperature and side effects that appeared during the intra-operative period.

Results

A total of 100 patients were enrolled in the study. From these, seven pregnant women were excluded. The median age was 31.5 (21.0-38.0) and 33.0 (20.0-42.0) years in groups NS and P, respectively. The median estimated blood loss was 400 ml in both groups. Most patients in both groups had the level of T4 anesthesia. All patients' baseline characteristics including age, weight, height, gestational age, duration of surgery, estimated blood loss, total IV fluid, and level of anesthesia were not statistically significantly different between the two groups. (Table 1)

Table 1 Patients' characteristics

	Normal saline (n=46)	Paracetamol (n=47)	*P*-value
Age (yr)	31.5 (21.0-38.0)	33.0 (20.0-42.0)	0.40
Weight (Kg)	71.3±11.1	75.5±13.2	0.10
Height (cm)	159.3±6.4	159.4±5.7	0.94
Gestational age (wk)	38.0 (38.0-41.0)	39.0 (37.0-40.0)	0.96
Duration of surgery (min)	60.0 (35.0-115.0)	60 (30.0-160.0)	0.83
Estimated blood loss (ml)	400.0 (200.0-1700.0)	400 (150.0-1000.0)	0.11
Total intravenous fluid (ml)	1100.0 (550.0-2100.0)	1100.0 (550.0-2700.0)	0.58
Level of anesthesia			0.68*
T4	43 (93.4)	42 (89.4)	
T5	1 (2.2)	1 (2.1)	
T6	1 (2.2)	4 (8.5)	
T7	1 (2.2)	0	

Data are presented as median (min- max), mean±SD and number (%).
*Fisher Exact test

Shivering (2-4 score) was noted in two patients (4%) in group NS and three patients (6%) in group P during surgery and was observed in seven patients (15%) in group NS and seven patients (15%) in group P at PACU. However, the incidence of shivering was not significantly different between the two groups both in the operating room and at PACU. (Table 2) The body temperature dropped after the spinal block, then gradually increased in both groups and there was no significant difference between both groups. (Table 3) During the operation, most patients had hypotension in the operating room 83% and 70% in groups NS and P, respectively. There was no significant difference in the incidence of hypotension and nausea/vomiting between groups (Table 4). At PACU, there were no postoperative side effects in both groups.

Table 2 Shivering score

Shivering score, n (%)	Normal saline (n=46)	Paracetamol (n=47)	*P*-value
Operating room			0.74*
0	44 (95.7)	44 (93.6)	
2	1 (2.2)	1 (2.1)	
3	0	2 (4.3)	
4	1 (2.1)	0	
Total shivering	2 (4.3)	3 (6.4)	
Postanesthesia care unit			>0.99*
0	39 (84.8)	40 (85.1)	
2	6 (13.0)	5 (10.6)	
3	1 (2.2)	2 (4.3)	
4	0	0	
Total shivering	7 (15.2)	7 (14.9)	

*Fisher Exact test

Table 3 Body temperature

	Normal saline (n=46)	Paracetamol (n=47)	*P*-value
BT0	36.7±0.4	36.7±0.5	0.67
BT1	36.2±0.4	36.2±0.3	0.40
BT2	36.1 (34.8-36.9)	36.2 (35.1-37.0)	0.36
BT3	36.2±0.3	36.3 (35.0-37.1)	0.34
BT4	36.3±0.3	36.4 (35.0-37)	0.49
BT5	36.4±0.3	36.5(35.5-37.0)	0.78

Unpair T-Test; BT0-1 and Mann-Whitney U test BT2-5

BT0; pre-anesthesia body temperature, BT1; post-anesthesia body temperature at 30 min, BT2; body temperature at end of surgery, BT3; first-assessed body temperature at PACU, BT4; body temperature at 30 min in PACU, BT5; body temperature at end of PACU

Table 4 Intraoperative side effects

	Normal saline (n=46)	Paracetamol (n=47)	*P*-value
Hypotension, n (%)	38 (82.6)	33 (70.2)	0.16
Nausea/vomiting, n (%)	1 (2.2)	4 (8.5)	0.36*

Chi-square test and *Fisher Exact test

Discussion

For the present study, we found that the administration of intravenous paracetamol did not present efficacy to prevent intraoperative and postoperative shivering in our anesthesia technique and situation. A previous study reported that the core body temperature setpoint increased after surgery. Theoretically, post-operative shivering can be explained as a heat-producing reaction to the postoperative increase in the core body temperature setpoint.[10] Postoperative shivering should be resolved when the body temperature reaches the elevated setpoint.[14] Antipyretic agents are believed to block endogenous pyrogen by inhibiting cyclooxygenase-mediated prostaglandin synthesis in the brain, the substances responsible for elevating the hypothalamic setpoint-leading to peripheral vasodilation and sweating.[5] Paracetamol is an antipyretic drug that has been used in various routes for a long time. Paracetamol acts through centrally mediated prostaglandin inhibition to decrease the hypothalamic temperature setpoint.[12] It can lower the body temperature of febrile and nonfebrile patients.[10]

A previous study demonstrated that orally administered paracetamol can suppress in a dose-dependent manner the increase in the body temperature of patients with acute ischemic stroke.[15] There were reports in the patients undergoing gynecological laparotomy suggested that intravenous paracetamol could prevent severe postoperative shivering by suppressing the postoperative increase in the body temperature set point.[10] Additionally, the study of Gholami and Hadavi showed the efficacy of prophylactic intravenous paracetamol on post-anesthetic shivering in elective cesarean section under general anesthesia.[12] Moreover, a two-blinded randomized control trial also confirmed that the prophylactic use of intravenous paracetamol reduced the rate of increase of shivering in pregnant women who underwent cesarean section under spinal anesthesia.[3]

Patients warmed can reduce heat loss due to convection to cold environments, radiation and evaporation from exposed sites, conduction to cold surfaces, and administration of un-warmed fluids. A retrospective observational cohort study showed that an underbody blanket with forced-air warm at 43°C alone for cesarean section was effective in decreasing the incidence of post-operative hypothermia in the cesarean section under spinal anesthesia. However, intraoperative lower body forced-air warming did not prevent intraoperative hypothermia or shivering in the cesarean section under spinal anesthesia.[16] The other report demonstrated that intraoperative lower body forced-air warming did not prevent intraoperative hypothermia or shivering in the cesarean section under spinal anesthesia.[17]

One reported that the application of warming intravenous fluids can be helpful in the prevention of hypothermia resulting from the cesarean section under general anesthesia.[4] Another showed that combined-modality active warming including a coload with warmed intravenous fluid and a lower body forced-air warming for scheduled cesarean delivery under spinal anesthesia increased maternal temperature on arrival at the PACU, minimized the perioperative temperature drop, decreased the incidence of perioperative hypothermia, and improved maternal thermal comfort compared with no interventions.[18]

In our study, intravenous paracetamol was designed to evaluate the preventive effect of perioperative shivering after spinal anesthesia. We found that there was no significant difference in the incidence of perioperative shivering between the saline and paracetamol groups that was different from the previous study.[3] There were no significant differences in body temperature and the incidence of nausea/vomiting between the two groups. The incidence of shivering in our study was slightly lower than the usual incidence due to we warmed the patients during the procedure. However, this study used different methods such as force-air warming blankets and warmed intravenous fluid. This was a routine practice for cesarean section in our hospital. So, this might affect the incidence of perioperative shivering in the study. In our opinion, the etiology of shivering in neuraxial anesthesia does not clear and involves a variety of mechanisms. During this anesthesia, autonomic regulation is impaired, resulting in a reduced body core temperature. A change in body heat distribution modulated the thermoregulatory response to hypothermia, generating shivering as an autonomic protective reflex mechanism to increase body heat through muscle contraction. Shivering in neuraxial anesthesia can be prevented by maintaining intraoperative normothermia, giving warmed fluids, using warmed clothing cover sites, or administering pharmacologic treatments liked tramadol and pethidine. Those were the known mechanisms. Suppression of the postoperative increase in the body temperature setpoint may not be prophylactic shivering.

Our study had some limitations. First, the measurement is biased regarding the shivering score due to variations in recorder personnel. In the study, experienced nurse anesthetists and PACU nurses demonstrated how to score a shivering score. Second, at Thammasat Hospital, we routinely warmed patients intraoperatively to keep them at normal body temperature. Third, we have studied a relatively small population. A larger sample size is required to assess the efficacy of paracetamol.

Conclusion

There was no statistically significant difference between intravenous paracetamol and normal saline in reducing perioperative shivering in pregnant patients undergoing cesarean section under spinal anesthesia in general practice at Thammasat Hospital.

Conflict of interest

The authors declare that they have no conflicts of interest including pharmaceutical company involvement. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subjects of this study.

Acknowledgments

We are grateful for the nurse anesthetists and PACU nurses who support and provide managerial service as well as the pharmacy unit and the Thammasat University Hospital Foundation for supplying the medicine. Additionally, the Routine Clinical Practice to Research Fund from the Faculty of Medicine, Thammasat University is also acknowledged.

References

1. Sessler DI. Temperature regulation and monitoring. In: Miller R, editor. Miller's anesthesia. 8th ed. London: Churchill Livingstone: Elsevier. 2010;1622-46.
2. Sung HC, Lee BS, Yang HJ, et al. Effect of preoperative warming during cesarean section under spinal anesthesia. Korean J Anesthesiol. 2012;62:454-60.
3. Rasoli S, Ansari E, Moslemi F, Ghojazadeh M. The prophylactic administration of intravenous paracetamol for control of shivering during and after cesarean section under spinal anesthesia. Arch Anesthesiol Crit Care. 2019;5:38-40.
4. Oshvandi K, Shiri FH, Fazel MR, Safari M, Ravari A. The effect of pre-warmed intravenous fluids on prevention of intraoperative hypothermia in cesarean section. Iran J Nurs Midwifery Res. 2014;19:64-9.
5. Jain A, Gray M, Slisz S, Haymore J, Badjatia N, Kulstad E. Shivering treatments for targeted temperature management: a review. J Neurosci Nurs. 2018;50:63-7.
6. Lema GF, Gebremedhn EG, Gebregzi AH, Desta YT, Kassa AA. Efficacy of intravenous tramadol and lowdose ketamine in the prevention of post-spinal anesthesia shivering following cesarean section: a double-blinded, randomized control trial. Int J Womens Health. 2017;9:681-8.
7. Nallam SR, Cherukuru K, Sateesh G. Efficacy of intravenous ondansetron for prevention of post-spinal shivering during lower segment cesarean section: a double-blinded randomized trial. Anesth Essays Res. 2017;11:508-13.
8. Sadegh A, Tazeh-Kand NF, Eslami B. Intrathecal fentanyl for prevention of shivering in spinal anesthesia in cesarean section. Med J Islam Republ Iran. 2012;26:85-9.
9. Kim YA, Kweon TD, Kim M, Lee HI, Lee YJ, Lee KY. Comparison of meperidine and nefopam for prevention of shivering during spinal anesthesia. Korean J Anesthesiol. 2013;64:229-33.
10. Kinjo T, Tadokoro T, Tokushige A, et al. Effects of perioperative administration of acetaminophen on postoperative shivering: a randomized, triple-blind, placebo-controlled trial. Anesth Analg. 2020;130:983-90.
11. Gholami A, Hadavi M. Prophylactic intravenous paracetamol for prevention of shivering after general anesthesia in elective cesarean section. J Obstet Anaesth Crit Care. 2016;6:81-5.
12. Crossley AW, Mahajan RP. The intensity of postoperative shivering is unrelated to axillary temperature. Anaesthesia. 1994;49:205-7.
13. Frank SM, Kluger MJ, Kunkel SL. Elevated thermostatic setpoint in postoperative patients. Anesthesiology. 2000;93:1426-31.
14. Fang J, Chen C, Cheng H, Wang R, Ma L. Effect of paracetamol (acetaminophen) on body temperature in acute stroke: a meta-analysis. Am J Emerg Med. 2017;35:1530-5.
15. Marin L, Höcker J, Esser A, Terhorst R, Sauerwald A, Schröder S. Forced-air warming and continuous core temperature monitoring with zero-heat-flux thermometry during cesarean section: a retrospective observational cohort study. Braz J Anesthesiol. 2022;72:484-92.
16. Butwick AJ, Lipman SS, Carvalho B. Intraoperative forced air-warming during cesarean delivery under spinal anesthesia does not prevent maternal hypothermia. Anesth Analg. 2007;105:1413-9.
17. Cobb B, Cho Y, Hilton G, Ting V, Carvalho B. Active warming utilizing combined iv fluid and forced-air warming decreases hypothermia and improves maternal comfort during cesarean delivery: a randomized control trial. Anesth Analg. 2016;122:1490-7.