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Original Article

Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension during cesarean delivery: a dose-dependent study

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Abstract: Objective: This study was to determine the optimal dosage of ondansetron for preventing maternal hypotension during cesarean delivery. Methods: One hundred and fifty parturient women scheduled for elective cesarean section were randomly assigned to five groups (n=30). Five minutes prior to spinal anesthesia, women were injected with 5 ml of physiological saline (S), 2 mg (02), 4 mg (04), 6 mg (06), or 8 mg (08) of ondansetron in saline, respectively. Maternal blood pressure and heart rate were measured at 2-min intervals for 30 min. The serum parameters in umbilical cord blood were analyzed after delivery. Results: Compared with group S, the incidence of maternal hypotension was significantly lower in groups 04 and 06 ($P < 0.05$). The umbilical venous pH was significantly higher in group 04 ($P < 0.05$); while the partial pressure of carbon dioxide (Pco_2) was significantly lower in groups 04, 06, and 08 ($P < 0.05$); and the bicarbonate (Hco_3^-) and base excess in extracellular fluid (BEecf) were significantly lower in groups 06 and 08 ($P < 0.05$). Moreover, minimal changes of systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure were observed in group 04 ($P < 0.05$). Conclusion: The optimal dose of ondansetron preloading was 4 mg during cesarean delivery.

Keywords: Ondansetron, hypotension, spinal anesthesia, optimal dose

Introduction

Maternal hypotension is the most common intraoperative complication after spinal anesthesia during cesarean delivery, with an incidence as high as 50-80% [1]. Maternal hypotension may cause maternal nausea and vomiting as well as detrimental neonatal effects, such as apnea. Thus, some vasopressive drugs including ephedrine and phenylephrine have been widely used to prevent maternal hypotension [2]. It has been demonstrated that ondansetron treatment preloading with crystalloid infusion reduces maternal hypotension in parturient women undergoing cesarean delivery [3, 4]. Our previous study also verified that 4 mg of ondansetron preloading with rapid crystalloid coloading significantly reduced maternal hypotension and nausea 4. However, the dose-dependent effect of ondansetron preloading on preventing maternal hypotension has not been investigated.

Ondansetron has been widely used in the clinic to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery [5, 6]. Ondansetron has been proven as a well-tolerated drug, but the most common side effects of ondansetron include headache, constipation, diarrhea, asthenia, and somnolence [7]. However, the specific treatment for ondansetron overdose has not been reported.

Therefore, in the present study, we designed a double-blinded and randomized study to compare the efficacy of different doses of ondansetron preloading combined with rapid crystalloid coloading on reducing maternal hypotension during cesarean delivery. We also assessed the effects of different doses of ondansetron preloading on maternal nausea, umbilical venous pH, partial pressure of carbon dioxide (Pco_2), bicarbonate (Hco_3^-) and base excess in extracellular fluid (BEecf), and neonatal outcome after delivery.

Materials and methods

Patients

This study was approved by the Ethics Review Committee of the Wuxi Maternal and Child Health Hospital, and informed consent was obtained from all participants. This study was registered at the Chinese Clinical Trial Registry (http://www.chictr.org/cn/; Registration number: ChiCTR-TRC-13003280). One hundred and fifty primiparous and parturient women with a single fetus scheduled for elective cesarean delivery were enrolled in this study from July 2013 to January 2014. Patients, aged 18-35 years, were at 37-42 weeks of gestation and classified as American Society of Anesthesiologists (ASA) grade I-II. All participants showed normal prenatal examinations, normal liver and renal function and fetal screening, and no medical history of heart or lung diseases. The exclusion criteria for participants were the same as in our previous study [4].

Grouping

All participants were randomly assigned to one of five groups according to computer-generated codes, 30 women in each group (n=30). Five minutes prior to spinal anesthesia, the participants in the five groups were intravenously injected with 5 ml of physiological saline (group S) or 2 mg (group 02), 4 mg (group 04), 6 mg (group 06), or 8 mg (group 08) of ondansetron (diluted to 5 ml with physiological saline), respectively. Ondansetron and saline solutions were prepared by an anesthesiologist who was blinded to this study.

Spinal anesthesia

Medication was not administered prior to spinal anesthesia. After a quiet resting period of 5 min, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP, MAP = (SBP + 2 × DBP)/3), heart rate (HR), and oxygen saturation (SpO_2) were measured at 2-min intervals using a noninvasive electrocardiography monitor. Mean SBP, DBP, MAP, HR, and SpO_2 from three measurements before surgery were set as the baseline SBP, DBP, MAP, HR, and SpO_2 levels. No subjects received oxygen.

Before spinal anesthesia, a standard venous angiocatheter (16-gauge) was placed into the superficial vein of the forearm, and warm lactated Ringer's solution was infused at a minimal rate to maintain vein patency. Five minutes after intravenous ondansetron infusion, spinal anesthesia was performed as described previously [4]. Briefly, 2 ml of 0.5% hyperbaric bupivacaine (10 mg) was intrathecally injected. After 2 min, maternal blood pressure, HR, and SpO_2 were measured at 2-min intervals for 30 min. After spinal anesthesia, the intravenous injection was adjusted to maximal speed until the dose reached 10 ml/kg body weight, and then the infusion speed was reduced to a minimal rate to maintain vein patency.

Five minutes after intrathecal injection, the block plane was assessed using the needle-puncture method, and the peak block height was evaluated every 5 min. The treatments for hypotension, bradycardia, low SpO_2, nausea or vomiting, and intractable pain were the same as previously described [4]. If hypotension occurred (defined as systolic blood pressure less than 80% of baseline), an IV bolus of 100 μg of phenylephrine was given in the study period (30 min).

Oxytocin (10 IU in 250 ml physiological saline) was given as intravenous drip after delivery. A blood sample (1 ml) was collected from the umbilical artery and vein to examine blood gas immediately on a fully automated blood gas analyzer (GEM Premier 3000, Instrumentation Laboratory; Bedford, MA). Neonatal Apgar scores were routinely performed at 1 and 5 min after delivery.

Statistical analyses

In our pretesting of 25 parturient women (5 in each group), the mean maximum decline in maternal SBP (baseline maternal SBP before spinal anesthesia-the lowest maternal SBP during the procedure) were 33.8 ± 8.5 mm Hg, and an intergroup difference decline of 20% in the mean maximum decline in maternal SBP was considered statistically significant. An estimated minimum of 26 women was required for each group according to significance ($\alpha = 0.05$) and power of the test ($\beta = 0.20$). Thirty parturient women were enrolled in each study group.

Intergroup comparisons were performed using analysis of variance or the Kruskal-Wallis test as appropriate and the Tamhane and Bonferroni procedures were used for *post-hoc* test, while the paired samples t-test was used to compare the mean differences with baseline values

Table 1. Side effects and vasopressor consumption

	Group S (n=30)	Group 02 (n=29)	Group 04 (n=30)	Group 06 (n=29)	Group 08 (n=30)
hypotension	18 (60.0%)	14 (48.3%)	9 (30.0%)*	9 (31.0%)*	12 (40.0%)
bradycardia	2 (6.7%)	1(3.4%)	0	0	0
nausea	10 (33.3%)	3 (10.3%)*	1 (3.3%)**	1 (3.4%)**	3 (10.0%)*
vomiting	1 (3.3%)	1 (3.4%)	0	0	0
consumption of Bphenylephrine (μg)	107.14±133.13	103.70±105.54	37.93±67.69*	55.56±69.29	82.76±107.13

Data are presented as *n* (%) and mean ± SD. *$P < 0.05$ vs. group S; **$P < 0.01$ vs. group S.

Table 2. Neonatal outcomes

	Group S (n=28)	Group 02 (n=28)	Group 04 (n=29)	Group 06 (n=29)	Group 08 (n=29)
Apgar score					
1 min	10 (7-10)	10 (8-10)	10 (9-10)	10 (8-10)	10 (7-10)
5 min	10 (8-10)	10 (9-10)	10 (9-10)	10 (9-10)	10 (9-10)
Neonatal birth weight (g)	3476±432	3310±343	3305±696	3444±424	3463±434
UA					
pH	7.286±0.036	7.287±0.032	7.287±0.037	7.289±0.035	7.286±0.034
Pco_2 (mm Hg)	54.89±7.24	54.42±5.06	56.03±6.23	52.50±5.37	53.93±6.72
PO_2 (mm Hg)	11.25±5.22	12.19±3.56	10.48±4.21	12.43±4.19	11.30±6.37
Hco_3^- (mmol/l)	26.14±2.50	25.94±1.71	26.97±2.39	25.12±1.48	25.58±2.13
BEecf (mmol/l)	-0.49±2.58	-0.69±1.85	-0.16±1.40	-1.47±1.57	-1.07±2.01
UV					
pH	7.333±0.035	7.340±0.031	7.357±0.028*	7.344±0.040	7.343±0.026
Pco_2 (mm Hg)	46.62±4.98	44.28±4.39	42.78±4.80**	43.11±6.17*	42.88±3.70**
PO_2 (mm Hg)	20.46±7.43	24.56±7.41	24.30±5.74	24.43±6.91	23.76±6.25
Hco_3^- (mmol/l)	24.63±1.42	23.95±1.13	23.89±1.48	23.31±1.36**	23.24±1.30**
BEecf (mmol/l)	-1.24±1.51	-1.94±1.17	-1.61±1.29	-2.39±1.24**	-2.49±1.33**

Data are presented as the mean ± SD or median (range). UA, umbilical arterial blood. UV, umbilical venous blood. *$P < 0.05$ vs. group S; **$P < 0.01$ vs. group S.

within groups. The chi-squared and Fisher's exact tests were used for categorical data. Changes in SBP, DBP, MAP, and HR at all time points after spinal anesthesia were analyzed by using the two-way analysis of variance (ANOVA). All statistical analyses were carried out using SPSS version 13.0 statistical software (SPSS Inc., Chicago, IL) and Excel 2003 (Microsoft Corporation, Redmond, WA). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Demographic data

The recruitment and exclusion of subjects are shown in Figure S1. One hundred and fifty parturient women scheduled for elective cesarean section were eventually enrolled in this study and used for analysis.

There were no significant differences in age, weight, height, body mass index, gestational age, estimated blood loss, or time from spinal anesthesia to delivery among the five groups ($P > 0.05$, Table S1). Moreover, no dose of ondansetron infusion affected block height during anesthesia (Table S2), suggesting no interference on the efficacy of spinal anesthesia.

Adverse reactions

Compared with group S, the incidence of maternal hypotension was obviously but not significantly reduced in groups 02 and 08 ($P > 0.05$), but significantly reduced in groups 04 and 06 ($P < 0.05$) (**Table 1**). The incidence of nausea in groups 02, 04, 06, and 08 was significantly lower than that in group S ($P < 0.05$). No bradycardia or vomiting were observed in groups 04, 06, and 08, while one or two women in groups

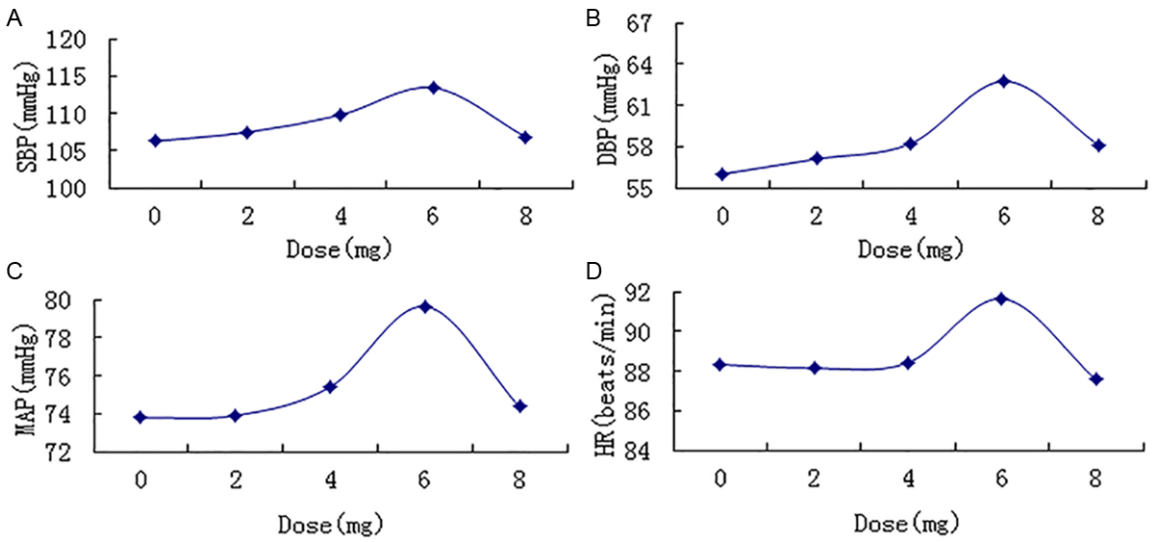

Figure 1. The means of maternal systolic blood pressure (SBP) (A), diastolic blood pressure (DBP) (B), arterial blood pressure (MAP) (C), and heart rate (HR) (D) after preloading different doses of ondansetron during the study period.

Table 3. Changes in maternal blood pressure and heart rate

	Group S (n=30)	Group O2 (n=29)	Group O4 (n=30)	Group O6 (n=29)	Group O8 (n=30)
ΔSBP_{max} (mm Hg)	30.86±16.23	31.89±10.96	20.52±8.80*	26.43±18.33	25.41±13.28
ΔDBP_{max} (mm Hg)	30.43±9.59	29.26±9.24	24.52±9.25*	25.96±10.81	28.03±10.84
ΔMAP_{max} (mm Hg)	29.45±11.20	28.67±9.27	21.86±8.60*	24.68±11.53	25.14±10.54
ΔHR_{max} (beats/min)	18.64±6.93	18.33±10.18	11.62±8.11	15.39±9.83	13.34±8.14

Data are shown as mean ± SD. ΔSBP_{max} = baseline maternal SBP-minimal maternal SBP during the study period; ΔDBP_{max} = baseline maternal DBP-minimal maternal DBP during the study period; ΔMAP_{max} = baseline maternal MAP-minimal maternal mean MAP during the study period; ΔHR_{max} = baseline maternal HR-minimal maternal HR during the study period. *$P < 0.05$ vs. group S.

S and O2 had bradycardia or vomiting (**Table 1**). Moreover, the consumption of phenylephrine in group O4 was significantly less than that in group S ($P < 0.05$) (**Table 1**).

Neonatal outcomes

There were no significant differences in Apgar scores at 1 and 5 min after neonatal delivery or neonatal birth weight among the five groups ($P > 0.05$, **Table 2**). The gas analysis results from umbilical arterial blood showed that there were no significant differences in pH, Pco_2, PO_2, Hco_3^-, or base excess ($P > 0.05$, **Table 2**). In addition, the pH of the umbilical venous blood was significantly higher in group O4 compared with group S ($P < 0.05$). Compared with group S, the Pco_2 in the umbilical venous blood was significantly lower in groups O4, O6, and O8, while the Hco_3^- and BEecf in umbilical venous blood were significantly reduced in groups O6 and O8 ($P < 0.01$, **Table 2**).

Variation in hemodynamic parameters

To assess the effect of different doses of ondansetron on maternal blood pressure and HR, the means of maternal SBP, DBP, MAP, and HR during the experimental period were evaluated. Compared with group S, the means of maternal SBP, DBP, MAP, and HR after spinal anesthesia were not or only minimally affected in groups O2, O4, and O8, but were dramatically increased in group O6 (**Figure 1**). Moreover, we also evaluated the changes of maternal SBP, DBP, MAP, and HR after spinal anesthesia. Compared with group S, the maximum decline of SBP, DBP, and MAP was significantly lower in group O4 (**Table 3**), while minimal changes of mean of SBP, DBP, MAP, and HR were observed in groups O4 and O6 (**Figure 2**).

Discussion

Maternal hypotension is one of the most common complications during spinal anesthesia

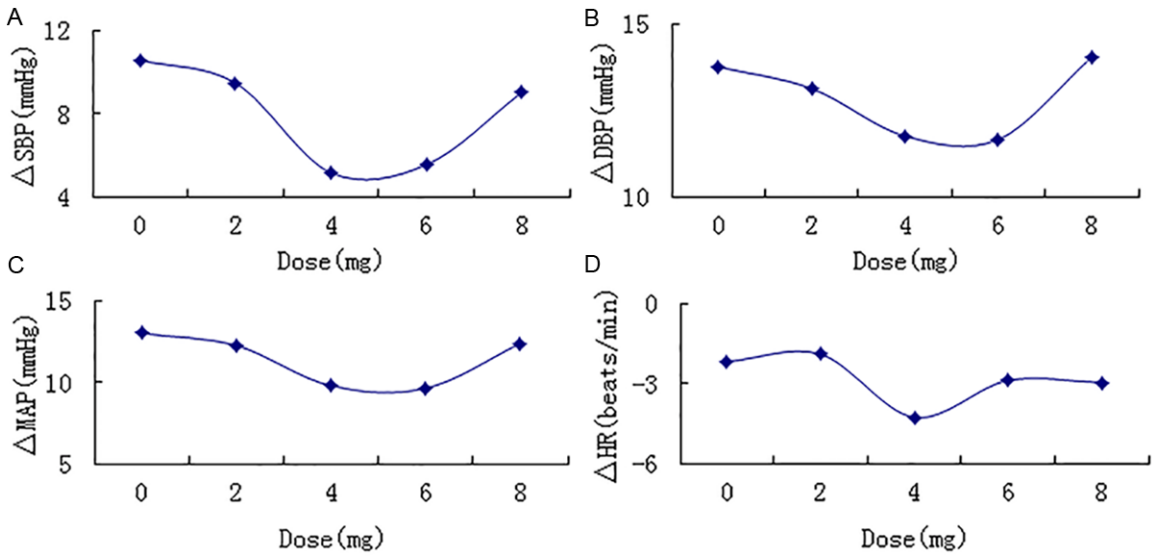

Figure 2. The curve of changes in SBP (A), DBP (B), MAP (C), and HR (D) after preloading different doses of ondansetron during the study period. ΔSBP = baseline SBP-mean of $SBP_{1\text{-}15}$; ΔDBP = baseline DBP-mean of $DBP_{1\text{-}15}$; ΔMAP = baseline MAP-mean of $MAP_{1\text{-}15}$; ΔHR = baseline HR-mean of $HR_{1\text{-}15}$.

because sympathetic nerve blockade can decrease blood return to the heart. Ondansetron, a highly effective and specific 5-HT_3 receptor antagonist, can block the binding of 5-HT from activated platelets to 5-HT_3 receptors [8-10], then alleviates the Bezold-Jarisch reflex (BJR) triggered by 5-HT [8, 11], and thus suppresses further expansion of peripheral vessels and increases blood return to the heart.

Previous studies have investigated the risk of adverse fetal outcomes relative to ondansetron administration during pregnancy [12, 13]. These studies found that appropriate exposure to ondansetron during pregnancy does not cause spontaneous abortion, stillbirth, any major birth defect, preterm delivery, or infants born with low birth weight or small for their gestational age [12]. Another prospective study has reported that ondansetron administration during the first trimester of pregnancy is not associated with an increased risk for major malformations above baseline [13]. Thus, appropriate ondansetron administration during pregnancy is safe to both the mother and fetus. However, ondansetron administration has potential puerperal risks, such as extrapyramidal symptoms [14], transient blindness [15], QT interval prolongation [16-18], coronary vasospasm and atrial fibrillation [19], fatal ventricular tachycardia [20], migraine-type headache [21], etc. Johannsen et al. reported that 50 μg/ml and 100 μg/ml ondansetron induced significant muscular contractures only in malignant hyperthermia-susceptible muscle, while 300 μg/ml ondansetron also induced muscular response in malignant hyperthermia-nonsusceptible muscle [22].

Moreover, previous studies have demonstrated that ondansetron preloading can effectively prevent maternal hypotension and nausea after spinal anesthesia during cesarean delivery [3, 4]. Although 4 mg of ondansetron preloading has been commonly used to reduce maternal hypotension and nausea [3, 4], the dose-dependent effect of ondansetron on reducing maternal hypotension has never been investigated.

In the current study, we investigated the dose-dependent effects of ondansetron preloading on maternal SBP, DBP, and MAP and neonatal outcomes. We demonstrated that intravenous injection of 4 or 6 mg of ondansetron preloading with rapid crystalloid infusion could significantly reduce the incidence of maternal hypotension and nausea, decrease the Pco_2 in umbilical venous blood, and stabilize the maternal hemodynamics. However, lower (2 mg) and higher (8 mg) doses of ondansetron preloading failed to reduce the incidence of maternal hypotension and nausea. We can assume that 2 mg of ondansetron may not be sufficient to prevent maternal hypotension and nausea. Although a previous study reported that 8 mg of ondansetron attenuated the decline of SBP

and MAP but not DBP and HR [23], here we observed that 8 mg of ondansetron had minor effects on hemodynamic parameters. The differences between the two studies may be due to the different methods used for surgery, ondansetron loading and anesthesia, and surgery or not during the study period. Studies by Sahoo et al. and us have demonstrated that 4 mg of ondansetron can effectively prevent maternal hypotension during cesarean delivery [3, 4], but both studies only used one given dose. The data in this study provide more convincing evidence that 4-6 mg of ondansetron is the optimal concentration to prevent maternal hypotension and associated complications during cesarean delivery.

Moreover, consistent with our previous findings, 4 mg of ondansetron could obviously increase the pH value but decrease Pco_2 in umbilical venous blood compared with the control. Constant hypotension in control subjects might result in high production of CO_2 and reduced pH, while 4 mg of ondansetron could effectively prevent hypotension and inhibit CO_2, thus increasing the pH. Interestingly, compared with the control subjects, the values of Pco_2 and Hco_3^- were significantly lower in the subjects treated with 6 mg and 8 mg of ondansetron, but the pH was not changed. Additionally, 6 mg and 8 mg of ondansetron might cause light lactate acidosis in the fetuses according to the reduced BEecf value. Therefore, application of the appropriate concentration of ondansetron during cesarean delivery is important to the health and safety of the mother and fetus.

In summary, considering its effects on hypotension, nausea, phenylephrine consumption, and neonatal outcomes, 4 mg of ondansetron preloading was the optimal dose to prevent maternal hypotension, nausea, and other adverse effects during cesarean delivery.

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Disclosure of conflict of interest

None.

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References

[1] Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010; 111: 1230-1237.

[2] Warwick D. Ngan Kee. Prevention of maternal hypotension after regional anesthesia for caesarean section. Curr Opin Anaesthesiol 2010; 23: 304-309.

[3] Sahoo T, SenDasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomised, placebo-controlled study. Int J Obstet Anesth 2012; 21: 24-28.

[4] Wang Q, Zhuo L, Shen MK, Yu YY, Yu JJ, Wang M. Ondansetron Preloading with Crystalloid Infusion Reduces Maternal Hypotension during Cesarean Delivery. Am J Perinatol 2014; 10: 913-922.

[5] Christofaki M, Papaioannou A. Ondansetron: a review of pharmacokinetics and clinical experience in postoperative nausea and vomiting. Expert Opin Drug Metab Toxicol 2014; 10: 437-444.

[6] Yeh YC, McDonnell A, Klinger E, Fowler B, Matta L, Voit D, Reddy P. Comparison of healthcare resource use between patients receiving ondansetron or palonosetron as prophylaxis for chemotherapy-induced nausea and vomiting. J Oncol Pharm Pract 2011; 17: 179-185.

[7] Goodin S, Cunningham R. 5-HT(3)-receptor antagonists for the treatment of nausea and vomiting: a reappraisal of their side-effect profile. Oncologist 2002; 7: 424-436.

[8] Martinek RM. Witnessed asystole during spinal anesthesia treated with atropine and ondansetron: a case report. Can J Anesth 2004; 51: 226- 230.

[9] Gyermek L. Pharmacology of serotonin as related to anesthesia. J Clin Anesth 1996; 8: 402- 405.

[10] Mao HZ, Chapleu MW. Platelet activation in carotid sinuses triggers sympathoinhibition and hypotension. Hypertension 1996; 27: 584-590.

[11] Aviado DM, Guevara Aviado D. The Bezold-Jarisch reflex: a historical perspective of cardiopulmonary reflexes. Ann N Y Acad Sci 2001; 940: 48- 58.

[12] Pasternak B, Svanström H, Hviid A. Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes. N Engl J Med 2013; 368: 2146.

[13] Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy a prospective comparative study. BJOG 2004; 111: 940-943.

[14] Spiegel JE, Kang V, Kunze L, Hess P. Ondansetron-induced extrapyramidal symptoms during cesarean section. Int J Obstet Anesth 2005; 14: 368-369.
[15] Cherian A, Maguire M. Transient blindness following intravenous ondansetron. Anaesthesia 2005; 60: 938-939.
[16] Charbit B, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J. Prolongation of QTc Interval after Postoperative Nausea and Vomiting Treatment by Droperidol or Ondansetron. Anesthesiology 2005; 102: 1094-1100.
[17] Charbit B, Alvarez JC, Dasque E, Abe E, Démolis JL, Funck-Brentano C. Droperidol and ondansetron-induced QT interval prolongation:a clinical drug interaction study. Anesthesiology 2008; 109: 206-212
[18] McKechnie K, Froese A. Ventricular tachycardia after ondansetron administration in a child with undiagnosed long QT syndrome. Can J Anaesth 2010; 57: 453-457.
[19] Havrilla PL, Kane-Gill SL, Verrico MM, Seybert AL, Reis SE. Coronary Vasospasm and Atrial Fibrillation Associated with Ondansetron Therapy. Ann Pharmacother 2009; 43: 532-536.
[20] Chandrakala R, Vijayashankara CN, Kumar KK, Sarala N. Ondansetron induced fatal ventricular tachycardia. Indian J Pharmacol 2008; 40: 186-187.
[21] Singh V, Sinha A, Prakash N. Ondansetron-induced migraine-type headache. Can J Anaesth 2010; 57: 872-873.
[22] Johannsen S, Roewer N, Schuster F. Ondansetron-Induced Muscular Contractures in Malignant Hyperthermia-Susceptible Individuals. Anesth Analg 2012; 111: 925-928.
[23] Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszułowicz R, Dylczyk-Sommer A, Wujtewicz MA, Sawicka W, Morzuch E, Smietanski M, Wujtewicz M. Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: a double-blind, placebo-controlled study. Reg Anesth Pain Med 2008; 33: 332-339.

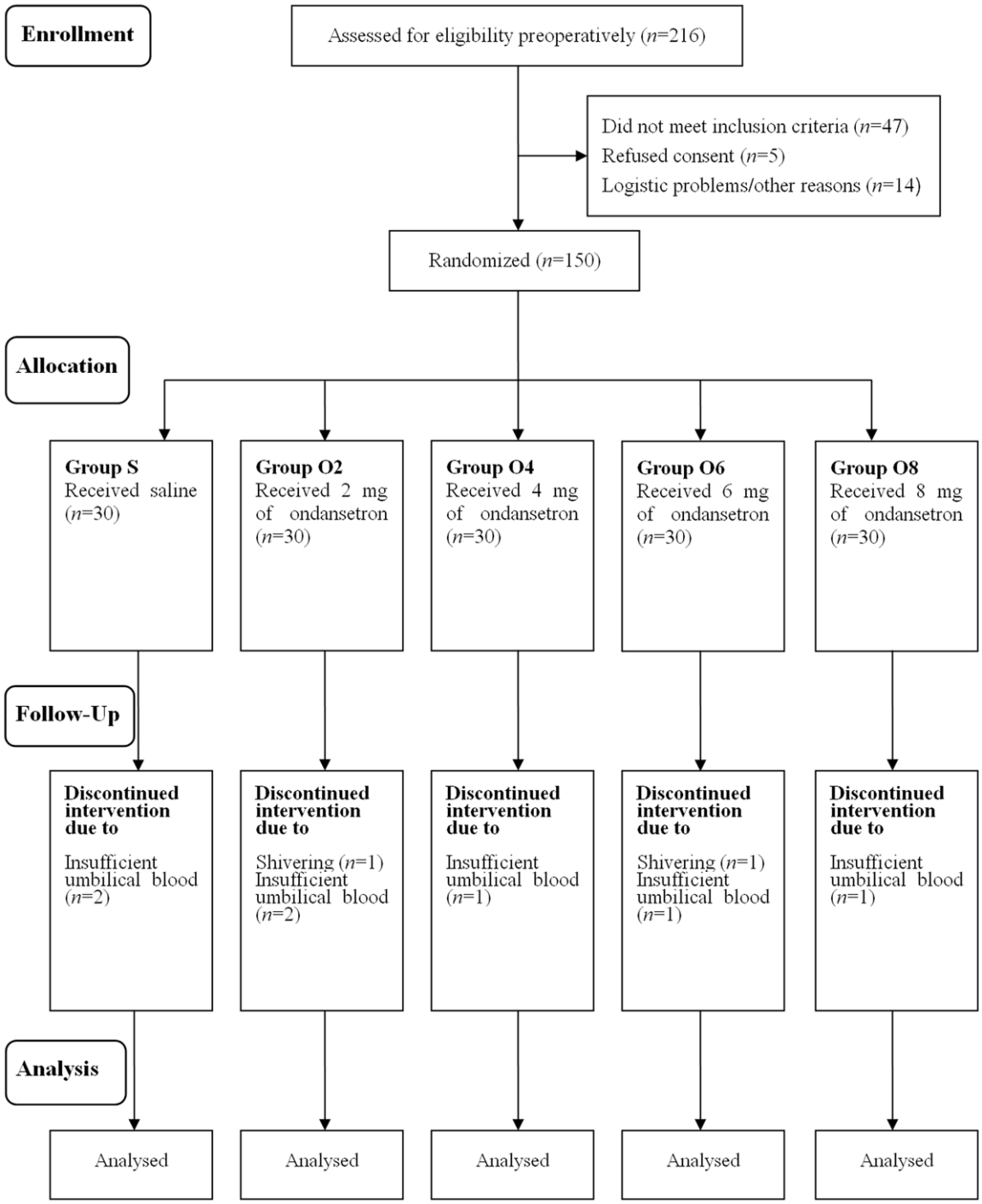

Figure S1. CONSORT flow diagram.

Table S1. Demographic and baseline characteristics

	Group S (n=30)	Group 02 (n=30)	Group 04 (n=30)	Group 06 (n=30)	Group 08 (n=30)
Age (years)	26.43±3.16	27.78±3.24	27.86±3.50	27.79±4.43	27.90±4.01
Weight (kg)	70.64±7.70	70.30±8.46	68.55±7.37	67.64±7.56	72.28±7.27
Height (cm)	161.75±3.88	162.19±3.77	162.66±3.68	160.75±3.72	161.55±5.19
BMI (kg/m^2)	27.00±2.77	26.72±3.07	25.94±2.96	26.18±2.82	27.72±2.81
Gestational age (weeks)	39.39±1.10	39.16±0.85	39.34±1.08	39.29±0.91	39.60±0.84
Estimated blood loss (ml)	253.57±50.79	268.52±41.94	270.69±64.80	267.86±53.08	265.52±48.37
Time from spinal anesthesia to delivery (min)	12.93±1.61	14.50±2.35	12.59±1.74	13.50±2.66	13.27±2.69

Data are shown as mean ± SD.

Table S2. Block height during spinal anesthesia

Time point (min)	Group S (n=30)	Group 02 (n=30)	Group 04 (n=30)	Group 06 (n=30)	Group 08 (n=30)
5	T5 (T4-T7)	T5 (T4-T6)	T5.5 (T4-T6)	T5.5 (T4-T6)	T6 (T4-T6)
10	T5 (T4-T6)	T5 (T4-T6)	T5 (T3-T6)	T5 (T4-T6)	T5 (T3-T6)
15	T5 (T4-T6)	T4 (T4-T5)	T4 (T3-T6)	T4 (T4-T6)	T5 (T3-T6)
20	T4 (T3-T6)	T4 (T4-T5)	T4 (T3-T6)	T4 (T4-T5)	T5 (T3-T6)
25	T4 (T3-T6)	T4 (T4-T5)	T4 (T3-T6)	T4 (T4-T5)	T4 (T3-T6)
30	T4 (T3-T6)	T4 (T4-T5)	T4 (T3-T6)	T4 (T4-T5)	T4 (T3-T6)

Data are shown as median (range).