Palonosetron might not attenuate spinal anesthesia–induced hypotension during orthopedic surgery

Department of Anesthesiology and Pain Medicine, Gachon University Gil Medical Center, Incheon, Korea

Jung Ju Choi, Young Jin Chang, Wol Seon Jung, and **Youn Yi Jo**

Background: 5-Hydroxytryptamine3 (5-HT$_3$) receptor antagonists have been reported to attenuate spinal anesthesia-induced hemodynamic changes. This study was conducted to determine whether the second generation 5-HT$_3$, antagonist palonosetron attenuates hypotension and bradycardia during spinal anesthesia.
Methods: Sixty adult patients scheduled for lower limb surgery were enrolled in this study. Patients were randomly assigned to receive either normal saline (Control group, N = 30) or palonosetron (0.075 mg, i.v.) (Palonosetron group, N = 30) prior to spinal anesthesia. Hemodynamic variables were recorded during anesthesia.
Results: The mean blood pressure (MBP) were 89.2 ± 11.4 mmHg in the control group and 87.6 ± 12.1 mmHg in the palonosetron group at 10 min after intrathecal injection (P = 0.609). The median blocked levels of the control group and the palonosetron group were T10 (interquartile range, 9–10) and T10 (8–10) at 20 min after intrathecal injection (P = 0.939). Requirements for ephedrine, phenylephrine, and atropine were similar (P = 0.652, 0.533 and 0.417, respectively). The incidences of hypotension (40% vs. 41%) and bradycardia (7% vs. 17%) were comparable (P = 0.562, P = 0.198, respectively) between the control and the palonosetron group. There were no significances in the changes of systolic blood pressure, diastolic blood pressure, MBP and heart rate by the group (P = 0.632, 0.287, 0.556, 0.733, respectively).
Conclusions: Intravenous palonosetron (0.075 mg) prior to spinal anesthesia might not attenuate spinal anesthesia-induced hypotension during low level of neuroaxial block for lower limb surgery. **(Anesth Pain Med 2016; 11: 195-200)**

Key Words: Hypotension, Palonosetron, Spinal anesthesia.

Corresponding author: Youn Yi Jo, M.D., Ph.D., Department of Anesthesiology and Pain Medicine, Gachon University Gil Medical Center, 21, Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea. Tel: 82-32-460-3636, Fax: 82-32-469-6319, E-mail: endless37@gilhospital.com

INTRODUCTION

Spinal anesthesia-induced hypotension is commonly encountered, and the incidences of spinal anesthesia induced hypotension and bradycardia were reported to be 33% and 13%, respectively, in a previous analysis of 952 non-obstetric patients [1], and to be 50–60% in obstetric patients [2]. Intrathecal injection of local anesthetics produces thoracolumbar sympathetic block, and this may lead to reduced systemic vascular resistance and venous pooling. Furthermore, during high level neuroaxial blocks, cardio-accelerator sympathetic block leads to bradycardia and reduced cardiac output. Relatively strong parasympathetic tone after sympathetic block also triggers Bezold-Jarisch reflex leading to sudden profound bradycardia [3-8].

5-Hydroxytryptamine3 (5-HT$_3$) receptor activation at sensory vagal nerve endings in the heart elicits bradycardia and hypotension [9], and thus, 5-HT$_3$ receptor antagonists had been used to attenuate spinal anesthesia-induced hemodynamic changes. Owczuk et al. [10] demonstrated that 8 mg of intravenous ondansetron attenuated spinal anesthesia-induced reductions in systolic and mean arterial pressures. In addition, Eldaba and Amr [11] reported 1 mg of granisetron before spinal anesthesia significantly reduced the incidences of hypotension and bradycardia and lowered vasopressor requirements as compared to a placebo control group during cesarean delivery.

Palonosetron is a second-generation 5-HT$_3$ receptor antagonist and has been reported to possess superior anti-emetic properties and greater receptor binding affinity than classic 5-HT$_3$ antagonists, such as ondansetron and granisetron [12,13].

Thus, we hypothesized that palonosetron might attenuate spinal anesthesia-induced hemodynamic changes more so than other classic 5-HT$_3$ antagonists, and thus, we conducted this

study to test the hypothesis that the use of intravenous palonosetron attenuates hypotension and bradycardia during spinal anesthesia.

MATERIALS AND METHODS

Subjects

After obtaining the Institutional Review Board approval from our center, 60 adult patients of American Society of Anesthesiologists physical status 1 or 2, aged 20–65 years and scheduled for elective lower limb surgeries from March 2015 to August 2015 were enrolled in this prospective randomized study. Patients with a history of uncontrolled hypertension or cardiovascular disease, uncontrolled diabetes mellitus, a severe respiratory disease, or any contraindications for spinal anesthesia were excluded.

Anesthesia and group assignments

All patients received 0.03 mg/kg of midazolam intra-muscularly as premedication 1 hour before anesthesia and no additional sedatives were administered during the operation. Patients were randomly assigned to receive either normal saline 1.5 ml (Control group, N = 30) or palonosetron (0.075 mg/1.5 ml, *i.v.*) (Palonosetron group, N = 30) 15 minutes before intrathecal injection for spinal anesthesia. On arrival at the operating room, non-invasive blood pressure monitoring, electrocardiography and pulse oximetry were applied. All patients received a fluid preload of 300 ml of crystalloid solution. Spinal anesthesia was performed in the lateral position using 0.5% hyperbaric bupivacaine and a 25 gauge Quincke needle at the L3-4 or L4-5 interspace by an anesthesiologist unaware of group identities and the dose of bupivacaine was determined as anesthesiologists' discretion.

Monitoring of hemodynamic variables

Vital signs were measured at 2 min intervals up to 20 min after intrathecal injection and changed to 5 min interval until the end of surgeries. Systolic (SBP), diastolic (DBP), and mean (MBP) arterial pressures, heart rate (HR), and pulse oximeter oxygen saturation (SpO2) were recorded 15 min before intrathecal injection (T0; immediate before administration of palonosetron or normal saline), 1 min after intrathecal injection (T1), and every 5 min after injection (T5-T40) by a senior trainee unaware of group identities. The blocked thoracic spinal level was checked at 1, 5, 10, 15 and 20 min after

intrathecal injection. All operative procedures were undergone in the supine position without urinary catheterization. Pneumatic tourniquet was placed in the patients' thigh (250 mmHg).

Hypotension was defined as a SBP fall to 80% of baseline or a fall to < 90 mmHg. Bradycardia was defined as HR of < 50 beats/min. Hypotension was treated with 50 µg of phenylephrine (heart rate ≥ 70 beats/min) or 5 mg of ephedrine (heart rate < 70 beats/min) and bradycardia was treated with atropine 0.5 mg (*i.v.*). Intravenous fluid was infused at a constant rate of 6 ml/kg/h.

Outcome variables

The primary outcome variable was MBP after spinal anesthesia. The secondary outcome variables were changes of SBP, DBP, and HR. Maximal changes of hemodynamic variables were calculated as differences between baseline and lowest values.

Statistics

To calculate sample sizes, we used previously reported differences of MBP at 10 min after spinal anesthesia [10]. To detect a mean inter-group difference of 6 mmHg in MBP, 23 patients per group were required for an α-error of 0.05 and a power of 80%. Considering 30% of possible drop outs, 30 patients were recruited per group.

The statistical analysis was performed using PASW Statistics ver. 13 (SPSS Inc, Chicago, IL, USA). Data are expressed as mean ± SD, median (interquartile range) or number of patients. Patient characteristics and perioperative clinical data were compared using the student's *t*-test or Fisher's exact test, as appropriate. Non-parameteric variables were analyzed with Mann-Whitney U test. Changes in hemodynamic variables over time between the two groups were analyzed using two way repeated measured ANOVA. Statistical significance was accepted for P values of < 0.05.

RESULTS

Of the 60 study subjects, one patient in the palonosetron group was excluded from the analysis due to operative plan changes. Demographic data, underlying medical diseases and perioperative clinical data including bupivacaine dose, anesthesia time, operation time and blocked sensory levels were similar in the palonosetron and control groups (Table 1).

The incidences of hypotension (40% vs. 41%) and bradycardia (7% vs. 17%) were comparable (P = 0.562, P =

Table 1. Patients' Characteristics and Perioperative Clinical Data

Variables	Control (N = 30)	Palonosetron (N = 29)	P value
Age (yr)	43.3 ± 14.2	45.1 ± 14.2	0.640
Weight (kg)	69.8 ± 16.0	70.5 ± 15.0	0.865
Height (cm)	168.6 ± 10.5	166.0 ± 9.3	0.313
Gender (M/F)	22/8	20/9	0.467
Diabetes mellitus (n)	2	2	0.513
Hypertension (n)	2	4	0.319
Hyperbaric bupivacaine (mg)	12.1 ± 1.4	12.7 ± 1.4	0.079
Anesthesia time (min)	109.8 ± 44.1	98.4 ± 35.2	0.278
Operation time (min)	72.8 ± 33.5	70.7 ± 34.2	0.809
Sensory blocked level at 20 min after intrathecal injection (n)			
T5−6	1	3	0.391
T7−8	6	8	
T9−10	23	18	
Infused fluid (ml)	478 ± 206	538 ± 310	0.387

Values are mean ± SD or number of patients. Infused fluid, total infused fluid except preloading.

Table 2. Incidences of Hypotension and Bradycardia and Requirements for Phenylephrine, Ephedrine and Atropine

| Variables	Control (N = 30)	Palonosetron (N = 29)	P value
Hypotension, n (%)	12 (40)	12 (41)	0.562
Bradycardia, n (%)	2 (7)	5 (17)	0.198
Requirements of hemodynamic drugs			
Ephedrine, n (%)	3 (10)	4 (14)	0.652
Phenylephrine, n (%)	1 (3)	2 (7)	0.533
Atropine, n (%)	3 (10)	5 (17)	0.417
Hemodynamic changes (baseline values − lowest values)			
Systolic blood pressure (mmHg)	31.8 ± 18.9	31.2 ± 12.7	0.540
Diastolic blood pressure (mmHg)	19.7 ± 12.4	18.8 ± 10.5	0.763
Mean blood pressure (mmHg)	27.7 ± 15.2	24.4 ± 11.9	0.365
Heart rate (beats/min)	13.5 ± 10.1	12.5 ± 9.4	0.681

Values are mean ± SD or number of patients (%).

0.198, respectively) between the control group and the palonosetron group. The median blocked levels of the control group and the palonosetron group were T8 (6−10) and T7 (6−8) at 1 min after intrathecal injection (P = 0.416), and T10 (9−10) and T10 (8−10) at 20 min after intrathecal injection (P = 0.391). Requirements for ephedrine, phenylephrine, and atropine were similar (P = 0.652, 0.533 and 0.417, respectively). Maximal changes in group hemodynamic variables were similar (Table 2).

Intraoperative changes in SBP, DBP, MBP, and HR are illustrated in Fig. 1. The MBP were 89.2 ± 11.4 mmHg in the control group and 87.6 ± 12.1 mmHg in the palonosetron group at 10 min after intrathecal injection (P = 0.609). The changes of each hemodynamic variables over time were significant (all P values < 0.001), but there were no significances in the changes of SBP, DBP, MBP and HR over time between the groups (interactive term 'time x group' in ANOVA) (P = 0.632, 0.287, 0.556 and 0.733, respectively).

DISCUSSION

This study shows the administration of palonosetron (0.075 mg, *i.v.*) prior to spinal anesthesia for lower limb surgery did not attenuate spinal anesthesia-induced hypotension or bradycardia in our cohort.
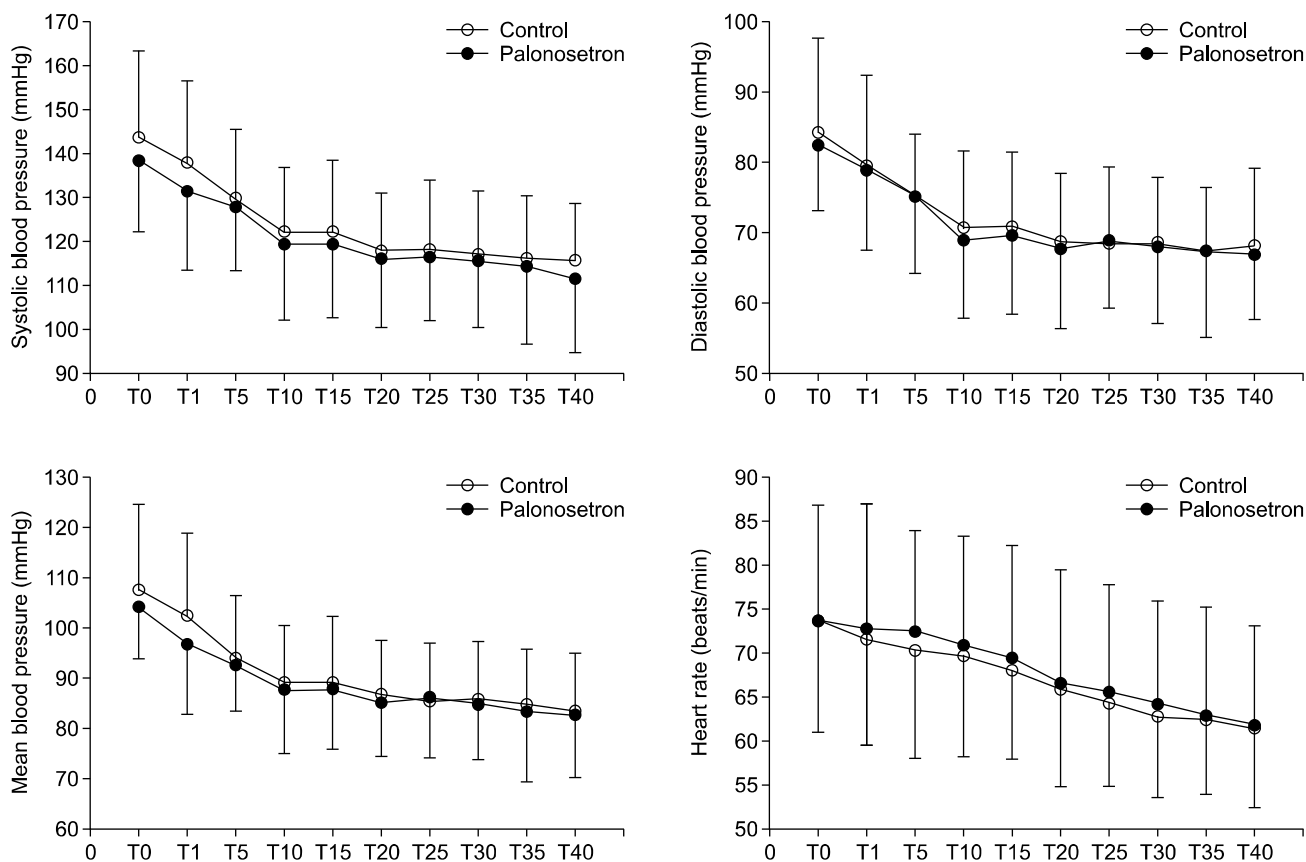
Fig. 1. Peri-operative changes in systolic and diastolic blood pressures, mean blood pressure, and heart rate in patients that received normal saline (Control group) or palonosetron (Palonosetron group) during spinal anesthesia. Error bars represent with standard deviations. T0: Before anesthesia induction, T1: 1 min after intrathecal injection, T5–T40: Every 5 min after intrathecal injection (from 5 min to 40 min after intrathecal injection).

For all study subjects, the overall incidences of hypotension and bradycardia were 41% (24/59) and 12% (7/59), which were consistent with previously reported incidences after spinal anesthesia [1] in non-obstetric subjects. However, response to 5-HT$_3$ receptor antagonist differed considerably from those described in previous clinical studies which had concluded various 5-HT$_3$ receptor antagonists effectively prevented spinal anesthesia-induced hypotension.

5-HT$_3$ receptor participates in cardio-inhibitory responses in the left cardiac ventricle. Under conditions of preload reduction, the left ventricular wall can collapse and trigger vagal nerve-mediated cardiac inhibitory reflex [7,10,14,15]. 5-HT$_3$ receptor is located in vagal nerve endings and activates thrombocytes to release serotonin [14-17], which leads to hypotension and bradycardia, referred to as Bezold Jarisch reflex. A sudden decrease in venous return induced by high neuroaxial anesthesia can activate this pathway. Palonosetron has unique structural, pharmacological characteristics compared to classic 5-HT$_3$ antagonists. Other 5-HT$_3$ antagonists such as

ondansetron and granisetron directly compete with serotonin, and attenuate the Bezold Jarisch reflex which mediated by serotonin in cardiac vagal nerve ending. However, palonosetron exhibit allosteric binding and the effects persisted beyond its binding to the 5-HT$_3$ receptor at the cell surface [18]. These functional and structural differences could contribute to the different result of our study to other studies which related with classic 5-HT$_3$ antagonists.

In a previous comparative study of ramosetron and ondansetron in the context of spinal anesthesia induced hypotension, they reported that 67–74% of the patients were above T5–6 and ramosetron attenuated hypotension more so than ondansetron [19]. In fact, the majority of studies that have addressed the effects of 5-HT$_3$ antagonists on spinal anesthesia-induced hemodynamic changes involved high levels of neuroaxial block [10,11,20]. On the other hand, in the present study, only 7% (4/59) of patients experienced high neuroaxial block. Singla et al. [21] reported that when the anesthetic level was under T10, there was little change in

systemic vascular resistance (SVR) with little hemodynamic changes and when the level was over T6, the reduction of preload was large because of blood pooling into hepatosplanchnic venous areas and therefore the risk of hypotension increased by about 2.4 times than lower than that level [21]. Thus, we considered 5-HT$_3$ antagonists might be effective against hypotension relevant to Bezold Jarisch reflex than hypotension induced by venous pooling. Further studies are needed to compare the effects of palonosetron on hypotension and bradycardia at different levels of neuroaxial block.

In this study we separately demonstrated BP as SBP, DBP, and MBP. Previous study demonstrated that ondansetron did not effect on SBP, but attenuate the decrements of DBP and MBP. They suggested that SVR was closely related to DBP than SBP and, so, the effect of ondansetron induced the changes of DBP and MBP [22].

One major limitation of our study is that we overlooked the effects of level of neuroaxial block and dose of intrathecal local anesthetics. Though the incidence of hypotension and bradycardia in this study was similar with previous study of non-obstetric patients [1], it was already known that the high thoracic block and large doses of local anesthetics were related with high frequency of Bezoled Jarisch reflex after regional anesthesia [15]. So, further study in the patients who are needed for high spinal block might help to generalizing the effect of palonosetron on spinal anesthesia-induced hypotension and bradycardia. Another limitation is that we failed to notice the effect of onset time. Although there was no unique report about onset time of palonosetron, palonosetron is recommended to administered immediate before anesthetic induction or 30 min before chemotherapy. We administered the study drug 15 min before intrathecal injection and we had to consider that only 15 min might not enough to reveal the antagonistic effect on 5-HT$_3$ receptor.

We conclude that intravenous palonosetron (0.075 mg) prior to spinal anesthesia might not attenuate spinal anesthesia-induced hypotension and bradycardia during low level neuroaxial block for lower limb surgery.

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