Original Article

# Comparison of IV granisetron and IV palonosetron on hemodynamics and sensory and motor block after spinal anesthesia with hyperbaric bupivacaine in patients undergoing abdominal hysterectomy

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## Abstract

**Background and Aims:** The present study evaluated the effects of two 5-HT3 serotonin receptor antagonists; granisetron and palonosetron on hemodynamics, sensory, and motor blockade induced by intrathecal bupivacaine in patients undergoing abdominal hysterectomy.

**Material and Methods:** In total, 126 female patients (ASA I and II physical status) undergoing abdominal hysterectomy under spinal anesthesia with intrathecal bupivacaine were randomly divided into three groups out of which 40 patients in each group were evaluated for final outcome. Group G received intravenous 1 mg granisetron, group P received intravenous palonosetron 0.075 mg, and group C received intravenous normal saline. Study drug was given 5 min before the spinal anesthesia. Systolic, diastolic and mean arterial blood pressure, heart rate, sensory and motor blockade were assessed.

**Results:** The systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate showed no significant differences among the three groups. Time to reach peak sensory block and modified Bromage 3 motor block, time to two segmental regression of sensory block, and motor regression to modified Bromage score of 0 were not statistically different among the three groups. Although statistically significant early regression of sensory block to segment S1 was seen in group G as compared to group P and group C, it was of no clinical significance. The incidence of nausea and vomiting was significantly lower in group G and P.

**Conclusion:** Intravenous administration of granisetron and palonosetron before intrathecal bupivacaine does not attenuate the hemodynamic changes in patients undergoing abdominal hysterectomy. Further, both 5-HT3 receptors antagonists do not have clinically significant effects on the spinal blockade produced by hyperbaric bupivacaine.

**Keywords:** Bupivacaine, granisetron, palonosetron, spinal anesthesia

## Introduction

Unwanted sequel such as nausea, vomiting, hypotension, and bradycardia are not uncommon with spinal anesthesia.[1] Hypotension and bradycardia are the most common complications after subarachnoid anesthesia with incidences of 15% to 33% and 9% to 13%, respectively.[2] Initially, hypotension is caused by a decrease in systemic vascular resistance secondary to blockade of sympathetic fibers. The Bezold-Jarisch reflex (BJR) has been proposed as an additional explanation for hypotension and bradycardia in patients undergoing subarachnoid anesthesia.[3]

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The selective 5-hydroxytrptamine-3 (5-HT3) receptors are located peripherally as cardiac chemoreceptors on cardiac vagal afferent and within the wall of cardiac ventricles and centrally in the chemoreceptor trigger zone. They are activated by serotonin released in response to systemic hypotension and cause an increase in efferent vagal signaling. The binding of serotonin to the 5HT3 receptor subtype also activates the BJR, leading to bradycardia and hypotension.[3,4]

The administration of granisetron has been found to significantly attenuate the decline of heart rate and blood pressure in rabbit model.[5] Infusion of granisetron (5-HT3 antagonist) diminishes heart rate fluctuations and decreases systolic blood pressure changes during head-up tilt table test that are likely related to BJR.[6] Various studies have demonstrated the role of granisetron and ondansetronin attenuation of hemodynamic response and faster regression of sensory levels if given prior to spinal anesthesia.[7-19] However, there are few studies, which have evaluated the effects of granisetron and palonosetron on spinal anesthesia in non – obstetric patients,[7,19] We conducted this study with the primary aim to examine the effects of serotonin receptor antagonists on hemodynamics changes after administration of intrathecal hyperbaric bupivacaine in patients undergoing abdominal hysterectomy. Secondary aims were to determine the effects of serotonin receptor antagonists on sensory and motor blockade resulting from spinal anesthesia and perioperative incidence of nausea and vomiting.

## Material and Methods

After local Hospital Ethical Committee approval and an informed written consent, 126 adult female patients of ASA grade I and II, aged 30 to 60 years, scheduled for abdominal hysterectomy surgery under spinal anesthesia were equally randomized in three groups in this prospective, double blind study over a period of 1 year from November 2014 to October 2015. There was no analgesic drug or sedative premedication given. The exclusion criteria included ASA grade >II, patients who have received antiemetic 24 h before surgery, taking drugs that act on serotonin receptors or affect the level of serotonin, history of allergy to the study drug, known prolonged QTc interval or bundle branch block and with contraindication for spinal anesthesia.

After securing an IV access, all patients were preloaded with 10 ml/kg of Ringer-lactate solution infused over 20 min before the beginning of spinal anesthesia. In the operating room, standard monitors including electrocardiograph, non-invasive blood pressure, and pulse oximeter were placed. All baseline parameters were recorded. The patients were randomly allocated into three groups using block permutation method. Group G received IV 1 mg granisetron, group P received IV 0.075 mg palonosetron, and group C received an equal volume of 0.9% of normal saline solution IV, 5 min before spinal anesthesia by an anesthesiologist who did not participate in the study. An anesthesiologist who was blinded to study protocol prepared the syringes. The study was double blinded. The anesthesiologist, data collectors, and patients were blinded to the assignment group.

Spinal anesthesia was performed in the sitting position at L3-L4 intervertebral space, through midline approach using a 26-G Quincke spinal needle. After obtaining a free flow of CSF, 3.0 ml of 0.5% hyperbaric bupivacaine was injected without barbotage in approximately 15 s with the level of the needle oriented cephalad. Thereafter, the patients were placed in the supine position to attain the level of T4-T6 block and maintained in this position until the end of surgery.

Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and $SpO_2$ were monitored and recorded every 2 min after the block for 20 min then every 5 min until the end of surgery. Time calculation was started considering the time of intrathecal injection as zero. The sensory level was assessed by loss of pinprick sensation using a blunt 25G needle at mid-axillary line every 2 min until the fixation of the sensory level. The peak sensory level and the time to reach peak sensory level were recorded before surgery. Thereafter, the sensory level was checked after every 15 min until sensory level regression to S1. Motor block was assessed every 2 min until maximum motor blockade, then every 15 min until complete motor recovery, according to the modified Bromage scale.[20]

Hypotension defined as a decrease in MAP >20% of the baseline or fall in systolic blood pressure <90 mmHg, which was treated with intravenous mephentermine 3 mg. Bradycardia (heart rate <50 beats/min) was treated with intravenous atropine 0.5 mg. In case of failed spinal anesthesia, general anesthesia was administered, and those patients were excluded from the study.

Patients were observed for complaints of nausea, vomiting, and need for rescue antiemetic. Intravenous metoclopramide 0.15 mg/kg was administered as rescue antiemetic. Side effects such as headache, dizziness, and myalgia were recorded for 24 h postoperatively.

The sample size was according to the study of hospital data for 3 ml of 0.5% intrathecal bupivacaine in non-obstetric

patients, which revealed MAP drop (difference between the initial value and the minimal value recorded within 20 min after the block) to be 26 ± 7.8 mmHg. The intergroup difference in MAP drop of 20% was assumed clinically significant. With this assumption, 80% test power and alpha level of 0.05, 36 patients were required in each study group.

The data were analyzed using computer software Microsoft Excel and IBM SPSS version 16.0 for Windows. The mean and standard deviation (SD) was calculated and reported for quantitative variables. The statistical difference in mean value was tested using paired *t* test and independent *t* test. The analysis of variance (ANOVA) was also performed to evaluate statistical significance in more than two groups. A $P$ value of $< 0.05$ was considered as statistically significance.

## Results

One hundred and thirty-four patients were screened. Two patients declined to participate, and six patients did not meet inclusion criteria. Remaining 126 patients were randomized into three equal groups. Subarachnoid block failed in 4 patients, and 2 patients were disqualified because of protocol violation. Finally, 120 patients were considered in analysis.

All the three groups were comparable with regard to age, weight, height, gender, and duration of surgery [Table 1]. The maximum cephalic spread of sensory block was similar ($P > 0.13$); T5 (range, T4–6) in group C, T 5 (range, T4–7) in the group G, and T6 (range T3-T6) in group P.

Time to reach peak sensory block was found to be statistically comparable among the three groups. Time to reach two segmental regression of sensory block was also comparable among three groups. Early regression of sensory block to segment S1 was seen in-group G as compared to group P and C. This difference was statistically significant. The results were comparable between group P and group C. Time to reach modified Bromage 3 motor block and time to motor regression to modified Bromage 0 was statistically comparable among the three groups [Table 2].

There were no significant differences among the three groups in hemodynamic variables except for diastolic blood pressure, which was statistically lower in granisetron group compared to Palonosetron group from 8 to 55 min intraoperatively [Figures 1-4]. However, the incidence of episodes of hypotension and bradycardia were not significant among three groups. There was no significant difference present in the incidence of bradycardia among the three groups. The number of patients requiring atropine and mephentermine were comparable among the three groups [Table 3].

The incidence of nausea and vomiting and need for rescue antiemetic were significantly lower in group G and $P$ in comparison to group C in the intraoperative period ($P < 0.0001$).The differences were not found to be statistically significant in the postoperative period in the three groups [Table 3].

**Table 1: Patients baseline demographic characteristics**

| Demographics | GROUP G ($n$=40) | GROUP P ($n$=40) | GROUP C ($n$=40) | $P$ |
|---|---|---|---|---|
| Age | 51±10 | 49±9 | 50±10 | 0.44 |
| Height (cm) | 158±3 | 158±3 | 157.2±3 | 0.68 |
| Body weight (Kg) | 64±5 | 66±6 | 66±5.2 | 1.45 |
| Body eight index | 24±3 | 24±3 | 24±3 | 0.97 |
| ASA status I/II | 31/9 | 27/13 | 28/12 | 0.57 |
| Duration of surgery | 106±12.2 | 109±16 | 111±17 | 0.38 |

*Values are mean±standard deviation .ASA-American Society of Anesthesiologists Physical Status. * < 0.05=statistically significant*

## Discussion

The main finding in this study was that intravenous granisetron and Palonosetron failed to have any effect on hemodynamic status.

Till date, five studies have evaluated the effects of IV granisetron spinal anesthesia with bupivacaine.[7-11] Four of them are in parturients undergoing cesarean section and one in patients undergoing knee arthroscopy.[7] Our results are in accordance to the study conducted by Mowafi HA *et al.* who found no significant

**Table 2: Sensory and motor characteristics of spinal anaesthesia**

| | GROUP G ($n$=40) | GROUP P ($n$=40) | GROUP C ($n$=40) | G vs P | G vs C | P vs C |
|---|---|---|---|---|---|---|
| Time to peak sensory block (min) | 6.2±1.4 | 7±1.4 | 7±2 | 0.086 | 0.287 | 0.541 |
| Time to two segmental regression (min) | 105±13 | 107±17 | 106±11 | 0.479 | 0.634 | 0.734 |
| Sensory regression to S1(min). | 187±10.4 | 196±11 | 193.3±10 | 0.002* | 0.004* | 0.257 |
| Time to reach modified bromage 3(min) | 9±1.1 | 9±1.3 | 9±1.2 | 0.534 | 0.927 | 0.491 |
| Motor regression modified Bormage 0(min) | 183±13.1 | 188.1±14.4 | 182±12.1 | 0.094 | 0.411 | 0.071 |
| Mephentermine used (mg) | 3.00±0.00 | 4.0±2.0 | 3.2±1 | 0.104 | 0.337 | 0.210 |

** < 0.05=Statistically significant*

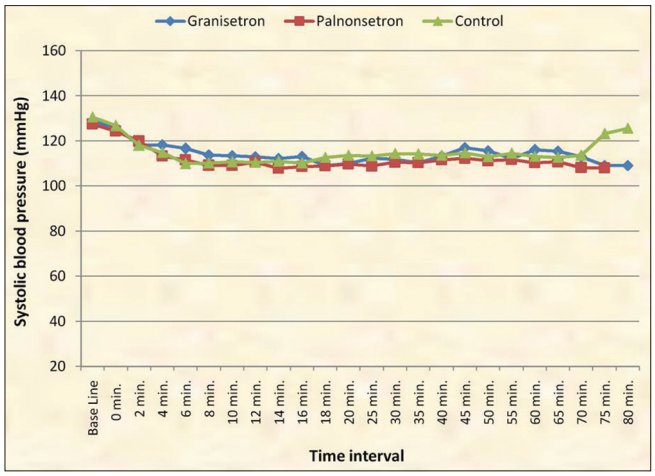


**Figure 1:** Intraoperative systolic blood pressure

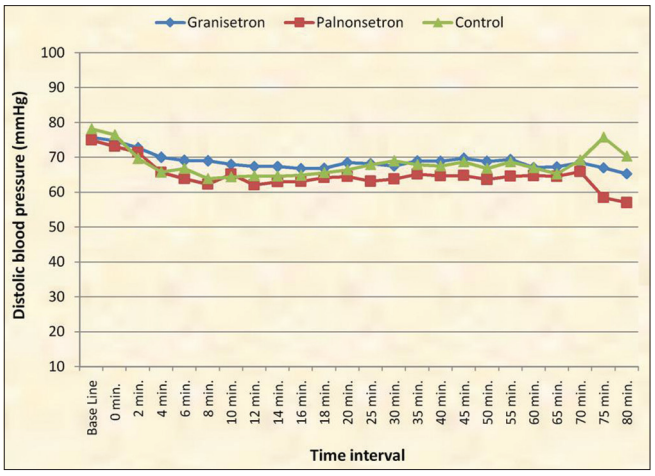


**Figure 2:** Intraoperative diastolic blood pressure devices

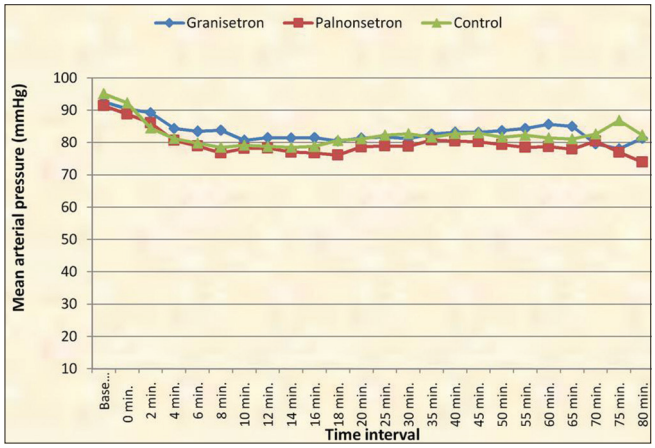


**Figure 3:** Intraoperative mean blood pressure

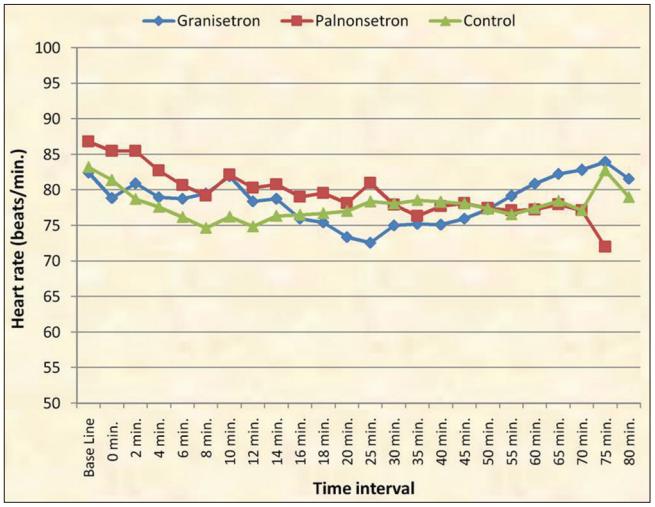


**Figure 4:** Intraoperative heart rate

**Table 3: Comparison of mephentermine, atropine, rescue antiemetic, and side effects in study groups**

| | GROUP G (*n*=40) | GROUP P (*n*=40) | GROUP C (*n*=40) | *P* |
|---|---|---|---|---|
| Rescue Mephentermine | 10 (25) | 11 (27.5) | 13 (32.5) | NS |
| Atropine | 2 (5) | 2 (5) | 3 (7.5) | NS |
| Rescue antiemetic intraoperative | 1 (2.5) | 0 (0) | 6 (15) | 0.001* |
| Rescue antiemetic postoperative | 1 (2.5) | 0 (0) | 2 (5) | 0.352 |
| Headache | 1 (2.5) | 2 (5.0) | 0 (0.0) | NS |
| Drowsiness | 2 (5.0) | 1 (2.5) | 0 (0.0) | NS |
| Diziness | 0 (0.0) | 0 (0.0) | 0 (0.0) | NS |
| Myalagia | 0 (0.0) | 0 (0.0) | 0 (0.0) | NS |
| Headache | 1 (2.5) | 2 (5.0) | 0 (0.0) | NS |
| Drowsiness | 2 (5.0) | 1 (2.5) | 0 (0.0) | NS |

*Data is expressed as number (%) compared with control group, NS-Non-significant*

effect on hemodynamics with prior administration of granisetron 1 mg in 40 patients undergoing elective knee arthroscopy under spinal anesthesia with 12.5 mg of 0.5% bupivacaine.[7]

Our results are also in agreement with the study conducted by Rashad MM *et al.*, Khalifa OSM, and Behdad *et al.* who found that there was no attenuation of hypotension or bradycardia in parturients receiving granisetron prior to administration of spinal anesthesia for cesarean section.[8-10]

Two recent meta-analysis including 19 trials (10 obstetrics and 9 non-obstetrics) with 1,744 patients evaluating the effects of 5-HT3 antagonists on prevention of spinal anesthesia induced hypotension and bradycardia have failed to confirm evidence that 5-HT3 antagonists reduces the incidence of hypotension and bradycardia after subarachnoid anesthesia in non-obstetric patients.[21,22]Although hypotension and bradycardia are attenuated in patients undergoing cesarean section, the effects are moderate. All the studies evaluating effects of granisetron on hemodynamic including our study, barring study by Eldaba AA *et al.* in obstetric patients have also failed to demonstrate any beneficial effect of granisetron in attenuation of hemodynamic response in both obstetric and non-obstetric patients, echoing

the finding of the above two meta-analysis. Till date, there is no study evaluating the effects of IV. Palonosetron administered before spinal anesthesia on hemodynamics.

Different effects of 5-HT3 antagonists on the hemodynamic parameters between obstetric and non-obstetric patients may be related to the hormonal changes in pregnancy and their effect on serotonin levels and sensitivity of serotonin levels. The estrogen level increase during pregnancy, and although studies have elucidated its interaction with 5-HT1A receptors, there are no studies to the effects of estrogen on 5-HT3 receptors. Pregnancy can also affect serotonin levels, which tend to increase during pregnancy.[18,23]

The sensory level achieved in our study was T4-T6 segments, and there was no difference in time to achieve these levels among three groups. The levels achieved in our study were similar to those achieved by numerous other studies evaluating effects of IV granisetron on spinal anesthesia, albeit using lower doses of 10 mg of intrathecal 0.5% hyperbaric bupivacaine.[7-11] It has been found that increasing the dose or volume of 0.5% hyperbaric bupivacaine does not increase height when dose of 10–20 mg are used. When doses of less than 10 mg of 0.5% hyperbaric bupivacaine are used, the blocks are 2.5 dermatomes lower than those achieved with doses more than 10 mg.[23] This explains the same block height achieved with 15 mg of 0.5% hyperbaric bupivacaine in our study in contrast to lower dose (10–12.5 mg) used in other studies.

Similar to these studies, we did not find any significant differences in maximum cephalic spread of sensory block, time to achieve maximum sensory level, time to attain peak sensory block, and level of sensory block with granisetron and palonosetron when compared to the control group. Similar results have also been seen with ondansetron administered to patient prior to spinal anesthesia.[8,15,16]

Time to two segments sensory regression indicates the duration of spinal block at the surgical site. We failed to show any beneficial effect of granisetron to hasten the two-segment regression in contrast to other studies where two segment regressions was hastened in patients receiving granisetron.[7-9] Although we did find a statistically significant early regression of sensory block to S1 segment as compared to group P, this difference was only 7 min and may not be of clinical significance in real world practice. These clinically insignificant effects may be attributed to higher dose of intrathecal bupivacaine in our patient as compared to other studies.

It has been demonstrated that increasing local anesthetics dose increases the duration of spinal block. If same height is achieved with different doses of local anesthetics, two segment regression is slow, and the duration of spinal block is longer with increasing doses of local anesthetics because of higher concentration of drug in cerebrospinal fluid and nerve roots.[24] This has been robustly demonstrated by Sheskey *et al*. who found a 40% increase in block duration at L2 when comparing 10 mg bupivacaine with 15 mg.[25] Similarly, Axelson *et al*. found that duration of sensory block at L2 was nearly double when comparing 10 mg bupivacaine with 20 mg.[26]

The dose used in our study (15 mg) was higher than the above three aforementioned studies, although block height achieved was same (T4-T6). This same block height with higher dose of 0.5% hyperbaric bupivacaine in our patients explains higher times to achieve two segment regression as compared to other three studies.[7-9] It may be possible that effect of 5-HT3 antagonists on sensory regression in our study, if any, may have been masked by very slow regression of block in our patients, and hence, failure to achieve clinically significant two segment regression and regression of sensory block to S1 level in our patients. Further higher sample size in our study (twice that of other studies[7-9]) may be responsible for differences in the results.

Our results are also similar to the study conducted by Kim MH *et al.*, which showed no significant difference in time to regression of sensory block by two dermatomes when IV 0.075 mg palonosetron was given prior to spinal anesthesia with 8 mg bupivacaine in patients undergoing transurethral surgery.[19]

Time to reach modified Bromage 3 motor block and motor regression to modified Bromage 0 motor block were not different in our patients who were administered granisetron or palonosetron compared to saline. Similar lack of effects on motor blockade has also been seen in other studies using other 5-HT3 receptors antagonists.[7-9,15,16,19]

The antiemetic effects of granisetron and palonosetron in our patients are in accordance with the literature demonstrating comparable efficacy of these drugs in preventing nausea and vomiting. Many studies have reviewed and studied the pharmacology of 5-HT3 receptors antagonist in postoperative nausea and vomiting and demonstrated that granisetron, ondansetron, and palonosetron all have comparable mechanism of action for prevention of postoperative nausea and vomiting.[1]

We did not evaluate higher doses of 5-HT3 receptor antagonists which indeed was a limitation of our study, as there may be a study dose response curve of these drugs on hemodynamics and characteristics of spinal anesthesia. Second issue is the standardization of dose of subarachnoid

hyperbaric bupivacaine. We evaluated a fixed dose of 15 mg 0.5% hyperbaric bupivacaine. The results could have been different with lower and higher doses. Future studies are required in non-obstetric patients.

In conclusion, IV administration of granisetron, in a dose of 1 mg and Palonosetron 0.075 mg before intrathecal bupivacaine does not attenuate the hemodynamic changes in patients undergoing abdominal hysterectomy. Further, there is no effect on the onset, intensity, duration, and regression of spinal block, block characteristics produced by hyperbaric bupivacaine.

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## Conflicts of interest

There are no conflicts of interest.

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