Granisetron's Preemptive Effect on Hemodynamic Changes in General Anesthesia During Laparoscopic Cholecystectomy

Burak Nalbant[1], Savaş Altınsoy[2], Gözde Bumin Aydın[3], Gulten Utebey[2], Fatma Kavak Akelma[1], Julide Ergil[2]

1 Department of Anesthesiology and Reanimation, University of Ankara Yildirim Beyazit, Ankara Bilkent City Hospital, Ankara, Türkiye
2 Department of Anesthesiology and Reanimation, University of Health Sciences, Ankara Etlik City Hospital, Ankara, Türkiye
3 Anesthesiology and Reanimation Clinique, University of Health Sciences, Sincan Training and Research Hospital, Ankara, Türkiye

Abstract

Aim: Laparoscopic cholecystectomy causes hemodynamic changes such as decreasing preload, compression on vena cava inferior. These effects are correlated with increased intraabdominal pressure due to pneumoperitoneum. This study aims to evaluate the effect of granisetron (1 mg) in the prevention of post-induction hypotension in adult patients with laparoscopic cholecystectomy under general anesthesia.

Methods: One hundred and forty American Society of Anesthesiologists (ASA) status I-II patients, aged 18 to 65 years, undergoing elective laparoscopic cholecystectomy surgery under general anesthesia were included. Mean blood pressure (MBP), heart rate (HR) and are measured and recorded 1 minute after induction, 1 minute before intubation, 1 minute after intubation and every 5 minutes during operation. Intubation quality was assessed by Evans score at one minute after intubation.

Results: The demographic variables (gender, age, weight, height and body mass index (BMI)) were similar in both groups. The mean blood pressure was decreased in 22 patients (%31.4) in saline group (Group S) and 8 patients (%11.4) in granisetron group (Group G) compared to baseline values after 15 minutes of granisetron administration at reverse Trendelenburg position. At the same period, the heart rate was decreased in 12 patients (%17.1) in group G 18 patients (%25.7) in group S

Conclusions: Granisetron prevented hypotension after reverse Trendelenburg position and CO_2 insufflation in 15th minute of granisetron administration. It can be used safely in adult patients and patients having risks of hypotension due to positions during general anesthesia.

Keywords: *Granisetron; hypotension; general anesthesia; propofol; laparoscopic cholecystectomy*

1. Introduction

Propofol is the most commonly used intravenous anesthetic agent for daily anesthesia due to its soft induction and fast recovery properties.[1] However, hypotension that occurs in induction is the most common disadvantage. The hypotensive effect of propofol was attributed to a combination of venous and arterial vasodilatation, a decrease in systemic vascular resistance and/or cardiac output, which was due to impairment of the baroreceptor reflex mechanism and depression of myocardial contractility.[2]

Preemptive treatments play a critical role in mitigating the hemodynamic side effects of anesthesia. Various strategies have been employed to prevent hypotension, including the administration of volume expanders, physical methods to enhance venous return, and the use of vasopressors 5-HT3 antagonists are primarily used to prevent postoperative nausea and vomiting (PONV).[3] Granisetron, a selective 5-HT3 receptor antagonist, belongs to this class. Ondansetron, another 5-HT3 antagonist, has been shown to be effective in preventing hypotension following both spinal and general anesthesia.[4] The Bezold-Jarisch reflex, which contributes to systemic hypotension, bradycardia, and vasodilation, is mediated by mechanoreceptors and serotonin-sensitive chemoreceptors located in the heart wall.[5] Serotonin is thought to play a central role in triggering this reflex, particularly in the context of post-spinal anesthesia-induced hypotension.

Laparoscopic cholecystectomy has become the gold standard for cholelithiasis and it's performed under general anesthesia. Laparoscopic cholecystectomy causes hemodynamic changes such as de-

Corresponding Author: Burak Nalbant, buraknalbant@gmail.com, Received: 05.05.2025, Accepted: 09.06.2025, Available Online Date: 30.06.2025 Department of Anesthesiology and Reanimation, University of Ankara Yildirim Beyazit, Ankara Bilkent City Hospital, Ankara, Türkiye. https://doi.org/10.36516/jocass.1691841

creasing preload, compression on vena cava inferior. These effects are correlated with increased intraabdominal pressure due to pneumoperitoneum.[6,7]

The primary aim of this study is conducted to determine the effectiveness of granisetron (1 mg) in the prevention of post-induction hypotension in adult patients with laparoscopic cholecystectomy under general anesthesia. Secondary aims were to evaluate the incidence of bradycardia and hypotension during the surgery.

2. Materials and Methods

Institutional Ethics Committee approval and written informed consent (Ref no 28/19, 04/04/2016) were obtained, and the study was registered in clinicaltrials.gov (NCT03180229). One hundred and forty American Society of Anesthesiologists (ASA) status I–II patients, aged 18 to 65 years, undergoing elective laparoscopic cholecystectomy surgery under general anesthesia was randomly allocated to two groups with sealed envelope technique. Patients with a history of hypertension, cardiorespiratory diseases, renal disorders, acute pancreatitis, cognitive disorders or which are using antihypertension medication and who written informed consent could not be obtained were excluded from the study. On the other hand, patients who have passed to open surgical intervention were excluded.

Peripheral venous catheterizations of patients were performed with 20-gauge needles and Ringer lactate (2 ml/kg) was administered before operation during the fasting period. Standard monitorization and BIS (BIS Quatro sensor and BIS VISTA monitor) were administered to all patients. After recording baseline heart rate and blood pressure, patients were randomly divided into two groups.

Group G (n=70) received 1 mg granisetron (KYTRİL® 3 mg / 3 mL, i.v. Assos Medical, Türkiye) diluted in 5 ml of saline and group S (n= 70) received 5 ml of saline before 5 minutes from anesthesia induction. Patients in both groups did not receive any premedication. Anesthesia was induced with propofol 2.5 mg/kg. i.v. mean blood pressure (MBP), heart rate (HR) and are measured and recorded 1 minute after induction, 1 minute before intubation, 1 minute after intubation and every 5 minutes during operation. All patients received fentanyl 1 µg/kg and rocuronium 0.8 mg/kg as neuromuscular blockade before intubation. Anesthesia was maintained using sevoflurane at 1 to 1.2 minimum alveolar concentrations with fractional inspired oxygen of 0.5. Controlled ventilation continued with a rate of 10-14 breath/min and a tidal volume of 6-10 ml/kg aiming for an end-tidal carbon dioxide (EtCO2) of 35-40 mmHg without positive end Expiratory Pressure (PEEP). Maintenance fluid of ringer lactate was infused at 5-10 ml/kg/h during operation in both groups. At the end of the surgery, neuromuscular blockade was antagonized with 0.01 mg/kg atropine and 0.03-0.05 mg/kg neostigmine. Tramadol 100 mg iv infusion was administered approximately 15 minutes before the end of surgery for postoperative analgesic treatment. All patients received dexketoprophen trometamol 25 mg (3×1) on the postoperative first day. When patients complained of pain, was administered intravenous tramadol (100 mg) as a rescue analgesic.

The primary outcome variable in this study was proportions of patients with marked hypotension defined as mean arterial blood pressure (MAP) at least 25% less than the basal value at any time during the procedure. If hypotension occurred vasopressors (5 mg doses of ephedrine) treatments were administered. Bradycardia was defined as heart rate below 60 or %25 dropped. Intubation quality was assessed by Evans score at one minute after intubation (Table 1). The patients were observed in the Post Anesthesia Care Unit for 30 minutes and then transferred to their ward.

2.1. Statistical methods

According to the results of a previous study in which the incidence of hypotension following induction was closed to 45%, 65 patients were required for each group to detect a 50% reduction in the incidence of hypotension (α= 0.05, β = 0.20). So, 75 patients were enrolled for possible dropouts in each group (4). Statistical Package for Social Sciences (SPSS) software (version 22.0, SPSS, Inc, Chicago, IL, USA) was used for the statistical analysis. Numerical variables were summarized with mean ± standard deviations. Qualitative variables were expressed as numbers and percentages. Differences in numerical variables among the groups and intra-groups were examined by a t-test in independent groups. Differences in quality variables in ASA status between groups were examined using the chi-square test. Differences in MBP and HR within and between groups were investigated by repeated measures of variance analysis and student t test. The statistical significance level was considered $p < 0.05$.

Table 1

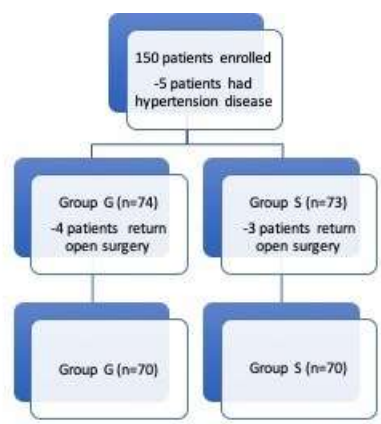
Evans (PRST) score

Systolic blood pressure	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Heart rate	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Sweating	No	0
	Moist skin	1
	Visible skin	2
Tears	No	0
	Yes	1
	Overflowing	2

Evans scores parameters determine the total score which can range from 0 to 8. Inadequate depth of anesthesia is scored as more than three. PRST: pressure, rate, sweating, tears

Figure 1

Flowchart



Group G: Granisetron group, Group S: Saline group

3. Results

One hundred fifty patients were enrolled to study. Four patients in group G and 3 patients in group S were returned to open surgery and excluded from the study. One patient in group G and 2 patients in group S had hypertension disease and they excluded from the study. One hundred forty patients were analyzed finally (Figure 1).

The demographic variables (gender, age, weight, height and body mass index (BMI)) were similar in both groups (Table 2) (p>0.05). The baseline blood pressure measurements were demonstrated in table 2 (p>0.05). The MAP and HR reduced after induction in both groups but there were no differences between groups (p>0.05). The mean blood pressure was decreased in 22 patients (%31.4) in group S and 8 patients (%11.4) in group G compared to baseline values after 15 minutes of granisetron administration (p <0.05) at reverse Trendelenburg position (Table 3). At the same period, the heart rate was decreased in 12 patients (%17.1) in group G 18 patients (%25.7) in group S (p<0.05) (Table 3). Although granisetron group was more stable and closer to baseline hemodynamic variables than the control group, there was no statistically significant difference in hemodynamic variables (MBP and HR) between the groups in other measurement times (p> 0.05) (Figure 2&3). Both groups were similar in respect to Evans Score (p>0.05) (Table 1).

Table 2

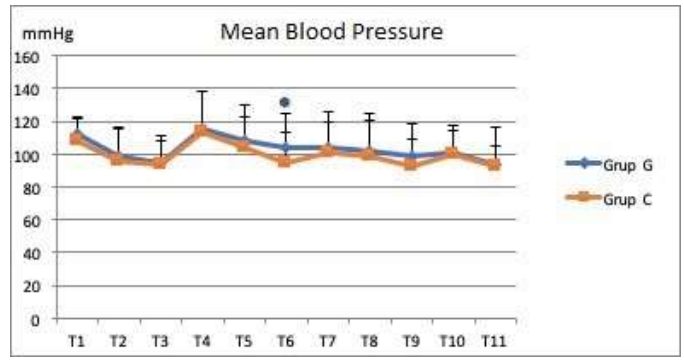
Demographic data

		Group S (n=70)	Group G (n=70)	p
ASA (n, %)	I	34 (%48.6)	35 (%50)	0.866
	II	36 (%51.4)	35 (%50)	
Gender (n, %)	Male	51 (%72.9)	48 (%68.6)	0.710
	Female	19 (%27.1)	22 (%31.4)	
Length (cm) (mean±SD)		168.8±9.5	168.5±8.3	0.821
Weight (kg) (mean±SD)		77.0±11.4	78.6±12.0	0.424
Age (yr) (mean±SD)		47.5±14.9	51.2±11.2	0.099
BMI (kg/m^2) (mean±SD)		27.2±4.6	27.8±4.3	0.491
Evans (PRST) score (mean±SD)		1.64±1.38	1.57 ±1.35	0.758
Systolic blood pressure (mmHg)		147.7±15.7	144.9±18.2	0.413
Diastolic blood pressure (mmHg)		87.4±9.9	84.4±11.4	0.146
Mean blood pressure (mmHg)		112.7±10.2	108.5±13.5	0.076

ASA: American Society of Anesthesiologists Status, BMI: Body mass index, PRST: pressure, rate, sweating, tears

Figure 2

Mean Blood Pressure



*Group G: Granisetron group, Group S: Saline group, T1: one minute before induction, T2: one minute after induction, T3: one minute before entubation, T4: one minute after entubation, T5: 10 minutes of granisetron administration, T6: 15 minutes of granisetron administration, T7: 20 minutes of granisetron administration, T8: 25 minutes of granisetron administration, T9: 30 minutes of granisetron administration, T10: 35 minutes of granisetron administration, T11: 40 minutes of granisetron administration, * p<0.05 between two groups*

Figure 3

Heart Rate

*Group G: Granisetron group, Group S: Saline group, T1: one minute before induction, T2: one minute after induction, T3: one minute before entubation, T4: one minute after entubation, T5: 10 minutes of granisetron administration, T6: 15 minutes of granisetron administration, T7: 20 minutes of granisetron administration, T8: 25 minutes of granisetron administration, T9: 30 minutes of granisetron administration, T10: 35 minutes of granisetron administration, T11: 40 minutes of granisetron administration, * p<0.05 between two groups*

Table 3

Patients data with hypotension and bradycardia

	Group G (n=70)	Group S (n=70)	p
T2 (n, %)			
· Hypotension	25 (35.7)	26 (37.1)	0.984
· Bradycardia	20 (28.5)	19 (27.1)	0.986
T6 (n, %)			
· Hypotension	8 (11.4)	22 (31.4)	0.001
· Bradycardia	10 (14.2)	21 (30)	0.025

T2: one minute after induction, T6: 15 minutes of granisetron administration

4. Discussion

This study showed that administrating preemptive granisetron couldn't prevent the incidence of hypotension after anesthesia induction in adult patients. But it prevented the incidence of hypotension after reverse Trendelenburg position and CO_2 insufflation in 15th minute after granisetron administration. On the other hand, we observed a more stable and closer to baseline hemodynamic variables in granisetron group than the saline group. As far as we are concerned, this may be the first study administering preemptive granisetron in adult patients for preventing hypotension under general anesthesia.

Hypotension occurs generally both during spinal and general anesthesia. Both the intravenous and inhalations anesthetics cause hypotension during in general anesthesia. Also in this study, we used propofol for induction and sevoflurane for maintenance of anesthesia. They were decreased the systemic vascular resistance and cardiac output. In spinal anesthesia venous return, cardiac output, and systemic vascular resistance were decreased and this was the main mechanism of hypotension.[8] Bradycardia and hypotension from stimulation of cardiac chemoreceptor and mechanoreceptor were established.[9] Spinal anesthesia-related triggering of BJR is known to result from stimulation of 5-HT3 receptors in vagal nerve endings.[10,11] In the previous study showed that the effects of serotonin administration on systemic hemodynamics variable on rabbits. It revealed that hypotension and bradycardia similar to that associated with BJR occurred. 5-HT3 receptors have been associated with anxiety, vomiting, and stress-induced gastrointestinal problems. Another study showed that granisetron was significantly prevented paradoxical bradycardia and reduce the systolic blood pressure (SBP) due to bleeding.[12] So, in this study, we observed that more bradycardia in group S after reverse Trendelenburg position with CO_2 insufflation in 15th minute of granisetron administration. We thought that this could be as the same mechanism (5HT3 receptor blockade inhibited the vagal reflex) of the previous studies.

When serotonin is administered iv, vasoconstriction and consequent increase in preload cause blood pressure elevation. Golparvar et al.[4] have shown that ondansetron used before induction in an elderly patient population is effective in prevented post-induction hypotension but no effects on heart rate. They used ondansetron 20 minutes before induction. Granisetron's peak onset time is 3-5 minute after iv. administration and hypotension caused by propofol have a peak effect after 1-3 minutes of induction. For this reason, we administered granisetron which was another 5HT3 antagonist, five minutes before induction but did not find any effect on post-induction hypotension. There is no study for the best time interval for granisetron administration for prevention of post-induction hypotension. Also, elderly people have different hemodynamic variable than adults. In our study, we included adult patients (18-65yr) as the elderly population lacks dramatic response to hypotension. So, we didn't observe any changes in this period in both groups. The depth of anesthesia is a common reason for hemodynamic changes due to laryngoscopy. The high level of serotonin may play a role in this effect. PRST score (pressure, rate, sweating, tears) was defined by Evans and proposed for the detection of inadequate depth of anesthesia. Evans scores parameters determine the total score which can range from 0 to 8. Inadequate depth of anesthesia is scored as more than three [13]. In our study, the scores were similar in both groups after intubation. We used BIS to monitored the depth of anesthesia and all intubation were performed at below 40. So, we didn't observe hypertension or tachycardia response due to laryngoscopy.

The exact mechanism of granisetron preventing hypotension after induction in adult patients is unknown and can't be explained by BJZ reflex since 5HT3 receptors are located intracardiac.[14] In the animal model, 5HT administration was caused by vasodilation and shivering and no side effects were observed in hemodynamic variables.[15] We observed that the granisetron group was more stable and closer to baseline hemodynamic variables than the control group without statistically significant variables. But in 15th minute after granisetron administration, it prevented hypotension in group G after reverse Trendelenburg position with CO_2 insufflation in 15th minute of granisetron administration.

James et al.[16] performed granisetron before the tilt test and they found that it reduced the early sympathetic component of the syncope with less decrease in systolic artery pressure. Laparoscopic cholecystectomy is a common procedure in general surgery. In this process, intraabdominal pressure increases due to CO_2 insufflation. As a result, increased intraabdominal pressure increases the vena cava pressure and causes a decrease in preload similar to that of spinal anesthesia and bleeding. And the reverse Trendelenburg position contributed to this decreased. In our study, we prevented hypotension at 15th minute of granisetron administration in reverse Trendelenburg position with CO_2 insufflation. Although we can not reveal its mechanism precisely, we think that the decrease in preload after vena cava pressure with increased intraabdominal pressure increase is since we have eliminated the effect of the heart reflex due to vagal stimulation because we have blocked intracardiac 5HT3 receptors.

Different regimens and type of 5-HT3 receptor antagonists have been used previously. Varying pharmacologic properties of different 5-HT3 receptor antagonists impede comparison. Granisetron has a plasma half-life of approximately 4.2–6.1 hours, which increases among elderly patients (>65 years); 12% of this drug is excreted unchanged via urine, with the remainder metabolized by the liver.[17] The previous study showed cardiovascular side effects after administrating 40 microgram/kg to 10 microgram/kg granisetron.[18] So, FDA advice to administered granisetron 3 mg/day total (3x1 mg). In this study, we limited by the dosage of granisetron to 1 mg like previous study about during spinal anesthesia in cesarean delivery [19]. Consequently, dosages and the type of used 5-HT3 receptor antagonists should be investigated in further studies.

There are some limitations to our study. First, we administered granisetron 5 min. before anesthesia induction. There is no study for the best time interval for granisetron administration for prevention of post-induction hypotension. Because of this many studies needs for granisetron application timing. The other, we used only the dosage of FDA suggested and we couldn't compare the effects of different dosage on hemodynamic response.

In conclusion, Granisetron prevented hypotension after reverse Trendelenburg position and CO_2 insufflation in 15th minute of granisetron administration. It can be used safely in adult patients and patients having risks of hypotension due to positions during general anesthesia.

Statement of ethics

Ethics committee approval was obtained from Ankara Dışkapı Yıldırım Beyazıt E&R Hospital Ethics Committee for our study. (Institutional Ethics Committee approval and written informed consent (Ref no 28/19, 04/04/2016) were obtained, and the study was registered in clinicaltrials.gov (NCT03180229).)

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Surgical and Medical Practices: S.A, B.N. Concept: B.N., F.K.A., Design: G.B.A, G.Ü., F.K.A., S.A. Data Collection or Processing: S.A., F.K.A. Analysis or Interpretation: S.A., G.Ü., Literature Search: B.N.,S.A. Writing: S.A., G.B.A., F.K.A

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