



Attenuation of spinal anesthesia induced hypotension with granisetron in type I diabetic parturients: A randomized controlled clinical trial

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ABSTRACT

Background: This study aimed to assess the safety and efficacy of intravenous granisetron as adjuvant therapy for spinal anesthesia-induced hypotension in type I diabetic parturients undergoing CS.

Methods: This double-blinded, parallel-group, randomized trial enrolled 68 adult parturients who were scheduled for CS under spinal anesthesia. The patients were randomly allocated to two groups (34 parturients each). In the granisetron (G) group, 1 mg of granisetron diluted in 10 mL of normal saline was administered intravenously 10 minutes prior to spinal anesthesia. While in the control (C) group, 10 mL of normal saline was administered in the same manner. The primary outcomes were total ephedrine consumption and frequency of use. Secondary outcomes included the total atropine consumption and frequency of use, nausea, vomiting, estimated intraoperative blood loss, patient satisfaction, Apgar score, and hemodynamic parameters.

Results: Group G had a significant reduction in the total ephedrine consumption ($P = 0.009$) and its frequency of use ($P = 0.034$). While the total atropine consumption and frequency of use, intraoperative blood loss, and patient satisfaction were not significantly different between the two groups. Nausea and vomiting were significantly reduced in group G. After 5 minutes of delivery, the Apgar score was significantly elevated in group G. The reduction of heart rate and hypotension was significantly lowered in group G.

Conclusion: In type I diabetic parturients, prophylactic use of granisetron can be effective in reducing ephedrine usage and attenuating the spinal anesthesia-induced hypotension during CS.

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1. Introduction

Spinal anesthesia is widely used for elective cesarean section (CS) in diabetic parturients [1]. Spinal anesthesia has little effect on the hormonal stress response and the blood glucose level. Thus, the incidence of hyperglycemia as well as other maternal and fetal complications is reduced [2].

Hypotension is considered the most common adverse effect of spinal anesthesia. It is defined as systolic blood pressure (SBP) of 90 or 100 mmHg in absolute terms or a relative decrease of 20% from baseline [3]. The frequency of hypotension can be as high as 70%–80% when pharmacological prophylaxis is not used [4].

The pathophysiology of post-spinal hypotension is mostly due to the parasympathetic power's predominance in dilating blood vessels, resulting in blood pooling in the dilated venous vessels [5]. Hypotension begins shortly after the local anesthetic is injected intrathecally, and it can last for several hours afterward. Sudden bradycardia can develop from this parasympathetic reflex. It is activated from the

contraction of unfilled left ventricular mechanoreceptors or chemoreceptors. This reflex is known as Bezold Jarisch reflex (BJR) [6]. Additionally, direct stimulation of cardiac serotonin (5-HT₃) chemoreceptors situated on cardiac vagal afferents with 5-HT or 5-HT₃ agonists induces the BJR [7].

The severity of hypotension is determined by the height of the block, the position of the parturient, the volume status, and whether the CS is elective or emergency. It can cause nausea and/or vomiting. Hypotension can be dangerous to both the mother and the baby. The mother may become unconscious, and pulmonary aspiration may develop, while the baby might suffer from hypoxia, acidosis, and neurological injury [8].

Diabetes mellitus is a widespread disease that is characterized by chronic hyperglycemia secondary to a reduction in the functional efficacy and/or a deficiency of insulin. Chronic hyperglycemia has been found to cause progressive autonomic neuronal dysfunction. Diabetic neuropathies, such as cardiac autonomic neuropathy are a prevalent chronic

consequence of type 1 and type 2 diabetes [9]. Cardiac autonomic neuropathy attenuates the compensatory response of the cardiovascular system to spinal anesthesia. Hence, hypotension becomes more severe in diabetic parturient than in non-diabetics. In addition, subclinical cardiac neuropathic dysfunction in the form of changes in heart rate (HR) variability may be detected within 2 years of diagnosis in type 1 diabetes [10].

Hypotension and bradycardia are commonly treated with intravenous fluid therapy, ephedrine, and atropine. Severe and/or quickly worsening bradycardia may necessitate immediate cardiac resuscitation [11]. However, fluid therapy can lead to fluid overload and urinary retention. Ephedrine has many drawbacks including tachyphylaxis and crossing of the placenta causing fetal acid base disturbance [12]. Atropine is an anticholinergic drug with adverse tachyphylaxis effect [13].

Granisetron is a 5HT₃ receptor antagonist used to treat nausea and vomiting in cancer therapy and post-operatively [14]. The proposed mechanism of granisetron in treating hypotension is blockage of the BJR through antagonism of the 5HT₃ receptors at the intracardiac vagal nerve endings [3].

This study aimed to assess the safety and efficacy of granisetron as an adjuvant treatment for spinal anesthesia-induced hypotension in type I diabetic parturients who were scheduled for CS.

2. Methods

2.1. Ethical considerations

The study was carried out following approval by the Ethics Committee of the Faculty of Medicine, Suez Canal University, Egypt. This trial was registered at the ClinicalTrials.gov (Trial ID: NCT03091881). A written informed consent was obtained from each participant after explanation of the purpose and procedures of the study. All participants' data were kept confidential.

2.2. Study design, setting, and date

This double-blinded, parallel-group, randomized trial was conducted at the day-case surgical theatres of Suez Canal University Hospital, Egypt between March and September 2018.

2.3. Eligibility criteria

The present study included 68 adult parturients, aged 21 years or more, with type I diabetes mellitus who were scheduled for elective CS under spinal anesthesia. We excluded patients who had apparent anatomical abnormalities, infection at the site of spinal injection,

a history of allergy to the used drugs, chronic hypertension, pregnancy-induced hypertension, congenital or rheumatic heart diseases, antepartum hemorrhage, fetal distress, as well as those with gestational age < 36 weeks. Patients who declined participation in the study or spinal anesthesia were also excluded.

2.4. Randomization, allocation concealment, and blinding

A computer-generated randomization software was used to randomly allocate the participants into two groups using a block size of 3. Within each block, the order of interventions was selected by a computer random number generator. This method was adopted to ensure that the number of patients in each group remained constant throughout the trial. The trial participants and the outcome assessor were kept blinded to the allocation of the intervention.

2.5. Interventions

2.5.1. Preoperative management

Sixty-eight type I diabetic parturients were randomly allocated into two groups (34 participants each). The granisetron (G) group received an intravenous (IV) injection of 1 mg of granisetron (GRANISETRON®, 1 mg/mL, European Egyptian Pharma Industries, Egypt) diluted in 10 mL of normal saline 10 minutes before spinal anesthesia. The control (C) group received an IV injection of 10 mL of normal saline as a placebo considering the same timing.

All participants were subjected to detailed history taking and thorough physical examination. Routine preoperative investigations were performed including prothrombin time, partial tissue thromboplastin time, international normalized ratio, and glycosylated hemoglobin (Hb A1c).

2.5.2. Intraoperative management

Upon arrival to the operating room, all patients received 500 mL of the lactated ringer IV over 10 minutes. The pre-anesthesia HR and mean arterial blood pressure (MABP) readings were reported just before spinal anesthesia.

Spinal anesthesia was performed in the sitting position using a 25-Gauge spinal needle. Either the L3-L4 or L4-L5 interspace was chosen, and 2.5 mL of 0.5% hyperbaric bupivacaine (Bupivacaine mylan®, Mylan medical SAS, Ramco, Paris, France) was injected over 30 seconds.

After spinal anesthesia, the parturients were put in the supine position with 15° of left lateral tilt. Supplemental oxygen was delivered through a nasal cannula at 2 L per min. The sensory level was assessed after 5 minutes of spinal anesthesia by checking for cold sensation and again with a forceps bite immediately before skin

incision. The motor block was assessed according to the Bromage's scale [15] (0 = none, 1 = just able to move the knee but not the hip, 2 = able to move the foot only, 3 = unable to move the knee or foot) after 5 min and repeated just before skin incision.

Up until 20 minutes into the procedure, the heart rate and MABP were monitored every two and three minutes respectively, and the monitoring was thereafter continued every five minutes up until the end of the first hour following spinal anesthetic. Maintenance fluid of lactated Ringer's solution was given at a rate of 10 mL/kg/h in both groups during the surgical procedure. When the MABP decreased by 20% less than the preoperative level or less than 65 mmHg, an additional rapid bolus infusion (100 mL) of lactated Ringer's was given at each episode of hypotension and intermittent doses of 6 mg of ephedrine were given and repeated if hypotension persisted for 5 minutes or recurred. If bradycardia occurred ($HR \leq 60$ beat/min), 0.5 mg of atropine was considered IV if bradycardia was not associated with hypotension.

The total consumption and frequency of use for both ephedrine and atropine were recorded. The incidence of nausea and vomiting and the total intraoperative blood loss were assessed and were managed according to the usual protocols. The patient's satisfaction and the baby's Apgar score were also recorded. Patients' satisfaction was determined by directly asking them to specify their level of satisfaction ultimately on a scale from 0 to 10, where 0 indicates they were completely dissatisfied and hoped would not have the same experience and 10 indicates they were completely satisfied and hoped to have the same experience afterwards.

2.6. Outcomes

The primary outcomes were the total ephedrine consumption and frequency of use. Secondary outcomes were the total atropine consumption and frequency of use, nausea, vomiting, intraoperative blood loss, the patient's satisfaction, Apgar score, and intraoperative hemodynamic parameters (heart rate and systolic, diastolic, and mean arterial blood pressures).

2.7. Sample size

According to Eldaba and Amr [16], an estimated 34 patients per group is needed to provide 80% power for independent populations, assuming that the total dose of ephedrine would be reduced in the granisetron group to 4.07 mg (corresponding to a mean dose of ephedrine in the control group of 10.7 mg), with a standard deviation of 8.9, and a unilateral α of 0.05. The calculated sample size was 28.255 subjects per

group. We added 20% to account for the loss to follow-up. The final sample size was then 34 subjects per group (total sample size was 68 subjects).

2.8. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics) for Windows, version 25 (IBM© Corp., Armonk, NY, USA). For quantitative data, the Shapiro-Wilk test for normality was performed. Normally distributed data were summarized as mean \pm standard deviation (SD). The studied groups were compared using ANOVA, the Student's unpaired t-test, or the Mann-Whitney U-test. Qualitative data were summarized as frequencies, and associations were tested using the Pearson's Chi-square test or Fisher's exact test. All tests were two-tailed. A p-value <0.05 was considered significant.

3. Results

Seventy-five patients were recruited, 3 patients refused to participate, 2 patients had coagulation disorders and 2 patients declined spinal anesthesia. Sixty-eight patients were enrolled in the study and were randomly allocated into two groups (Figure 1).

Patients' characteristic including the age, HbA1c, diabetes mellitus duration, height, weight, body mass index, and duration of surgery were non significantly different between the studied groups (Table 1).

The total ephedrine consumption was significantly reduced in group G than group C (0.53 ± 1.7 mg vs 2.65 ± 4.2 mg, $p = 0.009$). The frequency of ephedrine use was significantly lower in group G than group C ($p = 0.034$). However, the total atropine consumption was lower in group G than group C but did not reach a significant difference (0.015 ± 0.1 mg vs 0.059 ± 0.2 mg, $p = 0.168$). The Frequency of need to atropine was not significantly different between both groups. The incidence of nausea and vomiting was significantly reduced in group G compared to group C ($p = 0.008$). The intraoperative blood loss and patient satisfaction scores were non-significantly different between both groups. Neonatal outcomes depending on the Apgar score were comparable at 1 minute after delivery ($p = 0.631$), but after 5 minutes, the Apgar score was significantly higher in group G compared to group C ($p = 0.026$, Table 2).

Both groups were matched regarding the pre-spinal hemodynamic readings. However, intraoperative HR was comparable between both groups during the time interval from two minutes till 18 minutes. The HR fluctuation was significantly diminished in group G compared to group C at the time interval from 20 minutes onward till 60 minutes (Figure 2).

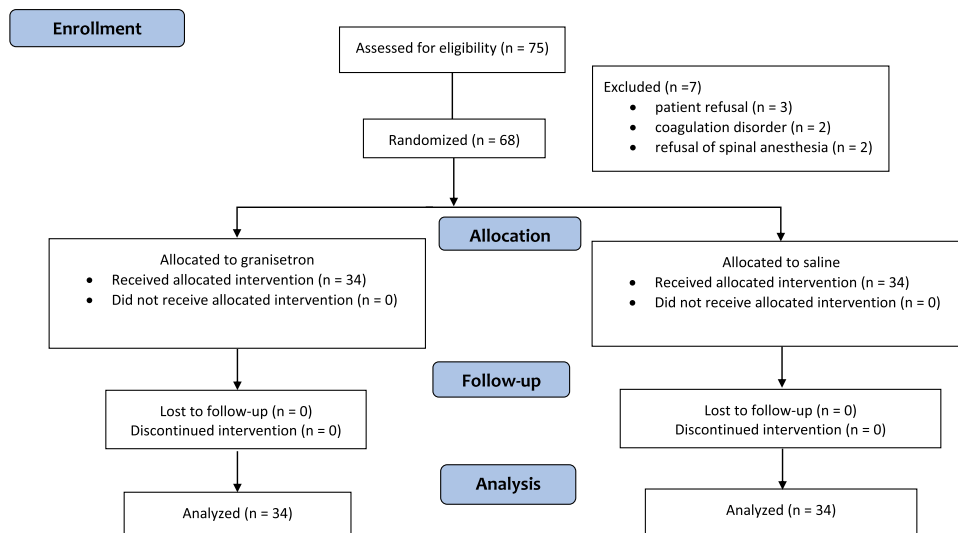


Figure 1. The trial flow chart.

Table 1. Patients' demographic and clinical characteristics (total n = 68).

	Granisetron Group (n = 34)	Control Group (n = 34)	P value
Age (years)	27 ± 3	26 ± 3	0.143
HbA1c	7.16 ± 1.0	6.68 ± 1.2	0.079
DM (years)	12.82 ± 2.5	12.12 ± 2.3	0.224
Height (cm)	163.41 ± 3.8	164.62 ± 3.4	0.176
Weight (kg)	88.68 ± 5.0	86.24 ± 5.3	0.054
BMI	32.96 ± 2.3	31.85 ± 2.3	0.052
Duration of surgery (minutes)	46.29 ± 6.9	46.44 ± 7.5	0.933

SD: standard deviation; n: number; HbA1c: glycosylated hemoglobin; DM: diabetes mellitus; cm: centimeter; kg: kilogram; BMI: body mass index. Data are presented as mean ± SD. P-values are based on independent samples Student T test.

The pre-spinal SBP was not significantly different between the study groups. After 3 minutes from spinal anesthesia, SBP was significantly reduced in group C compared to group G at different time intervals, except at the time interval from 20 to 35 minutes, the SBP was comparable between both groups (Figure 3).

The pre-spinal DBP was not significantly different between the study groups. At 3 minutes from spinal anesthesia, the DBP was significantly lower in group C than group G. However, the DBP was comparable between both groups at different time intervals, except for readings at T 25, T 30, and T 45, the DBP was significantly lower in group C than group G (Figure 4).

The pre-spinal MABP was not significantly different between the study groups. After 3 minutes from spinal anesthesia administration, the MABP was significantly reduced in group C compared to group G at 25 minutes and at the time interval from 40 to 55 minutes (Figure 5).

4. Discussion

Hypotension is a common problem that could affect the mother and the newborn during elective CS under spinal anesthesia. It may arise from

Table 2. Intraoperative ephedrine and atropine consumption, intraoperative blood loss, incidence of nausea, vomiting, patient's satisfaction, and Apgar score.

	Granisetron Group (n = 34)	Control Group (n = 34)	P value
Total ephedrine consumption (mg)	0.53 ± 1.7	2.65 ± 4.2	0.009*
Frequency of ephedrine use			
None	31 (91%)	23 (67%)	0.034*
One (6 mg)	3 (9%)	7 (21%)	
Two (12 mg)	0	4 (12%)	
Total atropine consumption (mg)	0.015 ± 0.1	0.059 ± 0.2	0.168
Frequency of atropine use			
None	33 (97%)	30 (88%)	0.163
One (0.5 mg)	1 (3%)	4 (12%)	
Nausea & vomiting			
None	23 (68%)	12 (35%)	0.008*
Once	11 (32%)	22 (65%)	
Estimated intraoperative blood loss (mL)	555.88 ± 88.6	565.88 ± 80.5	0.628
Patient satisfaction score	7.38 ± 1.1	6.94 ± 1.4	0.152
Apgar score at 1 min	8.41 ± 0.5	8.47 ± 0.1	0.631
Apgar score at 1 min			
8	20 (59%)	18 (53%)	0.625
9	14 (41%)	16 (47%)	
Apgar score at 5 min	9.74 ± 0.4	9.47 ± 0.5	0.036*
Apgar score at 5 min			
9	9 (26.5%)	18 (53%)	0.026*
10	25 (73.5%)	16 (47%)	

SD: standard deviation; n: number; min: minutes; mg: milligram.

Data are presented as mean ± SD or number (%). P-values are based on the independent samples Student T test or the Pearson chi-square test.

*Significant at p < 0.05.

sympathetic block and peripheral serotonin receptor (5-HT₃) stimulation, which is called BJR. Serotonin is the mediator that stimulates intracardiac 5-HT₃ receptors leading to significant hypotension. Diabetes mellitus aggravates the hypotension due to autonomic neuron dysfunction. Hence, the aim of our study was to assess the safety and efficacy of intravenous granisetron as an adjuvant therapy for spinal anesthesia-induced hypotension in type I diabetic parturients undergoing CS.

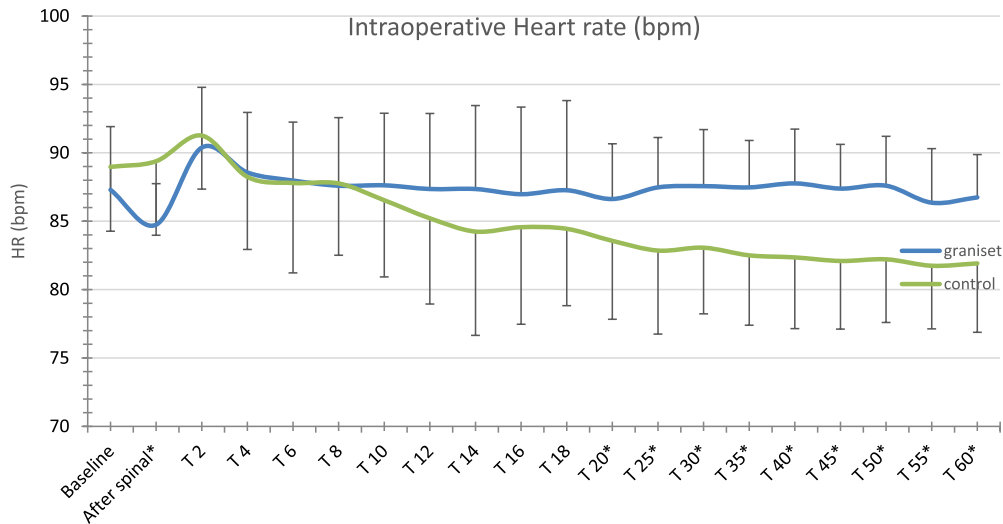


Figure 2. Intraoperative heart rate. bpm: beat per minutes; HR: heart rates; Independent samples T-test; * significant at $p < 0.05$; T: times; T2 – T20: values at every 2 minutes intervals after spinal anesthesia for 20 minutes. T20 – T60: values after 20 minutes of spinal anesthesia, every 5 minutes, to the conclusion of 60 minutes.

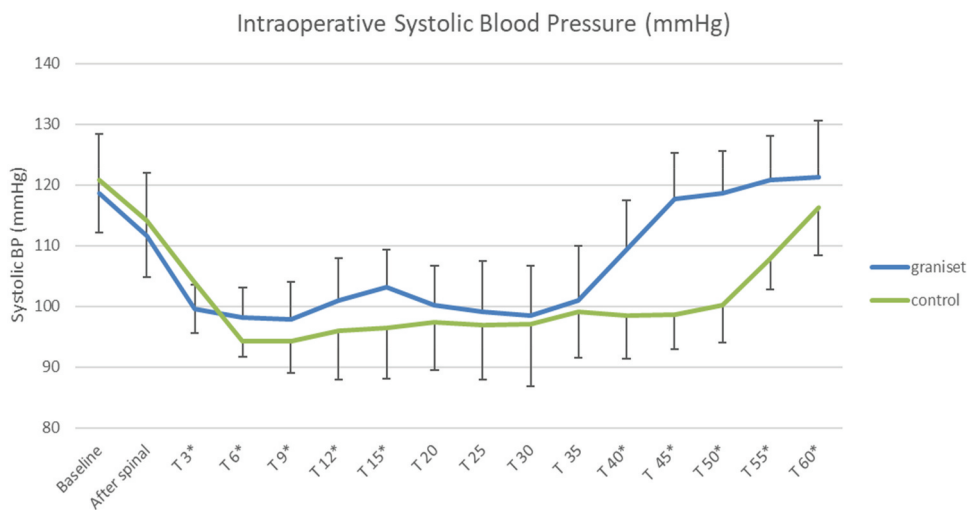


Figure 3. Intraoperative systolic blood pressure (mmHg). Independent samples T-test; * significant at $p < 0.05$; T: times. T3 – T20: values at every 3 minutes intervals after spinal anesthesia for 20 minutes. T20 – T60: values after 20 minutes of spinal anesthesia, every 5 minutes, to the conclusion of 60 minutes.

Our results revealed that granisetron caused a significant reduction in the total dose and the need for further bolus doses of ephedrine. In addition, granisetron significantly reduced nausea and vomiting. Apgar score after 5 minutes from delivery showed a significantly higher score in the granisetron group compared with the control group. The intraoperative HR and systolic, diastolic, and mean arterial blood pressures were significantly reduced in the control group compared to the granisetron group at different intraoperative time intervals.

Patients characteristics including the age, height, weight, and body mass index were not significantly different between both groups indicating similar maternal risk factors for spinal anesthesia-induced hypotension [5]. Also, the years since diabetes mellitus was discovered, HbA1c, and the duration of surgery showed no significant differences indicating similar clinical risk factors for spinal

anesthesia-induced hypotension. HbA1c is considered an indicator of long-term control of diabetes [17]. Thus, the effect of long-term control of diabetes on autonomic function could be established.

Ephedrine is an alpha and beta-adrenergic agonist used to treat anesthesia-induced hypotension, allergic conditions, bronchial asthma, and nasal congestion. Ephedrine produces tachycardia in the mother, has negative consequences on uterine blood flow, and lowers the fetal pH [12]. In the current study, the total ephedrine consumption and frequency of use were significantly reduced. Similarly, Khalifa [18], Eldaba and Amr [16], Chatterjee et al. [19], and Lamichhane et al. [20] reported that the prophylactic use of granisetron reduced the vasopressor need in CS and the severity of spinal anesthesia-induced hypotension, nausea, and vomiting. However, Mohammadi et al. [21] observed

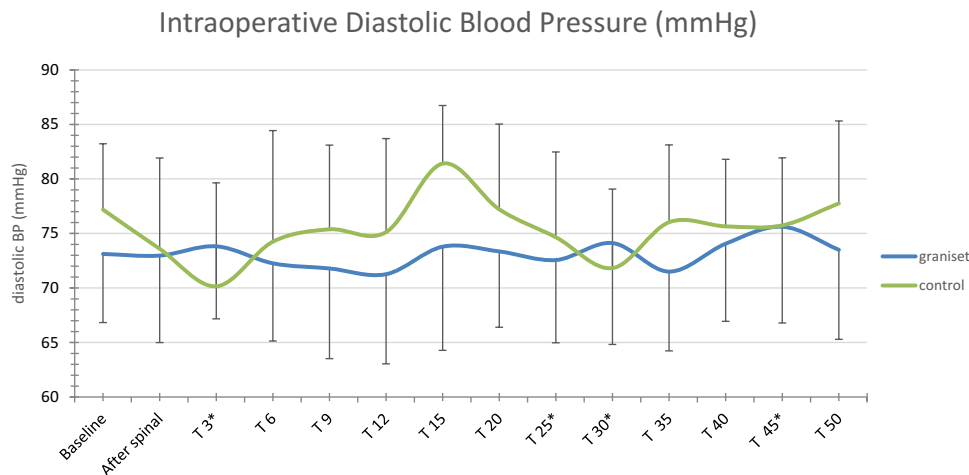


Figure 4. Intraoperative diastolic blood pressure (mmHg). Independent samples T-test; * significant at $p < 0.05$; T: times; T3 – T20: values at every 3 minutes intervals after spinal anesthesia for 20 minutes. T20 – T60: values after 20 minutes of spinal anesthesia, every 5 minutes, to the conclusion of 60 minutes.

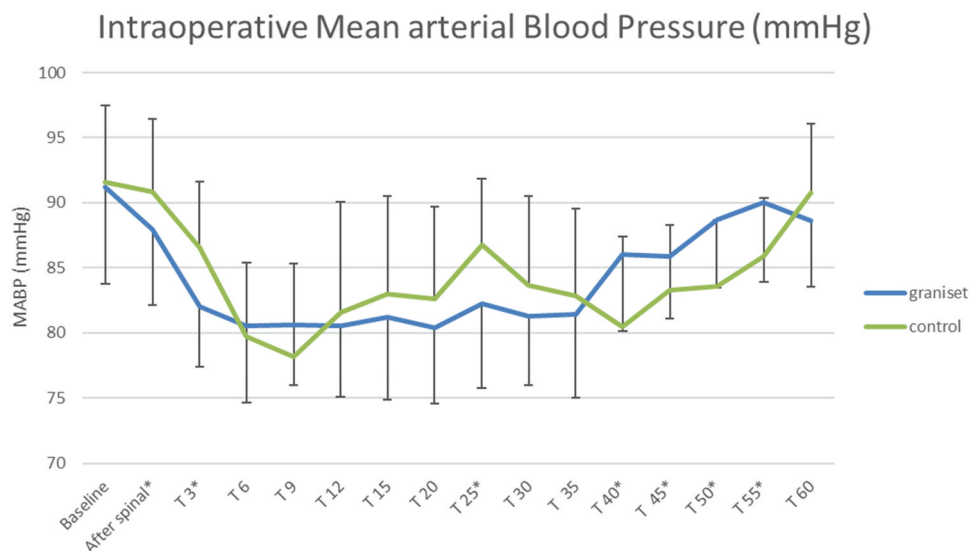


Figure 5. Intraoperative mean arterial blood pressure (mmHg). Independent samples T-test; * significant at $p < 0.05$; T: times; T3 – T20: values at every 3 minutes intervals after spinal anesthesia for 20 minutes. T20 – T60: values after 20 minutes of spinal anesthesia, every 5 minutes, to the conclusion of 60 minutes.

no significant effect of 3 mg granisetron on the vasopressor need for the management of post-spinal hypotension. This discrepancy could be attributed to different methodology. Mohammadi et al. [21] used both intrathecal fentanyl and bupivacaine, which could worsen the hypotension. Moreover, intraoperative blood loss and sensory block level that could influence the perioperative hypotensive episodes were not alleviated.

Spinal anesthesia-induced hypotension is caused by different mechanisms. The venous return is reduced in pregnant females due to aortocaval compression [22]. Spinal anesthesia reduces venous return even more due to sympathetic blockage, resulting in a drop in blood pressure [23]. The carotid baroreceptors detect the drop in blood pressure, causing sympathetic activation and fast contraction of the ventricles as

a compensatory response. Rapid contraction of under-filled ventricles activates serotonin receptors in the walls of the left ventricle, resulting in significant hypotension, bradycardia, and vasodilation due to vagal activation. This cardioinhibitory reflex is called BJR [6]. Additionally, hypotension is worsened in type I diabetic parturients due to dysfunction in the autonomic reflexes. Granisetron has a high affinity for 5-HT₃ receptors but a low affinity for other 5-HT receptors as well as adrenergic, histaminic, dopaminergic, and opioid receptors [24]. Granisetron action is attributed to its antagonism of the 5-HT₃ receptor and attenuation of the BJR. For treatment of spinal anesthesia-induced hypotension for caesarean section, IV fluids, the use of vasopressors such as ephedrine, and phenylephrine, and left lateral tilt have been used. However, none of these strategies was adequate on its

own to completely prevent hypotension associated with spinal anesthesia [11]. Also, as shown in our study, prophylactic use of granisetron could be an effective adjuvant in attenuation of hypotension induced by spinal anesthesia and reduction of the ephedrine use.

Atropine has an anticholinergic action and is used for bradycardia. Our results did not show significant difference in the atropine use between the granisetron and the control groups. This might be due to absence of significant bradycardia in our study. This agrees with Chatterjee et al. [19] and Lamichhane et al. [20] who did not report bradycardia in their study subjects. However, Eldaba and Amr [16] discovered a significant difference in the incidence of bradycardia, with more parturients in the saline group experiencing bradycardia than in the granisetron group. Eldaba and Amr [16] explained that by the inhibiting effect of granisetron on the BJR.

In addition, granisetron administration significantly lowered the incidence of nausea and vomiting, which conforms with the general antiemetic effect of granisetron. It is usually used for prevention of chemotherapy-induced nausea and vomiting [25].

The estimated intraoperative blood loss and spinal anesthesia have a compounding effect that might result in severe hypotension. As a result, we looked at how intraoperative blood loss affected the incidence of post-spinal hypotension in the two groups. Similar to Chatterjee et al. [19], we found that the intraoperative blood loss was comparable in both groups.

Patient's satisfaction was higher in granisetron group than the control group but did not reach a significant difference, which might be due to small number of patients. Granisetron reduced the morbidity, then, improved patient's satisfaction.

The Apgar score characterizes the state of babies shortly after birth and serves as a tool for systematic assessment [26]. In the current study, Apgar values at one minute after delivery were equivalent in the two groups, while Apgar values at 5 minutes after delivery were significantly higher in granisetron group than the control group. This could be explained by the effect of granisetron on the fetus, where it reduced the total ephedrine doses that can pass the placental and induce fetal adverse effects. Eldaba and Amr [16] and Chatterjee et al. [19] found that Apgar values were not significant and concluded that IV granisetron had no negative neonatal effects.

Regarding the HR, granisetron had a significant effect on HR fluctuation at the time interval from 20 minutes onward till 60 minutes. Our findings are consistent with Khalifa [18] and Tsikouris et al. [27], who found that granisetron infusions reduced HR variations during head-up tilt table testing, which were associated with the BJR blockage. Similarly, an earlier animal study [28] reported that granisetron

administration slowed the drop in rabbits HR. In contrast to our results, Rashad and Farmawy [29] and Lamichhane et al. [20] who used a similar dose (1 mg) of granisetron, and Shrestha et al. [30] who used 40 mcg/kg of granisetron, found that the drug did not have an acceptable impact. These contradictory findings are attributed to the intraoperative blood loss and the height of sensory block, which were not included in these studies. So, the patients in the granisetron group may have experienced more sensory block or more intraoperative blood loss than those in the placebo group.

In the current study, after three minutes from spinal anesthesia, the reduction of SBP in granisetron group was less than that in the control group at several time intervals. Likewise, Chatterjee et al. [19] and Zhang et al. [31] observed that spinal anesthesia-induced hypotension occurred after 3 minutes from the anesthesia administration and remained throughout the operation. However, Behdad et al. [32] and Shrestha et al. [30] found a non-significant difference in SBP between the two groups. Both studies did not account for surgical blood loss or other contributing factors, hence the results were different when compared to ours.

The trend of DBP was comparable in both groups throughout the study duration, except for the 3rd, 25th, 30th, and 45th minutes, indicating that granisetron had little effect on DBP when compared to SBP. Chatterjee et al. [19], Lamichhane et al. [20], and Behdad et al. [32] found a negligible effect of granisetron on DBP.

Both systolic and diastolic blood pressures are considered when calculating MABP. Because there was a little significant difference in DBP between the two groups at several time intervals, the changes in SBP were mirrored in a similar fashion, and we observed similar significant changes in the MABP. At the third minute after spinal anesthesia and from the 40th minutes onwards the trend of MABP was similar to the change in SBP between the two groups at the same time intervals. This agrees with Chatterjee et al. [19] who reported negligible effect of granisetron on DBP.

The current study is a single-center study with small sample size. Hence, larger, multicenter RCTs are needed.

5. Conclusion

In type I diabetic parturients, the use of granisetron before spinal anesthesia can reduce the usage of ephedrine and attenuate the spinal-induced hypotension during CS.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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