Original Article

A Comparative Study of Efficacy and Safety of Intravenous Ondansetron and Granisetron in Management of Intra-Operative Hypotension Induced Nausea and Vomiting in Patients Undergoing Caesarean Section under Spinal Anaesthesia

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ABSTRACT

Introduction: One of the cutting-edge therapeutic strategies being used to combat the well-known hemodynamic side effects of spinal anaesthesia namely bradycardia and hypotension, is the use of 5HT3 receptor antagonists. Two such widely used 5HT3 receptor antagonists are the antiemetic medications ondansetron and granisetron. It is important for anaesthesiologists to choose correct drug at right dose and right time to prevent haemodynamic instability after spinal anaesthesia.

Aims/ objective: To compare the efficacy of granisetron and ondansetron in caesarean section patients in reducing the hemodynamic reaction to spinal anaesthesia.

Materials and Method: Pregnant women of group O and group G were given ondansetron 4 mg and granisetron 3 mg through intravenous route as constituent of their pre-anaesthetic medication before giving spinal anaesthesia. Presence of (defined as heart rate exceeding 20% below baseline) and hypotension (defined as SBP less than 20% below baseline) was noted.7 To manage every case of bradycardia and hypotension, 0.5 mg of the drug atropine and 500 mcg of phenylephrine were given intravenously. For each patient, the total number of dosages utilised was recorded, and the total dose was computed.

Results: Both the drugs were effective in reducing intraoperative nausea and vomiting with no significant difference between two groups. There was appreciable decline in systolic blood pressure soon after spinal anaesthesia was given but it became stable after 10 minutes in both the groups. There was significantly lower incidence of hypotension in patients who were given granisetron before spinal anaesthesia as compared to patients who were given ondansetron ($p<0.05$). There was also less incidence of bradycardia in granisetron group but the difference was not significant ($p>0.05$).

Conclusion: Both drugs were effective in counteracting hypotension bradycardia but could not control early fall in blood pressure heart rate. High dose granisetron proved to be superior to low dose ondansetron in reducing incidence of hypotensive episodes caused by spinal anaesthesia.

Keywords: Granisetron, Ondansetron, Spinal Anaesthesia, Haemodynamic Instability, Hypotension, Bradycardia.

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INTRODUCTION

One of the cutting-edge therapeutic strategies being used to combat the well-known hemodynamic side effects of spinal anaesthesia namely bradycardia and hypotension, is the use of 5HT3 receptor antagonists.[1] Two such widely used 5HT3 receptor antagonists are the antiemetic medications ondansetron and granisetron.

Thirty-three percent of patients develop hypotension as a result of spinal anaesthesia, while thirteen percent experience bradycardia.[2] Due to the gravid uterus' additional constriction of the vasculature, these values spike to 75% in patients going through caesarean sections3. When hemodynamic instability is severe and goes unattended, it can cause cardiac arrest and mortality in addition to headache, nausea, and vomiting, which can be modest symptoms of the condition. Similar to this, as hemodynamic condition deteriorates, foetal distress is triggered.[3]

Currently, vasopressors (phenylephrine or ephedrine) and atropine are used as rescue drugs to treat these haemodynamic instabilities, both of which have their own negative consequences on the mother and/or the unborn child.[3]

While intrathecal administration of the local anaesthetic agent itself results in a halt of sympathetic outflow in the affected regions, causing parasympathetic overdrive and, consequently, a decline in blood pressure and heart rate, this decrease in hemodynamic variables causes the stimulation of 5HT3 receptors located in the inferoposterior wall of the left ventricle. The Bezold Jarish

reaction results in a blockage of the vasomotor centre, further lowering blood pressure and heart rate.[4] Therefore, blocking these receptors as a preventative measure will reduce the likelihood of hypotension and bradycardia, which will eventually result in less need for the above-mentioned rescue drugs.[5]

Ondansetron is often used in anaesthetic and surgical practise for the prevention of nausea and vomiting after surgery because it has an antiemetic action for approximately three hours and often needs numerous doses. [6] Its use as a pre-anesthesia medication to maintain hemodynamic state has recently undergone evaluation, and the results are encouraging. It is usable at doses ranging from 4 mg to 8 mg.[7] Ondansetron should be used at lower doses since, although its rarity, the risk of QT prolongation increases at greater doses while the effectiveness is steady. [8]

Yet another 5HT3 receptor inhibitor, granisetron, has a more potent and prolonged antiemetic action than ondansetron, lasting up to nine hours after administration.[6,9] It is frequently used to stop nausea and vomiting brought on by chemotherapy. Its effectiveness in reducing hemodynamic instability during anaesthesia as a pre-anaesthetic medication was recently clarified. The safe dosage range for this powerful 5HT3 receptor blocker is 1 mg to 3 mg, with a dose-dependent improvement in effectiveness and little to no risk of negative cardiac effects.[7,10]

The objective of this study was to compare the efficacy of granisetron and ondansetron in caesarean section patients in reducing the hemodynamic reaction to spinal anaesthesia.

MATERIALS AND METHODS

This was an open label randomised controlled trial with parallel 1:1 allocation in department of anaesthesiology in a tertiary care centre of eastern India from September 2022 to October 2022. The study was started after taking approval from institutional ethics committee and was conducted according to principles of declaration of Helsinki and Good Clinical Practice. Participant information sheet was provided to the future study subjects in their local languages and explained to them then written informed consent was taken from them.

With reported incidence of hypotension from previous studies[11], minimum sample size was calculated to be 62 with 31 women in each group to achieve power of 95% with 0.05 alpha value. With possible 10% attrition rate, we planned to recruit 35 patients in each group.

Inclusion Criteria: Pregnant women of age 21-35 years of age undergoing elective caesarean section, women with ASA Grade 2 or lower, duration of surgery less than or equal to 1 hour.

Exclusion criteria: Women with any contraindication to undergo spinal anaesthesia, patients taking sumatriptan or any other triptans, patients taking SSRI or MAO inhibitors, patients with history of pregnancy induced hypertension, patients with alcohol or other addiction, patients in which anaesthetic level achieved above T4, patients having more than 1 litre of bleeding during surgery, patients with neuropsychiatric, renal, hepatic, or cardiovascular disorders.

Pregnant women fulfilling our eligibility criteria were randomised into group O and group G. Pregnant women of group O were given ondansetron 4 mg through intravenous route and pregnant women of group G were given granisetron 3 mg through intravenous route as constituent of their pre-anaesthetic medication before giving spinal anaesthesia.

Prior to surgery, all participants received counselling. Eight hours of fasting were made sure of. Age, weight, and gestational age were all collected along with demographic information. Prior to the surgery, 1000ml of Ringer's Lactate had been administered onto each patient. Electrocardiogram, pulse oximetry, and non-invasive blood pressure monitoring were employed as monitoring modalities. Pre-anaesthetic drugs were given out in accordance with protocol. Heart rate and systolic blood pressure (SBP) were measured during rest.

All individuals received the same anaesthetic method. After being made to sit, a lumbar puncture was carried out, and a 25-gauge spinal needle was used to inject ten to fifteen mg of hyperbaric 0.5% bupivacaine into the midline of the intervertebral space between L3 and L4.

Throughout the entire process, a Ringer Lactate drip of 15ml/kg/hour was given. Following the onset of spinal anaesthesia, hemodynamic measurements were taken every two minutes for the first ten minutes, then every five minutes for the following 20 minutes.

Presence of (defined as heart rate exceeding 20% below baseline) and hypotension (defined as SBP less than 20% below baseline) was noted.7 To manage every case of bradycardia and hypotension, 0.5 mg of the drug atropine and 500 mcg of phenylephrine were given intravenously. For each patient, the total number of dosages utilised was recorded, and the total dose was computed.

Statistical analysis: Data recorded was presented into tabular form using Microsoft Excel 365 and then transferred to graph-pad version 8.4.3. Normal distribution of data was checked with the help of Shapiro Wilks test. Continuous data was presented in the form of mean ± standard deviation, and median and interquartile range as per finding of normality test. Unpaired t-test (for normally distributed) and Mann-Whitney U test (for non-normally distributed) was used to test statistical significance of difference in continuous data between groups. Categorical variables were presented in the form of frequencies and percentages, and analysed using Fisher's exact test. Measure of significance was taken as P-value less than or equal to 0.05.

RESULTS

Table 1: Comparison of baseline demographic and clinical characteristics of study participants between two groups

Parameters	Group O (n = 35)	Group G (n= 35)	P-value
Age in years (Mean ± SD)	28.39 ± 4.01	28.11 ± 4.72	0.79
Body Mass Index in kg/m^2 (Mean ± SD)	21.34 ± 3.22	21.77 ± 3.51	0.60
Duration of Surgery in minutes (Mean ± SD)	37.79 ± 7.52	38.08 ± 7.83	0.87
Time between anaesthesia and incision (Mean ± SD)	8 (7-10)	8 (6-9)	0.12
Intra-operative blood loss in ml (Mean ± SD)	231.63 ± 44.54	236.27 ± 51.15	0.69
Parity			
Primigravida, n	14	16	0.81
Multigravida, n	21	19	

here was no significant difference between two groups with respect to age, body mass index, parity, gestational age, intraoperative blood loss, duration of surgery or time interval between anaesthesia and incision (p>0.05).

Figure 2: Comparison of systolic blood pressure after spinal anaesthesia between two groups

Time after Spinal Anaesthesia in Minute	Mean SBP in mmHg (mean ± SD)		P-value (Unpaired t-test)
	Group O (n = 35)	Group G (n= 35)	
0	135.95 ± 10.31	131.79 ± 11.52	0.12
5	120.09 ± 10.24	122.16 ± 11.42	0.43
10	119.13 ± 10.11	119.17 ± 11.21	0.99
15	116.68 ± 9.98	123.75 ± 11.15	**0.007**
20	116.41 ± 9.95	121.93 ± 11.19	**0.03**
25	117.12 ± 10.03	119.15 ± 10.87	0.42
30	117.59 ± 10.09	121.54 ± 11.31	0.13

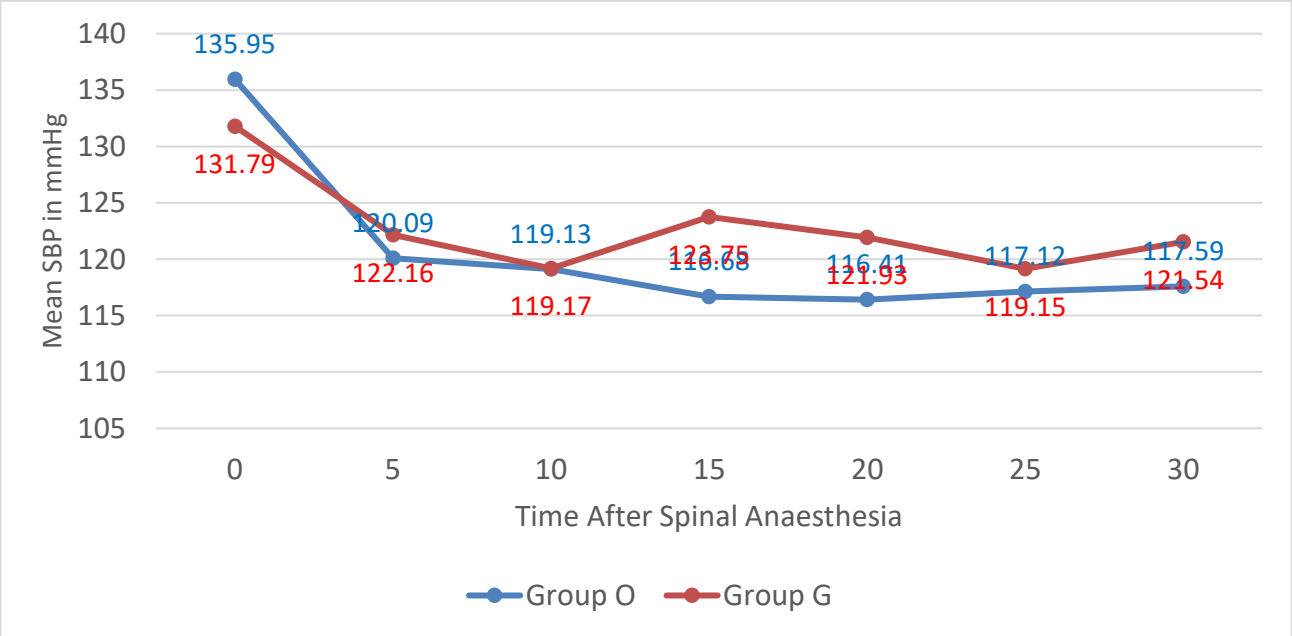

Figure 1: Comparison of Mean SBP between Two Groups

There was significant improvement in systolic blood pressure after 15 minutes of spinal anaesthesia in patients given granisetron before spinal anaesthesia as compared to patients given ondansetron (p<0.05). There was appreciable decline in systolic blood pressure soon after spinal anaesthesia was given but it became stable after 10 minutes in both the groups.

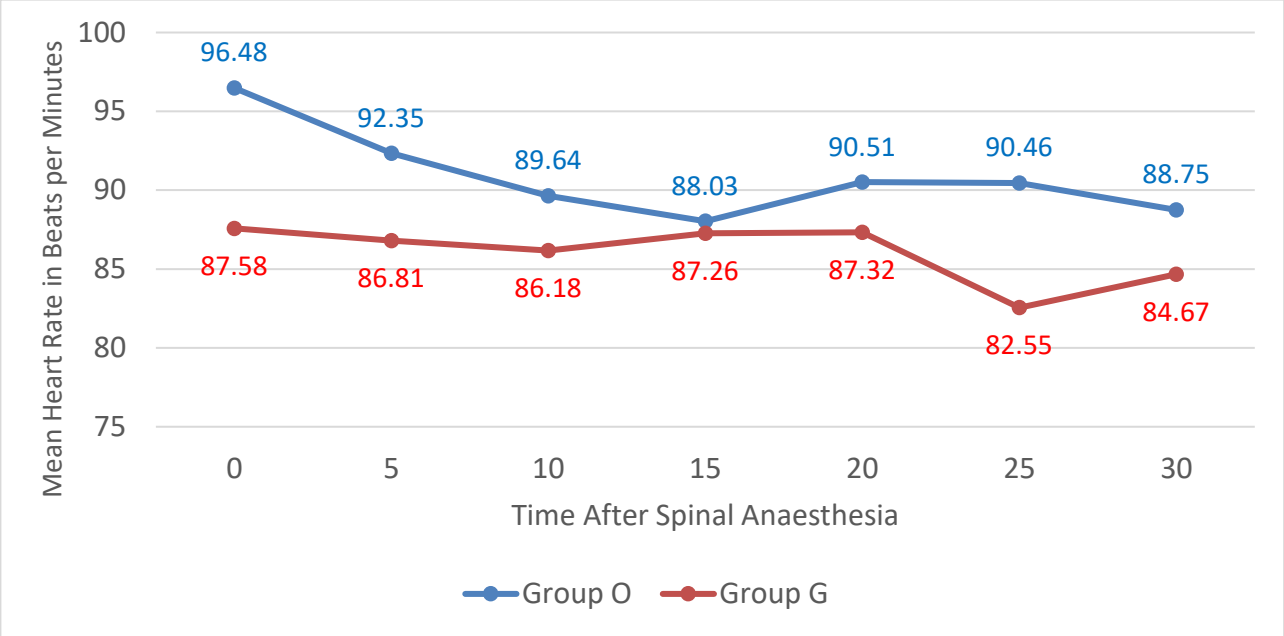

Figure 2: Comparison of Mean Heart Rate between Two Groups

The heart rate was more stable in patients who were given granisetron before spinal anaesthesia as compared to patients who received ondansetron. There was appreciable fall in heart rate after 20 minutes of spinal anaesthesia in patients who received granisetron but it became stable after 30 minutes.

Table 3: Comparison of incidence of intraoperative nausea & vomiting, haemodynamic fluctuation and dose of rescue medications between two groups

Parameters	Group O (n = 35)	Group G (n= 35)	P-value (Fisher's Exact Test)
Incidence of Nausea & Vomiting	10	4	0.1334
Number of patients with hypotension	21	6	0.0005
Number of patients with bradycardia	10	4	0.13
Dose of phenylephrine in mg, median (IQR)	100 (0-300)	0 (0-0)	<0.0001
Dose of atropine in mg, median (IQR)	2 (0-5)	0 (0-0)	<0.0001

Both the drugs were effective in reducing intraoperative nausea and vomiting with no significant difference between two groups. There was significantly lower incidence of hypotension in patients who were given granisetron before spinal anaesthesia as compared to patients who were given ondansetron ($p<0.05$). There was also less incidence of bradycardia in granisetron group but the difference was not significant ($p>0.05$). Rescue medication for bradycardia (atropine) or hypotension (phenylephrine) was not required in granisetron but these medications were used in group who were given ondansetron.

DISCUSSION

A widely recognised and infamous spinal anaesthesia-related complication, particularly in caesarean section, is hemodynamic imbalance. It is a significant clinical problem because the mother and child's livfe are in danger as a result of the patient's worsening hemodynamic status, which is worrisome for anaesthesiologists and surgeons as well as the patient. The administration of phenylephrine and atropine are just two of the many pharmacological treatments used to treat instances of hypotension and bradycardia. Unfortunately, these therapeutic methods have many negative side effects of their own, do more harm than good, and increase the patient's financial burden. Therefore, this hemodynamic catastrophe offers a serious conundrum in the therapeutic setting.

The 5HT3 receptors in the heart are partially responsible for the deteriorating hemodynamic stability. One of the cutting-edge therapy strategies being researched to combat this issue is the inhibition of these receptors. Ondansetron and granisetron, two 5HT3 antagonists, are being researched in this area. This study is the first to assess the effectiveness of high dose granisetron (3 mg) with low dose ondansetron (4 mg) in minimising hemodynamic fluctuations and reducing the need for rescue drugs.

In contrast to the control group in the current trial, prior to treatment with 4 mg of ondansetron returned blood pressure to normal levels. When compared to the control group, the ondansetron group experienced fewer cases of hypotension and bradycardia and used less phenylephrine and atropine. Similar results were shown in a study done in 2018 by Shabana and her colleagues, when 100 pregnant women were split into two distinct groups and given either 4 mg of ondansetron or 10 ml of normal saline five minutes before spinal blocks. [12] Additionally, Xiao and his co-investigators demonstrated that 4 mg of ondansetron is capable of controlling hypotensive episodes without the requirement for phenylephrine in their study in 2017.[13] The results of our investigation concur with this.

Our findings are in line with the research done by Wang et al. in 2014 in which 150 pregnant women were separated into five distinct groups, each of which received 2 mg, 4 mg, 6 mg, or 8 mg of ondansetron.[14] Similar to our results, this investigation found that 4 mg of ondansetron was the best dose to avoid spinal anaesthesia-induced hemodynamic instability.

When compared to the control group in the current investigation, 3 mg of granisetron was effective in returning the blood pressure and heart rate to their pre-anesthetic levels. In comparison to the control group, there were considerably fewer hypotensive and bradycardic episodes as well as a need for rescue medication. In a 2017 study by Abdalla and Ammar, 54 patients receiving various infraumbilical procedures were separated into two groups, with one given 1 mg of granisetron and the other receiving 5 ml of normal saline, 5 minutes prior to anesthesia.[15] Their results were identical to the findings of our study.

Another study conducted in 2015 with 200 pregnant patients by Eldaba and Amr found that premedication with 1 mg of granisetron significantly reduces hemodynamic disturbances brought on by spinal anaesthesia and the need for vasopressors.[16] In a study conducted in 2020 by Chatterjee and colleagues, 200 pregnant women were enrolled, and one group was given 1 mg of granisetron for 10 minutes during paranaesthesia, while the other group was kept as a control. Similar findings were also observed in this study.[17] In this trial, the use of vasopressors and the incidence and severity of hypotension were both successfully reduced with granisetron.

According to the results of our investigation, granisetron greatly outperforms ondansetron in avoiding spinal anaesthesia-induced hypotension and reducing phenylephrine utilisation. However, the need for atropine is reduced and both medications prevent bradycardia effectively. The improved efficacy of granisetron in preventing hemodynamic reactions linked to spinal block is thus the key finding of the current investigation. Ondansetron and granisetron were also compared by Aksoy and his associates in 2021 in 80 obstetric patients, and they came to the conclusion that both medications are equally effective.[1] While both medications are helpful in preventing hemodynamic changes, ondansetron is better, according to a similar study conducted by Khalifa in 2015 with 80 pregnant women.[18] These findings partially conflict with those of the current study, which may be because we utilised various drug doses in our research.

Granisetron's effect is dose-dependent. The drug's effectiveness is improved through raising the dose. This was proven in a study that used two doses of prophylactic granisetron to prevent shivering after spinal anaesthesia.[10] Ninety patients were randomised into two distinct groups, with one group receiving 1 mg of granisetron and the other group receiving 3 mg, for septorhinoplasty under general anaesthesia. According to this study, granisetron at a greater dose—3 mg as opposed to 1 mg—reduces post-spinal shivering more efficiently.

A comparable study in 2021 examined 3 mg and 1 mg of granisetron in 244 patients undergoing caesarean sections and concluded that high dose granisetron significantly reduced post-spinal shivering, nausea, and vomiting.[19] Granisetron's effect is hence dose-dependent. The medicine is used in our trial at a greater dosage of 3mg. When compared to 4mg ondansetron, this higher dose may have enhanced granisetron's efficacy in the current trial.

Granisetron poses little to no danger of having negative cardiac effects, hence greater therapeutic doses can be administered without risk. However, while ondansetron's effectiveness is not dependent on dose, it is advised to use it at a safe dose of 4 mg because greater therapeutic doses carry a danger of QT prolongation.[8]

In order to reduce hemodynamic instability, the present study is the first to demonstrate that high dose granisetron (3 mg) is better compared to low dose ondansetron (4 mg). Granisetron costs more than ondansetron, but in large doses it has superior and more durable antiemetic effects, improves hemodynamic reactions brought on by spinal anaesthesia, and reduces the need for vasopressors. This explains the drug's higher price because it will result in a lower financial burden per patient.[20]

Limitation of the study

The patients who were at high risk for hypotension were not identified as per study protocol and subgroup analysis could not be done.

CONCLUSION

Both drugs were effective in counteracting hypotension bradycardia but could not control early fall in blood pressure heart rate. High dose granisetron proved to be superior to low dose ondansetron in reducing incidence of hypotensive episodes caused by spinal anaesthesia. However, there was no difference in effectiveness of granisetron and ondansetron in preventing bradycardia. Study with much early dosage of these drugs should be conducted to evaluate their effectiveness in reducing early fall of blood pressure and heart rate.

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