Effect of prophylactic ondansetron on spinal anaesthesia-induced hypotension and bradycardia in lower limb and lower abdominal surgeries : A randomized controlled double-blinded study

Ashwini H.R[1], Pushpavathi S H[2]. Venkatesha K V[3], Avinash K[4]

[1,2,4]Department of Anaesthesia, [3]Department of Obstetrics and Gynaecology, Karnataka institute of medical sciences, Hubli. Karnataka, Indi

Abstract

Background: Ondansetron was effectively used to prevent spinal anesthesia-induced hypotension in the general population and women anesthetised for cesarean section. The aim of this study was to test the hypothesis that blocking type 3 serotonin receptors with intravenous ondansetron administration reduces hypotension and Bradycardia induced by spinal anesthesia.

Methods: Eighty patients participated in the study with 40 in the ondansetron group (received 8 mg intravenous ondansetron) and 40 in the placebo group (received 0.9% NaCl solution). The heart rate and arterial blood pressure were measured every 2 minutes after spinal anaesthesia for the first 20 min and every 5 min for the next 70 min.

Results: Decreases in both the heart rate and systolic, diastolic, as well as mean blood pressure compared to the baseline values were noted in both groups. The mean blood pressure values obtained over a 20-minute observation period were significantly higher in the ondansetron group. There were no significant differences in the systolic blood pressure and heart rate values between the groups.

Conclusion: Administration of intravenous ondansetron prior to subarachnoid block can decrease the incidence of hypotension following subarachnoid block in patients undergoing lower limb and lower abdominal surgeries.

Key words: Anesthesia, Hemodynamics, Ondansetron, Subarachnoid block

Introduction

Spinal anaesthesia has celebrated a long history of success and a centennial anniversary. Anaesthesiologists become sufficiently competent in spinal anaesthesia early in training with a 90% success rate after only 40-70 supervised attempts. The ease and long history of spinal anaesthesia may give the impression that it is a simple technique with little sophistication[1].

Inspite of simplicity and safety of spinal anaesthesia, rare complications like unresponsive hypotension and bradycardia are real anaesthetic challenges. It is preferred to prevent hypotension rather than treating it[2].The incidence of hypotension is around 33% and bradycardia 13% in non-obstetric populations. Hypotension results primarily from decreased vascular resistance, while bradycardia is secondary to relative parasympathetic dominance, increased baroreceptor activity or induction of the Bezold Jarisch Reflex (BJR). Reflex cardiovascular depression with vasodilation and bradycardia has been termed as Bezold Jarisch reflex. This is mediated through a neural mechanism rather than any cardiac dysfunction. Bradycardia and vasodilation are the principal changes triggered either centrally or peripherally.

Many animal studies suggest that serotonin is an important mediator associated with BJR[3]. Recently few studies have shown that 5HT3receptor antagonists when given intravenously over 2-5 min before spinal anaesthesia have reduced the incidences of hypotension and bradycardia[4].

In this study, we intend to test the hypothesis that the

Address for Correspondence:

Dr Ashwini H R

Department of Anaesthesia, Karnataka institute of medical sciences,
Hubli. Karnataka, India
Email: sunitaramaswamy@gmail.com

blockade of type 3 serotonin receptors by intravenous ondansetron administration will reduce hypotension and bradycardia induced by spinal anaesthesia.

Primary objective of the study is to test the hypothesis that ondansetron given intravenously before spinal anaesthesia decreases the incidence of hypotension. Secondary objectives included the incidence of bradycardia, level of sensory and motor blockade characteristics between the two groups and any untoward incidents.

Methods and materials:

After obtaining institutional ethical committee approval, 90 patients of either gender,in the age group of 18-60 years, belonging to American society of anaesthesiologists class 1and 2 were enrolled for the study. Patients posted for lower limband lower abdominal surgerieslasting for one and half to two hours, weighing 50 to 70 kgs were included in study. Aged patients (>60 years), pregnants, obese (with BMI> 30) patients, patients with contra indication to neuraxial anaesthesia and known allergy to study drug were excluded from the study. Written informed consent was taken from all the patients included in the study.

Patients were randomly allocated into 2 groups of 45 patients each, ondansetron with bupivacaine as group (O) and 0.9% saline as placebo (P) group. Randomization was done using a computerized randomisation chart. The serially labelled opaque and closed envelopes containing the group allocation were opened immediately before the study and the study drugs were prepared by an anaesthesia resident who did not participate in the process of anaesthesia and subsequent analysis. The bolus drug syringe contained ondansetron 0.15 mg/kg diluted to 5 ml with normal saline in group O and in group P, 5 ml of normal saline was injected. All preoperative and intra operative management were performed by the same anaesthesiologist who was blinded to the study drug and intraoperative data were noted by an investigator who was blinded to the patient group allocation.

In the operating room, the basal blood pressure (BP) and pulse rate were measured and intravenous (IV) accesswas secured with 18 gauge cannula. All patients received pre-hydration with lactated Ringer's solution 10 mL/kg. Monitoring included pulse oximetry (SpO2), non-invasive BP and electrocardiogram (ECG).

The study solution i.e., ondansetron 0.15mg/kg was administered intravenously over 2 minutes and 5 min later, the sub arachnoid block was performed in L3-4 space using 25 G Quincke's needle with the patient in the sitting position. After the confirmation of cerebrospinal fluid (CSF) flow, 0.5% hyperbaric bupivacaine 3.5ml was administered. Patients were made supine thereafter. Time of completion of subarachnoid injection were noted. Systolic BP (SBP), diastolic BP (DBP), mean BP (MBP) and pulse rate (PR) were recorded every 2 min for the first 20 min after sub arachnoid block and thereafter every 5 min for the next 45 min.

Sensory block level was evaluated by pin prick sensation using 25 guage blunted needle along the mid clavicular line every 2 min until T10 level and then every 5min until the highest level was attained. Highest level means there will be no change in 3 consecutive readings. Motor blockade was assessed according to modified Bromage scale[5].

Hypotension was defined as 25% decrease in SBP from baseline and was treated with fluids and vasopressors (mephentermine 6 mg IV) if needed. Bradycardia was defined as PR <50 bpm and was treated with 0.6 mg atropine IV.

Any episodes of nausea, vomiting and shivering intraoperatively or post operatively for the first 24 hours were recorded. Vomiting was treated with injection metoclopramide0.15 mg/kg intravenously. Inadequate analgesia and anaesthesia were considered as failed spinal anaesthesia and was converted into general anaesthesia resulting their exclusion from the study.

Based on the results of a study by T Sahoo et al., conducted with 23 patients in each group, a sample size of 31 patients was calculated to detect a difference of 8mmhg in the reduction of blood pressure between the groups at 5% level of significance and 80% power[4]. Considering the possibility of failure of block in some cases,45 subjects were included in each group. Statistical analysis was done using SSPS version 17(SPSS Inc., Chicago,Illinois,USA) Student`s t-test was used to compare demographic data. Qualitative data were analyzed using chi-square test and Fischer's exact test. ANOVA test was used to compare hemodynamic variables. Data were presented as mean ± standard deviation and p value less than 0.05 was considered significant.

Results

A total of 90 patients were randomized and included in the study. Later 5 patients were excluded due to surgical cancellations and another 5 were not included due to violation of protocol. (Fig 1)

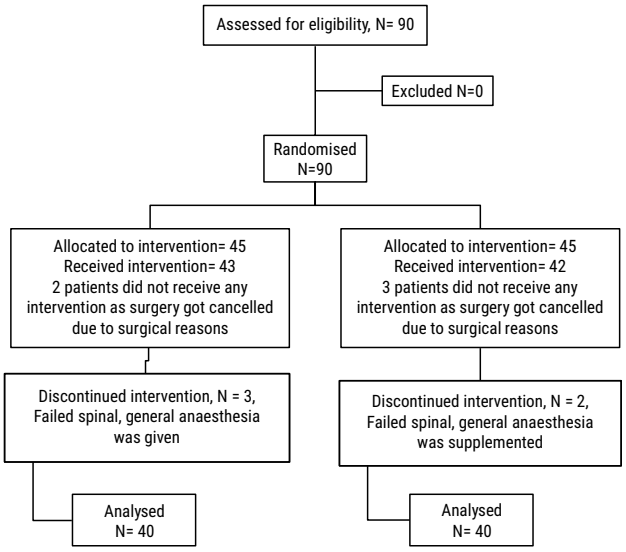

Figure no 1 : Consort diagram

Comparison of age, weight, sex and ASA physical status showed no significant difference between the groups (table 1)

Table 1: Comparison of demographic data of patients among groups

Parameter	Group O	Group P	P value
Age (year)	39±14.26	36±9.42	0.233
Weight (kg)	58 ± 7.3	57±7.86	0.455
Height (cms)	154.1±6.3	156.7±5.8	0.093
Sex (M:F)	16:24	19:21	0.499

Data are expressed as mean ± s.d except for gender distribution which is expressed as ratio (M: F) Male: Female. Group O- Ondansetron, Group P- Placebo.

The basal hemodynamic parameters of patients of both groups were comparable, (p=0.159 and p=0.972 for pulse rate and BP respectively. There was no statistical significant difference in the systolic as well as diastolic blood pressure between the two groups at all time interval. However, the mean blood pressure was significantly higher in group O at 4th,6th 20th, 25th, 30th and 35th min compared to group P as shown in figure 2.

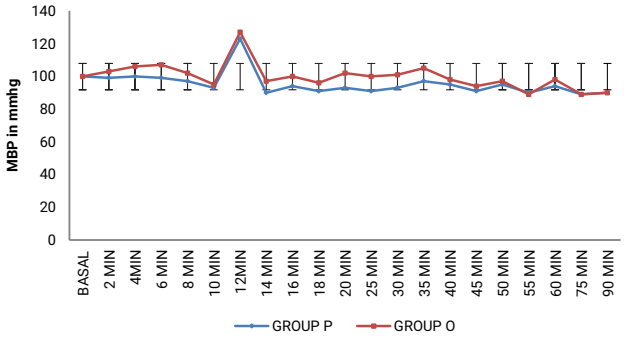

Figure 2: Comparison of mean blood pressure at different time intervals.

Data are expressed as mean± standarad deviation p < 0.05 is considered significant. Group O = Ondansetron group, Group P (control) = placebo group. MBP = Mean blood pressure

The pulse rate was significantly higher in group O at 2nd, 4th, 6th, 10th, 12th min when compared to group P as shown in figure 3.

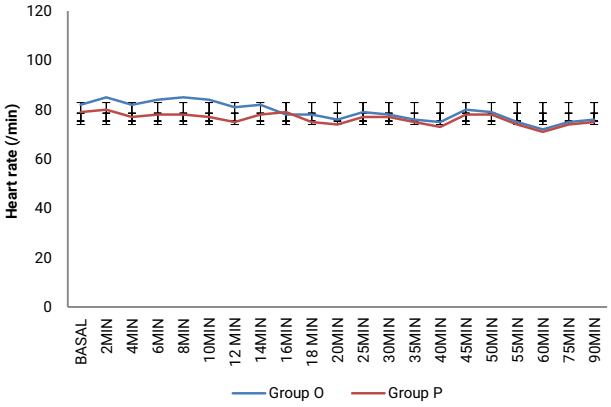

Figure 3: Comparison of heart rate at different time intervals.

Data expressed as mean ± standard deviation p < 0.05 is considered significant. Group O = Ondansetron group, Group P (control) = placebo group. Spinal anaesthesia characteristics such maximum sensory block (T6) and time taken to achieve the same were comparable between the two groups. All the patients achieved motor blockade of bromage score 3. There was no statistical significance in the time to attain complete motor block.

Incidence of intraoperative side effects were comparable in both the groups. Two (5%) patients in group P had vomiting which was treated with antiemetics and fluids. One patient (2.5%) from group O had nausea. Shivering was observed in three (7.5%) patients of group P and one (2.5%) patient of group O.

Discussion

Spinal anaesthesia causes vasodilatation, hypotension, and bradycardia by sympathetic blockade, the bezold zarisch reflex and stimulation of 5HT3 receptors in vagal nerve endings[6]. Blockage of 5HT3 receptors antagonizes the BJR induced by serotonin[7,8]. Hypotension results primarily from decreased vascular resistance, while bradycardia is secondary to relative sympathetic dominance, increased baroreceptor activity or induction of BJR. The incidence of hypotension and bradycardia is reported to be 33% and 13% respectively in non obstetric patients.

Although in our study the differences in two groups with respect to pulse rate is significant, no patients from either group needed atropine. Omyma et al., in

their study comparing the prophylactic IV granisetron and ondansetron, found that heart rate (HR) was significantly higher in 10th and 15th min in ondansetron group[9]. Our study correlates with study by T.Sahoo et al,. in decrease in HR in placebo group. Similar results were obtained by seyedmojtab et al., who showed 14% incidence in bradycardia in placebo group in comparison to two different doses of IV ondansetron (6mg, 12 mg)[10]. Ameta-analysis conducted by Tito et al., which included 13 RCTs showed decreased risk for Bradycardia with intravenous ondansetron[11]. Our results are comparable to study by Naseem et al., who reported 18% incidence in bradycardia in ondansetron group compared to 40% in placebo group[12].

Contrary to our study, Bipul Deka et al., and pouram et al., did not find any beneficial effects of the drug with respect to hemodynamics[13,14]. Study by Meenoti et al., though supported our study with regard to decreased incidence of hypotension in ondansetron group, did not report any effect on the HR[15].

Our study correlates with the study conducted by R.Owczucket al., and T.Sahoo et al., who reported decreased incidence of hypotension and mean blood pressure at 14 and 35th min respectively[16,4]. Clinically Ahmed A et al., showed the incidence of hypotension to be 3% with granisetron compared to 68% in placebo group[17]. Similarly, naseem abbas et al., showed incidence of hypotension to be 42% in ondansetron group compared to 68% in placebo group[11]. In a meta-analysis conducted by Cheng mao Zhou and Michael Heesen, the incidence of hypotension were significantly lower with ondansetron[18,19].

Limitations of our study being limited presentation of patient population as it was a single centre study and patients at risk for hypotension and Bradycardia like patients with obesity, elderly and pregnancy were not included. Comments on the incidence of bradycardia needs few more studies in larger group as studies done so far differ in conclusion due to differences in dose, age group and category (obstetric) of the patients.

Conclusion

We conclude that IV ondansetron 0.15 mg/kg given before subarachnoid block can decrease the incidence of hypotension following spinal anaesthesia in patients undergoing lowerlimb and lower abdominal surgeries.

References

1. *Spencer S. Liu, Susan B. Mc Donald. Current issues in spinal anaesthesia. Anesthesiology 2001; 94(5):888–906.*
2. *Tatikonda CM, Rajappa GC, Rath P, Abbas M, Madhapura VS, Gopal NV. Effect of intravenous ondansetron on spinal anesthesia-induced hypotension and bradycardia: a randomized controlled double-blinded study. Anesthessays Res. 2019 ;13(2):340-6.*
3. *S.M.Kinsella, J.P.Tuckey. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. Br J Anaesth 2001; 86:859-68.*
4. *T. Sahoo, C. Sen Dasgupta, A. Goswami, A. Hazra. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomised, placebo-controlled study. International Journal of Obstetric Anaesthesia 2012; 21: 24–8*
5. *Ahmed A, T Baig. Incidence of lower limb motor weakness in patients receiving post operative epidural analgesia and factors associated with it: An observational study. Saudi J Anaesth 2016; 10:149-253*
6. *Martinek RM. Witnessed asystole during spinal anaesthesia treated with atropine and ondansetron: a case report. Can J Anesth 2004;51:226–30*
7. *Yamano M, Ito H, Kamato T, Miyata K. Characteristics of inhibitory effects of serotonin (5-HT) 3 receptor antagonist, YMO60 and YM114 (KAE 393), on von BazoldJarisch reflex induced by 2 methyl 5 HT, veratridine and electrical stimulation of vagus nerves in anaesthetized rats. Jpn J Pharmacol1995;69:351–6.*
8. *Yamano M, Kamato T, Nishida A. Serotonin (5-HT)3- receptor antagonism of 4,5,6,7-tetrahydrobenzimidazole derivatives against 5-HT-induced bradycardia in anesthetized rats. Jpn J Pharmacol1994;65:241–8.*
9. *Khalifa OM. A comparative study of prophylactic intravenous granisetron, ondansetron, and ephedrine in attenuating hypotension and its effect on motor and sensory block in elective cesarean section under spinal anesthesia. Ain-Shams J Anaesthesiol 2015;8:166-72*
10. *Marashi S.M., Soltani-Omid S., Soltani Mohammadi S., Aghajani Y., Movafegh A. Comparing Two Different Doses of Intravenous Ondansetron with Placebo on Attenuation of Spinal-induced Hypotension and Shivering. Anesthesiol. Pain Med. 2014;18:4(2)*
11. *Tito D. Tubog, Terri D. Kane, Marilyn A. Pugh. Effects of Ondansetron on Attenuating Spinal Anaesthesia–Induced Hypotension and Bradycardia in Obstetric and nonobstetric Subjects: A Systematic Review and Meta-Analysis. AANA Journal. 2017; 85(2): 113-22*
12. *Abbas N, Shah S, Naqvi S. Role of prophylactic ondansetron for prevention of spinal anaesthesia induced hypotension in lower segment caesarean section. Pak Armed Forces Med J. 2016; 66(6):790-4*
13. *Bipul Deka, Bharat Talukdar, Amal Kumar Laha, Rupak Bhattacharjee. Effects of IV ondansetron during spinal anaesthesia with ropivacaine and fentanyl. Indian Journal of Basic and Applied Medical Research; March 2016: 5(2): 651-5*
14. *Hajian P, Malekianzadeh B, Davoudi M. Efficacy of intravenous ondansetron on hemodynamic complications in women undergoing spinal anesthesia for cesarean section: A randomized placebo controlled clinical trial. Galen Medical Journal 2016; 5(1): 13-8.*
15. *Potdar MP, Kamat LL, Jha TR, Talnikar AS, Mahevi ZM, Save MP. Effect of ondansetron in attenuation of post-spinal hypotension in caesarean section: A comparison of two different doses with placebo. J ObstetAnaesth Crit Care 2017;7:69-74.*
16. *Owczuk R, Wenski W, Twardowski P, Dylczyk-Sommer A, Sawicka W, Wujtewicz MA, et al. Ondansetron attenuates the decrease in blood pressure due to spinal anesthesia in the elderly: A double blind, placebo-controlled study. Minerva Anestesiol. 2015;81(6):598–607.*
17. *Ahmed A. Eldaba, Yasser M. Amr Intravenous granisetron attenuates hypotension during spinal anaesthesia in cesarean delivery: A double-blind, prospective randomized controlled study. Journal of Anaesthesiology Clinical Pharmacology 2015 ; 31 : 3.*
18. *Zhou C, Zhu Y, Bao Z, Wang X, Liu Q. Efficacy of ondansetron for spinal anesthesia during cesarean section: A meta-analysis of randomized trials. J Int Med Res. 2018;46(2):654–62.*
19. *Heesen M, Klimek M, Hoeks SE, Rossaint R. Prevention of spinal anesthesia-induced hypotension during cesarean delivery by 5-hydroxytryptamine-3 receptor antagonists: A systematic review and meta-analysis and meta-regression. Anesth Analg. 2016;123:977–88.*

Conflict of interest: Nil
Source of funding: Nil

Date received: 03rd Nov, 2022
Date accepted: 27th Feb, 2023