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Original Article

Anaesthesia Section

Effects of Intravenous Ondansetron and Granisetron on Haemodynamic Changes during Spinal Anaesthesia in Non-obstetric Population: A Randomised Double-blind Study

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ABSTRACT

Introduction: Two commonly used antiemetics in the peri-operative period may attenuate the spinal anaesthesia induced hypotension by attenuating the Bezold-Jarisch Reflex (BJR).

Aim: To evaluate and compare the efficacy of intravenous administration of ondansetron and granisetron five minutes prior to spinal anaesthesia on incidence of spinal anaesthesia induced hypotension and bradycardia.

Materials and Methods: Ninety patients scheduled for elective infraumbilical non-obstetric surgeries under spinal anaesthesia were enrolled for the study, after obtaining written informed consent. Patients were randomised to receive 4 mg ondansetron (group O), 1 mg granisetron (group G) or normal saline (control group) intravenously, five minutes prior to spinal anaesthesia. Changes in haemodynamics were noted after spinal anaesthesia to identify the number of episodes of hypotension and bradycardia necessitating treatment with ephedrine, atropine or both. The obtained data was analysed with one-way ANOVA or Chi-square test with post-hoc comparison to find out pairwise difference. Statistical significance was considered as $p<0.05$.

Results: The incidence of hypotension was highest in control group (46%) in contrast to 23% in granisetron and ondansetron group, however the difference did not reach the level of statistical significance ($p=0.07$). The usage of atropine was similar among the groups, whereas consumption of ephedrine was significantly different among the three groups ($p=0.037$) with granisetron group consuming the least dose of ephedrine to treat spinal anaesthesia induced hypotension.

Conclusion: We conclude that pretreatment with ondansetron, granisetron do not reduce the incidence of spinal anaesthesia induced hypotension and bradycardia.

Keywords: Antiemetics, Hypotension, Subarachnoid anaesthesia

INTRODUCTION

Hypotension after spinal anaesthesia using hyperbaric local anaesthetic agent is not very uncommon though the incidence may vary depending on the definition adopted by different investigators. Several investigators have advocated use of various strategies like preloading, coloading of intravenous fluids [1], fluid boluses vasopressors [2], and compression device [3] with varying success rate in counteracting spinal anaesthesia induced hypotension. Most of the above described spinal anaesthesia induced hypotension, avoidance strategy were carried out in obstetric population. However, a Cochrane review concluded that none of these techniques alone was sufficient in eliminating hypotension [4].

Hypotension results primarily from decreased systemic vascular resistance and central venous pressure from sympathetic block, whereas bradycardia is secondary to a relative parasympathetic dominance, increased baroreceptor activity or a result of the BJR [5]. This reflex is elicited by stimulation of peripheral serotonin receptors 5-Hydroxytryptamine (5-HT3 type) which are both mechanosensitive and chemosensitive. These receptors are located peripherally as cardiac chemo receptors on the cardiac vagal afferent pathway and centrally in the Chemoreceptor Trigger Zone (CTZ) [6]. Stimulation of cardiac chemoreceptors in the heart by decreased venous return increases the parasympathetic activity and decreases the sympathetic activity resulting in vasodilatation and bradycardia [7].

This study concentrated on two 5HT3 receptor antagonists, which can minimise the occurrence of hypotension and bradycardia after spinal anaesthesia. They are ondansetron and granisetron which are selective 5-HT3 receptor antagonists [8].

However, meta-analysis of randomised control trials does not opine favourably regarding attenuation potential of 5-HT3 antagonists for spinal anaesthesia induced hypotension and bradycardia in non-obstetric population [9,10]. Another meta-analysis observed that intravenous ondansetron prior to spinal anaesthesia is effective only in reducing the incidence of bradycardia, nausea and vomiting but not hypotension [11]. As there are only very few studies [9,10] to compare the effects of ondansetron and granisetron on spinal induced hypotension and bradycardia in non-obstetric population. The present study was designed to evaluate the effects of ondansetron and granisetron given five minutes before spinal anaesthesia on spinal induced hypotension and bradycardia in non-obstetric population.

MATERIALS AND METHODS

This randomised double blind active control trial was conducted in various surgical operation theatres of a tertiary care university teaching hospital, for one year (2016-2017) duration and after obtaining approval from Institutional Ethics Committee (A&E/08/IEC/SVIMS/09). The sample size was decided based on a previously reported incidence [12] of hypotension after spinal anaesthesia as 40% in control arm. Assuming a 50% relative decrease in incidence of hypotension with the use of study drugs, 27 patients per group were required for a significance level of 5% (alpha error) and a study power 80% (beta error). Considering possible attrition rate we recruited 30 patients per study group. Patients belonging to age group 18 to 60 years age group, American society of anaesthesiologists, physical status 1 or 2 scheduled for elective infraumbilical non-obstetric surgery under spinal anaesthesia were screened for the study.

Exclusion criteria: Patient's refusal, general contraindication to spinal anaesthesia, patients on medications known to alter cardiac rate and contractility, known allergic reaction to study drugs and bupivacaine. Ninety patients meeting the inclusion criteria were enrolled for the study after obtaining written informed consent. Randomisation sequence into one of the three groups was done before initiation of study by computer generated random number table and sealed opaque envelop technique.

The patients were randomised to receive Intravenous (IV) 0.9% normal saline (control group), granisetron 1 mg (Granisetron group) or ondansetron 4 mg (Ondansetron group). All the study drugs were diluted to equal volume of 10 mL using normal saline. Blinding was ensured by preparing the study drugs in a ready to inject 10 mL syringe by an independent anaesthesia resident trainee not involved in the study. All the patients received 10 mL/kg of intravenous lactated Ringer's solution over 30 minutes in the preoperative holding area before wheeling inside Operation Theatre (OT) and thereafter wheeled inside OT and received their IV study medication five minutes before spinal anaesthesia. Spinal anaesthesia was carried out by using a 25 gauze spinal needle at L3-L4 inter space in lateral decubitus position. After clear aspiration of spinal fluid 3 mL of 0.5% hyperbaric bupivacaine and 0.5 mL of fentanyl (25 mcg) (total 3.5 mL) injected into the subarachnoid space. All patients received a ringer's lactate intravenous infusion at a constant rate of 6 mL/Kg/hour. Hypotension was defined as a decrease in Systolic Blood Pressure (SBP) below 90 mmHg or 30% decrease from the baseline value. In either case, hypotension was treated with 3 mg of ephedrine IV. Bradycardia was defined as an absolute decrease in Heart Rate (HR) below 50 beats per minute and was treated with IV atropine 0.5 mg. If hypotension occurs, then the frequency of blood pressure monitoring is increased to one minute interval. Both vasopressor and atropine was repeated after one minute if, SBP and heart rate remains below the predefined hypotension and bradycardia values. Both patient and the investigator responsible for patient's haemodynamic were blind to study drug administration. Investigator was not blind to rescue vasopressor or inotropes administration.

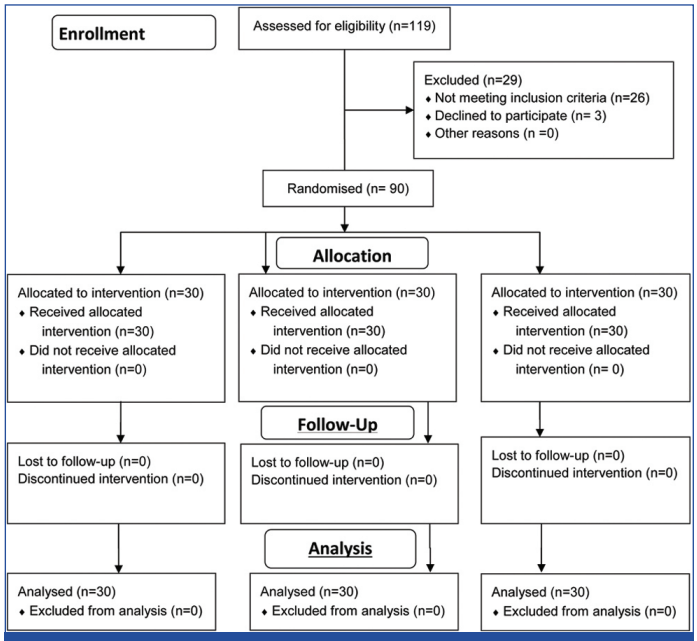
The upper level of sensory block was assessed using cold swab method at every five minutes for 25 minutes to ascertain the highest level of sensory block. The baseline heart rate and systolic blood pressure was recorded after preloading and thereafter every minute for first five minutes followed by every three minutes till the end of surgery or up to two hours whichever comes later. Blood pressure was measured by automatic non-invasive oscillometric methods using standard adult cuff size. The primary outcome variables were to find out the incidence of hypotension and bradycardia among study groups after spinal anaesthesia. The secondary outcome variables were number of episodes of hypotension, bradycardia that occurred during study period and the amount of dose of ephedrine or atropine needed to treat spinal induced hypotension and bradycardia respectively.

STATISTICAL ANALYSIS

Three groups were compared using one-way analysis of variance (ANOVA) with Turkey's multiple comparison post-hoc tests to identify the significant pair. The incidence and number of episodes of hypotension was analysed with cross tabulation using chi-square test. All statistical analysis was performed using statistical package for the social sciences version 20.0 (IBM, SPSS, Armonk, NY, USA). All statistical tests are two-tailed and p-value less than 0.05 were considered significant.

RESULTS

In total 90 patient completed the study protocol [Table/Fig-1], (consort flow chart). The study cohort was comparable in terms of ASA physical status, mean age, gender distribution type and duration of surgery. There was no statistical significant difference between base line clinical data like heart rate, systolic blood pressure among the study groups [Table/Fig-2].



[Table/Fig-1]: Consort flow diagram.

Variables		Control (n=30)	Granisetron (n=30)	Ondansetron (n=30)	p-value
Age (years)		43.0±13.2	40.7±11.9	45.6±13.6	0.347
Sex (Male/Female) (n)		24/6	14/16	21/9	0.181
ASA PS grades (I/II) (n)		25/5	25/5	24/6	0.710
BMI (kg/m^2)		22.6±2.9	22.7±2.7	22.7±3.0	0.986
Type of surgery					
Endoscopic procedures		15	18	13	1.000
Infra inguinal muscle cutting surgery		12	14	15	
Vesico vaginal Fistula repair		2	1	0	
Duration of surgery (min)		73.0±12.4	68.8±11.4	75.8±11.8	0.79
Systolic blood pressure		133±13.0	132±9.8	137±9.80	0.213
Heart rate		86.1±18.5	85.1±13.8	85.9±16.4	0.973
Sensory block height	T6-T8	6	3	6	0.487
	T9-T10	24	27	24	0.487

[Table/Fig-2]: Demographic distribution and baseline clinical data.
Data presented as mean±SD
N: number of participants or number of patients; ASA PS: American society of anaesthesiologists physical status; BMI: Body mass index

The incidence of hypotension was double in control group (n=14) in contrast to seven patients each from ondansetron and granisetron group. However this difference has not reached the level of statistical significance (p=0.079). Two patients each from control and ondansetron group had bradycardia in contrast to none from granisetron group (p=0.0351) [Table/Fig-3]. The sensory block height achieved at the end of 15 minutes was comparable between the group and none of the patient had attained a block height more than T6 level which could rule out the occurrence of Bain-Bridge reflux induced bradycardia and hypotension due to non-involvement of cardiac accelerator fibers (T1-T4). Seventy five patients out of 90 patients attained a sensory block height of T9-T10 and were equally distributed among the study groups [Table/Fig-2]. The control group needed a significantly higher dose of ephedrine compared to granisetron and ondansetron group (Group C, 2±2.40 mg; Group O, 0.9±1.78 mg; Group G, 0.8±1.56 mg=0.035). A further post-hoc analysis revealed that only granisetron and control group differed significantly in ephedrine requirement (p=0.051) with no statistical significant difference between control versus ondansetron

or ondansetron versus granisetron group. The atropine requirement among the groups for bradycardia was not significantly different (p=0.365) [Table/Fig-3].

Variable	Control	Granisetron	Ondansetron	p-value
Hypotension	14	7	7	0.079
Bradycardia	2	0	2	0.351
Ephedrine (mg)	2±2.40	0.8±1.56	0.9±1.78	0.035*
Atropine (mg)	0.06±0.2	0.0±0.0	0.02±0.1	0.365

[Table/Fig-3]: Incidence of hypotension, bradycardia and use of ephedrine and atropine.
*By kruskal-wallis H-test, p<0.05 is statistically significant

DISCUSSION

Hypotension and bradycardia are common side effects after spinal anaesthesia. Sympathetic block induced by spinal anaesthesia leads to decreased systemic vascular resistance and blood pooling in lower half of the body and this in turn gives rise to reduce preload and hypotension. The mechanism responsible for bradycardia is not clear. Bain-bridge reflux due to blockade of the sympathetic cardio accelerator fibers originating from T1-4 spinal segments is often suggested as one of the cause. The fact that bradycardia is more common with high blocks supports this mechanism which was not seen with the present study, another reflux BJR is a cardio-inhibitory reflex triggered by stimulation of 5-HT3 receptors in vagal nerve endings due to release of serotonin from activated thrombocyte, leading to an increase in parasympathetic activity and decreased sympathetic activity explains spinal induced bradycardia and hypotension. There are different studies which have revealed the effectiveness of different strategies for the prevention of spinal anaesthesia induced hypotension such as pre or co-loading of IV fluids, use of vasopressors, and compression devices. However, a Cochrane review concluded that none of these techniques alone was sufficient in eliminating hypotension. This emphasised the need for further research concerning other agents which prevent the action of serotonin on serotonin receptors in low volume states like spinal anaesthesia to prevent spinal induced hypotension and bradycardia and hence we conducted this double blind randomised controlled study to test the effectiveness of pretreatment with intravenous 5-HT3 antagonists for the prevention of spinal anaesthesia induced hypotension and bradycardia.

The current study results do not establish an association between incidence of hypotension and use of granisetron or ondansetron.

Our study findings are not in concordance with other studies comprising of non-obstetric patients who received 6-12 mg of ondansetron IV along with 15-20 mg of plain bupivacaine [13,14]. Our study protocol was different from the above two mentioned studies in two ways. First, we used only 4 mg of ondansetron and second our spinal anaesthetic regimen is of larger volume with addition of fentanyl 25 mcg along with bupivacaine which could have resulted in higher magnitude of hypotension, not amenable to counteracting effect of 5-HT3 antagonistic study drugs. However, other studies using low dose bupivacaine (10 mg) did not demonstrated a beneficial effect in use of 5-HT3 antagonist on spinal anaesthesia induced hypotension irrespective of their doses (2, 4, 8 mg of ondansetron) [15]. The current study is in accordance with Terkawi AS et al., who used bupivacaine plus opioid intrathecal regimen like us along with 8 mg IV ondansetron but did not observe any beneficial effect of ondansetron on spinal anaesthesia induced haemodynamic changes [16]. Terkawi AS et al., later conducted a meta-analysis of 14 randomised control trial and their subgroup analysis revealed that ondansetron has insignificant effect on attenuation of spinal anaesthesia induced hypotension {risk ratio, 0.58 (0.29-1.15)} and bradycardia {risk ratio, 0.56 (0.20-1.58)} in non-obstetric group [9].

An analysis comprising of 13 randomised control trial observed that unlike obstetric patients, 5-HT3 antagonist do not reduce the incidence of spinal induced hypotension in non-obstetric groups [10].

Investigators who worked on the potential of granisetron as an attenuator of spinal anaesthesia induced hypotension also demonstrated conflicting results. Abdalla W et al., concluded that 1 mg granisetron effectively reduces the incidence of hypotension and bradycardia after spinal anaesthesia [17]. However, unlike the current study, the hypotension is a relative definition in relation to the baseline SBP (20% decrease from SBP) so they might have excluded few episode of hypotension with SBP<90 but well above 80% of baseline values. However, a Nepalese [18] and Egyptian study [19] did not find beneficial effect of prophylactic granisetron on hypotension resulting from spinal anaesthesia. The Nepalese study [18] however used a higher dose of granisetron (40 mcg/kg) then our study and observed attenuation of diastolic blood pressure.

A very recently conducted meta-analysis [9] comprising of 13 randomised control trial observed that unlike obstetric patients, 5-HT3 antagonist do not reduce the incidence of spinal induced hypotension in non-obstetric groups. They further observed that though a trend appears to exist in all the 14 trial to favour the attenuation ability of 5-HT3 antagonist for reducing the incidence of bradycardia, it has not reached statistical significance and the effect size is very small (p=0.31;95% CI 0.19-0.50). In our study we found that the magnitude of fall in heart rate varies between 19-25% and there is a comparable incidence of bradycardia in ondansetron and control group, whereas none of the patients in granisetron group experienced bradycardia. A meta-analysis from Switzerland which included nine non-obstetric and seven obstetric spinal anaesthesia also observed that the 5-HT3 antagonist mediated attenuation of spinal induced hypotension and bradycardia is mostly confined to obstetric population with insignificant effect among non-obstetric population [20].

The low level of sympathectomy and pre-hydration before spinal anaesthesia are probably two reasons that partially explain why our study failed to observe 5-HT3 receptor antagonism effect on spinal anaesthesia induced haemodynamic change. Activation of BJR is responsible for potentiation of the natural sympathectomy induced hypotension and bradycardia after spinal anaesthesia in an under filled ventricle and 5-HT3 antagonist attenuate BJR activation and thereby could minimise incidence of hypotension and bradycardia after spinal anaesthesia. Singla D et al., reported that when the anaesthetic level was under T10, there was little change in Systemic Vascular Resistance (SVR) with little haemodynamic changes and when the level was over T6, the reduction of preload was large because of blood pooling into hepatosplanchnic venous areas and therefore the risk of hypotension increased by about 2.4 times [21].

LIMITATION

1) In our study, 80% of patient had a level of sympathectomy below T9-10 level and were pre-hydrated with 10 mL/kg of ringers lactate before spinal anaesthesia which might have prevented an acute volume under fill condition in the immediate post-spinal anaesthesia period. 2) We have included both SBP<90 mmHg or <30% from baseline SBP as definition for hypotension and this might have lead few additional case of hypotension in all the study groups. 3) We extended our study period to two hours without taking into account the other causes of hypotension like blood loss during surgery. However, the reason for extended study period is to reasonably include all the incidence of change in haemodynamic because of study drug effect unlike the other studies which mainly focussed on the drug effect in the first 20-30 minutes after spinal anaesthesia. Future studies with large cohort can be under taken only with muscle cutting type of surgery with objective calculation of blood loss during surgery to have a more generalizable result.

CONCLUSION

We do not advocate use of prophylactic ondansetron or granisetron either for prevention or attenuation of spinal anaesthesia induced hypotension and bradycardia in non-obstetric surgeries.

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