ORIGINAL ARTICLE

Does Prophylactic Use of Ondansetron and Phenylephrine Prevent Spinal Anesthesia Induced Hypotension in Adult Surgical Patients? A Cross-Sectional Analytical Study

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Article History

Received: 26th December, 2023

Acceptance: 24th July 2024

Online Access

DOI:

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Abstract

Introduction: Various drugs and techniques have been used to mitigate spinal anesthesia induced hypotension.We conducted this study to analyze whether prophylactic usage of ondansetron and phenylephrine would prevent spinal anesthesia induced hypotension.

Methods: This prospective cross-sectional analytical study was conducted in 135 adult patients who underwent orthopedic, general surgical, urological and gynecological surgery under spinal anesthesia . It was conducted after approval from institutional review board and getting written and informed consent. Convenient sampling technique was used.After spinal anesthesia; 2 mL bolus of study drug was injected. Group O received 4 mg Ondansetron, Group P received 100 µg Phenylephrine and Group N received 2ml Normal Saline. The episodes of hypotension,bradycardia, nausea/vomiting and dose of mephentermine was noted. Data was analyzed using SPSS 21.0.

Results: Hypotension was present in 34 patients (74.07) irrespective of pharmacologic prophylaxis. Hypotension was present in 14 patients (31.11%) in Group O; followed by patients in Group N; 12 (26.67%) and Group P; 8 (17.78%). This difference was not significant statistically when Group O and Group P were compared with Group N (p=0.64 and 0.34 respectively). Patients in Group P and Group O didn't experience severe nausea whereas 1 (2.22%) patient had severe nausea in Group N. Likewise, 1 (2.94%) patient each in Group N and Group O had vomiting. Bradycardia was present in 2 (5.88%), 1 (2.22%) and 7 (20.58%) patients in Group N, O and P respectively.

Conclusion: The prophylactic use of phenylephrine and ondansetron didn't prevent spinal anesthesia induced hypotension.

***Keywords*:** Anesthesia, hypotension, ondansetron, phenylephrine, prophylaxis Spinal.

Introduction

The most commonly encountered complications of spinal anesthesia (SA) is hypotension with the incidence of 33% in general population and 70-80% in pregnant female.[1–4] The sympathetic blockade associated with spinal anesthesia leads to loss of vasomotor tone resulting in hypotension. It may be associated with dizziness, nausea, vomiting, syncope and feeling of impending doom.[3,5] Several pharmacological and non-pharmacological methods have been tried to mitigate spinal anesthesia induced hypotension.[6] The preemptive administration of sympathomimetic drugs such as nor adrenaline, phenylephrine, metaraminol, ephedrine or serotonin receptor inhibitor such as ondansetron has been in clinical use with varied success rate.

Pre-loading or co-loading of crystalloids during the initiation of procedure has demonstrated mixed response in prevention of hypotension. The non- pharmacological interventions such as application of compression stockings or leg bindings in lower limbs is inadequate in itself to manage spinal anaesthesia induced hypotension.[7]

The role of ondansetron in spinal anesthesia induced hypotension comes from its association with Bejold Jarisch-reflex (BJR). The decrease in venous return and systemic vascular resistance (SVR) following spinal anesthesia triggers BJR mediated by peripheral serotonin receptors, 5-Hydroxytryptamine(5HT3), resulting in increased efferent vagal signaling and bradycardia,

How to Cite this Article in Vancouver Style:
Lakhe G, Pradhan S. Does Prophylactic Use of Ondansetron and Phenylephrine Prevent Spinal Anesthesia Induced Hypotension in Adult Surgical Patients? A Cross-Sectional Analytical Study. Med. J. Pokhara A. Health Sci. 2024;7(1):12-17.

ultimately exacerbating hypotension.[8] Hence, blocking the peripheral 5HT3 receptors with drugs such as ondansetron prevents BJR and associated hypotension and bradycardia. The pre-emptive administration to prevent SA induced hypotension was supported in cesarean section and geriatric patients. However, its response in non-obstetric population is controversial.[3] Hence, we conducted this study to analyze the effect of ondansetron in preventing SA induced hypotension in non-obstetric cases.

Phenylephrine, pure α-1 adrenergic agonist, is a preferred vasopressor for management of spinal anesthesia induced systemic vasodilation and associated hypotension. Phenylephrine increase SVR and blood pressure.[5] However, phenylephrine in high doses can cause a baroreceptor-reflex mediated bradycardia, a reduction in stroke volume due to increased afterload, and shift of blood into the splanchnic venous circulation. In combination with decreased venous return, this can lead to a dose-dependent fall in cardiac output.[9]

We conducted this study to find out whether prophylactic administration of ondansetron and phenylephrine can alleviate hypotension associated with spinal anesthesia in adult surgical patients.

Methods

This prospective cross-sectional analytical study was conducted in the Department of Anesthesia, Manipal Teaching Hospital, Pokhara, Nepal from 01/09/2022 to 31/08/2023. The study was conducted after the approval from institutional review board(reference number: MCOMS/IRC/530/GA).The written and informed consent was obtained from all cases. Convenient sampling technique was used. Sample size was calculated by using the formula given below:

$n= z^2 \times p \times (1-p)/e^2$

$= (1.96)^2 \times 0.5 \times (1-0.5)/ (0.05)^2$

$= 385$

Since, 185 patients underwent various surgical procedures under spinal anesthesia during the study period, adjusting the sample size for finite population.

$no= n \times N / \{(N + (n-1)\} = 125$

where,

n= minimum required sample size

Z= 1.96 at 95% Confidence Interval (CI)

p= prevalence taken as 50% for maximum sample size q=1-p

e= margin of error i.e., 0.05

n_o= adjusted sample size

N= total number of patients undergoing spinal anesthesia, 185

The minimum sample size calculated was 125, however we recruited 135 patients to compensate for any exclusion. The patientsaged 18 to 65 years,ASA grades I and II scheduled for elective orthopedic, general surgical, urological and gynecological procedures under spinal anesthesia were enrolled in study. The patients were divided into three groups of 45 patients in each group. Patients with contraindication to spinal anaesthesia, severe cardio-pulmonary disease, failed spinal anesthesia, pregnant female and emergency cases were excluded.

On arrival to operating room all patients were cannulated with 18 G intravenous (IV) catheter. Baseline blood pressure, heart rate (HR) and saturation was recorded. All patients were monitored with ASA standard monitors which included Non-Invasive Blood Pressure (NIBP), Mean Arterial Pressure (MAP), continuous electrocardiography, Heart Rate (HR) and pulse oximetry. HR, NIBP and MAP were recorded every three minutes for first fifteen minutes then every 5 minutes for rest of the procedure. The participants were allocated to one of three groups (with 45 patients in each group, respectively) in the ratio of 1:1:1; Group O (ondansetron) n=45, Group P (phenylephrine) n=45 and Group N (Normal Saline) n=45.

Subarachnoid block was performed with all patients in sitting position. After skin preparation and infiltration with 2% Lidocaine, a 27 G Sprotte needle was inserted at L3–L4 vertebral interspace. Once free flow of cerebrospinal fluid was obtained, 3 mL of hyperbaric bupivacaine 0.5% (15 mg) plus 6 µg Dexmedetomidinewas injected intrathecally. Patients were immediately turned supine and 2 mL bolus of the study drug was injected. Group O received 4 mg IV Ondansetron, Group P received 100 µg IV Phenylephrine and Group N received 2ml IV Normal Saline. The patients were co-loaded with 15 mL/kg of Ringer Lactate during induction of spinal anesthesia. Patients then received Ringer Lactate at a rate of 10 mL/kg/h during rest of the procedure. Total amount of IV fluid the patient received was recorded. Mephentermine (6mg) was given when systolic blood pressure (SBP) was< 90 mm of Hg or SBP falls > 20% from the baseline and repeated as necessary. Heart rate (HR) < 60 bpm or fall in HR > 20% from the baseline was treated with atropine 0.6mg. The block height was assessed by response to cold sensation using alcohol swab every 3 min until maximum block was achieved. Oxygen was supplemented via face mask at 5 liters/ min. Nausea/ vomiting was scaled on 3-point score 0: none, 1: nausea present but vomiting absent defined as severe nausea, 2: vomiting present. Those patients who scored 1 or 2 were treated with metoclopramide 10 mg.

Data analysis was done in SPSS (SPSS Inc., Chicago, IL, version 21.0 for windows). Continuous variable was analyzed with one way ANOVA, independent t- test or Mann Whittney U test whichever was applicable. Categorical variable was analyzed with chi square or fischer's exact test whichever was applicable. $p \leq 0.05$ was regarded statistically significant.

Results

A total of 135 patients were enrolled in the study and allocated to one of the three groups in the ratio 0f 1:1:1 with 45 patients in each group. The three groups were comparable with respect to age, gender, body mass index, ASA physical status, block height, volume of intravenous fluid received and duration of surgery and anesthesia (Table 1).

Table 1: Demographic and intraoperative variables in three groups (n=135)

Variables	Group N (n=45)	Group O (n=45)	Group P (n=45)	p value
Age; years	39.82±14.22	40.27±13.24	40.40±14.72	0.97
BMI; kg/m^2	25.46±4.04	24.29±4.66	24.33±4.66	0.37
Gender M/F	16 (35.5%)/28(64.5%)	24 (53.33%)/21 (46.67)	26 (57.78%)/19 (17.82%)	0.11
ASA 1 and 2	28 (62.22%)/17 (37.78)	30 (66.67)/15 (33.33)	26 (33.38)/19 (42.22%)	0.71
Block height	T6 (T4-T8)	T6 (T4-T8)	T6 (T4-T8)	0.09
Duration of anesthesia; min	62.93±25.47	70.91±25.56	68.33±24.47	0.31
Total IV fluid; ml	1053±350.71	1121.11±437.51	1082±377.96	0.71
Duration of surgery; min	58.31±25.88	66.31±25.62	63.33±24.47	0.32

BMI: body mass index, ASA: American Society of Anesthesiologists. Data presented as mean ±sd and median (IQR). Data analyzed by one way ANOVA. Gender and ASA presented as number (percentage) and analyzed using Fischer Exact test. p value ≤ 0.05 considered statistically significant.

Table 2 presents the baseline hemodynamic variables of three groups which were comparable among the groups.

Table 2: Baseline hemodynamic variables in three groups (n=135)

Baseline variables	Group N (n=45)	Group O (n=45)	Group P (n=45)	p value
HR (beats per min)	84.33 ± 16.78	83.36 ± 15.91	79.80 ± 15.82	0.37
SBP (mm of Hg)	134.51 ± 18.09	134.04 ± 15.71	134.20 ± 12.95	0.99
DBP (mm of Hg)	82.93 ± 11.23	84.80 ± 12.09	83.93 ± 11.97	0.75
MAP (mm of Hg)	102.38 ± 18.91	104.29 ± 13.30	103.80 ± 12.90	0.82

Data presented as mean ± sd and analyzed by one way ANOVA. p value ≤ 0.05 considered statistically significant.

We noted that overall prevalence of hypotension was 74.07% which was experienced by 34 patients irrespective of pharmacologic prophylaxis. The maximum number of patients in Group O; 14 (31.11%) experienced hypotension after spinal anesthesia followed by patients in Group N 12 (26.67%) and Group P 8 (17.78%). However, this difference in the prevalence of hypotension was not significant statistically when Group O and Group P were compared with Group N (Table 3).

Table 3: Prevalence of hypotension in three groups (n=135)

Group	Hypotension	p value
N (n=45)	12/26.67	
O (n=45)	14/31.11	0.64*
P (n=45)	8/17.78	0.34#

Data presented as number/ percentage and analyzed by using chi-square test. *p value between Group N and O, # p value between Group N and P. p value ≤ 0.05 considered statistically significant.

The mean rank of mephentermine used in Group N, O and P was 14.09, 11.15 mg and 9.07 mg respectively with p value 0.33 (Group N vs. Group O) and 0.79 (Group N vs. Group P)

The adverse events are presented in Table 4. None of the patients in Group O and Group P experienced severe nausea whereas 1 (2.94%) patient had severe nausea in Group N. Likewise, 1 (2.94%) patient each in Group N and Group O had vomiting. Bradycardia was present in 2 (5.88%), 1 (2.94%) and 7 (20.58%) patients in Group N, O and P respectively. The prevalence of adverse events was not statistically significant when compared with Group N (control group).

Table 4: Adverse events in three groups (n=34)

Nausea / Vomiting	Group N (n=12)	Group O (n=14)	Group P (n=8)	p value
Severe nausea	1 (2.94%)	0	0	0.31*, 0.31#
Vomiting	1 (2.94%)	1 (2.94%)	0	1.00*, 0.31#
Bradycardia	2 (5.88%)	1 (2.94%)	7 (20.58%)	0.55*, 0.07#

Data presented as number (percentage) and analyzed using chi square test. *p value between Group N and O, # p value between Group N and P. p value ≤ 0.05 considered statistically significant.

Discussion

We noted that pretreatment with ondansetron didn't decrease the episodes of hypotension associated with spinal anesthesia (SA) in our patients and there was no difference in consumption of mephentermine between two groups. Our finding is supported by previous study which concluded that prophylactic use of serotonin receptor antagonist whether ondansetron or granisetron didn't decrease the occurrence of hypotension in adult non obstetric cases who underwent surgery under

SA.[11] There is a difference on the choice of adjuvant in spinal anesthesia. We had used 6mcg dexmedetomidine in contrast to 25 mcg fentanyl in their study. However, the variation in the spinal adjuvant didn't seem to affect the outcome.

Several past studies have questioned the utility of serotonin receptor antagonist for prevention of SA induced hypotension with a conclusion that data is insufficient to clearly recommend it's use to alleviate SA induced hypotension.[1,12]

We differ from the findings of past study which proposed that prophylactic usage of ondansetron prevented hypotension. This difference in the findings may be due to the use of higher dosage of ondansetron 6 and 12 mg in their study vs. 4 mg in our study.[5]

One of the past studies have also emphasized the limited utility of prophylactic administration of 5-Hydroxytryptamine (5HT3), antagonist in young adults as compared to older population (≥ 60 years) to prevent hypotension after spinal anesthesia.[8] One of the plausible explanations for this is age related stiffening of blood vessel and decrease in blood volume. The vasodilation provoked by spinal anesthesia results in significant reduction in preload in geriatric patients which justifies that Bejold Jarisch Reflex (BJR) is more intense in geriatric population. Thus, it is reasonable that 5HT3 antagonist as ondansetron would be more effective in preventing hypotension induced by spinal anesthesia in elderly patients as compared to younger ones. As we conducted our study in patients aged 18-60 years, ondansetron didn't prove to be a useful adjunct to prevent spinal anesthesia induced hypotension.

The meta-analysis which included ten randomized controlled trials with 863 patients documented that effective dose of ondansetron as 8 mg in general population and 4 mg in obstetric patients to attenuate spinal anesthesia- induced hypotension, when used prophylactically.[13] The dose used in our study was less. This might be the reason for due to which there was no change in the prevalence of hypotension in patients who were pre-treated with ondansetron.

We differ in many ways from the abovementioned studies. First, we administered ondansetron after local anesthetic was deposited in the subarachnoid space whereas in most of the prior studies the study drug was given prior to performing subarachnoid block. Second, the dose of local anesthetic was high (15 mg). The time interval between the administration of ondansetron and onset of sympathectomy was too narrow in our study. These are possibly the reasons for in-effectivity of ondansetron to attenuate the hypotension associated with spinal anesthesia. We recommend further studies be conducted in our population using higher dose of ondansetron to shade light upon its role in alleviating hypotension associated with SA.

Likewise, we also noted that pre-treatment with phenylephrine was ineffective in attenuating the hypotensive effects of SA. There was no difference in consumption of mephentermine between Group N and Group P. Our findings are not congruent with several past researches which have documented the benefits of administration of phenylephrine immediately after instillation of intrathecal local anesthetic to prevent spinal anesthesia induced hypotension.[14–17] These studies have used infusion of phenylephrine in varied dosages rather than a single bolus dose and those studies were conducted in cesarean section and in geriatric patients.

Our finding is consistent with one of the past study conducted in similar set up using 15 mg Bupivacaine heavy for spinal anesthesia which also failed to document the utility of prophylactic use of phenylephrine to prevent SA induced hypotension.[4] The dose used in their study was much smaller 25 µg than that used in our study 100 µg.We differ from their study due to presence of 6 mcg dexmedetomidine as an adjuvant to 15 mg Bupivacaine heavy in spinal anesthesia. However, even with higher dose of phenylephrine, we failed to document the efficacy of single bolus dose of phenylephrine to prevent SA induced hypotension. Rather, there was a higher prevalence of bradycardia in patients receiving phenylephrine than those receiving ondansetron or normal saline.This was expected due to increase in blood pressure which led to reactive bradycardia. One of the previous study proposed that intrathecally added dexmedetomidine might have an additive effect for occurrence of bradycardia in patients pre-treated with phenylephrine. They had used 5mcg dexmedetomidine as an additive to spinal anesthesia.[18] However, there are further evidences which suggested that intrathecal dexmedetomidine in dosage less than 10mcg are not associated with bradycardia and hypotension.[19,20]

One of the previous study have highlighted that single prophylactic phenylephrine bolus of 50 µg was less effective than a prophylactic infusion of 0.15 µg/kg/min in reducing the incidence of hypotension, intraoperative nausea and vomiting in parturient.[21] Likewise, there is an evidence that prophylactic infusion of phenylephrine is superior in maintaining intraoperative blood pressure, with an incidence of hypotension of 13%–23% compared to an incidence of 85%–88% when phenylephrine boluses of 100 µg were used to treat a 20% decrease in arterial blood pressure.[22] We also noted that single prophylactic bolus dose was not sufficient to attenuate hypotensive effect of SA.

Likewise, while analyzing the prevalence of nausea and vomiting, we noted our patients in Group P didn't experience any episodes of nausea and vomiting in comparison to study conducted by previous researchers.[4] The plausible explanation could be lesser incidence of hypotension (17%) in comparison to 21% in their study which could have resulted in higher prevalence of nausea (16.66%) in their study because acute hypotension decreases cerebral perfusion which induces transient brainstem ischemia and activates the vomiting center.

In one of the past research where 4 mg ondansetron was given 5 minutes prior to spinal anesthesia, none of the patient experience nausea and vomiting whereas in our study even though we vary from them at the timing of giving ondansetron only one patient experienced vomiting.[23]

One of the previous studies which attempted to find the optimal dosage of intrathecal dexmedetomidine in Indian population highlighted that addition of dexmedetomidine to Bupivacaine led to overall decrease in the prevalenceof intraoperative nausea and vomiting as compared to the control group without dexmedetomidine as an adjuvant. We also noted very low

prevalence of nausea and vomiting in our patients which is similar to their findings.[20] In addition, ondansetron has proven antiemetic effect, this could also have been the plausible reason for lower prevalence of nausea and vomiting in Group O.

Limitations

The anesthesiologist was not blinded to the drugs that was used in the study. We have not taken into account the other causes of hypotension like blood loss during surgery.Another factor that may have influenced the lack of drug effect is the timing of administration. As we gave drug immediately after spinal anesthesia, sufficient time may have not been available for the drug to achieve its peak activity. Likewise, ondansetron in higher dosage 8mg, 10mg or 12 mg might blunt the hemodynamic response to spinal anesthesia. We suggest further research in our population using higher dosage of ondansetron.

Conclusion

Our findings do not support the prophylactic use of ondansetron and phenylephrine to attenuate spinal anesthesia induced hypotension in adult surgical patients.

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