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Original Article

Preemptive administration of ondansetron and phenylephrine for prevention of perioperative hypotension under spinal anesthesia for cesarean section: a quasi-experimental study

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Abstract

Background: Hypotension is the most commonly observed complications with the reported prevalence upto 90% without prophylaxis after spinal anesthesia in obstetric cases. Various methods have been implemented to mitigate spinal induced hypotension. Pharmacological agents as pure α2 adrenoceptor agonist as phenylephrine and 5HT3 antagonists as ondansetron have been used to prevent and treat spinal anesthesia induced hypotension. We aimed to find out whether or not pre-emptive administration of phenylephrine or ondansetron attenuates hypotension in elective cesarean section in healthy parturient under spinal anesthesia.

Methods: This quasi-experimental study was conducted in 120 ASA II parturient scheduled for elective cesarean section under spinal anesthesia with 10 mg 0.5% heavy bupivacaine. Patients in Group O received 4 mg ondansetron and patients in Group P received 100 µg phenylephrine immediately after spinal anesthesia. The occurrence of hypotension, total requirement of mephentermine was compared in both the groups. The complications such as bradycardia, nausea, vomiting were also compared.

Results: Hypotension was present in 31 patients in Group O (51.67%) and 33 patients in Group P (55%) (p=0.71). Consumption of mephentermine were comparable in both the groups (p=0.67) Bradycardia was not seen in any patients of Group O. It was present in five patients in Group P (8.33%) (p=0.02) which was treated with atropine. There were no cases of severe nausea and vomiting requiring treatment in any of the groups.

Conclusions: The pre-emptive administration of phenylephrine or ondansetron was not useful in attenuating intraoperative hypotension in healthy parturient undergoing elective cesarean section under spinal anesthesia.

Keywords: Cesarean section; Hypotension; Ondansetron; Phenylephrine

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Introduction

Hypotension after spinal anesthesia is the most common complications with the prevalence as high as 90% in obstetric cases.[1,2] Hypotension can have deleterious effects on both mother and neonate. Thus various techniques have been used alone or in combination to prevent and treat maternal hypotension. Non pharmacological techniques as leg elevation, left uterine displacement to relieve aorto-caval compression and pre hydration have limited efficacy. Hence vasopressors such as phenylephrine, ephedrine and norepinephrine have been widely used to mitigate sympathetic blockade induced reduction in systemic vascular resistance to maintain intraoperative blood pressure.[3]

Recent studies have shown that pure α-1 adrenoceptor agonists such as phenylephrine have more favorable effects on fetal acid-base balance. Hence, phenylephrine is now considered as a drug of choice for prevention and treatment of maternal hypotension in cesarean section.[4]

The pharmacologic and animal studies have suggested that serotonin is responsible for BJR induced hypotension and bradycardia and this effect can be blocked at serotonin receptor (5HT3).[5,6]Thus, there has been growing interest on 5HT3 receptor antagonist ondansetron as an alternative in attenuating spinal anesthesia induced hypotension and bradycardia.

The purpose of this study was to evaluate whether pre-emptive administration of intravenous phenylephrine or ondansetron reduces the occurrence of intraoperative hypotension associated with spinal anesthesia.

Methods

This quasi-experimental study was conducted in the Department of Anesthesiology of Manipal Teaching Hospital, Pokhara, Nepal from June 2019 to November 2019. The approval from institutional review board was obtained with protocol approval number of MEMG/IRC/198/GA. The written and informed consent was taken from all the participants. A total of 120 ASA II singleton term pregnant female, 18-35 years of age scheduled for elective lower segment cesarean section under spinal anesthesia were enrolled in the study. Patients with severe cardiopulmonary disease, chronic hypertension or pregnancy induced hypertension, allergy to

study drugs, failed spinal anesthesia and spinal anesthesia supplemented with intravenous analgesics and sedative drugs were excluded from the study.

The prevalence of hypotension under spinal anesthesia in parturient have been reported to range from 70-80 %.[7] Considering the prevalence as 70% with margin of error of 9%, the sample size was calculated as: $n \geq z^2pq/d^2$, where n: no of cases, z: 1.96 at 95% confidence interval, p: prevalence of hypotension in parturient= 0.7, q: 1-p=0.3, d: allowable error= 0.09, the minimum sample size calculated was 100 however we have enrolled120 cases to compensate for possible subject loss during the study. Convenience sampling technique was used to collect sample.

The patients were divided into two groups, Group O (ondansetron 4 mg, n=60) and Group P (phenylephrine 100 µg, n=60). The participants were allocated alternately in the ratio of 1:1 to one of the two groups.

The venous access was secured with18 G intravenous (IV) catheter in ward or in pre-operative holding area. On shifting the patients to operation theatre, baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), continuous electrocardiography, heart rate (HR) and pulse oximetry were recorded. The HR, SBP, DBP and MAP were recorded every minute for the first fifteen minutes then every five minute till the end of procedure.

Subarachnoid block was performed with all the patients in left lateral position. After skin preparation and infiltration with 2% Lidocaine, 25 G quincke needle was inserted at L2–L3 or L4-L5 interspinous space and once free flow of cerebrospinal fluid was obtained, 10 mg of 0.5% hyperbaric bupivacaine was injected. The time of drug injection into the intrathecal space was noted.

Patients were immediately turned supine. The operation table was tilted 15° towards left. The patients in Group O received 4 mg iv ondansetron and Group P received 100 µg iv phenylephrine. Both the drugs were constituted to a total volume of 2 ml. The patients were co-loaded with 15 mL/kg of ringer lactate during the 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 were recorded.

The block height was assessed by response to cold sensation using alcohol swab every minute until block height of T4 was achieved after which the surgery was started. Oxygen was supplemented via face mask at five liters/ minute.

Hypotension was defined as SBP less than 90 mm of Hg. It was treated with six mg bolus dose of mephentermine and repeated as necessary. The occurrence of hypotension, time to first requirement of mephentermine and total dose of mephentermine consumed were recorded.

Bradycardia was defined as HR less than 50 beats/minute. It was treated with iv 0.6 mg atropine. The occurrence of bradycardia was noted.

Nausea/ vomiting was graded as I: none, II: mild nausea, III: severe nausea, IV: vomiting Metoclopramide 10 mg iv was given for patients with severe nausea and vomiting.

The occurrence of hypotension was considered as the primary outcome measure. The secondary outcome measures were total dose of mephentermine used and time when mephentermine was used initially and other complications such as bradycardia, nausea, vomiting were considered as secondary outcome measure.

Data analysis was done using SPSS (SPSS Inc., Chicago, IL, version 20.0 for windows). Quantitative data were presented as mean ± sd and evaluated using one way ANOVA for repeated measures or independent t test. Qualitative data were presented as number/percentages and evaluated using chi square test and $p<0.05$ was regarded as significant.

Results

Total of 120 patients were enrolled in the study. The demographic and clinical variables in both the groups were comparable as presented in Table 1.

Table 1: Demographic and clinical variables.

Variables	Group O (n=60)	Group P (n=60)	P value
Age (years)	27.67 ± 5.89	27.20 ± 4.55	0.62
BMI (kg/m^2)	27.25 ± 3.76	27.92 ± 3.96	0.34
HR Baseline (bpm)	96.57 ± 17.37	91.50 ± 14.67	0.08
SBP Baseline (mm of Hg)	118.35 ± 13.05	122.93 ± 14.25	0.06
DBP Baseline (mm of Hg)	74.05 ± 12.65	76.30 ± 13.39	0.34
MAP Baseline (mm of Hg)	91.78 ± 11.23	95.87 ± 12.45	0.06
IV Fluid (millilitres)	1070 ± 291.86	1024.17 ± 221.60	0.33

DOA (minutes)	45.17 ± 10.25	44.92 ± 9.22	0.88

BMI: body mass index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, IV: intravenous, DOA: duration of anesthesia, bpm: beats per minute. Data presented as mean ± sd.

Hypotension was present in 31 patients in Group O (51.67%) whereas it was present in 33 patients in Group P (55%). The total dose of mephentermine used and time when mephentermine was used initially were comparable between the groups as presented in Table 2.

Table 2: Comparison of hypotension and consumption of mephentermine between the groups.

	Group O (n=60)	**Group P (n=60)**	**P value**
Hypotension	31/ 51.67%	33/55%	0.71
Mephentermine requirement (mg)	12 ± 7.09	12.73 ± 6.49	0.67
Time to first dose of mephentermine (minutes)	9.19 ± 5.26	10.70 ± 11.02	0.49

Data presented as number/percentage or mean ± sd.

Bradycardia was not seen in any patients of Group O whereas it was present in five patients in Group P (8.33%). Statistically higher frequency was observed in Group P (p=0.02) which was treated with atropine.

Severe nausea and vomiting did not occur in any patients of both the groups, thus metoclopramide was not used in any of the patients.

The heart rate was comparable between both the groups at all times except at 1,3,4,5,6 and 7 minutes where the heart rate was lower in Group P with p values of 0.002, 0.008,0.003,0.004,0.005,0.02 respectively (Figure 1).

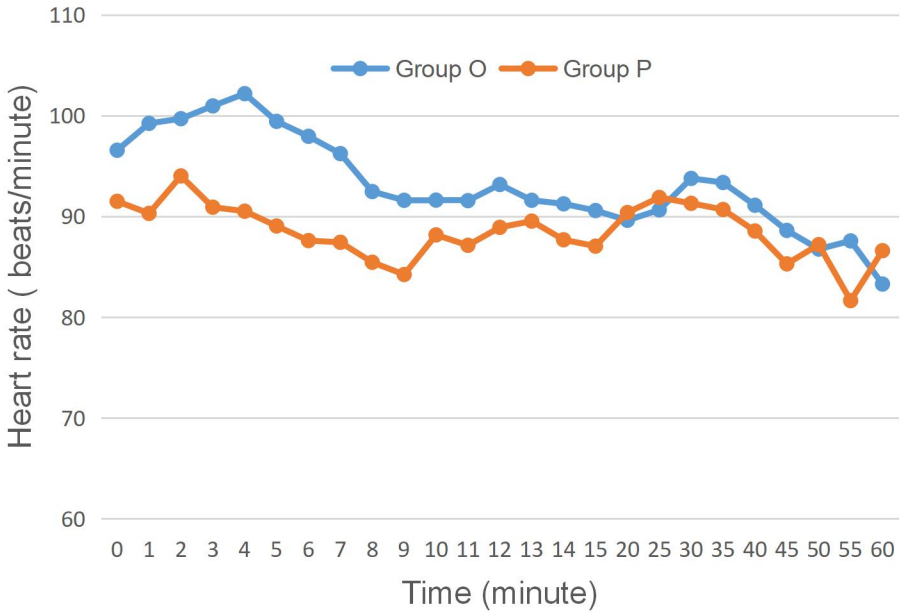

Figure 1. Comparison of heart rate between the groups. (Data points are mean)

The systolic blood pressure, diastolic blood pressure and mean arterial pressure were comparable between both the groups at all times as shown in Figure 2 and Figure 3.

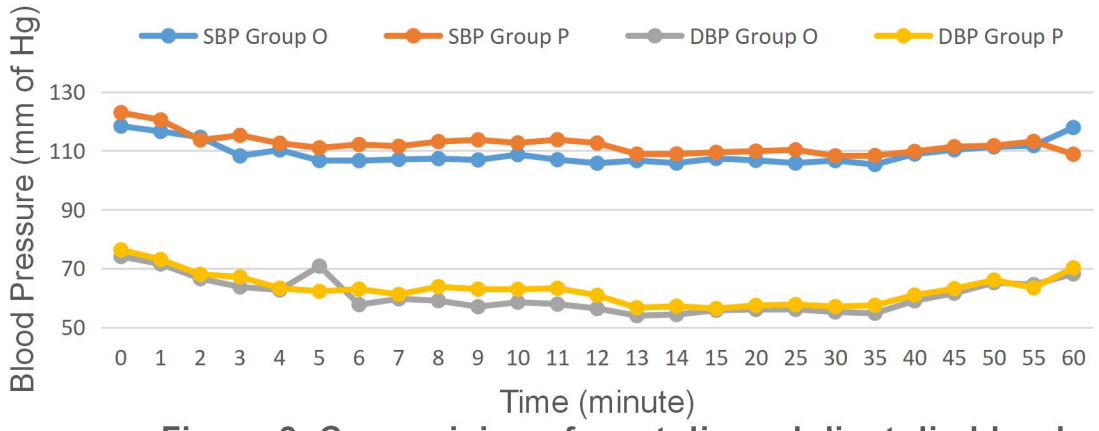

Figure 2. Comparision of systolic and diastolic blood pressure between the groups. (Data points are mean)

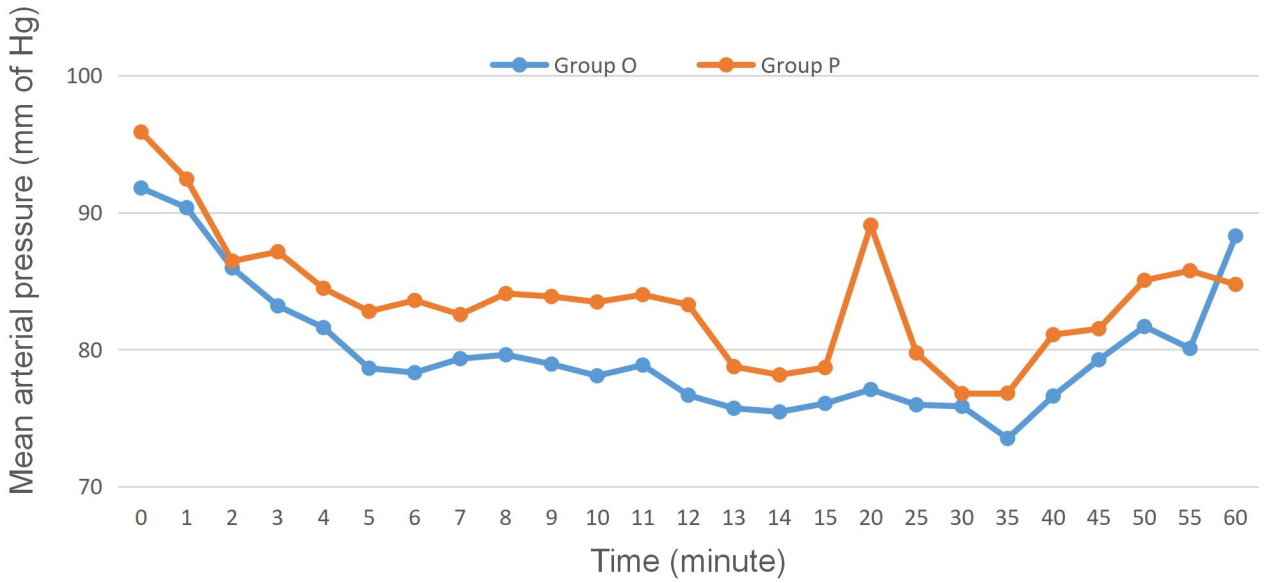

Figure 3. Comparision of mean arterial pressure between the groups. (Data points are mean)

Discussion

We found that pre-emptive instillation of intravenous phenylephrine or ondansetron didn't reduce the occurrence of hypotension in both the groups of term singleton parturient who underwent spinal anesthesia for cesarean section. Numerous studies have demonstrated the efficacy of phenylephrine in the prevention of hypotension after spinal anesthesia.[1–3,8,9] Agegnehu et al. compared two different doses of phenylephrine administered as a single bolus for prophylaxis, and found that phenylephrine 50 µg and 100 µg were more effective than placebo in maintaining intraoperative blood pressure in cesarean section.[8] Our findings are in contrast with their findings and the possible explanation is the small number of patients in their study, n=13 in patients receiving 100 µg phenylephrine. Moreover, the ineffectiveness of a single bolus dose of phenylephrine have been confirmed by Habib et al. They recommended phenylephrine to be used as continuous infusion to reduce the incidence of spinal anesthesia induced hypotension and intraoperative nausea vomiting.[9] Similarly, Neves et al. reported a lower incidence of hypotension (18% vs. 85%) when comparing a prophylactic phenylephrine infusion (0.15 mg/kg/min) with 50 µg phenylephrine boluses to treat a 20% drop in blood pressure.[10]

In this study, more patients experienced bradycardia who received phenylephrine than those receiving ondansetron. This is due to activation of baroreceptor reflex resulting in reactive bradycardia in response to increase in blood pressure due to administration of α-agonist. However, this was responsive to atropine.

The results of this study were in accordance with the study of Lee et al. where they have reported higher incidence of bradycardia in patients receiving phenylephrine as compared with

patients receiving ephedrine for prevention of hypotension under spinal anesthesia for cesarean section.[11]

A number of studies that investigated the efficacy of serotonin (5HT3) receptor antagonists in preventing spinal-induced hypotension have been published.[5,6,12–15]

Gao et al. in their meta-analysis have advocated 5HT3 receptor antagonists reduced the incidence of spinal anesthesia induced hypotension, bradycardia and requirement of vasopressor in cesarean section.[15] However, this finding has been challenged by Lee et al. for having a publication bias.[7] We differ from findings of Sahoo et al. as they have reported ondansetron 4 mg, given intravenously five minute before subarachnoid block reduced hypotension and vasopressor use in parturient undergoing elective caesarean section. This difference may be due to small number of patients, n=26 in patients receiving ondansetron in their study.[5]Likewise, Trabelsi et al. in their study also confirmed that prophylactic ondansetron 4 mg given five minutes before dural puncture decreased hypotension in healthy parturient undergoing spinal anesthesia with bupivacaine and sufentanil for elective caesarean section. The possible explanation of different finding may again be attributed to difference in sample size, 40 per group in their study. In contrast our study was larger as we had recruited 60 patients per group. Our hospital is a teaching institute and most of the procedure are performed by trainee residents, and we anticipated they would take longer time to perform spinal anesthesia, and considering the rapid onset of action of iv ondansetron we preferred to give it immediately after spinal anesthesia not five minutes before induction of anesthesia.

Our findings are comparable to findings of Gomez et al., who found that prophylactic ondansetron 2 mg, 4 mg or 8 mg didn't decrease the incidence of maternal hypotension in cesarean section.[14] Similarly, we agree with the findings of Nivatpumin et al. who found no difference in the occurrence of maternal hypotension in patients receiving prophylactic 8 mg ondansetron.[3] The limitations of our study were its non-randomized nature. Being an academic trial our study was not funded thus the financial constraint was one of the major barrier. In addition further logistic issues such as validity and long trial run time were other reasons why we failed to conduct a RCT. Though the investigators were not blinded to group allocation, we assigned patients alternately to each group in the ratio of 1:1 to minimize the allocation bias. We also have not analyzed umbilical blood acid base balance and Apgar scores of neonate.

Conclusions

Our study showed that prophylactic phenylephrine 100 µg or ondansetron 4 mg given immediately after spinal anesthesia in healthy parturient undergoing elective cesarean section with bupivacaine had no significant effect on maternal blood pressure.

Conflict of Interests: *The authors have filled the ICMJE COI form and have nothing to disclose.*

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