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Comparison between mephentermine and ondansetron for the prevention of post spinal hypotension: a prospective randomized trial

K. Shah, P.K. Dubey, A. Bharti, S. Singh

Abstract: *Background and Aims:* Spinal anesthesia is a technique often associated with side effects like hypotension and bradycardia. Recent studies have shown that the use of ondansetron leads to a decreased incidence of hypotension induced by spinal anesthesia. This prospective, randomized, controlled, double-blind study was done to compare the efficacy of the prophylactic use of intravenous (IV) ondansetron and mephentermine on post-spinal hypotension.
Methods: A total of 130 patients were randomly allocated to one of two groups: Group O received 4 mg IV ondansetron and Group M received 6 mg of IV mephentermine. All patients received spinal anesthesia using 3 mL of 0.5% hyperbaric bupivacaine. Assessment of blood pressure and heart rate (HR) was done for 30 minutes after spinal anesthesia was performed. Quantitative data were analyzed using ANOVA tests and qualitative data were analyzed using the Chi-square tests.
Results: Both groups were comparable regarding demographic data. Mean arterial blood pressure (MAP) in Group O was lower than Group M at 5 to 25 minutes and difference of MAP between the two groups was > 20% of baseline values ($p < 0.05$). HR was comparable between groups. No statistically significant differences were seen in side effects between the two groups.
Conclusion: Our study shows that the preemptive use of both ondansetron and mephentermine significantly decreases the incidence of post-spinal hypotension.

Keywords: ondansetron; spinal anesthesia; mephentermine; hypotension; hemodynamic.

Introduction

Spinal anesthesia is the preferred technique for lower limb and pelvic (urologic, gynecologic) surgeries, offering several advantages over general anesthesia. However, it is associated with significant side effects like hypotension, bradycardia, and shivering. An often-distressing symptom for the patient as well as the anesthesiologist is hypotension, which requires aggressive management. The mechanism involved in the occurrence of hypotension is the vasodilation caused by the sympathetic blockade, which in turn causes a decrease in vascular resistance, and finally leads to a drop in arterial blood pressure (1).

A combination of parasympathetic over activity, activation of Bezold–Jarisch reflex (BJR), and increased baroreceptor activity results in hypotension and bradycardia. BJR is triggered by chemoreceptors and mechanoreceptors, which are serotonin sensitive. This chemoreceptor triggering within the intracardiac wall by a reduction in blood volume causes increased vagal nerve activity, followed by bradycardia and vasodilation (2, 3, 4).

Multiple studies have shown that ondansetron, a serotonin (5HT3) receptor antagonist can prevent serotonin-induced BJR, thereby, preventing hypotension. (3, 5) Review of the current literature has shown that no study has been done to compare the efficacy of the prophylactic use of ondansetron with the one of mephentermine on the prevention of post-spinal hypotension. Frequent studies have been done in this field; many have shown contradictory and controversial results, which have necessitated the need for more exhaustive studies (6).

We designed this study, to compare the efficacy of the prophylactic use of Ondansetron and mephentermine on post spinal hemodynamic (blood pressure and heart rate) changes in the supine position. Our primary outcome was to compare the efficacy of the prophylactic use of ondansetron with mephentermine in reducing the incidence of hypotension caused by spinal anesthesia and perioperative adverse effects as secondary outcomes.

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Methods

After institutional ethical committee approval and informed written consent, 130 patients of both genders and aged between 18 and 60 years were recruited. They all had an American Society of Anesthesiologists (ASA) physical status I or II, and were scheduled for surgery below the umbilic under spinal anesthesia. The study period of ranged between December 2017 to July 2019. This double-blind, randomized-controlled trial was registered with qthe Clinical Trial Registry – India (CTRI/2017/11/010450).

Patients were evaluated the day before surgery by an anesthesiologist. They were randomized using a computer-generated randomization table into two groups: Group O received 4 mg ondansetron intravenously, and Group M received 6 mg of mephentermine intravenously. Each group received a total volume of 5 ml by adding normal saline, given five minutes prior to the spinal block.

Randomization schedule

Sample size was 65 in each group. A block randomization schedule was generated using https://www.sealedenvelope.com/. We took a block size of 10. A total of 13 blocks were generated. The randomization list was kept with the investigator not directly involved in the process of recruitment. The allocation was concealed.

Upon arrival to the operating room, standard monitors were placed and baseline parameters recorded. A peripheral 18G intravenous (IV) catheter was established on the ventral aspect of the left forearm, and all patients co-loaded with a lactated ringer solution at a rate of 5 ml/kg/hr throughout the study period. Patients were explained about the procedure and methodology of the study, as well as the monitoring methods. In Group O, a 5 ml syringe was given to the monitoring anesthesiologist and he/she injected intravenously its content intravenously, 5 minutes before performing spinal anesthesia. Spinal anesthesia was performed in the sitting position, under standard aseptic precautions, using a midline approach lumbar puncture at the L3-L4 intervertebral space, and a 25G Quincke spinal needle. Having confirmed the free flow of cerebrospinal fluid, 3 ml (15mg) of hyperbaric bupivacaine (0.5%) was injected intrathecally over a period of 10-15 seconds and patients were turned supine. No surgery-related procedure that included patient positioning, tourniquet placement and urinary catheterization was performed during the study period.

The level of sensory block was checked by pinprick sensation and motor blockade was assessed by the Modified Bromage scale. On achieving T-6 sensory blockade and Bromage scale 3, surgery was allowed. Heart rate (HR), mean arterial blood pressure (MAP) and peripheral saturation in oxygen (SpO_2) were recorded every 5 minute for 30 minutes. Hypotension, defined as a decrease in systolic blood pressure by more than 20% from baseline or a fall below 90 mmHg, was treated with incremental IV doses of mephentermine 6 mg and IV fluid as required. Bradycardia, defined as HR < 50 bpm or fall in HR of more than 20%, was treated with IV atropine 0.3 mg. The incidence of adverse effects, such as nausea, vomiting, hypotension, shivering, pruritus, and prolonged QT interval was recorded.

Statistical analysis

Earlier studies reported that 33% of the subjects receiving preemptive mephentermine experience hypotension. We expected a 50 percent reduction in the incidence of hypotension with the use of ondansetron, i.e. 17%. After applying continuity correction, the study would require a sample size of 63 for each group (i.e. a total sample size of 126, assuming equal group sizes), to achieve a power of 80% and a level of significance of 5%, for declaring that the ondansetron is superior to the mephentermine at a 5% margin of superiority (assuming that a larger proportion is desirable).

Statistical analysis was performed using the Statistical Package for Social Sciences version 17.0 (SPSS). Continuous variables were presented as mean [SD], and categorical variables were presented as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using ANOVA tests with post-hoc analysis. Nominal categorical data were compared using the Chi-square (χ^2) tests or Fischer's exact tests. A p value of less than 0.05 was considered statistically significant.

Results

The consort flow diagram for the study is depicted in Figure 1. Demographic profile was comparable in both groups (Table 1).

Baseline MAP was comparable between the two groups. MAP in Group O was lower than in Group M at 5, 10, 15, 20 and 25 minutes after the performance of spinal anesthesia (90.56 [10.23] vs 97.29 [9.24]; 85.93 [10.07] vs 95.76 [8.46]; 84.36 [10.83] vs 91.21 [6.89], 84.64 [9.67] vs 88.79

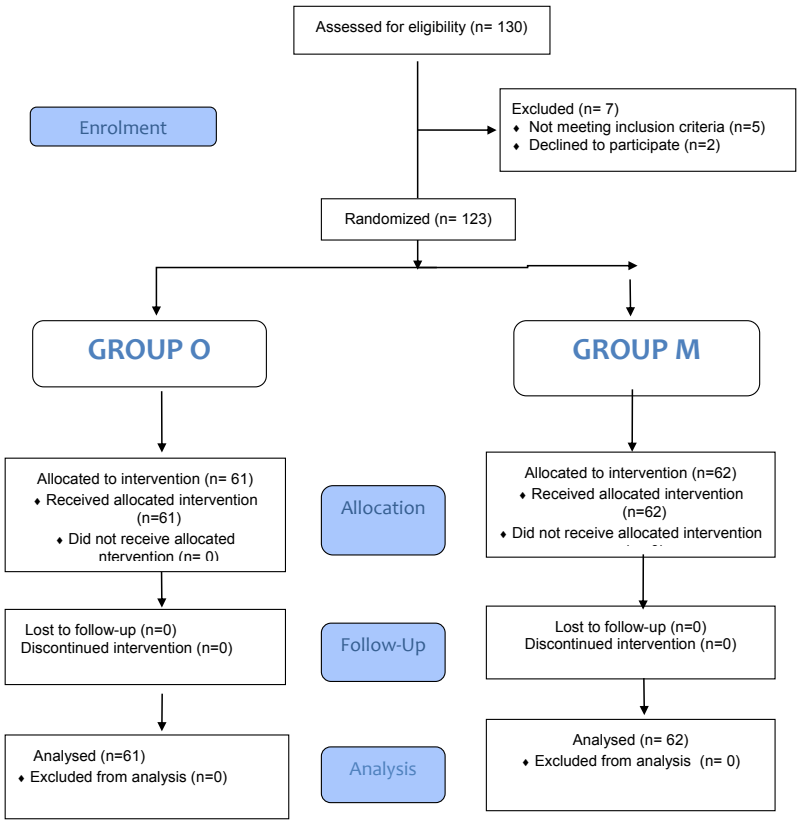

Figure 1. — Consort Diagram.

Table 1

Demographic data between two groups

	Group O (Mean [SD]	**Group M (Mean [SD]**	**95% CI**	**P value**
Age (years)	44.2 [12.73]	41.97 [11.38]	-2.36 - 6.36	0.35
Sex (%)				
Male (%)	43 (70.49)	42 (67.74)	-15.20 - 20.70	0.893
Female (%)	18 (29.51)	20 (32.26)	-15.20 - 20.70	0.893
Body Weight (Kg)	60.9 [8.91	57.5 [11.6	-0.21 - 7.21	0.064
ASA grade (%)				
Grade I	51 (83.61)	56 (90.32)	-6.77 - 20.19	0.402
Grade II	10 (16.39)	6 (9.68)	-6.77 - 20.19	0.402
Height (cm)	160.95 [5.41	161 [6.54	-2.04 - 2.24	0.92

[8.69]; and 84.56 [8.62] vs 88.6 [9.22], respectively) (Fig. 2), and the difference in MAP as compared to baseline was not higher than 20% in both groups (Table 2).

HR remained comparable between the two groups throughout the study period (Fig. 3) (Table 3). Nausea occurred in 1 patient in Group O and 3 patients in Group M. Two patients in Group O had an episode of shivering but none in Group M. There were no statistically significant differences in associated side effects between the two groups (Table 4).

Discussion

Spinal anesthesia is widely used for lower abdominal and lower limb surgeries. Despite its numerous advantages, side effects like hypotension and bradycardia that can evolve into severe bradycardia and cardiac arrest may occur (1,3), and

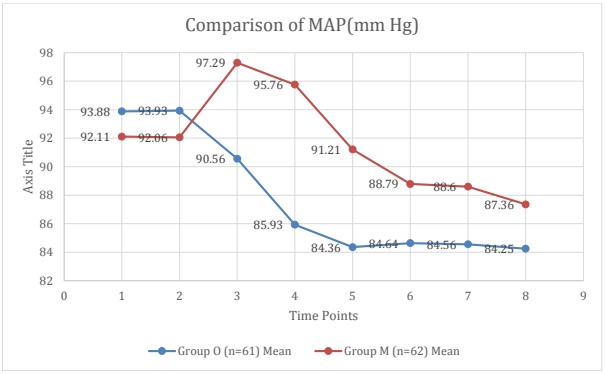

Fig. 2. — Comparison of Mean Arterial Pressure (MAP) between Group O and Group M.

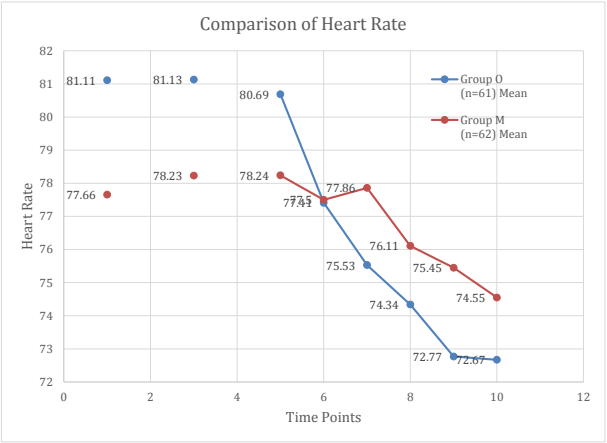

Fig. 3. — Comparison of Heart Rate (HR) between Group O and Group M.

Table 2

Comparison of MAP (mmHg) between the two groups

	Group O (n=61)		**Group M (n=62)**			
	Mean	SD	Mean	SD	95% C.I.	p value
MAP baseline	93.88	7.65	92.11	8.16	-1.05 - 4.59	0.217
MAP pre level	93.93	8	92.06	8.22	-1.03 - 4.77	0.203
MAP 5	90.56	10.23	97.29	9.24	3.25 - 10.2]	0.0002
MAP 10	85.93	10.07	95.76	8.46	6.51 - 13.15	0
MAP 15	84.36	10.83	91.21	6.89	3.62 - 10.08	0
MAP 20	84.64	9.67	88.79	8.69	0.87 - 7.43	0.014
MAP 25	84.56	8.62	88.6	9.22	0.85 - 7.23	0.0134
MAP 30	84.25	10.3	87.36	9.02	-0.34 - 6.56	0.077

Data are presented as mean [SD]; P value < 0.05 considered as significant; SD = Standard Deviation.

Table 3

Comparison of Heart Rate between the two groups

	Group O (n=61)		**Group M (n=62)**			
	Mean	SD	Mean	SD	95% C.I.	p value
HR Baseline	81.11	13.11	77.66	9.13	-0.58 - 7.48	0.092
HR Pre level	81.13	10.42	78.23	6.7	-0.22 - 6.02	0.06
HR 5	80.69	13.79	78.24	10.99	-2.00 - 6.90	0.277
HR 10	77.41	13.44	77.5	11.22	-4.33 - 4.51	0.97
HR 15	75.53	13.3	77.86	11.54	-2.11 - 6.77	0.301
HR 20	74.34	12.11	76.11	11.99	-2.53 - 6.07	0.42
HR 25	72.77	13.26	75.45	11.83	-1.80 - 7.16	0.24
HR 30	72.67	13.22	74.55	11.32	-2.51 - 6.27	0.39

Table 4

Comparison of associated side effects between the groups

Parameter	**Group O**	**Group M**	**P value**
Nausea	3 (61)	(62)	0.301
Shivering	1 (61)	2 (62)	0.5

led to a search for preventive methods, including preloading and co-loading with intravenous fluids, administration of sympathomimetics, administration of atropine, and patient positioning facilitating venous return (7, 8, 9, 10).

In the current study, the baseline MAP was comparable between groups. The difference in MAP between Group O and Group M was significant at 5, 10, 15, 20 and 25 minutes. Even though the difference between the two groups was significant, MAP fall was less than 20 % of baseline at all intervals, except in three patients of group O. Hypotension in one patient was managed with intravenous fluid administration, while a mephentermine bolus of 6 mg was given at 10 and 15 min in two patients.

A related study by Tatikonda et al. concluded that the prophylactic use of intravenous ondansetron 4 mg reduced the requirement of ephedrine in patients undergoing surgeries under subarachnoid block (11).

Rashad et al. studied the effect of intravenous ondansetron and granisetron on hemodynamic changes following spinal anesthesia for caesarean section, and found that the ondansetron group had significantly less blood pressure drop as compared to granisetron or the placebo group (12). Sahoo et al. studied 52 parturients scheduled for elective cesarean section and concluded that intravenous ondansetron reduced hypotension and vasopressor use in the group of patients who received ondansetron. (13)

The current study shows that there is a significant difference in MAP between the two study groups. This difference can probably not be attributed to confounders like difference in preloading, leg elevation, the application of bilateral leg wrapper, or Trendelenburg position.

In the present study, HR remained comparable between group O and Group M. Owczuk et al., who evaluated intravenous ondansetron 8 mg in patients undergoing surgeries under subarachnoid block found no significant difference in HR between their study groups (8). A possible explanation for the absence of significant differences in HR could be a compensatory increase in HR in Group O due to a significant fall in MAP, and increased HR in Group M due to the use of a sympathomimetic drug.

Incidence of shivering was 3.22 % in Group M, whereas no patient in Group O had shivering, but the difference between the groups is not statistically significant. Our study differ, in this respect, from the study of Marashi et al., who found a statistically significant difference in the incidence of shivering between their ondansetron group and control group (P = 0.02) (14). But this discordance in results might simply be a matter of sample size. Kelsaka et al. compared the incidence of shivering in patients who received intravenous ondansetron 8 mg and meperidine 0.4 mg/Kg immediately before spinal anesthesia. They concluded that ondansetron has similar effects as meperidine in reducing the incidence of shivering (15).

In present study 3 patients (4.9%) in Group O and no patient in Group M had an episode of nausea (not significantly different between groups). None of the patients, whatever the group, had an episode of vomiting. The episode of nausea can be explained by the significant fall in blood pressure, since hypotension is known to be an important factor that stimulates the chemoreceptor trigger zone in the medulla oblongata. Terkawi et al. conducted a study on 68 parturients, and concluded that an ondansetron 8 mg premedication before spinal anesthesia had no role in preventing nausea and vomiting (6).

Our study has the limitation that only ASA I and II patients were studied, hence results should not be generalized to other ASA categories. Second, further clinical trials are needed in a larger population to validate our study.

In conclusion, this trial demonstrates that the preemptive use of both ondansetron and mephentermine provides similar hemodynamic profiles during the minutes following the onset of spinal anesthesia. Ondansetron shows no significant effect on HR, as well.

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