

Ondansetron Is an Effective Alternative to Decrease the Incidence of Postspinal Hypotension in Healthy Subjects Undergoing Infra-Umbilical Surgeries Compared To Combined Volume Loading and Vasoconstrictors: Randomized Controlled Trial

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Abstract

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BACKGROUND: One of the important and predicted physiological effects of spinal anaesthesia is hypotension. A range of strategies including mechanical interventions, intravenous fluids and vasoconstrictor drugs have been used to minimise or prevent spinal anaesthesia-induced hypotension. Observational studies suggest that ondansetron reduces the incidence of post-spinal hypotension (PSH) and support the use of combined fluid preloading and vasoconstrictors for this purpose (but with limited doses) to avoid side effects as fluid overload and tachycardia respectively.

AIM: As no RCT had ever compared the use of Ondansetron alone with combined vasoconstrictors and fluid preload, so, this randomised controlled trial has evaluated the efficacy of the use of ondansetron alone compared to the combined use of fluid preload and vasoconstrictors to decrease the incidence of spinal hypotension.

METHODS: Ninety patients of ASA grade I between the age of 18 and 45 years scheduled to undergo elective surgical procedures on the lower extremity or lower abdomen under spinal anaesthesia were included in the study. The patients were randomly allocated into two groups of 45 each. Group I patients (ondansetron group) received 4 mg ondansetron in 5 ml normal saline (IV) 15 minutes before induction of spinal anaesthesia. Group II patients (combination group) received preloading with 7.5 ml/kg/min of Ringer's lactate over 10 minute period preceding the spinal block followed by intravenous bolus of 2.5 mg ephedrine in the first and second minute and 2.5 mg ephedrine every 5 minutes for the next 20 minutes after the injection of spinal anesthetic drug. Non-invasive measurement of mean arterial pressures, heart rate, reactive hypertension, nausea and vomiting were documented.

RESULTS: The incidence of hypotension following the subarachnoid block in Group I (ondansetron group) was 17.6% versus group II (combination group) was 13.3%, while difference among the groups is statistically insignificant ($P = 0.082$). Group IV fluids alone could reverse hypotension in 57.1% of patients in group I 33.3% in group II. 42.9% of patients in group I and 67.7% in group II could not be managed with IV fluids alone and had to be treated with 5 mg boluses of ephedrine for reversal of hypotension. The difference in the mean number of fluid boluses and a dose of ephedrine used between both groups was statistically insignificant ($P = 0.11$ and $P = 0.21$). HR showed a significant increase in group II and a statistically insignificant change in group I with a statistically significant difference in the heart rate (HR) between both groups ($P < 0.05$). Reactive hypertension, nausea and vomiting between both groups were statistically insignificant.

CONCLUSION: The preemptive use of Ondansetron alone versus combined vasoconstrictors with fluid preload significantly reduces the incidence of post-spinal hypotension (PSH) with no significant difference between both regimens. Furthermore, they also reduced consumption of the used vasoconstrictors and fluids to correct hypotension.

Introduction

Spinal anaesthesia was introduced by the German surgeon Karl August Bier in 1898 [1].

Nowadays it is one of the most commonly used techniques for lower limb and lower abdominal procedures, including cesarean section. Unfortunately one of its important adverse effects is hypotension [2] which occurs mainly as result of sympathectomy resulting from the neuroaxial blockade [3] and venous

pooling of blood in the legs, resulting in decreased venous return and cardiac output [4]. The incidence of hypotension was reported to be 92% in the control group during cesarean section with spinal anaesthesia [5] while in the nonobstetric patient was 33% [6]. In high-risk patients such as the elderly and those with underlying organ dysfunction, even a mild decrease in blood pressure must be avoided [7].

To prevent postspinal hypotension, mechanical techniques, volume preloading and loading and vasopressor drugs have been tried in several studies with variable results [8]. Most studies are centered around the effects of preloading [9], [10], [11] or vasopressors [12], [13], [14]. However, a large volume of fluids would be dangerous in elderly patients [8] and parturients [15] whom risky for pulmonary oedema. Ephedrine has alpha and beta actions [8] and is used as a vasoconstrictor in the treatment of spinal hypotension. Ephedrine causes tachycardia and hypertension [16] and should be used cautiously in ischemic heart patients [12].

Ondansetron is a serotonin 5-HT₃ receptor selective antagonist. Several studies revealed that it could prevent postspinal hypotension in pregnant and non-pregnant women [17], [18]. The mode of action is thought to be by prevention of the Bezold-Jarisch reflex (BJR). This reflex is cardiac inhibitory which produces a decrease in heart rate, blood pressure and cardiovascular collapse by type C fibres whose terminals lie in the heart [19]. Stimulating the peripheral serotonin receptors elicits the BJR [20].

As no one had ever compared the use of Ondansetron alone and combined vasoconstrictors with fluid preload, so, this randomised controlled trial evaluated in a single-blinded manner the efficacy of the use of ondansetron alone compared to the combined use of preloading and vasoconstrictors to decrease the incidence of spinal hypotension.

Methods

After approval of the ethical research committee, a prospective randomised single-blinded clinical trial was conducted in Kasr Alainy hospital theatres. Written informed consent was obtained from each patient. Ninety patients of the American Society of Anesthesiologists (ASA) grade I between the age of 18 and 45 years scheduled to undergo elective surgical procedures on the lower extremity or lower abdomen under spinal anaesthesia were included in the study. Patients with cardiovascular or respiratory disorders, abnormal cardiac anatomy, hypertension, pregnancy, diabetes, electrolyte imbalance, patients with hemoglobin concentration less than 10 gm%, weight more than 80 kg, height < 150 cm, fasting for less than 6 hours, those on medication which have

direct cardiac effects such as beta blockers, coagulopathy, hypersensitivity to the used drugs and patients who take antidepressants in the form of serotonin antagonists were not included in the study. In the preparation room, history was taken from all patients with documentation of the age, weight, height, American Society of Anesthesiologists score (ASA) and preoperative laboratory investigations as complete blood picture, coagulation profile, liver and renal functions and an 18 gauge cannula was secured with the entryway. The patients were randomly allocated into two groups of 45 each. Group I patients (ondansetron group) received 4 mg ondansetron in 5 ml normal saline intravenously (IV) 15 minutes before induction of spinal anaesthesia. Group II patients (combination group) received (IV) preloading with 7.5 ml/kg/min of Ringer's lactate over 10 minute period preceding the spinal block followed by intravenous bolus of 2.5 mg ephedrine in the first and second minute and 2.5 mg ephedrine every 5 minutes for the next 20 minutes after the injection of spinal anesthetic drug.

Then, the patient was transferred to the operating room and baseline vital signs were recorded 10 minutes before conduction of anaesthesia including non-invasive measurement of mean arterial pressures, heart rate, electrocardiogram (ECG), oxygen saturation.

No premedication was given, and the subarachnoid puncture was performed using a 25 gauge spinal needle at L3-4 interspace with patients in sitting position, 2.5-3 ml of hyperbaric bupivacaine 0.5% injected intrathecally according to height (< or = 160 cm - > 160 cm) and the patients returned to the supine position. The level of loss to pinprick sensation was assessed, and surgery was started when sensory loss of T10 was achieved.

Supplemental oxygen 5 L/min was given through face mask, and an infusion of lactated Ringer's solution at the rate of 2 ml/kg/hr was administered during anaesthesia, and the rate was not altered during the study period. Subsequently, the recording was done at 5, 10, 15, 20, 25, and 30 minutes after the subarachnoid injection of the anaesthetic drug. However, minute to minute monitoring was done to assess any hemodynamic changes and institution of corrective therapy. Non-invasive blood pressure (NIBP) around the upper arm and brachial artery pressure were recorded in the form of mean arterial pressure (MAP). Hypotension was defined as a decrease of MAP more than 20% of the baseline or less than 70 mmHg. During an episode of hypotension, an additional bolus of 2 ml/kg of lactated Ringer's solution was given. A maximum of three boluses was given. However, if supplementation of IV fluids failed to reverse hypotension, a bolus dose of ephedrine 5 mg was given intravenously then 2 ml/kg solution followed by 5 mg ephedrine are repeated if necessary. Pulse oximeter and ECG were used to record the oxygen saturation and heart rate

respectively. The patients were monitored for any reactive hypertension (MAP more than 20% of the baseline values), nausea and vomiting.

The sample size was calculated using the G-power software. Power analysis was done on the incidence of post-spinal hypotension (PSH) after spinal block as this is the primary outcome of our study. Previous studies reported an incidence of PSH in the nonobstetric patient as 33% [6]. The sample size was calculated to detect a 50% decrease in the incidence of PSH. Taking a study power of 80% and a P value less than 0.05 a minimum number of 45 patients were required for each group after exclusion of dropouts. Continuous data were presented as means (standard deviations) and medians (quartiles) and analysed using an unpaired t-test or Wilcoxon rank test as appropriate. Categorical data were presented as frequency (%) and analysed using Chi-square test. Repeated measures were analysed using two-way Analysis of variance (ANOVA). A p-value less than 0.05 were considered statistically significant.

Results

A total number of 145 patients were assessed for eligibility to be enrolled in the study while 52 were excluded as 44 didn't meet criteria and 8 declined to participate. The rest were randomized into group I with 92 patients and group II with 91 patients from group I and II, 3 patients were excluded due to failed spinal anaesthesia. Forty-five patients from each group received the allocated intervention and continued to be analysed with no further exclusions.

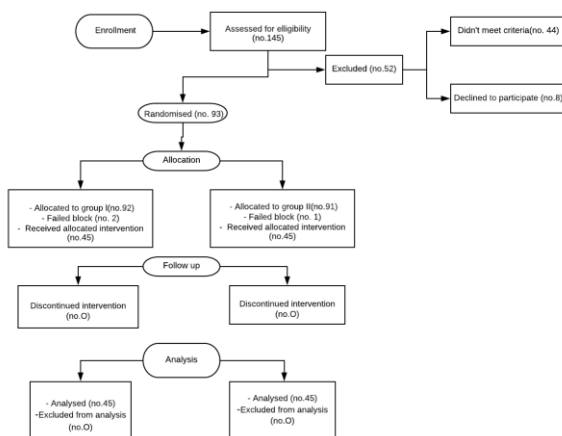


Figure 1: Flow chart for patient enrolment

The demographic data of the patients as shown in Table 1 showed that a number of 12 male and 18 female patients for group I with average age of

30.3 years, weight of 74.4 Kg and height of 171 cm while a number of 10 male and 20 female patients for group II with average age of 28.2 years, weight of 76 Kg and height of 173.6 cm are included in the study.

Table 1: Demographic data

	Group I (n = 45)	Group II (n = 45)
Age (yrs)	30.3 ± 10	28.2 ± 11.7
Sex (M/F)	12/18	10/20
Weight (kg)	74.4 ± 11.1	76 ± 7.8
Height (cm)	171 ± 9.3	173.6 ± 9.4

Values are mean ± SD.

Figure 2 shows that There was a significant decrease in mean arterial pressure (MAP) from baseline in group 1 at 10, 15, minutes while there was a significant fall in the MAP in group II from the baseline value at 15 and 20 minutes of the study with P < 0.05 while the rest of 30 minutes of the study MAP was insignificant in both groups to baseline value.

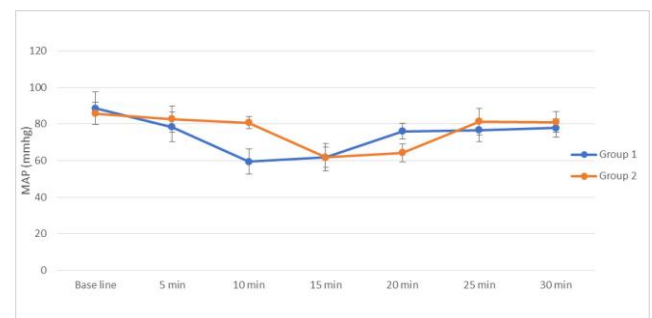


Figure 2: Mean arterial blood pressure. (Data are means, error bars are standard deviations. where the blue line is for the group I and a red line for group II)

Table 2 shows that seven patients in group I and six in group II had hypotension following the subarachnoid block and the difference among the groups is statistically insignificant. IV fluids alone could reverse hypotension in four patients in group I, two in group II. Three patients in group I and four patients in group II could not be managed with IV fluids alone and had to be treated with 5 mg boluses of ephedrine for reversal of hypotension. The difference in the mean number of fluid boluses and a dose of ephedrine used between both groups was statistically insignificant.

Table 2: Hypotension and its management

	Group I (n = 45)	Group II (n = 45)	p-value
No. of hypotensive patients	7 (15.6%)	6 (13.3)	0.082
(%) of patients managed by IV fluids bolus alone	4 (57.1%)	2 (33.3)	0.055
Mean No. of boluses of IV fluids	5	4	0.11
(%) of patients requiring bolus ephedrine	3 (42.9%)	4 (66.7)	0.14
Mean dose of bolus ephedrine	10	10	0.21

In Figure 3 the heart rate (HR) showed a significant increase in group II, throughout at 10 minutes till 30 minutes of the study and statistically insignificant change in group I and there was a statistically significant difference in HR between both groups with P < 0.05.

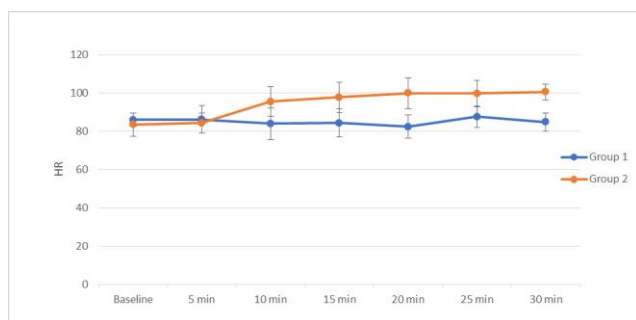


Figure 3: HR trends in both groups. (Data are means, error bars are standard deviations. where the blue line is for the group I and a red line for group II)

Table 3 showed that in group I, 2 patients had nausea while in group II, 3 patients had nausea but none had an episode of vomiting or reactive hypertension in either group and the difference among the groups is not statistically significant.

Table 3: Incidence of reactive hypertension, nausea and vomiting

	Group I (n = 45)	Group II (n = 45)	p-value
Hypertension	0	0	-
Nausea	2 (4.4%)	3 (6.6%)	0.075
Vomiting	0	0	-

Discussion

This randomised controlled trial (RCT) demonstrated that the preemptive use of both combined fluid preload and vasoconstrictors and use of Ondansetron alone significantly decreased the incidence of post-spinal hypotension (PSH) from 33% to 13.3% and 15.6 respectively. However no significant difference was shown between both regimens in reducing the incidence of PSH and also they reduced consumption of the used vasoconstrictors and fluids to correct hypotension while the difference in the mean number of fluid boluses and dose of ephedrine used between both groups was statistically insignificant which concludes that Ondansetron can be used as a sole agent in decreasing the incidence of post-spinal hypotension.

PSH is caused most probably due to reducing vascular tone and these results in decreases venous return and systemic vascular resistance [21]. Thus, measures used for prevention of PSH are directed to increase vascular tone and venous return which can be done by using vasoconstrictors, fluid administration, and positioning regimens [21], [22], [23], [24]. In many trials, fluid loading has been investigated to prevent PSH, but the results were not in its favour. With this in mind, investigators have turned their attention to vasoconstrictors protocols to prevent postspinal hypotension [25]. Conventionally,

ephedrine was used as the first-choice agent to maintain blood pressure [26]. Its stimulating action on alpha and beta-adrenergic receptors causes positive inotropic and chronotropic effects on the heart [27].

Malhotra HB compared the use of Preload alone, vasoconstrictors alone and a combined preload and vasoconstrictor with half volume and dose used in the previous 2 groups to prevent PSH. They found that a combination of preload and vasoconstrictors had maximum effect in preventing spinal hypotension, followed by the sole use of vasoconstrictor, while preload alone had the least protection against postspinal hypotension [28].

A Lee et al. used Prophylactic ephedrine prevents hypotension during spinal anaesthesia for Cesarean delivery in 12 RCTs over 571 women where significantly fewer women experienced hypotension with ephedrine, compared with control [29].

Kang YG et al. used Prophylactic intravenous ephedrine infusion during spinal anaesthesia for cesarean section and found that In patients given the infusion, systolic blood pressure did not change significantly from the baseline systolic blood pressure following spinal anaesthesia ($p > 0.1$) [30].

The mechanism of ondansetron in preventing PSH was mediated by inhibition of Bezold-Jarisch reflex (BJR). This reflex is mediated through vagal afferents. When activated, it causes hypotension and bradycardia. Triggering of chemoreceptors sensitive to serotonin in the intracardiac wall can occur by a reduction in blood volume. It may lead to increased vagal nerve activity, followed by bradycardia and vasodilatation [19]. In the ondansetron group, several studies have tested its use for prophylaxis against Postspinal hypotension (PSH).

The current study results were consistent with those of Sahoo T et al., who studied the effect of ondansetron in patients undergoing lower segment cesarean section (LSCS) [18], Wang M et al., which compared different doses of ondansetron for prophylaxis against PSH. They compared placebo with 2, 4, 6 and 8 mg of ondansetron. They found that 4 mg of ondansetron was the best dose [31].

Similar to this study, Trabelsi W et al., who used a dose of 4 mg of ondansetron with 10 ml/kg of crystalloid versus placebo. They found that hypotension, bradycardia and vasopressor consumption was less to occur in those received prophylactic ondansetron [32]. The study results were consistent with those of Gao L et al., who compared the effects of prophylactic ondansetron on PSH in a meta-analysis and found that it reduced its incidence as well as vasopressor consumption in both obstetric and non-obstetric patients. Also, it also reduced related adverse outcomes such as bradycardia, nausea and vomiting [33].

However, Ortiz-Gómez JR et al. found that ondansetron was not effective in the prevention of

drop in blood pressure in patients undergoing spinal anaesthesia for cesarean section [34], but they used bupivacaine combined with fentanyl while in our study we didn't use fentanyl. Omya Sh. et al. also supports our findings, they compared the effect of ephedrine versus ondansetron in the prevention of PSH in patients undergoing cesarean section (C.S) and found that results of both groups are nearly comparable and both had significantly fewer vasoconstrictors need and lower incidence of nausea [35].

Ondansetron has the advantage of more stable HR as Julius S. et al., studied the cardiovascular effect of rapid IV infusion of ondansetron in patients under general anesthesia and their results were consistent with our results as regards the change in heart rate as there were no clinically or statistically significant changes in heart rate during the five-minute period following administration of ondansetron [36].

Limitations: As no one had ever compared the use of Ondansetron alone versus combined vasoconstrictors with fluid preload, so we feel that further investigation and studies with larger groups are required to confirm our results, so as to eliminate the problem of hypotension associated with subarachnoid anaesthesia and as we used ephedrine as a vasoconstrictor so, repeated administration diminishes its vasoconstrictive effect and its slow onset of action and relatively long duration make accurate titration of blood pressure difficult, so another vasoconstrictor may be needed in future studies. Also, we didn't compare their effects on vulnerable groups as elderly and parturients.

In conclusion, the preemptive use of Ondansetron alone and combined vasoconstrictors with fluid preload significantly reduce the incidence of PSH with no significant difference between both regimens. Furthermore, they also reduced vasoconstrictors and fluids consumption.

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