Research Article

Assessment of the Effect of Two Doses of Prophylactic Ondansetron on Maternal Hemodynamics, Neonatal Outcome and Spinal Blockade Specifications in Parturients Scheduled for Cesarean Delivery

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Abstract
The aim of this randomized, prospective, double blinded placebo controlled study was to compare between two doses of ondansetron (2 mg, 4 mg) and ephedrine in prevention of maternal hypotension and bradycardia induced by spinal anesthesia, their effects on specifications of spinal blockade, neonatal outcome, and their side effects. **Patients and methods**: One hundred twenty parturients ASA I or II aged between 18 and 40 years, scheduled for elective cesarean section under spinal anesthesia. They were randomly divided into four equal groups. First group received intravenous I.V. 2 mg ondansetron, second group received I.V. 4 mg ondansetron, third group received 10 mg ephedrine, and the fourth group received normal saline. All the test drugs were administered as bolus dose five minutes before intrathecal injection. Mean blood pressure, heart rate, vasopressor use, spinal anesthesia specifications, neonatal outcome, and side effects were assessed. **Results:** The fall in mean blood pressure after spinal anesthesia in ondansetron 4mg group was the least and the greatest was in the control group. There was dropping in heart rate values after spinal anesthesia started from 5 minutes value with significance to the control group only. No significant difference between the four groups in the spinal anesthesia characters. Slight acidosis was noticed in the ephedrine group which doesn't affect the clinical neonatal outcome. **Conclusion**: Prophylactic bolus intravenous ondansetron 4 mg and to less extent 2 mg could decrease the fall in mean blood pressure of parturients following spinal anesthesia as well as intravenous ephedrine 10 mg with added advantage that it could decrease neonatal acidosis associated with ephedrine use .

Key Words: Ondansetron , Ephedrine, Post spinal hypotension, Cesarean delivery

Introduction
Cesarean delivery is usually performed under spinal anesthesia which has multiple advantages such as rapidity, reliability, safety, ease of performance, and avoiding the hazards of general anesthesia which made it the golden anesthetic technique for elective cesarean delivery[(1)]. It has a major problem which is hypotension and bradycardia with subsequent decrease in the utero-placental blood flow which leads to fetal acidosis and increase in fetal morbidity and mortality [(2)].

Spinal anesthesia induces sympathetic blockade below its level which leads to vasodilatation, pooling of venous blood, decrease of venous return, and low ventricular volume state which in turn leads to activation of chemo-and mechano-receptors in the cardiac wall with the abrupt withdrawal of sympathetic supply, and unopposed vagal tone to the heart which leads to bradycardia, and hypotension, this reflex is defined as Bezold-Jarisch reflex (BJR)[(3)] and it is triggered by serotonin (5-HT3) released from thrombocytes during low ventricular volume conditions[(4)]. Serotonin (5-HT3) antagonists suggested to be used in prevention of hypotension and bradycardia caused by BJR in response to spinal anesthesia [(5)].

Ondansetron is (5-HT3) antagonist which has been used to prevent nausea and vomiting caused by chemotherapy, radiotherapy, surgery[6] and there are clinical trials for its use in prevention of BJR after spinal anesthesia in obstetric patients [7].

Serotonin(5-HT3) receptors are present in the spinal cord and it was noticed that (5-HT3) level increased in the cerebrospinal fluid after spinal anesthesia with bupivacaine[8] so there was a query about the effects of (5-HT3) antagonist ondansetron on spinal anesthesia specifications[9].

Ephedrine is a non-catecholamine sympathomimetic that possesses α and β adrenergic activity, and it is the classical vasopressor of choice for treatment of post spinal hypotension in cesarean delivery but it can induce maternal cardiovascular adverse effects such as supraventricular tachycardia (SVT), tachyphylaxis, and fetal acidosis [10].

This study hypothesis was that ondansetron was effective as ephedrine in its ability to prevent post-spinal hypotension and can avoid side effects of ephedrine.

The aim of this study was to compare between two doses of ondansetron (2 mg, 4 mg) and ephedrine in prevention of maternal hypotension and bradycardia induced by spinal anesthesia (primary outcome), their effects on specifications of spinal blockade, neonatal outcome, and their side effects (secondary outcomes).

Patients and methods

This prospective, randomized, double blinded, clinical trial was performed in El-Minia University hospital in the period from April 2014 to September 2014. Written informed consent was obtained from every parturient included in the study. Ethical approval for this study was obtained from the Ethics Committee of El-Minia faculty of medicine. One hundred twenty parturients scheduled for elective cesarean delivery under spinal anesthesia, with their age ranged from 18 to 40 years with single viable fetus at full term and they were ASA physical status I or II. Parturients with contraindication to spinal anesthesia (infection, vertebral column deformity, or coagulopathy) or parturients refusal to participate in the study, morbid obesity, pregnancy induced hypertension, parturients with high risk pregnancy, parturients on treatment with selective serotonin reuptake inhibitors or on migraine therapy, and those with known hypersensitivity to the test drugs were excluded from the study. Parturients eligible for the study were randomly allocated into four equal groups each of which included 30 parturients using random allocation software (windows software, version 1.0, May 2004). The allocation ratio was 1:1, and the group identification card was put in a sealed and opaque envelop to hide allocation. This envelop was opened only in the operation room just before beginning of the study. Partutients were pre medicated with 150 mg oral rantidine. In the operating room electrocardiogram (ECG), non invasive blood pressure (NIBP), and pulse oximetry (SpO_2) were connected to the parturients to record heart rate (HR), mean blood pressure, and oxygen saturation. Insertion of 18 gauge cannula was done on the dorsum of the non dominant hand and they received preload of 5ml/kg of warm normal saline 0.9%. The test drugs were diluted in 10 ml of saline by another anesthesiologist not included in the study and labeled as A, B, C, and D. The test drugs were injected slowly intravenous 5 minutes before performance of spinal block. At the end of the study these labels were known as follow group A received 2 mg of ondansetron, group B received 4 mg of ondansetron, group C received 10 mg of ephedrine, and group D received normal saline only.

Technique of anesthesia: While the parturients were in sitting position and after sterilization of the back of the patients, spinal anesthesia was performed at L3-L4 using 25 gauge Quincke spinal needle (Typo Healthcare, Gasport, UK). Ten mg of hyperbaric bupivacaine 0.5% (Marcaine; AstraZeneca, Södertälje, Sweden) plus 15 µg fentanyl was injected. Time to complete intrathecal injection was considered as 0 time. Parturients lied in supine position with 15º left lateral tilt and supplemental oxygen through a nasal cannula at 4 l/min.

Partureints received warm normal saline 0.9% at a rate of 10 ml/kg/hr. Mean blood pressure (MBP), heart rate (HR), and oxygen saturation (SpO2) were recorded at the base line before spinal anesthesia, and then every 5 minutes until the end of the surgery. Hypotension was defined as a decrease in the mean blood pressure of more than 20% of the baseline value and it was treated by intavenous bolus dose of 50 µg phenylepherine repeated as needed, the total dose of phenylepherine was recorded. Bradycardia was defined as heart rate below60 beat/min and it was treated by 0.5 mg intravenous bolus dose of atropine followed by incremental doses of 0.1 mg as required. Vomiting was treated by 10 mg intravenous bolus dose of metclopromide. Sensory block was examined by loss of sensation to pin prick at midclavicular line every two minutes until fixation of sensory level in two consecutive times. Surgeon was allowed to start when the sensory block level was established at T6. Time to reach the highest sensory level from the injection time of bupivacaine in the subarachnoid space was recorded. Parturients who failed to reach this level were excluded from the study. Motor block was evaluated by Bromage scale (1-free movement of legs and feet; 2- unable to flex hip, able to move knee, ankle, and toes; 3- unable to move hip and knee, able to move ankle and toes; 4 - unable to move hip, knee, ankle, and toes)[(11)].

After delivery of the baby, parurients received bolus dose of 5 international units (IU) of oxytocin followed by infusion of 40 (IU). Blood sample of the umbilical vein and umbilical artery from double clamped segment was taken immediately after cord clamping and analyzed for PH and blood gases. Assessment of the neonates was done using Apgar score at 1 minute and 5 minutes. Maternal complications such as bradycardia, hypotension, rebound hypertension, nausea, vomiting, and shivering were recorded. Neonatal complications such as respiratory depression, and neonatal acidosis were also recorded.

Sample size: In previous study of Sahoo et al.,[(12)]., in which they found that the mean arterial blood pressure (MBP) in the control group was 82.2±10.5 mmHg. It was estimated that the least number of parturients required for the study to detect 10% decrease in (MBP) was 26 parturients to achieve α error of 5% and power of 80 % with 10% dropout, the number was increased to 30 parturients in each group.

Statistical analysis

This study used Statistical program SPSS (SPSS Inc., Chicago, Illinios, USA) version 20 for entry and analysis of the data. Data were examined for normal distribution using kolmogorov-Smirnov test. Quantitative data were presented as mean ± SD. Categorical data were presented as percentage and number. Independent T-test was used for comparison with the base line value in each group. ANOVA test was used for comparison between the means of the groups followed by post-hoc test. Chi-square test and fisher exact test were used for comparison between categorical data. All tests are two –tailed. *P* value < 0.05 considered statistically significant.

Results

One hundred twenty parturients were eligible for this study; all of them continued the study to statistical analysis (Figure 1). There was no significant difference between the four groups as regards demographic data of parturients and duration of the surgery (Table 1). As regards changes in the mean arterial blood pressure (MABP), there was no significant difference between the four groups in the baseline values. There was a significant drop in the blood pressure 5 minutes after spinal block when compared to the base line value in the four groups with the least drop was in 4 mg ondansetron group and the greatest was in the control group. There was a significant difference between the three test groups and control group in all study times started from 5 minutes reading. There was no significant difference between the two ondansetron groups between them and ephedrine group in all the study times (table 2).

There was no significant difference between the four groups as regards heart rate in the baseline values. There was a

descent in the heart rate values in the four groups in comparison to the base line values which became significant in ephedrine and control groups at 5, 10,15 minutes values. Heart rate values are highest in ondansetron 4 mg group and lowest in ephedrine group with significant difference between the two groups of ondansetron (2mg,and 4mg) and ephedrine, and control groups at 5, 10, 15 minutes values (Table 3).

There was no significant difference between the four groups as regards the characters of the spinal block(time to upper sensory block, time to two segment regression, time to complete motor block, and time to complete motor recovery) (table 4).

As regards the condition of the neonates, Apgar score values in control group was less than the other three groups and this difference was significant at 1 minute while no significant difference between the other three groups. There was no significant difference between the four groups in Apgar score at 5 minutes.

As regards pH values, there was no significant difference between the four groups with the least values was observed in ephedrine group (table 5).

As regards side effects, no one of partuteints complained from nausea in ondansetron 2 mg, and 4 mg while 5(16.6%) and 20(66.6%) parturients in ephedrine and control group respectively complained from nausea. No one of parurients complained from bradycardia in ondansetron group while 5(15.6%) and 7(23.3%) parturients in ephedrine and control group respectively complained from braycardia. Incidence of shivering was higher in control group (50%) in comparison to the other groups where it was 26.6% in ephedrine group, 20% in ondansetron2 mg group, and 13.3% in ondansetron 4 mg group (table 6).

Figure (1) Flow chart in the study.

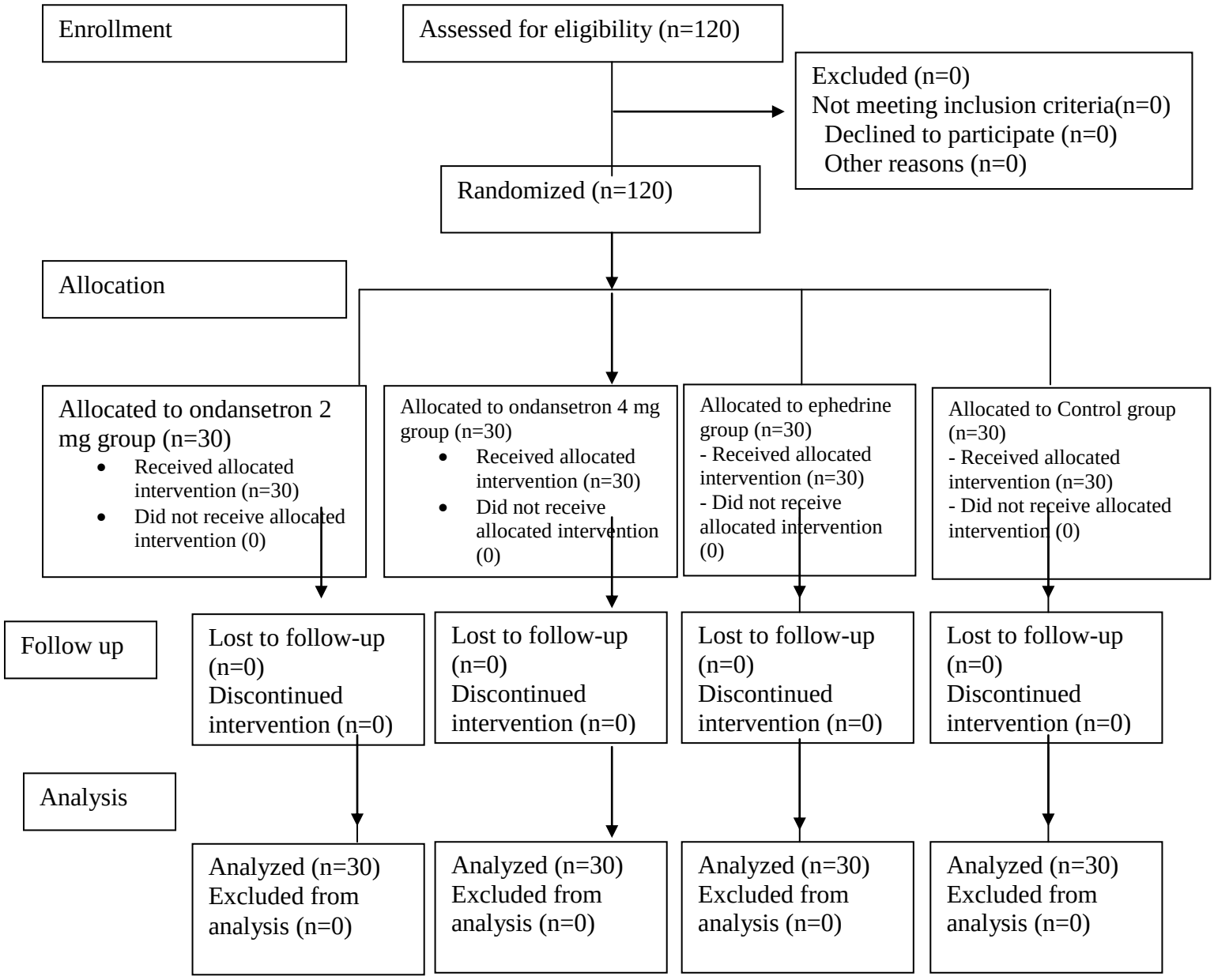

Table (1): Characteristics of the parturients and duration of surgery.

Item	Ondansetron 2 mg(n=30)	Ondansetron 4 mg(n=30)	Ephedrine (n=30)	Control (n=30)	P value
Age(years)	28.5 ± 6.1	27.3 ± 5.8	29.0 ± 5.7	27.6 ± 6.3	0.669
Weight (kg)	85.6 ± 8.9	86.3 ± 9.0	87.1 ± 8.2	88.2 ± 8.6	0.686
Height (cm)	170 ± 7.5	169 ± 4.9	167 ± 5.4	169 ± 6.2	0.283
Duration of surgery (min)	49 ± 5.5	51.2 ± 6.0	48.7 ± 4.9	49.5 ± 5.0	0.279

Data are expressed as mean ± SD. No significant difference between the four groups.
P value between the four groups. *P* value < 0.05 considered significant.

Table (2): Changes in mean arterial pressure (MAP) between the four groups and within the same group.

	Ondansetron 2 mg(n=30)	Ondansetron 4 mg(n=30)	Ephedrine (n=30)	Control (n=30)	P value
Base line	95.4 ± 5.0	95.5 ± 5.1	96.2 ± 5.0	95.0 ± 5.5	0.839
5 min	89.0 ± 2.8$^{\#}$*	90.4 ± 2.6*$^{\#}$	89.9 ± 4.6*$^{\#}$	76.1 ± 4.1*	<0.001
10 min	85.4 ± 3.0$^{\#}$*	87.4 ± 2.8$^{\#}$*	86.7 ± 3.9*$^{\#}$	75.2 ± 6.2*	<0.001
15 min	81.6 ± 2.8$^{\#}$*	82.1 ± 2.1$^{\#}$*	80.7 ± 3.9*$^{\#}$	74.9 ± 6.1*	<0.001
20 min	80.4 ± 2.0$^{\#}$*	82.0 ± 2.1$^{\#}$*	80.2 ± 3.5*$^{\#}$	76.7 ± 5.9*	<0.001
25 min	83.4 ± 1.8$^{\#}$*	85.1 ± 2.9$^{\#}$*	83.8 ± 4.1*$^{\#}$	78.1 ± 6.3*	<0.001
30 min	85.3 ± 3.1$^{\#}$*	86.0 ± 3.0$^{\#}$*	84.8 ± 2.1*$^{\#}$	79 .4 ± 5.6*	<0.001

Values in mmHg. Data are expressed as mean ± SD. *P* value between the four groups. * Significant with the base line. $^{\#}$ Significant with control group. $^{\Sigma}$ Significant with ephedrine group. † Significant with ondansetron 2 mg group. *P* value < 0.05 considered significant.

Table (3): Changes in heart rate (HR).

Item	Ondansetron 2 mg(n=30)	Ondansetron 4 mg(n=30)	Ephedrine (n=30)	Control (n=30)	P value
Base line	104.5 ± 6.8	103.4 ± 6.8	102.3 ± 7.4	103.2 ± 8.1	0.711
5 min	99.4 ± 5.1$^{\#\Sigma}$	100.1 ± 3.9$^{\#\Sigma}$	89.8 ± 5.1*	90.1 ± 6.4*	<0.001
10 min	98.1 ± 4.8$^{\#\Sigma}$	100.0 ± 4.1$^{\#\Sigma}$	88.2 ± 4.9*	89.0 ± 5.8*	<0.001
15 min	97.1 ± 4.3$^{\#\Sigma}$	98.9 ± 4.0$^{\#\Sigma}$	88.2 ± 3.8*	90.1 ± 4.3*	<0.001
20 min	98.0 ± 4.5	99.1 ± 2.1	98.2 ± 4.0	98.3 ± 5.0	0.734
25 min	97.4 ± 3.8	98.8 ± 3.7	97.2 ± 4.1	97.1 ± 4.6	0.335
30 min	98.7 ± 4.9	99.7 ± 4.8	98.1 ± 5.1	98.3 ± 3.2	0.536

Values in beat/min. Data are expressed as mean ± SD. *P* value between the four groups. * Significant with the base line. $^{\#}$ Significant with control group. $^{\Sigma}$ Significant with ephedrine group. † Significant with ondansetron 2 mg group. *P* value < 0.05 considered significant.

Table (4): Spinal anesthesia characters and incidence of vasopressor rescue need.

Item	Ondansetron 2 mg(n=30)	Ondansetron 4 mg(n=30)	Ephedrine (n=30)	Control (n=30)	P value
Need for rescue vasopressor.	10 (33%)[#]	8 (26.6%)[#]	10 (33%)[#]	24 (80%)	<0.001
Time to upper sensory level block (min)	12.1 ± 3.8	12 ± 2.9	11.8 ± 3	12 ± 3.5	0.988
Time to two segment regression (min).	79.4 ± 15.2	77.5 ± 13.4	81 ± 17.6	81 ± 18.4	0.815
Time to Bromage 4 (min).	10.4 ± 1.9	10.5 ± 2	10.1 ± 1.8	10.4 ± 2.1	0.871
Time to Bromage 1 (min).	179.1 ± 19.5	176.4 ± 21.2	177.8 ± 22	179.4±20.6	0.942

Data are expressed as mean ± SD. [#] Significant with control group. P value between the four groups. *P* value < 0.05 considered significant.

Table (5): Neonatal outcome.

Item	Ondansetron 2 mg(n=30)	Ondansetron 4 mg(n=30)	Ephedrine (n=30)	Control (n=30)	P value
Apgar score 1 min	10 (9-10) [#]	10 (9-10) [#]	9 (7-9) [#]	7 (6-8)	0.036
Apgar score 5 min	10 (9-10)	10 (9-10)	10 (9-10)	9 (8-10)	0.842
Umbilical vein pH	7.35 ± 0.03	7.36 ± 0.03	7.36± 0.03	7.35 ± 0.03	0.348
Umbilical artery pH	7.28±0.03	7.28±0.03	7.25±0.05	7.27±0.4	0.932

pH values are expressed as mean ± SD. Apgar score values are expressed as median (IQR). *P* value between the four groups. [#] Significant with control group. *P* value < 0.05 considered significant.

Table (6): Side effects.

Item	Ondansetron 2 mg(n=30)	Ondansetron 4 mg(n=30)	Ephedrine (n=30)	Control (n=30)	P value
Nausea	0 (0 %)[#Σ]	0(0 %)[#Σ]	5 (16.6 %)[#]	20 (66.6%)	<0.001*
Shivering	6 (20 %)[#]	3 (10 %)[#Σ]	10 (33.3 %)[#]	18(60 %)	<0.001*
Bradycardia	2 (6.6 %)[#Σ]	0 (0 %)[#Σ]	8(26.6 %)	10 (33.3 %)	0.001*

Data are expressed as numbers and percentage. P value between the four groups. *P* < 0.05 considered significant. [#] Significant with control group. [Σ] Significant with ephedrine group. *P* value < 0.05 considered significant.

Discussion

This study found that prophylactic bolus intravenous ondansetron (2mg or 4 mg) could prevent maternal hypotension after spinal anesthesia in cesarean delivery as well as ephedrine without any effect on motor and sensory block characters, with added benefit that it improved neonatal acidosis which observed with ephedrine use.

In agree with the results of this study Sahooo et al.,[12] in their study on 52 parturients scheduled for elective cesarean delivery under spinal anesthesia and they were treated with 4 mg ondansetron as a prophylaxis against hypotension and they found that ondansetron reduced the incidence and severity of post spinal hypotension and decreased the requirement of vasopressor use. Owczuk et al.,[13] in their study on 72 parturients scheduled for cesarean delivery with spinal anesthesia by 4 ml of 0.5 % bupivacaine and they were treated with 8 mg of ondansetron as a prophylaxis for post-spinal hypotension. The authors found that 8 mg ondansetron could attenuate the fall of systolic and mean blood pressure only but it had no influence on the drop of diastolic blood pressure or heart rate after spinal anesthesia which could be explained by the high dose (20 mg) of intrathecal hyperbaric bupivacaine 0.5% used in their study.

Marashi et al.,[14] in their study to compare between prophylactic intravenous ondansetron 6 mg, and 12 mg and placebo in attenuation of postspinal hypotension and bradycardia, concluded that intravenous pretreatment with either 6 mg or 12 mg ondansetron could reduce hemodynamic changes following spinal anesthesia without significant differences between the two doses of ondansetron.

Wang et al.,[15] in their study on 150 parturients scheduled for cesarean delivery with spinal anesthesia, they were divided into five groups according to the dose of prophylactic ondansetron 2,4,6,8 mg and placebo, each of which was 30 parturients, and they concluded that ondansetron was effective in prevention of post spinal hypotension, and could improve neonatal pH and neonatal clinical condition, also they concluded that the best dose of ondansetron for this purpose was 4 mg.

On the other hand Ortiz-Gomez et al.,[16] in their postoperative randomized placebo-controlled trial on 128 pregnant women scheduled for elective cesarean delivery under spinal anesthesia, and they found that prophylactic 2,4,8 mg of ondansetron had no role for prevention of post spinal hypotension or in reducing vasopressor consumption, this difference may related to the dose of intrathecal bupivacaine which individualized in each parturient to be (9.7 ± 0.4 mg) in placebo group and (9.6 ± 0.3 mg) in ondansetron group which was smaller than used in this study.

This study estimated the dose of ephedrine from previous researches which studied the effect of different doses of ephedrine in prevention of post spinal hypotension such as Loughrey et al.,[17] who compared between two doses of prophylactic ephedrine (6mg and 12mg) for prevention of post spinal hypotension in cesarean delivery and they found that ephedrine 12 mg was more effective. Magalhaes et al.,[18] concluded that ephedrine 10 mg would be effective prophylaxis for postspinal hypotension in parturients with slight neonatal acidosis but without serious clinical effects on the neonatal condition as shown by Apgar score.

As regards the condition of the neonates, it is better to use the Apgar score than umbilical cord blood gas analysis for prediction of the neonates condition as t is more reliable as recommended by Allen et al.,[19]. This study found that, there was significant difference of Apgar score at 1 minute between the ondansetron, ephedrine groups and the control group but this significant difference disappeared at 5 minutes measurement. There was no significant difference between ephedrine group and both ondansetron or between the two doses of ondansetron and as regards umbilical cord blood gas analysis, there was a slight acidosis the ephedrine group when compared to the other groups. This could be explained by the beta adrenergic activity of ephedrine which increase fetal metabolism,

anaerobic glycolysis, which leads to increased umbilical artery CO_2 and acidosis [20,21].

As regards the effect of ondansetron on the characters of spinal anesthesia, this study found that intravenous ondansetron had no effect on the onset, duration, and the level of sensory, and motor block of spinal anesthesia, this coincided with the study of smara et al.,[22] who evaluated the effects of systemic 4mg ondansetron on the characteristics of spinal anesthesia in urinary bladder tumors and they concluded that it had no effects on the intensity or the duration of motor or sensory block, these results were not suspected as ondansetron which is 5-HT3 antagonist would affect onset, duration, and intensity of spinal anesthesia as sertonin 5-HT3 level in cerebrospinal fluid CSF increased after spinal anesthesia[9].These results could be explained by the action of ondansetron on other receptors such as adrenergic, histaminic, dopaminergic, and opioid receptors.

Conclusion

Prophylactic bolus intravenous ondansetron 4 mg and to less extent 2 mg could decrease the fall in mean blood pressure of parturients following spinal anesthesia as well as intravenous ephedrine 10 mg with added advantage that it could decrease neonatal acidosis associated with ephedrine use .

Conflict of interest: Authors declared none; the fund of research was from the university budget.

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