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Original Article

Effect of Ondansetron on Blood Pressure during Elective Cesarean Section under Spinal Anesthesia at Baghdad Teaching Hospital

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Abstract

Background: Hypotension is a common consequence of spinal anesthesia for caesarean section. It is correlated with nausea, vomiting, dyspnea, and adverse effects on the fetus, including depressed APGAR scores and umbilical acidosis. ***Aim***: To investigate the effect of Ondansetron to prevent hypotension and the need for vasopressors after spinal anesthesia during elective Cesarean section. ***Methods***: This is a prospective double blind, randomized trial carried out in Obstetric Operation room of Baghdad Teaching Hospital, Medical city, Iraq from November, 2018 to August, 2019. Total number of 128 women assessed for eligibility and only 87 were included and allocated into 2 groups. The Ondansetron group (45 women) received 6 mg Ondansetron IV 1 min before induction of spinal anesthesia. The Placebo group received 3 ml normal saline as placebo before induction. The number of rescue drugs (vasopressors, antiemetic, anti-shivering), vital signs and side effects were recorded each 3 min from baseline to 45th min, fetal APGAR score was recorded after 1 min. ***Results***: The incidence of hypotension, nausea, vomiting and the need for vasopressors and metoclopramide were significantly lower in Ondansetron group than placebo group (P=0.001, 0.02, 0.003, <0.001, and 0.001, respectively). Shivering and the need of pethidine was non significantly lower in ondansetron group than placebo group. APGAR score after 1 min was not significantly differ between the two groups. ***Conclusion***: Preoperative administration of Ondansetron in cesarean section reduces the risk of spinal anesthesia-induced hypotension, prevents the nausea and vomiting attacks and decreases the need to vasopressors and metoclopramide.

Keywords: Spinal anesthesia, caesarian section, ondansetron, hypotension

تأثير أوندانسيترون على ضغط الدم خلال الجراحة القيصرية الاختيارية تحت التخدير الشوكي في مستشفى بغداد التعليمي

الخلاصة

الخلفية: انخفاض ضغط الدم هو نتيجة شائعة للتخدير الشوكي للولادة القيصرية، ويرتبط مع الغثيان والقيء وضيق التنفس، والآثار السلبية على الجنين، بما في ذلك خفض قيمة APGAR. **الهدف**: للتحقيق في تأثير أوندانسيترون لمنع انخفاض ضغط الدم والحاجة إلى مقبضات الأوعية بعد التخدير الشوكي خلال الجراحة القيصرية الاختيارية. **الطرائق**: هذه تجربة مزدوجة معشاة محتملة أجريت في غرفة عمليات التوليد في مستشفى بغداد التعليمي، المدينة الطبية، العراق من نوفمبر 2018 إلى أغسطس 2019. بلغ مجموع عدد النساء اللائي تم تقييم أهليتهن 128 امرأة، ولم تدرج سوى 87 امرأة توزعن في مجموعتين. تلقت مجموعة اوندانسيترون 6 ملغ اوندانسيترون وريديا قبل دقيقة من التخدير الشوكي. تلقت مجموعة الدواء الوهمي 3 مل محلول ملحي متوازن. تم تسجيل الحاجة لأدوية الإنقاذ (قابات الأوعية ، مضاد للقيء ، مضاد للرجفة) ، العلامات حيوية والآثار جانبية كل 3 دقائق من خط الشروع إلى الدقيقة 45، تم تسجيل درجة APGAR الجنينية بعد دقيقة واحدة. **النتائج**: كان معدل الإصابة بهبوط ضغط الدم والغثيان والقيء والحاجة إلى قابض للأوعية والميتوكلوبراميد أقل بكثير في مجموعة أوندانسيترون من مجموعة الدواء الوهمي. كما ان حصول الرجفة والحاجة إلى البثيدين كانا أقل بكثير في مجموعة أوندانسيترون من مجموعة الدواء الوهمي. لم تختلف نقاط APGAR بعد دقيقة واحدة بشكل كبير بين المجموعتين. **الاستنتاج**: أن استخدام أوندانستيرون أثناء الجراحة القيصرية يقلل من مخاطر انخفاض ضغط الدم الناجم عن التخدير الشوكي، ويمنع الغثيان والقيء الأرتجاف ويقلل من الحاجة إلى مقبات الأوعية والميتوكلوبراميد.

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INTRODUCTION

Cesarean delivery is a surgical procedure to deliver a fetus via a surgical incision through the mother's abdomen and uterus. It is done when recognized to be a safer method than a normal vaginal delivery for the mother, baby, or both [1]. Selection of the anesthesia method is based on the level of urgency and other patient-related risks including presence of a working epidural catheter, maternal preference, expectation or previous experience, the likely duration of surgery, and the presence of maternal pathology, especially cardiac, neurological, or previous back surgery. Local, institutional, anesthetic practice, and the experience of the physician may also play an important role [2]. Spinal anesthesia produced nociceptive effects, autonomic and motor block, and sympathetic blockade [3]. Furthermore, hypotension and bradycardia are the most common cardiovascular responses to spinal anesthesia [4]. Hypotension during spinal anesthesia is mainly a consequence of a decrease in systemic vascular resistance due to the blockade of preganglionic sympathetic fibers [5]. In addition, it causes decreased systemic vascular resistance resulting from arterial vasodilation rather than an increase in venous capacitances due to decreased venous return and cardiac output [6]. Spinal-induced bradycardia is multifactorial but is in part due to the Bezold–Jarisch reflex. This reflex is mediated by serotonin receptors within the wall of the ventricle in response to systemic hypotension [7]. It is thought that the stimulation of these peripheral 5-hydroxytryptamine subtype 3(5-HT3) receptors leads to increased parasympathetic activity and decreased sympathetic activity, resulting in bradycardia, vasodilatation, and hypotension [8]. Ondansetron, a widely used antiemetic agent and one of the new classes of 5-HT3 receptor antagonist, has been safely used to blunt the Bezold–Jarisch reflex, resulting in less bradycardia and hypotension in humans undergoing spinal anesthesia [9]. Ondansetron is known to inhibit the BJR by blocking serotonin binding to 5-HT3 receptors in the left ventricle, leading to hypertension and tachycardia [10]. Many studies have reported different methods to decrease the severity of hypotension, such as different regimens of volume preloading with various crystalloid and colloid fluids, mechanical methods of increasing auto-transfusion from the lower limbs by wrapping the legs, leg elevation, tilting the bed head down, thromboembolic stockings, the use of prophylactic and therapeutic vasopressors and also left lateral tilt, manual uterine displacement in pregnant patients, but no single regimen has eliminated clinically significant spinal anesthesia hypotension, and combination of techniques may be beneficial [6]. The present study aims to investigate the use of ondansetron to prevent hypotension and the amount of vasopressor needed during spinal anesthesia of women subjected to cesarean section delivery.

PATIENTS AND METHODS

This randomized double-blind, and placebo-controlled trial was carried out in the department of Obstetrics, Baghdad Teaching Hospital, Medical city, Iraq during the period from November, 2018 to August, 2019. The study protocol was approved by the Scientific Council of Clinical Pharmacy, Scientific Council of Anesthesia and Intensive Care, and the Iraqi Board for Medical Specialties. All participants were informed about the purpose of the study and asked to provide an informed written consent before inclusion. Selection of eligible women is based on the evaluation of those single pregnancy indicated for elective cesarean section presented to Baghdad Teaching Hospital before inclusion in the study. The inclusion criteria include 18-45-year age, ASA physical status II, bodyweight of 50- <100 kg, planning to undergo an elective lower segment Caesarean section under spinal anesthesia. The exclusion criteria include contraindications to spinal anesthesia, contraindication to ondansetron or any medication used during this study, cardiovascular disease or risk factors, the use of selective serotonin re-uptake inhibitors or anti-migraine medications, and women with placenta accrete or prepartum hemorrhage. Demographic and characteristic data were reported by the investigator and include age, weight, height, ASA class of pregnant women (as defined by the anesthetist), medical and surgical, and operative characteristics. At the surgical room, the investigator reported the mean arterial blood pressure and heart rate at baseline and thereafter each 3 min to the 45th min, type of vasopressor need as rescue drug, number of rescue drugs, and the time at rescue drug administration. Additionally, the expected side effects were reported from baseline to the 45th min (e.g., nausea, vomiting). The need for metoclopramide to treat nausea and vomiting, and the need for pethidine to treat shivering were also reported. The APGAR scores at the 1st min after delivery were also reported by a pediatrician. After 6-hr fasting, pregnant women were taken to the operating room and no premedication was given before surgery. Routine monitoring of ECG, BP and HR was performed. Intravenous access was established with two line 18-gauge cannula. Before the induction of spinal anesthesia, routine monitoring was performed through measurement of ECG, non-invasive blood pressure and heart rate. Pregnant women were randomly allocated to receive one of the two treatment options according to cards selected by them. Two syringes were prepared by the investigator who was blinded to the groups, and these were marked with a label. The syringes were identical and were made up to contain either 6 mg of ondansetron or the same volume (3 ml) of normal saline. The senior anesthetist administered the selected treatment (according to the card selected by the patients) 5 min before induction of spinal anesthesia, and as following: The first group (ondansetron group, n=45) received 6 mg ondansetron (3 ml) by slow IV injection 5 min before induction of spinal anesthesia. In this group, 3 cases lost due to inadequate data collection, and 2 cases dropped and converted to general anesthesia. The second group (Placebo group, n=42) received 3 ml normal saline in a similar way followed in ondansetron group. In this group, two cases lost due to inadequate data collection. Spinal anesthesia was performed when the patients was in a sitting position using a 25-gauge spinal needle through the L3–L4 or L4–L5 intervertebral space. Hyperbaric 0.5% bupivacaine (15 mg/3 ml) was injected into the subarachnoid space in both groups when free-flowing cerebrospinal fluid was observed. Each woman received 4 L/min oxygen via a mask to prevent the

expected adverse effects until the birth of the baby. Administration of ringer solution was started to a maximum of 2 L after which the flow rate was reduced to keep the vein open. Hypotension (the expected adverse effect) was defined according to Baghdad Teaching Hospital Operative Room local protocol, when MAP drops less than 30% of baseline and rescue therapy of vasopressors was urgently requested. The selection of vasopressors depends on the heart rate (when HR less than 100 bpm) then 5 mg of ephedrine was given; when HR is more than 100 bpm, 100 µg phenylephrine was given. Atropine was administered when HR less than 50 bpm. After delivery, all women were given oxytocin (10 IU) as bolus intravenous dose and 10 IU as infusion dose in fluid. Metoclopramide 10 mg was administered intravenously if either intolerable nausea and/or vomiting was witnessed. Reported shivering was treated by 25 mg/1 ml pethidine.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS) version 22. Descriptive data were presented as mean±SD and frequencies as percentages. Multiple contingency was analyzed using Chi square test categorical variables (Fishers exact test was used when expected variable was less than 20% of total variable). Independent sample t-test was used to compare between two means. In all statistical analysis, level of significance was set at $P < 0.05$.

RESULTS

Table 1 showed no significant differences observed between the two groups regarding age (P=0.1) and BMI (P=0.2).

Table1: Distribution of age and BMI according to study groups.

Variable	Ondansetron		Placebo		*P-value*
	No.	%	No.	%	
Age (year)					
<20	4	10.0	6	15.0	0.1*^{NS}
20-29	13	32.5	17	42.5	
30-39	21	52.5	12	30.0	
40-42	2	5.0	5	12.5	
Weight (mean±SD)	76±10.4		74.8±13.1		0.6***^{NS}
Height (mean±SD)	160.4±5		161.8±4.5		0.2***^{NS}
BMI (kg/m^2)					
Normal	4	10.0	10	25.0	0.2**^{NS}
Overweight	17	42.5	14	35.0	
Obese	19	47.5	16	40.0	

*Fishers exact test, **Chi-square test, ***Independent sample test, NS=Non-significant.

In the ondansetron group, the incidence of spinal hypotension during spinal anesthesia was significantly lower than those in the placebo group (P=0.001). Moreover, non-significant differences were observed between women in the ondansetron group and those in placebo group regarding neonatal APGAR score 1 min after delivery (P=0.6), arrhythmia (P=0.5) and type of arrhythmia (P=0.3). A highly significant increase in the incidence of nausea and vomiting was observed in the placebo group compared with ondansetron group (P<0.001 and P<0.002). The need for metoclopramide was significantly higher among women in the placebo group compared to those in ondansetron group (P=0.001) (Table 2).

Table 2: Distribution of operative outcomes according to study groups.

Variable	Ondansetron		Placebo		*P*-value
	No.	%	No.	%	
Incidence of hypotension					
1-2 times	20	64.5	10	25.0	0.001*^{VHS}
3-4 times	9	29.0	13	32.5	
≥5 times	2	6.5	17	42.5	
Neonatal APGAR score at 1 minute					
Low	4	10.0	3	7.5	0.6**^{NS}
Normal	36	90.0	37	92.5	
Nausea					
Yes	17	42.5	36	90.0	<0.001*^{VHS}
No	23	57.5	4	10.0	
Number of nausea attacks					
≤2 times	14	82.4	18	50.0	0.02*^{S}
>2 times	3	17.6	18	50.0	
Vomiting					
Yes	2	5.0	12	30.0	0.003*^{HS}
No	38	95.0	28	70.0	
Number of vomiting attacks					
1 time	1	50.0	9	75.0	0.4**^{NS}
2 times	1	50.0	3	25.0	
Need for metoclopramide					
Yes	6	15.0	20	50.0	0.001*^{VHS}
No	34	85.0	20	50.0	
Arrhythmia					
Yes	32	80.0	30	75.0	0.5*^{NS}
No	8	20.0	10	25.0	
Type of arrhythmia					
Tachycardia	31	96.9	30	100.	0.3**^{NS}
Bradycardia	1	3.1	0	-	

* Chi-square test, **Fishers exact test, S=Significant, HS=High significant, VHS=very high significant, NS=Not significant.

In table 3, the need for vasopressors was significantly higher in placebo group compared with ondansetron group (P=0.001). Meanwhile, no significant differences were observed between women of both groups regarding type of

vasopressor (P=0.5). Moreover, the mean time to first, second, and third vasopressor doses needed was significant earlier in placebo group (P<0.02). However, no significant differences were observed between the two groups regarding time to fourth and fifth vasopressor doses (P=0.2), and sixth or more doses were only given for women of the placebo group (Table 3).

Table 3: Distribution of vasopressor characteristics according to study groups.

Variable	Ondansetron		Placebo		*P*-value
	No.	%	No.	%	
Vasopressor					
Yes	31	77.5	40	100.0	0.001*VHS
No	9	22.5	0	-	
Type of vasopressor					
Ephedrine	14	45.2	15	37.5	0.5**NS
Phenylephrine	6	19.4	7	17.5	
Ephedrine & Phenylephrine	10	32.3	18	45.0	
Atropine	1	3.2	0	-	
Mean number of vasopressors administered					<0.001*** VHS
Mean±SD	2.4±1.4		4.3±2.3		
Time at first vasopressor dose					0.006***HS
Mean±SD (min)	10.6±8.1		5.9±5.7		
Time at second vasopressor dose					<0.001*** VHS
Mean±SD (min)	24.5±10.7		13.3±6.3		
Time at third vasopressor dose					0.001*** VHS
Mean±SD (min)	29.1±5.2		21.1±6.9		
Time at fourth vasopressor dose					0.2***NS
Mean±SD (min)	31.5±1.7		27.5±6.4		
Time at fifth vasopressor dose					0.2***NS
Mean±SD (min)	40.5±6.3		33.8±6.6		
Time at sixth vasopressor dose					-
Mean±SD (min)	-		37.3±7.1		

* Chi-square test, **Fishers exact test, ***Independent sample t-test, S=Significant, HS=High significant, VHS=very high significant, NS=Not significant.

Regarding the signs of shivering and the need for pethidine to treat the side effect of spinal anesthesia, Table 4 showed that the incidence was lower and non-significant in ondansetron group compared with the placebo group (P=0.2).

Table 4: Distribution of shivering and need for pethidine according to study groups.

Variable	Ondansetron		Placebo		*P*-value
	No.	%	No.	%	
Shivering					0.2*NS
Yes	6	15.0	10	25.0	
No	34	85.0	30	75.0	
Pethidine need					0.2*NS
Yes	6	15.0	10	25.0	
No	34	85.0	30	75.0	

* Chi-square test, NS=Not significant.

DISCUSSION

Continuous efforts are undertaken by specialists in obstetrical anesthesia to select a proper way of anesthesia in order to achieve safe delivery the mother and the baby. For that reason, the choice of safe and effect anesthesia is mandatory. Many anesthetists considered the spinal anesthesia as the best choice in Cesarean delivery procedures since it is accompanied by less effects on the fetus [11]. The present study showed a lower incidence of intraoperative hypotension in the ondansetron group compared with the placebo group. This finding was similar to results reported by Potadar *et al* [12] in India which stated that administration of ondansetron during Cesarean section is helpful in decreasing the incidence of hypotension during spinal anesthesia. Similarly, Wang *et al* [13] in China demonstrated that intravenous injection of 4 or 6 mg ondansetron could significantly reduce the incidence of maternal hypotension and nausea after spinal anesthesia. However, Wang *et al* that doses of ondansetron lower than 2 mg and higher 8 mg failed to reduce the incidence of maternal hypotension and nausea [13]. The spinal anesthesia used in Cesarean section has many benefits such as minimal chance of hemorrhage, relieving postoperative pain, low risk of fetal side effects, and lower need to other medications. In pregnancy, the venous return is diminished because of the aortocaval compression [14], in addition to the effect of sympathetic blockade that leads to hypotension [15]. These sympathetic changes and the ventricular lead to increased release of serotonin that causes profound hypotension [16]. Ondansetron is an antagonist of 5HT3 receptor which can be used prior to Cesarean section to prevent hypotension, nausea and vomiting [12]. In a study conducted by Sahoo *et al* [17] on 52 Indian women planned for elective Cesarean section, administration of 4 mg ondansetron 5 min before spinal anesthesia decreases the risk of hypotension and number of vasopressor doses administered during surgery. An American meta-analysis study conducted by Tubog *et al* [18] revealed that intravenous administration of ondansetron may attenuate the risk of spinal anesthesia-induced hypotension and bradycardia post spinal anesthesia. In the current study, a highly significant increase in the incidence of nausea was observed the placebo group, in addition to non-significant differences between the two groups regarding the APGAR score. A similar result was reported by Trabelsi *et al* [19] in

Tunisia; it indicates that the use of ondansetron is safe regarding neonatal status. The present study also showed a highly significant increase in the incidence of vomiting in the placebo group. Consistently, GAO *et al* [20] observed that prophylactic administration of ondansetron prior to spinal anesthesia decreases the chance of hypotension and also prevents many spinal anesthesia-induced adverse effects such as bradycardia, nausea and vomiting. In the present study, the need for metoclopramide was significantly higher in the placebo group, while the need for vasopressor agents was lower in the ondansetron group. These findings were in tune with that reported by Oofuvong *et al* [21] in Thailand which indicates earlier administration of other vasopressors in women received normal saline. The present study showed a decrease in the incidence of shivering and need for pethidine in the ondansetron group. These findings are inconsistent with results reported by Tie *et al* [22] in China; it shows higher efficacy for preoperative ondansetron administration in preventing post anesthesia shivering and decreasing the need for pethidine. This inconsistency might be due to differences in sample size and type of anesthesia used in in this study. The current study has many limitations, including follow up for few hrs post-operatively, inadequate acceptability of spinal anesthesia by women, high loss of follow up, single center study, and limited sample size.

Conclusion

The preoperative administration of ondansetron before spinal anesthesia in Cesarean section reduces the risk of spinal anesthesia-induced hypotension, prevents intraoperative nausea and vomiting, and decreases the need to vasopressors.

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Conflicting interests

The authors declared no conflicts of interest.

Data sharing statement

The datasets analyzed during the current study will be available from the corresponding author on a reasonable request.

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