



# Evaluation of the Effects of Ondansetron Administration in the ERAS Protocol on Regional Anesthesia in Cesarean Surgeries: A Prospective Randomized Study

## Sezaryen Ameliyatlarında ERAS Protokolünde Ondansetron Uygulamasının Rejyonel Anestezi Üzerine Etkilerinin Değerlendirilmesi: Prospektif Randomize Bir Çalışma

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### Abstract

**Objective:** The enhanced recovery after surgery protocol has been applied more frequently in cesarean surgeries, and regional anesthesia is the first choice because of its postoperative advantages. Hypotension and bradycardia are common side effects of spinal anesthesia. Bezold Jarisch reflex, which occurs by the stimulation of 5-HT<sub>3</sub> receptors, is thought to be effective. This study was planned as a prospective randomized study to investigate the effect of ondansetron, a 5-HT<sub>3</sub> receptor antagonist, on hemodynamics in pregnant women undergoing cesarean section under spinal anesthesia.

**Method:** Seventy-eight pregnant women scheduled for elective cesarean section with spinal anesthesia were included in the study. Patients were randomly divided into two groups; group 1 (n=38) received ondansetron 4 mg intravenously before spinal anesthesia, and group 2 (n=40) did not receive ondansetron. Blood pressure, peak heart rate, and vasopressor requirements were evaluated in both groups.

**Results:** The reductions in the mean arterial pressure were significantly lower in group 2 than in group 1 at 2 and 4 minutes (p<0.05). Patients in group 1 had a lower need for vasopressors (p=0.001) and a significantly lower incidence of nausea and vomiting (p=0.01).

**Conclusion:** When ondansetron was used before spinal anesthesia in pregnant women undergoing elective cesarean section, hemodynamics were more stable, vasopressor use was reduced, and nausea and vomiting were reported to be less.

**Keywords:** ERAS, nausea, ondansetron, spinal anesthesia, vomiting

### Öz

**Amaç:** Cerrahi sonrası hızlandırılmış iyileşme protokolü sezaryen ameliyatlarında daha sık uygulanmaya başlanmış olup, postoperatif avantajlarından dolayı rejyonel anestezi ilk tercihtir. Spinal anestezinin yan etkileri arasında hipotansiyon ve bradikardi sık görülmektedir. 5-HT<sub>3</sub> reseptörlerinin uyarılmasıyla meydana gelen Bezold Jarisch refleksinin etkili olduğu düşünülmektedir. Bu çalışma spinal anestezi altında sezaryen yapılan gebelerde 5-HT<sub>3</sub> reseptör antagonisti olan ondansetron uygulamasının hemodinamiye etkisini araştırmak amacıyla planlanmıştır.

**Yöntem:** Spinal anestezi ile elektif sezaryen planlanan 78 gebe çalışmaya dahil edildi. Hastalar rastgele iki gruba ayrılarak; spinal anesteziden önce grup 1 (n=38) 4 mg intravenöz ondansetron almış, grup 2 (n=40) ise ondansetron almamıştır. Her iki gruptaki hastaların kan basıncı, kalp tepe atımı ve vazopressör gereksinimleri değerlendirilmiştir.

**Bulgular:** Ortalama arter basıncındaki düşüşler grup 2'de 2. ve 4. dakikalarda grup 1'e göre anlamlı olarak daha düşüktü (p<0,05). Grup 1'deki hastaların vazopressör ihtiyacı (p=0,001) ve bulantı- kusma insidansı anlamlı olarak daha düşüktü (p=0,01).

**Sonuç:** Elektif sezaryen uygulanan gebelerde spinal anestezi öncesi ondansetron kullanıldığında hemodinami daha stabil olup, vazopressör kullanımı azalmış ve bulantı-kusmanın daha az olduğu görülmüştür.

**Anahtar kelimeler:** ERAS, kan basıncı, kusma, ondansetron, spinal anestezi



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## Introduction

The enhanced recovery after surgery (ERAS) is a standardized care program that includes preoperative, intraoperative and postoperative processes in colorectal, urological, gynecological and hepatobiliary surgery. ERAS has been shown to reduce the length of hospital stay, complications, readmissions, and cost (1). ERAS protocol is more frequently preferred in elective cesarean deliveries, which is one of the surgical procedures (2). According to this protocol, in planned births, follow-up is started between 10 and 20 weeks of gestation, while trying to optimize patient comorbidities. In unplanned or emergency situations, it is appropriate within 30-60 minutes of birth (3). This protocol involves preoperative thromboprophylaxis, antibiotic prophylaxis, ensuring perioperative fluid balance and normothermia, preventing postoperative nausea, early removal of urinary catheters, and effective pain relief (4). Thus, regional anesthesia in cesarean sections is preferred because it provides many advantages such as easier patient management, safety and low cost compared to general anesthesia in cesarean section surgeries (5).

In spinal anesthesia, hypotension may develop due to a decrease in systemic vascular resistance (SVR) and cardiac output due to sympathetic blockade (6,7). Hypotension is observed more frequently, especially in obstetric patients (8). Mechanisms causing hypotension include sympatholysis and the Bezold-Jarisch reflex (BJR). As a result of sympatholysis, venous return flow to the right atrium decreases and "5-hydroxytryptamine<sub>3</sub>" sensitive (5-HT<sub>3</sub>, serotonin) chemoreceptors (Bezold-Jarisch reflex) in the heart wall are stimulated. Vasodilatation, bradycardia and hypotension occur due to the release of serotonin (9-11). There are many studies evaluating 5-HT<sub>3</sub> receptor antagonists to prevent spinal anesthesia-induced hypotension. Some studies have shown that administering a 5-HT<sub>3</sub> receptor antagonist (ondansetron) before spinal anesthesia limits the decrease in blood pressure due to spinal anesthesia and reduces the incidence of hypotension (11-15). In a study by Chooi et al. (16), ondansetron administration was more effective in preventing hypotension and bradycardia requiring treatment.

Our study aimed to evaluate the effect of ondansetron (5-HT<sub>3</sub> receptor antagonist) administration on hemodynamics before spinal anesthesia in elective cesarean deliveries.

## Materials and Methods

After Ethics Committee approval of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol no: 2019/523, date: 09.12.2019)

was obtained, a total of 80 patients aged 18-45 years in the American Society of Anesthesiologists (ASA) II anesthesia risk group, who agreed to undergo cesarean section with spinal anesthesia between December 2019 and April 2020, were included in this study. The study was planned in accordance with the Helsinki Declaration. Written informed consent was obtained from all patients prior to the enrollment in the study. Type I error level (alpha level) was 0.2, number of patients per group was taken as 23 to obtain a statistical power of 80%. The number of patients was considered as 40 to add to the possibility of their possible separation. We created two patient groups of the same size according to the treatment: Group 1 (ondansetron group) and group 2 (ondansetron-free group). Patients above ASA III, those who were pregnant before 32 weeks of gestation, those who did not accept spinal anesthesia, and those who were randomized to general anesthesia perioperatively were excluded from the study. Two patients were excluded because they were switched to general anesthesia perioperatively. Patients included in the study were routinely given a supine position in the operation room according to the ASA standard, and heart rate (HR), pulse oximetry (SpO<sub>2</sub>), and non-invasive blood pressure monitoring were provided. All patients were preloaded with 5 mL/kg<sup>-1</sup> crystalloid solution. Group 1 received 4 mg ondansetron intravenous (IV) push. After being positioned in a sitting position, the patient was positioned in a supine position after hyperbaric bupivacaine + 10 µg fentanyl was administered in a total volume of 2 mL-2.5 mL (according to the patient's height) at a rate of 10 seconds following CSF inflow with a 25 G Quinke-type needle through the L3-L4 or L4-L5 interspinous space. A roller was placed under the pregnant woman's thigh for the left lateral decubitus position. The T6 dermatome block level was confirmed before the skin incision. Perioperative mean blood pressure below 60 mmHg or more than a 25% decrease from baseline was considered hypotension. If the heart rate dropped below 55 beats/min<sup>-1</sup>, 0.5 mg atropine IV was administered. IV ephedrine was administered to patients who developed hypotension. Demographic data of the patients, the total amount of fluids, ephedrine and oxytocin administered perioperatively, and atropine and methylazine requirements were recorded. Peak heart rate (HR) and mean blood pressure (MAP) values were recorded at the beginning of spinal anesthesia (T1), 2<sup>nd</sup> (T2), 4<sup>th</sup> (T3), 6<sup>th</sup> (T4), 8<sup>th</sup> (T5), 10<sup>th</sup> (T6), 15<sup>th</sup> (T7) higher at the end of the operation were discharged to the outpatient clinic.

### Statistical Analysis

Analyses were performed using NCSS 11 (Number Cruncher Statistical System, 2017 Statistical Software). In our study, frequency and percentage values were given for the variables. Mean, standard deviation, median, minimum and maximum values were given for continuous variables. The normal distribution test of continuous variables was performed with the Kolmogorov-Smirnov test. The chi-square analysis was used for the relationships between categorical variables. Categorical variables were assessed with the Fisher's Exact test and Fisher-Freeman-Halton test when appropriate.

Independent sample t-test was used to compare two groups in continuous independent variables with normal distribution. The Mann-Whitney U test was used in the comparison of two independent groups for the variables that did not meet the assumption of normal distribution. For dependent variables that did not have normal distribution, the Wilcoxon signed-rank test was employed for comparisons between two groups.  $P < 0.05$  was considered statistically significant.

### Results

Seventy-eight patients who underwent cesarean section under spinal anesthesia were included in the study. They were divided into the Ondansetron-treated group (group 1,  $n=38$ ) and the ondansetron-free group (group 2,  $n=40$ ).

Demographic data of the patients, duration of operation, the total amount of fluid, ephedrine and oxytocin are given in Table 1. The mean age of the patients was  $29.1 \pm 4.8 / 29.6 \pm 5.7$  years (group 1/group 2). ASA score, body mass index, perioperative bleeding and the total amount of fluid were similar in both groups. In group 2, the used amount of oxytocin and ephedrine was higher, and the operation time was longer ( $p < 0.05$ ) (Table 1). Nausea and vomiting were observed less in group 1 ( $p < 0.05$ ). Both groups had no statistically significant difference in atropine use and methylation requirement (Table 1). The patients' heart rates were similar in both groups (Figure 1). When the mean blood pressure was evaluated, it was statistically significantly lower in group 2 at 2<sup>nd</sup> and 4<sup>th</sup> minutes. The mean blood pressures of the patients before the spinal procedure (beginning) and at the end of the operation (ending) were similar (Figure 2).

### Discussion

In this study, hypotension and nausea-vomiting were less common, and perioperative hemodynamics were more

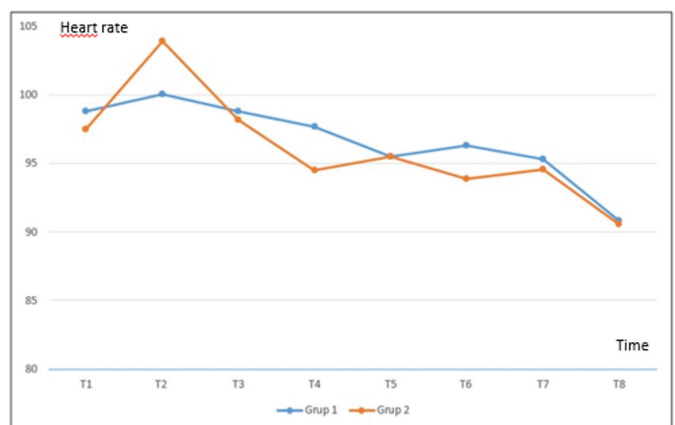
stable in the ondansetron group in patients undergoing cesarean section under spinal anesthesia. The used amount of ephedrine was also less than in the control group.

Hypotension due to peripheral vasodilation is common in cesarean surgeries performed with spinal anesthesia. Many studies investigate the effect of 5 HT-3 receptor antagonists on hypotension. Causes of hypotension include decreased SVR due to sympathetic blockade and BJR. As a result

**Table 1. Comparison of group 1 (ondansetron) and group 2 (ondansetron free) among demographic data of patients, duration of operation, amount of fluid and medication used perioperatively**

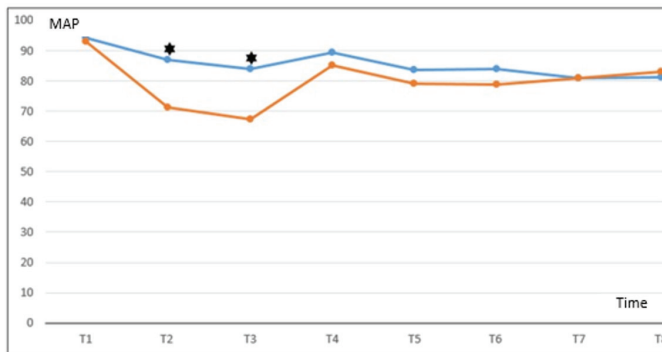
	Group 1 n (38)	Group 2 n (40)	p
Age	29.1±4.8	29.6±5.7	0.6
<b>ASA n (%)</b>			
II	31 (81.6)	32 (80)	0.86
III	7 (18.4)	8 (20)	
BMI, kg.m <sup>2</sup>	32.4±2.9	32.8±2.8	0.89
Presence of nausea and vomiting	5 (13.2)	15 (37.5)	<b>0.01</b>
Amount of bleeding (mL)	545.5±79.5	551.2±76.3	0.67
Fluid intake, mL	1378±78.9	1908±543	0.3
Amount of oxytocin, unite	31.5±0.8	36.7±1.4	<b>0.004</b>
Amount of ephedrine, mg	5.4±1.19	12.6±1.4	<b>0.001</b>
Duration of operation, min	50 (28-85)	55 (30-86)	<b>0.02</b>
Atropine use	1 (2.6)	5 (12.5)	0.1
Methylergonovine use	3 (7.9)	8 (20)	0.12

Categorical variables were shown as numbers (%). Numerical variables with normal distribution were shown as mean ± standard deviation. Numerical variables that do not show normal distribution are shown as median (minimum-maximum).  $p < 0.05$  shows statistical significance, BMI: Body mass index, ASA: American Society of Anesthesiologists



**Figure 1. Comparison of perioperative heart rate**

T1: The beginning of spinal anesthesia, T2: 2<sup>nd</sup> heart rate, T3: 4<sup>th</sup> heart rate, T4: 6<sup>th</sup> heart rate, T5: 8<sup>th</sup> heart rate, T6: 10<sup>th</sup> heart rate, T7: 15<sup>th</sup> heart rate and T8: The end of the operation



**Figure 2.** Comparison of perioperative mean arterial pressure (MAP)

*T1: The beginning of spinal anesthesia, T2: 2<sup>nd</sup> heart rate, T3: 4<sup>th</sup> heart rate, T4: 6<sup>th</sup> heart rate, T5: 8<sup>th</sup> heart rate, T6: 10<sup>th</sup> heart rate, T7: 15<sup>th</sup> heart rate minutes and T8: The end of the operation*

of stimulation of chemoreceptors (5-HT<sub>3</sub>, serotonin) in the heart wall with a decreased venous return to the right heart, BJR is activated; vasodilatation, bradycardia and hypotension occur (5). Accordingly, ondansetron is thought to inhibit BJR by binding to 5HT-3 receptors and preventing hypotension (6,7). There are studies suggesting that prophylactic ondansetron reduces hypotension and vasopressor use (8-13), and our results are similar to these studies. However, studies also support that ondansetron does not affect the risk of hypotension (14,15). Therefore, the mechanism by which ondansetron causes the observed effects on hypotension and vasopressor requirement is not fully understood.

Due to hypotension, uterine blood flow decreases and fetomaternal circulation is disrupted (11). Ephedrine, an alpha and beta agonist in treating hypotension related to neuraxial anesthesia, is preferred in obstetric anesthesia because it increases uterine blood flow (17). Thus, the side effects of hypotension are prevented by maintaining uterine blood flow. We believe that uteroplacental blood flow was well preserved in the ondansetron group, in which the requirement of hypotension and vasopressor (ephedrine) were less.

Prevention of nausea-vomiting in the ERAS protocol is essential for patient satisfaction, recovery and early discharge (1,15,16). In spinal anesthesia, cerebral blood flow decreases due to hypotension, and the vomiting center is stimulated, splanchnic blood flow decreases and serotonin release from the gastrointestinal system increases. Accordingly, nausea and vomiting are frequently observed (17). In cesarean deliveries, intraoperative nausea-vomiting increases with perioperative antibiotic use, pain, uterotonic drug use, removal of the uterine outside the abdomen and

peritoneal irrigation in addition to hypotension due to spinal anesthesia (18,19). In addition, hypotension may trigger nausea and vomiting and may pose serious risks for the mother (loss of consciousness, pulmonary aspiration) and the baby (hypoxia, acidosis, neurologic damage) (20). Studies have shown less nausea and vomiting with perioperative ondansetron use in cesarean surgeries (21,22). Our study also supports the findings.

### Study Limitations

The limitation of this study is that a fixed dose of ondansetron was used. Borgeat et al. (23) compared the effect of different doses of ondansetron on hypotension. Another limitation of our study is that only ondansetron was used among the 5 HT-3 receptor antagonists. Many studies evaluated the effects of ondansetron and granisetron on hemodynamics, and different results were found (13,24,25). Therefore, further studies with larger samples and different 5HT3 receptor antagonists are needed.

According to a Cochrane study, IV fluid loading, IV ephedrine or phenylephrine administration in caesarian sections have been shown to reduce spina anesthesia-related hypotension (26). However, studies have reported that prophylactic IV ondansetron effectively reduces the incidence of hypotension and vasopressor need due to spinal anesthesia in pregnant women undergoing cesarean section, and may even be an effective alternative to ephedrine (24,27,28).

### Conclusion

We believe that ondansetron administration will be beneficial in preventing hypotension and nausea due to spinal anesthesia's effect and decrease the need for vasopressors in cesarean deliveries.

### Ethics

**Ethics Committee Approval:** After Ethics Committee approval of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol no: 2019/523, date: 09.12.2019) was obtained.

**Informed Consent:** Written informed consent was obtained from all patients in this study prior to the enrollment in the study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: N.A., Concept: N.A., Design: N.A., P.K.E., İ.P., Data Collection or Processing: N.A., D.A.,



P.K.E., Analysis or Interpretation: N.A., D.A., P.K.E., Literature Search: N.A., D.A., İ.P., Writing: N.A., D.A., İ.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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