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Preoperative ondansetron does not reduce the incidence of maternal hypotension during elective caesarean delivery under spinal anaesthesia, but mitigate its severity: a double blind, randomized, placebo controlled trial

José Ramón Ortiz-Gómez[1], Francisco Javier Palacio-Abizanda[2], Francisco Morillas-Ramirez[2], Inocencia Fornet-Ruiz[3], Ana Lorenzo-Jiménez[2], Maria Lourdes Bermejo-Albares[2]

1 Department of Anaesthesiology, Complejo Hospitalario de Navarra, Pamplona, Spain
2 Department of Anaesthesiology, Hospital Gregorio Marañón, Madrid, Spain
3 Department of Anaesthesiology, Hospital Puerta de Hierro, Madrid, Spain

Abstract

Background. The prophylactic administration of ondansetron has been reported to provide a protective effect against hypotension in spinal anaesthesia (SA). ***Material and methods.*** This prospective double-blind, randomised, placebo-controlled study included 130 healthy pregnant women scheduled for elective caesarean delivery under SA randomly allocated to receive placebo (n = 65) or ondansetron 8 mg (n = 65) intravenously before SA. Demographic, obstetric, intraoperative timing and anaesthetic variables were assessed at 16 different time points, including blood pressure, heart rate, oxygen saturation, nausea, vomiting, electrocardiographic changes, skin flushing, discomfort or pruritus and vasopressor requirements. ***Results.*** There were no differences in the number of patients with hypotension: 33 (placebo) *vs.* 29 (ondansetron). However, as a single patient could had more than one hypotensive episode, we analysed the number of hypotensive events per patient (placebo 2.9 ± 4.0 *vs.* ondansetron 1.4 ± 2.2) (P = 0.011) and the percentage of time points with systolic hypotension (placebo 17.4% *vs.* ondansetron 8.7%) (P = 0.012). We also found differences at min 9 in diastolic blood pressure (DBP) (P = 0.014), mean arterial pressure (MAP) (P = 0.049), the variations from baseline of systolic blood pressure at min 5 to 13 and 20 (Figure 3), DBP at min 7 to 11, and MAP at 7 to 13 min between groups ($P < 0.05$) and the number of patients requiring ephedrine (P = 0.042). There were no differences in the number of patients with adverse effects excepting pruritus (P = 0.042). ***Conclusions.*** prophylactic administration of ondansetron 8 mg has a certain protective effect in the prevention of maternal hypotension in healthy women scheduled for elective caesarean delivery under spinal anaesthesia. *Anestezjologia i Ratownictwo 2016; 10: 19-27.*

Keywords: ondansetron, spinal anaesthesia, hypotension, caesarean delivery

Introduction

Spinal anaesthesia is a widely used anaesthetic technique, and the most common for caesarean delivery. However, it frequently produced hypotension, with an incidence of 33% in non-obstetric patients [1] and approximately twice this rate in the obstetric population [2]. Maternal hypotension is one of the most important causes of intraoperative nausea and vomiting [3] and may also be associated with dizziness and in severe cases unconsciousness, pulmonary aspiration and placental hypoperfusion with fetal hypoxia, acidosis and neurologic injury [2].

Much has changed in the way we manage hypoten-

sion during spinal anaesthesia for caesarean delivery. Several strategies have been used to decrease the occurrence of hypotension [2]; however none has been shown to eliminate the need to treat it.

Decreases in cardiac output and systemic vascular resistance are the main contributors to hypotension due to sympathetic nerve blockade in patients undergoing subarachnoid anaesthesia. The Bezold–Jarisch and reverse Bainbridge reflexes inducing bradycardia have been also involved as additional explanations. The Bezold–Jarisch reflex is caused by decreased filling of the right atrium, which reduces outflow from some intrinsic chronotropic stretch mechanoreceptors in the ventricular wall [4]. Serotonin may be an important factor in inducing this reflex [5-9], as has been described in hypovolaemic animal models. Therefore, ondansetron may attenuate arterial hypotension by blocking serotonin-induced bradycardia. Experimental results also suggest that a functional interaction between serotonergic and opioidergic pathways in the rat brain is part of the complex, multifactorial system that regulates blood pressure in the central nervous system [10-12]. Therefore, both peripheral and central mechanisms may be involved.

Ondansetron has been proposed to attenuate hypotension after subarachnoid anaesthesia in both non-obstetric [13-16] and obstetric patients [17-23]. However, results of these studies are limited by different studies designs and small sample size and are in some aspects contradictory. To clarify the utility of ondansetron in preventing hypotension, we evaluated in this study, the effect of intravenous ondansetron 8 mg compared with placebo on the haemodynamic response and side effects following spinal anaesthesia in healthy ASA I pregnant women undergoing elective caesarean delivery. The primary outcome, hypotension, was defined in this study as a SBP < 75% of baseline using the criteria outlined in the Cochrane review of hypotension in obstetrics [2].

Material and methods

This was a prospective double-blind, placebo-controlled, and randomized study. After institutional ethical committee approval, 150 American Society of Anaesthesiologists class I women scheduled for lower segment caesarean delivery under spinal anaesthesia were enrolled during anaesthesia consultation or early in the third trimester. Written informed consent was obtained from all patients to participate in this study. Exclusion criteria included refusal to participate, contraindication to spinal anaesthesia, age < 20 or > 45 years, obesity (body mass index (BMI) at term > 30 kg/m^2), ASA ≥ 2, previous fluid therapy and history of allergy to or side effects from ondansetron.

Women were fasted for eight hours before surgery. They did not receive premedication. Peripheral venous access was secured with an 18-gauge cannula. Ten minutes after arrival in the operating room, baseline values for oxygen saturation, electrocardiography and non-invasive blood pressure were recorded in the supine position with 15 degrees left tilt. These were considered the baseline data.

Women were previously randomly allocated by our Statistical Department into two groups according to receive placebo or intravenous ondansetron 8 mg (Zofran, GlaxoSmithKline, Parma, Italy). An anaesthesia nurse verified the allocation and prepared ondansetron 8 mg with 0.9% saline solution to a total volume of 10 mL or a placebo of 0.9% saline solution 10 mL. The syringes had no identifying markers indicating group allocation. The nurse injected the contents of the 10 mL syringe intravenously over 60 s five minutes before the lumbar puncture was performed. The anaesthetist caring for the woman was blinded to group allocation.

Spinal anaesthesia was induced in the sitting position at the L3-4 or L4-5 interspace, with a 27-gauge Whitacre (Braun, Melsungen, Germany) needle. We administered 0.5% hyperbaric bupivacaine (Inibsa, Barcelona, Spain), according to the following formula: bupivacaine (mg) = height (cm) x 0.06, with fentanyl (Kern Pharma, Tarrasa, Spain) 20 μg. Following injection, patients were immediately placed in supine with 15 degrees left tilt. All women were rapidly co-loaded with colloid 8 mL/kg (Voluven, Fresenius Kabi, Barcelona, Spain).

Sensory block height level was checking by assessing the perception of coldness using an alcohol swab, and motor block using the Bromage scale, both seven and 15 min after intrathecal injection.

Hypotension was defined as SBP < 75% of baseline [2,24] and in this case, treatment was initiated with intravenous ephedrine (Ephedrine, Genfarma Laboratorios, Toledo, Spain) 10 mg or phenylephrine 50 μg (if the maternal heart rate was >95 beats/min, given over 30 s to avoid bradycardia). Intravenous atropine (Atropine, Serra Pamies, Reus, Spain)

Table I. Demographic data

	Placebo (n = 65)	Ondansetron 8 mg (n = 65)	P value
Age (years)	35.6 ± 5.0	34.6 ± 4.3	0.24
Weight (kg)	75.6 ± 11.5	75.7 ± 12.6	0.95
Height (cm)	161.9 ± 5.8	161.2 ± 5.8	0.51
Body mass index (kg/m^2)	28.9 ± 4.6	29.2 ± 5.0	0.75
Dural puncture to skin incision (min)	10.4 ± 2.5	10.8 ± 2.1	0.31
Skin incision to fetal extraction (min)	11.8 ± 3.6	8.3 ± 2.8	0.0001
Total time (min)	49.0 ± 10.2	40.5 ± 6.7	0.0001
Sensory block height 15 min after intrathecal injection T3-4 T5-6	 44 (67.7%) 21 (32.3%)	 42 (64.6%) 23 (35.4%)	0.50

Data are mean ± SD or number (%)

0.01 mg/kg was administered if the maternal heart rate was < 45 beats/min.

The anaesthetist recorded demographic data (age, height, body mass index), obstetric data (indication for caesarean delivery, gestation, number of previous pregnancies, caesarean deliveries, uterine pathology), intraoperative timing (time from dural puncture to skin incision, time from skin incision to delivery, total time of the surgery) and anaesthetic variables, (SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), oxygen saturation (SaO_2), adverse effects (nausea, vomiting, electrocardiographic changes, skin flushing, discomfort, pruritus) and the need for atropine, ephedrine or phenylephrine. Anaesthetic variables were recorded before administration of the study drug and the at 2 min intervals for 15 min and 5 min intervals for a further 30 min after intrathecal injection, as well as at the end of surgery.

Our protocol allowed the administration of intravenous acetaminophen 1 g and supplementary doses of fentanyl 50 µg (maximum of three doses) if the patient felt pain during surgery. General anaesthesia could be administered if anaesthesia was still inadequate. The protocol dictated that women requiring supplementation analgesia were removed from the study.

Finally, we used low doses of oxytocin (1 U) after umbilical cord clamping, followed by an infusion of 2.5 U/h, to avoid side effects, which could affect haemodynamics.

Statistical analysis

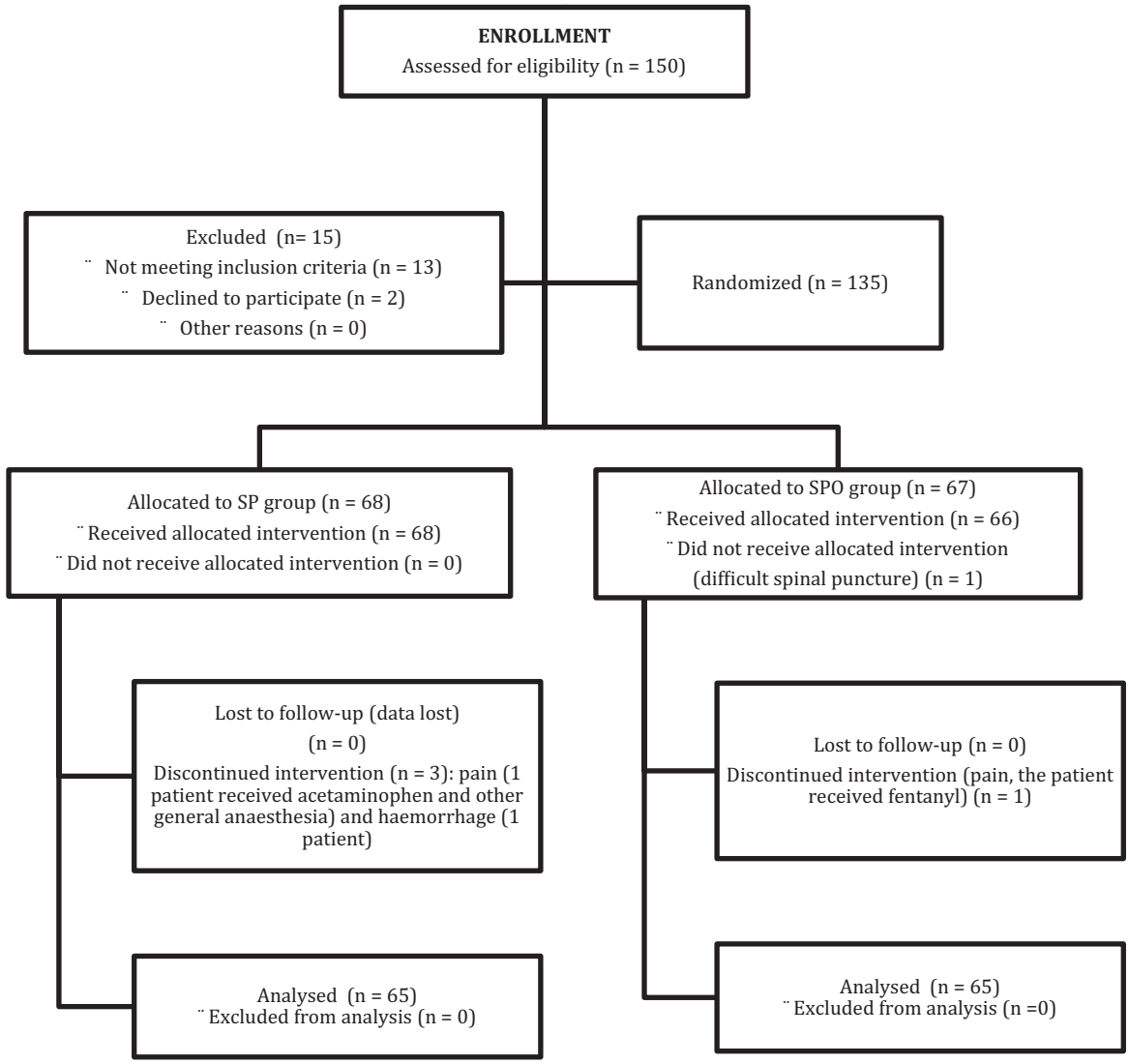
Data were analysed using IBM SPSS 21 statistical software package (IBM, New York, USA). Comparison of means of independent samples was performed using ANOVA, followed by Dunnett's test for post hoc testing, and repeated measures ANOVA was used for paired data. Association between qualitative variables was performed using the chi-square test with Fisher's exact test where appropriate. Trends were studied with the chi-square for linear trend test. A P value < 0.05 was considered significant. Haemodynamic data (SBP, DBP, MAP, heart rate and oxygen saturation), were re-plotted using a format where all values were expressed as the correspondent percentage related to the baseline value (considered as 100%) to reveal a more discrete pattern of change so that each patient served as her own control.

Results

A total of 150 women were recruited into the study (Consort flow diagram), 15 were excluded (2 declined to participate, 13 did not meet the inclusion criteria) and 135 women were randomized: 5 patients were withdrawn from the study (1 did not receive allocated intervention (difficult spinal puncture), 3 women had pain and received analgesics and 1 patient had a severe haemorrhage). Finally, 130 cases were considered valid: ondansetron group (n = 65) and placebo group (n = 65).

Demographic and anaesthetic data are presented in Table I. No differences between groups were observed in obstetric data including gestational age, previous pregnancies and caesarean deliveries excepting the times from skin incision to fetal extraction and the total time.

There were no differences ($P = 0.482$) in the number of patients with hypotension: 33 patients (50.8%) in the placebo group and 29 patients (44.6%) in the ondansetron group. As a single patient could have more than one hypotensive episode during the caesarean section,



we analysed also the number of hypotensive events per patient (every moment measured with arterial hypotension) and the percentage of time points when the patient had systolic hypotension.

We found statistically significant differences in the number of hypotensive events between placebo (2.9 ± 4.0) and ondansetron groups (1.4 ± 2.2) (P = 0.011) and the percentage of time points with systolic hypotension: 17.4% in the placebo group and 8.7% in the ondansetron group (P = 0.012) respectively.

Maternal arterial pressures (SBP, MAP and DBP) are shown in Figure 1. We found statistically significant differences between the groups at min 9 in DBP (P 0.014) and MAP (P 0.049). There were no differences in HR and SaO_2 values. However, differences ($P < 0.05$) were observed between groups in the variation from baseline of SBP at min 5 to 13 and 20 (Figure 2), DBP (at min 7 to 11), and MAP (Figure 3) from baseline at 7 to 13 min.

We found differences between groups in the number of patients requiring supplementary boluses of ephedrine (P = 0.042) but not phenylephrine or atropine (Table II).

There were no differences between groups in the number of patients with adverse effects (Table III) excepting pruritus (P = 0.042).

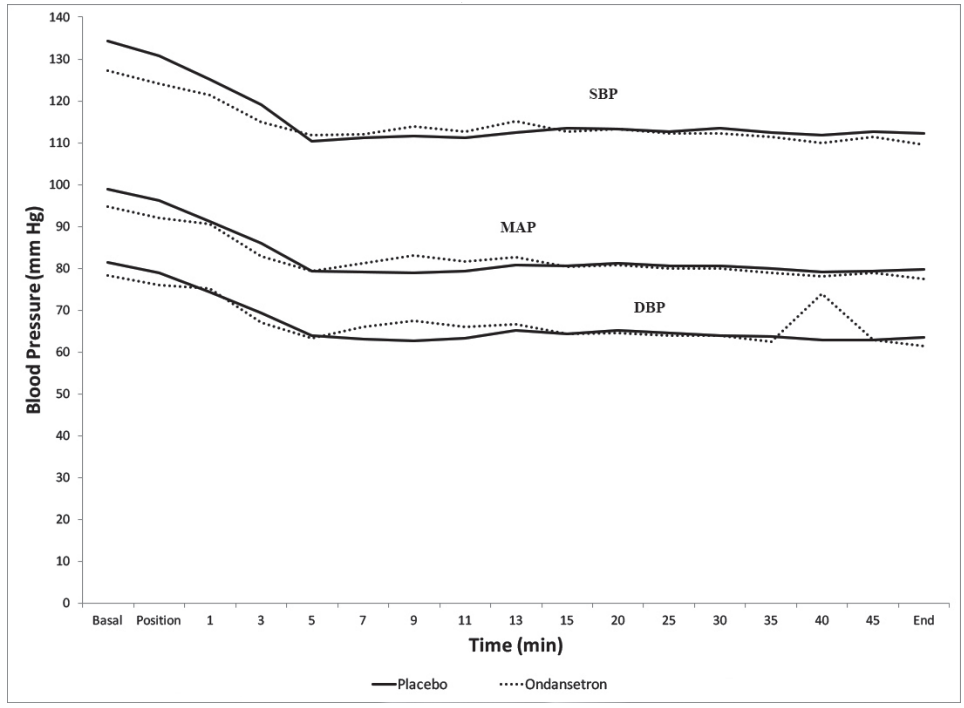


Figure 1. Maternal blood pressure

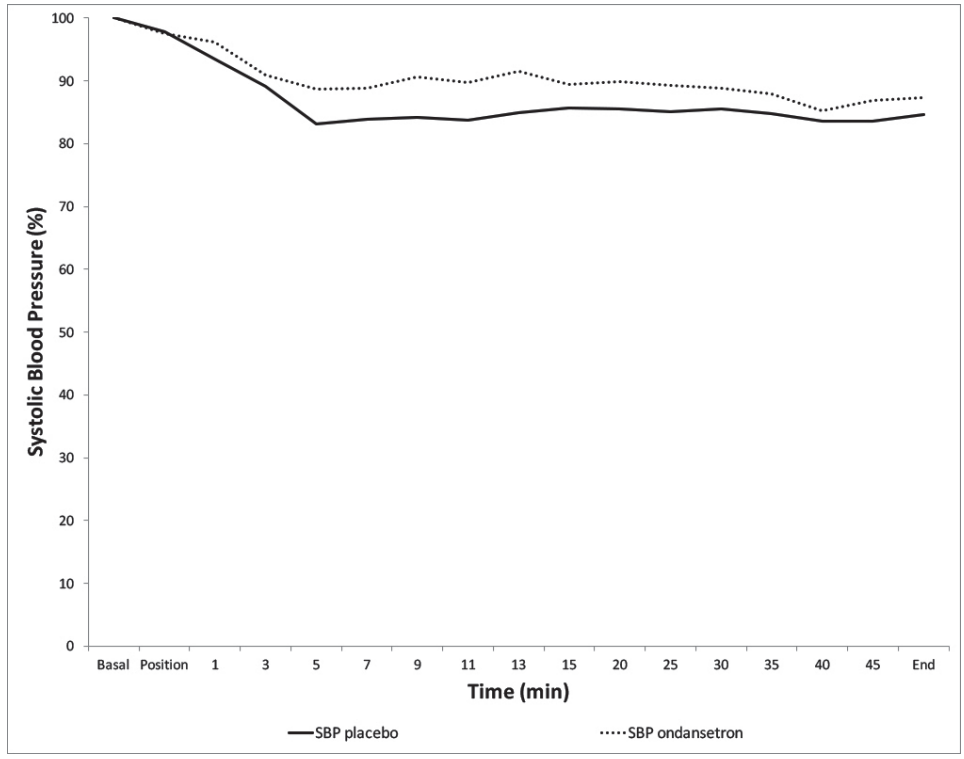


Figure 2. Variation in systolic blood pressure compared to baseline

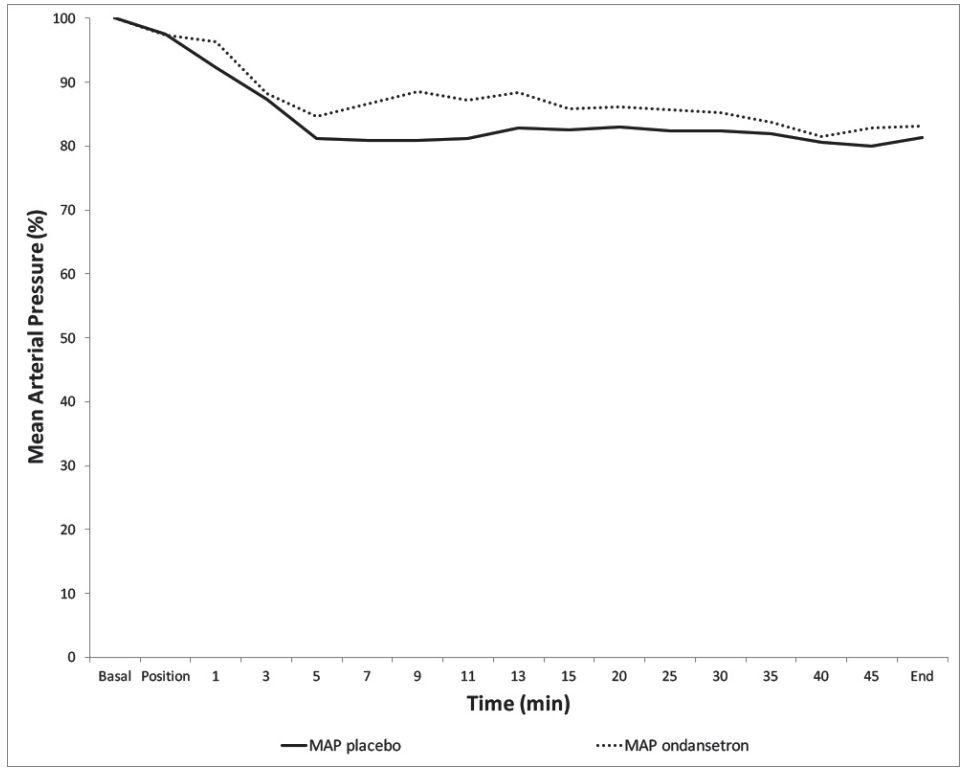


Figure 3. Variation in mean arterial pressure compared to baseline

Table II. Requirements of ephedrine, phenylephrine and atropine

	Placebo (n = 65)	Ondansetron 8 mg (n = 65)	P value
Ephedrine	21 (32.3%)	11 (16.9%)	0.042
Phenylephrine	5 (7.7%)	2 (3.1%)	0.244
Atropine	0 (0%)	0 (0%)	1

Data are number (%)

Table III. Adverse effects

	Placebo (n = 65)	Ondansetron 8 mg (n = 65)	P value
Electrocardiogram changes	0	0	1
Nausea	7 (10.8%)	7 (10.8%)	1
Vomiting	2 (3.1%)	0	0.154
Pruritus	0 (0%)	4 (6.2%)	0.042
Skin flushing	6 (9.2%)	12 (18.5%)	0.128
Discomfort	5 (7.7%)	4 (6.2%)	0.730

Data are number (%)

Discussion

It has been reported [25] that nearly one half of mothers had a 30% or greater decrease in their mean arterial pressure during neuraxial anaesthesia for caesarean delivery. This hypotension is well tolerated by healthy women with term infants, but in women with comorbidities or at-risk fetuses, hypotension may prove detrimental. Based on improved understanding of the physiological changes that occur following spinal anaesthesia, important advances have been made for preventing spinal hypotension during Caesarean delivery. Maintaining systemic vascular resistance, venous capacitance, and splanchnic venous tone are likely to be key factors in preventing a decrease in maternal cardiac output [26,27].

Several strategies, including uterine displacement, lower legs compression, patient position and administration of fluids, vasopressors or ondansetron have been used to decrease the occurrence of hypotension [2], but none is the definitive. The combination of dif-

ferent strategies could be a better solution.

Ondansetron is widely used in the prophylaxis and treatment of postoperative nausea and vomiting. This drug has been proposed to attenuate hypotension after subarachnoid anaesthesia in both non-obstetric [13,14] and obstetric patients [17-19]. However, results of these studies are limited by different studies designs and small sample size and are in some aspects contradictory: Sahoo et al. [18] and Wang et al. [19] reported that premedication with ondansetron (4 mg) mitigated hypotension in patients undergoing elective caesarean delivery whereas Ortiz-Gómez et al. [17] (2, 4, or 8 mg) and Terkawi et al. [20] (8 mg) did not find statistical significant haemodynamic effect. However, Ortiz-Gómez et al. [17] reported a significant dose-dependent trend in ephedrine dosing with ondansetron and significant differences in systolic blood pressure (SBP) between placebo and ondansetron 8 mg groups at 9, 11, 13 and 35 min.

In the present study we can see a better haemodynamic SBP profile with ondansetron *vs*. placebo (Figure 3) that is not statistically significant ($P = 0.486$) in the total number of patients with hypotension but it is relevant in the percentage of hypotensive effects ($P = 0.012$), because every patient who suffered hypotension could have various hypotensive events. So, ondansetron appears to reduce significantly the severity of maternal hypotension, with less number of hypotensive events per patient, and could reduce the possibility of maternal and fetal morbidity. Our results are similar to those reported by Trabelsi et al. [22] However, although methodologically close, those results differ from ours because of different hypotension's management (other loading fluids, vasopressor, dose of bupivacaine, intrathecal opioid and oxytocin protocol). Trabelsi et al. [22] also found that prophylactic ondansetron (4 mg) had a significant effect on the incidence of hypotension in healthy parturients undergoing spinal anaesthesia for elective caesarean delivery. They registered estimated variables based on continuous arterial waveform analysis system such as stroke volume, cardiac output and systemic vascular resistance (not measured in our study) and suggested that ondansetron may act at cardiac level (enhancing contractility and efficiency) and at vascular level (stable systemic vascular resistances) via vascular and/or medullar specific receptors. Trabelsi et al. [22] also reported that ondansetron can be helpful to improve metabolic and vital parameters of newborns.

The ideal ondansetron dose is not well established. We used 8 mg based on the previously reported results of Ortiz-Gómez et al. [17] who compared 2, 4 and 8 mg of ondansetron with placebo (32 patients/group). Wang et al. [23], however reported that the optimal dose appears to be 4 mg of ondansetron considering its effects on hypotension, nausea, phenylephrine consumption and neonatal outcomes (29 patients/group). Fattahi et al. [28] established this dose of ondansetron in 0.15 $mg.kg^{-1}$.

The type of the serotonin-receptor-antagonist could also be important. So, Shin et al. [15] described than ramosetron (0.3 mg) significantly attenuated the spinal anaesthesia induced arterial hypotension compared with 4 or 8 mg of ondansetron (39 patients/group).

Concerning the adverse effects, those most frequently related to ondansetron are diarrhoea, fever, headache and skin flushing, although more important clinically adverse effects have been reported such as electrocardiographic changes, proarrhythmic activity, coronary vasospasm and acute myocardial ischaemia. We only found statistical differences (Table III) in the incidence of pruritus. No electrocardiographic or cardiovascular changes were reported.

In conclusion, prophylactic administration of ondansetron 8 mg does not reduce the incidence of maternal hypotension in healthy women scheduled for elective caesarean delivery under spinal anaesthesia, but has a certain protective effect diminishing the number and severity of hypotensive events. It is important to remark that we can`t forget the addition of various techniques to achieve the optimal management of hypotension, including the patient's position, co-loading with colloid and the prophylactic administration of phenylephrine. Further studies are still needed to elucidate the definitive role of preoperative serotonin-receptor-antagonist in the prevention of maternal hypotension in Caesarean delivery.

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Conflict of interest

None

Correspondence address:
J. R. Ortiz-Gómez
Department of Anaesthesiology, Complejo Hospitalario de Navarra, Sección D.
Carretera Aoiz s/n, Planta Baja; 31486 Elcano – Egüés; Navarra, Spain.
☎ (+34) 848 422 222
j.r.ortiz.gomez.md.phd@gmail.com

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