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ORIGINAL ARTICLE

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The effect of intravenous ondansetron on maternal haemodynamics during elective caesarean delivery under spinal anaesthesia: a double-blind, randomised, placebo-controlled trial

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ABSTRACT
Background: Spinal anaesthesia for caesarean delivery is frequently associated with adverse effects such as maternal hypotension and bradycardia. Prophylactic administration of ondansetron has been reported to provide a protective effect. We studied the effect of different doses of ondansetron in obstetric patients.
Methods: This prospective double-blind, randomised, placebo-controlled study included 128 healthy pregnant women scheduled for elective caesarean delivery under spinal anaesthesia. Women were randomly allocated into four groups ($n = 32$) to receive either placebo or ondansetron 2, 4 or 8 mg intravenously before induction of spinal anaesthesia. Demographic, obstetric, intraoperative timing and anaesthetic variables were assessed at 16 time points. Anaesthetic variables assessed included 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 in the placebo (43.8%) and ondansetron 2 mg (53.1%), 4 mg (56.3%) and 8 mg (53.1%) groups ($P = 0.77$), nor the percentage of time points with systolic hypotension (7.3% in the placebo group and 11.1%, 15.7% and 12.6% in the ondansetron 2, 4 and 8 mg groups, respectively, $P = 0.32$). There were no differences between groups in ephedrine ($P = 0.11$) or phenylephrine ($P = 0.89$) requirements and the number of patients with adverse effects.
Conclusions: In our study, prophylactic ondansetron had little effect on the incidence of hypotension in healthy parturients undergoing spinal anaesthesia with bupivacaine and fentanyl for elective caesarean delivery.

Keywords: Ondansetron; Spinal anaesthesia; Hypotension; Caesarean delivery

Introduction

Spinal anaesthesia is the most widely used anaesthetic technique for caesarean delivery. However, it is frequently associated with adverse effects such as maternal hypotension and bradycardia. Although there is no single definition for hypotension, most authors agree that hypotension is present when the systolic blood pressure (SBP) decreases to <90–100 mmHg or when there is a reduction from baseline of <20–30%.[1,2] Hypotension may be associated with maternal nausea and vomiting and in severe cases unconsciousness, pulmonary aspiration and placental hypoperfusion with fetal hypoxia, acidosis and neurologic injury.[2] The incidence of hypotension after spinal anaesthesia is 33% in non-obstetric patients[3] and approximately twice this rate in the obstetric population.[2]

Several studies have reported that intravenous ondansetron (8 mg in the general population[4] and 4 mg in obstetric patients[5]) could attenuate hypotension in patients receiving spinal anaesthesia. Decreases in cardiac output and systemic vascular resistance are the main contributors to hypotension with sympathetic nerve blockade and the Bezold–Jarisch and reverse

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Bainbridge reflexes inducing bradycardia.[6] 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.[7] Serotonin may be an important factor in inducing this reflex,[7–12] 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.[13–15] Therefore, both peripheral and central mechanisms may be involved.

In this study, we evaluated the effect of three different intravenous ondansetron doses (2, 4 and 8 mg) and 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 as a systolic blood pressure <75% of baseline.

Methods

This was a prospective double-blind, placebo-controlled, randomised study. After institutional ethical committee approval, 128 American Society of Anesthesiologists 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) and a history of allergy to or side effects from ondansetron.

Women were fasted for 8 h 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 four groups to receive intravenous ondansetron (Zofran, GlaxoSmithKline, Parma, Italy) or placebo. An anaesthesia nurse verified the allocation and prepared the appropriate dose of ondansetron (2, 4 or 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 syringe intravenously over 60 s, 5 min 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 needle. We administered 0.5% hyperbaric bupivacaine, according to the following formula: bupivacaine (mg) = height (cm) × 0.06, with fentanyl 20 μg. Following injection, patients were immediately placed supine with 15 degrees left tilt. All women were rapidly co-loaded with hydroxyethyl starch (Voluven®, Fresenius Kabi, Barcelona, Spain) 8 mL/kg.

Sensory block height level was checked by assessing the perception of coldness using an alcohol swab, and motor block using the Bromage scale, both at 7 and 15 min after intrathecal injection.

Hypotension was defined as SBP <75% of baseline.[1,2] Treatment was initiated with intravenous ephedrine 10 mg or phenylephrine 50 μg if the maternal heart rate was >95 beats/min, given over 30 s to avoid bradycardia. Intravenous atropine 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), need for atropine, ephedrine or phenylephrine, and the initial and final haemoglobin values. Anaesthetic variables were recorded before administration of the study drug and then 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 were removed from the study.

Statistical analysis

Data were analysed using IBM SPSS 21 statistical software package (IBM, New York NY, 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