Original Article

Reducing by 50% the incidence of maternal hypotension during elective caesarean delivery under spinal anesthesia: Effect of prophylactic ondansetron and/or continuous infusion of phenylephrine - a double-blind, randomized, placebo controlled trial

ABSTRACT

Background: Prophylactic administrations of ondansetron or phenylephrine have been reported to provide a protective effect against hypotension in women undergoing cesarean delivery under spinal anesthesia (SA). The main hypothesis is that ondansetron improves the hemodynamic response, especially combined with phenylephrine infusion.

Methods: This prospective, double-blind, randomized, placebo-controlled study included 265 healthy pregnant women scheduled for elective cesarean delivery under SA. Women were randomly allocated into four groups to receive either placebo (control), ondansetron (O) 8 mg intravenously before induction of SA, phenylephrine infusion (50 mcg/min) (P) or ondansetron plus phenylephrine (OP). Demographic, obstetric, intraoperative timing, and anesthetic variables were assessed at 16 time points. Anesthetic variables assessed included blood pressure, heart rate, oxygen saturation, nausea, vomiting, electrocardiographic changes, skin flushing, discomfort or pruritus, and vasopressor requirements.

Results: There were differences ($P = 0.0001$) in the number of patients with hypotension (50.8% control, 44.6% O, 20.9% P, 25.0% OP), the percentage of time points ($P = 0.0001$) with systolic hypotension per patient (17.4% control, 8.7% O, 2.1% P, 6.7% OP) and the number of patients requiring supplementary boluses of ephedrine ($P = 0.003$), phenylephrine ($P = 0.017$) or atropine ($P = 0.0001$).

Conclusions: A 50 μg/min phenylephrine infusion reduces by 50%, the incidence of maternal hypotension compared with placebo, but infusions of phenylephrine are still not routine in our environment. Prophylactic ondansetron 8 mg might be considered in this situation, because it does not reduce the incidence of maternal hypotension but diminishes its severity, reducing the number of hypotensive events per patient by 50%.

Key words: Cesarean delivery; hypotension; ondansetron; phenylephrine; spinal anesthesia

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Introduction

Spinal anesthesia (SA) is the most common used anesthetic technique for cesarean delivery. However, it frequently produced hypotension[1,2] (30% or greater decrease in the mean arterial pressure (MAP) in nearly one-half of mothers[3]) that may induce maternal and/or fetal problems.[2,4]

Decreases in cardiac output and systemic vascular resistance are the main contributors to hypotension with sympathetic nerve blockade. The Bezold–Jarisch and reverse Bainbridge reflexes can also induce bradycardia. Maintaining systemic vascular resistance, venous capacitance, and splanchnic venous tone is likely to be key factors in preventing a decrease in maternal cardiac output.[5,6]

Several strategies have been used to decrease the occurrence of hypotension,[2] but none has been shown to eliminate the need to treat it. Ephedrine was historically considered the gold standard vasopressor for the management of SA-induced hypotension. However, phenylephrine is recommended now because of lower rate of fetal acidosis compared with ephedrine.[7] Hence, prophylactic infusion of phenylephrine is habitual in some institutions[8] but is not universally extended.

Previous administration of ondansetron[9] may attenuate arterial hypotension by blocking serotonin-induced bradycardia.

Methods

We evaluated in this study the effect of ondansetron 8 mg (with and without phenylephrine 50 μg/min) compared with placebo and phenylephrine infusion.

The main hypothesis is that the addition of intravenous ondansetron 8 mg improves the hemodynamic response following SA in healthy American Society of Anesthesiologists (ASA) I pregnant women undergoing elective cesarean delivery, especially combined with phenylephrine infusion.

This was a prospective, double-blind, placebo-controlled, and randomized study. The clinical trial was registered in the Australian New Zealand Clinical Trials Registry with allocation ID: ACTRN12616000884404, Web address: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12616000884404.

After institutional ethical committee approval, 300 ASA class I women scheduled for lower segment cesarean delivery under SA were enrolled during anesthesia 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 SA, 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 or phenylephrine.

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 (SaO_2), electrocardiography, and noninvasive blood pressure were recorded in the supine position with 15° left tilt. These were considered the baseline data.

SA was induced in the sitting position at the L3–L4 or L4–L5 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) × 0.06, with fentanyl (Kern Pharma, Tarrasa, Spain) 20 μg. Following injection, patients were immediately placed in supine with 15° left tilt. All women were rapidly coloaded with colloid 8 mL/kg (Voluven, Fresenius Kabi, Barcelona, Spain).

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.

Women were previously randomly allocated by our Statistical Department into four groups to receive placebo [control group], intravenous ondansetron (Zofran, GlaxoSmithKline, Parma, Italy) 8 mg [O group], phenylephrine (Phenylephrine, Genfarma Laboratories, Toledo, Spain) 50 μg/min [P group] or ondansetron 8 mg plus phenylephrine 50 μg/min [OP group]. An anesthesia 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 and phenylephrine 10 mg with 0.9% saline solution to a total volume of 49 mL or a placebo of 0.9% saline solution 50 mL.

The syringes had no identifying markers indicating group allocation. The nurse injected the contents of the 10-mL syringe intravenously over 60 s, 5 min before the lumbar puncture was performed, and then started the 50-mL syringe IV continuous infusion at 15 mL/h. The anesthetist caring for the woman was blinded to group allocation.

Hypotension was defined using the criteria outlined in the Cochrane review of hypotension in obstetrics as systolic blood pressure (SBP) <75% of baseline,[2,10] and in this case, treatment was initiated with intravenous ephedrine (Ephedrine, Genfarma Laboratories, Toledo, Spain) 10 mg or phenylephrine 50 μg (if the maternal heart rate [HR] was >95 beats/min, given over 30 s to avoid bradycardia). Intravenous atropine (Atropine, Serra Pamies, Reus, Spain) 0.01 mg/kg was administered if the maternal HR was <45 beats/min.

The anesthetist recorded demographic data (age, height, BMI), obstetric data (indication for cesarean delivery, gestation, number of previous pregnancies, cesarean deliveries, uterine pathology), intraoperative timing (time from dural puncture to skin incision, time from skin incision to delivery, total time of the surgery), and anesthetic variables SBP, diastolic blood pressure [DBP], MAP, HR, SaO_2, adverse effects (nausea, vomiting, electrocardiographic changes, skin flushing, discomfort, pruritus) and the need for atropine, ephedrine, or phenylephrine. Anesthetic 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 anesthesia could be administered if anesthesia was still inadequate. The protocol dictated that women requiring supplementation analgesia were removed from the study.

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 hemodynamics.

Finally, a complete umbilical cord blood gases analysis and Apgar values at 1st and 5th min were performed when continuous infusion of phenylephrine was used (due to the small but statistically significant increase in umbilical artery pH previously reported).[11]

Statistical analysis

Data were analyzed using IBM SPSS 21 statistical software package (IBM, New York, USA). The sample size was calculated to obtain a Cohen's *d* effect size = 1.0.

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. $P < 0.05$ was considered significant.

Hemodynamic data (SBP, DBP, MAP, HR, and SaO_2) were replotted 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 each patient served as her own control.

Results

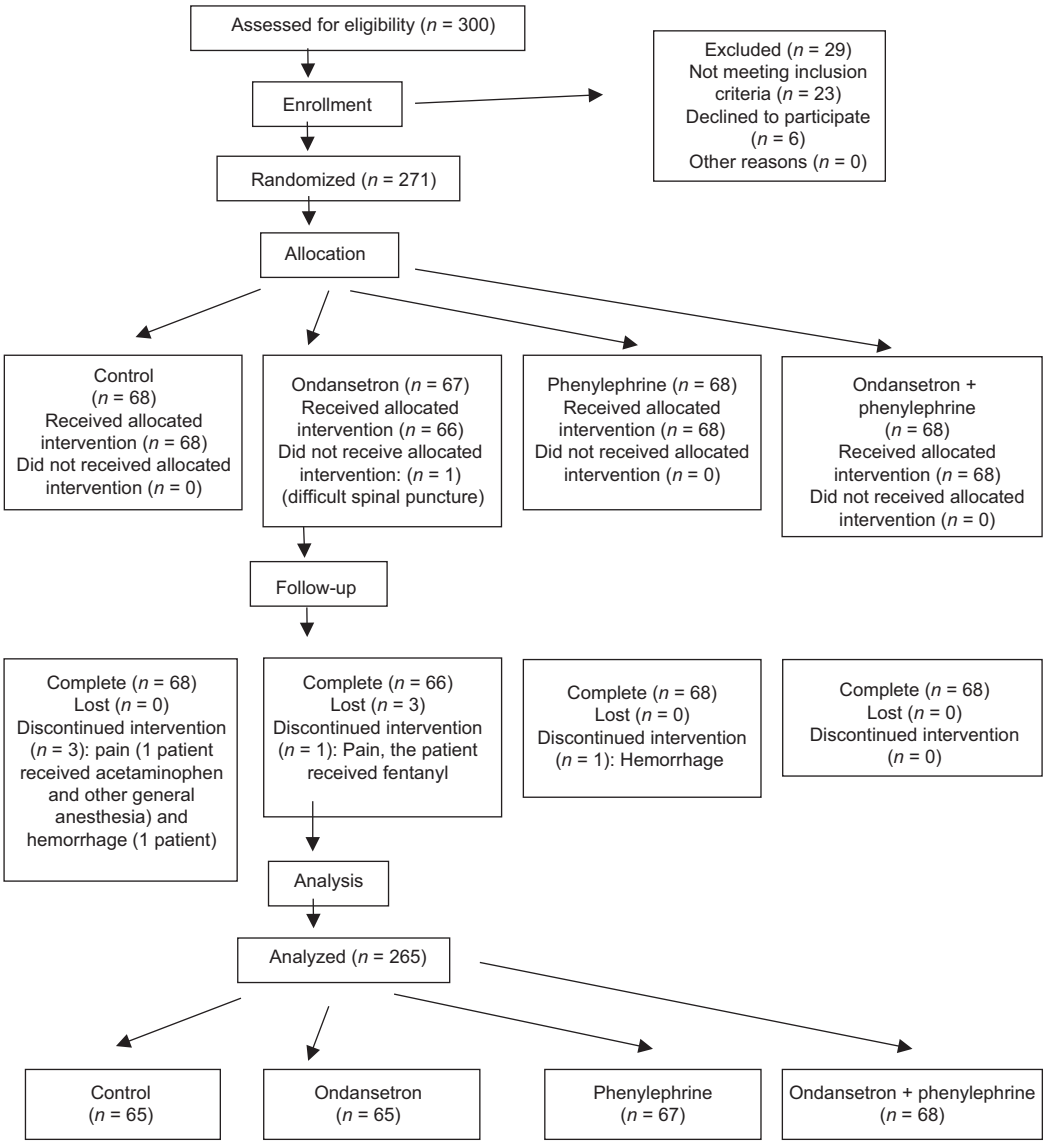
A total of 300 women were recruited into the study [Consort Flow Diagram]: 29 excluded, 271 randomized, and finally, 265 cases were considered valid (control group (n = 65), O group (n = 65), P group (n = 67), and OP group (n = 68)).

Demographic and anesthetic data are presented in Table 1. No differences between groups were observed in obstetric data including gestational age, previous pregnancies, and cesarean deliveries excepting the times from skin incision to fetal extraction and the total time.

Table 1: Demographic and anesthetic data

	Control (n=65), n (%)	Ondansetron (n=65), n (%)	Phenylephrine (n=67), n (%)	OP (n=68), n (%)	P
Age (years)	35.6±5.0	34.6±4.3	34.1±4.6	35.5±5.4	0.214
Weight (kg)	75.6±11.5	75.7±12.6	73.3±12.2	73.3±11.9	0.466
Height (cm)	161.9±5.8	161.2±5.8	162.5±6.0	161.9±6.2	0.638
BMI (kg/m^2)	28.9±4.6	29.2±5.0	27.8±4.8	28.0±4.3	0.227
Dural puncture to skin incision (min)	10.3±2.5	10.8±2.1	10.0±1.9	9.9±2.7	0.164
Skin incision to fetal extraction (min)	11.8±3.6	8.3±2.8	9.4±3.7	10.3±4.3	0.0001
Total time (min)	49.0±10.2	40.5±6.7	46.4±8.6	47.5±10.4	0.0001
Sensory block height 15 min after intrathecal injection					
T3-T4	44 (67.7)	42 (64.6)	32 (47.7)	35 (51.5)	0.052
T5-T7	21 (32.3)	23 (35.4)	35 (52.3)	33 (48.5)	

Data are mean±SD or n (%). SD: Standard deviation; BMI: Body mass index; OP: Ondansetron plus phenylephrine



Consort Flow Diagram: Consort flow diagram: distribution of patients

Table 2 shows the hypotensive events and the need of ephedrine, phenylephrine, and atropine. The patients who received ondansetron had differences in the number of patients with hypotension at O versus P groups ($P = 0.005$), O versus OP groups ($P = 0.024$) but no differences comparing O versus control groups ($P = 0.482$) and OP versus P groups ($P = 0.487$). As a single patient could have more than one hypotensive episode, we also analyzed the percentage of time points with systolic hypotension. The patients who received ondansetron had differences at O versus P groups ($P = 0.003$), O versus control groups ($P = 0.010$) but no differences comparing O versus OP groups ($P = 0.461$) and OP versus P groups ($P = 0.059$).

Hemodynamics is shown in Figure 1 (maternal arterial pressures). Variations from baseline are exposed in Figure 2 (SBP) and Figure 3 (MAP) and the adverse effects in Table 3. There were significant differences ($P < 0.05$) between the groups in HR at 1 min to end time points and no differences in SaO_2 values.

There were no differences between groups P and OP in the following fetal data (mean ± SD): weight (3.0 ± 0.4 kg), Apgar score at the 1st min (8.8 ± 0.6) and 5th min (9.9 ± 0.3), pH (7.32 ± 0.05), PCO_2 (50.1 ± 8.9 mm Hg), PO_2 (18.5 ± 8.9 mm Hg), and HCO_3^- (23.1 ± 2.4 mEq/L). The resuscitation was type I (no need of reanimation) and II (oxygen mask): 76.5% group OP versus 98.5% group P and 23.5% group OP versus 1.5% group P, respectively ($P = 0.0001$). There were no neonates with resuscitation type III (intermittent positive pressure oxygen therapy), IV (endotracheal intubation), or V (cardiac massage and/or drugs).

Table 2: Hypotension and requirements of drugs

	Control (*n*=65), *n* (%)	Ondansetron (*n*=65), *n* (%)	Phenylephrine (*n*=67), *n* (%)	OP (*n*=68), *n* (%)	*P*
Number of patients with hypotension	33 (50.8)	29 (44.6)	14 (20.9)	17 (25.0)	0.0001
Percentage of time points with systolic hypotension	17.4±23.7	8.7±13.7	2.1±4.9	6.5±14.4	0.0001
Requirements of					
Ephedrine	21 (32.3)	11 (16.9)	12 (17.9)	5 (7.4)	0.003
Phenylephrine	5 (7.7)	2 (3.1)	0	0	0.017
Atropine	0	0	17 (25.4)	13 (19.1)	0.0001

Data are mean±SD or *n* (%). SD: Standard deviation; OP: Ondansetron plus phenylephrine

Table 3: Adverse effects

	Control (*n*=65), *n* (%)	Ondansetron (*n*=65), *n* (%)	Phenylephrine (*n*=67), *n* (%)	OP (*n*=68), *n* (%)	*P*
Electrocardiogram changes	0	0	0	0	1
Nausea	7 (10.8)	7 (10.8)	4 (6.0)	4 (5.9)	0.564
Vomiting	2 (3.1)	0	1 (1.5)	2 (2.9)	0.530
Pruritus	0	4 (6.2)	1 (1.5)	1 (1.5)	0.097
Skin flushing	6 (9.2)	12 (18.5)	4 (6.0)	0	0.001
Discomfort	5 (7.7)	4 (6.2)	4 (6.0)	5 (7.4)	0.973

Data are *n* (%). OP: Ondansetron plus phenylephrine

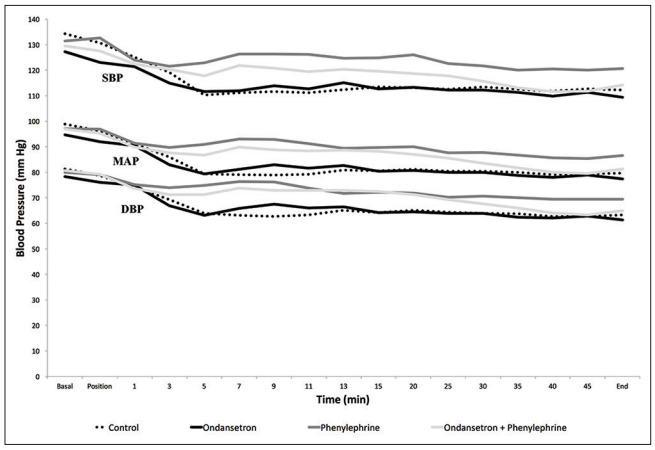


Figure 1: Maternal blood pressure. Significant differences (*P* < 0.05) between the groups in systolic blood pressure, diastolic blood pressure, and mean arterial pressure at 5 min to end time points

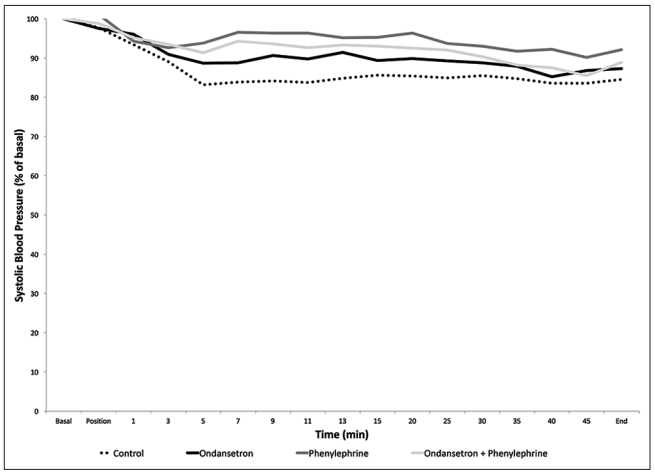


Figure 2: Variation in systolic blood pressure compared to baseline. Significant differences (*P* < 0.05) between groups in the variation from baseline of systolic blood pressure at 5 min to 40 min

Discussion

Infusion of phenylephrine is one of the most effective methods for preventing maternal hypotension and intraoperative nausea and vomiting.[12,13] The most usual initial bolus dose of phenylephrine for the treatment of postspinal hypotension in patients undergoing elective cesarean delivery is 100 μg although some authors recommend higher doses (125–150 μg).[14] However, we prefer a prophylactic infusion of phenylephrine, which has been used previously with doses ranging from 10 to 100 μg/min. We administered 50 μg/min because this rate appears to balance the risk of hypotension versus reactive hypertension.[13,15,16]

Various studies have reported that intravenous ondansetron (8 mg in the general population[17] and 4 mg in obstetric patients[18]) could attenuate hypotension in patients receiving SA. Ortiz-Gómez *et al*.[9] found that prophylactic ondansetron did not influence the incidence of maternal hypotension following SA for elective cesarean delivery.

Our results indicated that prophylactic ondansetron (group O) had no effect on the total number of patients with hypotension ($P = 0.482$) compared with control but has a certain protective effect diminishing the number of hypotensive events (1.4 ± 2.2 vs. 2.9 ± 4.0, $P = 0.011$), the percentage of time points with systolic hypotension per patient (8.7% in the O group vs. 17.4% in the control group, respectively, $P = 0.012$), and the number of patients requiring supplementary boluses of ephedrine ($P = 0.042$).

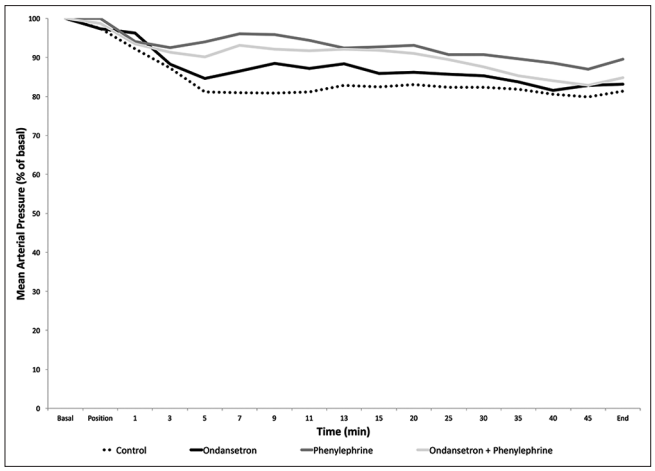


Figure 3: Variation in mean blood pressure compared to baseline. Significant differences ($P < 0.05$) between groups in the variation from baseline of mean arterial pressure at 5 min to end time points

Hence, prophylactic ondansetron appears to reduce significantly the severity of maternal hypotension and could reduce the possibility of maternal and fetal morbidity, but the combination of ondansetron and phenylephrine does not improve the hemodynamic in this clinical trial compared with phenylephrine infusion only.

Our results are similar to those reported by Trabelsi *et al*.[19] However, it should be noted that different hypotension's management protocols were used. They found that prophylactic ondansetron (4 mg) had a significant effect on the incidence of hypotension in healthy parturient undergoing SA for elective cesarean delivery. They suggested that ondansetron may act at cardiac level (enhancing contractility and efficiency) and at vascular level (stable systemic vascular resistances) through vascular and/or medullar specific receptors. This is an interesting hypothesis and could be the reason that explains the lack of differences between the groups of phenylephrine and phenylephrine plus ondansetron, found in this study.

Concerning the adverse effects, those most frequently related to ondansetron are diarrhea, 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 ischemia.[9] We only found statistical differences in the incidence of skin flushing in the O group (18.5%) ($P = 0.001$), but we cannot attribute it to ondansetron, because the OP group had no patients with skin flushing.

Finally, despite the previously reported absence of significant neonatal acid–base status changes when phenylephrine was administered,[13,20] we verified this affirmation in all patients receiving phenylephrine. Trabelsi *et al*. also reported that ondansetron can be helpful to improve metabolic and vital parameters of newborns.[19]

Conclusions

A 50 μg/min phenylephrine infusion reduces by 50%, the incidence of maternal hypotension in healthy women undergoing SA for elective cesarean delivery compared with placebo, but infusions of phenylephrine are still not routine in our environment. Prophylactic ondansetron 8 mg might be considered in this situation, because although it does not reduce the incidence of maternal hypotension, diminishes its severity, reducing the number of hypotensive events per patient by 50%.

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Conflicts of interest

There are no conflicts of interest.

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