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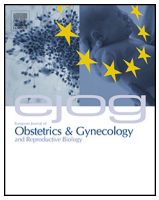

Carbetocin versus oxytocin for prevention of postpartum hemorrhage: a randomised controlled trial

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ABSTRACT

Objective: Postpartum hemorrhage (PPH) is the leading cause of maternal death worldwide. Prophylactic uterotonics are effective in reducing PPH, and the drug of choice is oxytocin. Carbetocin, a newer analog of oxytocin, has greater biological effect and longer half-life. It is also more heat-stable than oxytocin, which is of critical importance to resource poor settings. In this study, we compare the effectiveness of carbetocin with oxytocin.

Study design: A randomised controlled trial in a tertiary maternity hospital in Mexico. We randomised 1210 pregnant women with at least one risk factor for PPH to Carbetocin 100 mcg as a single intravenous bolus compared with oxytocin 20IU as a 6-h infusion, administered immediately after childbirth. The primary outcome was PPH more than 500 ml. Secondary outcomes were the volume of blood loss, severe PPH (blood loss > 1000 ml) and need for additional uterotonics.

Results: There was a reduction in PPH with carbetocin when compared with oxytocin (18.4% vs. 25.7%; RR = 0.67, 95% CI: 0.54–0.83; NNT 14, 95% CI: 8–37). The mean blood loss was less with carbetocin when compared with oxytocin (366 ± SE 7.8 ml vs. 400 ± SE 7.6 ml, $p < 0.001$). The incidence of severe PPH did not differ (1.3% vs. 1.6%; RR = 1.15, 95% CI 0.42–3.16), but fewer participants receiving carbetocin required additional uterotonics (1.5% vs. 5.8%; adjusted RR = 0.3; 95% CI 0.14–0.61).

Conclusion: This is the largest trial comparing carbetocin with oxytocin. An updated meta-analysis, combining the results from six randomised trials, including this study, found that carbetocin was associated with a reduction of PPH compared with oxytocin.

Contents

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Introduction

Improving maternal health is one of the eight Millennium Development Goals. Since 1990, maternal deaths worldwide have dropped by 47%, and yet an estimated 287,000 women died in childbirth in 2010, and maternal mortality levels are far away from the 2015 target [1]. Postpartum hemorrhage (PPH) remains the leading cause of maternal death worldwide, accounting for up to 25% of all deaths [2]. Even when death is avoided, the need for blood transfusion and the risk of morbidity are high [3]. The primary cause of PPH is uterine atony, which accounts for 75% of cases [4]. The use of uterotonic drugs in the management of the third stage of labor reduces the amount of bleeding, the need for blood transfusion and maternal deaths [5,6].

Oxytocin is currently the drug of choice for the prevention of PPH, recommended by WHO guidelines and national policies worldwide [6]. However, oxytocin is unstable to heat, and thus requires a 'cold-chain' from the manufacturer to the bedside, presenting logistical and storage difficulties in many poor resource settings. Furthermore, oxytocin has a short biological half-life, necessitating an intravenous infusion if prolonged uterotonic effect is needed, as it is often the case with women at high risk of PPH.

Carbetocin (Lonactene®/Pabal®/Duratocin®, Ferring Pharmaceuticals) is a synthetic oxytocin analog with a biological activity 10 times that of the parent drug [7]. It has 4–10 times longer average half-life when compared with oxytocin [7]. Therefore, it is administered as a single dose of 100 mcg, either IV or IM, thus eliminating the need for infusion and is more heat-stable compared with oxytocin, which is of particular importance in resource-poor settings [7].

There are four randomised trials comparing carbetocin with oxytocin, the largest of which recruited 659 women. These trials demonstrated the powerful uterotonic effects of carbetocin, with statistically significant reduction in the need for additional uterotonics. They also indicated a reduction in the incidence of PPH; however, this finding did not reach statistical significance even when the four studies were combined in a Cochrane meta-analysis [8]. As a result, the Cochrane reviewers called for additional large randomised trials to evaluate the effect of carbetocin against oxytocin. The aim of this randomised trial was to compare the effectiveness of a single dose of carbetocin (100 mcg, IV) against oxytocin infusion (20 IU in 1000 ml glucose, IV, over 6 h) for preventing PPH in women with at least one risk factor for PPH.

Materials & methods

Design, setting and participants

This is a two-arm parallel design randomised controlled trial. We recruited women delivering at one of the five hospitals considered as a high specialisation medical unit in Mexico City (Luis Castelazo Ayala Gynaecology and Obstetrics Hospital), which is a tertiary care centre of the Mexican Social Security Institute with 13,000 deliveries per year. Eligible participants were pregnant women from 18 to 35 years of age with at least one risk factor for PPH (obstetric bleeding history, previous caesarean section, retained placenta, multiparity, fetal macrosomia, induction of labor, multiple pregnancy, instrumental delivery or undergoing caesarean section). The inclusion criteria required that eligible women had attended at least 5 antenatal visits at the hospital. Patients with either incomplete clinical records or medical assessments were excluded.

Intervention and comparison

Carbetocin was given as a single IV bolus at a dose of 100 mcg. Oxytocin was given as a 6-h infusion at a dose of 20 IU in 1000 ml 5% glucose. The uterotonic drug was administered immediately after childbirth. In concordance with Mexican Guidelines for obstetric hemorrhage; the Mexican Social Security Institute (IMSS) uses a 6 h infusion of 20 IU of oxytocin as the standard of care for PPH prophylaxis as also recommended by Northern American guidelines [9,10]. Recently carbetocin has been introduced as a new uterotonic option.

Outcome measures

The primary outcome was PPH, defined as blood loss >500 ml. Secondary outcomes included average volume of blood loss (ml), incidence of severe PPH (>1000 ml), need for uterine massage, use of additional uterotonic drugs (number and type), need for transfusion of blood products, volume replacement with crystalloids or colloids, change in maternal hamodynamic variables (blood pressure and pulse assessed at 1, 2, and 24 h after birth), variation in hemoglobin and hematocrit levels at 24 h postpartum versus levels before delivery.

The volume of blood loss after delivery was measured in a strict and standardized manner. In women delivering vaginally, a nylon bag was placed below the buttocks for blood collection after birth and its content was quantified using a graduated cylinder once labor care was concluded. In those undergoing caesarean section, all dressings, surgical towels, and collecting bottles were replaced once the placenta was expelled in order to quantify blood loss from that moment onward.

Trial procedures

The trial protocol was reviewed and approved by the local research committee (IMSS R-2011-3606-1) and registered with CTMS on the 10th of January 2011. Eligible women were approached and offered study information at the time of admission to the hospital. Those who wished to participate provided written consent. The random allocation to either treatment group was made on a 1:1 ratio. For allocation of the participants, a central computer-generated list of random numbers was used, and the allocation sequence was concealed from the researchers and care providers. After the participants were assigned to carbetocin or

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oxytocin, participants and healthcare providers were unblinded to the assigned groups because of the nature of the two interventions. Specifically, it was deemed unethical to infuse a placebo drug for 6 h in the carbetocin group. Whereas participants and healthcare providers were aware of the allocated group, outcome assessors and data analysts were kept blinded to the allocation. The outcome assessment, data collection and validation were undertaken by an external blinded assessor through a clinical research organisation (Infinity Clinical Research).

Clinical progression was monitored during childbirth and up to 24 h following delivery; changes in vital signs were recorded. Whenever uterine atony was suspected, use of strategies such as uterine massage, additional doses of uterotonic drugs, and administration of crystalloid, colloids and blood products were allowed according to the attending physician's judgment.

Statistical analysis was performed using STATA, version 12.1 (StataCorp LP, Texas, USA). In order to detect a 7.5% difference in PPH with 90% power, and 5% type I error rate, while allowing 10% attrition for possible losses and exclusions, a sample size of 600 subjects per group was estimated. Analysis was by intention to treat. Chi-squared test was used for dichotomous and Mann Whitney *U* test for continuous variables. Relative risk estimation was performed with a log-binomial regression and planned adjustment for random imbalances in the PPH risk factors of the assigned groups at the conventional significance level ($p < 0.05$). The pre-specified subgroup was the mode of delivery (vaginal birth or caesarean section).

Results

Fig. 1 shows the participant flow in the trial. We enrolled 1222 pregnant women from January 2011 to November 2011, of whom 1214 were randomised in to the trial. In four women, the documentation went missing and these women were excluded from further analysis, leaving 1210 with available follow-up data for intention-to-treat analysis. Of those analysed, 602 received carbetocin and 608 oxytocin.

The demographic and baseline clinical characteristics of the participants are shown in Table 1. The mean age of women at delivery was 27.6 years, the median gestational age was 39 weeks (IQR 37.6 to 39.6) and parity was 1 (IQR 0 to 2). The majority of the deliveries was by caesarean section ($n = 1018$, 84.2%). The pre-delivery mean hemoglobin was 129 ± SD 13 g/l and 33 women were anaemic before delivery (2.7%, defined as hemoglobin <105 g/l).

Intention to treat analysis for the primary outcome found that there was a reduction in PPH (blood loss >500 ml) with carbetocin when compared with oxytocin (18.4% versus 25.7%; unadjusted RR = 0.71, 95% CI 0.58 to 0.89; adjusted RR = 0.67, 95% CI 0.54 to 0.83; NNT 14, 95% CI 8 to 37; Table 2).

For the secondary outcomes, the mean blood loss was less with carbetocin when compared with oxytocin (unadjusted mean difference = 34.1, 95% CI 55.5 to 12.7, $p = 0.001$; adjusted mean difference = 47.8, 95% CI 26.7 to 68.8, $p < 0.001$). The incidence of blood transfusion was similar in the two groups (1.7% versus 2.6%; unadjusted RR = 0.63, 95% CI 0.29 to 1.38; adjusted RR = 0.67, 95%

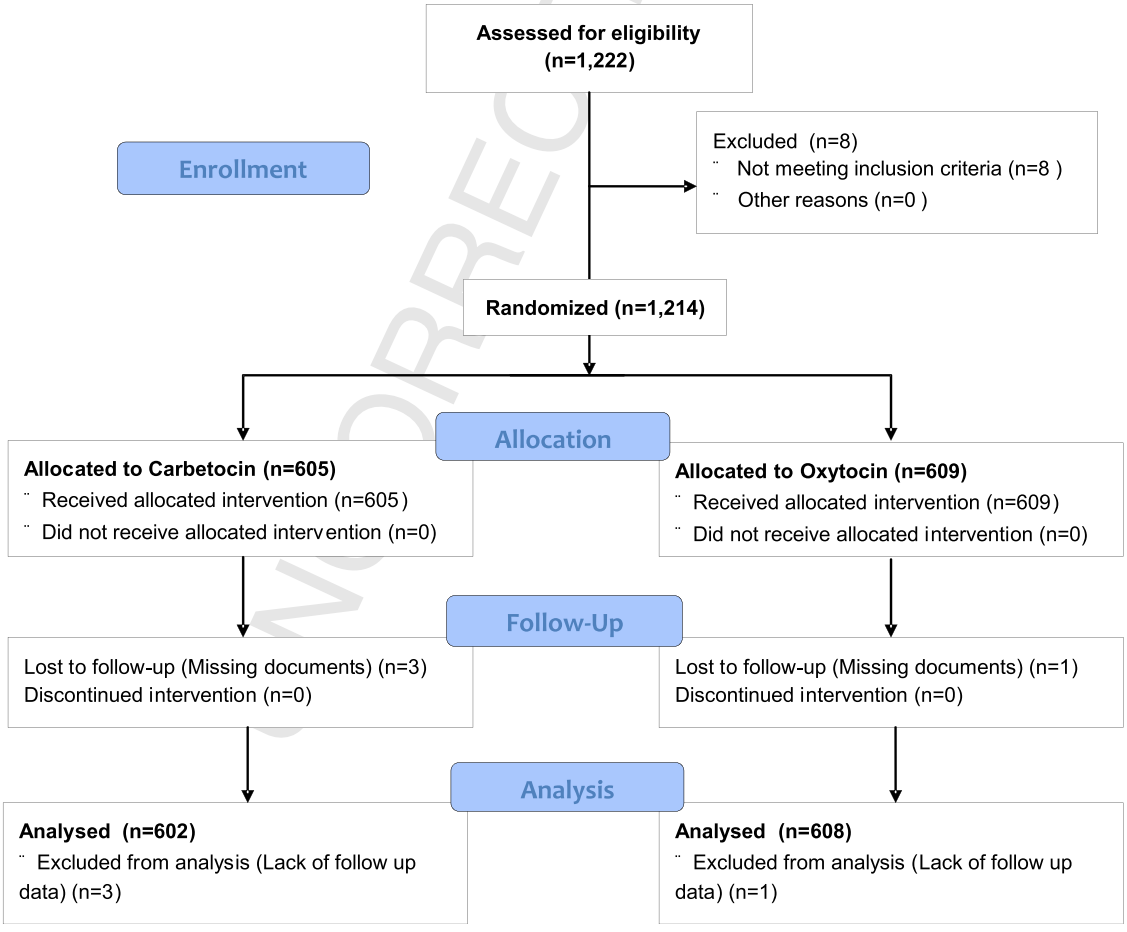

Fig. 1. CONSORT flowchart of study recruitment.

Table 1
Demographic and obstetric data for the study population.

		Carbetocin ($n=602$)	Oxytocin ($n=608$)
Age (years)		27.9 ± 5.3	27.2 ± 5.1
Gestational age at delivery (weeks)		38 ± 2.5	38.5 ± 1.8
Nulliparity		222 (36.9)	228 (37.5)
Grand multiparity (≥4 previous deliveries)		9 (1.5)	9 (1.5)
Previous PPH		7 (1.2)	3 (0.5)
Previous caesarean section		301 (50)	252 (41.6)
Induction of labor		144 (23.9)	230 (37.8)
Large for gestational age (>90th centile)		28 (4.6)	21 (3.4)
Multiple pregnancy		24 (4)	5 (0.8)
Duration of labor (min)		590.4 ± 573.9	473.5 ± 411.9
Route of delivery (index pregnancy)	Vaginal Delivery	68 (11.3)	123 (20.3)
	Caesarean section	534 (88.7)	484 (79.7)
Hemoglobin (g/l)		128 ± 12	129 ± 13
Hematocrit (%)		39.1 ± 3.4	39.4 ± 3.8
Before-birth systolic blood pressure (mm Hg)		114.3 ± 10.2	113.9 ± 11.3
Before-birth diastolic blood pressure (mm Hg)		73.7 ± 7.6	73.7 ± 8.1
Before-birth maternal pulse (beats per minute)		76.8 ± 6.5	78.1 ± 6.4

Q6 * Numbers are mean ± Standard Deviation for continuous variables and numbers with percentages in parentheses for dichotomous. PPH: postpartum hemorrhage.

CI 0.31 to 1.38). The incidence of major PPH, defined as blood loss more than 1000 ml, did not differ between the two groups (1.3% versus 1.6%; unadjusted RR = 1.15, 95% CI 0.42 to 3.16), but given the low number of cases it was not possible to adjust the risk for random imbalances on the risk factors. Participants receiving carbetocin required fewer additional treatments such as uterine massage (1.8% versus 4.3%; unadjusted RR = 0.43, 95% CI 0.21 to 0.86; adjusted RR = 0.43, 95% CI 0.21 to 0.86), use of additional uterotonics (1.5% versus 5.8%; unadjusted RR = 0.26, 95% CI 0.13 to 0.54; adjusted RR = 0.3; 95% CI 0.14 to 0.61), and fluid resuscitation (20.6% versus 24.2%; unadjusted RR = 0.86, 95% CI 0.69 to 1.05; adjusted RR = 0.77, 95% CI 0.62 to 0.95).

The use of carbetocin was associated with marginally higher hemoglobin (unadjusted mean difference = 2.1, 95% CI 0.2 to 4, $p = 0.03$; adjusted mean difference = 2.1, 95% CI 0.2 to 4, $p = 0.03$) and hematocrit (unadjusted mean difference = 0.62, 95% CI 0.07 to 1.17, $p = 0.027$; adjusted mean difference = 0.62, 95% CI 0.07 to 1.17, $p = 0.03$) levels at 24 h postpartum compared with oxytocin. No adverse effects were observed in either group during the study and no significant differences of blood pressure and pulse were recorded at 2 h from delivery (Table 2).

In the subgroup analysis by mode of delivery, we found consistent findings for both the caesarean group and the vaginal birth group, but for the caesarean group, the findings were more precise as this group had the larger sample size (84.2% of women randomised; Table 3). For women undergoing caesarean section the incidence of the primary outcome, PPH > 500 ml, was 19.8% in the carbetocin group compared to 29.3% in the oxytocin group ($p < 0.001$). However, for women undergoing vaginal delivery the incidence of PPH was 7.3% in the carbetocin group compared with 11.4% in the oxytocin arm ($p = 0.381$), but the power for this comparison was only 19%.

Discussion

Main findings

This trial is the largest randomised trial to date to compare carbetocin with oxytocin. It found that carbetocin (100 mcg, IV bolus) was more effective than a standard oxytocin infusion of 20 IU over 6 h for the prevention of PPH in patients with at least one risk factor for such complication. We also found that women having carbetocin had less blood loss and reduced need for additional uterotonics and fluid resuscitation, with higher hemoglobin and hematocrit levels when compared with the oxytocin group. Most women in this trial were delivered by caesarean section and within this subgroup the above findings were consistent and statistically significant; in the vaginal delivery group, the findings were consistent, but given the small sample size for this group, the findings did not reach statistical significance.

Table 2
Outcome for the comparison of carbetocin versus oxytocin for the prevention of post partum hemorrhage.

Characteristic n (%)	Carbetocin ($n=602$)	Oxytocin ($n=608$)	Unadjusted relative risk or mean difference (95%CI)	Adjusted† relative risk or mean difference (95%CI)
Blood loss (ml)	366 ± 7.8	400 ± 7.6	34.1 (55.5 to 12.7), $p=0.001$	47.8 (26.7 to 68.8), $p<0.001$
PPH > 500 ml	111 (18.4)	156 (25.7)	0.71 (0.58 to 0.89), $p=0.002$	0.67 (0.54 to 0.83), $p<0.001$
PPH > 1000 ml	8 (1.3)	7 (1.6)	1.15 (0.42 to 3.16), $p=0.78$	Not estimable
Additional uterotonics	9 (1.5)	35 (5.8)	0.26 (0.13 to 0.54), $p<0.001$	0.3 (0.14 to 0.61), $p=0.001$
Blood transfusion	10 (1.7)	16 (2.6)	0.63 (0.29 to 1.38), $p=0.249$	0.67 (0.31 to 1.47), $p=0.317$
Uterine massage	11 (1.8)	26 (4.3)	0.43 (0.21 to 0.86), $p=0.017$	0.43 (0.21 to 0.86), $p=0.017$
Fluid resuscitation	124 (20.6)	147 (24.2)	0.86 (0.69 to 1.05), $p=0.136$	0.77 (0.62 to 0.95), $p=0.016$
SBP (mmHg) 2 h	114 ± 12	113.8 ± 11.8	0.27 (1.1 to 1.6), $p=0.691$	0.09 (1.24 to 1.43), $p=0.89$
DBP (mmHg) 2 h	72 ± 8.7	72.5 ± 8.2	0.43 (−0.53 to 1.39), $p=0.377$	−0.59 (−1.55 to 0.37), $p=0.226$
Heart rate (bpm) 2 h	75.6 ± 5.9	75.9 ± 6	0.29 (−0.38 to 0.96), $p=0.395$	−0.25 (−1.26 to 0.77), $p=0.635$
Hemoglobin (g/dl) 24 h	117 ± 14	115 ± 19	2.1 (0.2 to 4), $p=0.03$	2.1 (0.2 to 4), $p=0.03$
Hematocrit (%) 24 h	35.7 ± 3.7	35.1 ± 5.8	0.62 (0.07 to 1.17), $p=0.027$	0.62 (0.06 to 1.17), $p=0.03$

† Adjusted for history of previous PPH, previous caesarean section, induction of labor and duration of labor in index pregnancy and mode of delivery.

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Table 3
Subgroup analysis for primary and secondary outcomes by mode of delivery.

Characteristic *n* (%)		Carbetocin (*n* = 602)	Oxytocin (*n* = 608)	Relative Risk or Mean Difference (95%CI), *p* value
Blood loss (ml)	Vaginal	273.1 ± 15.9	308.8 ± 16.9	−35.7 (−86.3 to 14.8), *p* = 0.165
	Caesarean	377.8 ± 8.5	422.6 ± 8.2	−44.8 (−66 to −21.6), *p* < 0.001
PPH > 500 ml	Vaginal	5 (7.3)	14 (11.4)	0.65 (0.24 to 1.72), *p* = 0.381
	Caesarean	106 (19.8)	142 (29.3)	0.68 (0.54 to 0.84), *p* < 0.001
PPH > 1000 ml	Vaginal	0	1 (0.8)	0.6 (0.02 to 14.51), *p* = 0.753
	Caesarean	8 (1.5)	6 (1.2)	1.21 (0.42 to 3.46), *p* = 0.724
Additional uterotonics	Vaginal	1 (1.5)	7 (5.7)	0.26 (0.03 to 2.06), *p* = 0.201
	Caesarean	8 (1.5)	28 (5.8)	0.26 (0.12 to 0.56), *p* = 0.001
Blood transfusion	Vaginal	1 (1.5)	3 (2.4)	0.6 (0.06 to 5.67), *p* = 0.659
	Caesarean	9 (1.7)	13 (2.7)	0.63 (0.27 to 1.45), *p* = 0.277
Uterine massage	Vaginal	2 (2.9)	5 (4.1)	0.72 (0.14 to 3.63), *p* = 0.694
	Caesarean	9 (1.7)	21 (4.3)	0.39 (0.18 to 0.84), *p* = 0.016
Fluid resuscitation	Vaginal	3 (4.4)	2 (2.4)	1.81 (0.38 to 8.72), *p* = 0.46
	Caesarean	121 (22.7)	144 (29.8)	0.76 (0.62 to 0.94), *p* = 0.01
SBP (mmHg) 2 h	Vaginal	110.5 ± 12	110.6 ± 9.3	0.1 (−2.3 to 3.2),*P* = 0.554
	Caesarean	114.5 ± 11.9	114.6 ± 12.2	0.09 (−1.4 to 1.6), *p* = 0.842
DBP (mmHg) 2 h	Vaginal	70.2 ± 8.8	71.2 ± 6.9	0.98 (−1.3 to 3.2), *p* = 0.406
	Caesarean	72.3 ± 8.7	72.8 ± 8.6	0.53 (−0.5 to 1.59), *p* = 0.431
Heart rate (bpm) 2 h	Vaginal	77.4 ± 5.4	78.1 ± 6.6	0.7 (−1.1 to 2.5), *p* = 0.562
	Caesarean	75.4 ± 6	75.4 ± 5.7	−0.02 (−0.7 to 0.7), *p* = 0.913
Hemoglobin (g/dl) 24 h	Vaginal	11.7 ± 1.4	11.4 ± 2.8	−0.2 (−1 to 0.5), *p* = 302
	Caesarean	11.7 ± 1.4	11.5 ± 1.6	−0.2 (−0.4 to −0.004), *p* = 0.147
Hematocrit (%) 24 h	Vaginal	35.5 ± 3.7	34.5 ± 8.4	−1 (−3.1 to 1.2), *p* = 0.346
	Caesarean	35.7 ± 3.7	35.3 ± 4.9	−0.5 (−1 to 0.05), *p* = 0.26

Q7 ¶ Data presented as median (quartiles). *Statistically significant differences. CI: confidence interval, PPH: postpartum hemorrhage, RR: relative risk. Volume replacement includes intravenous fluids and blood products.

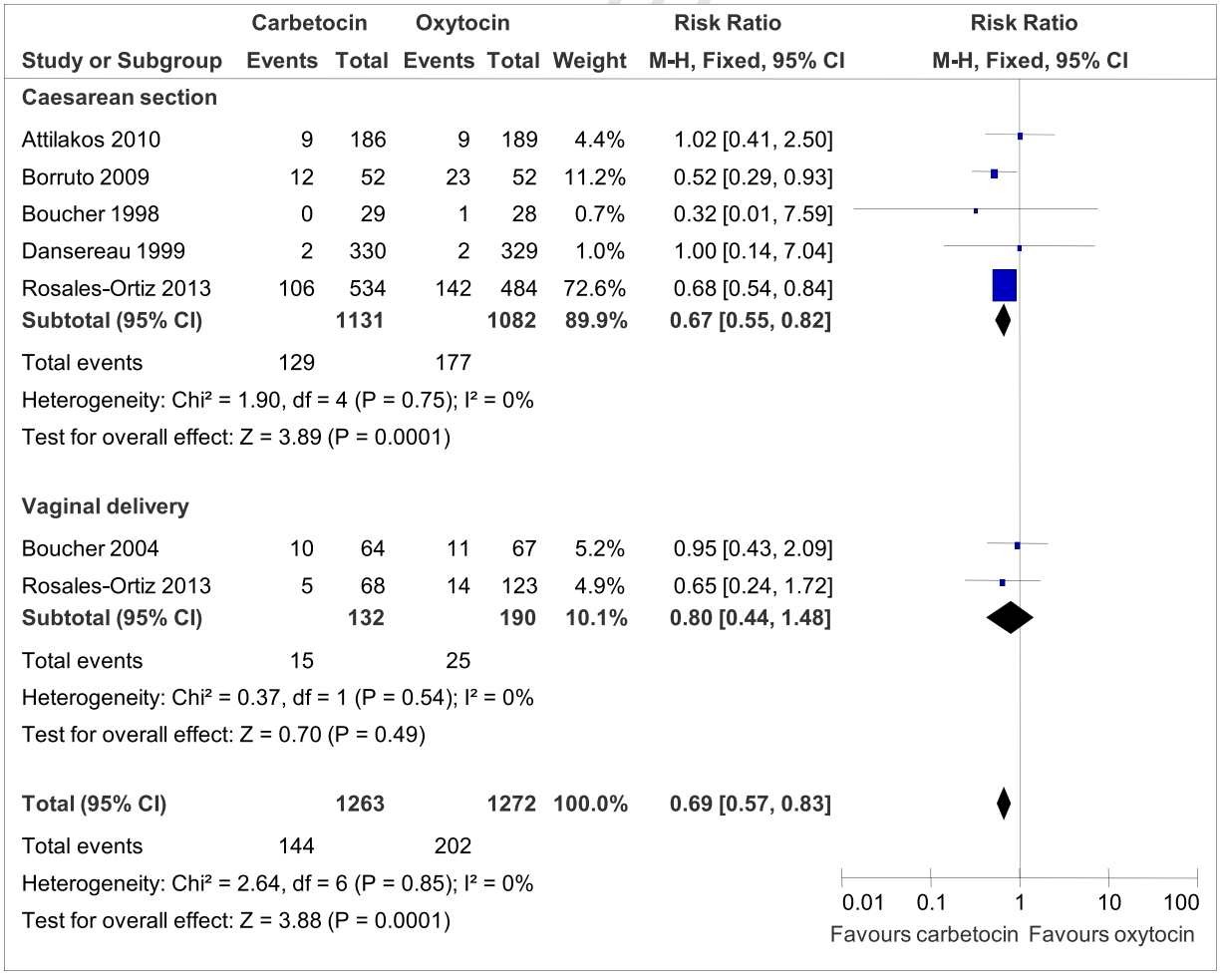

Fig. 2. Meta-analysis of randomised trials of carbetocin versus oxytocin showing the outcome of PPH > 500 ml. MH = Mantel–Haenszel homogeneity test.

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Strengths and limitations

The main strength of this trial is its high quality within the pragmatic context. The study was designed according to the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and national regulations for clinical research. The study's size provides reliable findings with narrow confidence intervals that can be applied in clinical practice. There were no violations to the protocol and all women received the assigned interventions. The loss to follow up was very small (0.3%). However, a pragmatic approach had to be taken for comparing a bolus of carbetocin administered over 1 min with an oxytocin infusion of 6 h. The infusion was preferred as it has a safer haemodynamic profile and offers longer duration of uterotonic treatment and hence, comparable with carbetocin. However, it was considered unethical to administer placebo infusions for 6 h, limiting the mobility of patients in the postpartum period and increasing their risk of thromboembolism. As a result, blinding was not implemented. There were no obvious clinician preconceptions about the efficacy of the two agents, and participants might have believed that an infusion was of superior efficacy, thus favoring oxytocin. We tried to limit assessment bias by blinding the outcome assessors and data analysts as those were undertaken by an external blinded CRO (Infinity Clinical Research). We therefore believe that lack of blinding is unlikely to have introduced bias. We did not use minimisation or stratification randomisation to avoid imbalance in the baseline characteristics it was considered that in a trial of this size, randomness would be expected to create balanced groups. However, imbalances emerged in multiple pregnancy rate, induction of labor rate, history of previous caesarean deliveries rate and route of delivery and we adjusted the estimates for these imbalances as planned in the protocol.

Interpretation

To put this randomised trial and its results into context; we undertook a meta-analysis of all randomised controlled trials comparing carbetocin with oxytocin for the prevention of PPH. This is an update of a recent Cochrane review that included all published trials up to March, 2011 [8]. We included 5 randomised trials [11–15], in addition to this study, with a total of 2535 women. The overall relative risk reduction of PPH more than 500 ml is consistent with the effect found in this study (RR = 0.69, 95% CI 0.57 to 0.83; Fig. 2) with no heterogeneity between the studies (I^2 = 0%). In a subgroup analysis with the five studies in which the comparison was evaluated in women undergoing caesarean section (n = 2213), meta-analysis found a relative risk reduction of 33% (RR = 0.67, 95% CI 0.55 to 0.82). There were only two studies in the vaginal birth sub-group, with a combined total of only 322 women randomised; meta-analysis of these two studies found a statistically non-significant reduction in PPH with carbetocin when compared with oxytocin (RR 0.8, 95% CI 0.44 to 1.44). The Cochrane meta-analysis [8], which had previously shown a statistically non-significant effect favoring carbetocin over oxytocin for caesarean section (RR 0.66, 95% CI 0.42 to 1.06), now shows significant difference in the primary outcome of PPH.

The prolonged uterine activity of carbetocin is a great advantage over oxytocin in preventing PPH. It is a long-acting synthetic analog of oxytocin and has a half-life of about 40 min, which is 4–10 times longer than that of oxytocin [7]. It can also be administered as an intramuscular injection. Carbetocin reaches peak plasma concentrations in less than 30 min, has 80% bioavailability and it has a longer duration of action compared with intravenous administration [7]. Oxytocin has been the standard uterotonic agent for the prevention of PPH [6]. However, the use of oxytocin as part of the active management of the third stage of labor is not completely risk-free. An oxytocin bolus can cause an increase in heart rate and a decrease in mean arterial blood pressure [16]. The intensity of the change depends on the dose used [16]. The intravenous infusion was preferred for this study as it causes fewer side effects than a bolus. In this study no difference in haemodynamic effects was found between the two agents.

Conclusion

From this study and the updated meta-analysis evidence, is shown that carbetocin significantly reduces PPH compared with oxytocin for women undergoing caesarean section. The side effects profile is similar to oxytocin. Carbetocin should also be considered as an option over syntometrine, due to the lower likelihood of adverse effects [17]. However, more randomised evidence is needed for the effectiveness of carbetocin in women delivering vaginally.

Declaration of competing interests

"All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf and declare: Dr. Sergio Rosales declares that he has received speaking fees from Ferring and has provided lectures and consultancy without funding to Schering-Plough, Ferring and MSD; Professor Arri Coomarasamy states that he has received funding to attend conferences from Ferring and other pharmaceutical companies. The remaining authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Contribution to authorship

SRO, RAPA, RSH, MIYTC, FGLC, MACG conceptualised and designed the trial and data collection tools, monitored data collection for the whole trial and undertook recruitment of participants. SRO and IDG cleaned and analysed the data, and drafted and revised the paper. AC revised the paper and he is guarantor.

Ethical approval

The trial protocol was reviewed and approved by the local research committee (IMSS R-2011-3606-1).

Funding

Financial support for the submitted work is from Ferring Pharmaceuticals.

Condensation

This is the largest trial comparing carbetocin with oxytocin. An updated meta-analysis, finds that carbetocin is associated with a reduction of PPH compared with oxytocin.

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