Changes in Blood Pressure and Cardiac Output during Cesarean Delivery

The Effects of Oxytocin and Carbetocin Compared with Placebo

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ABSTRACT

Background: Little is known about maternal hemodynamics after Cesarean delivery. Uterine contractions may increase cardiac output. Oxytocin is the first-line treatment for uterine atony, although the effects of the long-acting oxytocin analogue carbetocin are comparable with that of oxytocin. The authors analyzed the effects of i.v. oxytocin 5 U, carbetocin 100 μg, and placebo on hemodynamics, uterine tone, adverse events, and blood loss after Cesarean delivery.

Methods: This was a randomized, double-blinded, placebo-controlled, parallel-group comparison of carbetocin and oxytocin after elective Cesarean delivery of singletons under spinal anesthesia (n = 76). Continuously measured invasive systolic arterial pressure was the primary outcome measure.

Results: The mean systolic arterial pressure decrease was 28 mmHg (95% CI, 22–34) after oxytocin and 26 mmHg (95% CI, 20–31) after carbetocin. The decrease was greatest after 80 (95% CI, 71–89) and 63 s (95% CI, 55–72), respectively (P = 0.006). The differences were nearly undetectable after 2.5 min, although the effect of carbetocin was slightly greater than placebo (P < 0.001). The group differences in systolic arterial pressure decreased over 5 min and were gone at 1 h. Heart rate and cardiac output increased in all three groups. Stroke volume increased after oxytocin and carbetocin but was unchanged after placebo.

Conclusions: The hemodynamic side effects of oxytocin 5 U and carbetocin 100 μg were comparable. The lack of an increase in stroke volume in the placebo group challenges the theory that uterine contraction causes autotransfusion of uterine blood, leading to an increase in preload.

What We Already Know about This Topic

- Rapid oxytocin infusion can acutely reduce blood pressure, but the effect of the long-acting oxytocin analog, carbetocin, has not been examined
- Uterine contraction after cesarean delivery is thought to increase venous return and could mitigate the effects of oxytocin agents

What This Article Tells Us That Is New

- In women at cesarean delivery, oxytocin, 5 U and carbetocin 100 μg, produced a similar 25% reduction in mean arterial pressure, lasting less than 2 min
- Cardiac stroke volume was not increased in women receiving placebo, despite good uterine tone, questioning the autotransfusion hypothesis

POSTPARTUM hemorrhage remains a major healthcare problem and is a leading cause of maternal mortality and morbidity in developing countries.[1] The leading cause of postpartum hemorrhage is uterine atony. Surprisingly, the incidence of severe bleeding caused by uterine atony has increased in recent years even in some developed countries.[2] Administration of medications that increase uterine tone is important for preventing postpartum hemorrhage, but the usual first-line treatment, oxytocin, may put the woman in labor at risk for hypotension due to its prominent vasodilation effect.[3–5] Slow administration of reduced dosages of oxytocin is recommended for healthy women, and caution is needed for women in labor who

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have cardiac diseases[6] or preeclampsia.[7–9] Carbetocin, a long-acting synthetic analogue of oxytocin with a half-life of approximately 40 min,[10] may reduce bleeding compared with oxytocin.[11] Although the recommended i.v. dosage is 100 μg, the least effective dosage has not been established.[10] Similarly, the equipotency of carbetocin compared with oxytocin is not known. The rate of adverse events for carbetocin is reported to be comparable[12] with that of oxytocin. Only one recent randomized study compared the hemodynamic effects of carbetocin 100 μg and oxytocin 5 U during Cesarean delivery.[13]

The increase in maternal cardiac output (CO) observed directly after Cesarean delivery may be due, in part, to autotransfusion of uterine blood into the maternal systemic circulation when the uterus contracts, a phenomenon that has been shown during uterine contractions at the time of vaginal delivery.[14] The immediate hemodynamic changes after Cesarean delivery are not as well understood as those after vaginal delivery, and previous studies have been unable to assess the impact of oxytocin receptor stimulation.[15,16] We hypothesized that the pharmacological effect of an oxytocin receptor agonist is more important than the physiologic increase in CO after the preload increase caused by uterine contractions.

Even under spinal anesthesia for the Cesarean delivery, the mothers may release endogenous oxytocin in response to the presence of the newborn baby. In theory, endogenous oxytocin might increase the uterine muscle tone as a physiologic response to this endocrine stimulus, and in turn, increase the venous return to the heart immediately after delivery. Because of this, we felt it was important to compare oxytocin and carbetocin with placebo. This trial was designed to compare the effects of a 60 s i.v. injection of oxytocin 5 U, carbetocin 100 μg, and saline (placebo) on invasively measured hemodynamics, uterine tone, adverse events, and blood loss.

Materials and Methods

This was a randomized, double-blinded, placebo-controlled, parallel-group comparison of carbetocin and oxytocin given intravenously during elective Cesarean delivery under spinal anesthesia. The study was conducted at the Department of Anesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital, Rikshospitalet between November 2009 and September 2011. The Birth Clinic at Rikshospitalet is a tertiary care center, but the majority of the women in labor were healthy and representative of the general population in central Norway. The protocol was approved by the local representative of the Data Inspectorate at Oslo University Hospital, the Regional Committee for Medical and Health Research Ethics of Southern Norway (Oslo, Norway), and the Norwegian Medicines Agency (Oslo, Norway). The randomized controlled trial (RCT) was registered at clinicaltrials.gov (NCT00977769) and was conducted according to Good Clinical Trial practice and the principles of the Declaration of Helsinki. The data are reported according to the CONSORT guidelines.[17]

Eligible participants were screened by the primary author for inclusion at their last midwife consultation before their scheduled delivery. Oral and written information was given to each woman at least 24 h before her delivery and written informed consent was obtained before randomization. The inclusion criteria included an age limit of 18 years or older, in good health, a single gestation at 36 weeks or more, and a scheduled Cesarean delivery. The exclusion criteria included preeclampsia, placenta previa, placenta accreta, von Willebrand disease or other bleeding disorder, and preoperative systolic arterial pressure (SAP) less than 90 mmHg. A total of 185 patients were screened and 76 were randomized to three groups. Figure 1 shows a study flow chart that includes the number of patients screened, excluded, allocated, and analyzed in the RCT. Patient number 76 was excessive according to the protocol, but because consent had been obtained, we decided to randomize her, although it caused a minor imbalance.

The 76 patients included were randomly assigned to one of the three treatment groups: group P (placebo) received i.v. 5 ml sterile saline 0.9 mg/ml; group O received i.v. oxytocin (Syntocinon®; Novartis Pharmaceuticals, North Ryde, Australia) 10 U/ml (0.5 ml) + 4.5 ml saline; and group C received i.v. carbetocin (Pabal®; Ferring Pharmaceuticals, Kiel, Germany) 100 μg/ml (1 ml) + 4 ml saline.

To maintain blinding of the participants and investigators, the test medicine was delivered to the Department of Anesthesiology in 10-ml syringes containing 5 ml of solution marked only with trial identification and randomization numbers. The 10-ml syringes with the test medicines were prepared by a staff anesthesiologist, who was otherwise uninvolved in the study.

High body mass index may influence the hemodynamic response to spinal anesthesia or to vasodilators. Therefore, we decided upon a stratified randomization with two strata, body mass index less than 30 and body mass index of 30 or more. Maternal weight upon inclusion was used to calculate the body mass index. A computer-generated list of random numbers was used to randomize the participants.[18] The block size varied between six and nine. Sequentially numbered, sealed, opaque envelopes were prepared, which contained allocation information for the two strata. The person who was responsible for the randomization was otherwise uninvolved in the clinical course of the study. The randomization was not revealed to the other investigators until all data were entered into the database.

An arterial catheter was placed into the radial artery after infiltration of lidocaine (10–20 mg) immediately after arrival at the operating theatre. Peripheral i.v. catheters were placed on both forearms. Baseline measurements of calibrated invasive SAP, diastolic arterial pressure, and mean arterial pressure were recorded for 3 min, with the patient in a left lateral

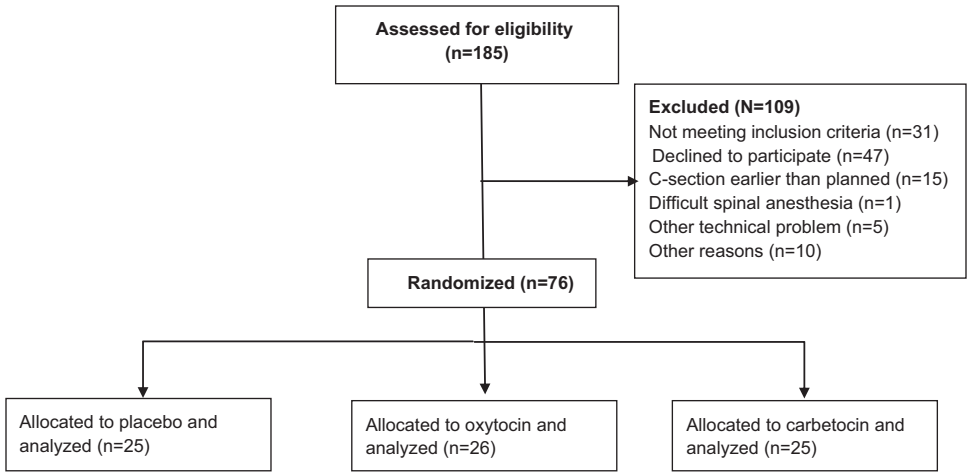

Fig. 1. Flow chart of the study showing the number of patients who were screened, included in the study, and analyzed.

position. Heart rate (HR) was recorded. Stroke volume (SV), CO, systemic vascular resistance (SVR), and other estimated variables based on continuous arterial waveform analysis system were recorded, using PulseCO (PulseCO™, Cambridge, United Kingdom), an integrated part of the LiDCO*plus* monitoring system (LiDCO Ltd., Cambridge, United Kingdom). We omitted the calibration of CO with the lithium dilution technique because the primary outcome was change in SAP. CO and all other hemodynamic variables were analyzed for group differences in relative changes.

With the woman in a right lateral position, spinal anesthesia was induced in the L2–L3 vertebral interspace, and bupivacaine 10 mg + fentanyl 20 μg was injected through a 25-gauge nontraumatic needle (Pencan®; B. Braun, Melsungen, Germany). Concomitantly, we started a rapid i.v. infusion of saline 0.9 mg/ml (37°C, 10 ml/kg) and a phenylephrine bolus (0.25 μg/kg). This was followed with a phenylephrine infusion (0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$). During surgery, the patient was supine with an operating wedge under her right hip (19° Tempur pillow; Trulife®, Dublin, Ireland). Hypotension (SAP <90 mmHg) was treated with an extra i.v. bolus of phenylephrine if the HR was above 60 beats/min or with i.v. ephedrine 5–10 mg if the HR was 60 beats/min or below. The level of anesthesia was tested by cold sensation 5 min after spinal anesthesia as well as by pinching with surgical tweezers before horizontal skin incision (pfannenstiel). The study drug was injected slowly, over the course of 60 s, starting when the baby's head and shoulders were delivered. Exteriorization of the uterus was performed routinely according to departmental policy. After approximately 5 min, each patient was asked if she experienced any side effects, and if so, she was asked to grade the intensity of the side effects as mild, moderate, or severe. The approximate duration of the side effects was also recorded.

The hemodynamic data were stored in the LiDCO*plus* monitor and were downloaded as .csv files and .lvu files for all the women, immediately after the operation. The dataset was constructed using MatLab version R2011a (MathWorks, Natick, MA). The beat-to-beat data that contained extreme values and artifacts were replaced using nonlinear interpolation. Extreme values, *i.e.,* values outside any reasonable range, often occur as blocks of data and may be the result of wire sway or kinking of the arterial line. Artifact values were defined as sharp but not extreme deviations from the adjacent beat-to-beat values and were often the result of an extra or skipped heartbeat. The LiDCO*plus* monitor registers the most extreme values as "bad"; in such a case, we have automatic identification of a corrupted record. However, there are some additional extreme values, particularly in records that are close to "bad" records. To identify the latter as corrupt, we set upper and lower acceptable limits for the following variables: SAP, diastolic arterial pressure, HR, and SVR. The limits, based on clinical discretion, were set individually for each patient file and were wide enough to ensure that only clearly corrupted records were replaced. A total of 1.23% of the records used in the analyses were identified as containing extreme values. All .lvu files were inspected visually in the software LiDCOview PRO (LiDCO Ltd.). Remaining artifacts in the sampled data were removed by running an artifact removal algorithm first, as described by Deegan *et al.*,[19] and then replacing the artifact values with interpolated values. Around 0.83% of the records used in the analysis were identified as containing artifact values. For statistical analysis, we transformed the beat-to-beat data into sliding averages with a window size of 10 s and a slide of 5 s. The transformation served several purposes: The uneven sampled beat-to-beat signal is transformed to an evenly sampled signal, the data are smoothed, and the number of observations for a given period of time is reduced. We noted that smoothing the data by computing sliding averages made the artifact removal procedure less critical.

In addition to the beat-to-beat hemodynamic variables that were stored electronically, we registered each patient's age, height, weight, fetal gestational age, indication for

Cesarean delivery, and hours of fasting (liquids and solids). Preoperative arterial blood hemoglobin and sodium concentrations were measured and used as baseline values for comparison with sodium and hemoglobin concentrations measured 1 and 2 h after inclusion.

The obstetrician in charge of the Cesarean delivery assessed uterine tone 1, 2.5, and 5 min after administration of study drug, using a numeric rating scale that ranged from 0 to 10, where a score of 0 meant "no effect", 10 meant "maximal uterus contraction", and 7 indicated "clinically satisfactory contraction". This uterine contraction scale was introduced to the obstetricians before the RCT to ensure reliability. The first assessment (at 1 min) was performed before exteriorization of the uterus. Repeated dosages of i.v. oxytocin 1 U were given as a rescue measure, if the uterine tone was insufficient (numeric rating scale <7 at 2 ½ min or more). Decisions about the need for secondary treatment, such as oxytocin infusion, rectal misoprostol, intramyometrial 15-methyl prostaglandin F2 alpha (prostinfenem), or other treatments, were left to the discretion of the obstetrician.

Because visual assessment of blood loss during delivery is of limited value, we calculated estimated blood loss using the formula[20]:

$$\text{Calculated estimated blood loss} = \left[0.75 \times (\text{Height in inches}) \times 50\right] + \left[(\text{Weight in pounds}) \times 50\right] \times \left[\frac{(\text{Predelivery hematocrit} - \text{Postdelivery hematocrit})}{(\text{Predelivery hematocrit})}\right]$$

We also tested whether the investigators could identify the treatment allocation group based on the observed effects. Ten minutes after delivery and injection of the study solution, the obstetrician and the anesthesiologist (the first author) independently answered the following question: "Which of the three treatments do you believe this patient received?" The answers were analyzed as a test of investigator unblinding.

The baby's birth weight, umbilical artery pH and base excess, umbilical vein pH and base excess, and Apgar scores at one and 10 min were recorded.

Statistical Analyses

The primary endpoint with respect to the hemodynamic effects of the interventions was group differences in SAP, which occurred during the first 5 min after intervention. The secondary outcomes were group differences in uterine contraction score, estimated bleeding (ml), decrease in hemoglobin, time to rescue drug, side effects, and hemodynamic variables other than SAP, in the time period from intervention (time = 0) to 2 h after intervention.

On the basis of the data from a previously published study, we expected a 40 mmHg (SD, 10) decrease in SAP after oxytocin 5 U.[5] To detect a clinically significant difference of 10 mmHg (SD, 10) with a two-sided 5% significance level and a power of 80%, a sample size of 17 is needed (SamplePower; SPSS Inc., Chicago, IL). We assumed that the difference between the two active treatment arms would be less prominent, so the group size was increased to 25.

Demographic data and baseline measurements are presented as mean (SD), if normally distributed, or as median and range, if not normally distributed, and group differences were tested using the one-way ANOVA or Kruskal-Wallis tests, respectively. Baseline hemodynamic values represent measurements collected before spinal anesthesia, with the patient in the left lateral position.

We used the linear mixed model in the Statistical Package for the Social Sciences (SPSS) version 18 (SPSS Inc.) to analyze group differences in hemodynamic variables as a function of time (5 min) in the three treatment groups, with *time*, *group,* and *time*group*-interaction as fixed effects. Nonlinear time sequences, which occurred during the first 2.5 min, were analyzed with a modified mixed model that included interactions between group and *time, time^2, and time^3*, and the last 2.5-min period was analyzed with a conventional linear mixed model. The statistical test of the interaction between group and *time*^2 in the time period 0–150 s was the key significance measure. The decision to divide the 5-min period into two and perform a modified analysis was made after the recognition of this nonlinear time sequence. The dependencies in the data were treated with an unstructured covariance matrix. Pairwise comparisons were Bonferroni-corrected. We decided to perform explorative statistical analyses on the secondary outcomes only if there were statistically significant differences in SAP, which was the primary outcome measure.

Results

There were no statistically significant group differences in demographic data, gestational age, surgical time, baseline maternal measurements (table 1), or neonatal characteristics (table 2). The indications for elective Cesarean delivery were: maternal request 43%, previous Cesarean delivery 25%, breech presentation 8%, other obstetric reasons 13%, and other nonobstetric maternal or neonatal medical conditions 11%.

As shown in figure 2, there was a prominent decrease in SAP in groups O and C compared with group P (fig. 2A). The mean decrease in SAP compared with baseline, which was determined in the 30 s before uterotomy, was 28 mmHg (95% CI, 22–34) in group O and 26 mmHg (95% CI, 20–31) in group C. This corresponds to SAP decreases of 21% and 19%, respectively, with a nonsignificant difference between groups O and C. The onset of the hypotensive effect of oxytocin and carbetocin was comparable and reached a trough 80 s (95% CI, 71–89) after study drug administration in group O and 63 s (95% CI, 55–72) after test drug administration in group C ($P = 0.006$). The hypotensive effect (table 3) was nearly abolished after 2.5 min, although the effect of carbetocin at 2.5 min was statistically

Table 1. Patient Characteristics

	Placebo	Oxytocin	Carbetocin	*P* Value
Age, yr	35 *(22–42)*	35 *(24–43)*	34 *(28–42)*	0.54
Height, cm	168.0 *(157–182)*	169.4 *(160–182)*	169.2 *(160–181)*	0.68
Weight, kg	82.6 *(60–128)*	80.2 *(51–115)*	81.8 *(62–113)*	0.82
BMI, kg/m^2	29.2 (SD 4.3)	27.9 (SD 4.0)	28.6 (SD 4.8)	0.60
Nulliparous	5 (of 25)	8 (of 26)	4 (of 25)	0.42*
GA, wk	39 *(36–39)*	39 *(38–39)*	39 *(37–40)*	0.24*
Surgery, min	30.4 *(18–50)*	29.8 *(15–49)*	30.4 *(17–47)*	0.93*
Induction time, min	17.1 *(12–34)*	21.4 *(11–47)*	19.5 *(10–57)*	0.43*
Preoperative Hb, g/100 ml	11.3 (SD 1.3)	11.2 (SD 1.0)	11.3 (SD 1.2)	0.90
Preoperative fasting, h	12.0 (SD 2.5)	12.3 (SD 3.2)	11.7 (SD 2.6)	0.75
Baseline†				
Systolic AP, mmHg	137 (SD 14)	133 (SD 15)	132 (SD 13)	0.37
Mean AP, mmHg	93 (SD 9)	90 (SD 10)	90 (SD 8)	0.38
Diastolic AP, mmHg	70 (SD 8)	68 (SD 8)	67 (SD 7)	0.44
HR, beats/min	78 (SD 11)	79 (SD 11)	76 (SD 11)	0.68

Values presented as mean (SD), *median (range)*, or proportion. Induction time is minutes from spinal anesthesia to delivery.

* Kruskal-Wallis test. † Baseline values representing a 60-s mean of intraarterial blood pressure (AP), and HR with the patient in the left lateral position 5 min before spinal anesthesia.

AP = arterial pressure; BMI = body mass index; GA = gestational age; HR = heart rate.

significantly different compared with placebo ($P < 0.001$). The group differences in SAP had decreased after 5 min (fig. 2) and were completely gone 1 and 2 h after inclusion (data not shown). Similar patterns were observed for mean arterial pressure and diastolic arterial pressure values (fig. 2, B and C).

There was an overall increase in HR in all groups, with the increases reaching a maximum 90 s after intervention (fig. 2D). The HR increased significantly in groups O and C compared with group P during the first 2.5 min (table 3). In the next 2.5 min, the differences between groups O and C were less prominent compared with the differences between these two groups and group P (fig. 2D); however, the between-group difference was still statistically significant ($P < 0.001$ for both comparisons). HR declined to baseline values in groups P and O at 5 min, whereas HR remained above baseline in group C (fig. 2D). In 8 min after intervention, there were no differences in HR between groups O and C compared with group P (fig. 2D).

The increase in CO was statistically significant in groups O and C compared with group P (table 3 and fig. 3A). The relative mean increase in CO (*i.e.,* the mean of the individuals' maximum measurements) from baseline was 82% (95% CI, 64–100) in group O and 96% (95% CI, 80–111) in group C (n.s. difference). The maximum CO increase occurred after 75 s (95% CI, 67–83) in group O and after 58 s (95% CI, 51–65) in group C ($P = 0.002$). The mean maximum increase in CO in the placebo group was 43%, which occurred a few seconds after delivery of the baby.

We observed a minor increase in SV between baseline and the start of the intervention in all three groups (fig. 3B). SV increased progressively and substantially after injection of oxytocin or carbetocin (increases of approximately 25%), and the values were statistically significantly different from those in group P, in which SV remained stable (table 3).

Table 2. Neonatal Characteristics

	Placebo	Oxytocin	Carbetocin	*P* Value
Apgar 1 min	*9 (6–10)*	*9 (9–10)*	*9 (8–10)*	0.07*
Apgar 5 min	*10 (7–10)*	*10 (9–10)*	*10 (9–10)*	0.62*
UV pH	7.36 (SD 0.04)	7.37 (SD 0.03)	7.36 (SD 0.02)	0.72
UV BE	−1.33 (SD 1.41)	−1.33 (SD 1.38)	−1.05 (SD 2.02)	0.65
UA pH	7.30 (SD 0.04)	7.31 (SD 0.03)	7.30 (SD 0.03)	0.43
UA BE	−0.50 (SD 1.65)	−0.39 (SD 1.48)	−0.36 (SD 1.91)	0.67
Birth weight, g	3,543 (SD 470)	3,509 (SD 405)	3,567 (SD 327)	0.88

Values presented as mean (SD) or *median (range)*.

* Kruskal-Wallis test.

BE = base excess; UA = umbilical artery; UV = umbilical vein.

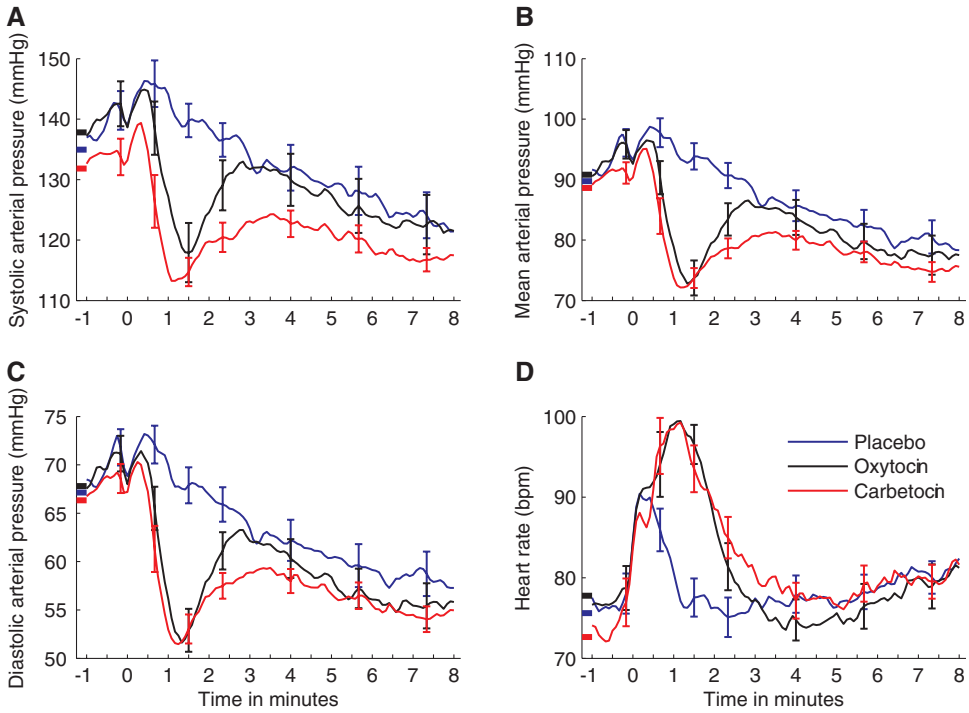

Fig. 2. Invasive hemodynamic variables are presented as mean (SD) in the three treatment groups 1 min before and 8 min after intervention (intervention = time 0). The group means of the measurements in the last 30 s before uterotomy are indicated on the y-axis with horizontal lines. (*A*) Systolic arterial pressure, (*B*) mean arterial pressure, (*C*) diastolic arterial pressure, and (*D*) heart rate.

Because SV changes might reflect changes in venous return, the uterine tone, or rather the lack of uterine tone, in the placebo group may represent a confounder. Rescue oxytocin was given to the first placebo patient 149 s after inclusion. Hence, the analysis of the first 150 s was not influenced by rescue oxytocin, and a *post hoc* analysis of SV in the placebo group corrected for uterine tone was performed. The interaction between time and the degree of uterine tension at 2.5 min (150 s) as a covariate was clearly nonsignificant (P = 0.98). This is in accordance with the observation of stability in venous return in group P. SVR decreased in group O and group C, but group P showed an initial minor increase in SVR (fig. 3C and table 3).

The calculated estimated blood loss was 853 ml (SD, 518) in group P, 841 ml (SD, 556) in group O, and 579 ml (SD, 623) in group C (fig. 4). The mean decrease in hemoglobin concentration 2 h after intervention was −0.84 g/100 ml in group P, −0.82 in group O, and −0.50 in group C. The differences between treatment groups were not statistically significant. The sodium concentration did not differ between the groups at any time point (data not shown). Both oxytocin and carbetocin elicited adequate uterine contraction (table 4), and rescue oxytocin 1 U was given to five patients in each group. One of the five patients in the oxytocin group and two of the five patients in the carbetocin group needed a second dosage of oxytocin. Two patients in the placebo group had adequate uterine contractions without any rescue medication, and 23 patients were given one (n = 17), two (n = 5), or three (n = 1) dosages of oxytocin. Two patients in group O and two in group P were given oxytocin infusion, rectal misoprostol, intramyometrial prostinfenem, balloon tamponade treatment, or B-lynch suture either alone, or in combination. Compared with group P, the number needed to treat was 1.34 for group O and 1.39 for group C. The median time to the first rescue oxytocin dosage was 227 s (range 184–368) in group C, 287 s (range 149–846) in group P, and 536 s (271–1,368) in group O (n.s. difference). To summarize, 23 of 25 group P patients, 7 of 26 group O patients, and 6 of 25 group C patients were given one or more rescue treatments (P < 0.001, Fisher exact test).

More patients in group O (9 of 26) and group C (9 of 25) reported one or more side effects after intervention compared with group P (2 of 25; table 5; P = 0.001; Fisher exact test). The patients in group O reported more types of side effects (table 5) and a higher degree of discomfort compared with group C, but the differences were not statistically significant. The reported median duration of side effects was 2 min in the population that reported one or more side effects. However, four of nine patients in group O had side effects of moderate degree that lasted from 5 to 19 min. The median side effect duration was 3.5 min (range 1–19) in group O and 2 min (range 1–3) in group C, but the difference was not statistically significant. On the basis of the self-reported rate of adverse events, the number needed to harm was 2.2 in group O and 3.6 in group C compared with group P.

Table 3. Estimates of Fixed Effects 0 to 150 Seconds after Inclusion

	Estimate	CI	*P* Value
SAP (mmHg), intercept	142.0	(135.2–148.8)	
Carbetocin†	–25.6	(–35.3 to –16.0)	<0.001
Oxytocin†	–17.9	(–27.5 to –8.4)	<0.001
Carbetocin*Time †	0.07	(–0.3 to 0.5)	n.s
Oxytocin*Time †	–0.7	(–1.0 to –0.3)	0.001
Carbetocin*Time^2†	0.09	(0.08–0.1)	<0.001
Oxytocin*Time^2†	0.08	(0.07–0.1)	<0.001
Carbetocin*Time^3†	–0.003	(–0.005 to –0.002)	<0.001
Oxytocin*Time^3†	0.001	(0.0001–0.002)	0.039
HR (min^{-1}), intercept	79.2	(74.0–84.4)	
Carbetocin†	17.3	(9.9–24.8)	<0.001
Oxytocin†	18.0	(10.6–25.3)	<0.001
Carbetocin*Time†	0.2	(–0.1 to 0.5)	n.s
Oxytocin*Time†	0.3	(–0.06 to 0.6)	n.s
Carbetocin*Time^2†	–0.09	(–0.10 to –0.08)	<0.001
Oxytocin*Time^2†	–0.09	(–0.10 to – 0.08)	<0.001
Carbetocin*Time^3†	0.002	(0.001–0.003)	<0.001
Oxytocin*Time^3†	0.0005	(–0.0006 to 0.0015)	n.s
SV (ml), intercept	93.3	(88.0–98.7)	
Carbetocin†	13.1	(5.5–20.7)	0.001
Oxytocin†	14.3	(6.8–21.8)	<0.001
Carbetocin*Time†	0.04	(–0.3 to 0.3)	n.s
Oxytocin*Time†	0.17	(–0.13 to 0.47)	n.s
Carbetocin*Time^2†	–0.09	(–0.10 to –0.08)	<0.001
Oxytocin*Time^2†	–0.08	(–0.09 to –0.07)	<0.001
Carbetocin*Time^3†	0.002	(0.001–0.003)	0.006
Oxytocin*Time^3†	0.0004	(–0.001 to 0.002)	n.s
CO (l/min), intercept	7.4	(6.5–8.3)	
Carbetocin†	3.1	(1.8–4.4)	<0.001
Oxytocin†	3.4	(2.1–4.6)	<0.001
Carbetocin*Time†	0.20	(–0.03 to 0.07)	n.s
Oxytocin*Time†	0.23	(–0.03 to 0.07)	n.s
Carbetocin*Time^2†	–0.02	(–0.020 to –0.016)	<0.001
Oxytocin*Time^2†	–0.02	(–0.020 to –0.017)	<0.001
Carbetocin*Time^3†	0.0004	(0.0002–0.0006)	<0.001
Oxytocin*Time^3†	0.0002	(0.0000–0.0004)	0.049
SVR (dynes · s^{-1} · cm^{-5}), intercept	984.3	(900.1–1,068.5)	
Carbetocin†	–406.6	(–525.6 to –287.6)	<0.001
Oxytocin†	–382.6	(–500.5 to –264.7)	<0.001
Carbetocin*Time†	–5.1	(–10.7 to 0.4)	n.s
Oxytocin*Time†	–11.8	(–17.3 to –6.3)	<0.001
Carbetocin*Time^2†	2.0	(1.8–2.1)	<0.001
Oxytocin*Time^2†	1.9	(1.7–2.1)	<0.001
Carbetocin*Time^3†	–0.04	(–0.06 to –0.02)	<0.001
Oxytocin*Time^3†	0.02	(0.0004–0.04)	0.045

The table presents the relevant results of the modified mixed model analyses of the hemodynamic variables, Y = β0 + β1 Time + β2 Time^2 + β3 Time^3 + β4 Group + β5 Group*Time + β6 Group*Time^2 + β7 Group*Time^3. The effect of time (Time) is centered, as such, time = 0 refers to 75 s after inclusion.

† The responses of the placebo group is redundant (0), to which the other factors and interactions are compared.

CO = cardiac output; HR = heart rate; SAP = systolic arterial pressure; SV = stroke volume; SVR = systemic vascular resistance.

The test for unblinding showed that both the obstetrician and the anesthesiologist were able to distinguish between placebo treatment and active treatment in most cases (19 of 25 and 24 of 25, respectively). The distribution between presumed oxytocin and carbetocin treatment was, however, close to random (data not shown).

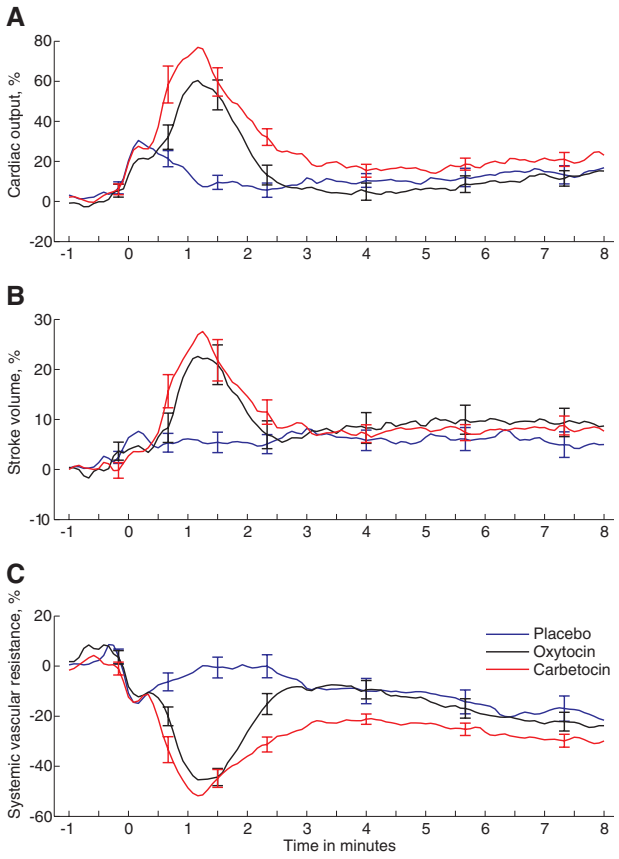

Fig. 3. Estimated cardiac output (*A*), stroke volume (*B*), and systemic vascular resistance (*C*) in the three treatment groups the minute before and 8 min after intervention (intervention = time 0) presented as the percentage change from baseline representing measurements from the last 30 s before uterotomy.

Discussion

Previous studies have shown that oxytocin and carbetocin have hemodynamic side effects of comparable magnitude and duration, whereas the uterotonic effect of carbetocin is documented to be significantly longer than that of oxytocin.[21] In this study, we found that the HR elevation after carbetocin lasted slightly longer than after oxytocin (fig. 2D), which may be of clinical interest for pregnant women with increased risk of cardiac events. Apart from this, none of our observed differences between carbetocin and oxytocin, even those that were statistically significant, have obvious clinical impact or relevance in healthy pregnant women.

The hemodynamic side effects of carbetocin and oxytocin were compared previously in a randomized study.[13] That study measured noninvasive blood pressure, HR, and hemodynamic variables estimated by impedance cardiography. Due to technical problems with the monitoring device, the drop-out rate was substantial, and only 56 of 84 included patients were analyzed. There was an increase in HR of 18 and 14 beats/min after 10-s injections of oxytocin 5 U or carbetocin 100 μg, respectively. The HR declined below baseline 200 s after injection in their oxytocin group, and to a lesser extent, 270 s after injection in the carbetocin group. Systolic blood pressure decreased by 27 and 23 mmHg, respectively, with no statistically significant differences in the hemodynamic variables. Overall, their results were comparable with ours. The strengths of our trial are that we measured blood pressure and hemodynamic variables invasively and continuously, we analyzed all included patients, and the statistical power was greater. In addition, we included a placebo group.

Compared with placebo, the differences in the hemodynamic effects of carbetocin and oxytocin were both statistically and clinically significant (fig. 3). The women that were randomized to placebo were hemodynamically more stable, and the observed increase in blood pressure and HR may

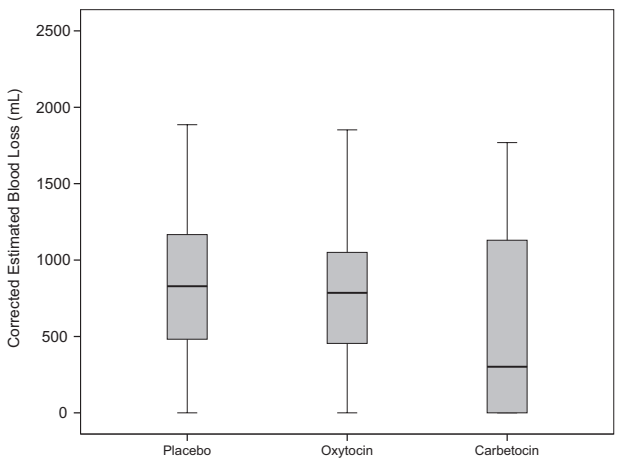

Fig. 4. Corrected estimated blood loss (ml) in the three treatment groups presented as boxplots.

Table 4. Median Numeric Rating Scale Scores of Uterus Contraction (Interquartile Range)

	Placebo	Oxytocin	Carbetocin
Time, min			
1	6 (2)	7 (2)	7 (2)
2.5	6 (2)	8 (1.25)	7 (2)
5	6 (1)	8 (1)	7 (2)

Table 5. Side Effects

	Placebo	Oxytocin	Carbetocin
No side effect	23 (of 25)	17 (of 26)	16 (of 25)
Feeling of warmth	1	2	2
Chest pain	0	2	2
Shortness of breath	0	0	1
Palpitations	0	3	0
Flushing	1	2	0
Headache	0	3	2
Nasal congestion	0	1	1
Xerostomia	0	0	1
Metallic taste	0	1	0
Total	2	14	9

be explained by the contextual physical and psychological stress. We observed substantial physiological changes when the obstetrician delivered the baby through the uterotomy before the randomized intervention started. Even when the woman is adequately anesthetized, giving birth is a large physiologic stress. SV, which is closely related to venous return (preload) through the Frank–Starling mechanism, did not seem to be affected by the delivery itself. Given an unchanged SV, the concomitant increase in HR will lead to an increase in CO. In our analysis of the placebo group, the CO changes were related to the increase in HR and seemed to peak when the baby's head and shoulders passed the uterotomy, which coincided with the start of the interventional trial. Elevated CO after vaginal delivery has been documented previously,[22] but repeated invasive measurements indicated a peak CO shortly after delivery of the baby, and a subsequent decrease after delivery of the placenta.[23,24] Echocardiographic measurements during uterine contractions have indicated that there is an autotransfusion of 300–500 ml of uterine blood into the maternal venous circulation, which may increase SV and CO.[14,25] Hemodynamic data during Cesarean delivery are sparse.[26,27] The studies that have been performed have included few patients, and CO levels were measured every 2 min, as opposed to being monitored continuously. To our knowledge, this is the first study to use continuous CO monitoring during Cesarean delivery in patients who were not given oxytocin prophylactically. Analyzing the data in the placebo group may provide new information about hemodynamic effects during caesarean delivery.

We postulated that lower uterine muscle tone in the placebo group and oxytocin given as rescue treatment for atony might have introduced a bias. To minimize this possible confounder, we reanalyzed data from the first 150 s to eliminate the effect of rescue oxytocin and corrected for uterine contraction score. The analysis supported the interpretation that SV remained stable in the placebo group. Taken together, the analyses of invasively measured beat-to-beat hemodynamic variables in the present study suggest that the physiological changes in SV are small and nearly negligible compared with the prominent vasodilatory effects of oxytocin receptor agonists. Thus, a rise in preload is less important during the first minutes after Cesarean delivery than assumed previously,[15,16,28] and autotransfusion of uterine blood into the maternal circulation does not seem to be the reason for CO elevation after Cesarean delivery (fig. 3).

One of the aims of this study was to observe the natural course of hemodynamics in patients given a placebo injection. In addition to the generation of interesting physiological data in a control group, we were able to prove the internal sensitivity of the clinical assay, regardless of whether there were statistically significant differences between the two active treatment groups. When effective rescue treatment is immediately available, placebo treatment does not represent an ethical problem.

We observed rapid onset and offset of undesirable hemodynamic side effects, and the differences between oxytocin 5 U and carbetocin 100 μg were minor. The dosages were based on the practice guidelines that were in place when the study protocol was approved. Our hospital guidelines have been changed since that time, with the oxytocin dosages reduced to 2.5 U. Carvalho *et al.*[29] have shown that the effective dosage of i.v. oxytocin (ED 95%) is only 0.35 U (95% CI, 0.18–0.52 U). The same research group found that the uterine contractions during elective Cesarean delivery were equally effective after carbetocin dosages that ranged from 80–120 μg.[30] We suggest that dosages lower than those which are currently used may reduce the undesirable hemodynamic effects of both drugs. The pharmacodynamic equipotency between the two drugs has not been tested, and we suggest that this merits study in the future.

Oxytocin causes myocardial ischemia.[31–33] Because i.v. oxytocin 10 U has probably contributed to maternal deaths,[4] lowering the dosages is strongly recommended.[34] One of the excipients in the oxytocin solution, chlorobutanol, may also affect the cardiovascular system and produce peripheral vasodilatation and reduced cardiac contractility.[35,36] The oxytocin preparation used in this study contains chlorobutanol 0.5%, so the effect of 0.5 ml of this solution is probably insignificant. The side effects reported by the patients were more frequent, lasted longer, and were graded as more severe in the oxytocin group compared with the carbetocin group. The study was underpowered in terms of detecting statistically significant differences in adverse events, and future controlled trials with sufficient group sizes are warranted. On the basis of the observed difference in the side effect rate, which was 53% in the oxytocin group and 36% in the carbetocin group, a controlled trial will have to include at least 133 patients in each group to have a statistical power of 80% ($\alpha = 0.05$, two-sided test; SamplePower version 3.0; IBM SPSS Inc.). Data from this and similar RCTs can be used to generate a systematic quantitative review.[37]

Carbetocin is documented to reduce the need for additional uterotonic therapy during Cesarean delivery by 50% compared with oxytocin.[37] The difference in the mean time to rescue oxytocin between group C and group O was not statistically significant in this study. The median time to rescue was longer in the oxytocin group, and the range was notably longer, probably due to a decline in uterotonic effects. As a consequence, we expected some patients to need supplemental oxytocin boluses or infusion or other uterotonic treatment. The difference in required rescue therapy was not significantly different between groups, and even though the calculated estimated blood loss was lower in group C compared with group O, the difference did not achieve a level of statistical significance. The study was underpowered to detect differences in bleeding, and the aim of this study was primarily to detect group differences in hemodynamic variables. In the future, studies are needed

that compare the difference in blood loss between the two oxytocin receptor agonists.

A high rate of unblinding of the physicians involved in a clinical trial can affect the data registration process and represent bias. In this trial, the physicians were often able to guess correctly when placebo treatment was given, but they failed to distinguish between oxytocin and carbetocin. The sampling of hemodynamic data were established before the test drug was injected and before it was possible for unblinding to occur. Most outcome measures were based on electronic sampling or on laboratory data, and the questions regarding self-reported side effects were presented to the patients during the first 5 min after inclusion. The test of unblinding took place approximately 10 min after inclusion. Thus, we do not believe unblinding introduced bias into the analyses in this RCT.

Conclusions

In this RCT, oxytocin 5 U and carbetocin 100 μg had comparable hemodynamic side effects with equal onset and offset times in the first few minutes after Cesarean delivery. Upon administration of these agents, SAP and SVR decreased, whereas HR, SV, and CO increased. The lack of a SV increase in the placebo group challenges the hypothesis that uterine contraction causes autotransfusion of uterine blood that leads to an increase in preload.

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