Efficacy and safety of carbetocin given as an intravenous bolus compared with short infusion for Caesarean section - double-blind, double-dummy, randomized controlled non-inferiority trial

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Abstract

Background. Carbetocin is a synthetic oxytocin-analogue, which should be administered as bolus according to manufacturer’s recommendations. A higher speed of oxytocin administration leads to increased cardiovascular side-effects. It is unclear whether carbetocin administration as short infusion has the same efficacy on uterine tone compared with bolus administration and whether haemodynamic parameters differ.

Methods. In this randomized, double-blind, non-inferiority trial, women undergoing planned or unplanned Caesarean section (CS) under regional anaesthesia received a bolus and a short infusion, only one of which contained carbetocin 100 mcg (double dummy). Obstetricians quantified uterine tone two, three, five and 10 min after cord-clamping by manual palpation using a linear analogue scale from 0 to 100. We evaluated whether the lower limit of the 95% CI of the difference in maximum uterine tone within the first five min after cord-clamping did not include the pre-specified non-inferiority limit of 0.

Results. Between December 2014 and November 2015, 69 patients were randomized to receive carbetocin as bolus and 71 to receive it as short infusion. Maximal uterine tone was 89 in the bolus and 88 in the short infusion group (mean difference 1.3, 95% CI 5.7 to 3.1). Bp, calculated blood loss, use of additional uterotonic, and side-effects were comparable.

Conclusions. Administration of carbetocin as short infusion does not compromise uterine tone and has similar cardiovascular side-effects as a slow i.v. bolus. In accordance with current recommendations for oxytocin, carbetocin can safely be administered as short-infusion during planned or unplanned CS.

Clinical trial registration. ClinicalTrials.gov NCT02221531 and www.kofam.ch SNCTP000001197.

Key words: Caesarean section; oxytocic drugs; uterine contraction
Uterotonic drugs are recommended to reduce blood loss and the risk of postpartum haemorrhage (PPH) after Caesarean delivery. Oxytocin is associated with a decrease in systemic vascular resistance leading to hypotension, tachycardia, and myocardial ischaemia. These side-effects depend on both the speed of administration and dose. There is a general recommendation for a slow administration of oxytocin, preferentially as a short infusion. Carbetocin is a synthetic oxytocin analogue with a longer half-life that was shown to reduce the need for additional uterotonics. It shares the same mechanism of action and same side-effects as oxytocin. Manufacturer’s instructions recommend a bolus injection of carbetocin over one min. So far, no trials have been designed to show non-inferiority of uterine tone using a slower mode of administration. Therefore, we aimed to investigate as primary efficacy endpoint whether carbetocin 100 mcg applied as a short infusion (short infusion group) had an equal effect on uterine contractility compared with the effect of a slow manual injection (bolus group), in a randomized controlled trial of women undergoing a planned or unplanned Caesarean delivery. Greater haemodynamic stability after a short infusion compared with a bolus administration was a secondary safety endpoint. Providing evidence for a similar efficacy would allow for a greater ease of administration as a short infusion, potentially avoiding pronounced hypotension. Preliminary results were presented at the annual meeting of the Obstetric Anaesthetists’ Association 2016 and published online as a supplemental abstract.

**Methods**

**Recruitment**

This prospective, single-centre, randomized, double-dummy, investigator-initiated, non-inferiority trial was conducted at the University Hospital Basel, Switzerland. Between December 8, 2014 and November 9, 2015, all patients presenting for an antenatal anaesthetic evaluation were screened for eligibility. Patients were eligible to participate in this trial if they were >18 yr old, presenting with a singleton pregnancy and undergoing a planned or unplanned CS under regional anaesthesia, after at least 37 completed weeks of gestation. Exclusion criteria were reported in detail in the published study protocol. Patients were given a one ml manual i.e. R, Fresenius Kabi, Oberdorf, Switzerland) was infused. While the patient was monitored according to our standard practice, a fluid co-load of 500 ml 6% hydroxyethyl starch (Voluven®, Fresenius Kabi, Oberdorf, Switzerland) was infused. Spinal anaesthesia by single-shot technique using 10 mg 0.5% hyperbaric bupivacaine, 10 mcg fentanyl, and 100 mcg morphine was established in a right lateral position. A pre-existing epidural catheter was topped up using 15-25 ml 2% carbonated lidocaine with 1:200,000 epinephrine. The patient was positioned in a left-tilted recumbent position for surgery. Bp and heart rate were recorded every min until 10 min after cord clamping. Systolic bp was maintained within 80% of the baseline values (i.e. definition of hypotension) using bolus administration of phenylephrine and, if not responding, ephedrine. After achieving a sensory block to dermatome T4, CS was performed according to the standard in-house procedure, applying the Misgav Ladach method for the laparotomy. After uterine incision, delivery of the baby, and cord clamping, the study drug was administered according to the group allocation. The placenta was delivered by cord traction or manually, if necessary. There was one follow-up visit on the second postoperative day to document side-effects of carbetocin. Haemoglobin and haematocrit concentrations were measured routinely preoperatively and two days postoperatively.

**Concomitant treatments**

In the event of uncontrolled bleeding or insufficient uterine tone after administration of the study drug, further measures were taken according to the current standard of care and at discretion of the treating obstetrician as described in the previously published study protocol.

**Primary efficacy endpoint**

The primary efficacy endpoint was the mean difference between study groups in maximum uterine tone within the first five min after cord clamping, assessed by manual palpation and rated on a linear analogue scale (LAS) from 0 (completely atonic) to 100 (fully contracted) by the obstetrician.

**Secondary efficacy endpoints**

The mean course over time of the uterine tone measured at two, three, five and 10 min after cord clamping was compared between both groups. The median time from the start of
administration of the study drug until the end of the short infusion and the time of placental removal was measured and recorded.

Mean blood loss within the first 48 h was estimated taking into account the calculated pregnancy blood volume and the percent blood volume lost.\textsuperscript{14, 15} A difference of 300 ml was considered clinically relevant.

Secondary safety endpoints
All secondary endpoints were described in detail in the published study protocol.\textsuperscript{12} In short, haemodynamic monitoring including ST segment changes served as a primary safety assessment, taking into account the amount of vasoactive drug administered before cord clamping and between cord clamping until one min after the end of the short infusion. The software application ixTrend (ixellence GmbH, Wildau, Germany) was used to ensure direct transfer of all haemodynamic data from the anaesthesia monitor (IntelliVue MX800, Philips AG Healthcare, Zurich, Switzerland) to the study computer. Further safety assessments included recording of type and amount of additional uterotonics drugs administered intraoperatively and immediately postoperatively, and the administration of blood products or coagulation factors.

Tolerability assessment included monitoring for side-effects including nausea, vomiting, facial flushing, headache, and chest pain, which were recorded during an interview conducted at the end of the CS and within 48 h on the maternity ward.

Statistical analysis
A detailed statistical analysis plan including a sample-size justification is reported in the published study protocol.\textsuperscript{12} Briefly, consistency checks were performed by logical data testing on a random sample of 5\% by an independent study member. Balance between study arms in patients and obstetric characteristics was investigated using descriptive statistics. To answer the primary research question, a confidence interval of the mean difference in LAS score of the maximal uterine tone from the model of uterine tone over time included the pre-specified non-inferiority limit of –10 (adjusted mean difference in maximal uterine tone –1.8, 95\% CI –6.1 to 2.6; and –2.5, 95\% CI, –6.7 to 1.7; appendix 1).

The haemodynamic parameters (lowest mean arterial pressure and highest heart rate) and calculated blood loss were analysed using a linear regression model, adjusting for the corresponding relevant confounders. The change over time of uterine tone and haemodynamic parameters were analysed using a generalized estimation equation (GEE) model with an exchangeable correlation matrix.\textsuperscript{17} As the data did not provide evidence for a relevant interaction between the effect of the treatment group over time (\textit{P} = 0.002, 95\% CI –0.352 to 0.347; \textit{P} = 0.989), the results of the less complex model without interaction term are shown. The planned knot at the average time of the lowest mean arterial pressure or the maximum heart rate did not reveal to be necessary as the course showed a steady increase or decrease, respectively. The incidence of any clinically relevant ST-segment changes in both groups was compared using a Fisher’s exact test. Further secondary endpoints were descriptively analysed.

We followed the CONSORT statement and its extension for non-inferiority trials.\textsuperscript{18, 19} We planned to perform a per-protocol and an intention-to-treat analysis, but they coincide as there were no post-randomization dropouts and no protocol violations. All analyses and graphs were performed using Intercooled Stata Version 14.1 for Macintosh (StataCorp, College Station, TX, USA).

Results
Out of the 627 women screened, 236 (38\%) did not meet the eligibility criteria, 139 (22\%) declined participation, and 252 (40\%) gave consent (Fig. 1). Of these, 140 were enrolled in the trial from December 17, 2014, to November 16, 2015. The two main reasons for non-enrolment (\textit{n} = 112) were vaginal delivery (\textit{n} = 63) and logistic reasons (\textit{i.e.} CS at night or during the weekend (\textit{n} = 37)). Of the 140 patients enrolled, two refused to give a statement about their side-effects during the follow-up two days postoperatively. As they did not deny the recording of their laboratory values (haemoglobin and haematocrit), we were able to calculate the perioperative blood loss of all patients.

Patient and obstetric characteristics are presented in Table 1. Baseline characteristics were balanced between the bolus group (\textit{n} = 69, 49\%) and the short infusion group (\textit{n} = 71, 51\%). Most of the CS (\textit{n} = 130, 95\%) were performed under spinal anaesthesia; another five each were performed under epidural or combined spinal-epidural anaesthesia.

Planned CS was performed in 117 (84\%) patients, and unplanned CS in 23 (16\%; Table 1). Previous CS was the most common reason for performing a planned CS; early onset of labour in case of a planned CS was the most common reason for performing an unplanned CS.

Carbetocin as short infusion was administered over a median of 3.52 min (IQR 3.20–4.39 min), carbetocin as bolus over approximately a min.

Efficacy endpoints
Uterine tone
The maximum uterine tone was 89 in the bolus and 88 in the short infusion group (mean difference –0.3, 95\% CI –0.5 to 0.7; \textit{P} = 0.542, Table 2). Both groups received the same dose of carbetocin bolus. In the short infusion group, an initial carbetocin bolus dose was administered and the remainder of the carbetocin dose was administered during the ongoing short infusion. In the bolus group, the whole carbetocin dose was administered as a bolus.

Estimated blood loss
The mean calculated blood loss in all patients was 543 ml (SD 479) with a mean difference between the short infusion and bolus group of –27 ml (95\% CI –188 to 134 ml; \textit{P} = 0.741, Table 2). The multivariable linear regression model adjusting for breastfeeding and the stratification variable planned or unplanned CS revealed a mean difference between the short infusion and the bolus group of -32 ml (95\% CI –192 to 127; \textit{P} = 0.688, appendix 3). A sensitivity analysis, excluding the three most extreme outliers did not significantly change the result (output not shown).

Tranexamic acid (1 or 2 g) was administered in eight patients (12\%) in the bolus group and in 10 patients (14\%) in the short infusion group. None of the patients received any packed red cells,
frozen plasma, or fibrinogen (Table 2). The overall incidence of PPH was 2.9% (4/140). One patient with PPH had received carbetocin as a bolus and three as a short infusion.

Safety endpoints

Haemodynamics
The minimum mean bp and maximum heart rate after carbetocin administration was similar in both groups (Fig. 3, appendix 2, 5, 6). In the bolus and short infusion group, phenylephrine was administered to 36 patients (52%) and 29 patients (41%), respectively (appendix 4). Even after adjustment for the amount of phenylephrine and ephedrine administered between cord clamping and one min after the end of the short infusion, there was no clinically relevant difference between both groups (appendix 2, 5). The amount of intraoperative crystalloid and colloid infusion was comparable in both groups.

Side-effects
No serious adverse events were observed in this trial. Except for facial flushing, side-effects were more frequently reported by patients in the short infusion than by those in the bolus group (Table 3). The incidence of chest pain was 17% in the trial population (n = 24). Chest pain was accompanied by ST-segment changes on the monitor screen in one patient in each group. Intraoperative ST-segment changes without chest pain were observed in three further patients in the short infusion group. The risk difference in incidence of ST-segment changes between the short infusion and the bolus group was 4.3% (95% CI: -1.9% to 10.4%; P = 0.366). Cardiac enzymes remained negative and ECG changes returned to normal within the intraoperative course.

As a result of insufficient regional anaesthesia, one patient required general anaesthesia for closing the abdomen more than 10 min after cord clamping. This patient was not excluded from the trial, but not all intraoperative side-effects could be recorded.

Discussion
This investigator-initiated trial shows that uterine tone after a short infusion of carbetocin is not inferior to that after a bolus administration. Calculated estimation of blood loss within 48 h
Table 1 Patient and obstetric characteristics of all women and of women in bolus and short infusion group. Values are mean (SD), median (IQR) or number (proportion). CS = Caesarean section; IQR = interquartile range; PPH = postpartum haemorrhage; SD = standard deviation

<table>
<thead>
<tr>
<th>Planned and unplanned CS</th>
<th>Bolus n = 69 (49%)</th>
<th>Short infusion n = 71 (51%)</th>
<th>All n = 140 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yr</td>
<td>35 (31–39)</td>
<td>35 (33–37)</td>
<td>35 (32–38)</td>
</tr>
<tr>
<td>BMI in kg m⁻²</td>
<td>28.0 (25.2–30.1)</td>
<td>29.4 (25.2–33.3)</td>
<td>28.5 (25.2–32.0)</td>
</tr>
<tr>
<td>Weeks of gestation</td>
<td>39 (38 to 39)</td>
<td>39 (38 to 39)</td>
<td>39 (38 to 39)</td>
</tr>
<tr>
<td>Primipara</td>
<td>20 (29%)</td>
<td>21 (30%)</td>
<td>41 (29%)</td>
</tr>
<tr>
<td>Primigravida</td>
<td>16 (23%)</td>
<td>15 (21%)</td>
<td>31 (22%)</td>
</tr>
<tr>
<td>Previous CS</td>
<td>40 (58%)</td>
<td>38 (53%)</td>
<td>78 (56%)</td>
</tr>
<tr>
<td>Abnormal placentation</td>
<td>–</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>History of PPH</td>
<td>3 (4%)</td>
<td>4 (6%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Polyhydramnion</td>
<td>4 (6%)</td>
<td>3 (4%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Planned CS</td>
<td>58 (84%)</td>
<td>59 (83%)</td>
<td>117 (84% of 140)</td>
</tr>
<tr>
<td>Reason for planned CS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous CS</td>
<td>34 (57%)</td>
<td>31 (53%)</td>
<td>65 (56%)</td>
</tr>
<tr>
<td>Breech position</td>
<td>6 (10%)</td>
<td>8 (14%)</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Patient’s preference</td>
<td>9 (16%)</td>
<td>11 (19%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>Abnormal placentation</td>
<td>–</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Others</td>
<td>9 (16%)</td>
<td>8 (14%)</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>Unplanned CS</td>
<td>11 (16%)</td>
<td>12 (17%)</td>
<td>23 (16% of 140)</td>
</tr>
<tr>
<td>Reason for unplanned CS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to progress</td>
<td>3 (27%)</td>
<td>5 (42%)</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>Abnormal foetal heart rate</td>
<td>1 (9%)</td>
<td>–</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Onset of labour and planned CS</td>
<td>7 (64%)</td>
<td>7 (58%)</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>Duration of labour in min</td>
<td>410 (225–1560)</td>
<td>520 (255–705)</td>
<td>500 (240–750)</td>
</tr>
<tr>
<td>Oxytocin infusion in labour</td>
<td>3 (27%)</td>
<td>3 (25%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Rupture of membranes</td>
<td>6 (55%)</td>
<td>5 (42%)</td>
<td>11 (48%)</td>
</tr>
</tbody>
</table>

Fig 2 Assessment of uterine tone during the first 10 min after cord clamping. Scatterplot of the assessment of uterine tone over time in the bolus and short infusion group. Lowess, locally weighted scatter plot smoothing, was carried out by locally weighted regression models to fit segments of the data.
Table 2: Procedural characteristics in all women and in women in bolus and short infusion group. Values are mean (SD) or number (proportion). FFP = fresh frozen plasma; Hb = haemoglobin; Hc = haematocrit; IQR = interquartile range; SD = standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Bolus n = 69 (49%)</th>
<th>Short infusion n = 71 (51%)</th>
<th>All n = 140 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience of obstetrician</td>
<td>Resident 34 (49%)</td>
<td>34 (48%)</td>
<td>68 (49%)</td>
</tr>
<tr>
<td></td>
<td>Junior consultant 12 (17%)</td>
<td>14 (20%)</td>
<td>26 (19%)</td>
</tr>
<tr>
<td></td>
<td>Senior consultant 23 (33%)</td>
<td>23 (32%)</td>
<td>46 (33%)</td>
</tr>
<tr>
<td>Placenta removal</td>
<td>Cord traction 58 (84%)</td>
<td>56 (79%)</td>
<td>114 (81%)</td>
</tr>
<tr>
<td></td>
<td>Manually 11 (16%)</td>
<td>15 (21%)</td>
<td>26 (19%)</td>
</tr>
<tr>
<td>Additional intraop. uterotonics</td>
<td>Sulprostone 2 (3%)</td>
<td>5 (7%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td></td>
<td>Misoprostol/oxytocin none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Additional intraop. Interventions</td>
<td>Uterine massage 4 (6%)</td>
<td>5 (7%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td></td>
<td>Bakri balloon none</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td></td>
<td>Tachosil sponge/Embolization/Surgical Intervention none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Coagulation factors</td>
<td>Tranexamic acid 8 (12%)</td>
<td>10 (14%)</td>
<td>18 (13%)</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Blood products (Packed red cells, FFP)</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Preop. Hb in g litre(^{-1})</td>
<td>123 (10.4)</td>
<td>124 (9.8)</td>
<td>124 (10.1)</td>
</tr>
<tr>
<td>Preop. Hc in %</td>
<td>36 (2.8)</td>
<td>36 (2.8)</td>
<td>36 (2.8)</td>
</tr>
<tr>
<td>Postop. Hb in g litre(^{-1})</td>
<td>110 (11.2)</td>
<td>112 (11.3)</td>
<td>111 (11.2)</td>
</tr>
<tr>
<td>Postop. Hc in %</td>
<td>32 (3.3)</td>
<td>32 (3.4)</td>
<td>32 (3.3)</td>
</tr>
<tr>
<td>Calculated blood loss in ml</td>
<td>557 (471)</td>
<td>530 (489)</td>
<td>543 (479)</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>66 (96%)</td>
<td>65 (92%)</td>
<td>131 (94%)</td>
</tr>
</tbody>
</table>

Fig 3: Course of mean arterial bp over time. Scatterplot of the mean arterial bp over time in the bolus and short infusion group. Lowess, locally weighted scatter plot smoothing, was carried out by locally weighted regression models to fit segments of the data.
was similar between both study groups. Therefore, carbetocin can be safely administered as a short infusion without compromising uterine tone in women undergoing a planned or unplanned CS. Changes in bp and heart rate over time were comparable between the groups.

Limitations
Precise measurement of intraoperative blood loss is difficult and laborious.\textsuperscript{20–23} Therefore, we chose uterine tone as our primary outcome variable assessed by manual palpation and in compliance with the standard in daily clinical practice in our hospital, accepting the limitation of a subjective outcome measure. To reduce bias, we maintained blinding in all patients and care providers until the statistical analysis was performed by using a double-dummy randomized design and widened the external validity of the results by including planned and unplanned CS in the trial population. We achieved complete primary outcome data and complete follow-up.

Findings in relation to other studies

Uterine tone
The number of patients reported to require additional uterotonic after carbetocin during CS ranges from 3.1%\textsuperscript{25} to 19%\textsuperscript{26} across all dosing groups. A meta-analysis summarizing the results of four randomized trials, reported an incidence of 13.7% of additional uterotonics after carbetocin.\textsuperscript{7} This is in line with our results, where 5% of women required additional uterotonics and 6% uterine massage.

Haemodynamics
Approximately 50% of patients in both study arms received boluses of phenylephrine. Other studies report an incidence of hypotension of 40–55%.\textsuperscript{24,26} However, a direct comparison cannot be made as those studies use a different definition for hypotension (i.e. decrease in systolic bp > 20% from baseline despite the use of phenylephrine). Additionally, in most other studies, crystalloids were used for co-loading whereas in this study, colloid was used (500 ml 6% hydroxyethyl starch).

The most likely explanation for the cardiovascular stability in both arms of our trial is the relatively low speed of injection of the bolus. In two studies, the bolus was injected substantially faster (over one or 10 s).\textsuperscript{5,11} In our trial, the bolus was administered over about one min and the infusion over an average of about four min. Although resolution of non-invasive bp measurement is reduced compared with invasive measurement, we believe that the cardiovascular stability we detected is not an artifact. This is confirmed by the stable heart rate. From a practical point of view, administering a one ml bolus over one min can be a challenge for the anaesthetist.

Side-effects
Despite haemodynamic stability, we observed incidences of nausea, vomiting, headache, and facial flushing in accordance with the incidences of previous studies.\textsuperscript{5,24,26} The high incidence of nausea and vomiting might also be associated with visceral stimulation secondary to manipulation and exteriorization of the uterus and not only by hypotension.

Oxytocin and carbetocin are both known to induce chest pain accompanied by signs of myocardial ischaemia.\textsuperscript{5,28} We recorded a relatively high incidence of chest pain (17%) and observed ST-segment changes (4%) in our trial. Only an incidence of 5–8% of chest pain was reported in two dose-finding studies for carbetocin.\textsuperscript{24,27} In many other trials investigating carbetocin or oxytocin, chest pain and ST-segment changes are not mentioned in the list of side-effects.\textsuperscript{5,9,26,28}

The risk for chest pain and ST-segment changes seemed independent of the mode of carbetocin administration.

Conclusions
Administration of carbetocin as a short infusion does not compromise uterine tone. There was no advantage in haemodynamic stability when using it as a short infusion as compared with a slow i.v. bolus. In accordance with current recommendations for oxytocin, carbetocin can safely be given as a short
infusion ensuring the desired slow administration of more than one min. Moreover, this allows the anaesthetist to have his hands free enabling him to focus on other more important tasks during this critical period of obstetric anaesthesia.

Authors’ contributions
Study design/planning: S.D.K., I.H., L.A.S., H.C.B., T.G.
Study conduct: S.D.K., I.H., O.L., E.S., T.G.
Data analysis: S.D.K.
Writing paper: S.D.K.
Revising paper: all authors

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

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Declaration of interest
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