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Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial

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Objective This study compares the maternal heart rate effects of carbetocin and oxytocin during elective caesarean delivery.

Design Double blind randomised single centre study (1:1).

Setting University hospital providing intrapartum care.

Population Fifty-six women undergoing elective caesarean section after spinal anaesthesia.

Methods Haemodynamic parameters were measured non-invasively using the Task Force® Monitor 3040i system. Measurements were taken for 500 seconds upon administration of a slow intravenous bolus of the clinically recommended doses of 100 μg of carbetocin or 5 IU of oxytocin to prevent postpartum haemorrhage (PPH).

Main outcome measure Effect on maternal heart rate (HR).

Results Statistically indistinguishable haemodynamic effects were seen for both drugs, with a maximal effect at about 30–40 seconds: HR increased 17.98 ± 2.53 bpm for oxytocin and 14.20 ± 2.45 bpm for carbetocin. Systolic blood pressure (sBP) decreased (−26.80 ± 2.82 mmHg for oxytocin versus −22.98 ± 2.75 mmHg for carbetocin). Following the maximal effect, women treated with carbetocin recovered slowly to baseline values asymptotically (HR and BP), whereas women treated with oxytocin displayed a slight rebound bradycardia at 200 seconds (−6.8 ± 1.92 bpm). Patients under both treatments showed a similar profile of side effects without any indication of unexpected adverse effects.

Conclusion Both oxytocins have comparable haemodynamic effects and are uterotonic drugs with an acceptable safety profile for prophylactic use. Minimal differences in the recovery phase beyond 70 seconds are in keeping with the fact that carbetocin has an extended half-life compared with oxytocin.

Keywords Caesarean section, carbetocin, cardiovascular effects, oxytocin, postpartum haemorrhage.

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Introduction

Postpartum haemorrhage (PPH) is a potentially life-threatening complication of both vaginal and caesarean delivery. The prevalence of PPH is approximately 6% of all deliveries.[1] The most frequent cause of PPH is uterine atony; therefore, active management of the third stage of labour rather than expectant management is recommended.[2,3] Currently intravenous injection of 5 iu of oxytocin is recommended as the prophylactic medication of choice to reduce the incidence and severity of PPH.[3,4] Oxytocin has a short half-life, whereas carbetocin, an oxytocin derivative exerting its effect via the same molecular mechanisms as oxytocin, has a longer half-life, and has been reported to decrease the use of additional oxytocics.[5,6] Currently 100 μg of carbetocin is routinely used for the prevention of PPH.

The haemodynamic effects of an oxytocin bolus consist of systemic vasodilatation, with hypotension, tachycardia, and an increase in cardiac output and pulmonary artery pressure, resulting in brief hypotension and tachycardia in a dose-dependent manner.[7–11]

* These authors contributed equally to the protocol, the study and the article.

Clinical trials comparing the contractile effect of carbetocin and oxytocin reported similar adverse symptoms with both drugs.[6,12–15] However, to the best of our knowledge—apart from animal experiments and single isolated observations—no detailed haemodynamic analysis has been reported, and thus no reliable clinical data about the haemodynamic side effects of carbetocin are accessible.[15] Because of the use as a prophylactic medication and the growing number of high-risk parturients—either pregnancy related or linked to pre-existing cardiovascular diseases—it appears timely and important to evaluate the haemodynamic side effects of both drugs.

We therefore compared the impact of carbetocin versus oxytocin for relevant maternal haemodynamic parameters in a non-invasive set-up during primary caesarean delivery in a double-blind randomised trial.

Methods

Setting

The study took place at the Medical University of Graz, Department of Obstetrics and Gynaecology, in Austria, with approximately 2500 deliveries per year.

Study design

Double blind randomised single centre study (ratio 1:1).

Primary outcome

Effects of both drugs on maternal heart rate (HR).

Secondary outcome

Additional haemodynamic effects on blood pressure (BP), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR). The impact of both drugs on pre- and postoperative haemoglobin, uterine tone, and incidences of other adverse effects.

Inclusion criteria

This study includes healthy pregnant women undergoing elective caesarean section at term with regional anaesthesia.

Exclusion criteria

Women with placenta praevia, placental abruption, and multiple gestation were excluded because these conditions are associated with an increased risk of PPH. Women with pregnancy-related complications and disorders such as pre-eclampsia, gestational diabetes, or pre-existing diseases such as insulin-dependent diabetes, cardiovascular or renal diseases, or hypo-/hyperthyroidism, were also excluded, as these conditions could possibly interfere with haemodynamic parameters. Additionally, women taking medication with a known impact on the cardiovascular system were excluded. Finally, women undergoing caesarean section with general anaesthesia were also excluded, as carbetocin is licensed for use only with regional anaesthesia.

Sample size estimation

As both drugs do act via the same mechanisms and no differences in adverse effects have been reported so far, we hypothesised that both drugs have the same acute haemodynamic profile following administration. From previous studies it has been predicted that changes in HR would be more reliable than changes in BP when using non-invasive monitoring; therefore, the sample size calculation was based on an HR difference between the groups. We hypothesised that a difference of 10 bpm (± 10 bpm SD) would be clinically relevant. Power analysis was performed using an online version of STATSUPPORT 1.0 (John Eng, Johns Hopkins University, Baltimore, MD, USA). We calculated that we would need 52 women (26 in each group) to detect significant differences (with a power of 95%; $\alpha = 0.05$). We decided to recruit 30 women for each group to counter participant withdrawal. As the study progressed we noticed that as a result of interference from high-frequency electrocautery, some measurements could not be analysed (Figure 1). We therefore extended the study until the number of 30 patients in each group had been reached.

Ethics

Ethical approval was granted by the Ethics Committee of the Medical University of Graz (reference number: 19-014 ex. 07/08). The study was registered with the European Clinical trials database (EudraCT 2007-005498-78). We followed

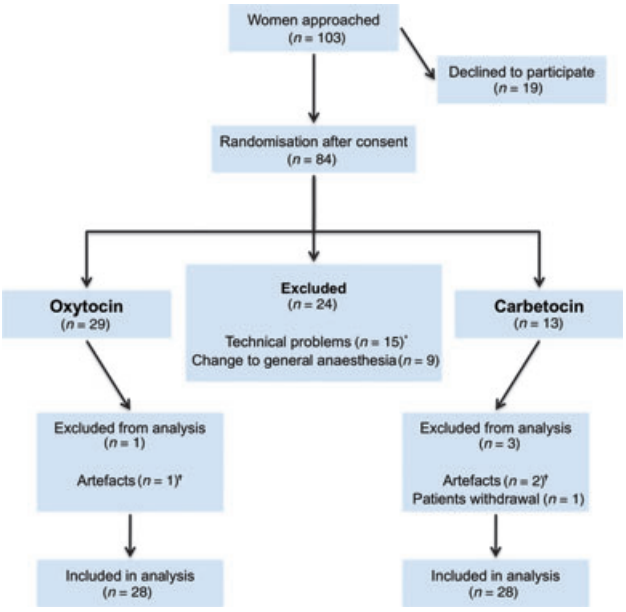

Figure 1. Randomisation flow chart. *Dislocation of electrodes, patient movements, interference with electrocautery; †recording artefacts.

the CONSORT statement for reporting the results of the study.[16]

Recruitment and consent

Women who were scheduled to undergo elective caesarean delivery with spinal anaesthesia were recruited, starting in November 2007. Signed informed consent was obtained from all women at the time of recruitment.

Randomisation

Randomisation was performed by computer (RANDLIST 1.2, randomisation sequence 1:1 ratio—blocks of ten, no stratification; DatInf GmbH, Tuebingen, Germany). Women randomised would receive either 5 iu of oxytocin or 100 μg of carbetocin (the standard clinical doses). According to the random list the study nurse, diluting either oxytocin or carbetocin with 10 ml 0.9% NaCl solution into a 25 ml syringe, prepared both study medications. Both drugs were prepared exactly 5 minutes before caesarean delivery, and were then handed to the anaesthesiologist. Study medication was double blinded to the clinical staff (obstetricians as well as anaesthesiologists) and the technicians performing the measurements.

Study drug administration and clinical management

Both drugs were administered as an intravenous bolus (delivered in 10 seconds) by the anaesthetist after the delivery of the baby. The monitoring and anaesthetic techniques were identical for all women. For a fluid preload, 500 ml of 6% hydroxyethyl starch (130/0.4) and 500 ml Ringer's solution were administered. After the patient had entered the operating theatre a local anaesthetic (lidocaine hydrochloride) was injected in preparation for spinal anaesthesia by a single-shot technique in a sitting position. The spinal anaesthetics (17 mg of ropivacaine and 20 μg of fentanyl) were injected intrathecally at L2/3. Fluid, as well as ephedrine infusion or boluses, could be given as required to achieve haemodynamic stabilisation.

The caesarean technique was as follows. Laparotomy was performed by a modified Misgav–Ladach technique or Pfannenstiel incision, if necessary. Following uterine incision, delivery of the baby, and cord clamping, the placenta was delivered by cord traction. For uterine repair the uterus was exteriorised.

Haemodynamic measurement and data collection

After the application of the spinal anaesthesia the women were positioned in a left-tilted recumbent position. A finger cuff for continuous BP and an arm cuff for the oscillating BP measurement, as well as the electrodes, were applied by the technician. The technician performed the measurement and reported (clinically) relevant actions, such as the administration of the study medication, delivery of the baby, specific surgery techniques, e.g. exteriorisation of the uterus (causing an increased venous return), sewing of the fascia, and other events considered to be a possible cause of significant haemodynamic effects. Additionally, further administration of drugs was recorded online during the measurement.

Haemodynamic measurement began after achieving the haemodynamic stabilisation of the women. Surgery was initiated after a calibration period of 3 minutes. We used the Task Force® Monitor 3040i system (CNSystems Medizintechnik AG, Graz, Austria) to retrieve and record the haemodynamic parameters, as previously described.[17,18] The Task Force® Monitor includes electrocardiography (ECG), impedancecardiography (ICG), beat-to-beat BP by the vascular unloading technique, all sampled with 1000 Hz each, and oscillometric BP recording for additional haemodynamic measurements. These data were used to calculate all haemodynamic parameters online.

Briefly, HR was derived by ECG from two separate adhesive monitoring electrodes, which were placed on the thorax to give maximal amplitude of the R wave. Continuous BP was measured from the finger using a refined version of the vascular unloading technique, and was corrected to absolute values with oscillometric BP measurements by the Task Force® Monitor. In comparison with intra-arterial BP, measurements with the Task Force® Monitor provided very comprehensive results, which produced reliable relative values of continuous BP.

The systems ICG hardware is based on the traditional four-wire method, where a constant current I_{const} (400 μA at 40 kHz) is passed through the thorax between an electrode placed around the neck and another electrode placed around the lower thorax aperture. The voltage is acquired by two further electrodes placed between the admitting electrodes, each at a distance of at least 3 cm from the outer electrodes in order to produce a homogeneous current field between them. The detected voltage $u(t)$ is proportional to the thorax impedance. The systems ICG measurement is performed using an improved estimate of the thoracic volume, and can eliminate respiratory artefacts. Furthermore, a patented set of short-band electrodes is used, which is able to create a particularly homogeneous field in the thorax, further increasing the reproducibility of the CO measurements. Standard formulae were used for the calculation of TPR; SV was calculated according to the method described by Kubicek.[19]

Furthermore, using a linear analogue scale from 1 to 10, the surgeon evaluated the tone of the uterus. Additionally, in order to evaluate blood loss, haemoglobin levels were recorded before and after the caesarean delivery.

Statistical analysis

All analyses were conducted using the statistical software program SPSS 13 (SPSS Inc., Chicago, IL, USA). Test results

are expressed as means ± standard errors of the means. Data were tested for normal distribution. Demographic and clinical data were compared by means of independent samples Student's *t*-test, or chi-square test if appropriate. Differences were considered as significant with $P < 0.05$. Pearson's correlation was used as a measure of the effect of size: a correlation coefficient <0.10 was considered to be very small and practically negligible; a correlation coefficient <0.30 was considered to be a small effect; a correlation coefficient of between 0.30 and 0.50 was considered to be a medium effect; and a correlation coefficient >0.50 was considered to be a large effect.

Results

The study was conducted over a continuous 6-month period (from January to July 2008). In total, 84 women were recruited. The randomisation flow chart is shown in Figure 1. Twenty-four patients had to be excluded because of technical problems, such as dislocation of electrodes, movement artefacts, and interference with electrocautery, and/or alterations in treatment by changing from spinal to general anaesthesia. From the haemodynamic measurement files of the remaining 60 patients, four additional patients had to be excluded because of a combination of several artefacts (three patients) and participant withdrawal (one patient). The remaining 56 patients were analysed in this study. In order to compare the haemodynamic changes in both groups, administration of the study medication was defined as the starting point of the graph.

All important maternal subject characteristics in both study groups were comparable, as summarised in Table 1. The number of patients in both groups was equal. No significant differences between both groups regarding exteriorisation of the uterus during surgery could be found. In both groups haemoglobin levels before and after the caesarean delivery—indicating the level of blood loss—were similar, as was the tone of the uterus (Table 1). In both groups no further contractile intervention, such as additional medication or uterine massage, was necessary. Any adverse effect was recorded, but no statistically significant differences were found. In both groups, three patients received ephedrine following the administration of the study medication in order to maintain an adequate BP.

Figures 2–5 demonstrate the progress of the haemodynamic parameters after the intervention. All calculations are based on similar haemodynamic parameters, with comparable baseline values in both groups, with a higher HR and concomitant lower BP for patients given carbetocin; however, the differences were not statistically significant.

Figure 2 demonstrates a rapid increase in HR by 17.98 ± 2.53 bpm (oxytocin) and 14.20 ± 2.45 bpm (carbetocin) at 30–40 seconds after the application of the study medication, with an apparent rebound bradycardia at 200 seconds (−6.80 ± 1.92 bpm) for oxytocin. The rebound bradycardia was both less pronounced and delayed (−3.04 ± 1.95 bpm at 270 seconds) in patients receiving carbetocin, although not to a statistically different level.

Table 1. Subject characteristics of the entire study group

	Carbetocin (n = 28)	Oxytocin (n = 28)
Age (years)	30.9 ± 5.8	30.4 ± 4.6
Gestational age at delivery (weeks)	39 ± 2	39 ± 2
Nulliparous	11	11
Body mass index (kg/m^2)	28.96 ± 5.36	27.95 ± 3.92
Indications for caesarean delivery		
Breech presentation	10	12
Previous caesarean delivery	12	10
Others	6	6
Difference in haemoglobin levels Before/after surgery (g/dl)	1.10 ± 0.99	1.14 ± 0.76
Uterine tone (scale from 1 to 10)	7.65 ± 1.56	7.83 ± 1.70
Side effects	10	11
Nausea	3	4
Symptoms of flushing	4	3
Headache	2	2
Tachycardia	0	1
Feeling warm	1	0
Shortness of breath	0	1

Data are given as means ± standard deviations or numbers.

The maximal hypotensive effect of both drugs was reached at approximately 30–40 seconds after receiving the study medication. In both groups systolic blood pressure (sBP) decreased by 26.80 ± 2.82 versus 22.98 ± 2.75 mmHg (Figure 3), diastolic blood pressure (dBP) decreased by 19.42 ± 1.78 versus 17.34 ± 1.88 mmHg (Figure 4), and mean arterial blood pressure (mBP) decreased by 22.42 ± 2.11 versus 19.38 ± 2.12 mmHg for oxytocin and carbetocin, respectively. The most pronounced effect was seen in total peripheral resistance (TPR), which decreased by 38.52 ± 3.11 and 32.00 ± 3.37% after the administration of oxytocin and carbetocin, respectively (Figure 5). All these effects peaked at about 30–40 seconds; however, differences between the treatments were statistically not significant.

Patients treated with carbetocin showed a slow recovery for HR after the peak, approaching the baseline values asymptomatically. In contrast, patients treated with oxytocin showed a more pronounced rebound bradycardia, slightly below their baseline levels (with a decrease of about 7%). The treatments differed between 100 and 300 seconds, with respect to recovery times, but these statistically significant differences appear to have no clinically relevant effects,

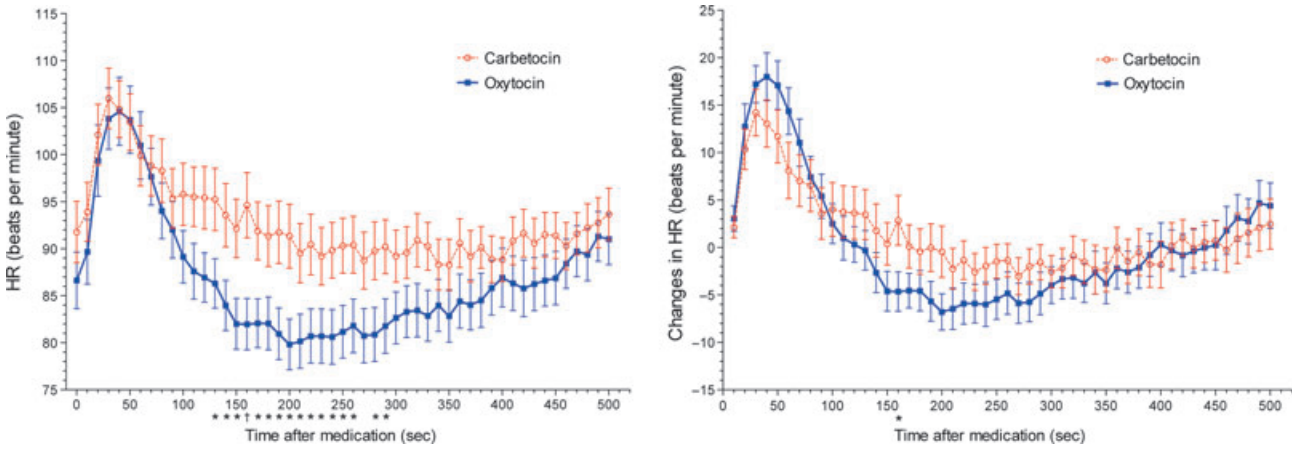

Figure 2. Left: maternal heart rate (HR) after the administration of the study medication. Right: changes in maternal HR following adjustment of different baselines between both groups. Data are displayed as means ± SEMs. Differences between both groups are indicated on the *x*-axis (*$P < 0.05$; †$P < 0.001$).

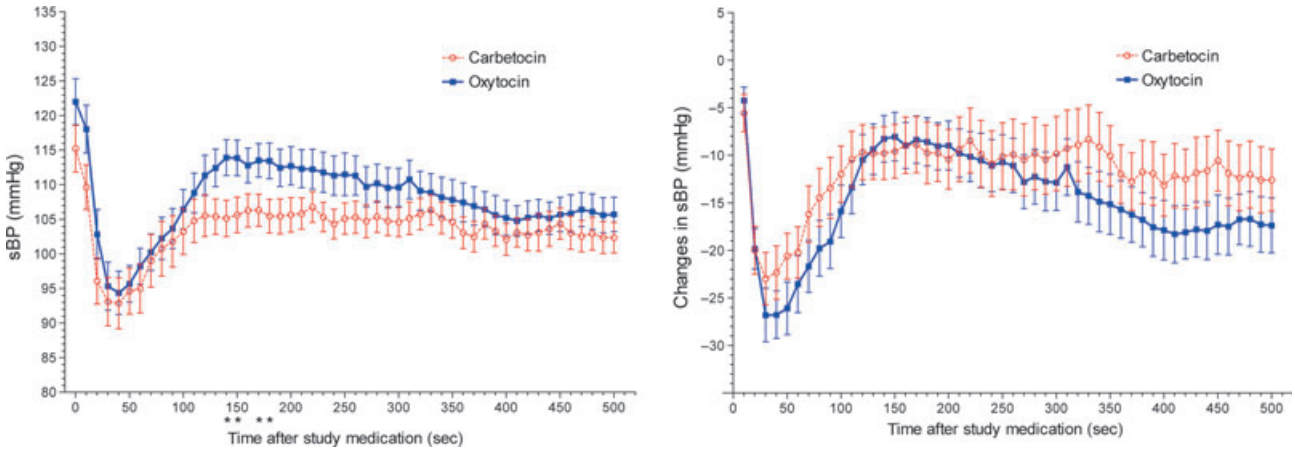

Figure 3. Left: maternal systolic blood pressure (sBP) after the administration of the study medication. Right: changes in sBP following adjustment of different baselines between both groups. Data are displayed as means ± SEMs. Differences between both groups are indicated on the *x*-axis (*$P < 0.05$).

and are within the acceptable clinical variation of HR. Similar effects were observed for BP parameters. However, after correcting for the increased HR and lower BP baseline values in patients treated with carbetocin, these effects were no longer statistically significant (Figures 2–5, right panels). Both groups of patients came back to their baseline haemodynamic levels after approximately 500 seconds.

The SV increased by about 10–12% (oxytocin) and 4.9–7.4% (carbetocin), reaching the maximum level between 80 and 150 seconds after administration, and remaining almost constant at this increased level, with only a slow decrease following the peak. The CO increased by about 26% (oxytocin) and 17% (carbetocin), reaching its maximal change between 30 and 60 seconds after administration of the medication (data not shown). After reaching the maximal effect, no statistically significant differences for SV and CO could be detected between both groups.

The observed effect sizes of the treatment effect, measured in terms of the correlation coefficient, ranged from 0.27 to 0.36 for the statistically significant results shown in Figures 2–5, and were below 0.27 for non-significant group differences. Therefore, all statistically insignificant group differences had a small effect and the effect sizes for the statistically significant results could be characterised as small to medium. Furthermore, it is notable that baseline levels of HR were slightly raised and BP fell during the observation period. This haemodynamic effect cannot be attributed to the administration of oxytocin or carbetocin.

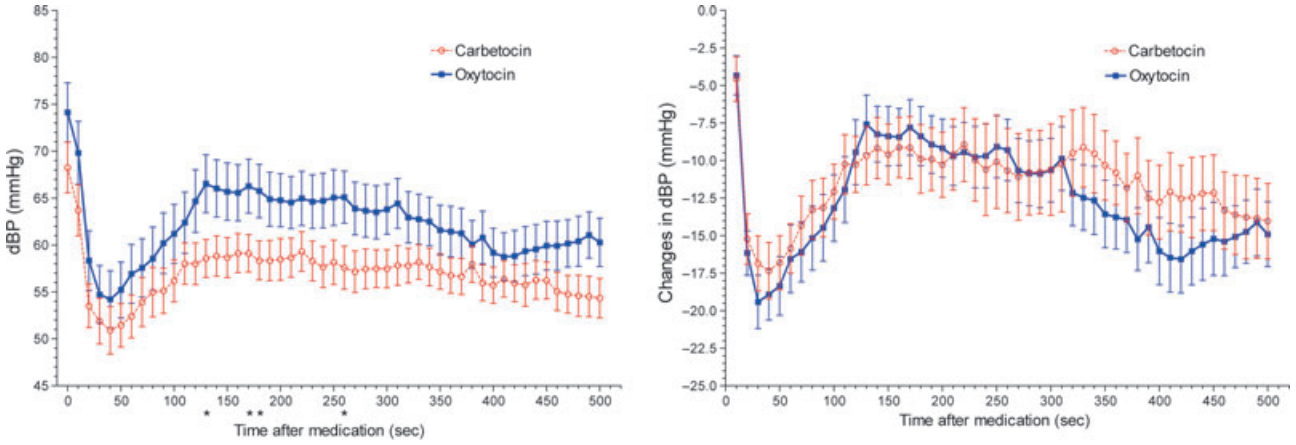

Figure 4. Left: maternal diastolic blood pressure (dBP) after the administration of the study medication. Right: changes in dBP following adjustment of different baselines between both groups. Data are displayed as means ± SEMs. Differences between both groups are indicated on the *x*-axis (*$P < 0.05$).

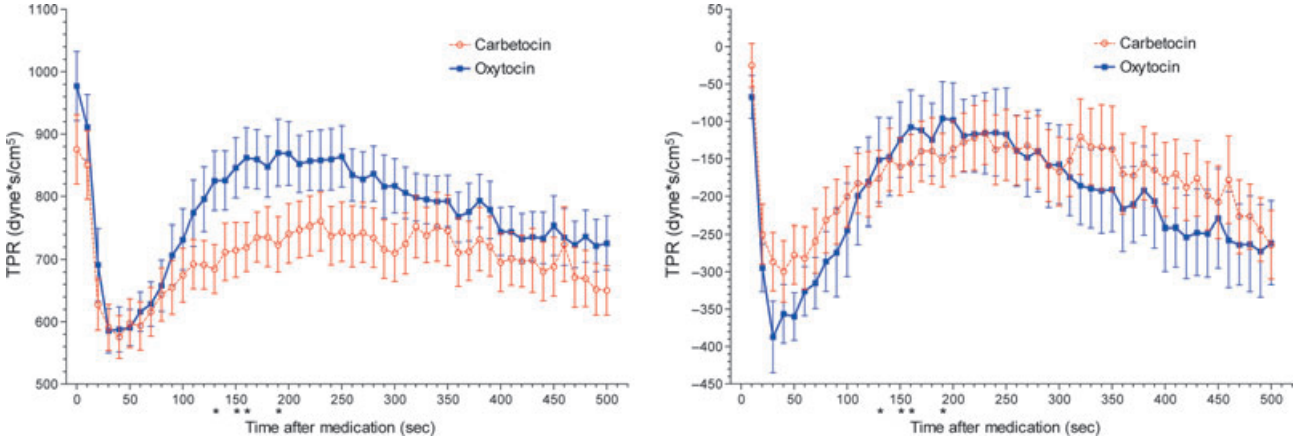

Figure 5. Left: maternal total peripheral resistance (TPR) after the administration of the study medication. Right: changes in TPR following adjustment of different baselines between both groups. Data are displayed as means ± SEMs. Differences between both groups are indicated on the *x*-axis (*$P < 0.05$).

Discussion

To the best of our knowledge this is the first study to compare the detailed immediate haemodynamic effects of licensed doses of oxytocin and carbetocin. This randomised, double-blinded study was designed to specifically compare the effect of the clinically recommended doses for carbetocin (100 μg) versus oxytocin (5 iu) on maternal haemodynamic parameters in a non-invasive set-up (TaskeForce® Monitor) during primary caesarean delivery. The results demonstrate that there is no statistically significant difference in immediate haemodynamic changes.

The prophylactic use of uterotonic drugs has significantly reduced maternal morbidity and mortality caused by PPH; however, oxytocin, which is the medication widely recommended in the current literature,[3,4] causes haemodynamic side effects that may lead to myocardial ischaemia,[9] especially in patients with hypovolaemia or cardiac diseases, which are steadily increasing because of the growing number of deliveries with relevant risk factors. Carbetocin, a synthetic derivate of oxytocin with a longer half-life, is reported by current studies to have advantageous effects on uterine contraction compared with oxytocin.[6,12–14]

In both groups and populations, HR increased while TVR and BP values decreased by comparable levels within the first 40 seconds of administration. This initial change until the maximum effect of the uterotonic drugs is reached is of clinical relevance. The course of the two graphs in this phase was very similar and showed no statistically significant differences. In the recovery phase, after

peak values were overcome, the two graphs showed minor but statistically significant aberrations of no clinical relevance. Whereas patients treated with carbetocin recovered slowly to baseline levels, patients treated with oxytocin showed a more pronounced rebound and recovery from beyond baseline levels. This can be regarded as a slight rebound bradycardia in the oxytocin group. However, this minor difference becomes statistically not significant if we correct the different baseline values for HR and BP between both groups. Therefore, we can conclude that both oxytocics do have comparable effects on the cardiovascular system, with no significant adverse clinical relevance. The incidence of other adverse side effects, such as headache, nausea or symptoms of flushing, was similar, as described in a previous study.[15]

We could not confirm earlier reports that carbetocin had a slightly better uterotonic effect.[6,12–14] The results on the intraoperative evaluation of myometrial contraction, the drop of haemoglobin and the need for additional contractile intervention were comparable for both groups. However, our study outcomes did not evaluate the necessity of additional drugs after surgery; therefore, these results may be biased. Every effort was taken to keep the clinical staff blinded as to which medication they were using. Nevertheless, as the study medication had to be prepared 'on site' we cannot rule out involuntary cancelling of the blinding.

The exact concordance of all the effects of oxytocin and carbetocin leads to the suggestion that they bind to the oxytocin receptor in exactly the same way and exert their effects through the same molecular mechanisms. The only differences seem to be the longer half-life and the lower biological activity of carbetocin.[5,6,20,21]

We therefore conclude that carbetocin and oxytocin are uterotonic drugs with an acceptable safety profile for prophylactic use at the indicated doses to reduce maternal morbidity and mortality caused by PPH. A slower injection of oxytocin was reported to minimise the cardiovascular side effects of a bolus dose without compromising the contractile benefits.[8] As our results show that oxytocin and carbetocin have the same effects and side effects, it is reasonable to speculate that the observed haemodynamic changes may be minimised when oxytocin or carbetocin are administered as a short infusion over, for example, 120 seconds, instead of in a bolus application. Additionally, carbetocin has been reported to reduce the need for additional uterotonic medication because of the longer half-life.[6] Our results of the same haemodynamic profile, together with the finding of a reduced need for additional uterotonics and the finding that repeated doses of oxytocin cause clinically and statistically significant haemodynamic changes,[10] support the suggestion of Attilakos et al.,[6] that 'carbetocin may become the medication of choice for women with hypertensive disorders or cardiac problems'. Given the current data it must be emphasised that both uterotonics should be administered as a slow infusion over at least 5 minutes, and that the oxytocin dose should always be as low as possible.

Disclosure of interests

All authors confirm no conflicts of interest with regards to the data reported here.

Contribution to authorship

MGM conceived the idea, performed the literature search, designed the study, applied for ethical approval and EudraCT registration, recruited women, performed the caesarean sections, and co-authored the article. SF performed measurements, recruited women, collected data, and co-authored the article. JK performed measurements, recruited women, collected data, and co-authored the article. CW and UL co-authored and reviewed the article. DS performed the literature search, designed the study, applied for ethical approval and EudraCT registration, assisted with statistical analysis, and authored the article.

Details of ethics approval

Ethical approval was granted by the Medical University of Graz ethics committee (reference number: 19-014 ex 07/08) on 15 October 2007. Clinical trial authorisation was granted by the Medicines and Healthcare Products Regulatory Agency (EudraCT number: 2007-005498-78). ClinicalTrials.gov identifier: NCT01277978.

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