Exploring cardiac effects after oxytocin 2.5 IU or carbetocin 100 µg: a randomised controlled trial in women undergoing planned caesarean delivery

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Key points

- Oxytocin and carbetocin are uterotonic agents used to prevent postpartum haemorrhage.

- This study explored cardiac effects of oxytocin and carbetocin.

- Healthy women (n=40) undergoing planned caesarean delivery were randomised.

- Oxytocin 2.5 IU and carbetocin 100 µg caused similar increase in QTc.

- Higher release of troponin was seen in the oxytocin group.

Abstract

Background: Oxytocin can stimulate release of myocardial biomarkers troponin I and T, prolong QTc and induce ST-depression.

Objective: To explore cardiac changes after either intravenous carbetocin or oxytocin.

Study Design: Exploratory phase 4 randomised controlled trial.

Setting: Obstetrics units of Oslo University Hospital, Norway between September 2015 and May 2018.

Participants: Forty healthy, singleton pregnant women aged 18 to 50 years at gestational age at least weeks with a planned caesarean delivery.

Interventions: Participants were randomised to receive either oxytocin 2.5 IU or carbetocin 100 µg immediately after delivery.

Main outcome measures: The primary endpoint was the assessment of troponin I within 48 h of study drug administration. Troponin I and T, and creatine kinase myocardial band assessments were measured before spinal anaesthesia (baseline), and again at 4, 10 and 24 h after delivery. QTc, ST-depression and relative increase in heart rate were recorded from start of study drug administration to 10 min after delivery. All adverse events were monitored.

Results: Compared with the carbetocin group, higher troponin I levels were observed in the oxytocin group at 4 h and 10 h after delivery. For both treatment groups, an increase from baseline in troponin I and T was most pronounced at 10 h after delivery, and it had begun to decline by 24 h. QTc increased with time after administration of both study drugs, with a mean maximum increase of 10.4 ms observed at 9 min $(P<0.001)$. No statistical differences were observed in QTc $(P=0.13)$ or ST-depression $(P=0.11)$ between the treatment groups.

Conclusions: Oxytocin 2.5 IU and carbetocin 100 µg caused a similar increase in QTc. The trial was underpowered with regards to ST-depression and the release of myocardial biomarkers and these warrants further investigation. Data from this trial will inform a larger phase 4 trial to determine potential drug differences in troponin release.

Trial registration: ClinicalTrials.gov Identifier: NCT02528136

Keywords: Arrythmia, caesarean delivery, carbetocin, oxytocin, troponin, uterine atony

Introduction

Oxytocin analogues are used for preventing postpartum haemorrhage (PPH) after vaginal and caesarean delivery.[1-4] At physiological concentrations, oxytocin exhibits cardioprotective properties by reducing inflammatory response and improving cardiovascular and metabolic function through the release of atrial natriuretic peptide (ANP) and nitric oxide–mediated vasodilation that leads to a reduction of arterial pressure.[5, 6] However, at the higher concentrations frequently used for preventing PPH, oxytocin induces dose-dependent hypotension and tachycardia, as well as ST-depression, prolongation of QTc interval, and arrythmias, all symptoms of myocardial distress.[4, 7, 8] Furthermore, high doses of oxytocin may cause circulatory collapse in hypovolemic patients and has been linked to myocardial infarction and death due to fatal arrythmia in patients with underlying myocardial pathology.[9] These cardiovascular symptoms are caused by oxytocin, and not due to pregnancy, delivery, surgical procedure or spinal anaesthesia.[8]

Carbetocin, a synthetic oxytocin receptor agonist with rapid onset of action (within 2 minutes of administration), has gained popularity for prevention of PPH due to its prolonged half-life of approximately 33 minutes[10] compared with the half-life of 2–3 minutes for intravenous oxytocin.[11] Several studies and meta-analyses have proved equal or improved effect on uterine contractions compared with oxytocin and both drugs are effective at preventing PPH.[12-15] The haemodynamic footprints of oxytocin 5 IU and carbetocin 100 μg are comparable;[16-18] however, the cardiac adverse events (AEs) of carbetocin are not well described and the effects of its prolonged half-life on these are unknown.

When oxygen supply to the heart is limited, circulating troponin I (cTnI) and troponin T (cTnT) are released into the circulating blood from myocardial myocytes, and these troponins can be used as an indirect measure of ischaemic heart damage and for making prognoses. As oxytocin causes dose-dependent symptoms of myocardial distress, our exploratory trial was to see whether there were any differences in troponin release between oxytocin and carbetocin. To the best of our knowledge, no previous study has compared the cardiac AEs of oxytocin and carbetocin when used to prevent PPH. In this exploratory Phase 4 study we investigated if carbetocin and oxytocin cause similar cardiac changes, including increases in cTnI and cTnT plasma concentrations, in women who have undergone a planned caesarean delivery.

Methods

Trial design

The Clinical Carbetocin Myocardium Trial was a randomised, double-blind trial conducted at the Division of Emergency and Critical Care, Oslo University Hospital between September 2015 and May 2018. The trial protocol was approved by the local Data Inspectorate´s representative at Oslo University Hospital, the Regional Committee for Medical and Health Research Ethics of Southern Norway (REC 2014/1210) and the Norwegian Medicines Agency (EudraCT number 2014-000507-27). The study was registered at clinicaltrials.gov (NCT02528136), and conducted according to Good Clinical Practice standards and the principles of the Declaration of Helsinki,[19] and the CONSORT and COS-STAR guidelines.[20, 21] We included all the core outcomes for PPH trials except breastfeeding and patient satisfaction.[22]

Trial population

Healthy women aged 18 to 50 years with a singleton pregnancy and undergoing planned CD at a gestational age of at least 36 weeks were eligible for inclusion. All participants were required to understand Norwegian to provide oral and written informed consent, obtained 24 hours prior to delivery. Women with placenta previa/accrete, preeclampsia/eclampsia, bleeding disorders, cardiac disease, prolongation of QT-time, organ failure, epilepsy, or any medical condition making the woman unfit for inclusion according to the investigator were not eligible.

Study drug administration and allocation

Participating women were randomised 1:1 to receive either 2.5 IU oxytocin (Syntocinon®, Novartis Pharmaceuticals, 5 IU ml^{-1}) or carbetocin 100 µg (Pabal®, Ferring Pharmaceuticals, 100 µg ml^{-1}), both used in accordance our department guidelines and with international consensus for the prevention of PPH in planned caesarean deliveries.[4] Both these doses represent approximately seven times the 90% effective dose (ED90) for a planned caesarean delivery (0.35 IU and 14.8 µg for oxytocin and carbetocin, respectively[23, 24]). Although the standard procedure according to its label is to administer 1 ml of carbetocin (100 µg ml^{-1}),[10] to maintain blinding both study drugs were diluted to 5 ml using 0.9% saline solution. The study drug was administered as a 1-minute intravenous injection immediately after delivery of the baby.

Randomisation

Identical syringes marked with trial identification and randomisation number were given to the anaesthesiologist in the operating theatre. Allocation information was kept in sealed, opaque envelopes marked with the randomisation number. All data were entered into the database, which was then locked before adding the randomisation codes for treatment allocation. The patients were randomised in block sizes of four, six and eight according to a computer-generated list of random numbers: this was to maximise blinding while also increasing the chances of an equal number of patients in each arm of the study.

Primary and secondary endpoints

The primary endpoint was group differences in release of cTnI (concentration of cTnI in blood serum) within the first 48 hours after baseline. cTnI levels were measured by one-batch analysis after inclusion of all patients. For safety reasons, cTnT levels, analysed consecutively at the local hospital at baseline and at 4, 10 and 24 hours, were used to detect patients who may have required an additional blood sample at 48 hours if cTnT levels were still elevated; however, additional blood samples at 48 hours were not necessary, as levels of cTnT were already decreasing in all patients at 24 hours after study drug administration. Secondary endpoints included group differences in release of other myocardial biomarkers (creatine kinase myocardial band [CK-MB], CK and NT-proBNP), QTc, ST segment depression, relative increase in heart rate (HR), uterotonic effect, need for additional treatment, estimated bleeding and reported adverse events.

For all neonates, we recorded umbilical vein and artery pH from a clamped portion of cord within 60 minutes of birth, and Apgar score at 1, 5 and 10 minutes after birth.

Anaesthesia procedure

Spinal anaesthesia was induced in a sitting or right lateral position at the discretion of the anesthetist. Hyperbaric bupivacaine 10 mg and fentanyl 20 μg were injected with a 27- or 25-gauge atraumatic needle at the L2–L3 or L3–L4 vertebral interspace. Spinal-induced hypotension (systolic arterial pressure <90 mmHg) was prevented with a rapid intravenous co-load of 0.9% saline solution (37°C, 10 ml kg^{-1}) and a phenylephrine bolus (0.50 μg kg^{-1}) followed by a phenylephrine infusion (0.25 μg kg^{-1} min^{-1}). Hypotension episodes were treated with an additional intravenous bolus of phenylephrine if the heart rate was more than 60 beats per

minute or with intravenous ephedrine 5 to 10 mg if HR 60 beats per minute or less. For surgery, the patient was placed in a supine wedged position: (19° Tempur pillow; Trulife®, Dublin, Ireland) under the patient's right hip.

Both study drugs were expected to lead to vasodilatation with a decrease in maternal blood pressure (BP) and increased HR. Spinal-induced hypotension was avoided by meticulous BP measurement, co-loading fluid with 10 ml kg^{-1} 0.9% saline and phenylephrine bolus and infusion titrated to maintain SBP at least 90 mmHg.

Myocardial biomarker assessments

Myocardial biomarkers were measured at baseline (before spinal anaesthesia), and 4, 10 and 24 hours after caesarean birth. A serum sample was collected at all time-points and stored in a local biobank freezer at below −70˚C . All samples were treated identically in terms of time waiting for sample to settle, spinning time and velocity to separate serum and storage. cTnI, a marker of ischaemic myocardial damage, was later analysed at Vestre Viken Trust, Drammen Hospital, after the last patient had been included. Batch analysis ensured that the same conditions applied for all the samples. cTnI was measured by a highly sensitive method using a chemiluminescent microparticle immunoassay (Architect ci16200®, Abbott, Illinois, U.S.A.). Normal values of troponin I in a female population (age 18 to 50 years) should be less than 15 ng l^{-1}, with the cut-off corresponding to the 99 percentile of a healthy reference population.[25] Serum concentration of creatine kinase, cTnT and N-terminal pro-brain natriuretic peptide (NT-proBNP) were analysed immediately using fresh samples on Cobas instruments (Roche Diagnostics, Mannheim, Germany) at the Department of Medical Biochemistry at Oslo University Hospital.

ECG assessments

The 12-lead ECG was performed 30 minutes before surgery. A Holter monitor (Medilog AR4®, Schiller, Baar, Switzerland) for recording continuous measurements during the surgery was also attached 30 min before surgery to allow for baseline stabilisation before the anaesthetic procedure. Baseline values for HR, ST segment (mV) and QTc interval (ms; Framingham method)[26] were recorded 1–2 minutes before administration of study drug. Beat-by-beat analysis was performed by two independent observers masked to treatment allocation; maximum values were recorded at baseline and then every minute until 10 min after study

drug administration.

Continuous QTc interval monitoring using a Holter monitor provided beat-by-beat analysis and allowed the investigators to capture the maximum QTc interval every minute during the observation time frame. As HR affects QT interval, it is routine practice to adjust the QT interval to a HR of 60 beats per minute, providing a corrected QT interval, QTc. Although Bazett described the first formula for QT interval correction in 1920, this formula tends to overcorrect the QT interval at higher HRs and under-correct at slower HRs.[27] In this study, we applied QT-correction according to Framingham, as this method provides improved rate correction and prediction of dangerous QTc prolongation compared with the Bazett method.[26]

Assessment of uterotonic effects, additional treatment, and blood loss

The obstetrician assessed uterine tone at 2.5 and 5 min after administration of the study drug using a numeric rating scale ranging from 0 to 10: a score of 0 meant 'no effect', 10 meant 'maximal uterus contraction', and 7 indicated 'clinically satisfactory contraction'.[18] As visual assessment of blood loss during caesarean delivery is of limited value, we calculated blood loss using the formula for calculated estimated blood loss as published by Stafford et al.[28] revised to use weight in kilograms (last measurement before surgery) and height in centimetres; the calculation also uses the change in haematocrit from predelivery to 24 h after delivery. If judged necessary by the obstetrician, additional uterotonics including oxytocin, misoprostol, methylergometrine or carboprost were administered to prevent excessive blood loss.

Adverse event monitoring

Noninvasive BP and HR were recorded before anaesthesia and repeated every 2 min throughout surgery. Adverse events were recorded at 0 to 2, 2 to 5 and 5 to 10 min after study drug administration. Prior to study drug administration, participating women were shown a list of possible adverse events: these were a feeling of warmth, chest pain, shortness of breath, palpitations, flushing, headache, nasal congestion, dry mouth and metallic taste or other events or reactions listed in the summary of product characteristics of the study drugs. Participants were asked to report the occurrence of any adverse event and grade the severity as mild, moderate or severe.

Statistical analyses

An intention-to-treat analysis was performed for the primary and secondary outcomes. Forty patients were planned to be enrolled to explore the potential differences in release of cTnI between the two treatment groups. There was no relevant information available about comparative cardiac effects of the study drugs to inform statistical power analysis.

We used descriptive statistics to analyse baseline values and patient characteristics, myocardial biomarkers and adverse events. Group differences were analysed by two-sample T-test, Mann-Whitney U test or Fisher's mid-P test, as appropriate. We used a linear mixed-effects model to analyse group differences in QTc as a function of time (10 minutes) in the treatment groups, corrected for baseline differences, with minutes and minute*treatment interaction as fixed effects, and a random intercept. Statistical analyses were performed using Stata/SE version 16.0 (StataCorp LLC, Texas, USA).

Results

Of the 223 women screened between September 2015 and May 2018, 41 women were randomised (Fig. 1). One woman randomised to receive carbetocin was excluded due to protocol deviation (failure of spinal anaesthesia and the need to convert to general anaesthesia).

There were no relevant differences between treatment groups regarding patient characteristics and baseline measurements (Table 1) or neonatal characteristics (Table 2). The duration of surgery was similar for the two groups. The primary indications for caesarean delivery were maternal request (35%), foetal malpresentation (32.5%), previous caesarean delivery (15%) and other obstetric reasons (17.5%).

Myocardial biomarker analysis

Compared with carbetocin, we observed a trend towards greater serum myocardial biomarkers with oxytocin (Fig. 2). Group differences in cTnI, cTnT and CK-MB over time are shown in Table 3 and Supplementary Table 1. No group differences were found for CK and NT-proBNP (data not shown). The largest differences from baseline in plasma cTnI levels were observed at 10 h: median [range] change from baseline for the oxytocin group was 0.4 [−0.5 to 20.1] ng l$^-$1, and for the carbetocin group, 0.2 [−0.6 to 2.9] ng l^{-1}. At 10 h after baseline, cTnI

was above the reference limit (>15 ng l^{-1})[25] in two women, both in the oxytocin group, but there were no ischaemic ECG changes or clinical symptoms of myocardial ischaemia. No women from the carbetocin group exceeded the reference limit for cTnI or cTnT.

ECG analysis

A similar relative increase in HR from baseline was observed for women in both treatment groups: oxytocin group, 57.1 ± 18.0%; carbetocin group, 66.8 ± 30.0%, *P*=0.22. Self limiting supraventricular tachycardia related to administration of study drug was observed in one patient in the carbetocin group. No other arrythmias were observed other than short episodes of sinus tachycardia related to onset of drug action and isolated supraventricular and ventricular extrasystoles. A similar number of extrasystoles were observed in both treatment groups before, during and after the period of observation, and was considered to be unrelated to the study drug.

The QTc interval from baseline until 10 min after administration of study drug is shown in Fig. 3. After an initial increase in QTc interval during the first 2 min, corresponding to the peak of tachycardia elicited by the vasodilatory effect of the study drugs,[18] a short decrease in QTc interval was observed at 3 min, followed by a gradual increase in both treatment groups. There was no difference between the groups. The QTc intervals remained in the normal range for age and sex of participants. In the entire cohort of patients, the peak QTc interval was seen 9 minutes after administration of the study drug, with a mean increase from baseline of 10.4 (95% CI 6.8 to 14.0) ms (Table 4). The overall *P* value for linear trend was less than 0.001. We found no difference between the treatment groups in QTc intervals (*P*=0.13).

ST-segment depression, defined as more than 0.1 mV depression, was observed in five women within the first minute after drug administration, one out of 21 in (4.8%) the oxytocin group and four out of 18 (22.2%) in the carbetocin group (*P*=0.11).

Use of additional uterotonic medication and estimated blood loss

Adequate uterine tone was obtained without additional treatment in 13 out of 21 (61.9 %) and 12 out of 19 (63.2%) women in the oxytocin and carbetocin groups, respectively (Table 5). The estimated calculated blood loss was comparable in both groups: 551.5 ± 381.8 vs. 559.5 ± 366.7 ml (*P*=0.95) for the oxytocin and carbetocin groups, respectively. The overall rate of PPH

more than 500 ml was 12 (57%) in the oxytocin group and 8 (42%) in the carbetocin group (*P*=0.37). Additional uterotonic (1 IU of oxytocin) was administered to eight out of 21 (38%) women in the oxytocin group and to seven out of 19 (37%) women in the carbetocin group. The time to administration of this additional uterotonic drug did not differ between the treatment groups. Four patients in the oxytocin group and two patients in the carbetocin group required rectal misoprostol, intravenous methylergometrine, intramyometrial carboprost or oxytocin infusion either alone or in combination. Group differences were not statistically significant. None of the participants required placement of a Bakri balloon or a B-lynch suture. There were no cases of maternal shock related to blood loss and none of the participants required transfusion, transfer to higher level of care or use of additional haemostatic interventions.

Safety analysis

There were no serious adverse events. Compared with the oxytocin group, more patients in the carbetocin group experienced adverse events during all intervals measured (Table 6). The differences were not statistically significant, except during the first 2 min when one (4.8%) woman in the oxytocin group and seven (36.8%) women in the carbetocin group experienced adverse events (*P*=0.01); however, group sizes were small, and we did not correct for multiple statistical comparisons for adverse events. There was no treatment difference for reported severity of adverse events, the majority of which were of mild or moderate severity.

The investigators were unable to distinguish between the study drugs: their guess as to which drug had been administered was close to random, confirming that treatment masking was maintained (*P*=0.28).

Discussion

This randomized trial is the first to explore the comparative myocardial effects of oxytocin 2.5 IU and carbetocin 100 µg when administered to preventing PPH in women undergoing a planned caesarean delivery. We observed increased levels of cTnI and cTnT in both groups compared with the baseline levels. These increases were most pronounced at 10 h after administration of either study drug. Although the mean concentrations of cTnI and cTnT were higher in the oxytocin group than in the carbetocin group, the differences were not statistically significant. The mean ± SD increases in cTnI at 10 h from baseline will be used for

statistical power calculations to help determine the sample size in a larger follow-up trial.[29] Increases in cTnI at 10 h exceeded the reference limit (>15 ng l^{-1}) in two patients, both in the oxytocin group; however, none of the patients experienced ECG changes or clinical symptoms of myocardial distress.

Recently, there has been an increased awareness of perioperative myocardial injury.[30, 31] Subclinical myocardial injury, as indicated by elevated troponin levels, may represent an increased risk of future cardiovascular events. Even minor changes of cTnI or cTnT could be of clinical relevance as increases of cTnT ≥5 ng l^{-1} have been shown to be associated with an increased 30-day mortality among a large cohort of male and female patients after noncardiac surgery, although the cohort was older and had more comorbidities than the participants in our study.[30] Moreover, perioperative myocardial injury, defined as an absolute increase of high-sensitivity cTnT at least 14 ng l^{-1}, is also associated with increased mortality after non-cardiac surgery.[32] As increases of cTnT are usually asymptomatic, it is possible that myocardial injury among postpartum women remains undetected. Nonetheless, the cut-off for ruling out myocardial ischaemia (elevations of cTnT <14 ng l^{-1}) remains applicable during pregnancy and after delivery, and elevations of cTnT at least 14 ng l^{-1} justify further attention.[33]

The clinical relevance of transient troponin release is not completely understood. There is increasing concern that exercise-induced troponin elevations may not be a benign physiological response to exercise, but an early marker of future mortality and cardiovascular events.[34] Indeed, transient troponin elevations comparable to our observations have been detected after prolonged endurance activities as marathon running, as well as after short-term exercise like 30 min of running or basketball.[35] The release of myocardial biomarkers, including high-sensitive cTnI, is potentially greater with oxytocin 2.5 IU than carbetocin 100 μg, and warrants further investigation to help inform prophylactic PPH treatment decisions for parturient women requiring caesarean delivery.

We found no group differences in blood loss, need for additional uterotonics or neonatal outcomes, but we did observe significantly more adverse events 0 to 2 minutes after study drug administration with carbetocin 100 μg vs. oxytocin 2.5 IU. The occurrence of adverse events is normally dose dependent. Previous studies have shown comparable haemodynamic changes with oxytocin 5 IU and carbetocin 100 μg;[16-18] however, in our study, we used half the

dose used in other studies. We chose a dose of 2.5 IU for oxytocin and 100 μg for carbetocin in accordance with our own departmental guidelines. Moreover, both these doses represent approximately seven times the ED90 for these drugs. Although the ED90 is estimated as 0.35 IU oxytocin and 14.8 μg for carbetocin for preventing of PPH after planned caesarean delivery,[23, 24] there is currently not enough evidence of the duration of uterotonic action with these lower doses to warrant their use in routine clinical practice.

Both study drugs resulted in comparable increases in QTc interval, reaching maximal values 9 min after study drug administration. Scant knowledge exists about the effect of carbetocin on QTc interval prolongation. Compared with our trial, a similar maximum QTc interval prolongation at 7 min after drug administration was reported among 20 women who received carbetocin 100 μg for prevention of PPH after elective caesarean delivery.[37] Another study that randomised 50 expectant mothers to receive either carbetocin 50 μg or 100 μg showed similar QTc prolongation interval in both groups with no dose-dependent effect.[38] As QTc values more than 500 ms are associated with high risk of arrhythmic events and sudden cardiac death,[39] we recommend that both oxytocin and carbetocin should be used with caution and preferably be avoided in patients with long QT syndrome.[40] Lowering the dose of oxytocin or carbetocin does not seem to reduce the degree of QTc prolongation. Cardiac disease is now one of the leading causes of maternal mortality in high-income countries,[41, 42] possibly because of the trend towards more advanced maternal age, increased BMI and increased occurrence of comorbidities such as hypertensive complications of pregnancy and cardiac disease, both inborn and acquired.[43-45]

Oxytocin is also known to stimulate release of myocardial biomarkers[46] and cause dose-dependent ST-depression.[7] ST-depression seems to be related to administration of oxytocin and not to the pregnancy itself, surgical procedure, delivery or an effect of spinal anaesthesia.[8] Knowledge of transient but profound haemodynamic alterations and dose-dependent ST-depression after intravenous oxytocin has led to a dose reduction for PPH prophylaxis during recent years. In our trial, although ST-depression changes were more frequent among the carbetocin group, these were not statistically significant. As previous studies have investigated higher doses of oxytocin 5 to 10 IU,[7] we speculate that the lower incidence of cardiac effects we observed may be attributed to the reduced dose of oxytocin in our trial.

Strengths and Limitations

No data have been previously published comparing the myocardial effects of oxytocin and carbetocin. This trial was conducted at two birth clinics, with a combined total of some 10,000 deliveries annually, and had few exclusion criteria. Women with common comorbidities, such as diabetes, chronic hypertension and hypothyroidism, were eligible for inclusion, as were women with singleton pregnancies resulting from assisted reproduction technologies. Inclusion was restricted to women who were able to read and understand Norwegian and may reduce generalisability of our results for patients with different ethnic backgrounds. As this trial was limited to patients undergoing planned caesarean delivery, this will also restrict interpretation for women who have vaginal deliveries or emergency caesarean delivery. However, the design was chosen to control for confounding variables that may affect troponin release and QTc prolongation. For each participant, we used the same method of anaesthesia, meticulous BP control and standardised perioperative follow up, allowing any differences in troponin release and QTc interval prolongation to be attributed to the study drug.

A potential limitation of the study is that we did not assess either participant satisfaction or initial breastfeeding rates, both of which are now considered core outcomes in trials for the prevention and treatment of PPH,[22] although this guidance was published after we completed the enrolment of women for this study.[22] All other core outcomes for PPH were included.

Conclusions

This is the first trial that has compared the myocardial effects of oxytocin and carbetocin when used to prevent PPH in in women undergoing planned caesarean delivery. We observed a greater change in cTnI from baseline with oxytocin 2.5 IU compared with carbetocin 100 µg, although the group differences were not statistically significant. cTnI elevations were most pronounced at 10 h after study drug administration for both treatment groups, and two women in the oxytocin group had cTnI levels that exceeded the reference limit (>15 ng l^{-1}) but had no symptoms of myocardial distress or ECG changes. Both oxytocin 2.5 IU and carbetocin 100 µg both caused a comparable increase in QTc. Both drugs should be administered with caution in patients with known QT prolongation. The data from this trial will be used to determine the appropriate number of individuals required for a future trial investigating

potential differences in the myocardial effects of oxytocin and carbetocin when used to prevent PPH after caesarean delivery.[29]

Presentation: Preliminary data for this study were presented as a poster presentation at the Euroanaesthesia 2020 virtual meeting, 28–30th November 2020.

Contribution to Authorship

MB: study conception and design, statistical analysis plan, data acquisition and analysis, drafting and review of manuscript; MWF: study conception and design, statistical analysis plan, data analysis, drafting and review manuscript; OGS: study conception and design, data analysis, manuscript review; LA: study conception and design, data analysis, manuscript review; OK: study conception and design, data analysis, manuscript review; JN: data analysis, data analysis, manuscript review; LAR: study conception and design, data acquisition and analysis, drafting manuscript and review. All authors critically reviewed multiple versions of the draft manuscript and approved the final draft for submission.

Details of Ethics Approval

The project has approval from the Regional Committee for Medical and Health Research Ethics (**REC 2014/1210**), The Norwegian Medicines Agency and the institutional data protection officer at Oslo University Hospital.

Data sharing

Requests for data sharing/case pooling may be directed to the project principal investigator Professor. Rosseland on email: lrossela@ous-hf.no

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Figure legends

Figure 1. Study flow diagram

Figure 2. Myocardial biomarkers from baseline to 24 h after administration of study drug

Lower box edge, 25th percentile; upper box edge, 75th percentile; middle box line, median; whiskers are the minimum and maximum values. For circulating troponin T, levels below the lower detection limit of 5 mg l^{-1} were designated as 0. Reference ranges are indicated by the horizontal dotted line.
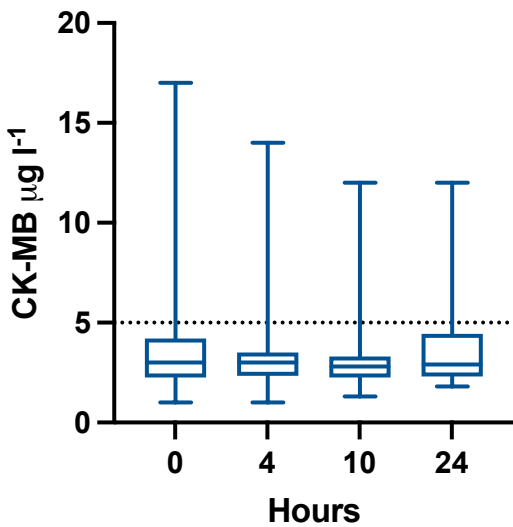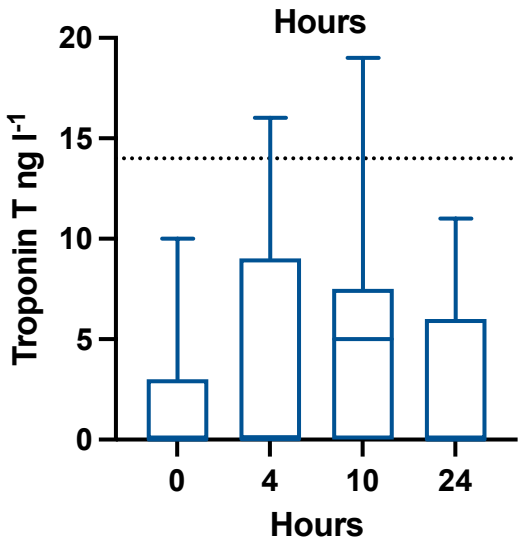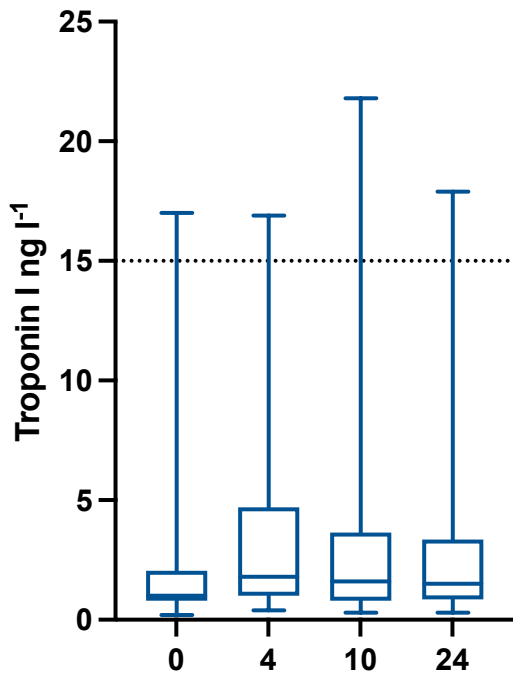
cTnI, circulating troponin I; cTnT, circulating troponin T; CK-MB, creatine kinase myocardial band; IV, intravenous.

Figure 3. QTc interval (Framingham) from baseline to 10 minutes after study drug administration
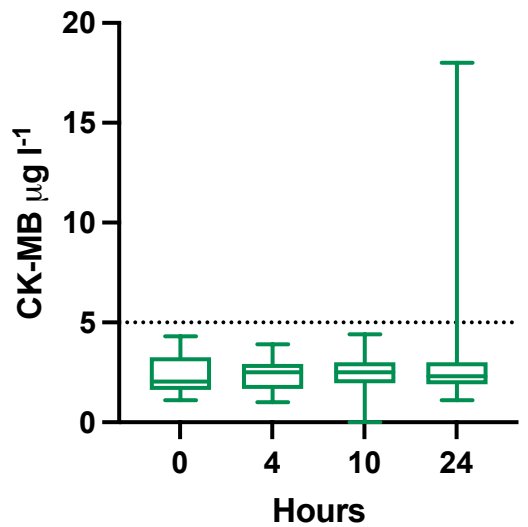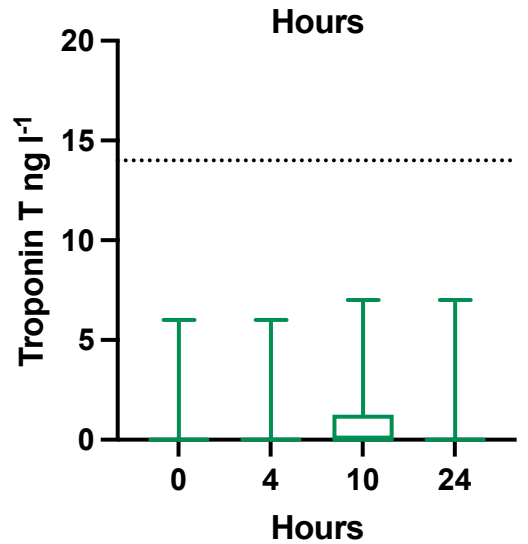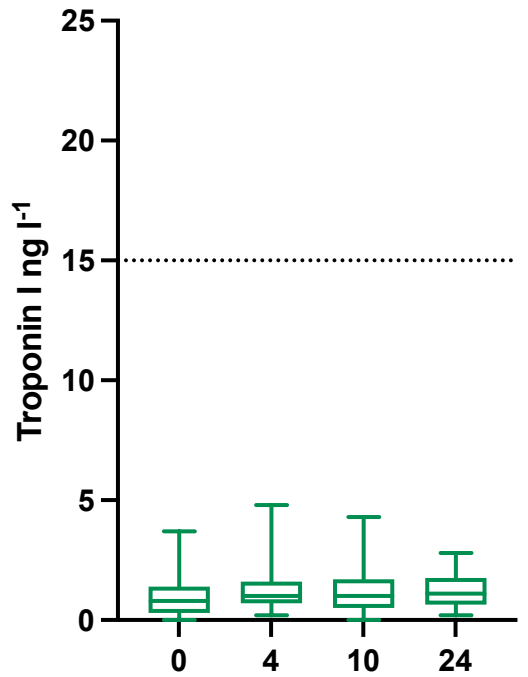
Normal QTc interval for ages 16–90 years is between 375 and 451 msec.[47]
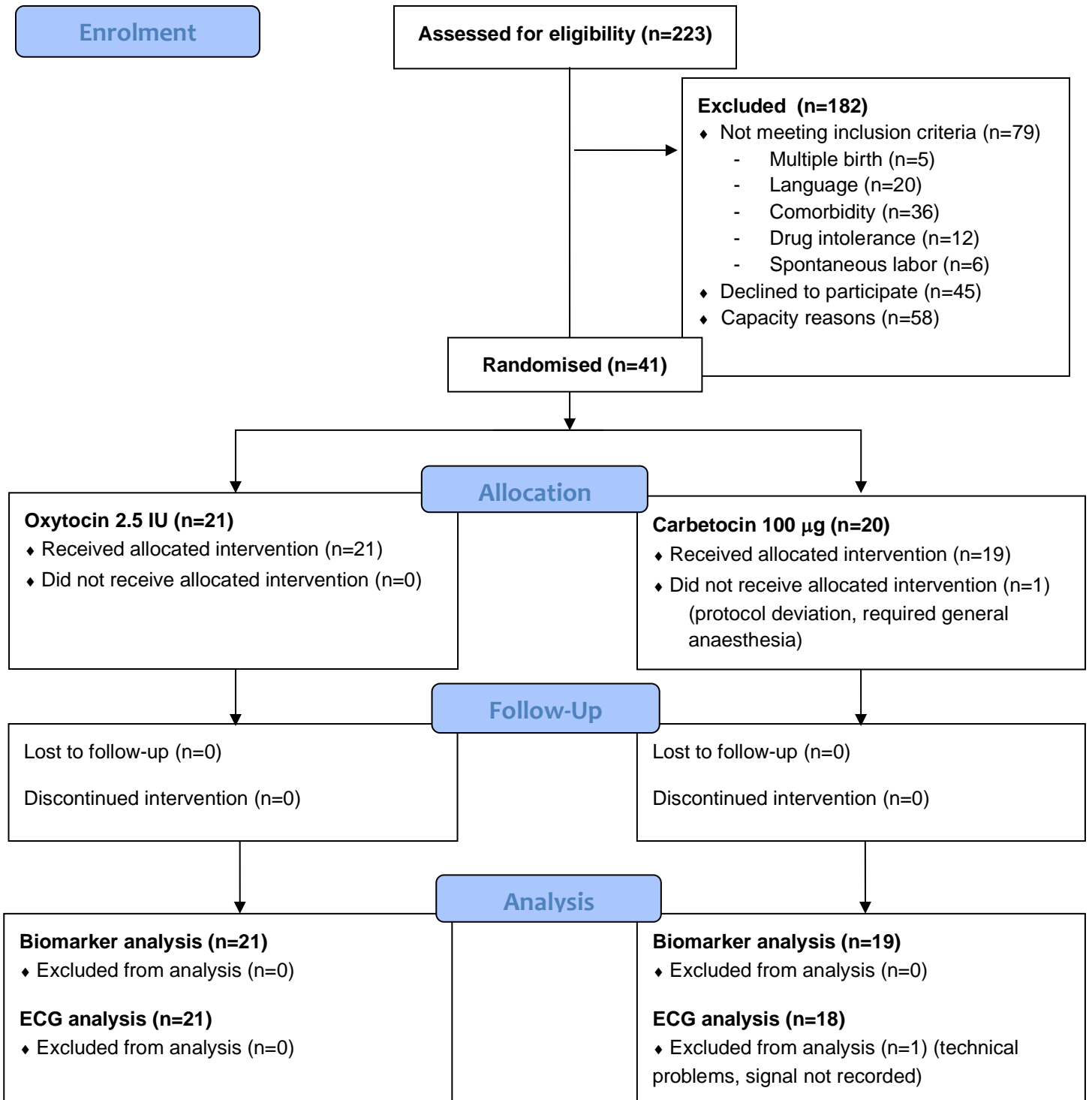
Oxytocin 2.5 IU IV   Carbetocin 100 μg IV
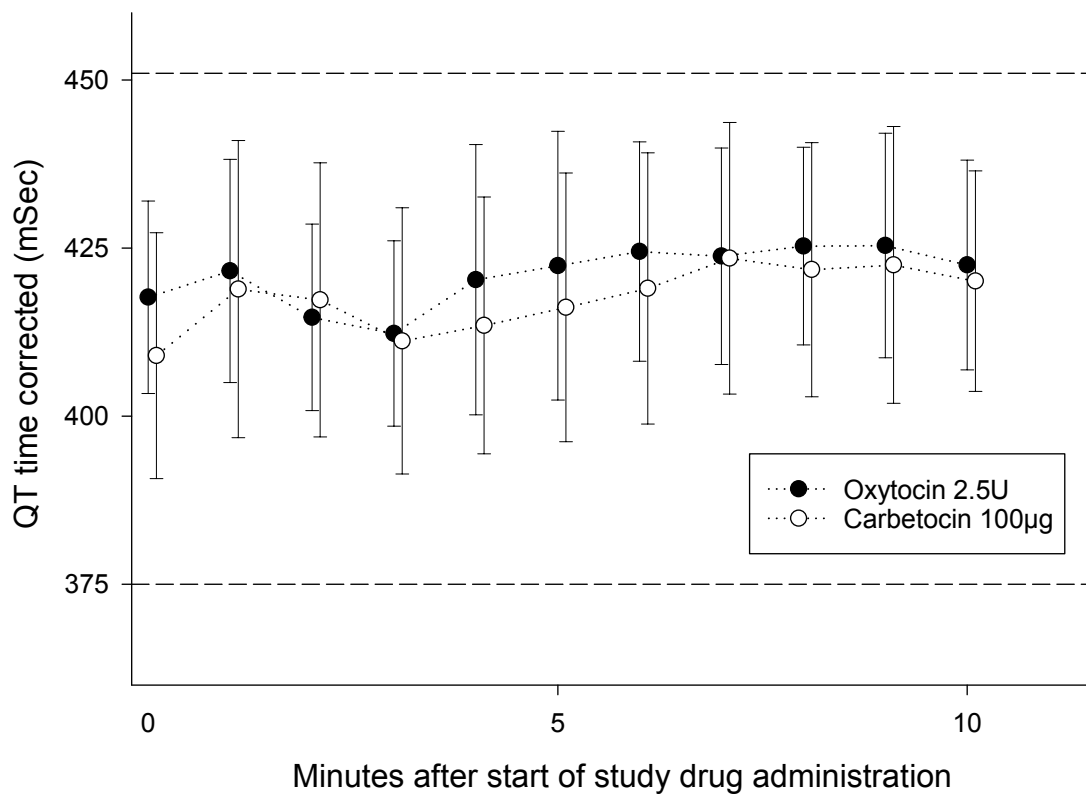
TABLE 1. Patients demographics, baseline characteristics and duration of surgery

CMT pilot trial (N=40)	Oxytocin 2.5 IU (n=21)	Carbetocin 100 µg (n=19)
Age, years	35.7 ± 4.1	36.6 ± 4.9
Parity	0.9 ± 0.7	1.2 ± 0.9
Gestational age, weeks	39.0 ± 0.5	38.7 ± 0.5
Prepregnancy weight, kg	63.5 ± 9.0	61.9 ± 8.6
BMI at day of delivery, kg m^{-2}	28.0 ± 4.1	28.3 ± 3.3
Mean arterial pressure, mmHg	89.0 ± 9.6	90.1 ± 23.8
Heart rate, bpm	83.3 ± 13.3	82.0 ± 17.7
Time from delivery until end of surgery	29.9 ± 15.8	28.2 ± 8.4

Values presented as mean ± SD. BMI, body mass index; bpm, beats per minute.

Table 2. Neonatal characteristics

	Oxytocin 2.5 IU (*n*=21)	Carbetocin 100 µg (*n*=19)
Umbilical vein pH	7.35 ± 0.05	7.35 ± 0.05
Umbilical artery pH	7.28 ± 0.05	7.28 ± 0.07
Apgar score at 1 min	9 [9 to 10]	9 [9 to 10]
Apgar score at 5 min	9 [9 to 10]	9 [9 to 10]
Apgar score at 10 min	10 [10 to 10]	10 [10 to 10]

Values presented as mean ± SD or median [range].

Table 3. Myocardial biomarker plasma concentrations at baseline and up to 24 hours after study drug administration

	Oxytocin	Carbetocin	
	2.5 IU (*n*=21)	100 µg (*n*=19)	*P*-value[a]
cTnI (ng l⁻¹) (primary endpoint)			
0 h	1.0 [0.2 to 17.0]	0.8 [0.0 to 3.7]	0.03
4 h	1.8 [0.4 to 16.9]	1.0 [0.2 to 4.8]	0.03
10 h	1.6 [0.3 to 21.8]	1.0 [0.0 to 4.3]	0.06
24 h	1.5 [0.3 to 17.9]	1.1 [0.2 to 2.8]	0.19
cTnT (ng l⁻¹)[b] (secondary endpoint)			
0 h	0 [0 to 10]	0 [0 to 6]	0.37
4 h	0 [0 to 16]	0 [0 to 6]	0.02
10 h	5 [0 to 19]	0 [0 to 7]	0.03
24 h	0 [0 to 11]	0 [0 to 7]	0.17
CK-MB (µg l⁻¹) (secondary endpoint)			
0 h	3.0 [1.0 to 17.0]	2.1 [1.1 to 4.3]	0.07
4 h	3.0 [1.0 to 14.0]	2.5 [1.0 to 3.9]	0.06
10 h	2.8 [1.3 to 12.0]	2.5 [0.0 to 4.4]	0.15
24 h	2.9 [1.8 to 12.0]	2.3 [1.1 to 18.0]	0.05

Values presented are median [range].

[a]Mann-Whitney U test. [b]Levels of troponin T below the lower detection limit of 5 mg l⁻¹ were designated as 0.

cTnI, circulating troponin I; cTnT, circulating troponin T; CK-MB, creatine kinase myocardial band.

Table 4. Linear mixed effect estimates of QTc from baseline to 10 min after administration of study drug

		Estimate (95% CI)	*P*-value
QTc (msec), intercept		413.7 (408.1 to 419.2)	
Minutes	1	6.7 (3.1 to 10.3)	0.000
	2	2.2 (−1.4 to 5.8)	0.23
	3	−1.9 (−5.5 to 1.7)	0.31
	4	3.6 (−0.0 to 7.2)	0.05
	5	5.9 (2.3 to 9.5)	0.001
	6	8.4 (4.8 to 12.0)	0.000
	7	10.0 (6.4 to 13.6)	0.000
	8	10.0 (6.4 to 13.6)	0.000
	9	10.4 (6.8 to 14.0)	0.000
	10	7.7 (4.1 to 11.3)	0.000

As there were no differences in the QTc changes between the groups over time, the QTc changes over time for all patients are shown as deviation from the respective baseline QTc values. The overall P-value for linear trend over time was calculated to be <0.001. We found no difference between the treatment groups in QTc intervals (P=0.13).

QTc, QT-time corrected according to Framingham, displayed in ms.

Table 5. Use of additional uterotonics, evaluation of uterine tone and estimated blood loss

	Oxytocin 2.5 IU (n=21)	Carbetocin 100 µg (n=19)	P-value
Women who required additional uterotonic treatment[a]	8 (38.1)	7 (36.8)	0.87
Oxytocin 1 IU x 2	6 (28.6)	5 (26.3)	0.86
Oxytocin 1 IU x 3 or more	3 (14.3)	3 (15.8)	0.83
Misoprostol 600 µg	1 (4.8)	0	0.74
Methylergometrine 200 µg	0	0	–
Carboprost 250 µg	1 (4.8)	1 (5.3)	0.74
Oxytocin infusion 50 IU per 500 ml 0.9% saline	2 (9.5)	1 (5.3)	0.80
Surgical/mechanical intervention	0	0	–
Time to additional treatment (min)	1.6 ± 2.5	2.3 ± 3.8	0.53[c]
Uterine tone			
Uterine tone 2.5 min (NRS 0–10)	7 [5 to 10]	8 [0 to 9]	0.58[b]
Uterine tone 5 min (NRS 0–10)	7.5 [5 to 9]	8 [0 to 10]	0.93[b]
Blood loss			
Estimated calculated blood loss (ml)	551.5 ± 381.8	559.5 ± 366.7	0.95[c]

Values presented as n (%), median [range] or mean ± SD. NRS, numerical rating scale.

[a]Fisher´s mid-P test; [b]Mann-Whitney *U*-test; [c]Two-sample *t*-test.

Table 6. Adverse events

Time period	0–2 min		2–5 min		5–10 min	
	Oxytocin (n=21)	Carbetocin (n=19)	Oxytocin (n=21)	Carbetocin (n=19)	Oxytocin (n=21)	Carbetocin (n=19)
Women with ≥1 adverse event(s)	1 (4.8)	7 (36.8)	4 (19.0)	8 (42.1)	7 (33.3)	11 (57.9)
*P**	*P*=0.01		*P*=0.13		*P*=0.16	
Chest pain	0	2 (10.5)	1 (4.8)	2 (10.5)	0	3 (15.8)
Shortness of breath	0	0	1 (4.8)	1 (5.3)	1 (4.8)	1 (5.3)
Palpitations	0	1 (5.3)	0	1 (5.3)	1 (4.8)	1 (5.3)
Flushing	0	1 (5.3)	0	3 (15.8)	1 (4.8)	2 (10.5)
Headache	0	0	1 (4.8)	0	1 (4.8)	1 (5.3)
Nasal congestion	0	0	0	2 (10.5)	0	2 (10.5)
Xerostomia	0	1 (5.3)	0	3 (15.8)	0	2 (10.5)
Metallic taste	0	0	0	0	0	0
Nausea/vomiting	0	1 (5.3)	0	1 (5.3)	1 (4.8)	2 (10.5)
Others	1 (4.8)	1 (5.3)	1 (4.8)	1 (5.3)	1 (4.8)	2 (10.5)

Data are *n* (%). Some women reported more than one adverse event.

*Fisher's mid-P test for women more than one adverse event at different timepoints.