The Clinical Carbetocin Myocardium Trial

Protocol Identification Number: CarbetocinHeart2014

EudraCT Number: 2014-000507-27

SPONSOR: **Kristin Sem Thagaard**

Address Division of Emergencies and Critical Care, Oslo University Hospital, Box 4950 Nydalen, 0424 Oslo, Norway

Tel : +4723070000

E-mail: E-mail: kristin.sem.thagaard@ous-hf.no

PRINCIPAL INVESTIGATOR: **Leiv Arne Rosseland, Professor DMSc MD**

Address Division of Emergencies and Critical Care, Oslo University Hospital, Box 4950 Nydalen, 0424 Oslo, Norway

Tel : +4723070000

E-Mail: l.a.rosseland@medisin.uio.no

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CONTACT DETAILS

Sponsor:

Kristin Sem Thagaard, MD

Address Division of Emergencies and Critical Care, Oslo University Hospital, Box 4950 Nydalen, 0424 Oslo, Norway

Tel : +4723070000

E-Mail: kristin.sem.thagaard@ous-hf.no

Coordinating Investigator:

Leiv Arne Rosseland, Professor DMSc MD

Address Division of Emergencies and Critical Care, Oslo University Hospital, Box 4950 Nydalen, 0424 Oslo, Norway

Tel : +4723070000

E-Mail: l.a.rosseland@medisin.uio.no

Principal investigator:

Leiv Arne Rosseland, Professor DMSc MD

Address Division of Emergencies and Critical Care, Oslo University Hospital, Box 4950 Nydalen, 0424 Oslo, Norway

Tel : +4723070000

E-Mail: l.a.rosseland@medisin.uio.no

Participating Departments:

Department of Cardiology, OUH, Department of Cardiology, Vestre Viken Trust, Drammen, Department of Obstetrics and Gynecology, OUH, Department of Clinical Biochemistry, OUH, Department of Clinical Biochemistry, Vestre Viken Trust, Drammen, Department of Biostatistics and Epidemiology, OUH, Department of Clinical Research Support, OUH, Department of Pain Medicine, Division of Emergencies and Critical Care, OUH.

SPONSOR SIGNATURE PAGE

Title **The Clinical Carbetocin Myocardium Trial**

Protocol ID no: CarbetocinHeart2014

EudraCT no: **2014-000507-27**

Sponsor signatory approval

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Kristin Sem Thagaard (sponsor)
Head of Department of Emergencies and Critical Care

Sponsor signature *Date*

PI signatory approval

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Leiv Arne Rosseland,
Professor DMSc MD

PI signature *Date*

PROTOCOL SYNOPSIS

The Clinical Carbetocin Myocardium Trial

Investigational Medicinal Product:	Carbetocin (Pabal®) inj + Oxytocin (Syntocinon®) inj
Centers:	Oslo University Hospital
Study Period:	Estimated date of first patient enrolled: 01-10-2014 Anticipated recruitment period: 2 years Estimated date of last patient completed: 31-12-2016
Treatment Duration:	1 minute
Follow-up:	48 h
Endpoints:	Primary endpoint: plasma Troponin I concentrations Secondary endpoint: Troponin T, ProBNP, other relevant myocardial markers, blood loss, uterine tone, adverse events rate, pain, and ECG changes.
Study Design:	Parallel group, blinded, randomized comparison with oxytocin
Main Inclusion Criteria:	Healthy pregnant women for elective caesarean section age 18 to 50 years
Sample Size:	40 patients
Efficacy Criteria:	Blood loss
Safety Criteria:	Plasma concentration of myocardial biomarkers. Adverse events.

TABLE OF CONTENTS

LIST **OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

Abbreviation or special term	Explanation
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electro Cardiography
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
MV	MetaVision
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SD	Stable Disease
SDV	Source Data Verification
SOP	Standard Operating Procedure
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1 INTRODUCTION

1.1 Background –Treatment

Caesarean delivery is a commonly performed surgical procedure. Uterus contraction after delivery of the baby is necessary to avoid excessive bleeding.

1.2 Background - Therapeutic Information

Adequate uterus contraction after delivery of the baby is necessary to avoid excessive bleeding. Prophylactic administration of an oxytocin receptor agonist is first line practice. Intravenous injection of oxytocin has been the standard procedure but serious cardiovascular adverse events have been reported. By lowering the dose or administer the drug as a 5 minutes infusion may increase safety. Carbetocin, a synthetic oxytocin receptor agonist, has significantly longer half life and may reduce blood loss compared with oxytocin. The hemodynamic vasodilatory effects are comparable to oxytocin(1), but potential differences in adverse effects on myocardium are not well described yet.

1.3 Pre-Clinical & Clinical Experience with Carbetocin (IMP) and Oxytocin

Carbetocin has been in clinical use in EU for some years and the efficacy is documented in several RCTs. In the proposed study, carbetocin will be used within the conditions of the marketing authorization. Oxytocin is the first line treatment and prophylaxis in Norway and most countries in the world. According to recently published goidelines fraom EU drug authorities (EMA) oxytocin should be given as a slow (5 minte) infusion in order to avoid hypotension. This has so far not been implemented in Norway. The pre-clinical and clinical experience of the two drugs are summarized in the Summaries of Product Characteristics.

1.4 Rationale for the Study

Pregnancy and delivery is a natural process, but for many women this period is stressful and not without risks of morbidity, and even mortality. Circulatory adverse events leading to death has been reported after intravenous injection of oxytocin.(2) Some studies indicate that oxytocin may lead to dose dependent ischemic ECG changes(3;4), prolongation of QT time and liberation of biomarkers of myocardial cell death.(3) Previously we have demonstrated comparable vasodilatory effects of oxytocin and carbetocin.(1) There is no clinical study comparing the specific myocardial effects of oxytocin with carbetocin. It may have great impact on the choice of standard medication if the cardiotoxicity of carbetocin is lower compared with oxytocin. The study of potential cardiotoxicity has to be performed in healthy women. Knowing that millions of laboring women have had uneventful injections of oxytocin and carbetocin after delivery, there is probably no reason to fear long lasting negative effects of either drug. If there are differences in cardiotoxicity, this new information should be taken into consideration when planning delivery in pregnant women with heart disease.

2 STUDY OBJECTIVES

The aims of this study are to compare 0h (before C-section), 4h, 12h, 24h, and 48h plasma concentrations of Troponin I (high sensitive methods), Troponin T, proBNP, CK, and other relevant myocardial markers in elective healthy C-section patients randomized to oxytocin 2.5 U or carbetocin 100 µg, 1 minute injection immediately after delivery.

2.1 Primary Endpoint

Primary outcome measure is difference in the interaction of time*group in plasma concentration of Troponin I. Plasma concentrations will be collected before C-section, 4h, 12h, and 24h after test drug administration. If indicated by increase in some of the specific myocardial biomarkers (troponin T, CK, etc), which will be analyzed consecutively, an additional sample at 48h will be included.

2.2 Secondary Endpoints

- Other myocardial biomarkers
- Uterus tone evaluated repeatedly
- Blood loss (estimated calculated blood loss)
- Postoperative pain and side effects.
- BP, heart rate and ECG changes

3 STUDY POPULATION

3.1 Selection of Study Population

3.2 Number of Patients

40 patients will be included in this trial. Based on analysis in this pilot trial, statistical power analysis and group size estimation will be performed in order to start a larger confirmatory study. This protocol will serve as protocol for the larger follow up study including up to 400 patients. Some endpoints may be omitted in this large randomized controlled trial.

3.3 Inclusion Criteria

1. Healthy pregnant women age 18 to 50
2. Singleton pregnancy at gestational age 36 weeks or more
3. Able to read and understand Norwegian.
4. Patients will be recruited from the general population at the birth clinic at Oslo University Hospital. Signed informed consent form (ICF) and expected cooperation of the patients for the treatment and follow up will be obtained and documented according to ICH GCP, and national/local regulations.

3.4 Exclusion Criteria

1. Patients with placenta pathology such as praevia, acreta, pre-eclampsia
2. Patients with bleeding disorders including vonWillebrand disease type I.
3. Known intolerance to one of the two drugs.
4. Patients with prolonged QT-time or other serious cardiac diseases.
5. Liver or kidney failure.
6. Epilepsy.

7. Any medical reason why, in the opinion of the investigator, the patient should not participate.

4 Overall STUDY Design

The study is a parallel, randomized, blinded phase 4 study (safety)

Study Period	Estimated date of first patient enrolled: 01-10-2014
	Anticipated recruitment period: 2 years
	Estimated date of last patient completed: 31-12-2016
Treatment Duration:	1 minute
Follow-up:	48h

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Dosage and Drug Administration

Carbetocin (Pabal, Ferring Medical, Copenhagen, DK) 100 µg/ml, 1 ml diluted in normal saline to 5 ml will be injected slowly intravenously (1 minute duration). Control intervention is oxytocin (Syntocinon, Swedish Orphan Biovitrum, Stockholm, Sweden) 5 U/ml, 0.5 ml diluted in normal saline to 5 ml will be injected slowly intravenously (1 minute duration).

5.2 Duration of Therapy

The IMPs will be injected slowly (1 minute). The patients will be followed 48h.

5.3 Premedication and Monitoring (if applicable)

Preoperative blood sample will be analyzed for baseline values of interest regarding the study outcome measures (Troponin I (high sensitive methods) and other myocardial biomarkers). There will be no premedication.

5.4 Schedule Modifications

N.a.

5.5 Concomitant Medication

In case of uterus atony, patients will be treated with oxytocin 1 U every 2 minute up to maximum 5 U. Misoprostol 200 µg rectally will be given if need of a second drug mechanism. Any additional treatment of uterus, medical or surgical, will be decided by the attending obstetrician and anesthesiologist according to departmental procedures. Spinal anesthesia will be given according to study procedure (isobaric Bupivacaine 5 mg/ml 2 ml + fentanyl 50µg/ml 0.4 ml), hypotension prophylaxis (phenylephrine 0.1 mg/ml 0.25 µg/kg followed by infusion rate 0.25 µg/kg/min) and intravenous volume (normal saline 10 ml/kg starting concomitantly with spinal anesthesia (see 6.2.2 for details). Pain treatment protocol includes oral paracetamol 1 g and ibuprofen 400 mg 4 times pr day and IV morphine administered according to

departmental procedure using a patient controlled analgesia pump (PCA). All interventions, including all administered medication will be registered with doses and timing.

5.6 Subject Compliance

N.a.

5.7 Drug Storage and Accountability

Drug preparation will be immediately before administration and prepared syringe will be destroyed if not used within 24h after preparation. All IMP use will be accounted for with registration of amount used, date given, batch, expiry date and the trial participant the IMP has been given to. Both oxytocin and carbetocin are in routine use in the department of anesthesiology and are easily accessible for the person responsible for preparation of study drug.

5.8 Drug Labeling

The investigational medicinal product will have a label permanently affixed to the outside and will be labeled according with ICH GCP and local regulations (4.4."Merking av utprøvingspreparatet "in FOR 2009-10-30-1321 Forskrift om klinisk utprøving av legemidler til mennesker and Veiledning til forskrift av 30. oktober 2009 om klinisk utprøving av legemidler til mennesker versjon 2.0./8.-sept-2011.)

- (In Norwegian)

Til klinisk utprøving

CarbetocinHeart2014 Batch nr:_____

Ansvarlig: Dr.Rosseland (Tlf 92204274)

PAS. NR. |__|__| Oslo Universitetssykehus

Til iv injeksjon (60 sek)

Carbetocin 100 µg eller Oxytocin 2,5 IE

Oppbevares i kjøleskap **(**2°C-8°C),

Holdbar 24 t til kl |__|__|:|__|__|

Dato: …… Signatur: ……

6 STUDY procedures

6.1 Flow Chart

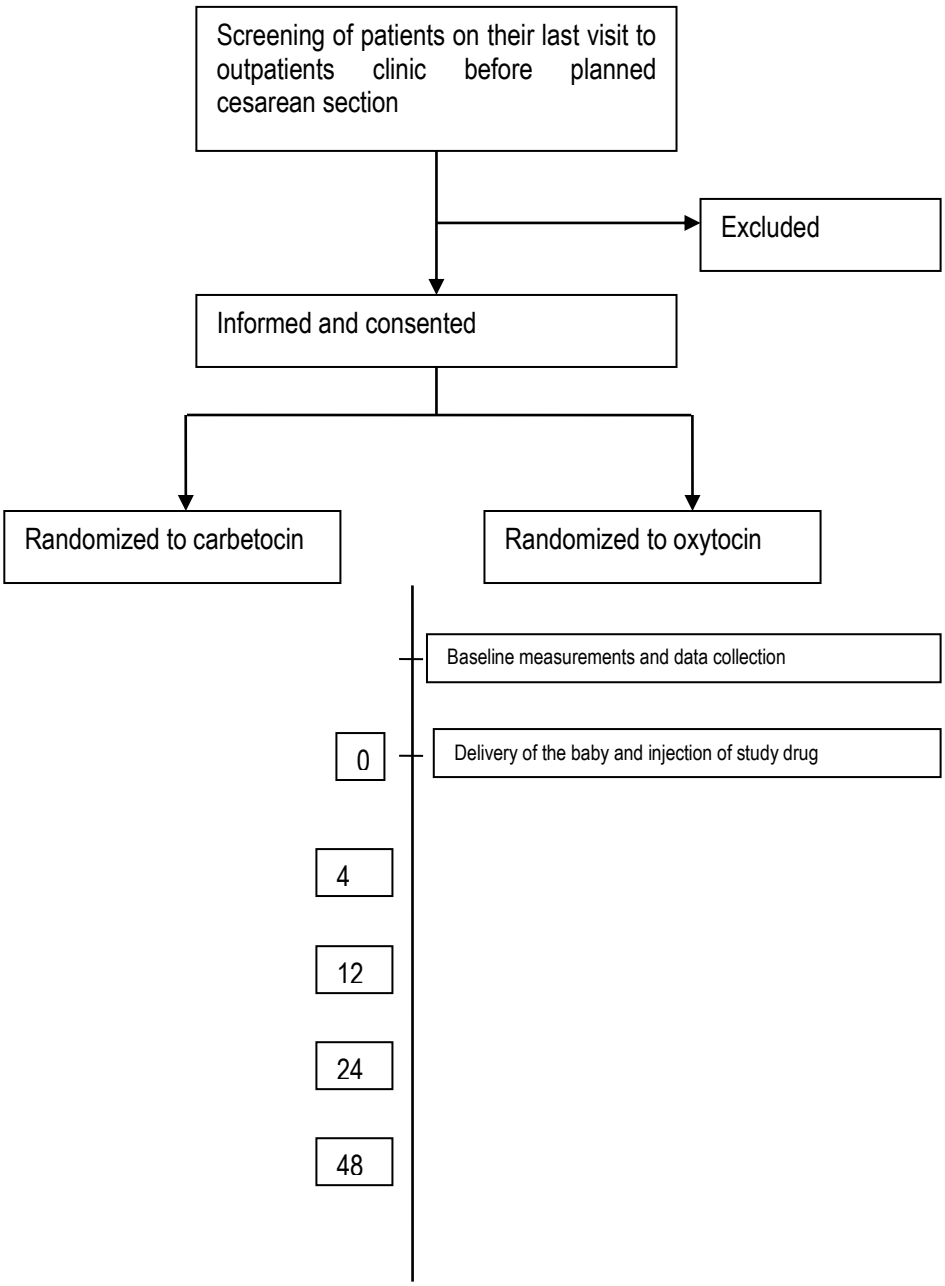

Table 1. Trial flow chart

	Screening Period		Treatment Period	Treatment Period	Treatment Period	Treatment Period			End of study
Time	**Within 14 days of treatment**	**Within 2 h of treatment**	**Time 0 (before C-section)**	**Time after C-section – 0 - 30 min**	**Time 4h**	**Time 12h**	**Time 24h**	**Time 48h**	**Time 48h**
Informed consent	X	X							
Inclusion/exclusion Evaluation	X								
Medical History	X								
Demographics[1)]			X						
Vital signs[2)]			X	X					
Blood samples[3)]			X		X	X	X	X	X
IMP administration/dispensation			X		X				
Uterine tone				2.5 and 5 min					
Adverse event, pain intensity			X	X	X	X	X	X	X
Record of concomitant medication		X		X	X	X	X	X	X

1. Demographics including pre-pregnant weight, actual weight, height, age, gestational weeks, parity at baseline.
2. Blood pressure, heart rate, ECG, at baseline and until 30 min.
3. Hb, Na, TropT, TropI, CK, CK-MB, ProBNP, etc. Sample after 48h only if Troponin T > 20 ng/L at 4h.

6.2 By Visit

6.2.1 Before Treatment Starts

Potentially eligible participants will be screened by the principal investigator for inclusion at their last midwife consultation before their scheduled delivery. An additional screening of psychological distress and pain catastrophizing will be administered by self-report during the visit in order to assess a potential association with adverse events (post-surgical pain). Oral and written information will be given to each woman at least 24 h before her delivery and written informed consent obtained before randomization. Consent (ICF), participation and redrawal of consent will be documented in electronic patient journal (see 9.2). Name of trial, eligibility, date of signed consent and randomization number will be documented. Screened, but not consented patients will be registered by number. Screened but not included due to exclusion criteria or unfulfillment of inclusion criteria will be registered by number and reason for non-inclusion/exclusion.

6.2.2 During Treatment

Vital signs, preoperative pain status, and baseline blood samples will be registered before anesthesia. With the woman in a right lateral position, spinal anesthesia will be induced in the L2–L3 vertebral interspace, and bupivacaine 10 mg + fentanyl 20 µg injected through a 27 or 25-gauge non-traumatic needle. Concomitantly, we start a rapid i.v. infusion of saline 0.9 mg/ml (37°C, 10 ml/kg), a phenylephrine bolus (0.25 µg/kg) followed by a phenylephrine infusion (0.25 µg·kg−1·min−1). During surgery, the patient will be supine with an operating wedge under her right hip (19° Tempur pillow; Trulife®, Dublin, Ireland). Hypotension (systolic arterial pressure <90 mmHg) is treated with an extra i.v. bolus of phenylephrine if the heart rate is above 60 beats/min or with i.v. ephedrine 5–10 mg if 60 beats/min or below. The level of anesthesia will be 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 will be injected slowly, over the course of 60 s, starting when the baby's head and shoulders is delivered. Exteriorization of the uterus is performed routinely according to departmental policy. The patient will be asked if she experienced any of the listed side effects, and to grade the intensity of the side effects as mild, moderate, or severe. The duration of the side effects will also be recorded. Side effects, pain intensity and medications will be registered until 48h. Registration of side effects will be performed 1, 2, 3, 4, 5 and 10 minutes after study drug administration. The rest of the observation period side effects will be registered when reported by the patient.

The obstetrician in charge of the Cesarean delivery assess uterine tone 2.5, and 5 min after administration of study drug, using a numeric rating scale that range from 0 to 10, where a score of 0 means "no effect", 10 means "maximal uterus contraction", and 7 indicates "clinically satisfactory contraction". This uterine contraction scale was introduced to the obstetricians before a previously published RCT. Because visual assessment of blood loss during delivery is of limited value, we will calculate estimated blood loss using the formula for calculated estimated blood loss as published by Stafford(5), revised with weight in kg (last measurement prior to operation), height in cm.(1)

Routine assessments of newborn status are registered (Apgar 1 and 5 minutes, umbilical vein and artery acid-base status).

6.3 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

1. Voluntary discontinuation by the patient who is at any time free to discontinue her participation in the study, without prejudice to further treatment.

2. Severe non-compliance to protocol as judged by the Principal Investigator.

3. Incorrect enrolment i.e., the patient does not meet the required inclusion/exclusion criteria for the study

6.4 Procedures for Discontinuation

6.4.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study, will stop further treatment.

Patients who withdraw or are withdrawn from the study before randomization, will be replaced.

6.4.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the sponsor (Kristin Sem Thagaard) or PI (Leiv Arne Rosseland) in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The principal investigator will inform the relevant regulatory authorities of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the relevant authorities should be informed within 15 days.

6.5 Laboratory Tests

The aims of this study are to compare 0h, 4h, 12h, and 24h plasma concentrations of Troponin I (high sensitive methods) and other myocardial biomarkers. Blood samples are collected by laboratory personnel who also store the plasma aliquots in the biobank freezer. The project will establish a research biobank at Oslo University Hospital. Some blood tests will be analyzed consecutively at Oslo University Hospital. Some biomarkers of specific scientific interest, such as Troponin I will be analyzed at Vestre Viken Trust, Drammen Hospital when the last patient has been included and after 48h follow up.

7 Efficacy assessments

7.1 Assessment of Efficacy

The primary outcome measure is the interaction of time and plasma concentrations of Troponin I. Group differences in this variable and other biomarkers (secondary outcomes) will be analyzed after the end of this pilot trial (N=40). Decisions will be made regarding primary outcome measure and group size in the final study based on these calculations. Maximum number of participants in the final study is 400.

7.2 Biobank

Blood samples will be handled by staff at Department of Clinical Biochemistry, OUH, stored in the specific biobank according to the internal regulations and procedures at OUH.

8 Safety assessments

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to inform the investigator immediately should they manifest any signs or symptoms they perceive as adverse.

The safety data are the outcome measures in the study (cardiovascular biomarkers, continuous monitoring of vital signs, ECG, blood pressure) and the registration of side effects and adverse events during the continuous bedside communication with the patient. Troponin I (high sensitive method) will be analyzed after entering all data on the last patient. Hence, these lab results can not lead to changes in the study, but may affect the procedure in the main study that follows this pilot study. Other biomarkers, such as troponin T, will be analyzed consecutively as routine laboratory tests. Patients with troponin T at 4h is above 20 ng/L will have a second ECG at 24h and additional blood tests at 48h as clinically indicated follow up.

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8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

Expected side effects are defined in 8.2. The participating patients will be informed about the expected side effects prior to inclusion and instructed to score grade of side effects every minute during the initial 5 minutes after injection and after 10 minutes. It is expected that all adverse events are unlikely after 10 minutes but possible AE occurring after 10 minutes will be registered until end of trial (48h). The patients are asked to grade the degree of side effects as mild, moderate and severe. In case of grades 4 and 5, according to NCI Common Terminology Criteria for Adverse Events, this will be registered by the investigator.

Patient follow up will be completed 48h after injection and this defines the AE period. Unexpected AE/SAE will be reported, also after this period, until discharge from the hospital.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

8.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered;

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction: Unexpected Adverse Reaction that:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

8.2 Expected Adverse Events

Expected side effects are feeling of warmth, chest pain, shortness of breath, palpitations, flushing, headache, nasal congestion, xerostomia, and metallic taste or other events or reactions listed in the SmPCs of the investigational medicinal products. Both drugs in the study will lead to vasodilatation with decrease in blood pressure and increasing heart rate.

8.3 Time Period and Frequency of Detecting AE and SAE

The standard time period for collecting and recording AE and SAEs will be 0 to 48h after study drug injection for each patient. Unexpected AE/SAE will be reported also after this period until discharge from the hospital.

During the course of the study all AEs and SAEs will be proactively followed up for each patient; events will be followed up to resolution. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

8.4 Recording of Adverse Events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset time and event ended data.
- The intensity of the adverse event will be described according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).
- The Causal relationship of the event to the study medication will be assessed as one of the following:

  Unrelated:

  There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

  Unlikely:

  There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.

  Possible:

  There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

  Probable:

  There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

  Definite:

  There is a reasonable causal relationship between the investigational product and the AE.

  Comment: Dechallange – rechallange of IMPs is not possible in this patient population.

8.5 Reporting Procedure

8.5.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

Every SAE will be documented by the investigator on the SAE pages (see CRF page 4). The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter. The principal investigator will inform the sponsor (Kristin Sem Thagaard, Division of Emergencies and Critical Care, Oslo University Hospital) within 24h.

The principal investigator keeps detailed records of all SAEs and performs an evaluation with respect to seriousness, causality and expectedness.

8.5.2 SUSARs

SUSARs will be reported to the Competent Authority. The following procedure will be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions will be reported in an unblinded manner to the Competent Authority concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor. In order to keep the investigator and other persons generating data to the study blinded, the unblinding and the reporting will be performed by Department of Clinical Research Support.

SUSARs will be reported using the CIOMS form since Oslo University Hospital is not connected to EudraVigilance.

8.5.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements and follow guidelines published at www.norcrin.no.

8.5.4 Clinical Study Report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

8.6 Procedures in Case of Emergency

Medical treatment of serious events will be according to international guidelines described in local procedures in Oslo University Hospital (E-håndbok). The PI and the sponsor will decide how to handle each serious patient event. Emergencies will be treated as usual, by the personnel specially trained in relevant medical emergencies.

9 The investigator recording of data and source verification

9.1 Case Report Forms (CRFs)

Case report forms (CRF) will be provided for the recording of all data. Data will be recorded legibly onto the record forms, in blue/black ink. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections if applicable, should be made legibly, dated and initialed. Correction fluid is not allowed.

9.2 Source Data

The medical records for each patient should contain information which is important for the patient's safety and continued care and to fulfill the requirement that critical study data should be verifiable. To achieve this, the medical records (MetaVision electronic anesthesia version (MV), or DIPS) of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code (CarbetocinHeart2014)(MV);

- Date when ICF was obtained from the patient and statement that patient received a copy of the signed and dated ICF (DIPS);
- Results of all assessments confirming a patient's eligibility for the study (DIPS);
- Diseases/patient history (past and current; both the disease studied and others, as relevant) (DIPS);
- Treatments given, changes in treatments during the study and the time points for the changes (MV);
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments (MV);
- Date of, and reason for, discontinuation from study treatment (DIPS);
- Date of, and reason for, withdrawal from study (DIPS);
- Additional information according to local regulations and practice (DIPS).
- Some blood analyses will be analyzed consecutively (troponin T. proBNP, Na, K, Ck, CK-MB etc) and these data will be entered into the database when made available.

  Some biochemical analyses (troponin I) will be performed in one batch when all patients are included and the follow up period is over (48h). A biobank consisting of blood samples marked by patient number (not initials or any person identification) will be established. This biobank will consist of aliquots of plasma, stored in a certified biobank freezer (-70 °C), and transported to department of clinical biochemistry, Vestre Viken Trust–Drammen Hospital for final analyses.

- Electronic files, including the data from CRF entered into an electronic database software (FileMaker PRO), will be stored at the research server at Oslo University Hospital. This data storage is administered by the Data Inspectorate's local representative who also will handle the application for approval of data storage and ICF.

9.3 Source Data Verification

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check and collect completed CRFs, discuss the progress of the study and monitor drug usage according to ICH GCP. The monitoring will also include source data verification (SDV).

All data will be entered into a computer database at Oslo University Hospital for further handling.

Sponsor's representatives, Department of Clinical Research Support, and Norwegian Medicines Agency will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

9.4 Storage of Study Documentation

The patient identification and the code list will be kept by the PI in a locked office. Patient files will be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc) will be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

10 Statistical considerations

10.1 Determination of Sample Size:

Based on the primary endpoint of interest, Troponin I, group size in order to detect statistically significant differences between the two treatments will be calculated. This is the first clinical study comparing these outcome measures and calculation of statistical power and group size estimations is not possible. The stage one of the study will be a parallel group (1:1 group size) randomized, double blinded study. After all data from the 40 patients have been collected and the database is locked, a blinded analysis based on these study data will be performed by a medical statistician (Are Hugo Pripp). He will get access to outcome measures and information about treatment allocation, but not the actual treatment. Unblinding will be performed when all analyses have been done

10.2 Randomization and blinding

After inclusion patients will be randomized to one of two arms. The randomization will be performed immediately before study start. The person responsible for preparing the syringes will open one sealed envelop with information about treatment allocation. Randomization list and envelops will be made by a researcher not involved in the data collection using an electronic random number generator or a randomization software. The randomization responsible will decide block size and if variable block size will be used.

Everybody will be blinded to treatment allocation with the exception of the person responsible for preparing the syringes and the person generating the randomization list. These persons will not be the same as the one responsible for analysis of the trial data. Department of Clinical Research Support will be responsible for sending SUSARs to the Competent Authority and will also have a randomization list available. Unblinding of one or more patients will be performed by this third party only.

There will be two sets of sealed envelopes containing the treatment allocation for the different patients; one set is kept by the personnel responsible for preparation of study drug and the other is kept by the principal investigator for emergency unblinding of one single patient, as described under 8.6.

Blinding of study drug will be secured by using standard 10-ml syringes marked with information as described under 5.8.

10.3 Statistical Analysis

The statistical test will be ANCOVA, probably MIXED MODEL in SPSS, or similar, for repeated measurements with main outcome group differences in the interaction of time and treatment allocation. *Ho hypothesis will be no difference between the treatments.* Level of statistical significance will be $\alpha<0.05$ and $1-\beta$ 0.8. These principles will be utilized in both stage one of the study and the main study.

Primary efficacy variable is troponin I. Intention to treat analyses will be performed and group differences in side effects will be analyzed and presented regardless of rejection of the H_0 hypothesis or not. All data will be entered and locked in the database, and treatment allocation information will not be revealed until complete dataset are obtained in the main study.

All adverse events, whether spontaneously reported by the patients or observed by the investigator, will be described and categorized both by their nature and severity using the NCI Common Terminology Criteria for Adverse Events, Version 4.03. An attempt to relate the incidence and severity of adverse symptoms to certain patient characteristics will be made.

11 STUDY MANAGEMENT

11.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) will be notified to and approved by the Norwegian Medicines Agency and the Ethics Committee according to EU and national regulations.

11.3 Audit and Inspections

Authorized representatives of a regulatory authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from monitor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 Ethical and regulatory requirements

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics Committee Approval

The study protocol, including the patient information and ICF to be used, will be approved by the regional ethics committee before enrolment of any patients into the study.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2 Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study, including local representatives of Data Inspectorate, Norway (“Personvernansvarlig” at Oslo University Hospital) and Norwegian Medicines Agency.

The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

12.3 Informed Consent

The investigator will give the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she wants. This will not prejudice the patient's subsequent care. Documented informed consent will be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent (ICF).

A copy of the patient ICF will be given to the patients. The signed and dated ICF will be filed in the Investigator File binder and also scanned to be part of the patient's electronic medical record at the hospital.

The information will be given to potential participants at least 24h prior to registration of consent followed by randomization.

12.4 Subject Identification

The investigator will keep a list of all patients (who have received study treatment or undergone any study specific procedure) including patient numbers, full names and last known addresses.

The patients will be identified in the CRFs by patient number and birth year.

Number of patients screened, informed, and non-consenting patients will also be registered.

13 Trial sponsorship and financing

The study is supported by an unrestricted grant by Inven2 funds from the manufacturer of carbetocin (Pabal), Ferring Medical, Copenhagen, DK. The funds are assigned M61631. Other expenses will be covered by Division of Emergencies and Critical Care or the University of Oslo. After End of study data will be shared with Ferring Medical. Data will be handled confidentially and the purpose is contact with Regulatory institutions, and not for further analyses or publication.

14 Publication policy

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors. Collaborators (+ main responsibility) in the project are: Tore Henriksen (Obstetrician, patient recruitment, data collection), Department of Obstetrics, OUS, Are Hugo Pripp (Statistical analyses), Division of Biostatistics, OUS, Ole Geir Solberg (Cardiology), Dep. Of Cardiology, OUS, Olav Klingenberg (Biomarker analyses), Dep. Of Medical Biochemistry, OUS, Bjørn Jørgensen (Cardiology), Dep. Of Cardiology, Drammen Hospital, and Jon Norseth (Biomarker analyses), Dep. Of Medical Biochemistry, Vestre Viken Trust, Drammen Hospital, Luis G. Romundstad (Randomization), Dep. Of Anesthesiology, Division of Critical Care, OUS, and Silje Reme (pain sub-study), Dep. Of Pain Medicine, Division of Critical Care, OUS. In addition a PhD candidate working in the project will be appointed.

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CMT2014

Statistical Analysis Plan (SAP)

Version: V1-5
Author: Leiv Arne Rosseland, Maria Egeland Bøgh Bekkenes, Morten Wang Fagerland
Date: 25-05-2021

APPROVAL PAGE

Biostatistician Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital

Signature: _____
Morten Wang Fagerland, PhD MSc

Date: _____

Principal Investigator/Project Leader

Signature: _____
Leiv Arne Rosseland, MD PhD

Date: _____

1.0 INTRODUCTION

Adequate uterus contraction after delivery of the baby is necessary to avoid excessive bleeding. Prophylactic administration of an oxytocin receptor agonist is first line practice. Intravenous injection of oxytocin has been the standard procedure, but serious cardiovascular adverse events have been reported. Lowering the dose or administering the drug as a 5-minute infusion may increase safety.
Carbetocin, a synthetic oxytocin receptor agonist, has significantly longer half-life, and may reduce blood loss compared with oxytocin. The hemodynamic vasodilatory effects are comparable to oxytocin(1), but potential differences in adverse effects on myocardium are not well described yet.
Carbetocin has been in clinical use in EU since 2007, and the efficacy is documented in several RCTs. In the proposed study, carbetocin will be used within then conditions of the marketing authorization. Oxytocin is the first line treatment and prophylaxis in Norway and most countries in the world.
According to recently published guidelines from EU drug authorities (EMA), oxytocin should be given as a slow 5-minute infusion in order to avoid hypotension. This has so far not been implemented in Norway. The pre-clinical and clinical experience of the two drugs are summarized in the Summaries of Product Characteristics.

Pregnancy and delivery is a natural process, but for many women this period is stressful and not without risks of morbidity, and even mortality. Circulatory adverse events leading to death have been reported after intravenous injection of oxytocin(2). Some studies indicate that oxytocin may lead to dose dependant ischemic ECG changes(3, 4), prolongation of QT time and liberation of biomarkers of myocardial cell death(3).
Previously we have demonstrated comparable vasodilatory effects of oxytocin and carbetocin(1). There is no clinical study comparing the specific myocardial effects of oxytocin with carbetocin. It may have great impact on the choice of standard medication if the cardiotoxicity of carbetocin is lower compared with oxytocin. The study of potential cardiotoxicity has to be performed in healthy women. Knowing that millions of labouring women have had uneventful injections of oxytocin and carbetocin after delivery, there is probably no reason to fear long lasting negative effects of either drug. Improved knowledge about the effects of the two drugs on heart and circulation will aid treatment decisions especially for women with underlying heart disease or hypertensive complications of pregnancy, but even for healthy women undergoing caesarean delivery.

The aim of the pilot study is to compare 0h (before C-section), 4h, 10h and 24h plasma concentrations of troponin I (highly sensitive methods), troponin T, NT-proBNP, CK-MB and other relevant myocardial markers and ECG changes in elective healthy C-section patients randomized to oxytocin 2.5 U or carbetocin 100 µg, by 1-minute injection immediately after delivery.

Based on the results from the pilot trial, sample size calculation for the main trial (CMT2) will be performed to answer which of the drugs causes more release of high sensitive troponin I.

Some clinical studies indicate that administering carbetocin will influence pain perception. One clinical study comparing carbetocin and oxytocin for prevention of PPH after caesarean

delivery, reported significantly reduced pain intensity in patients receiving carbetocin(5). A secondary analysis of postoperative opioid consumption in another clinical trial comparing hemodynamic effects of oxytocin and carbetocin, found a tendency of lower consumption of opioids in the carbetocin group, but the differences were not statistically significant(6).
The CMT-pain trial, a substudy of the CMT trial, will be conducted to investigate group differences in reported pain intensity and opioid consumption. Information on the patients level of anxiety, depression and pain catastrophizing traits will be obtained prior to the operation. In addition, biobank material will be analysed for levels of inflammatory markers related to pain.

2.0 DATA SOURCE

2.1 Patients

We will conduct a double blinded randomized controlled trial where healthy women undergoing C-section will receive either oxytocin or carbetocin immediately after delivery of the baby. Ratio between the groups will be 1:1.

2.1.1 CMT pilot trial

Forty patients will be recruited from the general population of the birth clinics of Oslo University Hospital (OUH). Based on blinded analysis in this pilot trial, statistical power analysis and group size estimation will be performed to prepare for a larger confirmatory main trial (CMT2).

2.1.2 CMT2 trial

240 patients will be included into the CMT2 trial from the general population of the birth clinics of OUH and Akershus University Hospital (AHUS).

2.1.3 CMT pain trial

This trial will include 40 patients from the pilot trial and the first 40 patients from the CMT2-trial included at the birth clinic of OUH, Rikshospitalet.

2.2 Inclusion and exclusion criteria

Inclusion criteria are healthy pregnant women aged 18 to 50, singleton pregnancy at gestational age 36 weeks or more, who are able to read and understand Norwegian.
Patients with placenta pathology, bleeding disorders, organ failure, prolonged QT-time or other serious cardiac diseases, epilepsy or known intolerance to any of the two drugs will be excluded from entering the trial.

2.3 Follow-up and timing of measurements

Patients will be followed for a period of 48 hours after the administration of study drug.
In the pilot trial, blood samples will be drawn at 0h, before C-section (=baseline), and at 4h, 10h and 24h after delivery (=test drug administration). The myocardial biomarkers including high sensitive troponin I, troponin T, CK, CK-MB and NT-proBNP will be measured at all time points. If indicated by increase in some of the specific biomarkers, which will be analysed consecutively, an additional sample at 48h will be included.

During the C-section the patients will be attached to a Holter-monitor that will allow us to read ECG changes that are triggered by administration of test drug. The first ten minutes immediately following administration of study medicine will be evaluated for ST-segment changes, duration of ST-segment changes, prolonged QT-time and occurrence of arrhythmia. Data on ECG changes will be analysed only in the pilot trial.

In the CMT2 trial, blood samples of high sensitive troponin I and levels of sodium and hemoglobin will be measured at 0h and at an interval of 6-10h after study drug administration.

Data on uterine contraction, routine assessments of newborn status, side effects of test drug, consumption of analgesics and reported level of postoperative pain, nausea and tiredness will be obtained. Prior to the C-section patients will be asked to fill in standardized self-reporting forms designed to determine level of anxiety, depression and pain catastrophizing traits.

3.0 STUDY OBJECTIVES

3.1 Primary objectives

3.1.1 CMT pilot trial

To measure the difference between oxytocin and carbetocin in changes over time in Troponin I release from baseline to 24h after test drug administration, and ECG changes from baseline to 10 minutes after test drug administration.

3.1.2 CMT2 trial

To measure the difference between oxytocin and carbetocin in changes over time in Troponin I release from baseline to an interval of 6-10h after test drug administration.

3.1.3 CMT pain trial

To measure the difference between oxytocin and carbetocin in changes over time in opioid consumption and reported pain intensity from baseline to 48h after test drug administration.

3.2 Secondary objectives

Plasma levels of sodium, hemoglobin and myocardial biomarkers such as troponin T, CK, CK-MB and NT-proBNP will be analysed for group differences in changes over time.

A study biobank is established both for the CMT pilot trial and the CMT2 trial.

To measure the difference between oxytocin and carbetocin in: uterine tone, blood loss, perioperative side effects, postoperative pain and side effects, consumption of analgesics, ECG changes, and time consumption from time of delivery till end of surgery.

To describe the relationship between the preoperative reported level of anxiety, depression and pain catastrophizing trait and opioid consumption and pain intensity during the first 48 hours after caesarean delivery.

3.3 Explorative objectives

We expect further analysis to be performed on the data set that may generate separate analysis and publications.

3.4 Study design

The study is designed as a double-blinded randomized controlled trial including healthy singleton pregnant women undergoing Caesarean delivery. The participants will be randomized 1:1 to oxytocin 2.5 U or carbetocin 100µg, 1-minute injection immediately after delivery.

3.4.1 CMT pilot trial

40 patients will be included from the birth clinics of OUH.

3.4.2 CMT2 trial

240 patients will be included from the birth clinics of OUH and AHUS.

3.4.3 CMT pain trial

40 patients from the pilot trial and the first 40 patients from the CMT2 trial included at OUH, Rikshospitalet will be included in the trial.

4.0 HYPOTHESIS AND DECISION RULES

4.1 Primary endpoint and statistical hypotheses

The protocol is designed to investigate group changes over time in patients receiving carbetocin compared to oxytocin.

The primary null hypothesis states that there is no difference between the treatment groups. The alternative hypothesis states that the changes over time differ between the treatment groups.

4.1.1 CMT pilot trial

The primary endpoint of interest is the treatment difference in changes over time in high-sensitive troponin I levels, measured at baseline 4h, 10h, and 24h after drug administration.

4.1.2 CMT2 trial

The primary endpoint is the treatment difference in changes over time in high-sensitive troponin I levels, measured at baseline and at an interval of 6-10h after drug administration.

4.1.3 CMT pain trial

The primary endpoint is treatment difference in opioid consumption and reported pain intensity within the first 48h after test drug administration.

4.2 Statistical decision rule

The primary and all secondary outcomes will be analysed with two-sided tests and confidence intervals and a statistical significance level of 5%.

5.0 ANALYSIS SETS

5.1 Enrolled

The enrolled set will include healthy singleton pregnant women undergoing Caesarean delivery at the birth clinics at OUH or AHUS, who have provided informed consent and have been included into the study data base.

5.2 Full analysis set

The full analysis set will be defined as all enrolled patients randomly assigned to a treatment group having received the study drug.

The patients are included in the study at an interval of 1-14 days prior to the set date of the planned C-section. Some of the patients will go into active labor prior to the planned date, and some of the planned C-sections will be shifted to an inconvenient time point for study completion due to competing acute activity at the maternity ward. These patients will be included in the study, but will end their study participation prior to receiving the study drug. The same is true for patients requiring general anaesthesia due to inadequate effect of spinal anaesthesia.
A modified intention to treat analysis will be performed on all the patients included in the study having received the study drug.

5.3 Safety analysis set

The safety analysis set will be equal to the full analysis set.

5.4 Per protocol analysis set

The per protocol analysis set will include all randomised patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy.
Major protocol deviations include entering into active labor prior to set date of planned C-section, planned C-section shifted to an inconvenient time point for study completion due to competing acute activity at the maternity ward, and need for general anaesthesia due to inadequate effect of spinal anaesthesia.

5.5 Treatment misallocation

If patients were randomized but not treated, the patients will appear on the study flowchart as randomized but not treated. This is the extent of how much the patient will be reported.

5.6 Protocol deviation

The following sections describe any protocol deviations that relate to the statistical analyses and forms the requirements for exclusion from the PPS.

5.6.1 Deviations to inclusion and/or exclusion criteria

Any patient who enters the study when the inclusion or exclusion criteria would have prevented entry, will be considered to have had a protocol deviation.

5.6.2 Deviations assessed post-randomization

Any patient who withdraw their consent during the observation period of 48 hours following administration of study medicine.
Randomised patients that for any medical reason will be prevented from completing the study according to study protocol.

6.0 ASSESSMENT, DEFINITION AND DERIVED VARIABLES

6.1 Primary outcome: High sensitive troponin I

Level of troponin I is measured at baseline (before administration of test drug) and at fixed time points following administration of test drug, and is a continuous variable measured in ng/L.

6.1.1 CMT pilot trial

Level of troponin I is measured at baseline and at 4, 10, 24 and if necessary 48 hours after study drug administration.

6.1.2 CMT2 trial

Level of troponin I is measured at baseline and at an interval of 6-10 hours after study drug administration.

6.2 Secondary outcomes

6.2.1 Other myocardial biomarkers.

The following myocardial biomarkers will be analysed at the same time points in the CMT pilot trial.

- Troponin T, a continuous variable measured in ng/L. The lower detection level of troponin T is 5 ng/L.
- CK, a continuous variable measured in U/L.
- CK-MB, a continuous variable measured in µg/L. The lower detection level of CK-MB is 1 µg/L.
- NT-proBNP, a continuous variable measured in ng/L. The lower detection level of NT-proBNP is 50 ng/L.

All measurements of biomarkers below their detection limits will be randomly imputed from a uniform distribution with lower limit equal to 0 and upper limit equal to the detection limit.

6.2.2 Other blood analyses

The following analyses will be performed at the same time points as for analysis of troponin I, for the CMT pilot trial at 0, 4, 10 and 24 hours and for the CMT2 trial at 0 and 6-10 hours after study drug administration.

- Hemoglobin, a continuous variable measured in g/100ml.
- Sodium (Na), a continuous variable measured in mmol/L
- Biobank analyses, continuous variables measured in units according to the specific variable.

6.2.3 Uterine tone

Uterine tone will be evaluated by obstetrician in charge of the C-section at 2.5 and 5 minutes after test drug administration
A numeric rating scale ranging from 0-10 is used (0 = no effect, 7 = clinically satisfactory contraction, 10 = maximal uterus contraction). The variable will be treated as continuous in the statistical analyses.

In case of need for additional uterotonic agent(s) for adequate uterine tone, time to rescue medication will be reported as a continuous variable in minutes.

6.2.4 Blood loss

Blood loss will be estimated by the formula for calculated blood loss as published by Stafford, revised with weight in kg and height in cm(7).
A continuous variable measured in mL.

6.2.5 Perioperative side effects.

During the first 10 minutes after administration of test drug, the patient will be asked to report any side effects. Severity of side effects will be registered in time gaps as follows 0-2 min, 2-5 min and 5-10 min.
Severity of side effects is an ordered categorical variable:

- 0 = no side effects at the given point
- 1 = mild side effects
- 2 = moderate side effects
- 3 = severe side effects.

Treatment given to alleviate side effects (a binary variable) will be registered as

- 0 = no treatment administered
- 1 = treatment administered

6.2.6 Postoperative pain and side effects

Pain at rest, pain after coughing, nausea and tiredness will be registered at 4h, 10h, 24h and 48 h after administration of test drug in the CMT pilot trial..
A numeric rating scale ranging from 0-10 is used (0 = no discomfort, 10 = maximal discomfort imaginable). The variables will be treated as continuous in the statistical analyses.

6.2.7 Consumption of analgesics

Postoperative pain treatment protocol includes oral paracetamol 1 g and ibuprofen 400 mg 4 times daily and IV morphine administered by a patient controlled analgesia pump (PCA).
In the CMT pain trial, overall postoperative morphine consumption in mg will be measured, as well as morphine consumption in the time periods 0-4h, 4-10h, 10-24h and 24-48h after test drug administration.
A continuous variable measured in mg.

6.2.8 QOL forms detecting level of anxiety, depression and pain catastrophizing trait

Prior to the operation the patients will be asked to fill inn QOL forms detecting level of anxiety, depression and pain catastrophizing trait. Only in the CMT pain trial.

6.2.8.1 Modified three simple questions

A numeric rating scale ranging from 0-100 is used to rate anxiety, anticipated level of pain, need for analgesics and coping with motherhood (0 = not at all, 100 = to an extreme degree). The variables will be treated as continuous in the statistical analyses.

6.2.8.2 Pain Catastrophizing Scale (PCS)

PCS consists of 13 questions scored as follows.

- 0 = not at all
- 1 = to a slight degree
- 2 = to a moderate degree
- 3 = to a great degree
- 4 = all the time

The overall score is achieved by summarizing the scores of the 13 questions. Results from the PCS will range from 0-52. The variable will be treated as continuous in the statistical analyses.

A PCS score of ≥ 30 is considered to be associated with clinical relevance. Reported level of PCS ≥ 30 will be reported as a binary variable (PCS $< 30 = 0$, and PCS $\geq 30 = 1$).

6.2.8.3 Hopkins Symtom CheckList (HSCL-25)

HSCL-25 consists of 25 questions measuring level of anxiety and depression. Each question is scored as follows.

- 1 = Not at all
- 2 = A little bit
- 3 = Quite a bit
- 4 = Extremely

The value for HSCL-25 is obtained by calculating the mean score of the 25 questions. The variable will be reported as a continuous variable.

HSCL-25 of ≥ 1.75 is considered clinically relevant, and will be reported as a binary variable (HSCL-25 $< 1.75 = 0$, HSCL-25 $\geq 1.75 = 1$).

6.2.9 ECG changes

In the CMT pilot trial, the patients will be attached to a digital Holter monitor (Medilog AR4, Schiller) during the C-section to evaluate ECG changes during the first 10 minutes following administration of test drug.
The following parameters will be registered:

- Occurrence of ischemic episode (ST-segment depression of ≥ 0.1mV). Registered as a binary variable (no ischemic episode = 0, one/more ischemic episodes = 1)
- Duration of ischemic episode. Continuous variable measured in seconds.

- Degree of ST-segment depression from baseline. Continuous variable measured in mV.
- Beat to beat analysis of QT time corrected according to Framingham. Continuous variable measured in msec.
- Occurrence of arrhythmia. Registered as a binary variable (no episodes of arrhythmia = 0, one/more episodes of arrhythmia = 1)

6.2.8 Time consumption

Time consumption from time of delivery until end of surgery and from time of delivery to time of discharge form postoperative ward unit.
A continuous variable measured in minutes.

6.3 Summary of endpoints (TABLE)

OUTCOME	ENDPOINT	TYPE
Primary	Troponin I level	Continuous
Other myocardial markers	Troponin T level	Continuous
	CK level	Continuous
	CK-MB level	Continuous
	NT-proBNP level	Continuous
Other blood analyses	Hemoglobin level	Continuous
	Sodium level	Continuous
	Biobank analyses	Continuous
Uterine tone	Uterine tone	Continuous
	Time till rescue, min	Continuous
Blood loss	Calculated blood loss, ml	Continuous
Perioperative side effects	Severity of side effects	Ordered categorical
	Treatment of side effects	Binary
Postoperative pain and side eff.	Pain at rest	Continuous
	Pain after coughing	Continuous
	Nausea	Continuous
	Tiredness	Continuous
Consumption of analgetics	Morphine consumption, mg	Continuous
QOL forms	Modified three simple questions	Continuous
	PCS	Continuous
	PCS $\geq$ 30	Binary
	HSCL-25	Continuous
	HSCL-25 $\geq$ 1.75	Binary
ECG changes	Occurrence ischemic episode	Binary
	Duration ischemic episode, sec	Continuous
	ST-segment depression, mV	Continuous
	Prolonged QTc interval	Binary
	Beat to beat analyses QTc interval	Continuous
	Occurrence of arrhythmia	Binary
Time consumption	Time consumption, min	Continuous

7.0 STATISTICAL METHODOLOGY

7.1 Sample size determination

7.1.1 CMT pilot trial

The predefined main outcome variable in this double blinded randomized controlled study is group differences in changes over time in high sensitive troponin I levels. This is the first clinical study comparing these outcome measures and calculation of statistical power and group size estimations are not possible. After all data from 40 patients (1:1 group size) have been collected, a blinded analysis based on these study data will be performed by a medical statistician, who will get access to outcome measures and information about treatment allocation, but not the actual treatment. Unblinding will be performed when all analyses have been completed.

7.1.2 CMT2 trial

Based on preliminary results of the CMT pilot trial, the largest difference in plasma troponin I concentration was found at 10 hours, with a mean±standard deviation change from baseline of 0.41±0.79 ng/L in the carbetocin group versus a mean change of 1.78±4.48 in the oxytocin group. The sample size calculation was based on 80% power to detect a between-group difference in change from baseline to 10 hours of 1.37, to be analysed using a two-sample T-test with adjustments for unequal variances. With a significance level of 5%, we will need to include 178 patients (89 in each treatment group) in the CMT2 trial. To adjust for loss of information from missing values and patient drop outs, 240 women will be enrolled. The drop-out rate after enrolment is expected to be low as the duration of the study is short.

7.2 Randomization

After inclusion, patients will be randomized to one of two study arms. The randomization will be performed immediately before study start. The person responsible for preparing the study drug will be unblinded and not otherwise involved in patient treatment. Research personnel involved in patient treatment, data collection and analysis will not receive information about actual treatment allocation until all data has been collected and analyses have been completed. Randomization will be performed by a researcher not involved in the data collection. The randomization responsible will decide block size and if variable block size will be used.

7.3 Blinding

All study participants will be blinded to the treatment allocation with the exception of the person responsible for preparing the study drug and the person generating the randomization list. These persons will not be the same as the one responsible for analysis of the trial data. Blinding of study drug will be secured by using standard 5 ml syringes marked with date and randomization number according to study protocol.

7.4 Statistical methods

7.4.1 Primary and secondary analyses

The primary analysis will be a modified intention to treat analysis of the primary outcome (highly sensitive troponin I) on the full analysis set.

Secondary analyses will be:
1. A per protocol analysis on the primary outcome (troponin I) on the per protocol analysis set
2. Modified intention to treat analyses of all secondary outcomes on the full analysis set
3. Sensitivity analyses to examine the impact of missing data (Section 7.4.5)

7.4.2 Repeated-measures continuous outcomes

The primary endpoint and all other continuous endpoints, including baseline and ≥1 follow-up measurements, will be analysed with linear regression models, with the follow-up measurement defined as the dependent variable and treatment group and baseline measurement defined as independent variables. Based on the fitted models, we will estimate treatment group differences in changes from baseline with 95% confidence intervals (CIs), together with a p-value for the null hypothesis of no treatment group difference. We expect at least some degree of skewness in the primary and some of the secondary endpoints, and maybe also in the residuals from the linear regression models. The amount of skewness will be assessed with histograms and descriptive statistics, such as mean, median, variance, and the skewness index. In cases where the distribution of the residuals deviates markedly from the normal distribution, or when the endpoints themselves are too skewed to use means as measures of central tendency, we will use median regression models instead of linear regression models, thus analysing between-group differences in median changes from baseline instead of mean changes from baseline. Standard errors and CIs in the median regression models will be obtained via bootstrapping with 100 replications.

7.4.3 Continuous outcomes measured at single time points

Continuous outcome variables measured at single time points will be analysed with two-sample t-tests (and 95% confidence intervals for the differences between means), with adjustment for unequal variances (the Welch U test). In situations where the distribution of the variable is difficult to assess or deemed to be highly skewed, median regression models will be used instead of t-tests to test and estimate differences in medians.

7.4.4 Categorical outcomes

Binary outcomes will be analysed with Fisher mid-P tests and Newcombe hybrid score confidence intervals for the difference between probabilities.

Ordered categorical outcomes will be analysed with score tests for effect in a proportional odds model (the Wilcoxon-Mann-Whitney test).

7.4.5 Handling of missing data

Due to a short interval of observation in the CMT trial, only 48 hours after test drug administration, we expect a low level of missing data in this trial.
For categorical outcomes and continuous outcomes measured at one or two timepoints, a complete case analysis will be the primary analysis. In addition, sensitivity analyses will be

performed for the primary outcome, where missing data will be imputed according to the following scenarios:

1. Best-case outcome in the oxytocin group and worst-case outcome in the carbetocin group.
2. Worst-case outcome in the oxytocin group and best-case outcome in the carbetocin group.

   Best case outcome = group mean + 2SD
   Worst case outcome = group mean - 2SD, levels below 0 are set to 0.

3. Group-specific mean values

Similar sensitivity analyses for missing data will be performed for other continuous and categorical secondary end points, if the proportion of missing outcome values is greater than 10%. Best and worst case for categorical variables will be the lowest or highest possible score according to each variable. For the binary variable occurrence of arrhythmia, for instance, best case score = 0 (no episodes of arrhythmia) and worst case score = 1 (one/more episodes of arrhythmia).

Continuous variables measured at more than two time points will be analysed with linear mixed models (Section 7.4.2), which automatically handle missing data under the missing at random assumption.

7.4.6 Statistical software

StataSE version 16 (StataCorp LLC, College Station, TX) will be used for all statistical analyses, except analyses of categorical outcomes, which will be done with MATLAB version R2019b (MathWorks, Inc.).

8.0 References

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