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Original Research Article

Protocol for a randomized trial on nausea, vomitus and arterial hypotension comparing carbetocin and oxytocin as prevention for hemorrhage after cesarean section

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ABSTRACT

Background: To prevent hemorrhage after cesarean section uterotonics are often administered after fetal extraction. At this moment two frequently used and available products are short working oxytocin and its long working analogue, carbetocin. Both have proven and similar efficacy. Side effects are nausea, vomitus and arterial hypotension resulting in dizziness. Differences in nausea, vomitus and blood pressure changes between oxytocin and carbetocin have been studied as secondary outcome measures only and results have been conflicting. The aim of the present study is to compare nausea, vomiting and changes in blood pressure between carbetocin and oxytocin used as prevention for postpartum hemorrhage after cesarean section.
Methods: Patients are women undergoing a planned term cesarean section for singleton pregnancy without other medical complications. One hundred patients will be randomized to receive either a single intravenous dose of 100 microgram carbetocin, either an intravenous bolus of 5 units of oxytocin followed by 10 units of oxytocin over 24 hours. As primary outcome nausea and vomitus are evaluated before, during and immediately after surgery, using a standard scale, blood pressure is automatically measured every three minutes. Secondary outcome measures are the difference between pre- and postoperative hemoglobin and the need for additional uterotonics. Analysis will be based on intention to treat.
Conclusions: This study will offer data on the difference in clinically relevant side effects between carbetocin and oxytocin helping clinicians to choose between both products in low risk cesarean sections.

Keywords: Pregnancy, Cesarean Section, Postpartum Hemorrhage, Nausea, Vomitus, Blood Pressure, Carbetocin, Oxytocin

Trial registration: Current Controlled Trials ISRCTN 95504420

INTRODUCTION

Postpartum hemorrhage (PPH) remains one of the most important causes of maternal morbidity and mortality, the most frequent cause of PPH is uterine atony, contributing up to 80% of cases.[1] Cesarean section (CS) is a well-known risk factor for PPH and it is advised to systematically administer uterotonic agents immediately after extraction of the fetus.[2]

Oxytocin (Syntocinon®) has long been the uterotonic most frequently used after cesarean section. Due to a short half live of 4 to 10 minutes it requires continuous or frequently repeated administration; carbetocin (Pabal ®) has been developed as a long acting oxytocin analogue and results in sustained uterine contraction. In a systematic review and meta-analysis of randomized controlled trials carbetocin is associated with reduced need for additional uterotonic agents but no differences are noted for PPH, severe PPH, mean estimated blood loss nor adverse effects.[3] Side effects including nausea and vomiting or arterial hypotension eventually resulting in dizziness or even syncope have only been studied as secondary endpoints of randomized controlled trials. Hypotension has been reported as an important medical event in randomized trials, a hypotensive effect has been described both by oxytocin and carbetocin in randomized studies comparing carbetocin with oxytocin mainly on hemodynamic effects.[4,5] In most studies high doses of oxytocin up to 20 units have been used and resulted in significant hypotension with this high dose of oxytocin.[5] When comparing carbetocin 100 µg with oxytocin 5 IU, hemodynamic side effects have been comparable in both groups, but nausea and vomiting have not been specifically been studied.[6] No difference in hypotension has been noted between different doses from 20 to 100 µg of carbetocin and generally hypotension is noted in 40 to 55%.[7,8]

In daily practice nausea and vomitus are side effects that are frequently encountered and have a negative impact on the experience of vaginal delivery and cesarean section, the very first moment of motherhood. As no randomized controlled trial has taken nausea, vomitus and symptomatic hypotension as primary endpoints comparing carbetocin and oxytocin after cesarean section, this study was set up.

METHODS

Study design

This study is a double blind randomized controlled trial. Two active intervention arms are compared, one with carbetocin the other with oxytocin so that all participants do receive effective uterotonic prevention of PPH. Neither the anesthesiologist nor the gynecologist nor the patient know what medication is administered. The study medication is prepared at the maternity department by a resident that will not attend the cesarean section. In this way a total blinding can be assured. The study protocol, information brochure and informed consent were approved by the Medical Ethics Company of Antwerp University Hospital, Belgian registration number D300201110299.

Inclusion and exclusion criteria

Included are all women undergoing a planned term cesarean section at Antwerp University Hospital in a term singleton pregnancy. Women with medical complications potentially influencing outcome measures (nausea vomitus and hypotension) are excluded: diabetes, pre-existing hypertension, pre-eclampsia, gestational hypertension and known gastro-intestinal diseases are exclusion criteria. Participants have to be 18 years or older. Gestational age has to be between 38 and 42 weeks.

Recruitment

Participants are recruited at the delivery ward of the Antwerp University Hospital at the moment they enter the hospital for planned cesarean delivery. Women are informed orally by the investigators in detail on the study and receive a written description of the study. If they agree and sign the informed consent form they are randomized.

Randomization

Participants are randomized in 1:1 ratio. A computer generated randomization list was generated using SPSS21. The medication is prepared by a resident not treating the patient to make sure that patient, gynecologist, anesthesiologist and midwife clinically in charge of the patient are blinded for the medication.

Intervention

The control group receives she standard dose of oxytocin (Syntocinon®, Sigma-Tau, Rome, Italy) as used in our hospital , 5IU oxytocin in 10 ml NaCl 0.9% over 3 minutes followed by 10IU oxytocin in 1 Liter of crystalloid (Plasma-Lyte®, Baxter S.A, Belgium) over 24 hours. The study group receives 100 µg of carbetocin (Pabal® , Ferring nv., Aalst, Belgium) in a single dose in 10 ml of NaCl 0.9% over 3 minutes followed by 1 Liter of crystalloid (Plasma-Lyte®, Baxter S.A, Belgium) over 24 hours.

Primary outcomes

From the entry of the patient in the operating room until one hour later blood pressure and heart frequency are automatically registered as during routine monitoring for every surgery. A computer outprint is generated with measurements every three minutes. Nausea and vomitus are evaluated before surgery, during surgery , before giving the intravenous medication and after 5, 10 and 15 minutes based on a simple dichotomous scale: 0 = no nausea no vomitus; versus symptomatic nausea/vomitus =1.

Secondary outcomes

As secondary outcomes the difference in hemoglobin taken 24 to 2 hours before the intervention and 48 hours after the intervention will be registered. This will serve as a substitute for the assessment of postpartum

hemorrhage. Furthermore a necessity of additional uterotonics will be noted as will be need for blood transfusion.

Sample size and statistical analysis

Analysis will be conducted according to intention to treat as well for protocol. A power analysis showed that 150 patients per group would provide 80% power and a statistical significance of 0.05 to detect a 15% to 5% decrease in the incidence of nausea and vomiting among the treatment groups; we considered this difference to be clinically relevant. Dichotomic variables including nausea and vomiting will be compared with a Chi-squared test, odds ratios and 95 % confidence intervals. Blood pressure in absolute values, delta blood pressures will be compared using a Students T-test. Delta hemoglobin will be compared using Students T-test

DISCUSSION

The aim of the study is to investigate the impact of two different uterotonics after cesarean section on clinically relevant side effects, namely nausea, vomiting and symptomatic hypotension.

As systematic review and meta-analysis did not demonstrate a clinically relevant difference in the effectiveness as far as the prevention of PPH is concerned between oxytocin and carbetocin.[3] Choice between both products will be guided by other determinants including side effects and cost. Some studies did note a difference in the need for additional uterotonics when using carbetocin as compared to oxytocin, but these have used oxytocin in more a dilute solution or stopped the oxytocin intravenous administration very shortly after delivery.[4,5] As this is not the routine protocol in our hospital, we do not expect any difference in postpartum hemorrhage. In a later secondary analysis retrospective costs of patients can be compared between both groups in our setting

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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