Statistics Plan: The Effect of Carbetocin Dose on Dispersion of Myocardial Repolarization in Healthy Parturients Scheduled for Elective Cesarean Delivery Under Spinal Anesthesia

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Research Study Protocol

Title: The effect of carbetocin dose on dispersion of myocardial repolarization in healthy parturients scheduled for elective Cesarean delivery under spinal anesthesia – A prospective, randomized, blind clinical trial

Abbreviated title: Carbetocin on myocardial repolarization dynamics in obstetrics (CaRDIO) Study

ClinicalTrials.gov Unique Identifier: Pending

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Background:
Postpartum haemorrhage (PPH) is a significant factor in maternal morbidity and mortality worldwide with uterine atony the commonest cause of PPH. In 2009, the Society of Obstetricians and Gynecologists of Canada (SOGC) recommended the use of an intravenous (IV) carbetocin bolus, instead of a continuous oxytocin infusion in elective Cesarean delivery for the prevention of PPH from uterine atony(1).

Carbetocin (1-deamino-1-carba-2-tyrosine (0-methyl)- oxytocin) is a synthetic analogue of human oxytocin and has a similar mechanism of action. The peak onset of action is 2 minutes, with a 60-minute duration of action following IV bolus. The dose recommended by the SOGC is 100mcg. However, recent studies have suggested that a 10-100mcg dose following low risk Cesarean delivery under spinal anesthesia can produce satisfactory uterine tone (2)(3). Carbetocin is currently used routinely at British Columbia Women's Hospital (BCWH) as a first-line pharmacological intervention at a dose of 50mcg or 100mcg during elective and emergency Cesarean deliveries. The range in dosing at BCWH stems from contemporary studies showing different effective dose 90 (ED90) doses. Khan et al showed that the ED90 dose producing satisfactory uterine contraction in women undergoing low risk elective Cesarean delivery was 14.8mcg(3). Nguyen-Lu et al showed a higher ED90 of 121mcg for women undergoing emergency Cesarean delivery after at least 3 hours of an oxytocin infusion in labour. They concluded that a 121mcg

dose could be an underestimation for this group of patients, but to use higher than the currently recommended doses with caution due to increased risk of arrhythmia(4).

A recent study involving 20 women undergoing Cesarean delivery suggested that carbetocin 100mcg IV bolus may be associated with prolongation of the QTc interval on the electrocardiogram (ECG)(5). They advocate that carbetocin should not be used in patients with prolonged QTc or LQTS. This issue has not been rigorously investigated, and the possibility of harm in patients with comorbid cardiac conditions remains unclear. Pregnant patients with pre-existing prolonged corrected QT (QTc) interval (drug induced) or congenital long QT syndromes (LQTS) are at significant risk for a cardiac event, especially during the post-partum period.

QTc interval prolongation is associated but not the cause of torsades de pointes (TdP)(6), a polymorphic ventricular tachycardia which can lead to cardiac arrest. QTc interval has been shown to be a poor predictor of the risk of TdP. Prior studies have demonstrated a more reliable predictor of risk of TdP is the interval between the peak and the end of the ECG T-wave (Tp-e), which is a surface ECG marker of dispersion of repolarization (TDR) across the myocardial wall(7)(8). Normal TDR reflects the way that different layers of the myocardial wall repolarize at different rates – the outside fastest, then the inside and finally the middle. It has been shown that exaggeration of TDR provides the right environment and trigger for TdP. This surface ECG marker can be used as a tool to assess the risk posed by a drug that prolongs the QT interval(9). The current evidence shows that, if TDR is not increased, the risk of TdP is not increased, even if the QT interval is prolonged. Conversely, if TDR is exaggerated, the risk of TdP is raised, even if the absolute QT interval is within normal limits.

The normal values for QTc and Tp-e are different in pregnancy. This has been elucidated by Tanindi et al who found that QTc, Tp-e and Tp-e/QT ratio were all increased in the third trimester of pregnancy but were still within the normal range of non-pregnant women(10).

Every patient undergoing Cesarean delivery must receive a uterotonic agent to prevent uterine atony. Currently carbetocin is the first line treatment including for those patients with LQTS. There is no clear evidence currently whether carbetocin is safe in these patients and whether there is a dose dependant effect on myocardial repolarisation. The alternative treatments to carbetocin used as 2nd and 3rd line agents include oxytocin, misoprostol, ergometrine and hemabate. Oxytocin poses a risk of prolonging the QTc and the Tp-e after a bolus dose of 5Units over 1 minute (11), although some data suggests the average prolongation may not be more than 40ms (+/- 20ms), in patients receiving 10Unit IV boluses(12). A reduced dose of oxytocin, 5Units per 1,000mL lactated ringers has been shown to not prolong the QT interval, while still effectively decreasing post-partum haemorrhage(12). However, a couple of case reports describe the use of oxytocin for induction of labour and to aid uterine contraction in women with LQTS without any effect. The current recommendation is to use oxytocin with caution in patients at increased risk of or with LQTS. There is no information on the effects of misoprostol, ergometrine or hemabate on QTc interval or repolarization dynamics. It is therefore important to carry out this study to determine the safe use of carbetocin in patients at risk of prolonged QT interval or with LQTS.

To date no study has explored the effect of carbetocin dose on TDR in pregnant patients. Therefore, this study aims to examine in detail the relationship between carbetocin dose and TDR in healthy women having Cesarean delivery under spinal anaesthesia.

Study design and methodology:
This will be a prospective, randomized, double blind study in healthy women undergoing Cesarean delivery. It will examine the effect of carbetocin dose on TDR using 50mcg and 100mcg intravenous boluses.

Arm 1: Intravenous injection of Carbetocin 50mcg (C50) + 0.9% Sodium Chloride (total volume 10 mL) over 1 minute.

Arm 2: Intravenous injection of Carbetocin 100mcg (C100) + 0.9% Sodium Chloride (total volume 10 mL) over 1 minute.

Hypothesis:
We hypothesize that carbetocin increases indices of myocardial repolarization (Tp-e and QTc) with a dose-dependent relationship following Cesarean delivery under spinal anesthesia.

Primary outcome:

1. Change in Tp-e from baseline to 5 mins post carbetocin

Secondary outcomes:

1. Change in QTc from baseline to 5 mins post carbetocin within and between groups (50mcg vs. 100mcg)
2. Changes in Tp-e and QTc between groups (50mcg vs. 100mcg) from baseline to 5 minutes and 10 minutes post carbetocin
3. Changes in Tp-e and QTc within and between groups (50mcg vs. 100mcg) from post spinal to 10 mins post carbetocin
4. The presence of atrial and ventricular arrhythmias within and between groups (50mcg vs. 100mcg)

Inclusion criteria:

- Pregnant patients ≥ 36 weeks gestation, for elective Cesarean delivery under single-shot spinal anesthesia
- American Society of Anesthesiologists (ASA) class 2
- Patients ≥ 19 years of age

Exclusion criteria:

- Long QT syndrome
- Cardiac disease or rhythm abnormalities
- Family history of long QT syndrome or abnormal cardiac conduction
- Currently taking medication that is known to prolong the QT interval (appendix 5(13))

- Women who are high risk for uterine atony as outlined in SOGC (History of PPH, Preeclampsia, hereditary coagulopathies, fetal death, polyhydramnios, multiple gestation, macrosomia, high parity, maternal fever, prolonged ruptured of membranes, fibroid uterus, abnormal placentation, induction of labor, uterine anomalies)(14)
- Known allergic reaction or hypersensitivity to carbetocin or any other oxytocin homologue
- Patients who are unable to give informed consent because of a language barrier as the study team only speaks English and will be unable to complete consent process and study procedure appropriately.

Withdrawal criteria:

- Post-partum haemorrhage requiring second-line uterotonic use
- Withdrawal of consent at any time

Recruitment:

Patients having an elective Cesarean delivery typically arrive 60-90 minutes prior to scheduled procedure. Upon arrival, patients check in at the admitting desk where the admitting nurse will provide eligible patients with a Patient Information Sheet (Appendix 1) describing the study. The patients and her support persons are brought to the pre-operative waiting area before their procedure. After about 30 minutes and once the patient has had a chance to read the information sheet, one of the study team members will approach the patients and fully explain the details of the study (i.e., why the study is being carried out and how it will affect her care if she chooses to participate) and answer any questions. The patients will also be shown the ECG machine and ECG leads which will be used if she chooses to participate. We will leave her with the consent form to further read about the study and discuss it with her support persons. Approximately 30 minutes prior to elective Cesarean delivery, we will ask the nurse what the patient has decided. If the patient agrees, one of the study team members will formally go through the consent process with the patient, obtaining informed written consent (Patient Consent Form in appendix 2).

We will not attempt to consent patients in the proceeding days before the surgery as this would often require an extra hospital visit and thus place burden on the patients' time. However, we will provide the Patient Information Sheet and Informed Consent Form to all women once the decision for a Cesarean delivery has been made. The decision usually occurs in the obstetric care provider's office where the patient is given an information pack detailing their Cesarean delivery. This information pack is compiled by the admissions team at BCWH, and they have agreed to allow study investigators to add their Patient Information Sheets and Informed Consent Forms to the packs sent out to obstetric care providers. The Patient Information Poster (appendix 3) will also be e-mailed to all obstetric offices to print and display on their notice boards. Finally, the information poster will also be placed in the operating room admissions area and research notice boards around the hospital, with the aim that patients will recognize the study when they come in for their elective Cesarean delivery.

Investigators will educate anesthesiologists, surgeons and operating room nursing staff about the study directly through departmental rounds and by e-mail.

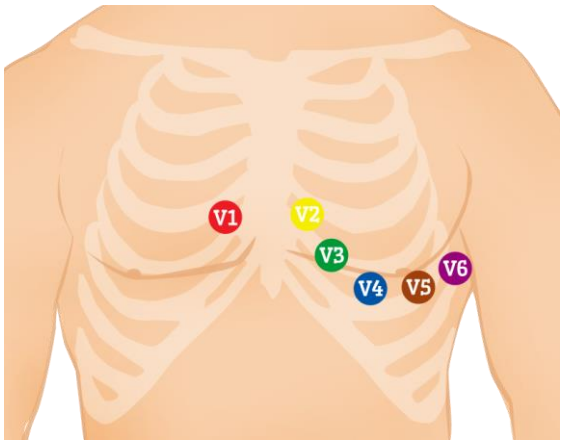
All study procedures will take place in the pre-operative area and operating room at BCWH. These will be conducted by one of the study team members; however, the study team will not then be involved with the participant's ongoing elective Cesarean delivery.

Randomization:
Microsoft Excel 2010 will be used to generate a randomization sequence that will be used to allocate participants to either Carbetocin 50mcg (C50) or Carbetocin 100mcg (C100). Allocation will be concealed using sequentially numbered opaque envelopes.

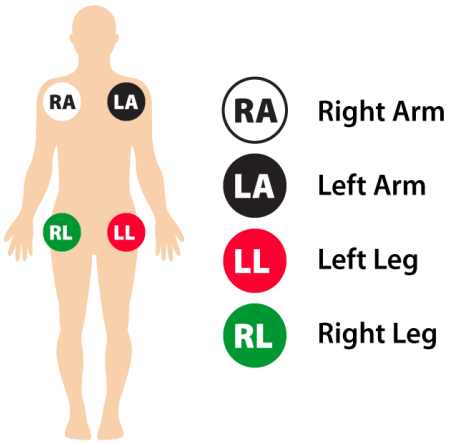
Blinding:
The ECG reviewer will be blinded to the study group and the status of the ECG recording (pre- or intra-operative). Each ECG will be given a random three-figure code to allow identification of the paired pre and intra-operative traces after analysis.

The ECG reviewer will not be involved in the recruitment or randomization of the patients, or in the conduct of the anesthesia or acquisition of the ECG recordings, all of which will be performed by one of the study team members.

Interventions (Study Protocol):
After obtaining written informed consent, enrolled patients will be randomized to one of two groups (C 50 or C100). Block randomization will be prepared using computer generated random numbers. Allocation



V1 - Fourth intercostal space on the right sternum
V2 - Fourth intercostal space at the left sternum
V3 - Midway between placement of V2 and V4
V4 - Fifth intercostal space at the midclavicular line
V5 - Anterior axillary line on the same horizontal level as V4
V6 - Mid-axillary line on the same horizontal level as V4 and V5
a)



RA (Right Arm) - Anywhere between the right shoulder and right elbow
RL (Right Leg) - Anywhere below the right torso and above the right ankle
LA (Left Arm) - Anywhere between the left shoulder and the left elbow
LL (Left Leg) - Anywhere below the left torso and above the left ankle
b)

will be concealed using sealed sequentially numbered opaque envelopes. In the pre-operative area ECG electrodes will be sited at standardized locations (figure 1) for acquisition of a pre-operative 12 lead ECG in the supine position – this will be the baseline ECG.

Participants' baseline ECGs will be analysed buy the study team in the preoperative area. If the QT interval is prolonged on the baseline ECG, the patient will be withdrawn from the study and an obstetric internal medicine specialist will be consulted. The ongoing care will then be determined by the attending obstetric, anesthetic and obstetric internal medicine physicians. . The QT interval range that we will be using as a reference is 435.9 ms ± 4.7. This is based on a study of third trimester pregnant parturients (10).

All ECGs will be recorded in duplicate at a paper speed of 50mm/s. Each trace will be allocated a three-digit random number code to allow
Figure 1(15)*: 12 lead Electrocardiogram (ECG) electrode placements in standard locations-a) pre-cordial electrodes and placement, b) Limb electrodes and placement.*

Identification of pre and intra-operative traces after analysis. Automated measurements, patient identifiers and times will be removed from the traces prior to analysis by study investigators. The anesthetic will be standardized for all patients. All patients will receive a Ranitidine 50mg IV infusion as a standard premedication.

After arrival in the operating room the patient will receive spinal anesthesia by single shot technique in the sitting position using a standardized dose consisting of hyperbaric 0.75% bupivacaine 12mg, 10mcg fentanyl and epidural preservative free morphine 100mcg. After the application of the spinal anesthesia, the patient is positioned in a left-lateral tilted recumbent position to avoid aorto-caval compression. A fluid pre-load using 0.9% normal saline or plasmalyte is infused while the patient is monitored with standard monitors including pulse oximeter, electrocardiogram and non-invasive blood pressure cuff around the upper arm. Each participant will receive an infusion of phenylephrine started after induction of spinal anesthesia at 50mcg/min to maintain BP at 100% of baseline. They will also receive Cefazolin IV 2g for surgical antibiotic prophylaxis.

An intra-operative 12 lead ECG, using the same electrode positions (figure 1) will be taken 5 minutes after induction of spinal anesthesia in the left lateral tilted position. Following delivery of the fetus and cord clamping, each patient will receive a bolus of carbetocin, 50mcg or 100mcg diluted in a 10mL normal saline syringe administered through a pump to be given over 1 min. The attending anesthesiologist will prepare the randomized carbetocin study dose and will not be involved in any other aspects of the study.

Further 12 lead ECGs will be acquired using the same electrode positions (figure 1) at 5 and 10 minutes after giving the study drug. Based on anecdotal clinical experience, the ECGs acquired at these time intervals do not interfere with any family or maternal-fetal bonding. The patient's involvement in the study will then be complete and the conduct of anesthesia continued at the discretion of the supervising anesthetist. Anti-emetics prophylaxis will be given after the final ECG recording, ondansetron 4mg and dexamethasone 5mg.

A postoperative 12 Lead ECG will be taken for safety purposes but will not be used for analysis. This postoperative ECG will be examined by the attending anesthesiologist and patients will be monitored in

the postanesthetic care unit (PACU) for up to 2 hours. If any abnormalities were found, an obstetric internal medicine specialist will be consulted.

All ECGs will be recoded in duplicate, at a paper speed of 50mm/sec and amplification of 0.1mV/mm and with no identifying data including time or automated analysis on the recorded traces. Each ECG will be given a random three-figure code to allow identification of the paired pre and intra-operative traces after analysis.

In case of insufficient uterine tone, the patient will be treated according to the current standard of care. Other options for ongoing care in case of uterine atony include uterine massage, ergometrine, oxytocin infusion, misoprostol, hemabate or Bakri balloon insertion. The choice of one or several of these interventions is according to severity of uterine tone and at the discretion of the obstetrician. In the event of any of these interventions occurring prior to the 10-minute ECG recording, the patients will be withdrawn from the study.

A summary of the protocol is shown in the flow diagram (Figure 2).

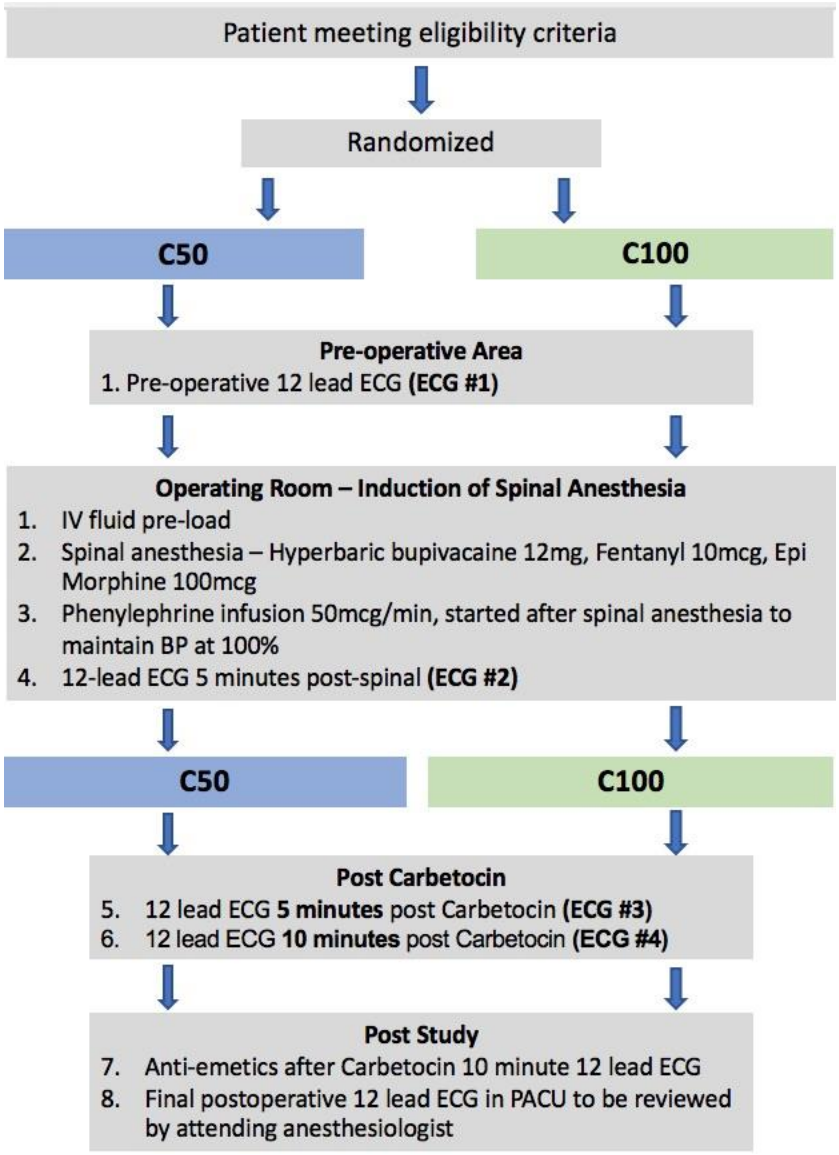


Figure 2: Study Flow Diagram. Abbreviations: Electrocardiogram (ECG), blood pressure (BP), heart rate (HR), Oxygen saturations (SpO_2).

Data to be collected (Data Collection Form):

- Participant demographics including age, height, most recent weight and body mass index, gravity and gestation
- Co-morbidities, complications of pregnancy and ASA grade
- Pre-operative blood pressure and heart rate
- Baseline pre-operative 12 lead ECG
- Spinal anesthesia drug doses
- Use and dose of any other vasopressors e.g. Ephedrine
- Post spinal 12 lead ECG at 5 minutes

- Blood pressure and heart rate at 5 minutes post spinal anesthesia
- 12 lead ECG post Carbetocin at 5 minutes and 10 minutes
- Blood pressure and heart rate at 5 minutes and 10 minutes post Carbetocin
- Evidence of arrhythmias at any time after study drug administration
- Skin-to-skin

Sample size:

The primary outcomes of our study are changes in Tp-e at 5 min post carbetocin administration compared to baseline for carbetocin 50mcg and carbetocin 100mcg. The published data(11) for the mean change in Tp-e for oxytocin at 5 min for pregnant patients undergoing spinal anesthesia for Cesarean delivery is 12ms with a standard deviation (SD) of 7. Using paired t-test, type I error of 0.05 and 99% power, 9 patients per group would be required. To adjust for two separate primary outcomes for 2 separate doses, an alpha correction factor of 2 is applied (i.e., 0.025), and assuming a wider SD for carbetocin of 10, 17 per group is needed. To account for attrition a total of 50 patients (25 per group) will be recruited.

Data analysis:

The QT and Tp-e intervals will be measured for all complete P-QRS-T cycles in lead II and V5 and averaged to give a mean QT interval and Tp-e interval for that lead. The QT interval will be measured from the start of the QRS complex to the end of the T-wave, defined as the point of return to the T-P baseline. If U waves are present, the end of the T-wave will be taken as the nadir of the curve between the T-wave and U waves. The Tp-e interval will be measured from the peak of the T-wave to the end of the T-wave. Monophasic T-wave peaks can be identified visually. For more complex T-wave morphologies, the peak will be identified according to the criteria Emori & Antzelevitch(16).

Within-group and between-group comparisons of pre and post carbetocin ECG indices will be performed using two-way analysis of variance.

ECGs will be interpreted by Dr Thomas Roston MD, cardiology fellow at the University of British Columbia, and a PhD student at the University of Alberta. If an abnormality is identified at the time of ECG analysis, the patient will be contacted and an internal medicine specialist and a cardiologist will be consulted if deemed necessary.

Normal values for QTc and Tp-e in pregnancy will be used from a study by Tanindi et al(10).

	Nonpregnant (n = 62)	First Trimester (n = 41)	Second Trimester (n = 45)	Third Trimester (n = 68)	P
Pmax	93.0 ± 9.1	93.9 ± 8.9	97.9 ± 5.6	99.0 ± 6.1	<0.001*
Pmin	62.4 ± 8.2	62.9 ± 6.8	64.4 ± 5.1	64.1 ± 4.9	0.83
QTc max (Bazett's)	425.98 ± 14.7	425.9 ± 15.05	428.5 ± 12.9	435.9 ± 4.7	<0.001†
QTc min (Bazett's)	397.7 ± 14.1	397.2 ± 14.1	399.9 ± 12.6	402.5 ± 4.7	0.19
QTc peak (Bazett's)	331.4 ± 13.1	333.1 ± 12.8	332.7 ± 11.9	335.6 ± 15.3	0.31
QTc max (Fridericia)	407.4 ± 14.2	408.5 ± 16.1	410.1 ± 13.1	415.1 ± 10.1	0.007‡
QTc min (Fridericia)	380.5 ± 13.7	381.1 ± 15.2	381.7 ± 13.7	383.6 ± 9.7	0.55
QTc peak (Fridericia)	315.1 ± 16.3	317.5 ± 11.6	317.2 ± 16.4	320.7 ± 16.6	0.25
Tp-e	72.7 ± 6.2	73.2 ± 6.5	77.2 ± 8.9	87.2 ± 9.6	<0.001†
Tp-e/QT	0.17 (0.14–0.20)	0.17 (0.14–0.20)	0.18 (0.15–0.23)	0.20 (0.16–0.25)	<0.001†

$P < 0.05$ is considered as statistically significant. For the comparisons where Bonferroni's correction was applied, $P < 0.008$ is considered as statistically significant.
*Significant difference is between nonpregnant group-second trimester, nonpregnant group-third trimester, first trimester–third trimester.
†Significant difference is between nonpregnant group-third trimester, first trimester–third trimester, second trimester–third trimester.
‡Significant difference is between nonpregnant group and third trimester; first trimester–third trimester.

Data Management:

De-identified participant data will only be collected by members of the research team using paper data collection forms. Once collated, the data will then be entered onto an encrypted and password protected Microsoft Excel spreadsheet on a password protected computer in the locked Research Assistant's office. The paper data collection forms will be stored for 5 years following publication of the study and then destroyed using the hospital's privacy and confidentiality shredding service. Participant identifiable data will not be recorded.

This study will be registered online with http://www.clinicaltrials.gov/.

The results will be written up and submitted for presentation at medical conferences and publication in a medical journal so that we can tell other doctors about the findings. This may help improve care for patients at other hospitals.

Safety:

No harm is expected from participating in this study. However, we are aware that this study aims to give a pre-determined low or high randomized carbetocin dose to women undergoing Cesarean delivery. The recommended dose of carbetocin form the SOGC is 100mcg IV bolus. Both study doses of carbetocin are well above the effective dose 90 (ED90) for pregnant women undergoing Cesarean delivery. Currently there is no firm consensus on the dose of carbetocin given to women undergoing low elective Cesarean delivery for the prevention of PPH secondary to uterine atony. It has been described that the ED90 dose of 14.8mcg produces satisfactory uterine contraction(3). Participants in this study will receive a dose greater than the ED90 dose in both groups. If there is any concern regarding the received blinded dose of carbetocin, the dose will be unblinded and the data collected for that participant will be removed from the data analysis. Data collection will always be secondary to the delivery of standard patient care and maternal wellbeing.

Feasibility:

At BCWH 15-20 elective Cesarean deliveries under neuraxial anesthesia occur each week. A conservative recruitment of approximately 10% of these patients equates to an average of 2 participants per week. The study should therefore be completed approximately 20 weeks from start of recruitment.

Financial cost:

Funding will be provided by the Department of Anesthesia at BCWH in the form of a research fellow and research assistant.

Disclosure:

Nothing to disclose

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Appendix 1: List of drugs increasing QT interval: http://www.crediblemeds.org