Prophylactic Methylergonovine in Patients Undergoing Cesarean Delivery With Twin Gestations: A Randomized Controlled Trial

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BACKGROUND

Study Purpose and Rationale

Obstetrical hemorrhage is a leading cause of maternal morbidity and mortality worldwide with a significantly higher frequency and severity following cesarean delivery. In 2020, 31.9 percent of pregnant women in the United States underwent cesarean delivery, [1] making it the second most common operation performed. Though multiple complications can occur following cesarean delivery, hemorrhage morbidities are among the most common with significant cardiovascular implications [2]. Twin gestations are at particularly higher risk for postpartum hemorrhage due to impaired myometrial contractility and atony following overdistention; increased maternal blood volume; and increased uterine blood flow compared to singletons, yet the management of obstetrical bleeding following twin delivery remains identical to singleton delivery [3]. Current strategies to address intrapartum hemorrhage have relied on pharmacological and mechanical treatments after intraoperative identification. However, there is extensive work on prophylactic therapies administered intraoperatively to prevent obstetrical hemorrhage [4-6]. Recent evidence has emerged about the utility of prophylactic Methylergonovine for the prevention of obstetrical hemorrhage [7-8]. Methylergonovine, a semisynthetic ergot alkaloid, acts primarily on alphaadrenergic receptors of uterine and vascular smooth muscle, increasing uterine tone and promoting vasoconstriction. Masse et al [8] in a randomized trial of 80 women undergoing intrapartum cesarean delivery found that fewer patients who were allocated to the methylergonovine group received additional uterotonic agents (20% vs 55%, relative risk [RR] 0.4, 95% CI 0.2–0.6). Participants receiving methylergonovine were more likely to have satisfactory uterine tone (80% vs 41%, RR 1.9, 95% CI 1.5–2.6), lower incidence of postpartum hemorrhage (35% vs 59%, RR 0.6, 95% CI 0.4–0.9), lower mean quantitative blood loss (967 mL vs 1,315 mL; mean difference 348, 95% CI 124–572), and a lower frequency of blood transfusion (5% vs 23%, RR 0.2, 95% CI 0.1–0.6). Investigators concluded that the administration of prophylactic methylergonovine in addition to oxytocin in patients undergoing intrapartum cesarean birth reduces the need for additional uterotonic agents. Similarly, Senturk et al [7], in a prospective study of 1210 participants found that intraoperative, prophylactic methylergonovine decreased post-operative blood loss with no adverse side effects. Randomized trials of Methylergonovine as prophylaxis to prevent hemorrhage in cesarean

delivery have exclude twin gestations [7-8]. Currently, there remains a paucity of research regarding prophylactic procedures for twin cesarean delivery. Similarly, the use of Hemabate (carboprost tromethamine) is an effective uterotonic to reduce obstetrical hemorrhage. Hemabate, a protaglandin F2 alpha agonist, similarly treats uterine atony by stimulating smooth muscle contraction. Unlike Methylergonovine, hemabate does not cause secondary vascular constriction and can be used in patients with blood pressure disorders. In a study of prophylactic Hemabate, Balki and colleagues assigned participants to receive either oxytocin 5 units intravenous alone, or with ergonovine 0.25 mg intravenous or carboprost 0.25 mg intramuscular immediately after delivery and found a reduction in postpartum hemorrhage.There is an opportunity to prophylactically address hemorrhage in high risk groups. Therefore, we propose a prospective randomized controlled trial which will compare maternal blood loss associated with prophylactic uterotonic treatment during cesarean delivery among patients with twin pregnancies. We hypothesize that prophylactic uterotonic therapy in cesarean delivery is associated with decreased maternal blood loss compared to standard care.

RESEARCH AIMS & ABSTRACTS

Research Question(s)/Hypothesis(es): To evaluate whether prophylactic uterotonic therapy reduces maternal blood loss among individuals with twin gestations undergoing cesarean delivery.

Primary Research Question: Is the administration of prophylactic uterotonic therapy at the time of scheduled cesarean delivery after cord clamping of the second twin associated with decreased maternal blood loss among patients with twin pregnancies (based on primary outcome of maternal hemoglobin drop from preop to postoperative day #1)?

Hypothesis: Prophylactic uterotonic therapy in cesarean delivery among patients with twin pregnancies is associated with decreased maternal blood loss compared to placebo.

Scientific Abstract

This is a randomized controlled trial of patients undergoing scheduled (daytime) cesarean section among patients with twin gestations. We propose a prospective randomized controlled trial which will compare maternal blood loss associated with prophylactic uterotonic therapy

during cesarean delivery among patients with twin pregnancies. We hypothesize that prophylactic uterotonic therapy in cesarean delivery is associated with decreased maternal blood loss compared to standard care. The target patient population for this study is women with twin pregnancies undergoing scheduled cesarean delivery. Subjects will be expected to do the following once they agree to participate: 1) Sign the informed consent 2) Enroll - randomized in preop to prophylactic methylergonovine or placebo.

STUDY DESIGN

We propose a prospective randomized controlled trial which will compare maternal blood loss associated with prophylactic uterotonic therapy during cesarean delivery among patients with twin pregnancies. We hypothesize that prophylactic methylergonovine 200mcg IM or Hemabate carboprost tromethamine (250mcg/mL, 1mL syringe) in cesarean delivery is associated with decreased maternal blood loss compared to placebo. This is a randomized controlled trial of patients undergoing scheduled (daytime) cesarean section among patients with twin gestations. For our primary research question, we will compare the change in maternal hemoglobin from pre-op to postoperative day #1.

Study Procedures

Consented subjects who remain eligible for study participation on the day of their scheduled cesarean delivery will be randomized 1:1 by trained research personnel to one of two groups: Intervention group (Prophylactic methylergonovine 200mcg IM) or Control group (placebo same volume). If a blood pressure disorder of pregnancy is diagnosed, study participants will be randomized to one of two groups: Intervention group (Prophylactic carboprost tromethamine 250mcg IM) or Control group (placebo same volume). Randomization will occur on labor and delivery while the subject is in the preoperative area prior to delivery. The subjects will be taken to the operating room where anesthesia will be administered and cesarean delivery will be performed in routine fashion until delivery of the fetuses. Obstetricians, anesthesiologists, intraoperative research staff, and subjects will be blinded to study arm allocation. A trained member of the research team will perform randomization prior to delivery. Upon delivery of the second twin neonate, the anesthesiologist will administer the study drug;

subjects will receive either prophylactic methylergonovine 200mcg IM or saline placebo (identical volume) IM.

If patients are not candidates to receive methylergonovine due to a blood pressure disorder of pregnancy (gestational hypertension, chronic hypertension, preeclampsia with or without severe features), they will be randomized to Prophylactic carboprost tromethamine 250mcg IM or Control group/placebo same volume Oxytocin will be administered (by the anesthesia team) in routine fashion immediately upon delivery. The remainder of the cesarean will proceed in routine fashion per surgical team. Uterotonics/blood transfusion may be administered per routine care as judged necessary by the surgical team. Blood loss at completion of the surgery will be estimated by the obstetric, nursing, and anesthesia teams with a final estimated blood loss (EBL) agreed on by all providers and recorded in the routine fashion in the medical record. Similarly, the quantitative blood loss (QBL) will be calculated and recorded. All mothers will receive routine postoperative and postpartum care. This includes administration of intravenous fluids (125 cc/h lactated ringers) until tolerating oral fluids. On postoperative day 1, maternal hemoglobin level will be assessed on a complete blood count per standard clinical care. Neonates will receive routine care. Race and ethnicity will be self-reported at the time of hospital registration and extraction from the medical record (fixed categories) to consider the generalizability of the results. All other data will be abstracted by the research team by review of both the maternal and neonatal medical records. All medical records will be reviewed through 30 days after delivery to identify any postpartum or postnatal complications.

Study Subjects

Inclusion Criteria:

- Twin gestation
- Scheduled cesarean delivery (>=34 weeks)

Exclusion criteria for methylergonovine:

- Subjects with known hypertensive disease: history of chronic hypertension, gestational hypertension or preeclampsia with or without severe features
- Use of protease inhibitors given known vasoconstrictive side effects with concomitant methylergonovine administration

- Hypersensitivity to methylergonovine or any of the ingredients

If patients meet any of the exclusions above, they will be assessed for the use of Hemabate and excluded if:

- Subjects with known asthma disease
- Hypersensitivity to Hemabate or any of the ingredients

Additionally, if subjects meet any of the following criteria, they will be excluded from participation:

- Participating in another intervention study where the primary outcome includes postpartum bleeding or thromboembolism, or the study intervention directly affects postpartum bleeding or thromboembolism
- Receipt of uterotonics, other than oxytocin, or planned or expected use of uterotonic prophylaxis
- Non-elective cesarean delivery

STATISTICAL ANALYSIS

Based on the following parameters, the sample size was calculated for the primary outcome of mean hemoglobin change from pre-op to post-op day 1 between placebo and treatment groups. The analysis was conducted in Stata 17. From the protocol: Based on a prior study of cesarean deliveries in twin gestations [9], a mean (SD) change in hemoglobin level for elective cesarean delivery of 1.40 (0.83) g/dL was estimated. Up to 20% crossover rate from the treatment group to the placebo group will be assumed. Because there is no accepted definition of a minimum clinically important difference in postoperative hemoglobin change, effect size was based on the published SD of the mean. Given the burden of maternal morbidity and mortality due to postpartum hemorrhage, the investigators decided that even a 1-SD greater drop in postoperative maternal hemoglobin level with Methylergonovine treatment arm might alter clinical decision-making. Hence the parameters are as follows:

Effect size / difference in means: 0.83SD: 0.83 (assumed to be the same for both groups)

Allocation ratio: 1:1

Crossover rate: 20%

Power: 0.90

Alpha: 0.05 (two-tailed)

Assumed dropout rate: 10%

The sample size is 33 per group, or 66 total on the more conservative end, including adjustment for potential loss to follow up.

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