Queens Hospital Center
Icahn School of Medicine at Mount Sinai
Department of Obstetrics and Gynecology

Clinical Investigation Protocol

EFFECT OF ADJUNCTIVE MISOPROSTOL TREATMENT ON BLOOD LOSS AT VAGINAL DELIVERY

Principal Investigator and Faculty Sponsor: Alexandr Fuks, MD
Co- Investigator: Tricia Yusaf, MD
Sub-investigator: Ayodeji Sanusi, MD
Sub-investigator: Anubha Arora, MD

Abstract

This document defines the Clinical Investigation Protocol for a study designed to determine whether blood loss after spontaneous vaginal delivery is altered by the addition of misoprostol administration to the standard use of intravenous oxytocin after delivery. The protocol is an open-label randomized prospective trial to be carried out at Queens Hospital Center.

Blood loss will be measured indirectly by comparing the maternal hemoglobin and hematocrit levels on admission in labor to those obtained within 24 hours after delivery.

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Principal contacts

Faculty Sponsor/
Principal investigator Alexandr Fuks, MD
Chairman of Obstetrics and Gynecology
Queens Hospital Center

Assistant Professor of Obstetrics and Gynecology
Icahn School of Medicine at Mount Sinai

Co- Investigator: Tricia Yusaf, MD
Attending Physician
Department of Obstetrics and Gynecology
Queens Hospital Center

Sub Investigator: Ayodeji Sanusi, MD
Resident Physician
Department of Obstetrics and Gynecology
Queens Hospital Center

Sub Investigator: Anubha Arora, MD
Resident Physician
Department of Obstetrics and Gynecology
Queens Hospital Center

Sponsoring Department: Department of Obstetrics and Gynecology
Queens Hospital Center
82-68 164th Street
Jamaica, New York 11432

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Background

Some maternal blood loss normally occurs at the time of vaginal delivery. The best estimates indicate that a loss of approximately 500 mL is average, with a range of about 250-700 mL.[1,2] Some of this bleeding arises from birth canal lacerations or surgical incisions (i.e., episiotomy), but most derives from the vessels exposed in the uterine wall at the placental site once the placenta has separated.

Under normal circumstances, shortly after placental separation intense myometrial contractions occur. These raise the pressure within the myometrial wall above that of the blood pressure in the vessels that traverse it, vessels that opened into the intervillous space. Flow in these vessels is thus mechanically attenuated by myometrial contraction, allowing for the formation of intravascular thrombi.

This mechanism for controlling postpartum uterine blood loss works well most of the time. If, however, the uterus remains hypotonic or atonic after delivery, excessive blood loss can occur. In the worst cases, severe uterine hemorrhage ensues. Postpartum hemorrhage is, in fact, the leading cause of maternal mortality in the world, accounting for at least 100,000 deaths annually.[3] Even in the absence of frank hemorrhage, postpartum blood loss can result in maternal anemia. Recuperation of iron stores to recover from this blood loss takes time, and may not occur, especially in low socioeconomic areas where dietary iron consumption is often deficient, and pregnancies tend to occur in close succession.

Postpartum anemia is a significant contributor to short- and long-term morbidity.[5-7] It increases the risk of infection and poor wound healing. Also, the associated fatigue may interfere with the mother's ability to administer child care and to bond appropriately with her infant. Anemic mothers tend to have more difficulty with nursing, and may produce iron-deficient milk. There is thus a strong rationale to minimize postpartum blood loss.

In most US hospitals, parturients receive a high dose of intravenous or intramuscular oxytocin immediately after delivery. This approach has been shown in several studies to reduce the risk of postpartum hemorrhage, [8-11] and is practiced routinely at Queens Hospital Center. We employ an intravenous infusion of oxytocin (Pitocin®) at a rate of about 50-100 mU/minute. Despite this approach, there is still substantial blood loss at delivery, based on our preliminary observations shown below. This provides the rationale to determine whether use of an adjunctive drug, namely misoprostol 600 µg rectally, administered after delivery, might reduce blood loss further than does oxytocin alone, thus decreasing the risk of morbidity related to postpartum anemia.

Preliminary Data

We examined the hemograms of a randomly chosen consecutive sample of 53 spontaneous vaginal deliveries performed at Queens Hospital Center between September 15 and October 1, 2010.

Among these patients, the admission hemoglobin concentration was 11.9±1.2 g/dL and that on the first postparutum day was 10.9±1.3. The mean fall was 1.02 (95% CI 0.74, 1.29), a statistically significant decrease (P<0.0001). Hematocrit levels fell in parallel, by an average of 7.8% of the predelivery value. The mean fall in hemoglobin and hematocrit levels after delivery (1.02 g/dL and 2.81%) is consistent with an average blood loss of about 500 mL. The consistency of these changes and the small associated variance indicate that the change in hemoglobin and hematocrit levels is a meaningful proxy for the assessment of blood lost during vaginal delivery.

Study Design

The study is a prospective randomized open-label clinical trial to be performed in a single institution. It will compare the intrapartum and postpartum maternal blood hemoglobin concentrations and hematocrit measurements in a group of parturients who received standard prophylactic intravenous oxytocin immediately after delivery with a group that received oxytocin and adjuvant misoprostol.

Sample size and analysis

A total of 800 subjects will enter this two-treatment parallel design study. With that sample size, the probability is 90% that the study will detect a treatment difference at a two-sided 0.05 significance level if the difference in hemoglobin concentration between treatments is 0.3 g/dL. This analysis is based on the assumption that the standard deviation of the postpartum and intrapartum hemoglobin concentrations is not larger than 1.3 g/dL.

Comparison of intrapartum and postpartum hemoglobin and hematocrit levels will be done using a paired t-test. A probability level of 0.05 will be used as the threshold for significance.

Inclusion and exclusion criteria

This study will include adult pregnant women regardless of age. Pregnant minors under the age of 18 will not be eligible.

A patient will be considered for inclusion in the study if she meets all of the following criteria:

- She has a term (≥37 completed weeks) live singleton gestation in cephalic presentation and has been admitted to the Labor and Delivery Unit
- She is in the latent phase of labor or has been admitted for induction of labor or at prenatal clinic visit
- She has had fewer than four prior vaginal deliveries.
- She reports no allergy to misoprostol.

The following factors or conditions will exclude a patient from consideration as a subject:

- The fetus has a known major fetal malformation or chromosome abnormality
- The gestation is multiple.
- There is a breech or other malpresentation
- The patient reports involvement in another clinical trial currently or previously in this pregnancy.
- The patient is expected to have a cesarean delivery.
- The patient had a prior cesarean delivery.
- There has been an intrauterine fetal death.
- There is polyhydramnios (amniotic fluid index >22 cm).
- Presence of acute or chronic renal disease
- Presence of preeclampsia

Of subjects who enter the study, the development of certain conditions will exclude them post hoc from receiving misoprostol under the protocol, and from the data analysis. These conditions include:

- Unanticipated cesarean delivery.
- Performance of episiotomy (third and fourth degree extensions will be excluded).
- Vaginal or cervical laceration, or perineal laceration of more than second degree in depth.
- Severe postpartum hemorrhage requiring intervention immediately after delivery.
- Uterine rupture
- Placental abruption.
- Patient withdrawal of consent.

Recruitment and Consent Procedures

Patients who meet the inclusion criteria for the study will be identified during their prenatal clinical visits, in early latent-labor, or prior to induction of labor or active labor. Informed consent will be obtained by one of the investigators. Consent will be obtained prior to active labor. The informed consenting process will not be initiated among patients in active labor. Patients will be recruited and consented with the consent document approved by the IRB. Patient recruitment will commence after IRB approval is obtained.

Once the subject has consented to participate in the study, it will be determined by the investigator whether the patient will receive oxytocin alone or oxytocin and misoprostol. Both drugs are on formulary and will be available on the Labor and Delivery Unit for immediate use.

Randomization

A computer-generated table of random numbers will be used to assign the recruited subject to a group. A locked file will be maintained in the Labor and Delivery area. The file will contain a series of sequentially-numbered sealed envelopes. Each envelope will contain a card with a randomly generated number. These numbers will have been taken in order from the computer-generated list. The investigator will choose the next envelope in sequence. If it contains an odd number, the patient will be assigned to the intervention group and will receive oxytocin and misoprostol. If the envelope contains an even number, the patient will be assigned to “oxytocin only” group.

Characteristics of Medication

Nature of misoprostol

Misoprostol is a synthetic prostaglandin E1 analog. It is marketed primarily as a drug to prevent the development of gastric ulcers associated with use of nonsteroidal anti-inflammatory drugs, and is part of the Queens Hospital Center formulary. Originally marketed as Cytotec®, misoprostol is available in a generic form as tablets containing contain either 100 µg or 200 µg. Misoprostol protects the gastric mucosa through several mechanisms. It also has the property of stimulating myometrial smooth muscle contraction.[12] That effect has resulted in the drug’s common use in obstetrics for termination of pregnancy, cervical ripening prior to induction of labor and, in large doses, for prevention and treatment of postpartum hemorrhage from uterine atony. [13-19]

Misoprostol can be administered by oral, sublingual, vaginal or rectal routes. It is well absorbed with all these modes of administration, but detailed pharmacokinetic data exist primarily concerning its oral administration. It is rapidly absorbed, and undergoes prompt de-esterification to its free acid, which is responsible for its clinical activity. Peak plasma levels after oral administration occur after 10-15 min. The half-life is 20-40 minutes. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs. Excretion is primarily in the urine.

Very little misoprostol appears in breast milk. [20,21] After a single 600 µg oral dose of misoprostol to nursing mothers, misoprostol acid was excreted in breast milk. One hour after dosing, the milk concentration was about 67% of the maternal serum level; by five hours, the misoprostol concentrations in breast milk declined to < 1 pg/mL. While no specific data exist for misoprostol concentrations in colostrum, given the very small ingested volume over the first few hours of life, neonatal exposure to the drug in our study can be expected to be minimal. There are no published reports of adverse effects of misoprostol in breast-feeding infants of mothers taking misoprostol

Misoprostol is classified by the FDA as a Pregnancy Category X drug. This label is related to its possible association with congenital anomalies when used in the first trimester, as well as its abortifacient properties. In our study, patients will no longer be pregnant when they receive the drug.

The use of misoprostol to enhance uterine activity postpartum is an off-label method, but one that has gained wide acceptance, and for which there is considerable experience.[8-10, 12-19] The drug can cause nausea, headache, dyspepsia, vomiting, and constipation or diarrhea with multiple doses. These side effects are usually mild to moderate and generally subside within a week. Serious side effects after a single dose are quite rare. In one study of 327 women who received 600 µg rectally (the dose we propose to use), the most common side effects were transient shivering (26%) and pyrexia (15%). Both were mild and short-lived. [16]

Benefits and Risks to Study Subjects

There will be no certain medical benefit to the subjects who participate in the study. It is possible that they will benefit from reduced postpartum blood loss.

Risks to the subjects are those associated with administration or misoprostol.

These include the following adverse events that have been reported in subjects receiving misoprostol for ulcer prophylaxis: diarrhea, abdominal pain, nausea, flatulence, headache, dyspepsia, vomiting, and constipation. All occurred in fewer than 5% of patients. Other reported effects that occurred in clinical trials of misoprostol, but for which no cause-effect relation has been established included fatigue, fever, chills, rash, alopecia, pallor, breast pain, abnormal taste, abnormal vision, conjunctivitis,

deafness, tinnitus, earache, chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope, myocardial infarction, thromboembolism, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, gout, polyuria, dysuria, hematuria, urinary tract infection, anxiety, depression, and thrombocytopenia. As with any drug, anaphylaxis is possible.

We emphasize that in a number of published studies using a single postpartum dose of misoprostol of 600-1000 µg and including in aggregate in excess of 1000 patients, no serious side effect has been reported.

Side effects after a single dose of misoprostol are rare. Misoprostol can cause nausea, headache, heartburn, vomiting, flatulence, and constipation or diarrhea with multiple doses. These side effects are usually mild to moderate and generally go away within a week. Mild shivering and slight fever are the most likely side effect of this medication. If they occur, they will probably disappear within an hour.

Oxytocin commonly causes vomiting and nausea. Oxytocin has the potential to cause muscle contractions. In rare cases, Oxytocin can cause heart palpitations (rapid heartbeat) and allergic reaction of a rash or swelling.

It is unknown whether Misoprostol and/or Oytocin are excreted in human milk. There is an unconfirmed relation with Misoprostol and/or Oytocin causing digestive problems, such as diarrhea, and abdominal cramps in breast-fed newborns. Pariticipants will be advised to discard breast mild for the first 24 hours to possibly avoid occurrence.

Study Procedure

Informed consent will be obtained by one of the investigators or informed consent delegates. The subject will then be assigned randomly to the control (oxytocin alone) or the study (oxytocin + misoprostol) group, as described above. The subject and her medical caretakers will be informed of which group she is in. If the labor eventuates in a vaginal delivery, all subjects will receive the standard dose of intravenous oxytocin, begun within one minute of delivery. Subjects in the study group who have not incurred any of the post-hoc exclusion criteria (episiotomy, major laceration, etc) will receive a dose of 600 µg of misoprostol in addition to their oxytocin. This will be administered in the form of six 100 µg tablets inserted approximately 2 cm into the anorectal canal by the obstetrician or midwife who has performed the delivery. The common method for administering Misoprostol for postpartum hemorrhaging is rectally for local absorption. Since this study is directed toward prevention instead of treatment, the dosage of 600mg is a lower dosage from the 1000mg administered, as standard practices, for treating postpartum hemorrhaging of more than 500cc estimated blood loss. The patient's vital signs will be recorded after delivery according to standard protocols of the obstetric service. The Data Collection forms will be filled out after the delivery by one of

the investigators. The measurement of postpartum hemoglobin and hematocrit (H & H) is automatically ordered at 06:00am for all patients who have delivered the day prior, constituting this measurement at "Postpartum Day 1", which is at a minimum of 6 hours after delivery and is enough time for H & H levels to stabilize.

Within 36 hours of delivery, additional information will be collected from the patient's record, including the postpartum hemogram and information about any symptoms or signs related to the misoprostol.

Confidentiality

After a subject has given informed consent, she will be assigned a Study Number. This number will be used on the study data collection form as the sole patient identifier, i.e., the form will not contain the subject's name or hospital number. A single hard copy list of the subjects' Study Numbers and their medical record numbers will be kept in a locked cabinet in the Principal Investigator's sponsor's office (Dr. Fuks). This list will be destroyed once the study has been accepted for publication. Only Dr. Fuks will have access to this list.

Costs

The cost of each 600 µg dose of misproostol will be $4.80. There will be no charge to the patient. The drug will be paid for through the research fund of the Department of Obstetrics and Gynecology at Queens Hospital Center.

Data Collection

Data collection will include the following elements:

Before Delivery

- Age
- Ethnicity/Race
- Gestational age (in weeks)
- Number of previous deliveries
- Number of Fetus
- Body-Mass Index (BMI)
- Amniotic Fluid Index (AFI)
- Cephalic presentation
- Fetal Heart Rate (FHR)
- Reported fetal Anomaly

- Preeclampsia
- Trial of Labor after Cesarean (TOLAC)

After Delivery

- Caesarean section (during delivery)
- Epidural
- Oxytocin in labor (if yes, number of hours before delivery
- Other medication used in labor
- Episiotomy
- Duration of stage 1, 2, and 3
- Degree and place of laceration
- Estimated Blood Loss (EBL)
- Transfusion
- Placental Abruption
- Birth weight

Results – includes Follow-up Data

- Hemoglobin and Hematocrit (H& H) on admission and on post- partum day #1
- Reported Side effect by patient
- Post partum temperature
- Reports of shivering
- Diagnosis of chorioamnionitis

Post- partum day #1- data collection
Postpartum Day 1 is delineated as the first 12:01am clock time from the time of delivery. Post-partum measurements, such as postpartum hemoglobin and hematocrit (H & H), are taken automatically at 06:00am for all deliveries that occurred before midnight (at least 6 hours prior).

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