Cover Sheet

Antibiotics During Intrauterine Balloon Tamponade Placement

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Intrauterine Balloon Tamponade (Bakri) and Antibiotics Protocol Narrative

IRB Protocol # _Pro00051005_

Title: Antibiotics during intrauterine balloon tamponade placement

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Purpose and Hypothesis

The goal of this study is to identify whether antibiotics given at the time of placement of an intrauterine balloon tamponade (IBT) will result in reduction of the risk of endometritis. We hypothesize that antibiotics given at the time of intrauterine balloon tamponade will reduce the likelihood of postpartum endometritis.

Significance of the Research

If we are correct that the use of antibiotics at the time of IBT placement will reduce the likelihood of postpartum endometritis, then the benefits would include a significant reduction in a major cause of postpartum morbidity in women. Apart from being an improvement for the patient's health, this could also result in a shorter duration of stay in the high-risk maternal-fetal care unit and shorter hospitalization overall which could result in significant cost savings.

Background

Postpartum hemorrhage is the leading cause of maternal mortality worldwide and the fourth most common cause in the United States. Intrauterine balloon tamponade (IBT) is one method of controlling bleeding and has been shown to be effective in as many as 84% of cases refractory to standard uterotonic medications. The balloon is typically inflated with 300-500 mL saline, and the hydrostatic pressure applied to the uterine wall results in reduced bleeding until the maternal coagulation system take effect. The balloon is then left in situ typically for 12-24 hours, at which time it is removed.

Postpartum endometritis is a common obstetric complication and the leading cause of postpartum febrile morbidity. Risk factors for postpartum endometritis include cesarean delivery, labor, prolonged rupture of membranes, as well as the number of vaginal exams. The risk also appears to be increased in patients who have had a postpartum hemorrhage and possibly increased further among those who have had an intrauterine balloon tamponade.

In a retrospective cohort study performed in our institution, we compared the incidence of postpartum endometritis in patients who received an IBT and noted that those who had received prophylactic antibiotics had a significant reduction in the likelihood of developing postpartum endometritis (5% vs 26%, $p < 0.002$; OR 6.53 [95% CI 1.76-24.25]). This association remained after adjustment for mode of delivery (OR 5.9 [95% CI 1.58-22.35]) which did differ between the two groups. The most commonly used prophylactic antibiotic in this cohort was cefazolin which was used in 55 of the 59 cases (93%).

Despite that the IBT is a common tool in obstetric management of postpartum hemorrhage and that the incidence of endometritis may be increased after placement of an IBT, no studies have evaluated

whether antibiotics should be given at the time of placement of an IBT would result in a reduction in the likelihood of postpartum endometritis.

Description of Protocol

We will perform a randomized, controlled trial of women who have had a postpartum hemorrhage and received an IBT.

Patients who are candidates for study enrollment will be identified on Labor & Delivery or in the Maternal-Fetal Care Unit by providers who would routinely have access to their medical records as a part of their regular clinical duties. If the patient is an appropriate study candidate, her primary obstetrician will be contacted to request permission to approach the patient and offer enrollment in the study. Those who give consent will be randomized by random number generator to receive either antibiotics (Group A) or no antibiotics (Group B).

If the patient is randomized to Group A, she will receive a 24-hour course of antibiotics. The primary antibiotic of choice will be cefazolin 1 gm iv q8 hours. If the patient has contraindications to the use of cefazolin including cefazolin allergy, hypersensitivity, or severe beta lactam allergy, then clindamycin 900 mg iv q8 hours will be used instead. Cefazolin is chosen for two reasons: (1) it was the antibiotic of choice for the great majority (93%) of the providers in our retrospective study and (2) this mirrors the recommendations from the World Health Organization regarding use of antibiotics during manual extraction of the placenta. The underlying etiology for endometritis both after manual extraction or IBT placement would be the analogous (vaginal flora which could cause an ascending infection during manual manipulation), and so our choice of first and second line antibiotics reflects this.

If the patient is randomized to Group B, she will not receive antibiotics as part of the study, though if at any time her provider chooses to administer antibiotics either prophylactically or for treatment she will not prohibited in any way from this or any other treatment as appropriate.

Both options (antibiotic prophylaxis vs not) are considered within the standard of care, and indeed our retrospective study of all IBT placements during the last five years suggests that (without research/protocol guidance) our providers opted for the use of antibiotics and to not use antibiotics almost equally (52% vs 48%).

At any time after randomization, the patient or provider may choose to discontinue participation in the study, including either to discontinue or initiate antibiotics as indicated.

Subjects' charts will then be reviewed to obtain demographic information (age, race, ethnicity, weight, BMI, payor status, prior medical [including diabetes] history, antepartum genital infections, prior social history, prior obstetric history), obstetric outcomes (gestational age at delivery, mode of delivery, time to delivery), endometritis risk factors (Group B strep status, use of internal monitors, duration of rupture of membranes), and obstetric complications (such as chorioamnionitis). We will also collect details about the IBT placement including time from delivery to placement of the IBT, duration that IBT remained in situ, and whether stepwise/rapid deflation was performed. We will identify whether additional methods to control PPH were employed including uterotonics, embolization procedures, or a return to the operating room. Infant birth weight and gestational age will also be obtained. Finally, our outcomes data will identify rates of endometritis, postpartum fever, postpartum vaginal or wound infection, and postoperative length of stay.

Abstractors will use CS-Link to abstract the required information. All abstracted information will be stored securely in a Cedars-Sinai Redcap database and the data will then be deidentified prior to statistical analysis.

Inclusion criteria are as follows:

1. Female
2. Able to give consent
3. Gestational age > 24 weeks
4. Postpartum
5. Placement of an IBT within the last 2 hours with plans for it to remain in situ for at least 2 hours
6. Primary obstetrician amenable to proceeding with either method of management during the study period.

Exclusion criteria are as follows:

1. Age < 18 years old
2. IBT removed within 2 hours of placement
3. Chorioamnionitis
4. Insufficient documentation of demographics, delivery outcomes, or peripartum events including postpartum hemorrhage, infectious outcomes

Primary Outcome

Incidence of postpartum endometritis. The presence of this outcome will be defined by any of the following:

- Clinical documentation reflecting a suspected diagnosis of endometritis
- Antibiotics initiated after randomization and clinical documentation supporting that the treatment has been initiated due to concern for endometritis
- T > 38.4 degrees beyond the first postoperative day associated with uterine tenderness or foul lochia

Secondary Outcomes

1. Postpartum febrile morbidities
    a. Fever > 38
    b. Wound infection
    c. Wound breakdown/dehiscence
    d. Receipt of postpartum antibiotics
    e. Hysterectomy
2. Control of PPH
    a. Need for additional uterotonics
    b. Need for return to OR / other procedures (e.g. repeat IBT, IR embolization)
3. Blood loss
    a. Estimated blood loss (EBL) prior to removal (for baseline comparison)
    b. EBL following removal (for intervention comparison)
    c. Total EBL

    d. Postpartum hemoglobin prior to discharge
    e. Change in hemoglobin from prior to removal and following removal
    f. Blood transfusions following removal
4. Maternal complications
    a. Fever > 38
    b. Endometritis
    c. Hysterectomy
    d. Maternal ICU admission
    e. Maternal death
5. Resource utilization measures
    a. Duration of admission to maternal-fetal care unit
    b. Duration of hospital admission
    c. Hospital readmission

Probable Duration

Based on our sample size calculation, we would need 168 total women for randomization (84 per group). To account for patients who withdraw, we will increase this value by 10% to include 185 patients total. Given that there are approximately 25 IBT successfully placed per year, taking into account patients who decline randomization, we anticipate completion of the study within 3 years.

Sample Size

In our retrospective cohort study on the same topic, the rate of endometritis among patients who have received an IBT was 15%. Within the subgroups, however, the rate of endometritis among those who did not receive antibiotics was 26% whereas among those who did receive antibiotics the rate was 5%.

Therefore, we will conservatively assume a rate of endometritis of 20% in the control group. Using Fisher's exact test, calculating sample size for an 80% power to detect a 15% difference in the proportion with endometritis in each group, the number needed per group is 84 (168 total). To account for patients who withdraw, we will increase this value by 10% to include 185 patients total.

Statistical Analysis

Statistical analysis will be performed using standard software such as SAS. Clinical variables will be analyzed using the chi-square test or Fisher's exact when appropriate for categorical variables and the student t-test for continuous variables.

Potential Benefits (Category)

To individual: We anticipate a reduction in the likelihood endometritis among those patients receiving antibiotics at the time of IBT placement. This would then result in a reduction in cost for the patient's admission which would benefit potentially the patient as well as her health plan and potentially societal health costs.

To society: This is the first study examining the use of prophylactic antibiotics at the time of placement of an IBT. If there is convincing evidence that IBT placement reduces the likelihood of endometritis, then there is the potential for significant benefit to reduction of the rate of endometritis.

Potential Risks (Category)

Both using and not using prophylactic antibiotics at the time of IBT placement are considered within the standard of care. The risks for the control group are that – in the event that it is shown that prophylactic antibiotics are of benefit for reducing the risk of endometritis – then they will not have received a potentially beneficial treatment. The risks for the intervention (antibiotics) group are that if it is shown there is no benefit to their use then they have received potentially unindicated exposure to a short course of antibiotics.

Since medical records will be accessed, the potential for breach of confidentiality exists.

Minimizing Risks

In order to minimize risks associated with review of medical records, only certified research personnel will have access to private and identifiable information. Data abstractors will not record patient name or Social Security Number; the only direct identifier made available to other team members for data abstraction will be MRN. Identifiers will be tagged in REDCap (e.g. MRN) and the relevant identifiers will be removed prior to downloading for statistical analysis and once data collection has been completed. Deidentified research records will be kept in a password protected computer file.

Do the anticipated benefits of participation outweigh the risks?

Yes.

Risk Rationale for Children

Inclusion of children will be limited to the review of medical records to obtain mode of delivery outcomes for newborns. The review of medical records poses minimal risk.

Pregnant teenagers who experience postpartum hemorrhage will not be eligible to participate in this study.

Risk Rationale for Pregnant Women

Inclusion of pregnant women will be limited to the review of medical records to obtain pregnancy outcomes, which poses minimal risk. Inclusion of postpartum women is necessary as the underlying condition only occurs in pregnant women.

Protecting the Privacy Interests of Individuals

Personally identifiable information such as medical record number, name, and date of birth will be used to identify subjects. These data will also be used to review their medical record to determine if they are eligible for inclusion in this study as well as to review the outcomes data as described above. The data sheets with this information will be kept in a password-protected file with only key investigators having access to it. The subjects can expect that any personally identifiable information will be removed once data collection is complete.

These data will be necessary to determine if subjects meet the inclusion/exclusion criteria. Additionally, the demographics will be used in data analysis to see if our outcomes are confounded by any other demographic factors such as age, gravidity/parity, etc.

References

https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html Pregnancy Mortality Surveillance System.

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