The University of Texas Medical Branch Galveston
Research Protocol

Validating a New Method to Assess Estimated Blood Loss in the Obstetric Population

Principal Investigators: Antonio F. Saad, MD
Co-Investigator: Fawzi Saoud, MD
Faculty Sponsor: George R Saade, MD.
Funding: Department of Maternal Fetal Medicine

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1. **Introduction/Background/Purpose:**
   According to the World Health Organization, postpartum hemorrhage (PPH) is the leading cause of maternal mortality in low-income countries and the primary cause of nearly one quarter of all maternal deaths globally (1). An estimated blood loss (EBL) in excess of 500 mL following a vaginal birth or a loss of greater than 1,000 mL following cesarean birth often have been used for the definition of postpartum hemorrhage, but the average volume of blood lost at delivery can approach these amounts when actually measured rather than estimated (2). More than half of all maternal deaths occur within 24 hours of delivery, most commonly from excessive bleeding (3). Worldwide, 140,000 women succumb to postpartum hemorrhage each year. The most common antecedents to postpartum hemorrhage are uterine atony, placental disorders, and trauma during delivery. Improving maternal health worldwide is one of the WHO's 8 Millennium Developmental Goals. The prevention and treatment of PPH is an essential step towards the achievement of that goal (4).

   Estimates of blood loss at delivery are notoriously inaccurate, with under-estimation more common than over-estimation (5). Traditionally, the surgeon performing the cesarean section would estimate the blood loss by visually assessing the blood collected in the surgical drape and counting the number of lap sponges used thru out the procedure. Current detection and management of hemorrhage is heavily based on clinical judgment, which often leads to delay in recognition and intervention. Often, interventions such as fluid resuscitation and blood transfusion are not initiated until significant hemorrhage has already taken place. The traditional method for estimating blood loss is based on the surgeon and surgical staff's subjective assessment that is severely limited by human error and the presence of large volumes of amniotic fluid, irrigation, or both (6). Another limitation is that blood loss is frequently estimated at the end of the procedure.

   Early detection and treatment of this potentially life threatening obstetric complication is of utmost importance in the field of obstetrics. Simulations and didactic training have been shown to improve visual estimations, but there are still poor associations between experience level and accuracy, and a

significant decay in blood loss estimation skills over time (7).

The Triton system (Gauss Surgical, Inc., Palo Alto, CA) is a novel mobile monitoring platform that combines mobile computing with Gauss Feature Extraction Technology (FET) to directly assess Hb mass (mHb) absorbed by surgical sponges from an image (8). The device is an iPad like imaging device that will assess blood loss via imaging of the surgical sponges used in the surgery. In 2014, Konig at al. showed that mobile blood loss monitoring using the Triton system is accurate in assessing mHb on surgical sponges across a range of ambient light conditions, sponge saturation, saline contamination, and initial blood Hb. Utilization of this tool could significantly improve the accuracy of blood loss estimates (9). Holmes et al. also showed that the novel mobile monitoring system provides an accurate measurement of mHb on surgical sponges as compared with manual rinsing measurements, and is significantly more accurate than the gravimetric method (10).

However, these studies were performed on patients undergoing a myriad of surgical procedures not just limited to obstetrical patients. To our knowledge, this technology has not been validated in the obstetrical population at risk for hemorrhage.

The gauss/triton colorimetric system is not standard of care at UTMB. Not enough data is available to support its use, despite being FDA approved to estimate blood loss. Most evidence is available in non-pregnant patients. In the obstetric population no definitive evidence exists, and the only trial that has been performed was recently published in AJP reports for which one of our co-PIs (Dr. Saade) is the chief editor (11). In that trial, only the accuracy was evaluated, and we believe that further evidence is needed to support its use.

Our hypothesis is that this device will enable clinicians to prospectively and objectively assess EBL. Ultimately after its validation, our results will be used to propose a multicenter clinical trial to the NICHD MFMU network to evaluate the clinical utility of this system.

This study will be a prospective cohort study, in which we will evaluate two methods of evaluating intraoperative blood loss during cesarean delivery (usual clinical assessment versus Device). Of note, the subjects consented will be used as self-controls.

2. **Summary of project:** This study will be a prospective cohort study. Patients who are scheduled for an elective cesarean and meet criteria for inclusion in the study will be approached for participation at same day of admission. Written informed consent will be obtained from the patients by the Co-PI (Dr. Fawzi Saoud) and by the study collaborators (Dr. Katherine Jelliffe,

Mauricio La Rosa, Joe Eid, Nadia Megahed, and Mahmoud Abdelwahab). If patients agree to participate, a CBC (complete blood count) will be obtained via venous puncture. The device will be used during the delivery in the operating room. The device will be used to assess EBL by the research staff only and results/ EBL assessment will be masked to the clinical team. Unmasking will only occur after collecting the data from the device with purpose to perform data analysis. Patient management will be according to the clinical team. All patients undergo a CBC postpartum. The drop in Hgb (ΔHgb) between the pre and post cesarean CBCs will be calculated for each patient. Patients will be divided into quartiles of ΔHgb. Cases will be those patients whose ΔHgb is in the upper quartile, while controls will be those patients whose ΔHgb is in the lower 3 quartiles. We will be comparing EBL by standard clinical assessment versus result from the device between cases and controls.

The colorimetric Triton system which comprises of the device, software analysis and staff training will be supplied by the manufacturer free of charge. We will be offering our skills, fellows and residents, who will be collecting data and we will be performing the data analysis. Results will be available to the manufacturer after results are completed. The results of this study will be presented in conferences or published in a peer-review journal.

Demographic information will be obtained from the electronic medical record. The data will be kept on a password secured UTMB computer. An encrypted USB flash drive will be used to transfer data. The data will be identified and linked to the patient using the medical record number (MRN). During data analysis, all patient identifiers will be deleted.

3. Study procedures: VISIT#1

3.1 Screening, Recruitment and Consenting: When a patient meets inclusion criteria for participation in our study, the obstetrical team will contact the research team. Written informed consent will be obtained from the patient by the PI, study coordinator, or collaborator. Study participation will be complete when the patient is discharged from the hospital. The data collected will be kept on a password secured UTMB computer. An encrypted USB flash drive will be used to transfer data. The data will be linked via MRN, which is needed to access the demographic data and will be deleted when the data is analyzed. Our target sample size is 242 subjects.

3.2. Baseline procedures: In some patients, there will be no baseline procedures aside from using the masked device for assessment of EBL. If a preop CBC is not indicated clinically or not available, then a preop CBC will be obtained after consent is signed. Funding from the Ob/Gyn department will cover the cost of this test. The device will be set by the manufacturer not

to reveal the EBL in order to mask the surgical staff hence not affecting the standard assessment of EBL already implemented in our surgical suite. Neither the subject's insurance nor the subject will be responsible for any charges relating to tests done only for research. Please see attached budget and departmental letter of support.

3.3. Study visits/Follow-up: One study visit will be needed during the trial. The subject participation will be considered complete when the subject is discharged home.

3.6. Withdrawals: Subjects who withdraw from the study after inclusion will be excluded from further follow-up. Data collected until the time of withdrawal will be analyzed.

3.7 Outcomes

- **Primary outcome:** Differences in EBL between cases and controls using clinical estimate versus device assessment.
- **Secondary outcomes: System performance (ROC sensitivity analysis and correlation).** Delta hemoglobin, transfusion requirements, administration of uterotonics, colloid resuscitation, post-partum hemorrhage or hemorrhagic shock.

4. **Criteria for inclusion of subjects**:
   Pregnant women between the ages of 18-50.
   Scheduled cesarean delivery.

5. **Criteria for exclusion of subjects:**
   • Incarcerated patients
   • Patient unwilling or unable to provide consent
   • Intrauterine fetal demise (no fetal heart beat identified and documented by two physicians)
   • Placenta previa or other known placental anomalies
   • Enrolled in another trial that may affect outcome.

6. **Sources of research material:** Electronic medical records.

7. **Recruitment methods and consenting process:** See 3.1 above.

8. **Potential risks**
   8.1 Loss of confidentiality: Any time information is collected, there is a potential risk for loss of confidentiality. Every effort will be made to keep the subject's information confidential; however, this cannot be guaranteed.

9. **Potential benefits**: With this novel approach of assessing blood loss more objectively during cesarean section, there are many potential benefits,

including: decrease in the delay in diagnosis of hemorrhagic shock, decrease in delay in interventions and improved postpartum surveillance. In addition, this data will be useful in designing a level 1 trial to measure outcomes such as transfusion rates, transfusion complications, hemorrhage and maternal death.

10. **Data monitoring:** The PI, research coordinator, and collaborators will ensure that all aspects of data quality adhere to the study design. This will include monitoring for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness and responsiveness to data queries. Data will be collected and stored with the participant ID code only. The master enrollment log linking patient identifiers with study ID numbers will be kept in a password protected database on the Ob/Gyn department's internal server. Several data collection forms will be used. Data on these forms will be devoid of personal identifiers and will be securely stored at the division offices. The research coordinator will be available to monitor the data and correct any discrepancies based on source documents if needed.

11. **Procedures to maintain confidentiality:** Each subject will be assigned a study number with personally identifiable information deleted or removed. If needed, charts will be reviewed in the medical records area. Subjects' information will be de-identified and tagged with a number. Data will be collected and stored on a UTMB password-protected computer.

Statistical approach: We will be performing a prospective study. After defining cases and controls using the cutoff of upper quartile for pre- to postop- hemoglobin drop. We will use univariable and multivariable analysis to check for association between both blood loss assessment techniques using the device and the subjective clinical assessment among our cases and controls. We will be comparing cases versus controls (two groups) and EBL (continuous variable and primary outcome) hence t tests/means were used for our sample calculation; For the purpose of the study, we believe a sample size of 220 will be able to evaluate our primary outcome. Accounting for 10% loss of data or follow-up: **N total is 242 subjects**. This was based on a study of 50 patients having cesarean deliveries using the Triton System (the mean measured blood loss was 555.8 ml with a standard deviation of 317 ml (11). For a power of 80% and alpha of 0.05 and 25% effect size 1: 3 allocation (25%ile versus 75%ile PP delta hemoglobin):

Estimated sample sizes for a two-sample means test
t test assuming sd1 = sd2 = sd
Ho: m2 = m1 versus Ha: m2 != m1

Study parameters:

alpha = 0.0500
power = 0.8000
delta = -139.0000
m1 = 555.0000
m2 = 416.0000
sd = 317.0000
N2/N1 = 3.0000

Estimated sample sizes:

N = 220
N1 = 55
N2 = 165

We will also be using multiple model correlation (Pearson correlation coefficient) (secondary outcome) between EBL Device and EBL Standard. We will also perform ROC curve analysis (secondary outcome) to compare the area under the curve (AUC) to predict ΔHgb in the upper quartile by clinical estimate versus device assessment. The coefficient of multiple correlation takes values between 0 and 1; a higher value indicates a better predictability of the dependent variable (EBL Device) from the independent variable (EBL standard).

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