The University of Texas Medical Branch Galveston
Research Protocol

Estimating Blood Loss Using Triton™ in Vaginal Deliveries: A Validation Trial (ELUSIVE Trial)

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1. Introduction/Background/Purpose:

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 has often been used for the definition of PPH, 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 clinicians performing the vaginal delivery would estimate the blood loss by visually assessing the blood collected in the delivery drape drain and counting the number of lap sponges used thru out the delivery. 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 clinician and nursing staff's subjective assessment that is severely limited by human error and the presence of large volumes of amniotic fluid (6).

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 L&D system (Gauss Surgical, Inc., Menlo Park, CA) is an FDA-cleared mobile application on a tablet computer (iPad) that facilitates quantification of blood loss (QBL) by providing an easy to use process and user interface. Dry weights of all potential blood containing substrates are built-in to the device allowing batch weighing with automatic subtraction of dry weights. There is also a V-drape simulator accounting for collected fluids with automatic subtraction of a measured amount of amniotic fluid.

QBL is not regularly used at UTMB. Although widely recommended, little data is available to support its use in the obstetrical population. We believe that gathering further evidence regarding its value is appropriate.

Our hypothesis is that use of this device for QBL will enable clinicians to objectively measure blood loss in real-time.

This study will be a prospective cohort study, in which we will evaluate two methods of evaluating blood loss during vaginal delivery (usual visual EBL assessment versus Device QBL). 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 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 and by the study collaborators. If patients agree to participate, a CBC (complete blood count) will be obtained via venous puncture routine in our facility as part of the admission labs which will be around 10 cc of blood. The device will be used during the delivery in laboring room. The device will be used to assess QBL by the research staff only and results/ QBL assessment will be masked to the clinical team. Unmasking will only occur following study completion with purpose to perform data analysis. Patient management will be according to the clinical team without the knowledge of the QBL. All patients undergo a CBC postpartum as part of post-partum evaluation, this will also be performed by venipuncture where 10 cc of blood will be collected. The drop in Hgb (ΔHgb) between the pre and post partum CBCs will be calculated for each patient. The post-partum CBC will be collected approximately 24-30 hours from delivery as standard in our unit. The blood will be collected from each patient by the nursing staff who are experienced in withdrawing blood. 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 visual EBL by standard clinical assessment versus the QBL result from the device between cases and controls.

The Triton L&D system which comprises of the device, software analysis and staff training will be supplied by the manufacturer free of charge. Research staff will be trained by the manufacturer. We will be offering our skills, fellows, midwifes 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 completed 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 556 subjects.

3.2. Baseline procedures: In some patients, there will be no baseline procedures aside from using the masked device for assessment of QBL. Every effort will be made to mask the clinical staff from the QBL information so as not to affect the standard assessment of visual EBL and medical decision making. During blood loss assessment, clinicians will be instructed not to place any sponges and other junk or materials into the callibrated v-drape following placental delivery (before placenta is delivered this is allowed), since it can artificially inflate or interfere with the accuracy of QBL. Subjects , where this protocol deviation occurs, will be removed from the final analysis and replaced by other cases in order to meet our final sample size. Neither the subject's insurance nor the subject will be responsible for any charges relating to tests done only for research.

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 blood loss between cases and controls using clinical estimate (visual EBL) versus device assessment (QBL).
- **Secondary outcomes:** System performance (ROC sensitivity analysis and correlation)**.** Delta hemoglobin, hemorrhage recognition (defined as >500 ml blood loss), transfusion requirements (timing, rate, dose, etc.), 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.
   Plan of care is vaginal 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.
   •Any contraindications to vaginal delivery.
   •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 the QBL approach of assessing blood loss more objectively during vaginal delivery, there are many potential benefits to future patients, 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/QBL (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 500 will be able to evaluate our primary outcome. Accounting for 10% loss of data or follow-up: **N total is 556 subjects**. This was based on a study of 30,937 patients having vaginal deliveries using the Triton™ System (the mean measured blood loss was 383.87ml with a standard deviation of 330.52 ml (unpublished data supplied by the manufacturer). 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 = -95.9700
m1 = 383.8700
m2 = 287.9000
sd = 330.5200
N2/N1 = 3.0000

Estimated sample sizes:

N = 500
N1 = 125
N2 = 375

We will also be using multiple model correlation (correlation coefficient) (secondary outcome) between QBL 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 (QBL Device) from the independent variable (EBL standard).

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