# The Effect of Intravenous EACA on Blood Loss and Transfusion Requirements After Bilateral VRO

**Protocol and Analysis Plan**

**NCT # NCT02257580**

**Approved 12/10/2014**

## 1. What is the Study Design

### Experimental:

Randomized controlled clinical trial (RCT)

## 2. Who will be recruited and enrolled?

### *Inclusion Criteria*:

Patients will be recruited from the practices of Dr. Scher and Dr. Dodwell. Inclusion criteria will include the following:

- Age less than or equal to 18
- Scheduled for elective bilateral VRO with or without associated soft tissue and osseous procedures

### *Exclusion Criteria*:

All patients will be asked to discontinue acetylsalicylic acid (ASA), antiplatelet agents, and hormone replacement and hormonal contraceptive agents at least 7 days prior to surgery. Other than ASA, these agents will be held 6 weeks postoperatively.

- Preoperative use of an anticoagulant (Plavix, warfarin, lovenox, etc.)
- History of hypersensitivity to EACA
- History of thromboembolic event (e.g., PE or DVT)
- History of renal insufficiency or failure
- Congenital or acquired coagulopathy as evidence by INR >1.4 or PTT > 1.4 times normal, or Platelets <150,000/$mm^3$ on preoperative laboratory testing
- Use of hormone replacement therapy or hormonal contraceptive agent within 7 days prior to surgery
- Pregnant
- Breastfeeding
- Older than 18 years of age
- Patients <u>not</u> receiving neuraxial anesthesia

This trial will be registered on ClinicalTrials.gov. All patients undergoing bilateral VRO by the study surgeons (DS and ED) will be identified in their office and screened for eligibility as potential patients for participation in the study. A research assistant will review the office and operative calendars of the study surgeons each week to identify and recruit potential patients. The assistant will record on the CONSORT diagram any reasons for ineligibility/exclusion.

The surgeon, a co-investigator or research assistant will obtain consent prior to surgery, at the patient's preadmission screening visit. All authors on the protocol, in addition to their research assistants, will be designated to obtain consent.

We will power the study to detect a 250mL difference in calculated intra-operative blood loss between groups. This effect size has been used in the total hip literature, and it is considered to be a clinically significant difference in blood loss[15]. Our analysis shows that 12 patients are required in each arm of the study (24 patients total) to achieve 81% power with an independent-sample t-test and statistical significance set to alpha equal to 0.05. Expecting that 10-25% of patients will be excluded, we will aim to enroll a total of 30 patients in this study.

Patients aged 18 or younger will be screened for study eligibility

3. **Interventions or Observations – what data are going to be collected and from what source?**

Only anesthesiologists agreeing to participate in the study will be paired with the study surgeons. Anesthesia will be conducted in a standardized fashion. The anesthesiologist will perform a neuraxial block (epidural, spinal, combined-spinal epidural) as well as administer general anesthesia. A neuraxial block will be placed using bupivicaine. A balanced general anesthetic utilizing a combination of either isoflurane, sevoflurane with or without nitrous oxide, vecuronium, midazalam and either fentanyl, morphine or dilaudid as the narcotic will be used at the discretion of the anesthesiologist. If a combined-spinal epidural is unsuccessful and an epidural and/or spinal are successfully obtained, the patient will still be included in the study. Patients not receiving neuraxial anesthesia will be excluded from the study. Arterial and venous access will be obtained in the usual sterile manner for monitoring.

The blood pressure target will be 20-25% below baseline, which will be achieved primarily with the combination of the general anesthesia and the neuraxial anesthesia. For blood pressure above this range, the epidural will be dosed with a short-acting local anesthetic, and/or the depth of the general anesthetic and will be titrated as per the anesthesiologist's judgment. For hypotension below this range, intravenous pressors, crystalloid, colloid or blood will be given. The technique of induced hypotension will not be utilized during these cases. Additional maintenance IV fluids or colloid will be given to maintain urine output of at least 0.5-1ml/kg/hr. Toradol and IV acetaminophen may be given towards the end of the case per the anesthesiologist's discretion.

Bilateral VRO will be performed as per the surgeon's routine practice. In general, the operative extremity will be prepped and draped in the usual sterile fashion. Prior to incision, the anesthesiologist will administer a loading dose of 100 mg/kg of EACA with a max of 4-5 grams up to 1 hour prior to incision. During the case, an infusion of 33 mg/kg/hr (max of 1 gram/hr) will be maintained. The use of EACA will be terminated at the end of the case. Patients randomized to the placebo arm will be

infused with a comparable volume of normal saline prepared by the pharmacy. All participating anesthesiologists will not be blinded in this study. A direct lateral approach to the femur will be used, and standard surgical techniques for intra-operative hemostasis will be utilized. The surgeon will perform bilateral femoral osteotomies and associated soft tissue surgery and pelvic osteotomy. After all hardware is placed, the wound will be thoroughly irrigated and suctioned. A deep drain will be placed on each operative side, and the wound will be closed in layers. Intra-operatively, a cell saver will be used, and the volume (mL) of auto-transfusion will be recorded.

Hematocrit levels will be monitored regularly in the post-operative period. As per protocol, a post-op hematocrit will be drawn in the PACU, and subsequently, daily labs will be obtained unless specified by the medicine or surgical attending. Routine, daily inpatient CBC data and drain output will be reviewed. Inpatient and office records will be accessed to help identify postoperative complications. The criteria for transfusion of blood products will be a hemoglobin level of < 7.0 g/dL or a hemoglobin level of < 10.0 g/dL with clinical signs of symptomatic anemia (e.g., unexplained tachycardia, hypotension unresponsive to fluids or vasopressors, change in mental status, low urine output, and shortness of breath). Blood will be administered 1 unit at a time, and the presence of symptoms or signs will be reassessed after each unit. This algorithm may be altered by the treating physician (e.g., PACU attending, surgeon, pediatrician, or the OR anesthesiologist), however all decisions will be supported by reasonable documentation. Drains will be removed on POD 2 unless specified by the attending surgeon, and the 24-hour clock will begin once the patient is in the PACU. All drains, patient charts, and patient rooms will be clearly labeled in order to identify study patients.

Attending surgeons, orthopedic surgery residents, physician assistants and research assistants involved with this study will assist in data collection. For each patient, we will collect demographic data, pre-operative CBC data, intra-operative cell saver auto-transfusion volumes, post-operative number of packed red blood cell units transfused, post-operative CBC data, post-operative drain outputs, and post-operative complications. This information will be gathered from the peri-operative medical records and electronic medical records.

A sticker will be place on the front of each participating patient's chart identifying him or her as a study patient. Their enrollment will also be communicated in the clinician rounding notes for each patient. Drains will be labeled for each study participant as well, and nurses will record the drain outputs per their floor protocol.

Data recorded from the electronic medical record will include:

- Date of surgery
- Patient age at the time of surgery
- Patient sex
- Patient height (cm) and weight (kg) at time of admission
- Preoperative CBC data and coagulation study data

- Postoperative hemoglobin on all inpatient days postoperatively (g/dL)
- Transfusion requirement during inpatient stay (units required)
- Transfusion reaction
- Total 24-hour drain output
- Postoperative day and time of discharge
- Chart review of progress notes for evidence of clinically significant VTE
- Chart review of progress notes for evidence of reoperation, hematoma, seroma, or postoperative infection

Data recorded from the operating room record will include:

- Anesthetic used (e.g., spinal/epidural, general, etc.)
- Operative times (minutes)
- Intra-operative transfusion requirements (units of blood)
- Use of cell saver intraoperatively (auto-transfusion volume, mL)
- Intra-operative complications

Data recorded from outpatient postoperative office records will include:

- Chart review of progress notes for evidence of clinically significant VTE through six weeks post-operatively
- Chart review of progress notes for evidence of re-operation, hematoma, seroma, or postoperative infection through six weeks post-operatively

Patients will be randomized to either the intervention or control group, as per randomization protocol described elsewhere in the proposal. For patients who are randomized to the control group, study data will be collected in the same manner as for the intervention group.

All tests and imaging used in this study are considered standard of care.

*Randomization Process:*

The patients will be randomized into one of 2 groups: (1) Loading dose and infusion of EACA (2) Equivalent volume of normal saline prepared by the pharmacy. An EACA loading dose of 100 mg/kg with a max of 4-5 grams will be given up to 1 hour prior to incision. During the case, an EACA infusion of 33 mg/kg/hr (max of 1 gram/hr) will be maintained. The use of EACA will be terminated at the end of the case. Assignment of patients will be made based on a sequential treatment assignment or minimization strategy in order to ensure an even distribution of patients in each treatment arm. More specifically, each patient will be randomized to the treatment arm that would minimize differences between groups. Randomization will be stratified by sex and surgery type (bilateral VRO, bilateral VRO with associated soft tissue or osseous procedure) so that the number of male/female patients and VRO/associated procedure patients will be balanced in each study group between trial arms.

The Biostatistics Core of the HSS Healthcare Research Institute will randomize each patient based on the minimization strategy. It will be a double-blind experiment with all parties, except the pharmacy, anesthesiologist, and designated research assistant, being blinded to the randomization schedule (surgeon, medical staff, and patient). Patient recruitment will continue until a total of 30 patients are enrolled.

*Treatment Groups*:
Bilateral VROs will be performed as per the study surgeon's routine practice. In general, the operative extremity will be prepped and draped in the usual sterile fashion. Prior to incision, the anesthesiologist, will administer a loading dose of 100 mg/kg of EACA with (max of 4-5 grams) or an equivalent volume of normal saline prepared by the pharmacy. The loading dose may be give up to 1 hour prior to incision. During the case, an EACA infusion of 33 mg/kg/hr (max of 1 gram/hr) will be maintained. Only anesthesiologists agreeing to participate in the study will be paired with the study surgeons, and all anesthesiologists will be aware of a patient's randomization to the treatment or placebo group.

*Outcome Measures*
Primary outcome: Calculated total blood loss.
Secondary outcomes of interest: Postoperative transfusion requirements (allogeneic blood transfusion and intraoperative cell saver utilization), post-operative blood loss, length of stay, and post-operative complications.

Calculated total blood loss will be determined from the difference between the preoperative hemoglobin and the postoperative hemoglobin (or the lowest postoperative hemoglobin during the hospital stay prior to transfusion). Based on hemoglobin balance, the estimated blood loss will be calculated according to the formula by Nadler et al.[17]:

Estimated Blood Volume (EBV) = ($k_1$ x Height$^3$ (m)) + ($k_2$ x Weight (kg)) + $k_3$
For men, $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$
For women, $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$

Multiplying the EBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level[23,24]:

Total RBC volume loss = EBV x (Hct Preop – Hct Postop)

Transfusions (mean volume per unit at HSS, 250 mL) can be taken into account by calculating the total blood loss[16]:

Total blood loss (L) = Total RBC volume loss + (No. of Units Transfused x 0.25) / (Hct Preop – Hct Postop) / 2)

The rate of perioperative blood transfusions, both intraoperative and postoperative, will be documented for analysis.

The criteria for transfusion of blood products will be a hemoglobin level of < 7.0 g/dL or a hemoglobin level of < 10.0 g/dL with clinical signs of symptomatic anemia (e.g., unexplained tachycardia, hypotension unresponsive to fluids or vasopressors, change in mental status, low

urine ouput, and shortness of breath). Blood will be administered 1 unit at a time, and the presence of symptoms or signs will be reassessed after each unit. This algorithm may be altered by the treating physician (e.g., PACU attending, surgeon, or the OR anesthesiologist), however all decisions will be supported by reasonable documentation. Drains will be removed on POD 2 unless specified by the attending surgeon. Of note, the chart of the patient will clearly indicate him/her as a study patient.

VTE prophylaxis is not commonly used for pediatric patients at our institution. However, all patients will also receive a comprehensive approach to postoperative care comprised of mechanical (sequential compressive device) prophylaxis in-house, early mobilization with physical therapy, medical optimization, and regional anesthesia (if appropriate).

**4. What is the long-term significance**?

There are certain risks associated with blood loss and blood transfusion after elective orthopaedic procedures in young patients. Blood loss and transfusion requirements can be reduced with several blood conservation measures, including the use of pharmacological agents such as EACA. If the use of IV EACA is shown to decrease blood loss and transfusion requirements after bilateral VROs, it will provide an efficacious and inexpensive method to reduce post-operative morbidity and improve patient outcomes after bilateral VROs.

## D. SAMPLE SIZE AND DATA ANALYSIS

**Sample Size –**

1. Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):
Independent samples t-test will be utilized if the data is normally distributed (or non-parametric Mann-Whitney U test if assumption of normality is not met).

2. Alpha level: 0.05

3. Beta or power level: 0.81

4. Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):
The primary outcome of interest in total intra-operative blood loss, which will be summarized as mean +/- standard deviation. Based on an analysis of the twenty-four consecutive cases of bilateral VROs, the mean calculated intra-operative blood loss was 671.24mL (SD: 233.69).

5. Number of groups being compared (use 1 for paired analysis within the same subjects):
Two groups are being compared: Treatment Group (Loading Dose + Infusion) vs. Placebo Group (NS)

6. Effect size or change expected between groups: 250cc

7. Resulting number per group: 12

8. Total sample size required: 24

## Data Analysis

The primary outcome of interest (calculated total blood loss) will be presented as a mean +/- standard deviation and compared between the EACA and placebo groups with a two-sample t-test. Multivariable linear regression models will also be used to adjust for any potential confounding due to total blood loss volume between arms after adjustment for age, sex, BMI, and anesthesia type. To adjust for any patients lost due to early withdrawal, we will increase our sample size by 3 patients in each group for a total sample size of 30 patients.

Calculated total blood loss will be determined from the difference between the preoperative hemoglobin and the postoperative hemoglobin (or the lowest postoperative hemoglobin during the hospital stay prior to transfusion). Based on hemoglobin balance, the estimated blood loss will be calculated according to the formula by Nadler et al.[17]:

Estimated Blood Volume (EBV) = ($k_1$ x Height$^3$ (m)) + ($k_2$ x Weight (kg)) + $k_3$
For men, $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$
For women, $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$

Multiplying the EBV by the hematocrit (Hct) gives the red blood cell (RBC) volume. As such, a change in the RBC volume can be calculated from a change in the Hct level[23,24]:

Total RBC volume loss = EBV x (Hct Preop – Hct Postop)

Transfusions (mean volume per unit at HSS, 250 mL) can be taken into account by calculating the total blood loss[16]:

Total blood loss (L) = Total RBC volume loss + (No. of Units Transfused x 0.25) / (Hct Preop – Hct Postop) / 2)

All continuous secondary outcomes such as postoperative allogeneic blood transfusion requirement, intraoperative cell saver utilization, and length of hospital stay, will be analyzed in the same manner as the primary outcome.

Complications will be reported as incidence rates with 95% confidence intervals.

All hypotheses will be evaluated with two-sided tests with statistical significance set at $\alpha = 0.05$.

Bibliography

1. Murray-Weir M, Root L, Peterson M, et al. Proximal femoral varus rotation osteotomy in cerebral palsy: A prospective gait study. *J Pediatr Orthop*. 2003;23(3):321-329.

2. Thomason P, Selber P, Graham HK. Single event multilevel surgery in children with bilateral spastic cerebral palsy: A 5 year prospective cohort study. *Gait Posture*. 2013;37(1):23-28.

3. Spiegel D, Flynn J. Evaluation and treatment of hip dysplasia in cerebral palsy. *Orthop Clin N Am*. 2006;37:185-196.

4. Tomak Y, Piskin A, Ozcan H, Tomak L. Subtrochanteric derotation osteotomy using a bent dynamic compression plate in children with medial femoral torsion. *Orthopedics*. 2008;31(5):453-458.

5. Pirpiris M, Trivett A, Baker R, Rodda J, Nattrass GR, Graham HK. Femoral derotation osteotomy in spastic diplegia. proximal or distal? *J Bone Joint Surg Br*. 2003;85(2):265-272.

6. Risberg B. The response of the fibrinolytic system in trauma. *Acta Chir Scand Suppl*. 1985;522:245-271.

7. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. *J Am Acad Orthop Surg*. 2010;18(3):132-138.

8. Faraoni D, Goobie SM. The efficacy of antifibrinolytic drugs in children undergoing noncardiac surgery: A systematic review of the literature. *Anesth Analg*. 2014;118(3):628-636.

9. Thompson GH, Florentino-Pineda I, Poe-Kochert C. The role of amicar in decreasing perioperative blood loss in idiopathic scoliosis. *Spine (Phila Pa 1976)*. 2005;30(17 Suppl):S94-9.

10. Thompson GH, Florentino-Pineda I, Poe-Kochert C, Armstrong DG, Son-Hing J. Role of amicar in surgery for neuromuscular scoliosis. *Spine (Phila Pa 1976)*. 2008;33(24):2623-2629.

11. Gill JB, Chin Y, Levin A, Feng D. The use of antifibrinolytic agents in spine surgery. A meta-analysis. *J Bone Joint Surg Am*. 2008;90(11):2399-2407.

12. Florentino-Pineda I, Blakemore LC, Thompson GH, Poe-Kochert C, Adler P, Tripi P. The effect of epsilon-aminocaproic acid on perioperative blood loss in patients with idiopathic scoliosis undergoing posterior spinal fusion: A preliminary prospective study. *Spine (Phila Pa 1976)*. 2001;26(10):1147-1151.

13. Florentino-Pineda I, Thompson GH, Poe-Kochert C, Huang RP, Haber LL, Blakemore LC. The effect of amicar on perioperative blood loss in idiopathic scoliosis: The results of a prospective, randomized double-blind study. *Spine (Phila Pa 1976)*. 2004;29(3):233-238.

14. McLeod LM, French B, Flynn JM, Dormans JP, Keren R. Antifibrinolytic use and blood transfusions in pediatric scoliosis surgeries performed at US children's hospitals. *J Spinal Disord Tech*. 2013.

15. McConnell JS, Shewale S, Munro NA, Shah K, Deakin AH, Kinninmonth AW. Reduction of blood loss in primary hip arthroplasty with tranexamic acid or fibrin spray. *Acta Orthop*. 2011;82(6):660-663.

16. Molloy DO, Archbold HA, Ogonda L, McConway J, Wilson RK, Beverland DE. Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: A prospective, randomised controlled trial. *J Bone Joint Surg Br*. 2007;89(3):306-309.

17. Nadler S, Hidalgo J, Bloch T. Prediction of blood volume in normal human adults. *Surgery*. 1962;51(2):224-232.

18. Chimento GF, Huff T, Ochsner JL,Jr, Meyer M, Brandner L, Babin S. An evaluation of the use of topical tranexamic acid in total knee arthroplasty. *J Arthroplasty*. 2013;28(8 Suppl):74-77.

19. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev*. 2011;(3):CD001886. doi(3):CD001886.

20. Makhija N, Sarupria A, Kumar Choudhary S, Das S, Lakshmy R, Kiran U. Comparison of epsilon aminocaproic acid and tranexamic acid in thoracic aortic surgery: Clinical efficacy and safety. *J Cardiothorac Vasc Anesth*. 2013;27(6):1201-1207.

21. Martin K, Breuer T, Gertler R, et al. Tranexamic acid versus varepsilon-aminocaproic acid: Efficacy and safety in paediatric cardiac surgery. *Eur J Cardiothorac Surg*. 2011;39(6):892-897.

22. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: A systematic review of randomized trials. *Thromb Res*. 2009;123(5):687-696.

23. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement . *Br J Anaesth*. 2003;90(5):596-599.

24. Bjerke-Kroll BT, Sculco PK, McLawhorn AS, Christ AB, Gladnick BP, Mayman DJ. The increased total cost associated with post-operative drains in total hip and knee arthroplasty. *J Arthroplasty*. 2014;29(5):895-899.