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Effect of Intravenous Aminocaproid Acid on Blood Loss and Transfusion Requirements After Bilateral Varus Rotational Osteotomy: A Double-blind, Placebo-controlled Randomized Trial

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Background: ε-Aminocaproic acid (EACA) is an antifibrinolytic agent that has been shown to decrease blood loss and transfusion requirements in several populations undergoing various surgical procedures. However, the efficacy of EACA has not been assessed in pediatric patients with cerebral palsy undergoing bilateral varus rotational femoral osteotomies. The purpose of this study was to assess the efficacy of intravenous EACA in reducing calculated intraoperative blood loss and transfusions in this population.

Methods: Patients aged 18 years or younger were eligible. Patients were randomized to receive EACA or placebo (saline), and randomization was stratified based on sex and whether or not additional soft tissue or osseous procedures were performed. On the basis of retrospective data, the calculated sample size was 12 patients per arm to detect a difference of 250-mL blood loss. The primary outcome was calculated intraoperative blood loss. Secondary outcomes included transfusion requirements, 24-hour drain output, length of stay, and incidence of complications.

Results: The mean age of patients in this study was 8 years (SD: 2.4 y). There were no differences in age, sex, height, weight, type of anesthesia, operative time, and associated procedures between the EACA and placebo groups ($P > 0.05$). Preoperative hematocrit was lower in the EACA group (37.1 vs. 40.0, $P = 0.04$). Calculated intraoperative blood loss was 536 mL in the EACA group and 628 mL in the placebo group ($P = 0.45$). Transfusions were required in 62% of patients in the EACA group and 67% of patients in the placebo group ($P = 0.68$). Total 24-hour drain output was 72.5 mL in the EACA group and 103.3 mL in the placebo group ($P = 0.37$). Length of stay was similar between both groups, and there were no drug or placebo-related complications in either group.

Conclusions: There was no difference in blood loss or transfusion requirements associated with EACA compared with placebo; however, this study is underpowered to detect smaller differences in blood loss. Additional studies with larger sample sizes are needed to confirm these findings and further elucidate the indications for antifibrinolytic agents in pediatric patients.

Level of Evidence Level I.

Key Words: aminocaproic acid, osteotomy, blood loss, transfusion, cerebral palsy

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Neuromuscular hip subluxation, coxa valga, and excessive femoral anteversion are common causes of gait disturbance and disability in children with cerebral palsy (CP).[1] Varus rotational osteotomy (VRO) of the femur corrects the femoral neck-shaft angle and torsional abnormalities, which allows the hips to be concentrically reduced and adequately covered.[2] Children with CP commonly require bilateral VROs to maintain symmetry for both walking and sitting, and routine practice is to perform these during 1 surgical event.[2,3] Given the extent of osseous and soft tissue surgery involved in bilateral VRO, blood loss and transfusion requirements are a major source of morbidity in the perioperative period.[4,5] In 1 study, all patients that underwent bilateral femoral osteotomies required a blood transfusion in the perioperative period.[4]

Antifibrinolytic agents are commonly used in orthopaedic surgery, and they have been shown to be efficacious in reducing perioperative blood loss and transfusion requirements after total joint arthroplasty, pediatric scoliosis surgery, and adult reconstructive spine surgery.[6] ε-Aminocaproic acid (EACA) is a synthetic lysine analog that

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competitively inhibits the activation of plasminogen to plasmin and subsequently decreases the degree of fibrinolysis.[7] Multiple studies have shown that EACA decreases blood loss and transfusion requirements after orthopaedic surgery,[8–13] and recent meta-analyses by Faraoni and Goobie[7] and Gausden et al[14] concluded that antifibrinolytic agents such as EACA are efficacious in children undergoing noncardiac surgery. However, there are no studies assessing the efficacy of EACA in patients undergoing bilateral VROs.

The purpose of this double-blinded, randomized controlled trial was to assess the efficacy of intravenous (IV) EACA in reducing calculated intraoperative blood loss compared with placebo (normal saline) in patients undergoing bilateral VROs. We hypothesized that patients receiving IV EACA would have decreased intraoperative blood loss and transfusion requirements in the setting of bilateral VRO+/− additional procedures.

METHODS

This prospective, double-blinded, placebo-controlled, randomized clinical trial included patients aged 18 years or younger with CP indicated for bilateral VRO with or without associated soft tissue or osseous procedures. Patients with a history of a thromboembolic event, renal insufficiency or failure, known hypersensitivity to EACA, and congenital or acquired coagulopathy, as well as patients that could not receive neuraxial anesthesia were excluded. Patients that were being treated with anticoagulants, hormone replacement therapy or hormonal contraceptive agent were also excluded. Patients undergoing bilateral VRO were identified by the study surgeons (E.D. and D.S.) and screened for eligibility. Any reasons for ineligibility or exclusion were recorded by the research staff in a CONSORT diagram (Fig. 1). All patients included in the study were consented by the study surgeon before surgery. This study received institutional review board approval and was registered on clinicaltrials.gov (NCT02257580).

Randomization and Study Protocol

Following confirmation of eligibility, patients were randomized by our statistician (J.N.) into 1 of 2 groups: (1) loading dose and infusion of EACA (2) equivalent

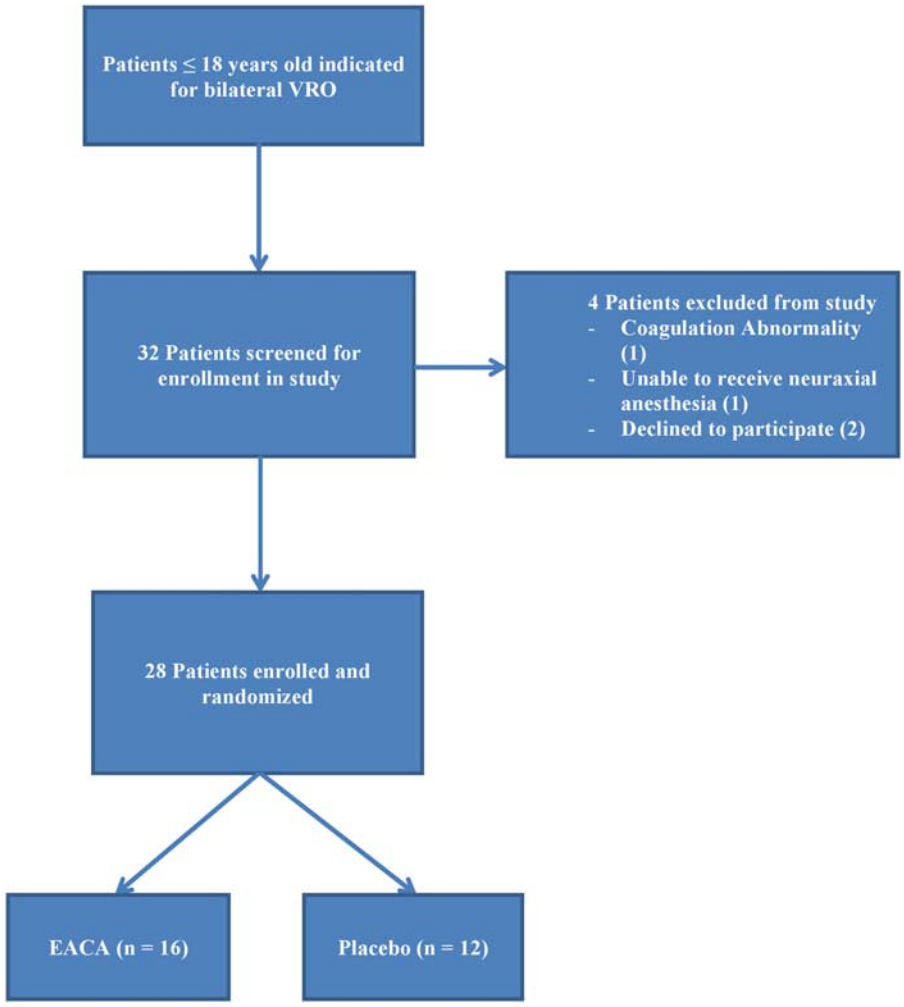

FIGURE 1. Trial CONSORT diagram. EACA indicates ε-aminocaproic acid; VRO, varus rotational osteotomy.

volume of normal saline. Patients were randomized using a minimization strategy to ensure equal numbers of patients in each group over the course of the study and decrease the likelihood of differences between groups.[15] Randomization was 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 were balanced in each study arm. The statistician, anesthesiologist, and pharmacist were not blinded to treatment arm, although patients, families and other members of the care team were blinded. The anesthesiologist was not blinded in this study to ensure patient safety when administering this medication in an experimental manner.

Bilateral VRO and associated procedures (if indicated) were performed by the study surgeons using standard surgical techniques. Within an hour before skin incision, the anesthesiologist administered a loading dose of 100 mg/kg of EACA (maximum of 4 to 5 g) or an equivalent volume of placebo (normal saline) prepared by the pharmacy. During the case, an EACA infusion of 33 mg/kg/h (maximum of 1 g/h) or placebo infusion was maintained and then terminated at the end of the case. Intraoperative fluid and blood management were guided by the patient's hemodynamics but at the discretion of the anesthesiologist. Surgical drains were placed at both hip incisions and standard postoperative care was initiated including postoperative labs in the postanesthesia care unit and subsequent postoperative days (PODs). Physical therapy and mobilization were commenced on POD 1. Our patients routinely received ketorolac as part of their postoperative pain regimen.

Perioperative medical care was administered by the pediatric hospitalist service. The study criteria for postoperative transfusion of blood products was a hemoglobin level of <7.0 g/dL or a hemoglobin level of <10.0 g/dL with clinical signs of symptomatic anemia (eg, unexplained tachycardia, hypotension unresponsive to fluids or vasopressors, change in mental status, low urine output, and shortness of breath). Surgical drains were removed on POD 1 unless specified by the treating surgeon. Patients were discharged once they had met all discharge criteria as determined by the surgical team, pediatric hospitalist team, and physical therapy.

Data were extracted from the electronic medical record and recorded in data collection sheets (I.S.). A data safety monitoring board was established to periodically review all complications and results. The study data was saved in a secure, password-protected electronic database. We did not routinely collect data relating to nutrition and G-tube dependence in the datasheet or preoperative visit.

Outcome Measures

The primary outcome of this study was calculated intraoperative blood loss. Calculated total blood loss was determined from the difference between the preoperative hemoglobin and postoperative hemoglobin measured in the postanesthesia care unit. On the basis of hemoglobin balance, the estimated blood loss was calculated according to the formula by Nadler et al.[16] This calculation was adjusted for intraoperative transfusions and it has been used in previous studies.[17–19]

Secondary outcome measures included transfusion requirements (units), postoperative blood loss (total 24-h drain output, mL), length of hospital stay (days), and incidence of complications from POD 0 through 6 weeks postoperatively (%), specifically venous thromboembolic disease (deep vein thrombosis and pulmonary embolism), infection (superficial and deep), wound dehiscence, hematoma/seroma formation, gastrointestinal and pulmonary complications, reoperation, and transfusion reaction.

Sample Size Calculation and Statistical Analysis

The sample size calculation was based on 2 sample *t* test with a nonparametric adjustment for the primary outcome of calculated intraoperative blood loss. Blood loss during bilateral VRO cases with or without additional procedures was calculated at 671 mL (±234 mL) based on unpublished, retrospective institutional data for 2 years before the start of this study. A difference of 250 mL of blood loss was selected as the clinically significant effect size since it has been previously defined as a clinically significant difference in the literature,[20] and it is the standard volume of a unit of blood at our institution. Twelve patients in each arm were needed to show a clinically significant difference of 250 mL blood loss with 80% power, and the goal of enrollment was 30 patients to account for exclusions and patients with incomplete data.

Descriptive statistics were used to summarize baseline characteristics of patient demographic and clinical data. Continuous data were analyzed using nonparametric Mann-Whitney *U* test. Discrete variables were analyzed using Fisher exact tests. Multivariable regression models were generated to identify those potential factors associated with total blood loss. Variables were defined a priori as candidate variables in the regression model (ie, study group, age, transfusion requirements, additional osteotomy) as well as those variables that achieved a *P*-value of ≤ 0.05 in the comparative analysis (preoperative hematocrit). We hypothesized that additional osteotomy would be associated with increased blood loss, and we specifically controlled for this in the regression analysis. Given the limited sample size available, iterative stepwise techniques were used to identify a reduced model that allowed for the best goodness of fit of the data to the model. Because of the exploratory nature of the regression modeling, variables that achieved a *P*-value of ≤ 0.10 were retained in the final model. Statistical significance was defined as all variables that achieved a *P*-value of ≤ 0.05. All analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY).

RESULTS

A total of 28 patients were enrolled in this study (16 EACA, 12 placebo). All patients underwent bilateral VROs+/− additional procedures by 2 fellowship-trained pediatric orthopaedic surgeons between 2015 and 2018. The mean age was 8 years (SD: 2.4 y), and 64% of patients were male. There were no differences in age, sex, height, weight, and type of anesthesia between the EACA and placebo groups ($P > 0.05$) (Table 1). The majority of patients were

TABLE 1. Patient Demographics and Baseline Data

	Mean (SD)/n (%)			
	Total	Placebo	EACA	*P*
Age (y)	8.0 (2.4)	8.1 (2.8)	8.0 (2.1)	0.93
Height (m)	1.2 (0.1)	1.2 (0.2)	1.2 (0.1)	0.65
Weight (kg)	23.8 (6.9)	25.0 (7.1)	23.0 (6.8)	0.45
Sex				
Male	18 (64)	8 (67)	10 (63)	1.00
Female	10 (36)	4 (33)	6 (38)	
Hematocrit				
Preoperative	38.3 (3.7)	40 (3.2)	37.1 (3.6)	0.04
Postoperative	27.7 (3.9)	28.4 (3.1)	27.1 (4.4)	0.40
Associated procedure				
No	2 (7)	2 (17)	0	0.18
Yes	26 (93)	10 (83)	16 (100)	

EACA indicates ε-aminocaproic acid.

either Gross Motor Function Classification System IV (n = 9) or V (n = 12). Almost all patients had an associated procedure (Table 2), and there was no difference in the rates of associated procedures between groups ($P > 0.05$). However, additional osteotomies were performed in 14/16 patients receiving EACA and 5/12 patients receiving placebo (88% vs. 42%, $P = 0.02$). Preoperative hematocrit was also lower in the EACA group compared with the placebo group (37.1 vs. 40.0, $P = 0.04$).

Calculated mean intraoperative blood loss in the EACA group was 535.7 mL (SD: 356.6 mL) and the placebo group was 628 mL (SD: 235.8 mL) ($P = 0.45$). There was no difference in surgeon or anesthesia reported estimated blood loss between groups (407 mL in placebo group vs. 425 mL in the EACA group, $P = 0.77$). Patients in the EACA group lost 32% (SD: 19.7%) of their total blood volume, and patients in the placebo group lost 36.2% (SD: 9.8%) of their total blood volume ($P = 0.51$). Overall, there was no difference in the number of total transfusion units required between EACA (62.5%) group and placebo (66.7%) groups ($P = 0.68$) (Table 3). Intraoperative transfusions were required in 44% of patients in the EACA group and 64% of the placebo group ($P = 0.44$), and postoperative transfusions were required in 25% of patients in both the EACA and placebo groups ($P > 0.99$). Total 24-hour drain output was

TABLE 2. Associated Procedures in Patients Undergoing Bilateral Varus Rotational Osteotomies

Associated Procedure	Total [n (%)]
Adductor lengthening or tenotomy	17 (61)
Psoas lengthening	4 (14)
Rectus transfer	5 (18)
Hamstring lengthening or release	6 (21)
Gastrocnemius recession	6 (21)
Open reduction	1 (4)
Pelvic osteotomy	17 (61)
Distal femoral osteotomy	1 (4)
Tibial osteotomy	1 (4)
Foot reconstruction	1 (4)
Removal of hardware	1 (4)

TABLE 3. Intraoperative and Postoperative Transfusion Requirements

	n (%)			
	Total	Placebo	EACA	*P*
Intraoperative transfusion requirement (U)				
0	13 (48)	5 (41)	9 (56)	0.44
1	14 (52)	7 (58)	7 (44)	
Postoperative transfusion requirement (U)				
0	21 (75)	9 (75)	12 (75)	> 0.9
1	7 (25)	3 (25)	4 (25)	
Total transfusion requirement (U)				
0	10 (36)	4 (33)	6 (38)	0.68
1	15 (54)	6 (50)	9 (56)	
2	3 (11)	2 (17)	1 (6)	

EACA indicates ε-aminocaproic acid.

72.5 mL (SD: 68.9 mL) in the EACA group and 103.3 mL (91.4 mL) in the placebo group ($P = 0.37$). The mean length of stay was similar between both groups (5.1 d in placebo group vs. 5.5 d in the EACA group, $P = 0.64$). There were no drug or placebo-related complications or postoperative complications in either group.

The variables assessed in the multivariable regression analysis for calculated intraoperative blood loss included study group (EACA or placebo), age, preoperative hematocrit, other osteotomies (in addition to bilateral VRO), and transfusion requirements (intraoperative and total). Higher preoperative hematocrit was the only variable significantly associated with greater calculated intraoperative blood loss ($\beta = 35.0$, $P = 0.04$).

DISCUSSION

The primary objective of this study was to determine the efficacy of EACA in reducing calculated intraoperative blood loss associated with bilateral VROs. There was no difference in calculated blood loss or transfusion requirements between patients who received IV EACA versus placebo. Similarly, transfusion rates and all secondary outcomes were similar between the EACA and placebo groups. This study does not currently support the routine use of EACA in pediatric patients undergoing bilateral VRO; however, differences in preoperative hematocrit despite randomization, heterogeneity in associated procedures, and high variability in calculated blood loss may have impacted results.

Given the extent of osseous and soft tissue surgery and baseline patient factors such as poor nutrition and concomitant use of medications that inhibit coagulation, blood loss and transfusion requirements are relatively high in this patient population. This phenomenon has been noted in our clinical experience and corroborated by Tomak et al,[4] who reported the need for a blood transfusion in all patients undergoing bilateral femoral osteotomies. Other authors have found that the mean blood loss after bilateral VRO can range from 260 to 400 mL.[4,5] In this study, we report similar estimates of blood loss and over half of patients in each group required a blood

transfusion. Since these surgeries are commonly performed in children, these blood volumes comprise a greater percentage of total blood volume and have significant physiologic implications.

At the initiation of this study, there were no retrospective or prospective studies in the literature focusing on the use of antifibrinolytic agents in the setting of bilateral VROs. However, EACA was shown to be efficacious in reducing blood loss and transfusion requirements after other orthopaedic procedures in retrospective and prospective studies.[7–11,13,14] Three recent studies have shown that antifibrinolytic agents are not effective in reducing blood loss associated with pelvic and femoral osteotomy. McLawhorn et al[21] showed that aminocaproic acid did not reduce calculated blood loss or transfusion requirements after periacetabular osteotomy, and Majid et al[22] showed that tranexamic acid did not reduce blood loss or transfusion requirements in patients with CP that underwent hip reconstruction. In addition, Nazareth et al[23] performed a retrospective study on the efficacy and safety of tranexamic acid in patients with CP undergoing VDRO. The authors did not find any association with thromboembolic events, but they also did not find any difference in transfusion rates or blood loss as estimated by the surgeon and anesthesiologist. However, all of these studies were retrospective in nature and their findings are susceptible to several biases and confounding. Although these studies support our findings, the current study provides a greater level of evidence to guide clinical practice and recommendations.

There are several possible explanations for our findings. For instance, it is possible that drug efficacy and dosing may have affected our outcomes. Although tranexamic acid has been shown to be more potent in vitro,[24] EACA and tranexamic acid have been shown to be equally effective in pediatric patients.[7,8] Additional studies are needed to compare the efficacy of antifibrinolytic agents, specifically in children. In this study, we used EACA given its favorable safety profile. More specifically, tranexamic acid has been associated with postoperative seizures in pediatric patients, and this association has not been observed with the use of EACA.[25,26] Since patients with CP may have an underlying seizure disorder, we considered that it was safer to study EACA in a randomized manner. Similarly, we used a dosing strategy that has been reported in the literature and recommended by our anesthesia department. This study was not designed to determine the relationship between drug dosing and efficacy; therefore, additional studies are needed to determine optimal drug dosing.

Furthermore, differences in the coagulation response in pediatric patients may help to explain our findings. In particular, developmental hemostasis occurs in children and it is generally protective against bleeding and thrombosis.[27] These changes in the setting of long-bone surgery may offset the effect of antifibrinolytic agents. Similarly, patients undergoing bilateral VRO are younger than patients undergoing spinal deformity surgery or total joint arthroplasty, and their physiology likely differs from patients that are known to benefit from antifibrinolytic agents. Last, a bilateral VRO is inherently different from the other procedures studied in orthopaedic surgery. For example, the closure of the joint capsule in total joint arthroplasty allows for a tamponade effect which may be synergistic with the use of antifibrinolytic agents. Similarly, bony surfaces are usually covered with cement in total joint arthroplasty, which may further limit blood loss.[21] In bilateral VRO, there is a large potential space for blood loss as well as large areas of exposed bony surfaces from the osteotomies. This is particularly the case for VROs with a large correction, where the cut bone surfaces are not closely opposed, and for pelvic osteotomies where the osteotomy surfaces are intentionally displaced and remain separated.

This study is not without its limitations. Despite randomizing patients, there was more variation in the surgeries performed within groups and a high standard deviation in blood loss for each group resulting in an underpowered study. A resulting post hoc power analysis with the observed findings of our study (112 mL difference in mean blood loss with an approximate SD of 300 mL), determined that 167 patients would be needed in each arm to detect the difference found in this study. In addition, even though the rate of associated procedures was similar between groups, more additional osteotomies were performed in patients receiving EACA. However, additional osteotomies were not associated with increased calculated blood loss in the regression analysis. Similarly, the effect size selected in this study may be too large for this patient population, which contributed to this study being underpowered. Second, there was a small yet statistically significant difference in preoperative hematocrit between groups despite randomization. In the regression analysis, a higher preoperative hematocrit was associated with increased calculated blood loss, and it is possible that the higher blood loss observed in the placebo group was secondary to higher preoperative hematocrits in this group. Third, there was an unequal number of patients in each arm, which is an inherent limitation of the minimization strategy or stratified randomization since it aims to limit differences in each group. Finally, this study was powered to assess a difference in calculated intraoperative blood loss, and additional studies are needed to further determine the effect of EACA on transfusion requirements and other secondary outcomes.

In conclusion, this randomized, double-blind study found no difference in calculated intraoperative blood loss or transfusion requirements between EACA and placebo in patients undergoing bilateral VROs. However, further prospective studies with larger sample sizes are required to confirm our findings and to elucidate whether or not there is a role for EACA in minimizing blood loss and transfusion requirements in children undergoing VROs or other multilevel surgery.

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