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Epsilon Aminocaproic Acid to Reduce Blood Loss and Transfusion After Total Hip and Total Knee Arthroplasty

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ABSTRACT

Background: Total hip and knee arthroplasty (THA and TKA) are associated with significant blood loss and some patients require postoperative blood transfusion. While tranexamic acid has been studied extensively among this population, we tested the hypothesis that epsilon aminocaproic acid (EACA) can reduce blood loss and transfusion after joint arthroplasty.
Methods: In April 2014, our Veterans Affairs Medical Center introduced a protocol to administer EACA during THA and TKA. No antifibrinolytics were used previously. We retrospectively compared blood loss and incidence of transfusion among patients who underwent primary arthroplasty in the year before standardized administration of EACA with patients having the same procedures the following year. Blood loss was measured as delta hemoglobin (preoperative hemoglobin − hemoglobin on postoperative day 1). All patients undergoing primary THA or TKA were included. Patients having revision surgery were excluded.
Results: We identified 185 primary arthroplasty patients from the year before and 184 from the year after introducing the EACA protocol. There were no changes in surgical technique or attending surgeons during this period. Delta hemoglobin was significantly lower in the EACA group (2.7 ± 0.8 mg/dL) compared to the control group (3.4 ± 1.1 mg/dL) ($P < .0001$). The incidence of blood transfusion was also significantly lower in the EACA group (2.7%) compared to the control group (25.4%) ($P < .0001$). There was no difference in venous thromboembolic complications between groups.
Conclusion: We demonstrated reductions in hemoglobin loss and transfusion following introduction of the EACA protocol in patients undergoing primary arthroplasty. EACA offers a lower cost alternative to TXA for reducing blood loss and transfusion in this population.

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Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are associated with substantial blood loss, sometimes requiring postoperative transfusion [1,2]. There is a clear association between transfusion and several serious postoperative complications, most notably infection [3–7]. Additionally, transfusions are costly and expose the recipient to the possibility of transfusion-transmitted infection, transfusion-related lung injury, or more commonly in this population, transfusion-associated circulatory overload [8]. Several methods have been employed to decrease blood loss and transfusion rate after THA and TKA. These include optimization of preoperative hemoglobin, use of bipolar electrocautery, fibrin spray, use of tourniquet for TKA, and more restrictive transfusion criteria [9–13].

The most dramatic single change has come with the introduction of antifibrinolytic medications for THA and TKA. Antifibrinolytic drugs have been shown to decrease blood loss and improve outcomes in a number of settings, including cardiac surgery [14–18], trauma [19,20], spine surgery [21,22], liver transplant [23–25], obstetrics [26–28], subarachnoid hemorrhage [29–32], as

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well as orthopedics [1,33–38]. The most commonly used and reported drug in the orthopedic literature is tranexamic acid (TXA). This has been in use sporadically in orthopedics since the mid-1990s [33,34,36], but only became widely used in the United States over the past several years. Numerous reports have documented significant decreases in transfusion rates when using TXA both parenterally and topically within the surgical wound [37,38].

Epsilon aminocaproic acid (EACA) is also in the lysine analog class of antifibrinolytics and has been extensively and effectively used in cardiac surgery [14,15,17,18] with evidence that it is associated with fewer seizures [39]. TXA reduces the seizure threshold by binding to glycine and $GABA_A$ inhibitory neurotransmitter channels [40]. EACA has been studied much more sparsely in orthopedics than TXA, although the available evidence suggests efficacy and safety for this indication [35].

In order to reduce bleeding and transfusion among hip and knee arthroplasty patients at our local Veterans Affairs Medical Center (VAMC), we introduced an EACA protocol in 2014. We elected to use EACA rather than TXA due to the favorable side effect profile and lower cost. As a quality control evaluation of this process, we tested the hypothesis that, compared to historical controls, introduction of an EACA protocol reduced perioperative hemoglobin loss and incidence of blood transfusion without increasing the incidence of venous thromboembolism (VTE).

Materials and Methods

The EACA protocol was created by a committee of orthopedic surgeons, anesthesiologists, and transfusion medicine specialists, and the protocol adopted for this study is detailed below. Patients were screened as candidates to receive EACA during their preanesthesia assessment appointment, which is conducted within 30 days of surgery. Contraindications to EACA in this protocol included: (1) history of deep venous thrombosis (DVT), pulmonary embolus (PE), or other hypercoagulable state; (2) current atrial fibrillation or flutter; (3) coronary artery stents <2 years old; (4) medically managed coronary artery disease requiring sublingual nitroglycerin; (5) history of cerebrovascular accident; or (6) current use of oral contraceptives. If a patient had no contraindications to receive EACA, the drug was ordered for the day of surgery. The final decision to administer the drug was made by the attending anesthesiologist during the preoperative briefing immediately before surgery. The drug was given as 5 g intravenous over 20 minutes just before incision, and the same dose again during closure. In TKA cases, the second dose was typically given shortly before the tourniquet was released. For patients with impaired renal function (creatinine >2.0 mg/dL) only the first dose was given.

This study was approved by the local VAMC Institutional Review Board. Since it is a retrospective review of medical records, informed consent was waived. We retrospectively reviewed the electronic medical records and electronic anesthesia records of patients who underwent primary TKA or THA between April 1, 2014 and March 30, 2015. The control group included all patients who underwent primary TKA or THA in the year prior to starting the protocol, April 1, 2013 to March 30, 2014. Patients undergoing revision or bilateral arthroplasty were excluded. Outcomes included delta hemoglobin, incidence of blood transfusion, number of units transfused, and incidence of VTE. Delta hemoglobin was defined as the difference between preoperative hemoglobin and hemoglobin measured on postoperative day (POD) 1. All patients undergoing total joint arthroplasty had routine measurement of hemoglobin within 30 days preoperatively as well as on POD 1. Incidence of blood transfusion and number of units transfused were defined as any transfusion during the postoperative hospital stay and were determined from the blood bank report in the electronic medical record. VTE was defined as any new diagnosis of DVT or PE within 90 days of surgery.

The intraoperative anesthetic (general anesthesia vs regional anesthesia) during the study period was at the discretion of the attending anesthesiologist. No formal changes to postoperative blood management occurred during this time period. We did not have a formal transfusion trigger in place during either time period. In general, patients with ischemic risk factors, such as coronary artery disease or history of ischemic stroke, were transfused at higher hemoglobin levels. Otherwise, the decision to transfuse was made individually, and was based on vital signs, hemoglobin level, and symptoms.

Statistical Analysis

Descriptive summary statistics were computed, including the mean and standard deviation for continuous variables and the count and percentage for nonmissing categorical variables. Continuous variables were evaluated for normality using the Kolmogorov-Smirnov test and normality plots. Since major deviations from normality were not detected, the t-test was used to compare continuous variables between the 2 treatment groups (control and EACA), while categorical variables were compared using either the chi-square test or Fisher's exact test (expected cell counts <5).

The independent association of the 2 primary outcome variables (delta hemoglobin level from preop to POD 1 and incidence of blood transfusion) with administration or no administration of EACA was further investigated with univariable and multivariable regression models as appropriate for the underlying distribution of each dependent variable. Baseline predictors considered in each model were preoperative hemoglobin, age, gender (male or female), American Society of Anesthesiologists (ASA) status (1 or 2 vs 3 or 4), VTE prophylaxis use (ASA, enoxaparin, or other), surgery (TKA or THA), and side (left or right). Results are presented using the least square mean (LSM) difference or odds ratio (OR), as appropriate, with 95% confidence intervals (CIs).

The variables that demonstrated univariable associations with P value <.15 were considered in each multivariable model to investigate the independent effect of each predictor on hemoglobin change and blood transfusion. The variables that remained in each multivariable model were significant predictors at a P value <.05. Preoperative hemoglobin was forced into each univariable and multivariable model for change in hemoglobin regardless of its significance. Underlying assumptions of each multivariable regression model and model fit were assessed. Metrics examined for predictability and model fit were coefficient of determination (R^2), C-index, and P value from Hosmer-Lemeshow goodness-of-fit test, as appropriate to the dependent variable.

Descriptive comparisons were made using an analysis of covariance model adjusted for preoperative hemoglobin or Breslow's test for homogeneity of OR to further explore if an interaction between treatment group and VTE prophylaxis existed for each change in hemoglobin and transfusion incidence, respectively.

Statistical significance was set at P value <.05 (2-sided) for all tests unless otherwise specified. All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc, Cary, NC) by a statistician at our affiliated University Department of Biostatistics and Bioinformatics.

Results

Patient demographics are presented in Table 1. A total of 405 patients underwent elective primary THA and TKA from April 1, 2013 to March 30, 2015. The control group initially included 186