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# Antifibrinolytic Therapy and Perioperative Blood Loss in Cancer Patients Undergoing Major Orthopedic Surgery

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# *Antifibrinolytic Therapy and Perioperative Blood Loss in Cancer Patients Undergoing Major Orthopedic Surgery*

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***Background:*** **Aprotinin has been reported to reduce blood loss and transfusion requirements in patients having major orthopedic operations. Data on whether ϵ amino–caproic acid (EACA) is effective in this population are sparse.**

***Methods:*** **Sixty-nine adults with malignancy scheduled for either pelvic, extremity or spine surgery during general anesthesia entered this randomized, double-blind, placebo-controlled trial, and received either intravenous aprotinin (n = 23), bolus of $2 \times 10^6$ kallikrein inactivator units (KIU), followed by an infusion of $5 \times 10^5$ KIU/h, or EACA (n = 22), bolus of 150 mg/kg, followed by a 15 mg/kg/h infusion or saline placebo (n = 24) during surgery. Our goal was to determine whether prophylactic EACA or aprotinin therapy would reduce perioperative blood loss (intraoperative + first 48h) >30% when compared to placebo.**

***Results:*** **The mean age of the study population was 52 ± 17 yr. The groups did not differ in age, duration of surgery, perioperative blood loss or number of packed erythrocyte units transfused. When compared to the placebo group, the two treated groups had a significantly lower D-Dimer level immediately after surgery, $P < 0.01$.**

***Conclusions:*** **Under the conditions of this study, we were unable to find a clinical benefit to using aprotinin or EACA to reduce perioperative blood loss or transfusion requirements during major orthopedic surgery in cancer patients.**

MAJOR orthopedic surgery can be associated with substantial perioperative blood loss requiring transfusion of multiple units of blood. One of the contributing mechanisms to increased blood loss during orthopedic operations involves an imbalance of the coagulation and fibrinolytic systems in response to major bleeding, endothelial and bone trauma, and absorption of bone cement.[1] Transfused blood has been associated with immunomodulation and increased postoperative infection, transmission of infectious diseases, acute lung injury and increased costs.[2] Patients with cancer frequently present with various degrees of anemia secondary to chemotherapy, bleeding, or the malignancy itself, and are therefore more likely to require transfusion during surgery. As a group, they represent an immunocompromised population who suffer greater morbidity from postoperative infection. Several of the blood salvage techniques available to other surgical populations such as preoperative autologous blood donation or intraoperative cell salvage and retransfusion are controversial and often contraindicated in patients with malignancy or certain systemic diseases.[3]

The prophylactic administration of the antifibrinolytic agent aprotinin was shown to reduce perioperative blood loss in patients undergoing cardiac or major orthopedic surgery including that for tumor resection.[4–10] The ϵ-aminocaproic acid (EACA), an antifibrinolytic agent with potential advantages over aprotinin including substantially lower cost and no risk of anaphylaxis, has been shown to be as cost-effective as aprotinin in cardiac surgery but has not been studied in well-controlled trials of patients undergoing orthopedic surgery.[11] Thus, the primary objectives of the study were to compare the efficacy of EACA *versus* aprotinin or placebo to reduce perioperative blood loss and the number of units of packed red blood cells (PRBC) transfused during major orthopedic or spine surgery. We also examined whether the incidence of postoperative wound infection or deep venous thrombosis (DVT) was affected by the use of these agents.

## Methods

### *Study Population*

This study was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center and written informed consent was obtained from each patient before operation. Included were adult patients scheduled for any of the following operations to treat primary or metastatic musculoskeletal neoplasms: total hip replacement, long bone rodding, total knee replacement, sacrectomy, resection of tumor in bone, spinal fusion or posterior spinal fixation and stabilization. Excluded were patients who were <18 yr of age, and had a known or suspected allergy to either drug, previous exposure to aprotinin, preoperative renal insufficiency (creatinine level >1.3 mg/dl), preoperative hepatic insufficiency defined as an elevation >1.5 times normal of lactic acid dehydrogenase, or serum glutamic oxaloacetic transaminase, or serum glutamic pyruvate transaminase, history of thromboembolic disease, preoperative coagulopathy, coronary artery disease, cerebrovascular disease, congestive heart failure, or current pregnancy. Five patients were excluded from the study after ran-

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domization but before the study medication was given. These patients were not included in the intention-to-treat analysis since the exclusion criteria were identified before initiating the study.

*Anesthesia, Operation, and Perioperative Care*

Preoperative medications were continued until the time of surgery. During and after surgery all patients received DVT prophylaxis with compression/decompression boots. All patients received standard anesthetic management that consisted of isoflurane and nitrous oxide in oxygen supplemented by intravenous fentanyl and morphine as needed. During surgery, an attempt was made to maintain a mean arterial pressure between 60 and 70 mmHg using isoflurane and small (5 mg) incremental doses of intravenous boluses of labetalol if needed. Fluid warmers and heated body blankets were used to maintain the patient's temperature above 35.4°C. Patients were randomized to one of three experimental treatment arms: aprotinin, EACA, or placebo. Randomization of patients in blocks of 20 were done by the Biostatistics Department and the hospital pharmacy using sealed, opaque treatment-code envelopes. All patients and clinical and study personnel were blinded to the study group assignments throughout the trial. Intravenous preparations of the active drugs and placebo were prepared by the hospital pharmacy according to a computer-generated list that was kept confidential until formal unbinding by the biostatistician at the preselected analysis.

After anesthetic induction, patients randomized to aprotinin received a bolus of $2 \times 10^6$ kallikrein inactivator units (KIU) given over 30 min followed by an infusion of $5 \times 10^5$ KIU/h until the end of surgery. Patients randomized to EACA received 150 mg/kg EACA bolus in an equal volume given over 30 min, followed by an infusion of 15 $mg \cdot kg^{-1} \cdot h^{-1}$ until the end of surgery. Patients randomized to the placebo arm received an equal volume of normal saline bolus and infusion. Perioperative blood loss was estimated by suction losses and weighed sponges during surgery and by the volume of wound drainage for the next 48 h postoperatively. Serial hemoglobin and hematocrits were measured intraoperatively based on the extent of surgical bleeding and daily after surgery. The PRBC were administered if the hemoglobin was less than 8.0 g/dl or hematocrit was less than 24% with a goal to maintain the hematocrit at approximately 28%. Platelet concentrates were administered only when clinically significant bleeding was observed and platelet count was <100,000 per microliter. We used these trigger points based on our transfusion practice considering our patients often present for surgery after extensive antineoplastic and radiation therapy which may cause residual bone marrow suppression and platelet dysfunction. The number of PRBC units transfused was totaled through postoperative day 2. Determination of complete blood count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) was done during surgery if bleeding was extensive or there was evidence of a clinical coagulopathy, upon arrival of the patient to the postanesthesia care unit and on postoperative day 2. Postoperative pain relief was provided to all patients by continuous administration of intravenous opioid (usually morphine) patient-controlled analgesia. The patients were evaluated for the presence of wound infection and for proximal DVT by daily clinical exam and Doppler ultrasonography performed once between postoperative days 4 and 6. Major postoperative cardiac complications recorded were: unstable angina defined as recurrent or persistent ischemic cardiac pain at rest with electrocardiogram changes, myocardial infarction documented by new Q waves of at least 0.04 s duration and a minimum of 1 mm depth on 12-lead electrocardiograph or elevation of creatine kinase–myocardial band (CK-MB) or troponin I levels, and congestive heart failure defined as a clinical diagnosis based on the presence of rales, increased pulmonary capillary wedge pressure, or classic chest radiographic findings. Major postoperative pulmonary complications recorded were: pulmonary embolism diagnosed by spiral computed tomography and/or ventilation/perfusion lung scans when clinical parameters (pleuritic chest pain, hypoxemia, pulmonary rub) were present, pneumonia requiring antibiotic therapy or respiratory failure requiring mechanical ventilation. Other clinical end points recorded throughout the hospital stay were renal failure or insufficiency and death. Patients were monitored for similar complications as outpatients for 30 days.

*Statistical Analysis*

The calculation of sample size for this trial was based on retrospective data from our institution showing that similar consecutive patients (n = 50) had an average of 1.2 ± 0.9 l intraoperative blood loss. In order to detect at least a 30% difference (considered clinically important) in total (48 h) blood loss between the three arms with a power of 80% and a type 1 error of 5% and using a group sequential design with one interim analysis at mid-study, we estimated that a sample size of 105 patients per arm would be needed. However, due to a much slower accrual rate (25%) than anticipated and the inherent risk of administering these drugs to cancer patients at a greater risk for postoperative thromboembolic events, it was decided to perform an early interim analysis. Four different stochastic curtailment methods (three conditional power approaches[12–14] and one of predictive power[15]) were used with calculations using a FORTRAN program written by one of the authors (D.H.L.). In the method of stochastic curtailment current data are used to project the power for finding a significant difference between two treatment arms if the trial were to continue to completion. These methods showed

**Table 1. Patient Characteristics according to Treatment Group**

| Variable | Aprotinin (n = 23) | EACA (n = 22) | Placebo (n = 24) |
|---|---|---|---|
| Age, yr | 48 ± 17 | 53 ± 18 | 55 ± 16 |
| Gender (M/F), n | 13/10 | 11/11 | 13/11 |
| Weight, kg | 80 ± 24 | 76 ± 17 | 83 ± 20 |
| Operation type, n | | | |
| Spine | 7 | 7 | 3 |
| Hip | 5 | 8 | 11 |
| Other | 11 | 7 | 10 |
| Operative time, min | 291 ± 160 | 368 ± 203 | 284 ± 148 |
| Intraoperative fluids | | | |
| Crystalloid, l | 4.8 ± 2.7 | 5.0 ± 3.1 | 4.3 ± 2.1 |
| Colloid, l | 0.4 ± 0.6 | 0.3 ± 0.5 | 0.4 ± 0.6 |
| Controlled hypotension, n (%) | 10 (43) | 7 (32) | 9 (38) |
| Hospital stay, days | 9.8 ± 5.3 | 11.9 ± 7.3 | 9.0 ± 5.9 |

There were no significant differences among the groups.

EACA = ϵ-aminocaproic acid.

that even if we had accrued the planned 315 patients, the power to detect a significant treatment effect of aprotinin or EACA over placebo was extremely low.[16] Upon consultation with members of the Institutional Review Board it was decided to stop the trial. Other statistical analyses were performed with the software SPSS version 10.1 (SPSS, Chicago, IL). All analyses were performed on an intention-to-treat basis and all *P* values are two-tailed. A *P* value less than 0.05 was considered significant. Data that were not normally distributed (estimated blood loss, number of PRBC units transfused, D-Dimer levels) were log transformed before analysis. Univariate analysis consisted of Student *t* test, chi-square test or Fisher exact test. Repeated measures analysis of variance was done for testing differences in laboratory values among the study groups. Data are presented as mean value ± SD unless otherwise indicated.

## Results

Patient characteristics and type of operation are shown in table 1. The groups did not differ in age, duration of surgery, percent of patients in whom controlled hypotension was achieved throughout the operation or in duration of hospital stay. Estimated blood loss measured during surgery and in the first postoperative 48 h did not differ among the groups (table 2). Similarly, the number of PRBC units transfused during surgery or in the first 48 h after surgery did not differ among the groups (table 2). To evaluate the effect of controlled hypotension on bleeding, we compared total blood loss measurements between patients who did and did not achieve hypotension throughout the study infusion and found that none of the comparisons were significantly different within the three groups: placebo 1.6 ± 0.8 *versus* 1.6 ± 1.7 l, $P = 0.99$; aprotinin 1.6 ± 1.2 *versus* 1.8 ± 1.0 l, $P = 0.56$; EACA 1.7 ± 1.1 *versus* 1.5 ± 1.2 l, $P = 0.75$, respectively. The use of fresh frozen plasma or platelets was low and did not differ among the groups: two patients required both fresh frozen plasma (3–4 units) and platelets (6 units) and were assigned to placebo or EACA and two patients required only fresh frozen plasma (2–4 units) and were treated with aprotinin or EACA. The aPTT levels in the postanesthesia care unit

**Table 2. Perioperative Blood Loss and Erythrocyte Transfusion**

| | Aprotinin (n = 23) | EACA (n = 22) | Placebo (n = 24) |
|---|---|---|---|
| EBL, l | | | |
| Intraoperative | 1.0 (0.3, 2.0) | 0.9 (0.5, 1.6) | 0.9 (0.4, 1.4) |
| | 1.2 ± 1.0 | 1.3 ± 1.1 | 1.0 ± 0.9 |
| Total | 1.4 (0.9, 2.6) | 1.2 (0.6, 2.3) | 1.3 (0.6, 1.9) |
| | 1.7 ± 1.0 | 1.6 ± 1.1 | 1.6 ± 1.4 |
| Packed erythrocytes, number of units | | | |
| Intraoperative | 0 (0, 3) | 0 (0, 2) | 0.5 (0, 2) |
| | 1.1 ± 1.4 | 1.4 ± 2.2 | 1.3 ± 1.8 |
| Total | 0 (0, 3) | 1 (0, 2) | 1 (0, 2) |
| | 1.8 ± 1.5 | 1.7 ± 2.5 | 1.8 ± 2.5 |

Data are shown as median (25%, 75% quartiles) followed by mean ± SD. Total includes intraoperative and first 48 h after surgery. There were no significant differences among the groups.

EACA = ϵ-aminocaproic acid; EBL = estimated blood loss.

**Table 3. Perioperative Laboratory Values**

| | Aprotinin (n = 23) | EACA (n = 22) | Placebo (n = 24) |
|---|---|---|---|
| Hemoglobin, g/dl | | | |
| Preoperative | 13.2 ± 2.1 | 12.7 ± 2.2 | 12.6 ± 1.6 |
| PACU | 11.2 ± 1.3 | 10.4 ± 1.4 | 10.5 ± 1.3 |
| POD2 | 10.2 ± 1.4 | 10.5 ± 1.3 | 9.9 ± 1.3 |
| Hematocrit, % | | | |
| Preoperative | 37.9 ± 8.5 | 38.3 ± 5.6 | 37.8 ± 4.7 |
| PACU | 33.2 ± 3.7 | 31.4 ± 4.4 | 31.0 ± 3.7 |
| POD2 | 30.5 ± 4.3 | 31.8 ± 3.4 | 29.7 ± 4.0 |
| Platelet count, $\times 10^3$/dl | | | |
| Preoperative | 261 ± 75 | 279 ± 108 | 306 ± 134 |
| PACU | 220 ± 85 | 213 ± 86 | 262 ± 137 |
| POD2 | 201 ± 86 | 194 ± 85 | 244 ± 121 |
| Prothrombin time, s | | | |
| Preoperative | 11.9 ± 1.0 | 11.7 ± 0.9 | 12.1 ± 0.8 |
| PACU | 13.0 ± 1.5 | 13.2 ± 1.8 | 13.0 ± 1.0 |
| POD2 | 14.2 ± 5.1 | 12.4 ± 1.4 | 13.2 ± 1.1 |
| aPTT, s | | | |
| Preoperative | 29.1 ± 2.9 | 27.3 ± 3.2 | 29.1 ± 2.7 |
| PACU | 34.5 ± 8.2* | 26.5 ± 4.3 | 26.4 ± 2.2 |
| POD2 | 29.7 ± 7.6 | 26.6 ± 2.6 | 26.7 ± 2.1 |
| D-Dimer, ng/ml | | | |
| PACU | 1.0 ± 1.1 | 0.6 ± 0.5 | 2.6 ± 2.5† |

*$P < 0.01$, aprotinin *versus* ε-aminocaproic acid (EACA) or placebo groups. †$P < 0.01$, placebo *versus* EACA or aprotinin groups.
aPTT = activated partial thromboplastin time; POD2 = postoperative day 2.

were modestly greater for aprotinin *versus* EACA ($P < 0.01$) or placebo ($P < 0.01$) groups (table 3). Hemoglobin, hematocrit, platelet count, and PT measurements did not differ perioperatively among the groups (table 3). When compared to the placebo group, the two treated groups had a significantly lower D-Dimer level immediately after surgery, $P < 0.01$, respectively (table 3). A subgroup analysis for estimated blood loss and transfusion requirements omitting patients who had spine surgery showed no significant differences among the groups (table 4).

*Compliance with Treatment and Adverse Effects*

One patient developed acute intraoperative bronchospasm after receiving aprotinin for 30 min, which was possibly related to aprotinin administration and therefore discontinued. All other patients completed the study infusion protocol. DVT occurred in three patients who received EACA and three in the placebo group. Pulmonary embolism occurred in two patients randomized to aprotinin and in one patient in the placebo group. The overall incidence of postoperative DVT (9%) or pulmonary embolism (4%) did not differ among the groups, $P = 0.72$. Other postoperative complications included: one case of thrombocytopenia (placebo group), one case of respiratory failure in a patient who received 9 units of PRBC following a thoracic laminectomy for metastatic renal cell carcinoma (EACA group) and two cases of wound infection (EACA and placebo groups).

**Table 4. Perioperative Blood Loss and Erythrocyte Transfusion in Patients Undergoing Nonspine Surgery**

| | Aprotinin (n = 16) | EACA (n = 15) | Placebo (n = 21) |
|---|---|---|---|
| EBL, l | | | |
| Intraoperative | 1.0 (0.3, 2.0) | 0.9 (0.6, 1.2) | 0.7 (0.3, 1.1) |
| | 1.2 ± 1.0 | 1.1 ± 0.8 | 0.9 ± 0.9 |
| Total | 1.7 (0.7, 2.3) | 1.1 (0.6, 2.2) | 1.1 (0.6, 1.8) |
| | 1.7 ± 1.0 | 1.5 ± 1.0 | 1.5 ± 1.4 |
| Packed erythrocytes, number of units | | | |
| Intraoperative | 0 (0, 2) | 0 (0, 2) | 0 (0, 2) |
| | 0.8 ± 1.2 | 1.0 ± 1.6 | 1.1 ± 1.7 |
| Total | 1 (0, 2) | 1 (0, 2) | |
| | 1.1 ± 1.6 | 1.2 ± 1.8 | 1.6 ± 2.4 |

Data are shown as median (25%, 75% quartiles) followed by mean ± SD. Total includes intraoperative and first 48 h after surgery. There were no significant differences among the groups.
EACA = ε-aminocaproic acid; EBL = estimated blood loss.

## Discussion

Under the conditions of this study, neither aprotinin nor EACA reduced perioperative blood loss or red blood cell transfusion requirements when compared to placebo treated controls. Our study was terminated before full accrual of the projected sample size based on the results of an early interim analysis showing that intraoperative blood loss was nearly identical across all three arms and similar to that of a historical cohort on which the study sample-size power calculation was based. For the treatment to be clinically meaningful we hypothesized that there would need to be a reduction in estimated blood loss of at least 30% with either treatment in comparison to placebo. Our futility analysis indicated that unless the remaining patients to be enrolled into the treatment arms of this study had at least a 50% reduction in blood loss in comparison to the placebo group, we would not be able to show a benefit to using either drug in this patient population.[16] As this was very unlikely we decided to end the trial. Although not accruing the full sample size is a limitation of the study, we had a comparable or greater number of patients in each of the treatment arms as in other studies examining the use of antifibrinolytic agents in orthopedic surgery.[6–10] We acknowledge that there is some anatomic heterogeneity in our population but our patients were a physiologically homogenous group selected based on our historical review of similar cases at risk for major blood loss during resection. These patients had similar exposure to antineoplastic therapy and were treated by a focused group of surgeons. The results showing no differences in blood loss among the groups with all the patients included or with the spine patients removed further validate our decision to include these patients in the study.

Our study used general anesthesia, and moderate hypotensive technique throughout the operation was achieved in an average of 38% of our patients. A separate analysis of blood loss with or without controlled hypotension showed no differences among the groups. The antifibrinolytic effect of aprotinin or EACA was confirmed by significantly lower immediate postoperative D-Dimer levels when compared to placebo. Aprotinin treated patients had a statistically but not clinically significant increase in aPTT immediately after surgery. This rise in aPTT but not in PT is likely associated with aprotinin's known inhibition of kallikrein and the intrinsic coagulation system.[6,7] Although our study was not powered to detect differences in thromboembolic complications among the groups, the incidence of DVT seen in this study was lower than that reported in other patients with malignancy recovering from orthopedic surgery while that of pulmonary embolism was greater in our patients.[17] Possible explanations for the differences in side effects between the two studies may be that Lin *et al.*[17] excluded patients undergoing extensive spine surgery, had a larger sample size of patients and did not use antifibrinolytic agents.

Our results are in contrast to a prior study showing a benefit to using an identical dose regimen of aprotinin in combination with moderate hypotensive anesthesia (systolic blood pressure between 80 to 90 mmHg) to reduce blood loss and red blood cell transfusion in cancer patients undergoing major orthopedic surgery.[8] In that study of 23 patients, five of nine patients had malignancy and received aprotinin and 16 patients had infected hardware removed, of whom half were treated with aprotinin. Although the authors reported a 58% reduction in the overall transfusion rate with aprotinin, it is difficult to extrapolate their data to our population since most of the patients had infection and few had cancer.[8] Two other randomized, double-blind studies examined the effects of aprotinin in noncancer patients undergoing total hip replacement with general anesthesia.[6,7] Both studies did not use controlled hypotension and showed that aprotinin use was associated with similar and modest reductions in blood loss. Only one of the studies found that aprotinin reduced blood transfusion requirements slightly and recommended its use,[6] while the other investigators questioned whether the slight reduction in blood loss justified the routine use of an expensive drug.[7] More recent studies using aprotinin in major orthopedic surgery showed that a "large" but not "small" dose regimen of aprotinin as used in our study was associated with a significant reduction of homologous PRBC use.[9,10]

We chose to include a group of patients treated with EACA because it has been reported to have similar benefits on blood loss and transfusion requirements as aprotinin in patients undergoing cardiovascular surgery, with no reports of anaphylaxis and at a fraction of the cost.[11] To the best of our knowledge, this is the first study to compare EACA with placebo or aprotinin in a controlled double-blind study of patients undergoing orthopedic surgery. In contrast to aprotinin, which is a serine protease inhibitor that rapidly neutralizes plasmin, EACA acts as a competitive inhibitor of plasmin by blocking lysine sites on fibrinogen, fibrin and platelet receptors. Tranexamic acid, an antifibrinolytic agent that works similarly to EACA, has been used during orthopedic surgery and shown to have little or no benefit in reducing blood loss or homologous blood transfusion needs.[18–20] Taken together, the above mentioned studies and our data suggest that the benefit of antifibrinolytic agents to reduce perioperative transfusion requirements in orthopedic surgery is not clear and perhaps dose related.[6–10,18–20]

In conclusion, in this randomized, double-blind study of patients with malignancy undergoing major orthopedic surgery we were unable to show that the use of EACA or aprotinin is associated with a reduction of

perioperative blood loss or transfusion requirements when compared to placebo treated patients.

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