The effect of epsilon aminocaproic acid on blood loss in patients who undergo primary total hip replacement: a pilot study

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Objective: To determine if the use of an antifibrinolytic agent (epsilon aminocaproic acid [EACA]) decreased perioperative and postoperative blood loss in patients who underwent total hip arthroplasty (THA). **Design:** A prospective, double-blind, randomized, controlled clinical trial. **Setting:** A university-affiliated tertiary care hospital with a large joint arthroplasty population. **Participants:** Fifty-five patients who were scheduled for a primary THA. **Method:** Patients were randomly assigned to 2 groups to receive either EACA or saline placebo perioperatively. Preoperatively, the groups were similar with respect to gender, mean age, mean hemoglobin level, operative time and prosthesis type. **Outcome measures:** Blood loss from the start of surgery until the Hemovac drain was removed, and the transfusion rate and hemoglobin levels. **Results:** Mean (and standard error) total blood loss for patients receiving EACA was 867 (207) mL and for patients receiving placebo was 1198 (544) mL ($p < 0.025$). Four patients in the EACA group received 7 units of packed red blood cells and 7 patients in the saline group required 12 units. **Conclusions:** Patients receiving the placebo sustained greater total blood loss than EACA patients and were more likely to require blood transfusion. In the current climate of concern over blood transfusions during surgery, EACA administration can reduce blood loss and consequently transfusion and transfusion-related risk.

Objectif : Déterminer si l'utilisation d'un antifibrinolytique (acide epsilon amino-caproïque [AEAC]) a permis de réduire la perte sanguine périopératoire et postopératoire chez des patients ayant subi une arthroplastie totale de la hanche (ATH). **Conception :** Étude clinique contrôlée, randomisée et prospective à double insu. **Contexte :** Hôpital de soins tertiaires affilié à une université, où sont effectuées un grand nombre d'arthroplasties d'une articulation. **Participants :** Cinquante-cinq patients chez lesquels on devait pratiquer une ATH de première intention. **Méthode :** Les patients ont été répartis au hasard en deux groupes, pour recevoir de l'AEAC ou un placebo de solution saline en période périopératoire. Avant l'intervention, les deux groupes étaient semblables quant au sexe, à l'âge moyen, au taux moyen d'hémoglobine, à la durée opératoire et au type de prothèse. **Mesures de résultats :** La perte sanguine entre le début de l'intervention et le moment où le drain Hemovac a été enlevé, le taux de transfusion et les taux d'hémoglobine. **Résultats :** La moyenne (et l'erreur type) de la perte sanguine totale s'établissait à 867 (207) ml chez les patients ayant reçu de l'AEAC et à 1198 (544) ml chez les patients ayant reçu le placebo ($p < 0{,}025$). On a administré 7 unités de concentré de globules rouges à 4 patients du groupe de traitement par AEAC, et 12 unités à 7 patients du groupe placebo. **Conclusions :** Comparativement aux patients ayant reçu de l'AEAC, les patients du groupe placebo ont subi une perte sanguine totale plus importante et étaient plus susceptibles d'avoir besoin d'une transfusion sanguine. Dans le contexte actuel des préoccupations que soulèvent les transfusions sanguines au cours des chirurgies, l'administration d'AEAC peut réduire la perte de sang et par conséquent les transfusions et les risques qui s'y rattachent.

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Total hip arthroplasty (THA) may be associated with marked blood loss. Because of the risks of homologous blood transfusions, which have been well publicized,[1] surgeons are enlisting the use of various blood-conserving techniques to reduce patient requirements for homologous blood. Autologous predonation programs have become a common method of blood replacement in recent years. Pharmacologic therapies that boost hemoglobin levels preoperatively have also been shown to reduce transfusion requirements.[2] Normovolemic hemodilution and hypotensive anesthetic techniques reduce intraoperative blood loss, but they are not preferred techniques for elective THA.[3] Although all of these techniques can reduce the requirement for homologous blood transfusion, they do not eliminate the need for homologous blood.

Perhaps the greatest change in homologous blood transfusion therapy has occurred because of modification to the routine practice of transfusion for hemoglobin values less than 100 g/L.[4–6] As medical experience with hemoglobin levels in the 80 g/L to 90 g/L range increases, the indications for homologous blood transfusion continue to evolve.[7]

Administration of pharmacologic agents to decrease surgical blood loss has been well described. The use of epsilon aminocaproic acid (EACA) as a therapeutic agent was first described in 1960.[8] EACA inhibits fibrinolysis as a result of its reversible complex formation with the lysine-binding sites of plasminogen and the active protease plasmin. It therefore acts by preventing the premature dissolution of the normal fibrin clot. The use of EACA for the prevention of surgical blood loss has been well established in the field of cardiothoracic surgery,[8,9] and it has also been found to reduce bleeding associated with neurosurgical and urologic procedures.[8]

The experience with antifibrinolytic agents in orthopedic surgery is limited. A small number of clinical trials have investigated the administration of the synthetic antifibrinolytic tranexamic acid in total knee arthroplasty, and 3 studies examined the use of the natural antifibrinolytic aprotinin in THA.[10–15] All of these studies documented reductions in blood loss and decreased blood transfusion requirements. Importantly, the safety of antifibrinolytic agents was clearly demonstrated in these clinical studies. These studies, as well as the cardiothoracic surgery literature, have consistently shown no increased risk of venous thromboembolism as a result of their administration. We know of no study that has examined the effectiveness of EACA in hip or knee replacement surgery.

The primary objective of this study was to determine if the use of EACA reduced blood loss in patients who underwent primary THA. The secondary objectives were to compare hemoglobin levels in patients who received EACA to those who received a placebo, to compare the coagulation profiles in these 2 groups, and to determine if the use of EACA reduced the number of transfusions required. We hypothesized that administration of EACA preoperatively and intraoperatively would reduce blood loss in these patients and thus help to reduce exposure to homologous blood products. Using dosages drawn from the experience in cardiac surgery, we undertook a randomized study of EACA in primary THA.

Patients and methods

This prospective randomized clinical trial comprised patients presenting for primary THA at a major teaching hospital between February 1998 and September 1999. All patients scheduled to undergo a primary THA by 1 of 4 experienced surgeons were eligible for the study. Exclusion criteria included a known allergy to EACA, a history of renal or hepatic failure, coagulopathy, uncontrolled hypertension, symptomatic cardiac or pulmonary failure, or known upper urinary tract bleeding. Ethical approval was received from the regional internal ethics review committee.

Fifty-five patients were enrolled into the study and provided informed written consent. Patients were randomly assigned to receive either EACA or saline placebo administered from uniformly blinded bottles. Patients, anesthesiologists, surgeons and clinical evaluators were blinded to the patient allocation. The anesthetic technique applied was at the discretion of the anesthesiologist and patient. All arthroplasties were performed through a Hardinge lateral approach. The use of cemented or press-fit technique for the femoral component was based on the surgeon's preference. All patients received a press-fit acetabular component. A volumetric drain was placed deep into the wound through a separate skin site in all patients.

Perioperative protocol

An EACA loading dose of 150 mg/kg, or the equivalent dose of placebo, was administered as a bolus load over 20 minutes on the patient's arrival in the operating room. An hourly EACA infusion of 12.5 mg/kg, or equivalent placebo, was subsequently administered for an additional 5 hours. Crystalloid was administered at a maintenance rate at the start of each procedure and was also used in a 3:1 ratio to match ongoing blood loss. Colloid preparations or homologous blood products were not used unless clinical evidence of excessive bleeding was supported by laboratory documentation. Measurement of suction losses and weight of sponges were used to assess intraoperative blood loss. Blood samples were drawn when blood loss exceeded 500 mL and every 45 minutes thereafter. If the hematocrit decreased to 0.24 or lower, intraoperative packed red blood cell were transfused in addition to crystalloid to maintain a hematocrit of 0.24 or

more. In the recovery room, a complete blood count and a coagulation profile, including international normalized ratio (INR), partial thromboplastin time (PTT) and D-dimers, were obtained.

Postoperative blood loss was measured from the drain output, with drain removal occurring when drainage was less than 30 mL over an 8-hour period. Drain removal typically occurred on postoperative day 2. Hemoglobin concentrations and hematocrits were measured at the following intervals postoperatively: 5 hours, 24 hours, 3 days and 7 days or prior to discharge. Packed red blood cells were transfused according to standardized guidelines that exist for orthopedic patients at the study institution. These guidelines consist of the following: a hemoglobin level less than 80 g/L or a hematocrit less than 0.24; patients having symptoms from their anemia (including tachycardia, dyspnea, chest pain or recurrent syncope); or medical conditions that render the patient unable to compensate for diminished oxygen-carrying capacity.

The THA clinical pathway currently in use at the study institution directed all routine postoperative care. Standard postoperative anticoagulation consisted of 5000 units of heparin administered subcutaneously every 12 hours until the INR became greater than 2.0 with daily coumadin administration. Heparin was then discontinued and patients were continued on coumadin for 6 weeks postoperatively. Patients were assessed for deep venous thrombosis and pulmonary embolism while in hospital through daily clinical examination. Any suspicious symptoms or signs were investigated further with Doppler ultrasonography or ventilation–perfusion scans. All patients received physiotherapy postoperatively and were mobilized as tolerated according to clinical pathway guidelines.

Descriptive statistics and univariate analyses were performed on all variables. χ^2 tests were used to identify any systematic differences between categorical variables. Nonparametric tests (Mann–Whitney U test) were used for categorical variables that were not normally distributed. Student's *t*-tests and analysis of variance were used to identify systematic differences between continuous variables that were normally distributed. Statistical analyses were performed using the SPSS software version 7.5. All statistical analyses were performed with 2-tailed tests and at a 0.05 level of significance.

The sample size calculations of this pilot study were based on postoperative blood loss of 800 mL ± 300 mL, 2-tailed distribution with a 0.05 level of significance and a power of 80%.[13,14,16–18] A 2-tailed test was used because we were indifferent to the direction of the difference between the means for EACA and placebo groups. Moreover, the use of a 2-tailed test was more stringent than a 1-tailed test and would reduce the likelihood of a type I error. The sample size required to detect a clinically important difference of 250 mL was 50 patients. Anticipating a 10% attrition rate, we recruited 55 patients.

Results

No significant differences were detected in demographics between the EACA and placebo groups in any category except for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 1). A significantly greater number of patients in the EACA group were using NSAIDs preoperatively than in the placebo group (21 v. 15 patients, respectively, $p = 0.02$).

Although 55 patients were enrolled, 4 patients in the EACA group and 5 patients in the placebo group were excluded postoperatively due to breaches in the anesthetic protocol or operating room instructions: use of a cell-saver system (2 patients), colloid use (2 patients), incorrect administration of the drug bolus (2 patients), errors in measurement of intraoperative blood loss (2 patients) and packed red blood cell transfusion for an incorrectly reported postoperative hemoglobin level (1 patient).

Randomization resulted in an equal distribution of hybrid and cementless implants, as well as regional and general anesthesia techniques

Table 1

Demographics and Surgical Characteristics of 55 Patients Who Underwent Total Hip Arthroplasty With or Without Epsilon-Aminocaproic Acid (EACA)

	EACA (*n* = 26)	Placebo (*n* = 29)	*p* value
Demographics			
Mean (and SD) age, yr	69 (11)	69 (10)	0.28
Gender, male:female	10:16	11:18	0.99
Diagnosis, no. (and %) of patients			0.22
Primary osteoarthritis	24 (92)	29 (100)	
Secondary osteoarthritis	1 (4)	0	
Rheumatoid arthritis	1 (4)	0	
Mean (and SD) body mass index, kg/m^2	27.6 (5.7)	30.1 (5.1)	0.12
NSAID use, no. (and %) of patients	21 (81)	15 (52)	0.02
Surgical characteristics			
Implant fixation, no. (and %) of patients			0.53
Hybrid	11 (42)	11 (38)	
Cementless	15 (58)	18 (62)	
Mean (and SD) operation time, min	77 (17)	80 (20)	0.17
Type of anesthetic, no. (and %) of patients			0.83
Spinal	15 (58)	13 (45)	
General	10 (38)	14 (48)	
Both (general and spinal)	1 (4)	2 (7)	

NSAID = nonsteroidal anti-inflammatory drug.

between the groups. No significant difference in blood loss was attributable to the implant type or anesthesia technique in both treatment and control groups ($p > 0.05$). When the effect of the surgeon on blood loss and operative time was examined across the 2 groups, no differences were seen ($p > 0.05$). Thus, the 2 groups were homogeneous and not stratified according to these factors.

The mean postoperative blood loss in patients receiving EACA was significantly less than in patients receiving saline ($p < 0.003$), as was the mean overall blood loss ($p < 0.025$) (Table 2). The intraoperative blood loss was not significantly different between the 2 groups ($p = 0.58$).

In the EACA group, 4 (18%) of the 22 patients received 7 units of packed red blood cells, whereas 7 (29%) of the 24 patients in the placebo group required 12 units of packed red blood cells ($p = 0.40$). The increased transfusion rate in the placebo group was required to maintain a hemoglobin concentration similar to the that in the EACA group throughout the perioperative and postoperative course (Fig. 1).

EACA administration had no demonstrable effect on the intrinsic or extrinsic coagulation pathways in the perioperative period, but fibrinolysis was reduced. No differences could be detected in recovery room INRs ($p = 0.96$) or PTTs ($p = 0.47$), whereas analysis of D-dimers from samples drawn in the recovery room showed a significant difference between the 2 groups ($p < 0.001$) (Table 3). The administration of EACA did not alter the course of postoperative anticoagulation. Similar INRs were documented in the 2 groups from recovery room through to discharge (Fig. 2).

Few drug-related side effects were observed in this study. One patient in the EACA group reported a rash postoperatively, which resolved after diphenhydramine was administered. No patients required investigation for deep venous thrombosis or pulmonary embolism postoperatively as a result of clinical examination.

Discussion

The administration of EACA during primary THA resulted in a 27% reduction in the mean total blood loss. This rate is similar to published results of tranexamic acid used in knee arthroplasty and aprotinin used in THA.[10–15] The most notable effect occurred in the postoperative period: total blood loss for patients receiving EACA was, on average, 331 mL less than for patients receiving the saline placebo.

In contrast to the results of studies by Janssens and associates[13] and Murkin and colleagues[14,15] on the use of aprotinin in primary THA and revision THA, we did not find a significant difference in intraoperative blood loss. However, the mean operative

Table 2

Details of Mean (and SD) Blood Loss (mL) in 46 Patients Who Underwent Total Hip Arthroplasty With or Without Epsilon-Aminocaproic Acid (EACA)

Blood loss	EACA ($n = 22$)	Placebo ($n = 24$)	p value
Intraoperative	552 (331)	607 (331)	0.580
Postoperative	315 (207)	591 (374)	0.003
Total	867 (207)	1198 (544)	0.025

Table 3

Recovery Room D-Dimers in 49 Patients* Who Underwent Total Hip Arthroplasty With or Without Epsilon-Aminocaproic Acid (EACA)†

D-dimers	EACA ($n = 24$)	Placebo ($n = 25$)
< 0.5	18 (75)	3 (12)
> 0.5	6 (25)	22 (88)

*6 patients did not undergo D-dimer testing.
†$p < 0.001$. Bracketed numbers are percentages.

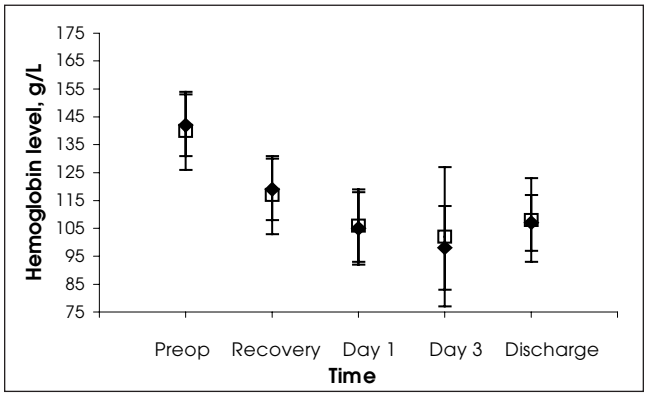

FIG. 1. Time course of mean (and standard error) hemoglobin levels in patients who underwent total hip arthroplasty with or without the administration of epsilon aminocaproic acid (EACA). Squares = EACA group, diamonds = placebo saline group, Preop = the day before surgery, Recovery = recovery room, Day 1 and Day 3 = postoperative days 1 and 3 respectively.

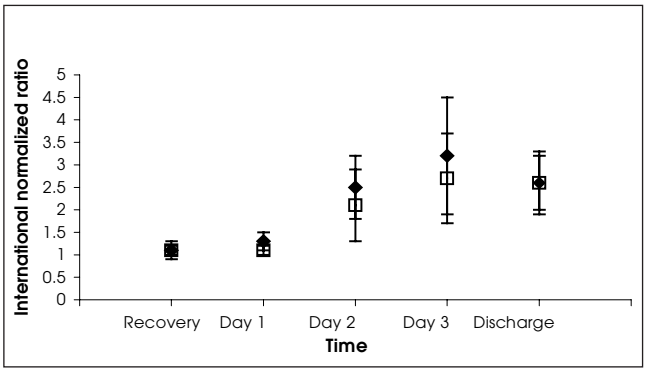

FIG. 2. Time course of mean (and standard error) international normalized ratios in patients who underwent total hip arthroplasty with or without the administration of epsilon aminocaproic acid (EACA). Squares = EACA group, diamonds = placebo saline group, Preop = the day before surgery, Recovery = recovery room, Day 1, Day 2 and Day 3 = postoperative days 1, 2 and 3 respectively.

time in this trial was less than half the losses reported in their series. It may be that the reduction in blood loss attributable to aprotinin in those studies was a result of the antifibrinolytic effect over a more prolonged operative course. This presumption is supported by the findings of Benoni and associates[19] who demonstrated that administration of tranexamic acid (an antifibrinolytic of mid-potency) during total knee arthroplasty reduced blood loss only in the postoperative setting. We found that D-dimer measurements from peripheral venous blood samples in the recovery room were generally within normal limits in the EACA group, whereas they were significantly more elevated in the placebo group. This postoperative inhibition of fibrinolysis in patients administered EACA likely accounts for the reduced blood loss in the recovery room and postoperative period.

Patients receiving placebo were more likely to require blood transfusions than the patients administered EACA. The 27% reduction in mean blood loss and the 11% reduction in blood transfusion rates in our study are similar to the rates reported in a recent study of aprotinin in a primary THA by Murkin and colleagues[14] (24% and 16% respectively). The reduction in transfusion rate was not significant, however, because of the overall low transfusion rates and the relatively small size of the treatment and placebo groups. Further study likely should be limited to a population with an overall higher rate of transfusion (e.g., those with a preoperative hemoglobin level < 135 g/L), so that a manageable sample size could be obtained in a relatively short period of time. Whether our finding of a reduction in transfusion requirements is clinically significant may be a separate and important question.

No patient in this study had clinical symptoms of deep venous thrombosis postoperatively. Routine screening for deep venous thrombosis was not performed for 2 reasons. First, antifibrinolytic agents are used routinely in cardiac surgery, and previous studies in both orthopedic and nonorthopedic populations have failed to show any increased thrombogenic potential from these agents.[8–13,19–21] In fact, a study on the use of aprotinin in hip arthroplasty noted a decreased rate of deep venous thrombosis with routine screening.[15] Second, a considerably larger sample size than that used in our study would have been required to define a significant difference in deep venous thrombosis rate. Although no increase in venous thromboembolic events was noted, we recognize that clinical examination is an unreliable measure for deep venous thrombosis, and therefore we cannot accurately comment on the rate of this condition between the 2 groups.

Analysis of possible confounding variables between the groups revealed that the randomization process was very effective. Operative time, surgeon factors and anesthetic technique were equally distributed and were found not to be responsible for any of the observed differences in blood loss. Similar numbers of hybrid and cementless arthroplasties were performed in each group, and no differences in blood loss or transfusion requirements could be attributed to the choice of technique, which is consistent with the results reported by Trice and colleagues.[22] All patients were instructed to discontinue NSAIDs 5 days before surgery; however, patients were not surveyed to ensure compliance. Benoni and Fredin[10] found that compliance of patients instructed to discontinue NSAIDs before total knee replacement was moderate. Given the uneven distribution of NSAIDs used in this trial, a larger number of patients in the EACA group may have failed to discontinue their medication before surgery. Any increase in blood loss due to impaired platelet function as a result of continued NSAID use would therefore underestimate the effectiveness of EACA.

A clinical limitation of this study concerns the measurement of intraoperative and postoperative blood loss. Assessment of intraoperative sponge weight and suction loss fails to take into account blood loss on the drapes, gowns or instruments. Likewise, postoperative assessment of only drain quantity fails to account for blood loss on the dressings or any hematoma present beneath the incision. The parameters assessed in this study provide a quantitative measure that is the most reliable one possible in this setting. These measures represent the accepted standards for blood loss evaluation in the literature.[10–15] As all personnel who performed the measurements were blinded to the patient's study status, measurement errors would be expected to be similar in both groups.

Transfusion of homologous blood has traditionally been used to replace the blood loss associated with primary THA. The use of homologous blood is associated with a significant risk of viral and bacterial infection, however, and costs a minimum of Can$700 per unit.[1,23,24] Development of techniques to reduce the requirement for homologous blood during THA is therefore important for both financial and medical reasons.

The search for a cost-effective pharmacologic intervention that reduces requirements for homologous blood transfusion in primary total joint replacement is ongoing. Blood conservation strategies including autologous predonation (PAD) programs, red blood cell salvage, erythropoietin and potent antifibrinolytic agents have been proven to reduce rates of homologous blood transfusion, but they are all associated with a high financial cost.[15,25–28] Accurate cost–benefit analysis is beyond the scope of this study, but none of these techniques have been proven to be so cost-effective as to become standard medical practice. The cost of the preparation and administration of EACA as described in this study is Can$80 per patient, so this agent represents one of the most cost-effective modalities currently un-

der investigation. EACA administration did not, however, completely eliminate the need for homologous blood transfusion, and like other blood-conservation strategies, it does not represent a perfect solution.

In the current climate of concern about homologous blood transfusions during surgery, any technique or therapy that reduces the likelihood of even a single unit transfusion can significantly reduce transfusion-related risk.[4,5,17,23,24] The routine administration of EACA in patients who undergo THA results in a significant reduction in blood loss and a trend to a decreased requirement for packed red blood cell transfusion. Furthermore, no evidence exists in this study or in the literature that would suggest that the administration of EACA can cause increased morbidity in patients who undergo THA. We believe that with further study, the routine use of an antifibrinolytic agent like EACA may prove beneficial in primary THA.

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