Epsilon-Aminocaproic Acid Has No Association With Thromboembolic Complications, Renal Failure, or Mortality after Liver Transplantation

Ramona Nicolau-Raducu, MD, PhD,* Timothy C. Ku, MD,† Donald R. Ganier, MD,* Brian M. Evans, MD,* Joseph Koveleskie, MD,* William J. Daly Jr, MD,* Brian Fish, MD,* Ari J. Cohen, MD, MSc, FRCSC, FACS,‡ Trevor W. Reichman, MD, PhD,‡ Humberto E. Bohorquez, MD, FACS,‡ David S. Bruce, MD,‡ Ian C. Carmody, MD,‡ George E. Loss, MD, FACS, PhD,‡ Marina Gitman, MD,§ Thomas Marshall, MD,* and Bobby D. Nossaman, MD*

Objectives: **To examine the role of epsilon-aminocaproic acid (EACA) administered after reperfusion of the donor liver in the incidences of thromboembolic events and acute kidney injury within 30 days after orthotopic liver transplantation. One-year survival rates between the EACA-treated and EACA-nontreated groups also were examined.**

Design: **Retrospective, observational, cohort study design.**

Setting: **Single-center, university hospital.**

Participants: **The study included 708 adult liver transplantations performed from 2008 to 2013.**

Interventions: **None.**

Measurements and Main Results: **EACA administration was not associated with incidences of intracardiac thrombosis/pulmonary embolism (1.3%) or intraoperative death (0.6%). Logistic regression (n = 708) revealed 2 independent risk factors associated with myocardial ischemia (age and pre-transplant vasopressor use) and 8 risk factors associated with the need for post-transplant dialysis (age, female sex, redo orthotopic liver transplantation, preoperative sodium level, pre-transplant acute kidney injury or dialysis, platelet transfusion, and re-exploration within the first week after transplant); EACA was not identified as a risk factor for either outcome. One-year survival rates were similar between groups: 92% in EACA-treated group versus 93% in the EACA-nontreated group.**

Conclusions: **The antifibrinolytic, EACA, was not associated with an increased incidence of thromboembolic complications or postoperative acute kidney injury, and it did not alter 1-year survival after liver transplantation.**

KEY WORDS: epsilon-aminocaproic acid, antifibrinolytics, thromboembolic complications, acute kidney injury, intracardiac thrombosis/pulmonary embolism, liver transplantation

FIBRINOLYSIS AND ITS role in coagulopathy in patients undergoing orthotopic liver transplantation (OLT) have been reported for decades.[1-3] A meta-analysis by Molenaar et al reported decreases in surgical blood loss and transfusion requirements without an associated increased risk of thromboembolic events during OLT when prophylactic antifibrinolytics were used.[4] However, case reports of thromboembolic risks associated with antifibrinolytics cautioned against acceptance of this class of agents during OLT.[5,6] Excessive activation of coagulation secondary to the dissection, massive bleeding, venous stasis secondary to clamping of the cava and portal vein, and the use of veno-venous bypass have been shown to be the leading factors associated with increased risk for thromboembolic complications during OLT.[4]

Past OLT studies have focused on the use of aprotinin,[4] now removed from the US market because of increased incidences of renal failure or mortality in patients undergoing cardiac surgery.[7-9] Subsequently, only 2 synthetic lysine derivative antifibrinolytics now are available in the United States: epsilon-aminocaproic acid (EACA) (Amicar; Akorn, Marietta, GA) and tranexamic acid. Considering the substantial cost difference and the comparable efficacy and safety reported in non-OLT studies, EACA is used widely in liver transplant programs in the United States.[4] However, the safety of EACA in OLT is not well-studied.

The purpose of this study was to investigate the effect of EACA administered during the neo-hepatic phase of OLT on the incidences of thromboembolic events, acute postoperative renal failure within 30 days after OLT, and 1-year survival rates.

METHODS

After institutional review board approval, data from 708 adult OLT performed from 2008 to 2013 were abstracted. Endpoints of the study were risks associated with EACA administration during the neo-hepatic phase of OLT. All patients, including patients with antecedents of thrombotic events/thrombophilia, were included. All recipients received deep venous thrombosis (DVT) prophylaxis with both mechanical compression stockings and 5,000 U of subcutaneous heparin every 8 hours once platelet counts were $>70 \times 10^3/\mu L$. Combined organ transplants were excluded. The standard surgical technique was OLT with caval replacement, with the exception of 9 piggy-back cases. None of the cases included veno-venous bypass. All patients received a tacrolimus-based immunosuppressant protocol. Of the 708 transplants, 702 liver grafts originated from deceased donors (626 brain dead and 76 donations after cardiac death), and 6 liver grafts (right lobe graft) were from living donors. The quality of donor organs was assessed using the donor risk index: demographic characteristics (age, race, and height), causes of death (cerebral vascular accident, trauma, anoxia, other), type of death (donations after cardiac death), split/partial graft, cold ischemia time, and donor location (local, regional, national).[10]

*From the *Department of Anesthesiology, Ochsner Clinic Foundation, New Orleans, LA, †Department of Anesthesiology, Tulane Medical Center, New Orleans, LA, ‡Department of Surgery/Transplantation, Ochsner Clinic Foundation, New Orleans, LA; and §Department of Anesthesiology, University of Illinois at Chicago, Chicago, IL.*

Address reprint requests to Ramona Nicolau-Raducu, MD, PhD, Department of Anesthesiology, Ochsner Medical Center, 1514 Jefferson Highway, New Orleans, LA 70121. E-mail: rnicolauraducu@ochsner.org

1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2015.12.003

This study analyzed the role of EACA administration on the incidences of thromboembolic complications, renal failure within the first month after transplant, and 1-year survival rates. The decision to administer EACA during the neo-hepatic phase was based on the presence of fibrinolysis, analyzed using thromboelastography (TEG; Haemonetics, Braintree, MA) at 5 and/or 30 minutes after reperfusion and on clinical observation of the surgical field by the surgeons. Presence of fibrinolysis using TEG analysis was defined as $\geq 8\%$ reduction in the post-maximum amplitude signals up to 30 minutes from the start of the test.[11] Bolus intravenous (IV) dosing and/or continuous infusion of EACA were based on clinical conditions. Continuous infusion of EACA (total of 5 g) was discontinued either in the operating room or intensive care unit. Since 2012, thromboprophylaxis has been initiated routinely with IV heparin (average dose of 2000 U) administered before caval cross-clamping in 39% (275/708) of patients (Fig 1). Protamine, average of 57 ± 30 mg IV, was administered after hepatic artery reperfusion in 54% (381/708) of the patients. A heparin effect was documented with paired TEG tracings (kaolin *v* heparinase), with a correction of more than 30% to 50% of the r+k time interval after addition of heparinase[12,13] or activated partial thromboplastin time >50 seconds (reference range: 21.0-32.0 seconds).

Intraoperative blood product administrations were recorded from the induction of general anesthesia until transport to the intensive care unit. Transfusion targets with packed red blood cells (pRBC) and cell-saver and blood products (fresh frozen plasma [FFP], platelets [PLTS], or cryoprecipitate [CRYO]) were based on the amount of bleeding, hourly TEG analysis, and laboratory results. In surgical situations with massive bleeding, an optimal FFP:pRBC ratio of at least 1:2 was used. Control of surgical and medical bleeding at the end of surgery was required with target hematocrit values of 28% to 30% (reference range: 37.0%-48.5%), hemoglobin values of 8 to 9 g/dL (reference range: 12.0-16.0 g/dL), platelet values $>50{,}000$ K/uL (reference range:150-350 K/uL), international normalized ratio <2 (reference range: 0.8-1.2), fibrinogen >180 mg (reference range:182-366 mg/dL), and/or TEG values within normal limits (r time 4-9 min; k time 1-3 min; alpha angle 59-74 degrees; maximum amplitude 55-74 mm).

Acute kidney injury (AKI), both before transplant (pre-TX) and/or after transplant (post-TX) was defined as an increase in serum creatinine (sCr) of ≥ 0.3 mg/dL over 48 hours or an increase in sCr ≥ 1.5 times the baseline sCr value within 7 days before or after OLT.[14] Pre-TX and post-TX renal replacement therapy (RRT) were defined as any form of renal dialysis before and within 1 month after OLT, respectively.

The following thromboembolic complications within 1 month of transplantation were recorded: myocardial ischemia (MI), defined as an increase in cardiac biomarkers in the presence of electrocardiographic changes suggesting ischemia

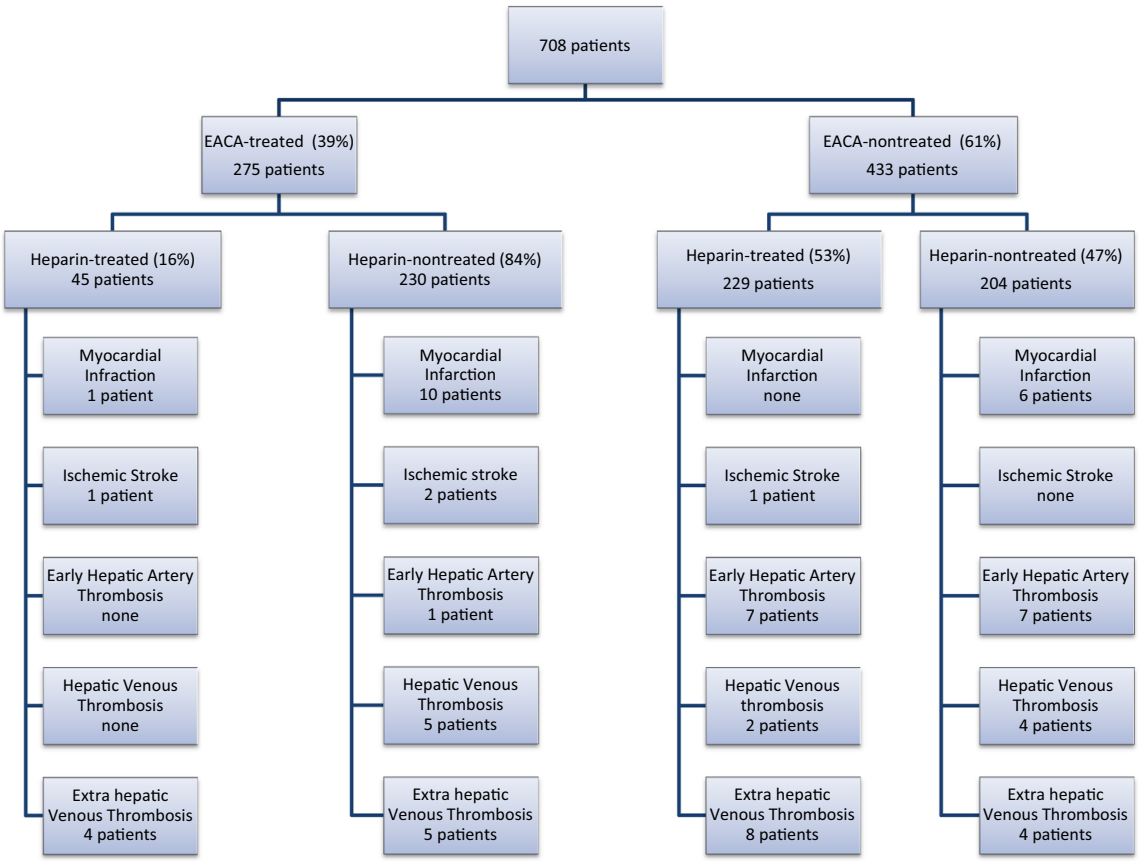

Fig 1. The incidence of thrombotic events with or without epsilon-aminocaproic acid (EACA) and with or without heparin.