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Aminocaproic acid for the management of bleeding in patients on extracorporeal membrane oxygenation: Four adult case reports and a review of the literature

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ABSTRACT

Background: Extracorporeal membrane oxygenation (ECMO) is associated with a significant risk of bleeding and thrombosis. Despite high rates of bleeding and bleeding-related mortality in patients on ECMO, there is little evidence available to guide clinicians in the management of ECMO-associated bleeding.
Methods: We report the use of aminocaproic acid in four patients with bleeding on ECMO and a review of the literature.
Results: High D-dimer levels and low fibrinogen levels suggested that an antifibrinolytic agent may be effective as an adjunct to control bleeding. After aminocaproic acid administration, bleeding was controlled in each patient as evidenced by clinical and laboratory parameters. One patient suffered a cardiac arrest and care was withdrawn.
Conclusions: In patients on ECMO with evidence of fibrinolysis, aminocaproic acid may be an effective option to control bleeding and to stabilize clot formation.

Introduction

The extracorporeal membrane oxygenation (ECMO) device was developed as a long-term mechanical support device based on the design of the cardiopulmonary bypass (CPB) circuit.[1] Due to mortality rates between 40% and 56%, the indication for ECMO is limited to a temporary, last-line measure for patients with reversible, single organ dysfunction refractory to conventional management.[1] The primary contributors to the high mortality rate in these patients are thrombosis and hemorrhage.

Approximately 5–15% of patients on ECMO develop a venous thrombus. The hemostatic dysfunction associated with ECMO is mediated by activation of coagulation factors, such as thrombin and fibrin, as well as platelets.[2] Anticoagulation is required to prevent thrombus formation within the circuit. Bleeding occurs in approximately 33%–52% of patients on ECMO.[1] In adults, the reported rates of intracranial hemorrhage range from 8% to 20%. Cannula (40–52%) and surgical (34–43%) site bleeding are also common. Persistent activation of the coagulation cascade consumes the endogenous supply of coagulation factors at a rate greater than the ability to regenerate this supply.

Hemostasis is compromised by the administration of anticoagulation and a potent fibrinolytic state. Contact of factor XII, prekallikrein or high molecular weight kininogen with the anionic surface of the circuit leads to the downstream release of tissue plasminogen activator (tPA), a potent fibrinolytic, from the vascular

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endothelium.[3,4] The circuit itself may also induce tPA release, further propagating fibrinolysis. Redistribution due to hemodilution or organ sequestration and destruction due to nonlaminar blood flow lead to a decrease in platelet count and increased risk of bleeding.

There is limited evidence available to guide clinicians in the management of ECMO-associated bleeding (Table 1) and the majority of available studies have been conducted in the pediatric population. We present a single center case series of four adult patients with ECMO-associated bleeding who were managed with ε-aminocaproic acid (EACA) followed by a review of the available literature on the medical management of ECMO-associated bleeding.

Case 1

A 26 year-old male with end-stage cystic fibrosis received veno-venous (VV) ECMO support after bilateral lung transplantation. Bleeding from the surgical site continued through post-operative day (POD) 2. During this time, the hematocrit decreased from 31.5% pre-operatively to 22.9% post-operatively, chest tube output exceeded 900 mL/h and fibrinogen was depleted at 60 mg/dL.

Intravenous EACA was started at a rate of 1 g per hour and continued for 7 h. The patient underwent an exploratory washout with removal of several blood clots from the right hemithorax and placement of topical hemostatic agents. Packed red blood cells (PRBC) (16 units), fresh frozen plasma (FFP) (74 units), platelets (PLT) (2 units) and cryoprecipitate (1 unit) were administered as well. Hematocrit remained low but stable at 28%. On POD6, international normalized ratio (INR) was 1.7, fibrinogen 187 mg/dL and functional antithrombin III level 48%. The elevated INR was reflective of a high level of coagulation factor consumption thought to be due to continued bleeding.

EACA was started as a continuous infusion with rates between 1 and 1.25 g/h without a bolus dose to stabilize clot formation. Concomitant with EACA administration, the patient received PRBC (51 units), FFP (55 units) and PLT (3 units). Bleeding was controlled, EACA was discontinued after 72 h. Patient was successfully weaned off ECMO support and discharged home.

Case 2

A 34 year-old female with rheumatoid arthritis-associated interstitial lung disease required VV ECMO support as a bridge to lung transplantation. Her post-operative course was complicated by an expanding right retroperitoneal hemorrhage and a left-sided hemothorax.

The right retroperitoneal hemorrhage required surgical removal of two large hematomas and placement of two surgical drains on POD33. Continued bleeding required re-exploration on POD34 and EACA was started as a continuous infusion at a rate of 1.25 g/h for a duration of 2 h. Two units of PRBC and 1 unit of PLT were administered. The fibrinogen level increased from 279 mg/dL to 323 mg/dL while D-dimer remained >4000 ng/mL. Three days later, bleeding was noted to have ceased upon re-exploration for placement of a vacuum-assisted closure device.

On POD39, the patient was taken to the operating room for suspected increase in retroperitoneal bleeding. Although two large hematomas were removed, no sites of active bleeding were found. EACA was given post-operatively at a rate of 1.25 g/h followed by a rate of 1 g/h. PRBC (18 units), PLT (5 units) and cryoprecipitate (3 units) were administered concurrently. Fibrinogen increased from 228 mg/dL to 260 mg/dL with the use of EACA. INR (1.2) and D-dimer (>4000 ng/mL) remained stable and no further retroperitoneal bleeding was noted.

EACA 1 g/h was again administered on POD65 for a left hemothorax that expanded despite initial surgical intervention. Additionally, 11 units of PRBC, 6 units of FFP and 19 units of PLT were given. Over the course of the approximately 84 h EACA infusion, fibrinogen doubled from 224 mg/dL to 462 mg/dL. Hematocrit stabilized, ranging between 23.2% and 32.8%. However, hematocrit dropped from 32.5% to 24% on POD73 (off EACA) and the patient underwent a repeat washout and hematoma removal from the same area.

EACA was then administered as a 5 g oral loading dose followed by 1.5 g orally every hour for 8 doses. Therapy was then transitioned to parenteral administration at an initial infusion rate of 1.5 g/h for 8 h followed by 1 g/h for 24 h. In addition to EACA, PRBC (17 units), FFP (2 units), PLT (10 units) and cryoprecipitate (4 units) were administered. Fibrinogen levels increased from 190 mg/dL to 282 mg/dL and bleeding stabilized. The following day, the patient underwent successful bilateral lung transplantation.

Case 3

A 23 year-old male with pulmonary veno-occlusive disease underwent VV ECMO cannulation after bilateral lung transplantation. His operative course was notable for persistent thoracic cavity hemorrhage which was managed initially with blood transfusions, 5 doses of 4-factor prothrombin complex concentrate (50 units/kg) and vitamin K.

After surgical evacuation of a thoracic hematoma and ligation of mediastinal and right paratracheal lymphatics on post-transplant day 2, EACA 1.25 g/h was started. PRBC (14 units), FFP (24 units), PLT (16 units) and cryoprecipitate (6 units) were administered. Fibrinogen increased from 161 mg/dL prior to EACA to 290 mg/dL after EACA, chest tube output slowed and transfusion requirements decreased. D-dimer levels were unavailable. With bleeding controlled, EACA was discontinued after a treatment duration of 50 h. The patient was successfully decannulated from ECMO.

Case 4

A 64 year-old male with idiopathic pulmonary fibrosis was initiated on VA ECMO during right lung transplantation. Bleeding from chest tubes, cannulation sites and multiple orifices continued through (post-operative day) POD5 despite significant transfusion support and stable systemic anticoagulation with unfractionated heparin (UFH). D-dimer was 795 ng/mL, fibrinogen 238 mg/dL, INR 1.3. Anticoagulation with UFH at 4 units/kg/h resulted in a PTT of 40.6 s and a heparin anti-factor Xa <0.10.

To facilitate clot stabilization, intravenous EACA was started with a 4 g loading dose followed by a continuous infusion at a rate of 0.25 g/h. The infusion rate was increased to 1 g/h after 4 h. During EACA infusion, the patient also received 28 units of PRBC, 8 units of FFP and 13 units of PLT. The bleeding slowed. Fibrinogen remained stable (Fig. 1), D-dimer was halved to 302 ng/dL (Fig. 2) and hemoglobin remained stable (Fig. 3). EACA was continued for a total of 48 h.

ECMO was discontinued on POD9, however mixed a respiratory and metabolic acidosis prompted the re-initiation of ECMO on POD13. Within 24 h of ECMO initiation, the patient developed bleeding in his left lung which continued through POD15. At that time, his INR was 1.6, fibrinogen 201 mg/dL and D-dimer 1037 ng/m. Anticoagulation was temporarily held. Intravenous EACA was restarted with a 5 g load and 1 g/h infusion. The patient also received 35 units/kg of 4-factor prothrombin complex concentrate (Kcentra®, CSL Behring, Kankakee, IL) and desmopressin 0.3 mcg/kg.