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Original Contribution

Comparative effectiveness of epsilon-aminocaproic acid and tranexamic acid on postoperative bleeding following cardiac surgery during a national medication shortage☆

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Abstract

Study objective: The aim of this study was to compare the effectiveness of epsilon-aminocaproic acid (εACA) and tranexamic acid (TXA) in contemporary clinical practice during a national medication shortage.

Design: A retrospective cohort study.

Setting: The study was performed in all consecutive cardiac surgery patients (n = 128) admitted to the cardiac-surgical intensive care unit after surgery at a single academic center immediately before and during a national medication shortage.

Measurements: Demographic, clinical, and outcomes data were compared by descriptive statistics using χ^2 and *t* test. Surgical drainage and transfusions were compared by multivariate linear regression for patients receiving εACA before the shortage and TXA during the shortage.

Main results: In multivariate analysis, no statistical difference was found for surgical drain output (OR 1.10, CI 0.97–1.26, $P = .460$) or red blood cell transfusion requirement (OR 1.79, CI 0.79–2.73, $P = .176$). Patients receiving εACA were more likely to receive rescue hemostatic medications (OR 1.62, CI 1.02–2.55, $P = .041$).

Conclusions: Substitution of εACA with TXA during a national medication shortage produced equivalent postoperative bleeding and red cell transfusions, although patients receiving εACA were more likely to require supplemental hemostatic agents.

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1. Introduction

Nearly 1 in 5 blood products transfusions in the United States occurs in the setting of cardiac surgery [1]. Blood conservation techniques are used to minimize perioperative transfusions during and after cardiac surgery [2]. These techniques include intraoperative cell-salvage devices, improved surgical techniques, topical hemostatic agents, and conservative transfusion thresholds [3]. Anti-fibrinolytic agents are often used as a pharmacological adjunct to maintain clot stability and minimize bleeding.

Contemporary antifibrinolytic agents include aprotinin, ε-aminocaproic acid (εACA), and tranexamic acid (TXA). In 2007 to 2008, the most thoroughly studied agent, aprotinin, was removed from the market in the US, UK, Canada, and European Union due to safety concerns [4,5]. Since 2012, aprotinin has been returned for use in Canada and Europe following a systematic review of multiple studies concluding with a favorable the risk/benefit ratio [6]. Aprotinin remains unavailable in the United States.

The alternative antifibrinolytic agents, εACA and TXA, have been compared in small trials published between 1994 and 2001 [7-11] which did not establish the clinical superiority of either agent. The Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) was the only large study to include TXA (n = 770) and εACA (n = 768) arms, and demonstrated equivocal outcomes in mortality for a composite 'massive transfusion' endpoint (including greater than 1.5 L blood loss within 8 hours, >8 U red blood cells (RBCs) transfused, or surgical re-exploration for hemorrhage) [12]. The results are difficult to interpret as major hemorrhage following surgery is multifactorial and often involves compromised surgical hemostasis. It is unrealistic to expect an antifibrinolytic agent alone to prevent perioperative catastrophe. A recent Cochrane review reported insufficient evidence (particularly for εACA) to recommend either lysine analog over the other [13]. Studies included in that analysis were limited by small size, remote publication dates, and surgical indications often limited to primary coronary revascularization surgery (for which many patients today might receive percutaneous coronary angiography). Contemporary antifibrinolytic agents are used for a variety of cardiac procedures beyond coronary revascularization, such as valve surgery or ventricular assist device placement, for which they have not been well studied. Finally, since the 1990s when many of these trials were conducted, thresholds for transfusions have lowered such that today small differences in blood may be more relevant towards the decisions to transfuse than they would have been in an era where most patients would receive blood regardless. While some clinicians favor a particular agent, at present, the use of εACA and TXA remains in a state of equipoise.

In 2012–2013, the United States experienced a national shortage of εACA following FDA-mandated upgrades to the manufacturing process (W. Fridich, Luitpold Pharmaceuticals, personal communication, August 8, 2015). The blood conservation practice at our institution included eACA exclusively until stores of this medication were exhausted on March 30, 2013. There was an immediate substitution of TXA for all cardiac procedures from April 1, 2013, until supplies were replenished on June 4, 2013. The shortage presented an opportunity to compare retrospectively the effectiveness of εACA and TXA on postoperative bleeding in the ICU following cardiac surgery under contemporary surgical conditions and with minimal patient risk.

2. Materials and methods

2.1. Study population

The study population includes all consecutive patients undergoing cardiac surgery with cardiopulmonary bypass between February 1 and June 3, 2013, who received either TXA or εACA. The protocol was approved by the Research Compliance Office and Institutional Review Board of Stanford University School of Medicine with a waiver of informed consent. Patients were included for the first cardiac or proximal aortic surgery of the hospitalization. Patients were required to have a planned post-operative admission to the cardiothoracic surgical intensive care unit with surgical drains in situ. Patients who died or required surgical exploration within 8 hours were excluded, as antifibrinolytic agents alone were unlikely to prevent these complications.

Prior to April 1, 2013, all cardiac surgery patients at our institution received εACA (loading dose 10-15 mg/kg over 10-15 min, 2-3 mg/kg bolus into the bypass priming solution, then 1-2 mg/kg per hour infusion for 6 hours). During the shortage, all patients received TXA (loading dose 10-15 mg/kg over 10-15 min, 2-2.5 mg/kg bolus in the bypass priming solution, then 1-2 mg/kg per hour for 6 hours) until εACA was again available on June 4, 2013. Allotment of either εACA or TXA was assigned based on medication availability and was independent of clinician judgment.

2.2. Data collection

Patient charts were accessed for the following data: patient demographics including age on admission, sex, and race; preoperative co-morbidities including hypertension, diabetes mellitus, chronic pulmonary obstructive disease, chronic renal insufficiency (baseline Cr >1.5 g/dL), congestive heart failure with New York Heart Association functional class; ASA Physical Classification; unstable pre-operative coronary artery disease (as evidenced by electrography, echocardiography, cardiac catheterization, perfusion scan, or unstable angina defined by chest pain at rest with electrocardiogram or echocardiographic changes); pre-operative atrial fibrillation; pre-operative hemoglobin, platelet count, and INR; type of surgical procedure; duration of surgical procedure; duration