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Case Report

Left ventricle thrombus after tranexamic acid for spine surgery in an HIV-positive patient

Neal Stuart Gerstein, MD, FASE*, Janet Kathryn Brierley, MBBS, FRCA, Matthew Douglas Culling, MD

Department of Anesthesiology and Critical Care Medicine, University of New Mexico School of Medicine, MSC 10 6000, 2211 Lomas Blvd NE, Albuquerque, New Mexico 87106, USA

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Abstract

BACKGROUND CONTEXT: Our case highlights the underappreciated thrombotic risks of tranexamic acid (TXA) use in non-cardiac surgery and emphasizes the need to elucidate these risks with appropriate clinical trials.

PURPOSE: The use of TXA in non-cardiac surgery has significantly expanded in the past 5 years, especially after the 2010 publication of the CRASH-2 Trial. We submit a case with the intent to highlight the thrombotic risk of TXA use during non-cardiac surgery and discuss the need for careful risk stratification before the use of TXA in this context.

STUDY DESIGN: A 66-year-old man with long-standing HIV infection, hypertension, and no history of coronary artery disease (CAD) presented for revision spinal fusion surgery with the use of TXA is presented.

METHODS: To limit perioperative blood loss, the case patient received TXA intraoperatively. His operative course was uneventful.

RESULTS: During the first 12 hours postoperatively the patient was noted to have persistent tachycardia and ST-elevation on electrocardiogram. Echocardiography showed a new apical wall motion abnormality and a left ventricle thrombus; cardiac catheterization confirmed two-vessel CAD, treated with a bare-metal stent and anticoagulation.

CONCLUSIONS: The thrombotic risks of TXA use in non-cardiac surgery have yet to be adequately studied in clinical trials. Hence, TXA use in this context is still an area of uncertainty, and its thrombogenic risks have yet to be studied as a primary outcome in any large prospective trial to date. Patients with any hypercoagulable risk factors, including HIV infection or any prior thrombotic history in which TXA use is being considered, should prompt a discussion among the perioperative physicians involved.

Keywords: HIV; Hypercoagulable; Left ventricle thrombus; Spine surgery; Tranexamic acid

Introduction

This is the first report of a patient undergoing elective spine fusion surgery developing a left ventricle thrombus and an ST-elevation myocardial infarction (MI) within 12 hours of receiving tranexamic acid (TXA).

Case description

The patient, a 66-year-old man, had a history of human immunodeficiency virus (HIV) infection first diagnosed over 30 years ago. His most recent CD4 count was 794. He was on highly active antiretroviral therapy at the time of presentation for surgery. Other significant medical history included chronic obstructive pulmonary disease, a prior deep vein thrombosis (DVT), and a transient ischemic attack several years previously, thought to be associated with his HIV

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* Corresponding author. Department of Anesthesiology and Critical Care Medicine, University of New Mexico School of Medicine, MSC 10 6000, 2211 Lomas Blvd NE, Albuquerque, NM 87106, USA. Tel.: +505 272 2610; fax: +505 272 1300.

E-mail address: ngerstein@gmail.com (N.S. Gerstein)

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medications. He suffered from chronic back pain and presented to the operating room for a revision T3–L2 posterior spinal fusion. The patient had undergone multiple prior spine surgeries, including a lumbosacral posterior fusion without instrumentation more than 10 years ago. He developed significant degenerative lumbar scoliosis and spinal stenosis for which he underwent decompression surgeries and then later a posterior fusion with instrumentation from T11 to S1. During the current admission, he presented with T10–T11 proximal junctional kyphosis (acquired kyphosis) above a prior T11–S1 posterior spinal fusion, thoracic post-laminectomy syndrome (failed back syndrome), and refractory back pain with forward sagittal imbalance. The patient had a normal transesophageal echocardiogram 2 years before his surgery, and 7 months before his surgery he had a normal exercise stress echocardiogram.

On the day of surgery, induction of anesthesia was performed with midazolam, fentanyl, lidocaine, and propofol. The patient received a 1-g bolus of TXA after induction and a 1 mg/kg/hr infusion of TXA intraoperatively. General anesthesia was maintained with sufentanil, propofol, and desflurane, and there were no adverse intraoperative events. Surgically, the fusion of T11–L2 was explored, and revision posterior spinal fusion was performed. This was extended to include arthrodesis of T3 down to T11. The prior construct was revised and segmental instrumentation T3 through L2 was applied (see Figs. 1 and 2). The estimated surgical blood loss was 500 mL. He received 2 L of crystalloid and 500 mL of 5% albumin. No blood products were administered.

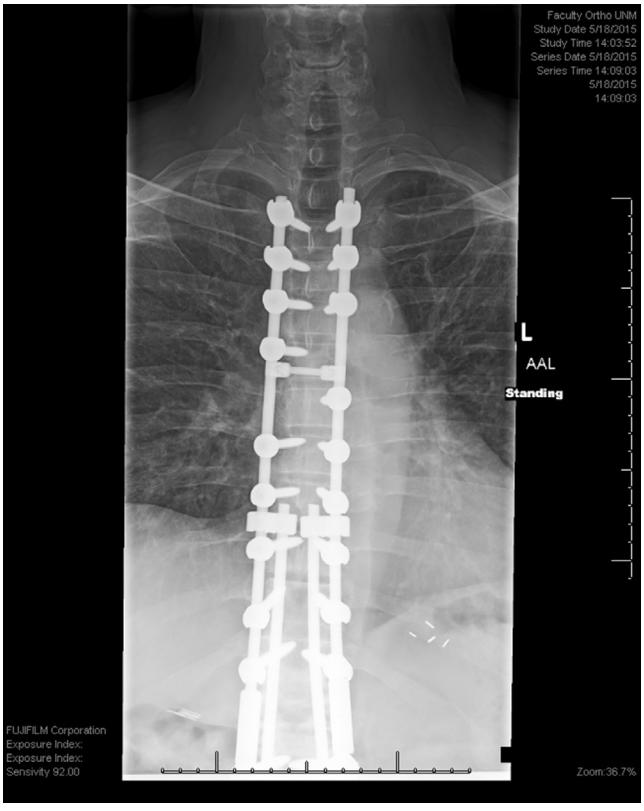

Fig. 1. Anterioposterior postoperative follow-up spine film.

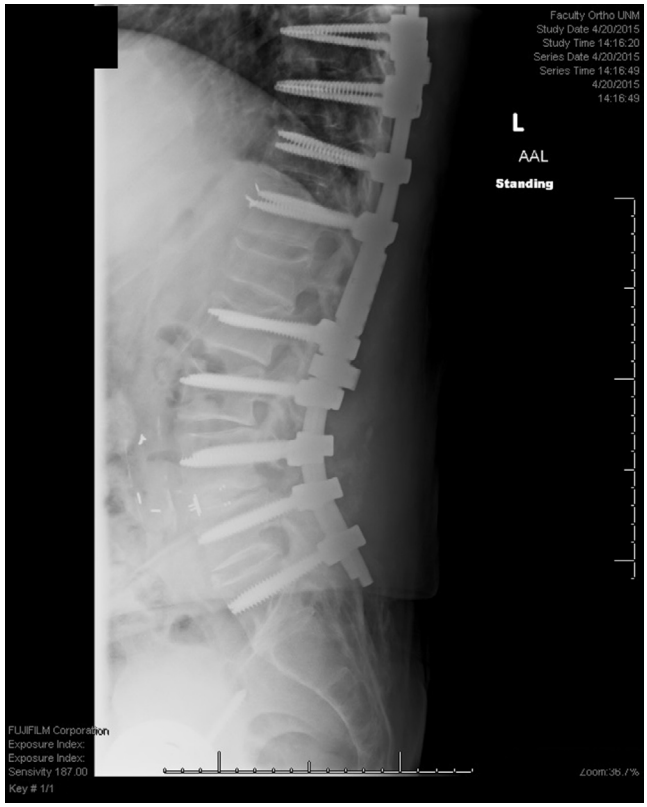

Fig. 2. Lateral postoperative follow-up spine film.

In the postanesthesia care unit, the patient had persistent tachycardia that was attributed to severe postoperative pain, which was controlled with both analgesics and labetalol. He was transferred to a subacute care unit where he complained of back pain in the thoracic area and was noted to have ST elevations in the anterior and anterolateral leads. His serum troponin-I level was 4.04 ng/mL (normal high<0.06 ng/ml) during this period. He was given aspirin, and a heparin infusion commenced. A postoperative transthoracic echocardiogram demonstrated a large apical thrombus (see Fig. 3), apical akinesis, and moderate anterolateral wall hypokinesis. Cardiac catheterization revealed a severe proximal left anterior descending lesion and complete occlusion of a diagonal branch. A bare metal stent was deployed into the left anterior descending. The patient was bridged to warfarin; clopidogrel and aspirin treatment commenced. A repeat transesophageal echocardiogram on postoperative day 6 demonstrated left ventricular (LV) apical akinesis and a persistent thrombus in the LV apex. The remainder of his hospital course was uneventful, and he was discharged on postoperative day 9.

Discussion

This case represents the first reported LV thrombus associated with the administration of TXA in the perioperative period and highlights its significant thrombotic potential.

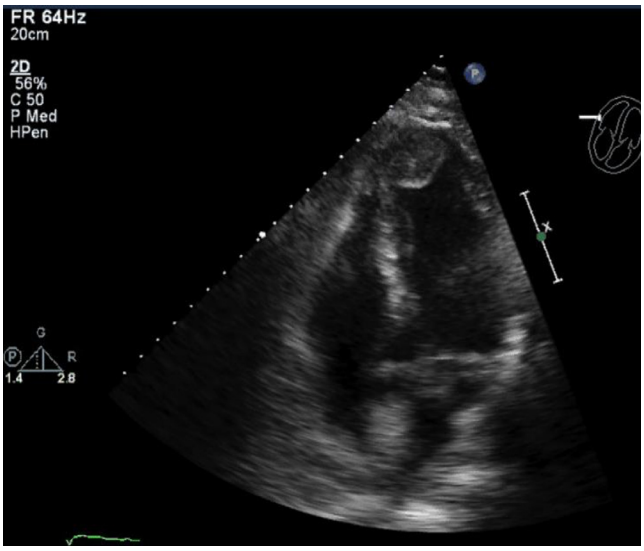

Fig. 3. Apical four-chamber transthoracic echocardiogram demonstrating apical thrombus.

The use of TXA has undergone a resurgence in the past few years, especially after the 2010 publication of the large (n=20,211) CRASH-2 Trial which demonstrated significant decreases in death caused by bleeding and all-cause mortality in adult trauma patients with significant bleeding who received TXA versus placebo within 3 hours of their injury [1,2]. Moreover, there was no increase in the rate of thromboembolic events in the treatment group [1]. Based upon the results of CRASH-2, the World Health Organization added TXA to their list of "Essential Medicines," resulting in the addition of TXA into various international trauma protocols [3,4]. Similar to the findings of CRASH-2, a 2012 systematic review and meta-analysis of TXA use in 10,488 elective and emergent surgical patients encompassing 129 trials found significant decreases in transfusion rates. Data related to differences in mortality as well as thromboembolic complications (stroke, MI, DVT, and pulmonary embolism) were mixed and in total non-significant [5].

Historically, TXA and epsilon aminocaproic acid were first developed in 1962 for their use in the treatment of hemophilia followed by the evolution of their use in on-pump cardiac surgery in the 1990s [6,7]. Tranexamic acid use has evolved into an agent used in a broad array of non-cardiac surgical contexts, including: urology [8], orthopedics [9], liver [10], trauma [4], neurosurgery [11], and obstetrics [12,13]. Specifically, the use of TXA in spine surgery has been examined in two recent studies. One was a 2013 meta-analysis of six placebo-controlled randomized clinical trials that demonstrated TXA's effectiveness in reducing total blood loss and the need for transfusion without any increase in venous thromboembolic (VTE) complications [14]. A 2015 meta-analysis in spine surgery examining similar parameters found TXA to have similar positive effects on blood loss without an increase in thrombotic complications [15].

The primary contraindications for using TXA include ongoing or risk of venous or arterial thrombosis, history of thrombosis or thromboembolism, and allergy to the drug [2].

With regard to thrombotic risk, Berntorp et al. retrospectively examined the temporal relationship of TXA administration in women with and without a recent DVT and found no correlation with prior TXA use [16]. In a group of 3,512 patients treated with TXA after subarachnoid hemorrhage, the rate of DVT and pulmonary embolism was only 1.9% [17]. These findings corroborate those of the CRASH-2 Trial as well as large retrospective reviews of non-traumatic surgical patients which also demonstrate no increase in thrombotic complications [15,18]. However, the thrombogenic risks of TXA have not yet been studied as a primary outcome in any large prospective trial to date. There remains uncertainty about precisely where TXA should or should not be used in terms of patients or procedures. In orthopedics, in a recent small (n=254) prospective trial in hip arthroplasty, a greater rate of distal DVT was found in the TXA arm; however, these were primarily in the superficial system rather than the deep veins [19]. In three recent meta-analyses examining TXA use in orthopedic surgery, the overall VTE complication rate was not increased compared with controls [20–22]. However, each of these studies was limited because of the exclusion of either patients or related trials with certain important thrombotic risk factors (thromboembolic history, pregnancy, significant cardiovascular, renal, and liver disease). All three studies still leave the true safety of TXA use, especially in the context of one or more VTE risk factors, in question, and all conclude that the need for large prospective randomized controlled trials in this area is needed. Tables 1 and 2 display the advantages and disadvantages to TXA use in spine surgery as well precautions for its use in spine surgery, respectively.

Additionally, HIV infection as well as highly active antiretroviral therapy are known risk factors for accelerated atherosclerosis, peripheral artery disease, coronary artery disease, hypercoagulability, thrombosis, and cardiomyopathy [39,40]. There are numerous theories as to how HIV infection negatively impacts the cardiovascular system. It likely involves a combination of free radical production, inflammation, and augmented susceptibility to ischemic and toxic injury [41]. With regard to thrombotic risk, HIV-infected patients have been reported to have a 2- to 10-fold increased risk of thrombosis as compared with the general population [42]. The rate of venous to arterial thrombosis is approximately twofold greater. In a review of 109 consecutive HIV-infected patients, 16% developed a symptomatic thrombus of which 10% were venous and 6% were arterial [43]. The increased thrombotic milieu in HIV patients is multifactorial and includes abnormalities in fibrinolysis, protein C and S deficiencies, increased levels of factor VIII, and excess serum fibrinogen [44]. With regard to intracardiac thrombus and HIV, there are limited reports with most of the focus on right-sided venous thrombus [45]. There are two reported cases of LV thrombus in HIV-positive patients. One was a non-perioperative case of an LV apex thrombus in a 41-year-old

Table 1
Advantages and disadvantages of TXA use in spine surgery

Advantages	Disadvantages
• Reduces total surgical blood loss [23–25]	• Multiple precautions and contraindications (see Table 2)
• Decreases need for transfusion [23–25]	• Limited information on optimal dosing regimen [27]
• Decrease in total volume of blood transfused [23–25]	• Epsilon-aminocaproic acid possibly more efficacious for complex procedures [24,25]
• Anti-inflammatory properties [23]	• Epileptogenic potential [28,29]
• Inexpensive/cost-effective [9,23,26]	• Possible concern with use of free-flap coverage [30]
• Minimal side effects [23,26]	• Needs dose reduction in renal sufficiency [27]
• Minimal drug interactions [23,26]	• Placental transfer occurs [23]
• Minimal plasma protein binding [23]	• Crosses blood-brain barrier/potential cerebral edema exacerbation [23]
• No significant metabolites [23]	• Use in orthopedic procedures not FDA approved [23]
• No effect on blood coagulation parameters [23]	

man with HIV who had severe LV systolic dysfunction (LV ejection fraction of 10%) and a severely dilated LV cavity [46]. The second case involved a 47-year-old man with HIV who presented with a stroke, mildly depressed LV function (LV ejection fraction 50%), normal size LV, and was found to have a large mobile LV apex thrombus [47].

There are a number of possibilities that led to our patient's thrombus development. It could be attributed to a

Table 2
Precautions to TXA use in spine surgery

Clinical scenario/Patient condition	Description
Allergy or hypersensitivity to TXA [23]	Possible anaphylaxis with use
History of significant venous or arterial thrombosis or thromboembolic event [9,23,31–33]	• Deep vein thrombosis • Pulmonary embolism • Coronary thrombosis—*additional consideration should be taken with coronary stenting* • Cerebral thrombosis • Acute renal cortical necrosis • Central retinal vein or artery obstruction
Inherited hypercoaguable states [9,23,32]	• Antithrombin deficiency • Factor V Leiden mutation • Prothrombin gene mutation • Protein C and S deficiencies • Dysfibrinogenemias • Factor XII deficiency
Acquired and non-primary hypercoaguable states (including risk factors for) [9,23,27,32–35]	• Prior thrombosis/thromboembolism • Malignancy—*especially advanced disease* • Antiphospholipid syndrome • Recent major operative procedure • Immobilization • Prior heparin use (Heparin-induced thrombocytopenia with thrombosis) • Hormone replacement therapy/oral contraceptive use • Nephrotic syndrome • Polycythemia vera; thrombocythemia • HIV infection/HAART therapy • Congestive heart failure • Central venous catheters/hardware • Pregnancy • Bevacizumab, tamoxifen, or testosterone therapy
Renal insufficiency [27]	Primarily renal excretion and toxicity potential increased with renal insufficiency.
Concurrent subarachnoid hemorrhage or traumatic brain injury [23,36]	Cerebral edema or infarction has been associated with TXA use. Traumatic brain injury is independently associated with hypercoaguable state.
History of significant seizure disorder or poorly controlled seizure disorder [23,28,29]	TXA has epileptogenic potential; seizure activity has been reported in use in cardiac surgery.
Concomitant treatment with other procoagulants [23,27]	Thrombosis risk increased with use of Factor IX Complex and anti-inhibitor coagulant concentrates.
Disseminated intravascular coagulation [37]	Risk of thrombosis; may require concomitant heparin use.
Visual disturbances [38]	Chromatopsia and visual impairment has been reported in use in hemophiliacs.
Pregnancy [32]	Category B agent but no well-controlled studies of use during pregnancy; use in pregnancy should be limited.

HAART, highly active antiretroviral therapy; TXA, tranexamic acid.

combination of TXA administration in the context of his increased coagulability related to HIV infection alone. Alternatively, his perioperative MI, possible stunned myocardium, and resultant regional wall motion abnormality may have contributed to his apical thrombus formation; TXA in this context could have been an inciting or contributing factor for thrombus formation. Moreover, the patient's subclinical coronary artery disease (possibly HIV-related) was unmasked by the prothrombotic state of the perioperative period and TXA administration—both contributing to the apical thrombus formation. Regardless of the exact mechanism, it is highly likely that TXA administration was a significant contributing element in what could have possibly been a catastrophic event.

Enthusiasm for the use of TXA outside of the cardiac surgery realm is expanding. However, as our case report illustrates, the thrombotic potential of TXA is clearly extant. The risks and benefits of TXA use need to be carefully considered in each patient for whom it is prescribed. The thrombotic risks of TXA have yet to be adequately examined by prospective clinical trials in elective surgical patients and are still an area of uncertainty. Commenced in 2006 and still enrolling patients, the Aspirin and Tranexamic Acid for Coronary Artery Surgery is examining TXA use in patients at high risk for thrombotic complications and should help clarify this issue [48]. Until the thrombotic risks of TXA are fully elucidated, patients with known hypercoagulable risk factors in whom TXA is being considered should prompt a discussion among the perioperative physicians involved. As stated previously, TXA use is contraindicated in those with known hypercoagulable disorders; HIV infection should be part of this contraindication list.

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