

# ANESTHESIOLOGY™ 2014

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## **Antifibrinolytic Use in Major Orthopedic Procedures: What's the Bloody Controversy?**

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### **Stem Case and Key Questions Content**

#### **CASE STEM**

75 year-old, 100 kg female is scheduled for a left total hip implant revision surgery. Her medical history is significant for hypertension, morbid obesity with a BMI of 40 who denies having sleep apnea, a history of breast cancer, anemia, and end stage renal disease. In addition, she is a Jehovah's Witness. Her medications include amlodipine 5mg daily, metoprolol 25mg daily, calcium, darbopoeitin alpa 40mcg subcutaneous every week, intravenous iron 125mg every 3 days, and hydromorphone 0.5mg intravenous every 3 hours as needed. Her airway exam is significant for good neck mobility, adequate mouth opening, neck circumference of 30cm, and a Mallampati class II airway. Cardiopulmonary physical exam revealed no significant abnormalities. She has a stress echocardiogram with no evidence of induced ischemia and an ejection fraction of 50%. She underwent dialysis 12 hours ago and her electrolytes are within normal limits. Her hemoglobin is 9.0 g/dl and platelets are 150K. The surgeon requests tranexamic acid (TXA) to be administered intraoperatively.

#### **GUIDING QUESTIONS**

- 1. Is this patient medically optimized to undergo the planned procedure?*
- 2. What are the current antifibrinolytic agents available to decrease surgical bleeding? Compare and contrast their efficacy, safety, and cost effectiveness.*
- 3. How does TXA work to decrease surgical bleeding? What is its mechanism of action?*
- 4. What other modalities of blood conservation techniques should be discussed with this patient?*
- 5. What is the current evidence on the efficacy, effectiveness, and risks of TXA in orthopedics compared to other surgical procedures in the literature?*
- 6. How can we optimize perioperative outcomes by reduction in anemia and transfusion rates?*
- 7. Are there subgroups of patients at increased risk for complications from TXA?*
- 8. What is a reasonable dosing schedule of TXA for the orthopedic population? Are there standardized dosing guidelines for this patient with renal impairment?*
- 9. What role can anesthesiologists play to address clinical barriers and facilitate timely dialogues with the hospital pharmacy, nursing staff, residents, and other surgeons regarding TXA use?*
- 10. What is the relationship between severe renal impairment and chronic anemia? How effective are erythropoiesis-stimulating agents in raising hemoglobin levels? Are there major adverse effects with these agents?*
- 11. Is there a target hematocrit that is safe for proceeding with this case? What are the global*

*benefits and risks of proceeding or delaying this procedure? How should the anesthesiologist approach the initial discussion with this patient?*

Further history reveals that this is the second left hip revision that this patient is undertaking. She had a left total hip replacement one year ago at an outside hospital followed by a revision on the same hip three months prior to this hospitalization. On this admission, the patient reports that she felt something “popped” when she moved her legs on her bed two days ago. Now, she can barely move her left leg secondary to severe hip pain. Additional investigations in her medical chart confirmed diagnoses of a pulmonary embolism in her right lower lung segment one year ago and a history of drug-eluting coronary stent placed in her left circumflex artery two years ago. She has not been adherent to her anticoagulation regimen for the past month. After a full discussion about the risks of surgical hemorrhage, the patient refused all human blood and plasma products but will accept the use of a cell saver and synthetic colloid solutions.

- 12. Has TXA been shown to impact the incidence of reoperation in variety of surgical settings?*
- 13. Is there a significant increase in the risk of hemorrhage for patients undergoing revision of joint prosthesis?*
- 14. What are the considerations for using cell saver in this patient undergoing a hip revision procedure?*
- 15. Is there a difference between hip arthroplasty and hip fractures with the use of TXA?*
- 16. What are the available synthetic colloid solutions? What are the associated adverse effects?*
- 17. What is the appropriate documentation for a Jehovah’s Witness patient refusing life-saving interventions?*
- 18. How do the benefit-risk analyses change regarding TXA use in the high risk patient? What insights, if any, do the current evidence based literature offer?*
- 19. Does TXA use affect her perioperative venous thromboembolism prophylaxis regimen?*
- 20. How should we proceed with her history of drug-eluting stent and cessation of anti-platelet therapy?*

On arrival to operating room, a central line and arterial line were placed. Anesthetic induction and endotracheal intubation are uneventful. The patient was placed in the right lateral decubitus position and surgery proceeded. During a difficult exposure of the acetabular component, the patient lost 750ml of blood over a period of 30 minutes. After adequate resuscitation with 1L of crystalloid solution, 500ml of hydroxyethyl starch, and 500ml of autologous blood via cell saver, the patient remained hemodynamically stable for the remainder of the case. Her trachea was extubated uneventfully and arterial line was removed in the operating room. On postoperatively day 1, her hemoglobin was 7.5g/dL and DVT prophylaxis regimen was started on postoperatively day 2.

- 21. What is the reported reduction in total blood loss associated with TXA in major orthopedic procedures?*
- 22. Should TXA be continued postoperatively? Is there any standardized dosing regimen used in the literature?*
- 23. What is the relationship between TXA and strategies for optimizing postoperative thromboembolic risks?*
- 24. Is there a role for TXA in other joint procedures such as knee replacements where there is limited intraoperative blood loss secondary to tourniquet use?*

25. What are the indications for placing an arterial line for this patient who refused blood transfusion?

## Model Discussion Content

### CASE DISCUSSION

#### *Introduction*

The number of total joint replacement procedures has increased exponentially in the last decades for the aging surgical population. Among Medicare patients, the number of primary total knee replacements has increased 160% over the past 20 years. Approximately 10% of these patients will require revision of their prosthesis and the absolute number of revisions will increase by 137% in the next 20 years. Thus, the management of perioperative hemorrhage in these procedures has a major impact on patient morbidity and mortality. Recent studies have repeatedly demonstrated that perioperative anemia and transfusion are independent risk factors associated with increased patient mortality and complications in noncardiac surgery. The anesthesia provider plays a pivotal role in optimizing patient outcomes by employing strategies to minimize intraoperative and postoperative bleeding. In order to facilitate an effective discussion on patient safety with our surgeons, the anesthesiologist has to be familiar with the current literature on antifibrinolytic therapy as an important form of blood conservation. The following provides a pharmacological overview of antifibrinolytic agents as well as a summary of existing evidence for their use with a specific emphasis on tranexamic acid (TXA) in orthopedic procedures.

#### *Jehovah's Witness: Special Considerations and Unique Challenges*

There are more than 7 million Jehovah's Witness (JW) followers residing in more than 200 countries around the world. In these patients, major perioperative concerns are preoperative anemia and the refusal of blood transfusion even in life-threatening hemorrhagic conditions. However, this refusal of products is not absolute. Some JW patients can accept certain blood fractions (below dotted line on image 1), allowing them to participate in invasive procedures with relative safety. Nevertheless, patients should be thoroughly educated and counseled on surgical risks and alternatives. Notably, this discussion is highly individualized and each itemized decision should be fully documented for clinical and medico-legal considerations. Not surprisingly, cardiothoracic surgery remains the best and most comprehensive source for insights to blood conservation in the JW population. In a recent 2012 paper from France, Vaslic et al. report on outcomes associated with performing bloodless cardiothoracic surgery on 500 JW patients in over two decades. Notably, 10% of patients in this cohort have preoperative renal failure. The overall 30-day mortality ranges from 1-3% with low perioperative complication rates that are equivalent to standard cardiac surgery. At the same time, Jassar et al published a comparable report for 91 JW patients who underwent cardiac surgery over a 10-year period. Their findings include an in-hospital mortality of 5.5% and a postoperative renal failure rate of 1% requiring hemodialysis. Both authors attribute their success to institutional commitment and a multidisciplinary approach to bloodless surgery. Their programs consist of a dedicated perioperative bloodless medicine team, use of erythropoietic stimulating agents such as parenteral iron and erythropoietin for preoperative hemoglobin optimization, use of a detailed "itemized" blood product consent form, use of acute normovolumic hemodilution, use of cell saver, use of surgical hemostatic adjuncts and minimally invasive techniques, use of warm cardioplegia and maintaining normothermia, use of antifibrinolytics intraoperatively, and minimizing blood tests postoperatively. In his conclusion, Vaslic et al. explains that cardiac

surgery has become safer in these patients partly because of advances in pharmacological blood conservation.

Although there is much less experience with JW patients undergoing major orthopedic procedures, Harwin et al. provides a snapshot of their long-term surgical outcomes, as well as a summary of the available literature (see Image 2) in his 2012 multi-center review article on 10 JW patients over a 10-year period. The authors explain that hip revisions are known to carry higher risks of bleeding compared to primary hip arthroplasty. The blood loss involved in revision procedures is in the range of 2L requiring blood transfusion in almost 45% of cases. Using a similar comprehensive blood management program, the investigators report 0% mortality, 100% implanted prosthesis survival at 69 months, and only 1 case of DVT in this cohort. Harwin et al. state that hip revisions are a viable treatment options for JW patients with no mortality reported to date in highly specialized bloodless surgery centers. In a 2013 A&A article titled, "Current Status of Pharmacologic Therapies in Patient Blood Management", Drs. Goodnough and Shander advocate for a patient-centered, evidenced based and multidisciplinary blood management approach to improve patient outcomes. This article provides an extensive and current overview of erythropoiesis-stimulating agents (ESAs), recombinant activated factor VII, hemo[[Unsupported Character - Codename &shy;]]static agents such as antifibrinolytics and prothrombin complex concentrates, parenteral iron therapy, and artificial oxygen carriers. According to the authors' review, aggressive use of ESAs to achieve target hemoglobin >12 g/dL instead of treating symptomatic anemia is associated with more thrombotic events and increased mortality trends in renal failure and cancer patients. As a result, black box warnings have been inserted advising cautious use of ESAs in renal failure patients undergoing elective surgery. One way to mitigate these risks is the use of intravenous iron supplementation. Compared to oral formulations, parenteral iron has been shown to reduce ESAs dosages by 46% while maintaining efficacy in anemia optimization. While this article serves as an excellent reference to effective blood management, it is outside the scope of this discussion to review every strategy for blood conservation. Nevertheless, as the authors point out, "Both patients and physicians will require effective information to make the appropriate health decisions in the context of informed consent". Overall, vulnerable populations such as JW patients present unique challenges for the anesthesiologist and the use of a patient-centered and evidence-based approach should be the basis of a global multi-specialty perioperative plan.

### *Antifibrinolytics: Pharmacology, Efficacy, and Adverse Effects*

The antifibrinolytic agents exert their inhibitory effect by reversible competitive antagonism of plasminogen and plasmin binding sites for fibrin. This ultimately suppresses fibrinolysis (See Images 3 and 4). There are three commonly used antifibrinolytics including TXA, aminocaproic acid (EACA), and aprotinin. Aprotinin is a polypeptide derived from bovine lungs and acts as a serine protease inhibitor. Due to the apparent association between aprotinin and perioperative cardiovascular, cerebrovascular, and renal complications as well as an increase in mortality in the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) in high-risk cardiac patients published in NEJM in 2008, aprotinin was withdrawn from the market. After further analyses of BART data and outcomes from other major trials, aprotinin was reinstated in Europe (2013) and Canada (2011) but currently pending approval in the US. In equipotent doses, EACA has been reported to have equivocal efficacy when compared to TXA in a single trial in total knee replacement. However, in a meta-analysis of antifibrinolytic agents used in major orthopedic procedures, Zufferey et al. concludes that EACA is not efficacious compared to TXA or aprotinin. Also, EACA has been linked to higher incidence of arrhythmias, hemodynamic

# ANESTHESIOLOGY™ 2014

OCTOBER 11-15 | NEW ORLEANS, LA

instability, myopathy, and rhabdomyolysis. Hence, TXA emerged as the agent of choice in major orthopedic surgery.

TXA has been in clinical use for over 40 years, with widespread applicability in cardiathoracic, orthopedic, obstetrical, and urological procedures. In these settings, TXA has consistently shown to result in reductions in total blood loss by at least 30% on average. Furthermore, there is a significant decline in transfusion requirements and need for reoperation without significant increased risk for thromboembolic events. In general, TXA is an effective intravascular adjunct to surgical hemostasis in settings where fibrinolysis is a significant contributing factor to bleeding.

TXA is available in both intravenous and oral formulations. Oral dosing regimen varies among practitioners. For menorrhagia (over-the-counter formulations are available in United Kingdom), conisation of cervix, hereditary angioneurotic edema, or traumatic hyphaema secondary to ocular hemorrhage, 1.5g orally every 8 hours for 4 days is recommended. Plasma concentrations of 5-10 mg/L are sufficient for antifibrinolysis and studies in human volunteers show that peak plasma TXA concentration of higher than 30 mg/L is achieved from 0-30 minutes after intravascular injection. The half life of TXA is 3 hours and adequate plasma concentrations are maintained for 3-5 hours. TXA crosses blood-brain and placental barriers and the majority is renally cleared. Uncommon adverse effects associated with TXA include nausea, diarrhea, and orthostatic hypotension. Rare isolated case reports of arterial and venous thrombotic events, renal insufficiency, and coronary graft occlusion have been documented. Postoperative seizures have been reported with high doses (100mg/kg) of TXA used in cardiac surgery.

### *TXA: Evidence-based use in Trauma, Surgery, and Orthopedics*

In 2010, TXA experienced a much deserved boost in popularity when the results of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage Trial (CRASH-2) from the United Kingdom were published in *Lancet*. This randomized controlled study with over 20,000 trauma patients from 40 countries at clinical risk of bleeding provided major insights into the efficacy and safety of this drug. The CRASH-2 group showed that all-cause mortality as well as death due to bleeding was significantly reduced with the early administration (within three hours of injury) of TXA (See Image 5). Their intervention was a loading dose of 1 gram of TXA at randomization and 1 gram subsequently infused over 8 hours. Perhaps even more surprising was the data on vasoocclusive events, defined as myocardial infarction, stroke, and pulmonary embolism. In this population of patients, TXA not only failed to increase thromboembolic burden but there was actually a trend toward reduced vasoocclusive events (See Image 6). In fact, in a subsequent subgroup analysis of the CRASH-2 data that is stratified for baseline risk of death published in *BMJ* in 2012, the investigators reveal that there were significantly less nonfatal and fatal arterial thrombotic events in the TXA group. Based on this encouraging data, the *BMJ* article recommends, "Tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding."

As compelling as the CRASH-2 data are, the trauma population is not identical to the surgical population. For instance, less than half of the CRASH-2 cohort underwent surgery of any kind (48%). Inconsistent with previous studies, the TXA group failed to demonstrate any effect on the need or the number of transfusions in those who had an operation. The investigators attribute

# ANESTHESIOLOGY™ 2014

OCTOBER 11-15 | NEW ORLEANS, LA

this to the possibility of difficult clinical diagnoses of bleeding in trauma patients and subsequent survival bias in the TXA group.

In 2012, Ker et al. published a systematic review looking at the effect of TXA on surgical bleeding, mortality, and thromboembolic events. The study reviewed 129 randomized controlled trials (RCTs) with over 10,000 patients spanning 4 decades. The review included all types of surgery with orthopedic being the second most prevalent after cardiac procedures. Consistent with the past 10 years of surgical research, TXA reduces the probability of receiving blood transfusion by 32-38%. In fact, the authors conclude that further studies examining this known efficacy on transfusion reduction will likely be futile. Nevertheless, there was a mild mortality reduction with the TXA group, but this effect was lost when the analysis was limited to studies with better concealment methods. The study was inconclusive when it comes to myocardial infarction, stroke, DVT, or PE despite a lowered or equivocal trend. There were no suggestions of any changes in thromboembolic risks compared to placebo. The authors recommend that large pragmatic surgical trials examining these uncertain and specific factors are desperately needed.

Although no such large trial exists in orthopedics, meta-analyses looking at the use of TXA in major spine and joint procedures have been undertaken. In 2013, Huang et al. published a meta-analysis of 46 RCTs of major orthopedic procedures and found that TXA reduces total blood loss by an average of more than 400ml (mostly postoperative blood loss) and reduces transfusion requirement by 49% with no increase in DVT rates. No meta-analyses published have identified any increased incidence of DVT or PE associated with TXA. Although these results appear promising, the authors acknowledge that the majority of the studies they included often had a small sample sizes and the study designs often suffered from inherent methodological flaws. Also, their overall analyses were subjected to publication bias. Still, the impartial effect that TXA has on venous thromboembolic risks is duplicated in another large retrospective study published in 2012 looking at over 2,000 hip and knee arthroplasty patients stratified to three different DVT prophylaxis regimen including aspirin, warfarin, and dalteparin. The authors conclude that the use of TXA did not incur increases in thromboembolic complications.

Nonetheless, primary joint arthroplasty or non-infected prosthetic revisions are mainly elective in nature and are distinct from emergent or urgent hip fracture operations. Some argue that risks of thromboembolism may be inherently higher in the geriatric population suffering from long bone fractures that have multiple comorbidities and greater incidence of preoperative anemia. Moreover, the effectiveness of TXA may be diminished since one third of total blood loss in hip fractures occurs preoperatively, in contrast to primary hip arthroplasty or revisions. In a 2009 RCT of 110 patients undergoing surgery within 48 hours of hip fracture, Zufferey et al. again showed a 30% relative risk reduction in transfusion with TXA as a result of fewer postoperatively hemorrhagic events. Interestingly, there was a three-fold increase (9 in TXA patients vs. 3 in placebo) in vascular events (most frequent being DVT) during a 6-week follow up that was inconsistent with other studies. It is important to note that this finding is not statistically significant, and the authors attribute the discrepancy to mandatory ultrasound monitoring of DVT in all asymptomatic patients. Furthermore, none of the patients with positive ultrasound findings became symptomatic or developed PE. Finally, the investigators used a higher TXA dose (15mg/kg) that may have implications on their validity. In their conclusions, Zufferey et al state, "the clinical significance of these findings could not be assessed... no definite conclusions

# ANESTHESIOLOGY™ 2014

OCTOBER 11-15 | NEW ORLEANS, LA

regarding the clinical benefit-risk ratio of the use of tranexamic acid can be derived from our trial”.

In 2013, a single center retrospective review of high risk orthopedic patients who received TXA may provide insights to the uncertain safety profile of TXA to date. In this cohort of over 1,000 mostly ASA 3 patients, 788 of them received 1 gram of TXA at incision and then 1 gram at closure. The primary outcome, which was the incidence of postoperative symptomatic thromboembolism (TE) at 30 days, was no different between TXA group (2.5%) and placebo (2.6%). 402 out of the 1,002 patients were categorized as a high risk subgroup because they were diagnosed with having at least 1 of the 7 risk factors for thromboembolic events (TE). These risk factors include a history of cardiac stents, DVT, PE, MI, CVA, CABG, or prothrombotic conditions. Prothrombotic conditions range from factor V Leiden, Protein C or S deficiencies, and antiphospholipid or anticardiolipin syndromes. When this high risk subgroup was compared to the others regardless of TXA use, there is a 7 fold increase in the incidence of TE (5.7% vs. 0.8%). This confirmed that the high risk subgroup carries a higher TE burden. 240 of this 402 high risk subgroup received TXA. Within this subgroup of 402 high risk patients, TXA use is associated with a higher trend of TE (6.7% vs. 4.3%) but this is not statistically significant. In order to show a significant difference in high risk patients, the authors calculated that an additional 3,000 high risk patients are needed. The only 3 deaths that occurred in this study were in the non-TXA group. Despite the ongoing uncertainty regarding its risk, this study in high risk patients provides a significant step toward closing the gap in the understanding and establishment of safety profile for TXA.

Another major drawback to the TXA studies in orthopedics is the absence of standardized dosing regimen. A typical dose for major spine and orthopedic cases is a 10mg/kg loading dose over 10-30 minutes prior to skin incision follow by 1mg/kg/hr infusion for the remainder of the case. Practitioners remain variable in their use of TXA postoperatively ranging from 0-24 hours. Nevertheless, some argue that a more precise dosing scheme that is tailored to timing of the procedure (THR) and pneumatic tourniquet application in TKR should be utilized. In a recent 2012 RCT titled, “Most Effective Regimen of Tranexamic Acid in Knee Arthroplasty”, 240 patients were randomized into 6 groups varying in the timing and routes of TXA administration. All 4 intravenous intervention groups had better outcomes when compared to placebo. Looking at the primary outcome of total blood and drain loss, the most effective dosing regimen appears to be a 10mg/kg loading dose given at the beginning of surgery, one before tourniquet deflation, and the third, three hours after the last dose. In addition, the authors conclude that a single dose regimen was ineffective and at least a double dosing regimen is needed. Despite a few well-designed dose ranging and efficacy studies, there is no consensus on the best dosing regimen that will suit every institution, system, and practice.

Similarly, there is a dearth of data on TXA dosing in renal impairment patients despite the long history of its use in cardiac surgery. Nutall et al. implemented a renal dosing regimen in 20 cardiac surgery patients in a 2008 prospective randomized study. Based on their calculations, the authors believe that the initial loading dose of 10mg/kg is reasonable for all patients. The alternate regimen is based on a 25-75% reduction of the 2mg/kg/hr maintenance dose used for cardiac surgery that continued 2 hours postoperatively after arrival to ICU.

Finally, in terms of economic impact and cost effectiveness, multiple studies have shown that TXA reduces total hospital cost of up to more than \$700 per healthy patient undergoing joint

# ANESTHESIOLOGY™ 2014

OCTOBER 11-15 | NEW ORLEANS, LA

arthroplasty. This should be considered in the global context of severe blood product shortages and escalating healthcare costs.

## *Conclusion*

The bloody controversy persists, but certain parts of the debate are clear. First, there is little doubt that TXA reduces total blood loss and the need for transfusion by at least a third perioperatively. The benefits to preventing perioperative anemia and reducing transfusion are well established including a reduction in mortality and in-hospital complications. In orthopedics, postoperative anemia is associated with a shorter walking distance on discharge, higher infection rates, increased length of stay, and higher mortality in hip fracture patients. Second, a majority of well designed RCTs and meta-analyses with substantial number of patients repeatedly and consistently validated the favorable efficacy and safety profiles of TXA in multitudes of surgical settings. Third, TXA appears to be the best antifibrinolytic agent. Lastly, cautious use of TXA in major joint replacement procedures has the potential to become an important centerpiece for patient blood conservation and management.

Still, perplexing inquiries remain that demand answers from future trials. Importantly, the TE risks for high-risk patients are yet to be determined in a definitive way. Other less significant factors that might contribute to TE risks such as pregnancy, morbid obesity, malignancies, age, organ impairment, medications (hormone replacement therapy), immobility, and emergent operations are yet to be explored. Other emerging topics include TXA dosing in renal impairment, the efficacy of TXA in procedures with minimal to moderate hemorrhage, the use of topical TXA, and TXA use in the context of newer postoperative thromboprophylaxis agents.

## **References**

1. Llyod, Janice. Knee replacements on the increase among older adults. USA Today. Posted 9/25/2012. <http://usatoday30.usatoday.com/news/nation/story/2012/09/25/knee-replacements-on-the-increase-among-older-adults/57841616/1>.
2. Beattie WS, et al. Risk associated with preoperative anemia in noncardiac surgery: a single cohort study. *Anesthesiology* 2009 Mar; 110:574-81.
3. Shander A, et al. What is really dangerous: anaemia or transfusion? *British Journal of Anaesthesia* 2011; 107: i41-59.
4. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of literature. *Anesthesiology* 2010; 113:482-95.
5. Vaislic CD, et al. Outcomes in cardiac surgery in 500 consecutive Jehovah's Witness patients: 21 year experience. *J Cardiothorac Surg* 2012 Sep 27; 7: 95.
6. Jassar AS, et al. Cardiac surgery in Jehovah's Witness patients: ten-year experience. *Ann Thorac Surg* 2012 Jan; 93(1): 19-25.
7. Harwin SF, et al. Revision total hip arthroplasty in Jehovah's Witnesses. *Orthopedics* 2012 Aug 1; 35(8): e1145-51.

8. Goodnough, LT, Shander, A. Current Status of Pharmacologic Therapies in Patient Blood Management. *Anesth Analg* 2013 Jan; 116(1): 15-34.
9. Schulman, S. Pharmacologic tools to reduce bleeding in surgery. *Hematology Am Soc Hematol Educ Program*. 2012 Dec; 2012: 517-521.
10. Dunn CJ, et al. Tranexamic acid: A review of its use in surgery and other indications. *Drugs* 1999 Jun; 57: 1005-1032.
11. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. *J Am Acad Orthop Surg* 2010 Mar; 18(3): 132-8.
12. Henry DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011 Mar 16;(3): CD001886.
13. Fergusson DA, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008 May 29; 358(22): 2319-2331.
14. Camarasa MA et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. *British Journal of Anaesthesia* 2006; 96(5): 576-82.
15. Zufferey P, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *Anesthesiology* 2006; 105: 1034-46.
16. CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010 Jul 3; 376(9734): 23-32.
17. Roberts I, et al (CRASH-2 Collaborators). Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. *BMJ* 2012 Sept 11; 345: e5839.
18. Ker K, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012 May 17; 344:e3054.
19. Huang F, et al. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: a meta-analysis. *J Surg Res*. 2013 Sept; 1-10.
20. Gillette BP, et al. Low risk of thromboembolic complications with tranexamic Acid after primary total hip and knee arthroplasty. *Clin Orthop Relat Res* 2013 Jan; 471(1): 150-4.
21. Zufferey PJ et al. Tranexamic acid in hip fracture surgery: A randomized controlled trial. *Br J Anaesth* 2010 Jan; 104(1):23-30.
22. Whiting DR, et al. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. *Clin Orthop Relat Res* 2013; Epub.

# ANESTHESIOLOGY™ 2014

OCTOBER 11-15 | NEW ORLEANS, LA

23.

Maniar RN, et al. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. *Clin Orthop Relat Res* 2012 Sep; 470(9): 2605-12.

24.

Tanaka N, et al. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. *J Bone Joint Surg Br* 2001 Jul; 83(5): 702-705.

25.

Nuttall GA, et al. A Preliminary Study of a New Tranexamic Acid Dosing Schedule for Cardiac Surgery. *J Cardiothorac Vasc Anesth* 2008 Apr; 22(2): 230-5.

26.

Gillete BP, et al. Economic impact of tranexamic acid in healthy patients undergoing primary hip and knee arthroplasty. *The Journal of Arthroplasty* 2013; 28(1): i37-39.

27.

Irisson E, et al. Tranexamic acid reduces blood loss and financial cost in primary total hip and knee replacement surgery. *Orthop Traumatol Surg Res* 2012 Sep; 98(5): 477-83.