Can Topical Application of Tranexamic Acid Reduce Postoperative Blood Loss in Shoulder Arthroplasty and Primary Hip Arthroplasty?

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Can Topical Application of Tranexamic Acid Reduce Postoperative

Blood Loss in Primary Hip Arthroplasty?

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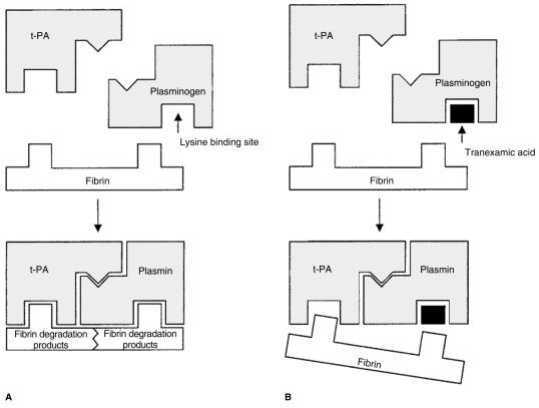
Investigation will be performed at the Steadman Hawkins Clinic of the Carolinas, Greenville, SC; Simpsonville, SC; Greer, SC

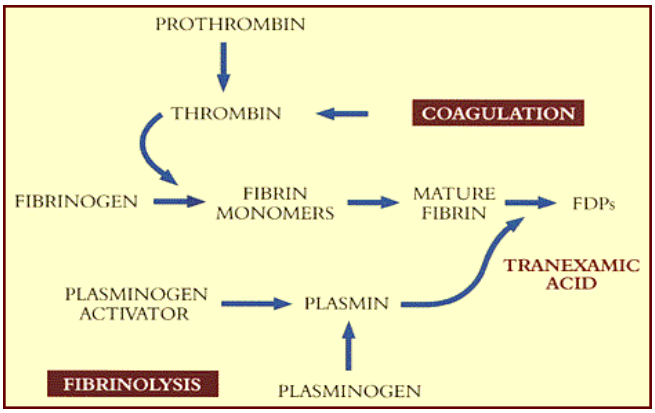
Specific Aim/Hypothesis: The objective of this study is to evaluate the efficacy of topical tranexamic acid in decreasing blood loss following primary total hip arthroplasty. We hypothesize that topical application of tranexaminic acid (TXA) prior to closure reduces postoperative bleeding as measured by absolute changes in postoperative hemoglobin levels and surgical drain output. In addition, use of topically applied tranexaminic acid may reduce the need for transfusions, the rates of hematomas, infections, and length of hospital stay.

Significance: Post-operative blood transfusion is often required and variable depending on primary, revision, or reverse procedures, with reported rates ranging from 8% to 45% in several studies. (Sperling, J JSES 2005) (Millet, P JBJS 2006). Following hip and knee arthroplasty, estimated blood loss ranges from 450-1500 ml and 180-330 ml, respectively (Bierbaum JBJS 1999).

TXA is an antifibrinolytic agent that has been studied extensively in major orthopaedic and cardiac procedures and has been found to efficacious in reducing blood loss and transfusion requirements. Applied either systemically or topically, TXA functions to decrease blood loss through the inhibition of clot degradation. Its mechanism of action is via a reversible interaction with plasminogen and the active protease, plasmin. TXA saturates the lysine binding site of plasminogen, inhibiting plasminogen from binding to the surface of fibrin. It has a relatively short half life (1-2h) and is rapidly excreted unchanged in urine (Eubanks, JAAOS 2010). TXA has been associated with nausea, vomiting, diarrhea, orthostatic reactions, and rare dermatitis reactions. No increased risk of

thromboembolism has been reported.





Topical application of tranexaminic acid to bleeding wound surfaces has been shown to reduce blood loss in patients undergoing major orthopaedic surgeries, without an increased risk of systemic complications. Numerous studies have shown that systemic use of TXA in hip and knee arthroplasty is safe and effective in reducing blood loss following hip or knee replacement (Sepah JOSR 2011) (Yang JBJS 2012). A recent RCT showed that topical TXA in knees could reduce post-operative bleeding by 20%-25%, or 300 to 400ml, resulting in roughly 16% higher postoperative hemoglobin levels compared to placebo (Wong JBJS 2010). In a recent meta-analysis investigating the effectiveness and safety of tranexamic acid in total knee arthroplasty, the amount of blood loss and the number of patients requiring blood transfusions was lower in patients receiving tranexamic. Similar results have also been demonstrated in posterior lumbar spine surgery (Endres BMC Surgery 2011). However, to date, no studies have shown the effectiveness of topical TXA application in primary hip arthroplasty procedures.

From a financial perspective, the application of TXA has many benefits. In one study, the use of TXA reduced the cost of blood salvage by as much as 25%, prompting the institution to eliminate routine use of intra-operative blood salvage (Cell Saver) in primary total hip and knee arthroplasty given its limited impact in patients treated with TXA (Irrison OTSR 2012). The same study suggested a cost-saving effect of TXA therapy related to decreases in anesthesia costs and length of hospital stays. Topical application of tranexaminic acid is simple and inexpensive compared with other commonly used topical fibrin sealants. Approximate costs for fibrin sealants from one study was $585 US compared with a $6 cost of administering TXA as noted in the Wong (JBJS 2010) article.

Double blind randomized prospective trial:

Sample Size Estimate: Provided by Chad Cook PhD

Hip: Using a 2-tailed t-test for independent groups and post-op blood loss as the primary outcome measure with an estimated effect size of 0.59, at 80% power, a standard error of 0.05, and a drop-out rate of 20%, we estimate the need for a minimum sample size of 100 (50 in each group) for statistical significance and 120 to account for the drop outs. The study will use an intention to treat analysis.

Current Standard Of Care: Non Study Patients undergoing a THA may receive TXA intravenously depending on their surgeon's current standard of care. This decision is made on a case by case basis depending on their surgeon's standard of care. Intravenous application is approved by GHS. The study treatment arms will not change, however potential patients will be informed of the standard of care as well as the randomization options. The topical application may offer less risk or a more direct effect to patients as compared to the intravenous application.

Age and Gender Matched Control (Intravenous TXA) Group: A group of patients who previously received TXA intravenously and have completed the same standard post-operative protocol will be age and gender matched to the study participants who were randomized to the topical TXA group for comparison. Using a 2-tailed t-test for independent groups and post-op blood loss as the primary outcome measure with an estimated effect size of 0.55 at 80% power, a standard error of 0.05, and no drop outs, we estimate the need for a minimum single arm sample size of 53 for statistical significance. The study will use an intention to treat analysis.

Inclusion Criteria: .

Hips: All adult patients over the age of 18 scheduled for a primary total hip arthroplasty will be eligible for the inclusion in the study.

Exclusion Criteria:

The exclusion criteria will include allergy to TXA, refusal of blood products, preoperative use of anticoagulant therapy within 5 days of surgery, history of seizures, renal failure (creatine clearance <30ml/min), bleeding disorders, venous thromboembolism (deep vein thrombosis and/or pulmonary embolism), significant cardiac history (myocardial infarction, angina, stroke, lower limb ischemia), or perioperative anemia (hemoglobin <11g/dl in females and < 12g/dl in males).

At the time of surgery, via randomization patients will receive either:

1) **Control:** Irrigation of 100ml of normal saline
2) **TXA:** 1g (100mg/ml) of tranexaminic acid (Cyklokapron) Pfizer, New York,NY in 100ml normal saline solution. This dosage was chosen as this has been utilized in previous studies and was shown to be safe and effective in reducing blood loss following total knee arthroplasty (Craik Eur J Orthop Surg Traumatol 2013). Effective TXA dosing has shown to range from 1-1.5g, with 1 g being the most cost effective to the patient. A higher dose of 3g was also used in a study and no difference in efficacy was observed. (Wong JBJS 2010). The solution will be prepared by our surgical pharmacy and provided at the time of surgery to the operative circulating staff. Both the patient and the surgical staff will be blinded as to the treatment regimen.

Surgical Intervention:

After all components are secured into place, the joint will be thoroughly irrigated and the study medication applied to open joint surfaces with use of a bulb syringe, solution soaked sponges will be left in contact with the tissues for five minutes, and then removed. The wound will then be closed without any irrigation or manipulation. Surgical drains will be placed for <24 hours. Postoperatively, all patients will receive aspirin, Coumadin, or LMWH (Low molecular weight heparin) based on our current thromboprophylaxis protocols).

Outcome Measures

Primary outcome will be blood loss as calculated from the difference between the preoperative hemoglobin and the lowest postoperative hemoglobin during the hospital stay or the lowest postoperative hemoglobin prior to blood transfusion. Based on hemoglobin balance, the estimated blood loss will be calculated according to the formula described by Good et al.[7] and Nadler et al.[23]

A standard H/H will be measured post op Day 1, and any subsequent hospital day stays. Other data that will be collected and compared: Age, BMI, Weight, **American Society** of **Anesthesiologists** (ASA) Physical Status **classification**, Smoker, OR time (minutes), EBL (ml), cemented vs non-cemented , Inpatient Length of Stay (Days), Direct Discharge to home (%), and any complications, such as infection, thromboembolism, revisions, or hematomas. Secondary outcomes will be assessed and will focus on the rate of perioperative blood transfusions, the number of blood units transfused, the rate of surgical infections, the length of hospital stay, the time until the start of a rehabilitation program, the postoperative changes in joint function (i.e., the range of motion and the severity of pain at rest as determined with use of a visual analog scale [possible range, 0 to 10] on postoperative day 2, and at 3 and 9 weeks and 6 months after surgery for hip patients. General Outcome measures include EQ-5D, GROC, SANE, Harris Hip score and WOMAC.

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http://www.bjjprocs.boneandjoint.org.uk/content/93-B/SUPP_II/95.2.abstract (Appendix A)

3. http://www.nytimes.com/2012/03/21/health/tranexamic-acid-cheap-drug-is-found-to-staunch-bleeding.html?_r=0 (Appendix B)

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Appendix A:

RANDOMISED CONTROLLED TRIAL OF THE USE OF TOPICAL APPLICATION OF TRANEXAMIC ACID IN PRIMARY TOTAL KNEE REPLACEMENT

1. Sattar Alshryda,
2. Praveen Sharda,
3. Anup Shetty,
4. Manesh Vaghela,
5. Raj Logishetty,
6. Chris Tulloch,
7. Nargol Antoni and
8. James Mason

Abstract

Introduction: Today's aging population has resulted in an increase in the number of major orthopaedic surgical interventions in the elderly. Total knee replacement (TKR) is one of the commonest operations in orthopaedic practice. The fourth annual report of the National Joint Registry showed that there were 60 986 TKR performed in England and Wales in 2006. The true figure is probably much higher. Literature showed that 20–70% of patients who had TKR needed 1–3 units of blood.

Although safer than ever, allogeneic transfusion is still associated with risks for the recipient (haemolysis, infection, immunosuppression, transfusion-related acute lung injury and even death).

Tranexamic acid (TA) is a synthetic antifibrinolytic agent that has been successfully used to stop bleeding after dental operation, removal of tonsils, prostate surgery, heavy menstrual bleeding, eye injuries and in patients with Haemophilia.

In this study Tranexamic acid was applied topically to the exposed tissue around the knee joint prior to the wound closure and tourniquet release. It is anticipated that this method of administration is quick, easy, associated with less systemic side effect. Also, it provides a higher concentration of the Tranexamic acid at the bleeding site.

Objectives: To find out whether Tranexamic acid can reduce blood loss and subsequent blood transfusion significantly after total knee replacement when applied topically without extra side effects.

Design: A double blind randomised controlled trial of 150 patients who underwent unilateral primary cemented total knee replacement. This number gives a 90% power to detect a 50% reduction in blood loss and 80% power to detect a reduction in blood transfusion from current local standard 30% to 10%.

Outcome Measures: Blood loss, transfusion, Length of stay, complications, Euroqol and Oxford Knee Score.

Results: The two groups were comparable in age, weight, height, BMI, Tourniquet time, and type of anaesthesia. There has been significant differences in the amount of blood loss and blood transfusion in favour of tranexamic acid (p-values are 0.001 and 0.007 respectively). Fourteen patients needed blood transfusion ranged from 2–6 units. Thirteen were in the Placebo group and only one in the Tranexamic acid. There has been no significant difference among other outcomes in particular complications rates such as DVT and pulmonary embolism.

Appendix B: NY Times
March 20, 2012

A Cheap Drug Is Found to Save Bleeding Victims
By DONALD G. McNEIL Jr.

For months, a simple generic drug has been saving lives on America's battlefields by slowing the bleeding of even gravely wounded soldiers.

Even better, it is cheap. But its very inexpensiveness has slowed its entry into American emergency rooms, where it might save the lives of bleeding victims of car crashes, shootings and stabbings — up to 4,000 Americans a year, according to a recent study.

Because there is so little profit in it, the companies that make it do not champion it.

However, the drug is edging slowly closer to adoption as hospitals in New York and other major cities debate adding it to their pharmacies. The drug, tranexamic acid, has long been sold over the counter in Britain and Japan for heavy menstrual flow. After a groundbreaking 2010 trial on 20,000 hemorrhaging trauma patients in 40 countries showed that it saved lives, the British and American Armies adopted it. The World Health Organization added it to its essential drugs list last year, and British ambulances now carry it.

But outside Britain, it is used in very few civilian hospitals, though almost six million people around the world die each year of trauma — 400,000 of them in hospitals. A study published March 1 in BMC Emergency Medicine estimated that the drug could save up to 128,000 of those lives a year, 4,000 of them in the United States.

The slowness of American hospitals is due to "inertia," said Dr. Ian Roberts, clinical trials director for the London School of Hygiene and Tropical Medicine and leader of the 2010 trial, which was called Crash-2. "The people who do the urging and the talking about new drugs are the pharmaceutical companies, and if they're not interested, it's not done."

Many companies in India and China make tranexamic acid. Pfizer, which makes an injectable form for hemophiliacs (and donated thousands of doses to the Crash-2 trial), declined to give sales figures or even discuss administering it to trauma patients because the Food and Drug Administration has not approved that use. A company spokeswoman declined to say whether Pfizer had applied for approval. (Doctors may prescribe approved drugs for "off-label" uses, but drugmakers cannot endorse off-label uses without F.D.A. permission.)

The drug is believed to block plasmin, an enzyme that dissolves blood clots.

New York City's public hospital trauma doctors "are excited about the possibilities and discussing the risks and benefits" said Ana Marengo, a spokeswoman for the city's Health and Hospitals Corporation. A decision will be made "in a couple of months," she said.

Spokesmen for Cook County Hospitals in Chicago, San Francisco General Hospital and Grady Memorial Hospital in Atlanta said they too were moving toward using it, probably within two months. Los Angeles

County hospitals have no such plans yet, a spokesman said.

Crash-2, which showed that getting the drug within three hours reduced the risk of fatal hemorrhage by 30 percent, “was an amazing study,” said Dr. John B. Holcomb, chief of trauma surgery at the University of Texas Health Science Center in Houston, which does use the drug. “Twenty thousand patients, and it was done in some places that had no lab tests.”

The United States Army took note when the drug was used on its soldiers in British Army hospitals.

“So we had a dog in that fight,” said Dr. Todd E. Rasmussen, an Air Force colonel who is now deputy commander of the Army Institute of Surgical Research in San Antonio.

American surgeons were skeptical, he said, until he led a follow-up study, called Matters, which looked at the fates of 896 British patients.

It found that severely wounded patients who got the drug survived twice as often as those who had not; that convinced his American colleagues.

Recent wars have taught combat surgeons many new lessons that later caught on in civilian emergency rooms, said Dr. David E. Lounsbury, a retired colonel and co-author of a 2008 Army textbook, “War Surgery in Afghanistan and Iraq: A Series of Cases, 2003-2007.”

Traditional hemorrhage treatment — giving intravenous saline solution to restore blood pressure — actually killed patients, he said, because it diluted clotting factors. Army doctors switched to giving blood and plasma; then, in the mid-2000s, added recombinant factor VIIa, a very expensive new clotting drug. But use of it faded, he said, after some patients got life-threatening clots on evacuation flights.

Tranexamic acid was never even in his combat hospital’s pharmacy. “An old generic doesn’t have any hair-on-your-chest bravado, so we didn’t even take it to the battlefield,” Dr. Lounsbury said.

That the British pioneered it “makes complete sense to me,” he added. “I worked in their hospitals, and they did pretty much everything we did — but much more cheaply.”

Dr. Holcomb, in Houston, said his hospital, the only one he knew that was now using it, gives it only to patients whose blood fails a clotting test. He insists on the test, even though it adds half an hour, because he is skeptical of one Crash-2 conclusion: that there are no side effects.

“Every drug has side effects,” he said. “Even aspirin.”

Dr. Roberts, in London, responded, “Well, John Holcomb’s intuition may be that there must be side effects, but we looked at 20,000 patients and the data doesn’t show it.”