Single versus Multi-Dose Oral Tranexamic Acid in Patients at High Risk for Blood Transfusion After Total Joint Arthroplasty

Purpose: As tranexamic acid (TXA) becomes more prevalent, all patients are receiving the same dose regardless of their pre-operative risk of transfusion. Therefore the aim of the study is to determine whether or not repeated dosing of oral TXA reduces the post-operative reduction in hemoglobin, hematocrit, number of transfusions, and post-operative blood loss following primary TKA and THA surgeries in patients with low pre-operative hematocrit and high risk for transfusion.

Hypothesis: The regimen that utilizes multiple doses of oral TXA will significantly minimize post-operative blood loss and transfusion requirements compared to the use of a single dose regimen.

Background/Scientific review:
Total joint arthroplasty is associated with the risk of moderate to significant blood loss. Because TXA has been shown to significantly reduce the need for blood products during total joint replacement, it is now the standard of care at many institutions.[1-3] Oral and intravenous TXA are equivalent, but oral TXA is cheaper and allows for ease of repeat dosing.[1] Although low preoperative hemoglobin is a risk factor for transfusion, no studies that have compared standard TXA dosing to risk stratified dosing of TXA.

Study Design: Prospective, randomized, double-blinded study

Inclusion Criteria: Any patient > 17 years of age scheduled for a primary cemented TKA or cementless THA with preoperative hematocrit less than 36%.

Exclusion Criteria: Known allergy to TXA, acquired disturbances of color vision, refusal of blood products, pre-operative use of anticoagulant therapy within five days before surgery, a history of arterial or venous thrombotic disease (including a history of DVT, PE, CVA, TIA), pregnancy, breastfeeding, or major co-morbidities (myocardial infarction or stent placement within one year, severe pulmonary disease, renal impairment, or hepatic failure), any patient undergoing a revision TKA, revision THA, hip resurfacing, or UKA, and patients who decline to participate

Screening Procedures and Randomization: At the pre-operative clinic appointment and before the day of surgery, the study staff will assess the potential subject's eligibility. Once eligibility is established, the potential subject will be approached regarding their participation in this clinical trial. We will provide 48 hours before the date of surgery to allot for questions and consideration of the Informed Consent document. Once all patient questions have been answered,

1. Fillingham YA, Kayupov E, Plummer DR, Moric M, Gerlinger TL, Della Valle CJ. A Randomized Controlled Trial of Oral and Intravenous Tranexamic Acid in Total Knee Arthroplasty: The Same Efficacy at Lower Cost? The Journal of arthroplasty. 2016 Mar 19.
2. Irwin A, Khan SK, Jameson SS, Tate RC, Copeland C, Reed MR. Oral versus intravenous tranexamic acid in enhanced-recovery primary total hip and knee replacement: results of 3000 procedures. The bone & joint journal. 2013 Nov;95-B(11):1556-61.
3. Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. The Journal of bone and joint surgery British volume. 2011 Jan;93(1):39-46.
4. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. The Journal of bone and joint surgery American volume. 2010 Nov 3;92(15):2503-13.
5. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962 Feb;51(2):224-32.

patients willing to be in the study will sign the Informed Consent. Patients will be randomized, via standard randomization tables that provide a 1:1 distribution of subjects between the two groups through blocked randomization, no later than the morning of surgery to either of the two treatment groups: Conventional Oral TXA Group or Multi-Dose Oral TXA Group.

Sample Size Calculation: We estimate that the rate of transfusion for patients with HCT <36% who receive one oral dose of TXA preoperatively is 15%. After discussions within our group, we determined that a reduction by half to 7.5% would be clinically meaningful. Using these parameters, sample size calculation determined that 151 patients per treatment group (302 patients total) are required to provide an alpha of 0.05 and beta of 0.80. This total of 302 patients includes a 10% drop-out rate to allow for protocol deviations.

Demographics/Patient Specifics: Age, sex, ASA score, weight, height, estimated intra-operative blood loss, intra-operative fluids (crystalloid, colloid), operative time, hospitalization days, BMI, pre-operative hemoglobin, hematocrit, PT/INR, PTT, and platelet count.

Treatment Groups:

1. Conventional Oral TXA Group (76 TKAs, 76 THAs) – Three 650mg tablets of oral TXA 2 hours prior to incision with three 250mg tablets of ascorbic acid (oral TXA placebo) given 6 hours postoperatively and a final 750mg ascorbic acid dose given the morning of postoperative day 1.
2. Multi-Dose Oral TXA Group (76 TKAs, 76 THAs) – Three 650mg tablets of oral TXA 2 hours prior to incision with a second 1950mg oral TXA dose given 6 hours postoperatively and a final 1950mg oral TXA dose given the morning of postoperative day 1.

Outcome Measurements: (Assessed during hospital stay and at routine outpatient follow-up visit which occurs about 3 weeks after discharge and within 30 days of surgery)

1. Number of patients transfused (primary outcome) and units transfused
2. Post-operative reduction in hemoglobin and hematocrit
3. Calculated blood loss – Based on predicted blood volume and hemoglobin balance[4,5]
4. Cost comparison – Cost differences resulted from differences in the blood transfusion rate, length of hospital stay, and management of complications as well as from the cost of the TXA itself
5. Complications – DVT/PE, return to the OR within 30 days, superficial or deep infection, and cerebrovascular accident, transient ischemic attack or MI

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