A Different Approach to Preventing Thrombosis (ADAPT): A Randomized Controlled Trial Comparing Low Molecular Weight Heparin to Acetylsalicylic Acid in Orthopedic Trauma Patients

Study Protocol and Statistical Analysis Plan

NCT02774265

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Study Design
ADAPT was a single-center randomized controlled trial that compared safety of low molecular weight heparin (LMWH) versus aspirin with respect to bleeding and wound complications in orthopaedic trauma patients within 90-days of their fracture. Ethics approval was obtained by the University of Maryland Institutional Review Board and informed consent was obtained for all enrolled patients.

Eligibility Criteria
All adult trauma patients (age ≥18 years) with operative extremity fracture proximal to the carpals/metatarsals or any hip or acetabular fracture requiring VTE prophylaxis were included in the study. We excluded prisoners, pregnant patients, non-English speaking patients, patients with an indication for therapeutic anticoagulation or high dose aspirin (greater than 81mg daily) and patients receiving pre-existing confounding prophylaxis or therapeutic anticoagulation prior to admission or greater than two doses of prophylaxis in our hospital prior to consent. Patients with recent VTE within the last 6 months, impaired creatinine clearance, history of heparin-induced thrombocytopenia or aspirin or non-steroidal anti-inflammatory allergy or another contraindication to receiving one of the study medications were also excluded.

Randomization and masking
Patients were randomly assigned venous thromboembolism prophylaxis by LMWH or aspirin using block randomization (6 per block) with the assistance of the trial's REDCap system by research staff at the study site after enrollment. Surgeons and patients were not masked to the treatment groups.

Intervention and Procedures
Patients allocated to the LMWH group received two 30mg BID doses daily with allowance for dose adjustment based on BMI or Xa levels. Patients allocated to the aspirin group received 81mg doses, twice daily. The duration of prophylaxis was at the treating surgeon's discretion, with no minimum or maximum duration. Mechanical prophylaxis with intermittent pneumatic compression devices is also ordered as part of clinical protocol for all inpatients. Study follow-up was conducted at 3-months post-fracture either at the patient's clinic appointment or over the phone. A chart review was also conducted at this time.

All prophylaxis doses were monitored daily during the index admission by the study's research staff. Additionally, outpatient adherence was assessed at all clinical follow-up visits. Any contamination or unplanned crossover was closely monitored.

Outcomes
The primary endpoint was bleeding complications within 90-days from the date of injury. Bleeding complications included a 2g/dL or greater drop in hemoglobin, blood transfusion, gastro-intestinal (GI) bleeding, surgical site hematoma requiring reoperation, or other bleeding events requiring intervention or resulting in death. Secondary exploratory outcomes included wound complications defined as a deep surgical site infections (SSI) based on the Centers for Disease Control and Prevention criteria that required operation, and VTE (including massive, sub-massive, or clinically significant pulmonary embolism and clinically significant deep vein thrombosis (either distal or proximal)). No screening of asymptomatic patients for VTE events

was done. All adverse events were reported to the IRB as per local requirements. Two medical monitors reviewed the safety of the trial and all serious adverse events.

Statistical Analysis

The study's sample size calculations were based on a retrospective review of the study centers database, which determined a 1-year historic bleeding complication rate of 15% in the study population. Based on arthroplasty literature, we hypothesized that aspirin would be associated with a 5% absolute reduction bleeding complications. Using a one-sided Fisher's Exact sample size calculation, an alpha of 0.05, and an allocation ratio of 1:1, a sample of 1150 patients would provide 80% power. This target sample was inflated to 1380 to allow for up to 20% loss to follow up. Within a year of starting the trial, funding was obtained to commence a large pragmatic trial comparing these two interventions with a primary endpoint of pulmonary embolism-related death. This trial was subsequently stopped after the enrollment of 329 participants, for which the safety of these two interventions was assessed

Analysis followed the intention-to-treat principle and included all patients in the groups to which they were randomly assigned. Bivariable analysis and multivariable logistic regression model were used to assess the association between type of VTE prophylaxis and the primary and secondary endpoints. The treatment effects were reported as odds ratios (OR) and 95% confidence intervals (CI). The analyses adjust for the time each patient is at risk of the analyzed study event, to a maximum of 90 days. Patients who did not complete the 90-day follow up were deemed at risk from their time of enrollment until their last documented follow-up. Kaplan-Meier curves were used to plot the time to study events by treatment arm.

Patient crossover and contamination was assessed at several thresholds including $\geq 5\%$, $\geq 10\%$, $\geq 25\%$, $\geq 50\%$ of the patient's total study doses being the non-allocated prophylaxis medication. All thresholds were assessed in a secondary as-treated analysis. A threshold of more than 50% of the patient's total study doses being the non-allocated prophylaxis medication is presented for the as-treated analysis in the results. Factors associated with patient crossover in this study sample were also assessed.

At the completion of the trial, we investigated possible effect measure modification by patient smoking status, history of VTE, mechanism of injury (high energy versus low energy), fracture location (upper extremity versus lower extremity), fracture severity (open fracture versus closed fracture), and non-orthopaedic injury (abdomen, head, or chest) determined by an Abbreviated Injury Scale score of ≥ 2. Each variable was added into the primary analysis as an interaction term. Statistically significant interactions were then analyzed stratifying by the effect measure modifier. The treatment effects in the stratified analysis were reported as odds ratios (OR) and 95% confidence intervals (CI), adjusting for time at risk.

All analyses were performed using JMP Pro Version 13 (SAS Institute, Cary, NC). This study was registered with ClinicalTrials.gov (NCT02774265).