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# Oral Xa Inhibitors *versus* low molecular weight heparin for thromboprophylaxis after nonoperative spine trauma

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ABSTRACT

*Background:* Thromboprophylaxis with oral Xa inhibitors (Xa-Inh) are recommended after major orthopedic operation; however, its role in spine trauma is not well-defined. The aim of our study was to assess the impact of Xa-Inh in spinal trauma patients managed nonoperatively.

*Methods:* A 4-y (2013-2016) review of the Trauma Quality Improvement Program database. We included all patients with an isolated spine trauma (Spine-abbreviated injury scale $\geq$3 and other-abbreviated injury scale <3) who were managed nonoperatively and received thromboprophylaxis with either low molecular weight heparin (LMWH) or Xa-Inh. Patients were divided into two groups based on the thromboprophylactic agent received: Xa-Inh and LMWH and were matched in a 1:2 ratio using propensity score matching for demographics, vitals and injury parameters, and level of spine injury. Outcomes were rates of deep venous thrombosis, pulmonary embolism, and mortality.

*Results:* We analyzed a total of 58,936 patients, of which 1056 patients (LMWH: 704, Xa-Inh: 352) were matched. Matched groups were similar in demographics, vital and injury parameters, length of hospital stay ($P = 0.31$), or time to thromboprophylaxis ($P = 0.79$). Patients who received Xa-Inh were less likely to develop a deep venous thrombosis (2.3% *versus* 5.7%, $P < 0.01$). There were no differences in the rate of pulmonary embolism ($P = 0.73$), postprophylaxis packed red blood cells transfusions ($P = 0.79$), postprophylaxis surgical decompression of spinal column ($P = 0.75$), and mortality rate ($P = 0.77$).

*Conclusions:* Oral Xa-Inh seems to be more effective as prophylactic pharmacologic agent for the prevention of deep venous thrombosis in patients with nonoperative spinal trauma compared to LMWH. The two drugs had similar safety profile. Further prospective trials should be performed to change current guidelines.



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## Introduction

Approximately 860,000 trauma admissions occur annually, with over 41,000 of these admissions are secondary to spine injury.[1] Venous thromboembolism (VTE) includes both deep venous thrombosis (DVT) and pulmonary embolism (PE) which can present itself via spectrum of symptoms ranging from occult events to life-threatening.[2,3] Patients after trauma are particularly at high risk of developing DVT and PE as trauma induces direct endothelial injury. Moreover, this risk is further aggravated by subsequent immobilization following spine trauma. In literature, VTE ranges from 4% to 32% depending upon the demographic and injury parameters of the patients, the methods of detection, and type of thromboprophylaxis used.[4-6]

With increasing burden of VTE in trauma patients, the American College of Chest Physicians and the Eastern Association for Surgery of Trauma recommends the use of either low-dose unfractionated heparin (UFH), low molecular weight heparin (LMWH) with or without mechanical prophylaxis after trauma.[7,8] However, like any other drug, thromboprophylaxis is associated with certain complications including hemorrhage which is a major concern for prescribing physician. Novel oral anticoagulants (NOACs) are relatively new anticoagulants that offer benefits over warfarin. The two classes of NOACs that have been introduced in the last decade include direct thrombin inhibitors and direct factor Xa inhibitors (Xa-Inh). Although the American College of Chest Physicians and the Eastern Association for Surgery of Trauma guideline recommend the use of UFH or LMWH, NOACs particularly the oral Xa-Inh has gained popularity as thromboprophylactic agent after elective orthopedic surgery.[9,10] However, the role of oral Xa-Inh as thromboprophylactic agent after trauma is still not well established. Therefore, the aim of our study was to assess the impact of thromboprophylaxis with oral Xa-Inh on outcomes in trauma patients with acute spine injury managed nonoperatively. We hypothesized that thromboprophylaxis with oral Xa-Inh is associated with lower rates of DVT and PE without increasing the rate of hemorrhagic complications in patients after nonoperative spine trauma.

## Methods

### *Study design and population*

We performed a 4-year (2013-2016) retrospective analysis of the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) database and identified all the patients who had a diagnosis of spine trauma on presentation using ICD-9 and ICD-10 codes and were managed nonoperatively. The TQIP is a well-known effort to improve the quality of trauma care using a risk-adjusted benchmarking methodology. As of 2014, more than 700 hospitals are participating in TQIP. Trained personnel abstract more than 100 patient and institutional variables, including patient demographics (age, gender, and race), comorbidities, injury parameters (type and mechanism of injury, injury severity score [ISS], and abbreviated injury scale [AIS]), prehospital and emergency department (ED) vitals, in-hospital procedures, complications and mortality, and discharge disposition. The TQIP began collecting VTE prophylaxis data (type and timing of initiation) from participating trauma centers in 2013.[5] Although the TQIP is administered by ACS, the authors of this study are solely responsible for the analyses and conclusions presented here. The institutional review board approval was exempted because the TQIP only contains deidentified data.

### *Inclusion and exclusion criteria*

We included all adult patients (age $\geq$18 y) who had an isolated spine injury (defined as spine-AIS $\geq$3 and other body region with AIS <3), a diagnosis of vertebral fracture, received pharmacologic thromboprophylaxis with either Xa Inhibitors or LMWH, and underwent nonoperative management for spine injury. Patients with hospital stay <2 d who were transferred from other institutes or were dead within first 24 h of arrival were excluded from the analysis.

### *Data points*

We abstracted the following data points for each patient: demographics (age, gender, race, and ethnicity); injury parameters (mechanism of injury, ISS, spine-abbreviate injury scale score [s-AIS]); admission vitals (systolic blood pressure [SBP], heart rate [HR], temperature, and Glasgow coma scale [GCS]); type of thromboprophylaxis agent used (Xa-Inh or LMWH); timing of initiation of thromboprophylaxis; and length of hospital stay (LOS), in-hospital complications, and mortality.

### *Patient stratification*

Patients were stratified into two cohorts based on the type of thromboprophylactic agent; those who received Oral Xa-Inh and those who received LMWH.

### *Outcomes*

Our primary outcome measures were rates of DVT and/or PE in both groups. Secondary outcome measures were postprophylaxis packed red blood cells (pRBCs) transfusion, any surgical decompression of the spinal column, and in-hospital mortality. Postprophylaxis pRBCs transfusion was taken as a surrogate marker for any bleeding complications, while surgical decompression of the spinal column was considered the marker for intraspinal hematoma development secondary to thromboprophylaxis.

### *Missing data analysis*

Missing data were treated as missing completely at random. Multiple imputations using a missing value analysis technique to account for the missing values were performed. For multiple imputations, the original data set was analyzed for random missing data points using Little's missing completely at random test. The Markov Chain Monte Carlo method was