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ORIGINAL PAPER

# Tranexamic acid with a pre-operative suspension of anticoagulation decreases operative time and blood transfusion in the treatment of pelvic and acetabulum fractures

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## Abstract

**Purpose** The purpose was to evaluate the impact of intra-operative administration of tranexamic acid (TXA) and pre-operative discontinuation of prophylactic chemoprophylaxis in patients undergoing internal fixation of pelvic or acetabular fractures on the need for subsequent blood transfusion. Operative time and the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) were also assessed.

**Methods** Data from a single level one trauma centre was retrospectively reviewed from January 2014 to December 2017 to identify pelvic ring or acetabular fractures managed operatively. Patients who did not receive their scheduled dose of chemoprophylaxis prior to surgery but who did receive intra-operative TXA were identified as the treatment group. Due to the interaction of VTE prophylaxis and TXA, the variables were analyzed using an interaction effect to account for administration of both individually and concomitantly.

**Results** One hundred fifty-nine patients were included. The treatment group experienced a 20.7% reduction in blood product transfusion (regression coefficient (RC): − 0.207, $p = 0.047$, 95%CI: − 0.412 to − 0.003) and an average of 36 minutes (RC): − 36.90, $p = 0.045$, 95%CI: − 72.943 to − 0.841) reduction in surgical time as compared to controls. The treatment group did not experience differential rates of PE or DVT (RC: 1.302, $p = 0.749$, 95%CI: 0.259–6.546) or PE (RC: 1.024, $p = 0.983$, 95%CI: 0.114–9.208).

**Conclusions** In the study population, the combination of holding pre-operative chemoprophylaxis and administering intra-operative TXA is a safe and effective combination in reducing operative time and blood product transfusions.

**Keywords** Venous thromboembolism · Deep vein thrombosis · Tranexamic acid · Pelvic ring · Acetabulum · Fracture · Operative time · Transfusion

## Introduction

Pelvic and acetabular traumas are known risk factors for venous thromboembolism (VTE) [1]. This increased risk may be related to disruption of the pelvic vasculature at the time of the trauma, manipulation of the vasculature during subsequent operative fixation or secondary to the prolonged period of protected weight bearing required thereafter [2]. The estimated incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE) has ranged from 0.51 to 61% [2–7] and 0.2 to 10% [4, 6, 8], respectively. Subsequent mortality resulting from PE is estimated to occur in 0.5% to 4% of patients [8]. The use of chemo-thromboprophylaxis such as with low molecular weight heparin (LMWH) has proven effective in decreasing VTE rates in this high-risk population

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[9]. To the authors' knowledge, the optimal timing of initiation, discontinuation, and resumption of chemoprophylaxis in regard to operative reconstruction of pelvis or acetabulum fractures are not clearly defined in the literature.

Due to the lack of data regarding exact protocols for VTE prevention in patients with pelvic and acetabulum trauma, there are no official guidelines, and most surgeons use guidelines developed for total joint replacement and hip fracture management to help guide practice. There is much more information regarding VTE prevention protocols in patients undergoing total hip and knee replacement as well as hip fracture management. Despite the greater amount of available literature, there is controversy and conflicting guidelines for VTE prevention exist. The American Academy of Orthopaedic Surgeons (AAOS) recommends the use of VTE prophylaxis in hip fracture patients but does not specify type or duration [10]. Their recommendations recognize the need for a multi-armed randomized controlled study to answer many questions that remain [10]. Similarly, the AAOS recommends pharmacologic and/or mechanical prophylaxis for patients undergoing elective total hip or knee arthroplasty; however, there is insufficient evidence to recommend for or against a specific strategy [11]. In contrast, the American College of Chest Physicians (ACCP) recommends administration of chemoprophylaxis 12 hours or more prior to and following surgery rather than within four hours pre- or post-operatively in patients undergoing hip and knee arthroplasty or hip fracture surgery [12]. The ACCP goes on to list recommended medications which include low molecular weight heparin and aspirin. Beyond organizational recommendations, many authors have commented on the timing of chemoprophylaxis in cases of hip and knee arthroplasty and hip fracture surgery [13–21].

In regard to minimizing intra-operative blood loss, tranexamic acid (TXA) (Cyklokapron, Pfizer, New York, New York) is an increasingly popularized synthetic derivative of lysine which competitively inhibits the conversion of plasminogen to plasmin. This prohibits fibrin degradation and dissolution of formed clots [22]. The use of TXA as a safe means to control intra-operative blood loss and need for transfusion has been incorporated into many elective orthopaedic procedures, especially in joint arthroplasty [23–27]. Many studies have also found TXA to be both safe and effective in controlling bleeding within spine surgery [28, 29]. Within orthopaedic trauma literature, routine use of TXA for fracture fixation has been suggested given safety and efficacy; however, the majority of these studies focus on hip fractures and do not address pelvic or acetabular injuries [30, 31]. One randomized clinical trial specifically looking at the use of TXA in acetabular 88 patients failed to find show a difference in transfusion rates and average blood loss [32]. To the authors' knowledge, this is the only study directly assessing TXA use in pelvic or acetabular fracture patients.

Given the paucity of literature regarding peri-operative chemoprophylaxis and the use of TXA in a subset of trauma patients with pelvic and acetabulum fractures, the purpose of this study was to evaluate the impact of pre-operative discontinuation of prophylactic chemoprophylaxis and intra-operative administration of TXA in polytrauma patients undergoing internal fixation on the need for subsequent blood transfusion. The authors hypothesized that the combined effects of pre-operative discontinuation of VTE chemical prophylaxis in addition to intra-operative administration of TXA would reduce operative time and the need for blood transfusion. Secondary measures included an assessment of operative time and the safety of these measures by evaluating the frequency of DVT and PE.

## Patients and methods

After institutional review board approval, patients either admitted to or followed by the orthopaedic trauma service between January 2014 and December 2017 at a single, level 1 trauma centre were retrospectively reviewed. Patients were included if they had pelvic ring or acetabular fractures managed operatively. From that cohort, the authors identified those patients whose fractures required an open approach and internal fixation. Thus, patients were then excluded if their pelvic fractures were managed with external fixation, INFIX, trans-sacral or sacroiliac screw placement in isolation or in combination so long as there was no open approach performed. The above listed procedures are often minimally invasive with minimal dissection and expected blood loss thus obviating the indication for TXA administration. Additionally, the authors felt this helped bring uniformity to the cohort. No other exclusion criteria were applied.

Demographic information including age and body mass index (BMI) were recorded. Risk factors for VTE such as a history of malignancy and history of previous DVT or PE were documented based on patient history recorded in the electronic medical record. Other orthopaedic and non-orthopaedic injuries necessitating surgical intervention were recorded. The presence of an intra-cranial haemorrhage was recorded based on the attending radiologists' impression of the admission-computed tomography brain scan, if performed. Embolization of intra-pelvic vessels by the interventional radiologists was similarly recorded. The AO/Orthopaedic Trauma Association fracture classification system was used to catalog both pelvic ring and acetabulum fractures.

Operative data, operative time, estimated blood loss, and peri-operative changes in haemoglobin/haematocrit were then collected for all patients. Intra-operative Cell Saver (Braintree, MA, USA) transfusion records were included. For the purposes of the study, the authors defined a blood transfusion

event if a patient received an autologous transfusion from the use of Cell Saver or an allogeneic transfusion intra-operatively or within 48 hours of surgery. At the authors' institution, there were no set protocols for transfusion of blood products and are largely performed at the discretion of the primary team—whether that be the orthopaedic or trauma surgery team. Clinical evaluation of the patient, including but not limited to their vital signs, age, and medical comorbidities, was paramount when considering transfusing blood products. However, patients were typically transfused to maintain a haemoglobin above 7.0 g/dL or a haematocrit above 21%. Intra-operative transfusions are administered at the discretion of the anesthesiologist at the time of surgery. Administration of tranexamic acid (TXA) and discontinuation of prophylactic anti-coagulation prior to surgery were recorded. Type of prophylactic anti-coagulation was recorded as either unfractionated heparin, or low molecular weight heparin (LMWH), with LMWH being the standard of care at this institution. Most patients received 30 mg LMWH subcutaneously twice daily for DVT prophylaxis. Upon discharge, most patients were converted to 40 mg LMWH subcutaneously daily for 14 days. If the patients had bilateral injuries such that they could not weight bear on either extremity, the prophylaxis was continued until they were allowed to weight bear. The use of intra-operative Cell Saver and TXA was at the discretion of the attending surgeon and anesthesiologist at the time. No institutional protocols were in place. All TXA was administered intravenously; however, the rate of administration varied among patients and was not recorded in the medical record.

Screening tests for deep venous thrombosis (DVT) and pulmonary embolism (PE) were performed at the discretion of the trauma or orthopaedic teams. DVT screening was performed with ultrasonography, while PE screening used computed tomography angiography (CTA) or ventilation-perfusion (VQ) scan. Patients treated empirically for pulmonary embolism without radiographic confirmation based on clinician judgment were treated as having a PE for the purposes of the chart review.

Patients who received their pre-operative dose of prophylactic anticoagulation prior to surgery and did not receive intra-operative TXA served as the control group. Statistical analysis was performed using Stata 15 Software (College Station, Texas, USA). Due to the interaction of prophylactic anticoagulation and TXA, the variables were analyzed using an interaction effect to account for administration of both individually and concomitantly. A logistic regression model using the interaction effect condition was used to test for significance. Coefficients from the model are reported along with standard error (SE) and 95% confidence interval (95%CI) for binary variables only. Significance was defined as $p < 0.05$.

No funding was received for this study.

## Results

A total of 195 patients with pelvic ring or acetabulum fractures managed operatively were identified. After exclusion criteria were applied, 159 patients (109 male, 50 female) with ages ranging from nine to 86 years (mean = 39.18 years, standard deviation (SD) = 16) were included for analysis. Two patients expired due to their injuries. Neither mortality occurred during pelvic nor acetabular fixation. Other patient characteristics of the cohort are summarized in Table 1.

Of the 159 patients, 50 patients had isolated pelvic ring injuries while 92 had isolated acetabulum fractures. Seventeen patients had both pelvic ring and acetabulum fractures. Table 2 summarizes the AO/OTA fracture classifications treated in this cohort.

During the study period, 102 patients had their chemical DVT prophylaxis discontinued prior to surgery. Forty-six patients received an average of 1.33 g of TXA (range 1–3 g) intra-operatively. Variability in the amount of TXA administered was secondary to the anaesthesia department's initial hesitation and unfamiliarity administering TXA in trauma patients. The preferred dosage schedule was one dose of 1 g prior to incision and an additional gram at the time of wound closure. Initially, 1 g just prior to incision was administered. However, as the institution has become more comfortable with the use of TXA, the preferred dosing regimen was allowed. The two patients who received 3 g of TXA had a mean operative time of 363.5 minutes. The retrospective nature of the study does not allow for evaluation of the indication or justification for administration of a third dose. Over the three year period, 26 patients received TXA intra-operatively and had their chemoprophylaxis discontinued prior to surgery.

Eighty-two patients (51.6%) received blood product transfusions within 48 hours of their pelvic or acetabulum fracture surgery. Of those, 56 (68.2%) transfusions were intra-operative. These included 36 patients who received autologous transfusions using a cell salvage system.

Patients whose chemoprophylaxis was held pre-operatively and who received intra-operative TXA experienced a 20.7% reduction in blood product transfusion (regression coefficient (RC): − 0.207, $p = 0.047$, 95%CI: − 0.412 to − 0.003) and an average reduction in operative time by 36 min (RC): − 36.90, $p = 0.045$, 95%CI: − 72.943 to − 0.841) as compared to the remainder of the patients in the cohort.

Six and ten patients, respectively, experienced non-lethal pulmonary emboli and deep venous thromboses. Table 3 summarizes the frequency of PE and DVT as it pertains to intra-operative TXA administration and discontinuation of peri-operative DVT prophylaxis. In the logistic regression model, the combination of TXA and holding pre-operative chemoprophylaxis did not result in statistically significant increases in the rate of DVT (RC: 1.302, $p = 0.749$, SE: 1.073, 95%CI:

**Table 1** Patient characteristics

| | |
|---|---|
| Age | Mean: 39.18, range: 9–86, standard deviation: 16 |
| Female | 50 (31%) |
| Mortality | 2 (1.3%) |
| Mechanism of injury | |
| Fall | 31 (19.5%) |
| Pedestrian hit by motor vehicle | 25 (15.7%) |
| Motor vehicle collision | 78 (49.1%) |
| Motorcycle collision | 21 (13.2%) |
| Jet ski | 3 (1.9%) |
| Gun shot wound | 1 (0.6%) |
| BMI (%) | |
| BMI < 25 | 31.45 |
| BMI 25–29.9 | 33.96 |
| BMI 30–39.9 | 25.79 |
| BMI > 40 | 8.81 |
| Patients with a history of DVT or PE | 4 (2.5%) |
| Intracranial bleed | 14 (8.8%) |
| Interventional radiology procedure | 15 (9.4%) |
| Patients with additional orthopedic injuries managed operatively | 75 (47.2%) |
| Patients with additional non-orthopedic injuries managed operatively | 35 (22%) |
| Pulmonary embolism | 6 (3.8%) |
| Deep venous thrombosis | 10 (6.3%) |

**Table 2** Fracture classification

| | |
|---|---|
| Pelvic ring | 50 |
| Acetabulum | 92 |
| Combined | 17 |
| Acetabulum | |
| 62A1.1 | 12 |
| 62A1.2 | 18 |
| 62A2.1 | 3 |
| 62A2.3 | 5 |
| 62A3.2 | 1 |
| 62A3.3 | 1 |
| 62.B1.1 | 1 |
| 62B1.2 | 17 |
| 62B1.3 | 16 |
| 62b2.2 | 4 |
| 62b2.3 | 8 |
| 62B3.2 | 1 |
| 62B3.3 | 3 |
| 62C1 | 4 |
| 62C2 | 9 |
| 62C3 | 6 |
| Pelvic ring | |
| 61B2.1 | 3 |
| 61B2.3 | 25 |
| 61b3.1 | 1 |
| 61b3.3 | 2 |
| 61C1.1 | 1 |
| 61c1.2 | 8 |
| 61c1.3 | 8 |
| 61c2.1 | 4 |
| 61c2.2 | 3 |
| 61c2.3 | 7 |
| 61c3.1 | 3 |
| 61c3.2 | 1 |
| 61c3.3 | 1 |

0.259–6.546) or PE (RC: 1.024, $p = 0.983$, SE: 1.147, 95%CI: 0.114–9.208) as compared to the remainder of the cohort.

## Discussion

The data presented above demonstrate that holding pre-operative chemoprophylaxis in combination with intra-operative administration of TXA decreased operative times and reduced requirement for blood product transfusions without increasing the rate of DVT or PE in patients with operative fractures of the pelvis and acetabulum. To the authors' knowledge, this is the first study addressing the utility and safety of both peri-operative DVT prophylaxis and TXA in this population.

Reduction of operative time and blood product transfusion are important considerations in preventing morbidity and mortality. Prolonged operative times have been shown to result in increased rates of infection in extremity fracture surgery [33]. Similarly, recipients of blood products are at risk for several complications including acute lung injury, circulatory overload, HIV, and hepatitis C [34, 35]. Moreover, transfusions have been previously shown to have detrimental immunomodulating effects through impaired T cell-mediated immunity [36, 37]. Clinically, these immunologic effects manifest as increased rates of infection in trauma [38–40], spine [41], and joint arthroplasty patients [42, 43]. Blood product transfusion has also been shown to be an independent predictor of mortality in trauma patients after controlling for severity of shock [44]. Conflicting evidence exists regarding the impact of leukoreduction of blood products as it pertains to the transfusion-related immunomodulation (TRIM). Some have shown that leukoreduction reduces the frequency of post-operative infections in orthopaedic procedures [45]; however, other studies failed to demonstrate benefits as it pertains to infection [46] and mortality [47]. Nevertheless, avoidance of blood product transfusion when possible precludes the possibility of these undesirable outcomes and therefore should be the goal.

**Table 3** Venous thromboembolism

| | |
|---|---|
| Deep vein thrombosis (DVT) | |
| Pre-operative DVT prophylaxis held and intra-operative TXA administered | 2 |
| Pre-operative DVT prophylaxis held, NO intra-operative TXA administered | 5 |
| Pre-operative DVT prophylaxis administered and intra-operative TXA administered | 0 |
| Pre-operative DVT prophylaxis administered, NO intra-operative TXA administered | 3 |
| Pulmonary embolism (PE) | |
| Pre-operative DVT prophylaxis held and intra-operative TXA administered | 1 |
| Pre-operative DVT prophylaxis held, NO intra-operative TXA administered | 4 |
| Pre-operative DVT prophylaxis administered and intra-operative TXA administered | 0 |
| Pre-operative DVT prophylaxis administered, NO intra-operative TXA administered | 1 |

The literature specifically focusing on patient's undergoing acetabular fracture surgery echoes that cited above. Blood product transfusion, estimated blood loss, and operative time were identified as risk factors for surgical site infection by both Suzuki et al. and Li et al. [48, 49].

In efforts to mitigate intra-operative blood loss, TXA has emerged as a reliable tool. Among the most referenced studies in the trauma literature involving TXA is the CRASH-2 trial. In this randomized, controlled study, early administration of TXA within three hours of injury reduced mortality from haemorrhage without increasing the risk of thromboembolic events. It is important to note that there was no reduction in the frequency of blood product transfusion in TXA group as compared to the placebo group (relative risk 0.98, 95% confidence interval 0.96–1.01, $p = 0.21$) and that administration of TXA between three and eight hours after injury increased the risk of death from bleeding [50].

The role of TXA in orthopaedic trauma surgery has yet to be elucidated [27]. Two recent meta-analyses evaluating TXA usage in orthopaedic trauma surgery concluded that its use is associated with decreased rates of transfusion and lower estimated blood loss with no associated increase in VTE risk [30, 31]. Farrow et al. reached similar conclusions regarding decreased rates of transfusion without concomitant increase in VTE in a review of hip fractures [51]. In contrast, Zufferey et al. reported a non-significant trend towards increased DVT in a randomized controlled study evaluating TXA use in hip fracture surgery [52]. TXA has repeatedly demonstrated its strong therapeutic potential and safety profile by attenuating blood loss and therefore decreasing the need for transfusions while avoiding increased VTE rates in total knee arthroplasty (TKA) [53–56] and total hip arthroplasty (THA) [53]. It is worth noting that as compared to total joint arthroplasty patients, orthopedic trauma patients have relatively increased risk of fatal pulmonary embolism [57].

As discussed above, there is limited literature specifically evaluating TXA in pelvic ring and acetabular fractures. Lack et al. failed to demonstrate a difference in transfusion, estimated blood loss, DVT, and PE in a randomized controlled study evaluating TXA use in acetabular fracture surgery [32]. In contrast to the current study, no mention of peri-operative DVT prophylaxis was included.

There are important limitations to this study through which the results should be interpreted. The absence of a treatment protocol during the study period and the retrospective nature of the study generate inherent variability in treatment exposures. For instance, patients received between 1 and 3 g of intravenous TXA at the discretion of the operating surgeon and the anaesthesia provider. Additionally, there was no uniformity if the type (unfractionated heparin versus low molecular weight heparin) or timing of DVT prophylaxis administered. As such, for patients who did not receive a pre-operative dose, there is the potential for variability in the time from last dose to surgery. However, standardization of chemoprophylaxis administration in this setting would be logistically difficult due to varying surgical start times as well as the unpredictable nature of a level 1 trauma centre. Lastly, while this patient cohort is at high risk for VTE, its incidence remains low enough that the current study is underpowered to accurately detect a difference in PE and DVT. Further investigation of this topic with a prospective, randomized trial is needed as demonstrated by the results herein. Strengths of this study include the number of patients included relative to the available studies.

## Conclusion

In summary, in patients with operative pelvic ring and acetabular fractures, the combination of holding pre-operative chemoprophylaxis and administration of intra-operative TXA is a safe and effective combination in reducing operative time and blood product transfusion. Further prospective studies are needed to better evaluate the treatment effects; however, the findings herein contribute to addressing a gap in the available literature specific to pelvic and acetabular fractures.

## Compliance with ethical standards

Investigation Performed at Jackson Memorial Hospital, Miami, FL

The University of Miami Institutional Review Board approved this study. This research was previously presented at the American Academy of Orthopaedic Surgeons Annual Meeting, Mar 12–16, 2019.

**Conflict of interest** Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

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