Review Article

The Use of Tranexamic Acid in Hip and Pelvic Fracture Surgeries

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ABSTRACT

Tranexamic acid (TXA) use has expanded across many surgical specialties. It has been shown to reduce blood loss, decrease transfusion rates, and, in some cases, improve mortality. Within orthopaedic surgery, its popularity has primarily grown within arthroplasty and spinal surgery. It has only recently gained traction within the field of orthopaedic trauma and fracture care. At this time, most literature focuses on hip fracture and pelvic trauma surgery. For hip fractures, the results are encouraging and generally support the claim that TXA may lower overall blood loss and decrease transfusions. Conversely, less support exists for TXA use in fractures of the acetabulum or pelvic ring. Based on the current fracture-related studies, TXA does not seem to carry an increased risk of thromboembolism or other complications. In addition, few studies have been noted discussing the route of administration, timing, or dosage. This article reviews the most current literature regarding TXA use in fracture care and expands on the need for further research to evaluate the role of TXA in orthopaedic trauma populations who carry a high risk for transfusion.

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The first clinical trial of tranexamic acid (TXA) was published in 1968 and highlighted the use of TXA in the management of heavy menstrual bleeding.[1] Over the following decades, clinical application expanded to areas such as dental, urologic, cardiac, and transplant surgery.[2-5] It was not until the 21st century that the use of TXA began in orthopaedic surgery, such as arthroplasty and spinal surgery.[6,7]

More pertinent to the patient cohort in orthopaedic trauma, the role of TXA in the management of the polytraumatized patient has been investigated. A large multicenter double-blinded randomized controlled trial known as the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2, referred to as CRASH-2, evaluated more than 20,000 trauma patients in 274 hospitals across 40 countries who were at risk for hemorrhage within eight hours from injury.[8] Each patient was randomized to receive either TXA or placebo within eight hours from injury. The results of this landmark study demonstrated a statistically notable decrease in all-cause mortality risk by

9%. In addition, the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study was a retrospective observational study that compared TXA versus no TXA in combat injury patients. Nearly 900 patients were examined and revealed a 6.5% absolute reduction in mortality rate. This observation was even more substantial in patients undergoing massive transfusion (>10 units packed red blood cells) with a 13.7% absolute reduction in mortality.[9] These studies provided valuable insight into the use of TXA as an antifibrinolytic agent for trauma patients. As the use of TXA has gained traction within the general management of the trauma patient, research has expanded to include the field of orthopaedic trauma and fracture surgery. Although not comprehensive, this review summarizes the most recent and highest-level data on TXA use during surgical management of hip and acetabular and pelvic ring injuries.

Mechanism of Action of Tranexamic Acid

Fibrinolytic mechanisms are essential for maintaining vascular hemostasis and patency. The foundation of these mechanisms is regulated by the conversion of inactive plasminogen to plasmin, which is an enzyme that cleaves fibrin and leads to clot degradation. Several regulatory pathways modulate plasmin activation under physiologic conditions. Tissue injury disrupts this equilibrium, which may result in coagulopathy and bleeding.[10] Pharmacologic interventions have been developed that focus on these derangements in efforts to reduce blood loss and transfusion rates secondary to trauma.

TXA is a drug that competitively inhibits plasminogen activation and reduces plasmin activity, thus limiting fibrinolysis. It achieves this by occupying lysine-binding sites on plasminogen, which prevents binding to lysine residues located on the molecule fibrin (Figure 1). By reducing fibrinolysis, existing clot is stabilized without the promotion of new clot formation. Subsequently, other parameters such as platelet counts and coagulation have been shown to be unaffected by this process.[11,12]

Potential Benefits of Tranexamic Acid Utilization in Fracture Patients

Hip fracture and trauma patients commonly require blood transfusions, which are associated with numerous adverse outcomes.[1,13-16] The literature clearly shows an increased risk for 90-day mortality[1] and cardiac complications after transfusions.[13] In addition, infectious complications such as urinary tract and surgical site infections are more common in patients receiving transfusions. It has been suggested that this is related to immune modulation secondary to the transfusion.[14,15] For fracture patients, postoperative mobilization is vital for recovery and transfusions may hinder this process. The increased immobility may lead to delirium,[16] longer inpatient stays,[13] and an increased risk for thromboembolism and pneumonia. Therefore, the major benefit in reducing transfusions in hip fracture and orthopaedic trauma patients is avoiding the associated risks and reducing costs.

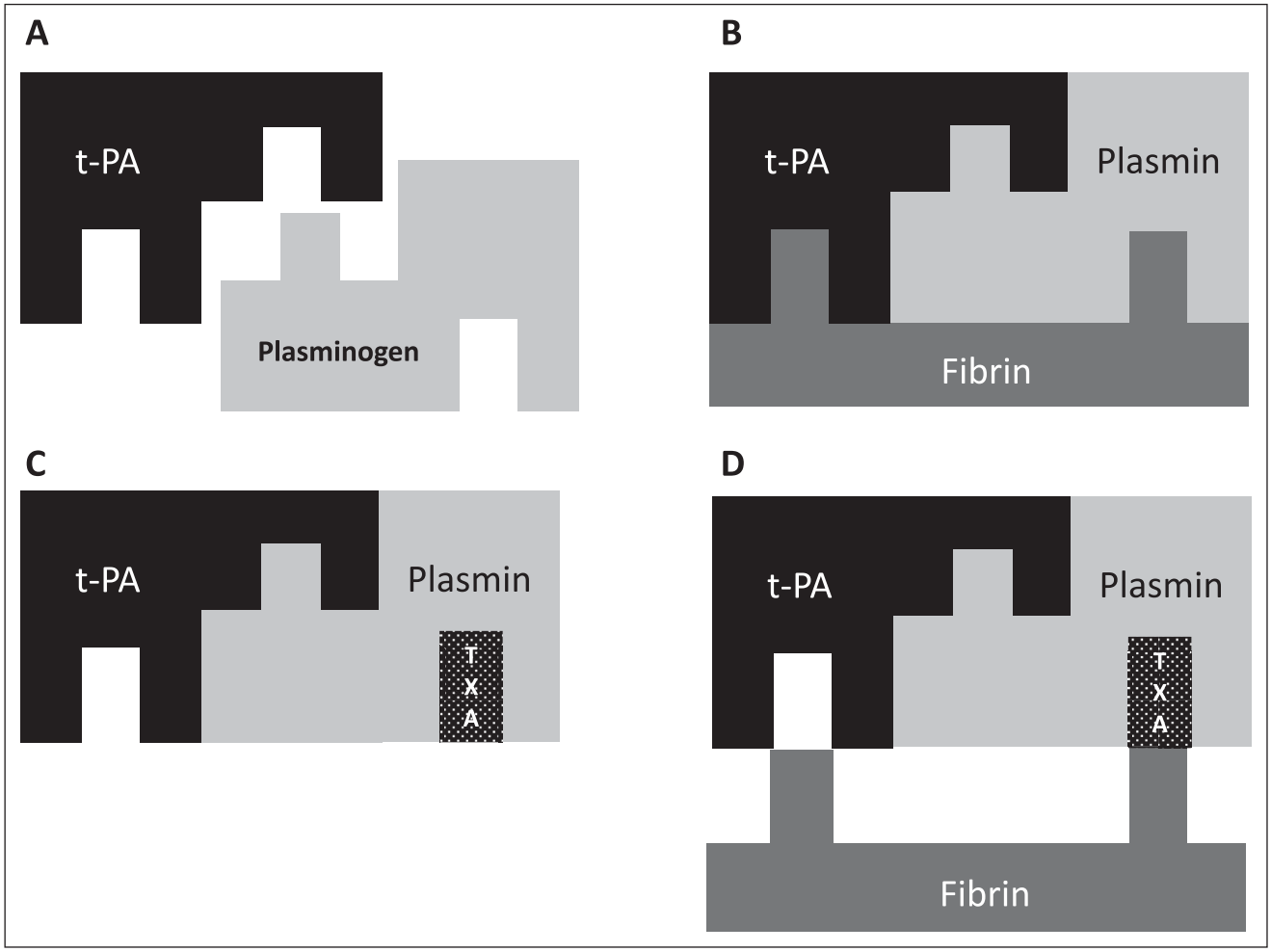
Tranexamic Acid Use in Hip Fractures

Zufferey et al[17] conducted one of the original randomized controlled trials investigating the use of TXA in all types of hip fractures. They demonstrated a 30% relative risk reduction in transfusion requirements for patients receiving TXA. In contrast to previous data on elective orthopaedic procedures, they found a higher incidence of vascular events among patients receiving TXA. Most events were asymptomatic deep vein thromboses and discovered via mandatory ultrasonography on all patients. It is unclear whether these deep vein thromboses were present before the initiation of the study, which may have falsely elevated the incidence of this complication. Therefore, it is difficult to make a definitive conclusion on the safety of TXA based on these results.[17] Because of this conflicting evidence for hip fracture patients, other studies were done to better define the risk-benefit profile of TXA in this patient cohort. In addition, these later studies were designed to focus on a specific type of hip fracture.

Extracapsular Hip Fractures

In 2016, two randomized-controlled trials investigated the efficacy of locally administered TXA in patients undergoing surgical treatment for an extracapsular hip fracture. Drakos et al [18] conducted the largest study, which included two-hundred patients with AO type 31A1, 31A2, and 31A3 fractures. All patients in their study underwent surgical fixation with a short intramedullary nail. Patients were randomized to receive either 3 g of TXA or normal saline injected directly adjacent to the fracture site under fluoroscopic guidance at the conclusion of the case. The control group demonstrated a larger drop in hemoglobin on postoperative day one, and 29% of patients required a transfusion compared with 22% in the treatment group. In

Figure 1



Mechanism of action of tranexamic acid (TXA). **A**, Plasminogen is activated to plasmin by binding to tissue plasminogen activator (t-PA). **B**, Fibrinolysis occurs when plasmin binds to fibrin. **C**, TXA occupies the lysine binding site of fibrin to plasmin, thus (**D**) inhibiting fibrinolysis by preventing the binding of plasmin and fibrin.

total, an additional 21 transfusion units were required in the control group. The indication for transfusion was a hemoglobin value less than 8 g/dL, unless felt to be clinically relevant based on symptoms. Cost analysis revealed a savings of 77.8 euros per patient. Rates of thromboembolic complications were similar between treatment and control. The control group was found to have more hematomas and postoperative infections, yet the authors did not comment on the statistical significance of this.[18]

Similarly, Virani et al[19] conducted a randomized-controlled trial with local infiltration of TXA versus saline for 137 extracapsular hip fracture patients. All patients were treated with sliding hip screw fixation. Patients were randomized to 2 g of TXA or saline injected intramuscularly at the conclusion of the case. A drain was placed in each patient, and the output was recorded. Although a trend exists toward decreased blood loss, less drain output, and lower transfusion rate for patients who received TXA, it failed to reach statistical significance. Therefore, they concluded that TXA did not play a notable role in blood conservation for patients undergoing surgery for peritrochanteric fractures. In addition, similar rates exist of thromboembolism and other complications between the intervention and control groups.[19]

In contrast to local administration, investigations with intravenous (IV) administration of TXA for extracapsular hip fractures have also been done. Tengberg et al[19] conducted a double-blinded placebo-controlled trial with IV TXA versus IV saline for 72 patients treated with a short intramedullary nail. One gram of TXA or saline was administered immediately before surgery and a postoperative 24-hour infusion of 3 g of TXA or saline. The results

Table 1. Summary of Literature Using TXA in Hip, Pelvic, and Acetabular Fractures

Study	Study Type	Fracture Pattern	Surgical Treatment	TXA Route	Transfusion Rate	VTE Rate
Zufferey et al [18]	RCT	All hip fracture patterns	Variety	IV	30% reduction in the transfusion rate for the TXA group ($P = 0.055$)	Increased by 3.1%
Drakos et al[19]	RCT	Extracapsular hip fractures	IMN	Local (fracture site)	43% reduction in the transfusion rate for the TXA group ($P < 0.01$)	No difference
Virani et al[20]	RCT	Extracapsular hip fractures	SHS	Local (intramuscular)	14.9% transfusion rate in the TXA group vs 17.1% in the control group ($P > 0.05$)	No difference
Tengberg et al[21]	RCT	Extracapsular hip fractures	IMN	IV	81.8% transfusion rate in the TXA group vs 84.6% in the control group	No difference
Jiang et al[22]	Meta-analysis	Extracapsular hip fractures	SHS and IMN	Local and IV	17.5% reduction in the transfusion rate for the TXA group ($P < 0.05$)	No difference
Watts et al[25]	RCT	Intracapsular hip fractures	Arthroplasty	IV	17% transfusion rate in the TXA group vs 26% in the control group ($P = 0.22$)	No difference
Kwak et al[26]	Retrospective cohort	Intracapsular hip fractures	Arthroplasty	Local	36.1% transfusion rate in the TXA group vs 65.2% in the control group ($P = 0.002$)	No difference
Lee et al[27]	Observational cohort	Intracapsular hip fractures	Arthroplasty	IV	6% transfusion rate in the TXA group vs 19% in the control group ($P = 0.005$)	No difference
Xie et al[28]	Retrospective cohort	Intracapsular hip fractures	Arthroplasty	IV	8.65% transfusion rate in TXA group vs 24.06% in control ($P < 0.001$)	No difference
Spitler et al[29]	RCT	Pelvic ring and acetabular and proximal femur fractures	ORIF	IV	17% transfusion rate in the TXA group vs 30% in the control group ($P = 0.138$)	No difference
Lack et al[30]	RCT	Acetabular fractures	ORIF	IV	50% transfusion rate in the TXA group vs 32% in the control group ($P = 0.097$)	No difference

IMN = intramedullary nail, IV = intravenous, ORIF = open reduction and internal fixation, RCT = randomized control trial, SHS = sliding hip screw, TXA = tranexamic acid

demonstrated a statistically notable reduction in total blood loss of nearly 600 mL in the IV TXA group. In addition, a trend exists toward lower transfusion rates for patients who received TXA, despite a statistically notable higher preoperative hemoglobin level for the control group. They did not see any difference in thromboembolic events between groups. However, a trend exists toward higher 90-day mortality in patients who received TXA. The cause of death was not verified for these patients, making it difficult to ascertain the implication of this finding.[20]

A recent meta-analysis of trials investigating IV administration of TXA for extracapsular hip fractures demonstrated a reduction in overall blood loss and transfusion requirement with no additional complications.[21]

Table 2. TXA Administration Routes and Dosing Strategies Used in Published Fracture Studies

Factor	Dosage					
Local administration	3 g at fracture site at conclusion of case[18]	2 g intramuscularly at conclusion of case[19]	1 g throughout surgical site at conclusion of case[25]			
IV administration	1 g at draping. 3 g infused over 24 hr [21]	15 mg/kg at incision. Again, at closure[24]	1 g at induction[26]	15 mg/kg 10 min before incision[27]	15 mg/kg at incision. Again, 3 hr later[28]	10 mg/kg 30 min before incision. 10 mg/kg infusion over 4 hr [30]

IV = intravenous, TXA = tranexamic acid

Although consistency exists in fracture types, fixation methods and TXA dosing were inconsistent among the studies. Additional meta-analyses are available that include studies on both extracapsular and intracapsular hip fractures, which necessarily introduces various surgical treatments. Regardless of the variability, these studies generally support the use of TXA for blood conservation in extracapsular hip fractures.[22,23]

Intracapsular Femoral Neck Fractures

In 2017, Watts et al[23] published the only available randomized controlled trial that specifically focuses on TXA use during management of intracapsular femoral neck fractures. The trial enrolled 138 participants undergoing hemiarthroplasty or total hip arthroplasty who received either 15 mg/kg of IV TXA or saline before incision and again at closure. On all postoperative days, a statistically notable lower cumulative blood loss was noted for patients who received TXA. Although statistical significance was not reached, trend exists toward a lower transfusion rate and less total blood products required in the TXA group. Adverse events at 30 and 90 days were comparable between groups; however, the study was not powered to detect these differences. Within this study, various surgical approaches and implants were used. Most cases were done through an anterolateral approach and with a cemented implant. Although hemiarthroplasty and total hip arthroplasty were both included, equal numbers were allocated to treatment and control groups.[24]

A more recent retrospective cohort study included 226 patients who underwent hemiarthroplasty for femoral neck fracture between the years 2015 and 2017.[25] Their TXA protocol was implemented in 2016; therefore, patients treated before April 2016 did not receive TXA and those thereafter received topical TXA. As opposed to the trial by Watts et al, this study included a single surgeon with the same surgical technique and noncemented femoral implant. One gram of TXA was injected throughout the surgical site at the conclusion of the case and a vacuum drain was left in place. They found a notable reduction in calculated blood loss, drain volumes, transfusion rate, and total blood transfusion volumes for patients who received TXA. Thromboembolic events, surgical complications, and mortality were similar between cohorts, but the control group had a higher incidence of medical complications. They attributed this to a decrease in postoperative mobility secondary to the higher transfusion rate.[25]

In addition, two retrospective reviews of patients who underwent hemiarthroplasty for femoral neck fractures are available in the current literature.[26,27] Similar to the abovementioned trials, they both determined that TXA was beneficial for total blood loss and transfusion rates with no reciprocal increase in adverse events. Lee et al, who published their results of 271 patients in 2015, specifically calculated an absolute risk reduction of 12% in transfusion rate. This extrapolated to a number needed to treat of eight.[26] The study by Xie et al[27] included 609 patients and found that TXA was associated with faster mobilization and shorter hospital stays. It is important to recognize the retrospective nature of these studies, which introduces bias, and the effect on each outcome is unknown.

Acetabular and Pelvic Fractures

Although an abundance of literature tends to support the use of TXA in hip fracture surgery, less available and less convincing data exist for pelvic trauma. Spitler et al[28] randomized a total of 93 patients undergoing open reduction and internal fixation for high-energy proximal femur fractures, pelvic ring injuries, and acetabular

fractures to receive either IV TXA or placebo. At the time of incision, the treatment group received 15 mg/kg of TXA, followed by a second dose 3 hours later. Most cases (84%) were pelvic ring and acetabular fractures, followed by proximal femur fractures (16%). Any patient with open fracture, additional injury that contraindicated immediate VTE prophylaxis use, and patients undergoing other urgent procedures such as exploratory laparotomy were excluded. Notable findings included lower total blood loss and smaller postoperative hematocrit changes in the TXA group. Postoperatively, 17% of patients who received TXA were transfused compared with 30% of patients in the control group. Although these results are promising, several factors need to be considered. A higher intraoperative transfusion rate and higher intraoperative blood loss was noted in the TXA group, which may have introduced selection bias. Furthermore, the TXA group had a lower preoperative hematocrit, potentially predisposing them to the aggressive intraoperative resuscitation efforts directed by the anesthesia team. Other confounders include a heterogeneous group of injuries and highly variable surgical times (2 to 12.5 hours). In addition, the use of intraoperative intraoperative cell salvage was not controlled.[28]

A randomized controlled trial focused solely on IV TXA use in acetabular fractures was published by Lack et al in 2017.[29] Given the known strong effect of preoperative anemia on transfusion rates, randomization was stratified based on preoperative hemoglobin levels. A total of 88 patients were included. The TXA group received 10 mg/kg 30 minutes before incision and 10 mg/kg infusion over 4 hours during surgery. The control group received an equal volume of normal saline. The primary outcome measure was incidence of transfusion. Secondary outcomes were number of units transfused, estimated blood loss, and incidence of VTE. Contrary to expected results, a trend exists toward inferiority in the TXA group in all outcome measures. The TXA group demonstrated a higher transfusion rate, average estimated blood loss, and received more transfusion units than the control group. One incidence of venous thromboembolism was also noted in a patient who received TXA. Although none of these findings reached statistical significance, a decision was made to preemptively terminate enrollment. Analysis of the available data demonstrated that a preoperative hemoglobin <11 g/dL, complex acetabular fracture patterns, and surgical time >4.5 hours were notable risk factors for transfusion. As a conglomerate, these factors were even more tightly associated with transfusion. Overall, more complex fracture patterns and longer surgical times were observed in the TXA cohort, which may have introduced bias. The authors concluded that these risk factors, along with the variability in fracture severity, likely overwhelmed any effect of TXA (Table 1).[29]

Shortcomings of the Literature

Interest in the use of TXA as an antifibrinolytic drug has heightened over the past decade. Although its use for elective orthopaedic procedures such as total joint arthroplasty is widely accepted, there does not seem to be a clear consensus regarding its use in fracture surgery. As such, we should be critical while reviewing the available literature on this topic.

The literature on TXA use for orthopaedic trauma is centered around hip and pelvic fracture surgery. This represents a largely heterogenous group of injuries. Many of the current studies fail to narrow their focus on an isolated injury pattern or type of surgery.[17,30] This introduces a number of confounding variables, which potentially obscures outcomes. Therefore, this review attempted to focus on studies that emphasized a specific fracture pattern and fixation strategy to reduce the inherent variability in surgical times, blood loss, and complications. In addition, it is important to recognize the difficulty in controlling for the range of fracture severity or displacement, which may influence results.

To date, no standardized regimen has been found for TXA administration. This introduces a wide variety of routes, dosages, and timing (Table 2). Local infiltration during hip fracture surgery has been done in various ways. For example, Drakos et al[18] injected 3 g of TXA at the fracture site, whereas Virani et al[19] injected 2 g of TXA intramuscularly. This could certainly make an impact, especially if most blood loss is from the fracture site during reduction and at the trochanteric entry for an intramedullary device. IV administration of TXA also varies. Some studies provide a single preoperative bolus, whereas others provide multiple doses. The second dose varies based on the timing and duration of infusion. It is unknown how these variables affect the efficacy of the drug.

Several primary outcome variables are used in the current literature, including blood loss, hemoglobin values, and transfusion requirements. It is difficult to know which of these is most suitable to gauge efficacy of TXA. In addition, each of these variables has inherent weaknesses that should be discussed. Blood loss

calculations include intraoperative, hidden, and/or total blood loss. One should be cautious when using blood loss as a surrogate for efficacy. Estimating intraoperative blood loss is most often done by a visual assessment and has been shown to be highly unreliable.[31,32] Alternate methods such as gravimetric and photometric analysis are error prone, laborious, and costly.[33,34] Outside the surgical suite, a plethora of methods exist to determine blood loss. These calculations use an estimated total blood volume that can be swayed by erroneous data such as hydration status, height, and weight. Each equation has unique features, some are quite cumbersome, and accuracies vary.[35,36] In some instances, such as in the study by Virani et al,[19] drain output is used as a measure of postoperative blood loss. Drain placement is not universally accepted, and output may be affected by technical errors in placement and clotting within the line. All of these methods, prone to inaccuracies, may have notable ramifications on the conclusions of a study. Hemoglobin values, although more objective, have the potential to be misinterpreted. For example, Drakos et al[18] concluded that TXA reduced blood loss and improved hemoglobin values based on a difference of 0.5 g/dL. Although this was statistically notable, it does not necessarily translate to clinical relevance. Regarding transfusions, various thresholds exist in the reviewed literature, ranging from 7 to 10 g/L, which makes interpretation challenging. To complicate matters further, some studies allow for a more subjective transfusion trigger such as tachycardia or hypotension, which may be explained by pain or certain physiologic traits.[19]

Summary

Based on the current literature, TXA likely decreases blood loss and, more importantly, transfusion requirement in hip fracture patients without posing a notable risk for increased complications. A smaller amount of literature exists on TXA use during acetabular and pelvic ring surgeries. The benefits seen during hip fracture surgery have not been reflected in the limited number of reports available. Patients with acetabular fractures and pelvic ring disruption are often multiply injured and have large variations in fracture severity. Therefore, it is difficult to design a study that accounts for such a wide range of confounding variables. It is possible the efficacy of TXA is merely overwhelmed by the complexity of these patients. Protocols for administration vary, with studies supporting both IV and local TXA use. Neither of these routes have been shown to increase complications. Oral administration is supported by the arthroplasty literature because of its low cost and efficacy, but this route has not been studied in fracture patients.[37] Data exist to suggest that a substantial portion of blood loss for a hip fracture patient occurs at the time of injury, and admission hemoglobin values may in fact be falsely elevated because of dehydration.[36,38] Afterward, potential exists for a "second-hit phenomenon" during the time of surgery with manipulation of the fracture, surgical exposure, and instrumentation.[39] It is presumed that this could be extrapolated to other trauma-related fracture injuries. Given this information, we suggest that future studies should focus on determining a superior regimen for administration of TXA to potentially include an initial dose of TXA on arrival to the ED, followed by an additional dose at surgery. Until this is established, the routine use of TXA in hip fracture patients using any of the described methods in the literature is likely safe and effective for blood conservation. The same recommendation cannot be made for acetabular or pelvic ring injuries because the efficacy of TXA is uncertain in this patient cohort.

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