Chapter

Hemostatic Adjuncts in Orthopedic Surgery: Innovations in Technique, Technology, and Biosurgical Applications

Andrew Konopitski and Chinenye Nwachuku

Abstract

Significant blood loss is an obstacle frequently encountered in orthopedic surgery in both elective and trauma settings. Notwithstanding the nature of orthopedic surgery creates a unique environment, where hemostasis may be difficult to achieve. In total hip and knee arthroplasty, freshly cut bone edges bleed persistently and often do not respond to typical hemostatic methods utilized in soft tissues. Spine surgery requires strict adherence to hemostatic principles as uncontrolled bleeding can result in compression of neural elements. Blood loss in orthopedic trauma presents a highly variable environment where methods of hemostasis must match the severity of the injury. Lastly, orthopedic tumor procedures often require bloodless fields in order to limit the risk of hemostatic spread. The following chapter takes a subspecialized approach to blood loss management in orthopedic surgery, including perioperative management of anticoagulant medications, protocols for utilization of pharmacologic agents, and techniques for the application of topical hemostatic compounds.

Keywords: hemostasis, blood management, topical, biosurgical, orthopedics

1. Introduction

Orthopedic procedures are among the most common elective and non-elective surgeries performed in the United States every year. Though common, these procedures are associated with excessive bleeding and a high demand for transfusions [1–3]. Common surgeries where significant blood loss can be expected include total hip and knee replacements, instrumented spinal fusion or deformity correction, wide resection for bone or soft tissue tumors and trauma to long bones, especially those of the lower extremities and pelvis. Maintaining hemostasis in these environments is of utmost importance, but many orthopedic subspecialties have surgical cases which present unique challenges in blood management. During decompression of the spinal canal, surgeons must be vigilant of the effects that hemostatic agents may have on neural structures. Joint arthroplasty procedures are often associated with bleeding from the bony edges which is not amenable to techniques commonly used for hemostasis in soft tissues, and orthopedic traumatologists must frequently manage mangled limbs with multifaceted approaches.

To put the importance of blood management in perspective, one must look at the prevalence of transfusions among orthopedic populations. Though the rate of hip and knee arthroplasty has steadily increased over the last decade, transfusion rates have remained stable, but the type of transfusion has shifted from pre-donated autologous blood to allogenic blood transfusions [1]. Between total hip arthroplasty (THA) and total knee arthroplasty (TKA), it has been demonstrated that THA is associated with higher rates of perioperative transfusions, especially if the patient is anemic pre-operatively. In their study of national trends in transfusion requirements in lower extremity arthroplasty, Yoshihara et al. cited transfusion rates of 18% and 11% for THA and TKA, respectively [1].

Similarly, spine surgery has seen a significant increase in allogenic transfusions, while pre-donated autologous blood transfusion has declined [2]. When translated to the pediatric population, major deformity corrections of the spine have consistently found that 30% of patients will require a transfusion and these rates may increase with the presence of neuromuscular syndromes or non-neuromuscular comorbidities [3]. The PREPARE study performed in 2015 was a large observational study assessing the value of patient blood management (PBM) programs in the context of major joint or spine surgery. This study found that PBM centers not only optimized patients better pre-operatively, but also found that patients who entered surgery anemic had higher complication rates [4].

In the realm of tumor surgery, orthopaedists are often called upon to stabilize compromised long bones in the setting of metastatic disease to avoid pathologic fracture. In this setting, patients are often deconditioned and can be expected to receive an average of 2.5 units of packed red blood cell (PRBC) transfusions in the post-operative period [5].

Lastly, orthopedic trauma to the lower extremities and pelvis are associated with an extremely high rate of transfusion. Over one-third of the patients who sustain a fracture of the femur will require a transfusion within 48 h with an average transfusion volume of 2 units PRBC [6].

While transfusions themselves place the patient at risk for transfusion reactions, disease transmission, and increased overall cost of care, there is a preponderance of data which shows that receiving a transfusion in the perioperative period places the patient at risk for post-operative complications. Across all subspecialties, transfusions have been shown to increase length of stay, cardiac events, sepsis, wound infections, and even mortality [7–10].

It is imperative to develop a comprehensive approach to blood management, as many orthopedic surgical procedures place patients at risk for blood transfusions, leaving both patients and the healthcare system at risk of negative outcomes. The goal of this chapter is to outline several options by which surgeons can optimize patients in the perioperative setting. This includes pre-operative management of anticoagulant and antiplatelet agents, intra-operative techniques, new technology, and use of biosurgical innovations throughout the perioperative period to minimize blood loss.

1.1 Perioperative management of anticoagulant and antiplatelet medications

Given the expected blood loss associated with certain orthopedic surgeries, patients taking prophylactic or therapeutic anticoagulants may require the effects of these medications to be reversed in a controlled fashion. Unfortunately, this reversal can place patients at risk for arterial thromboembolism (ATE) or venous thromboembolism (VTE) due to a rebound hypercoagulability resulting from increased thrombin generation. The risk of ATE is relatively low in patients with mechanical valves or atrial fibrillation (0.6%), but up to 70% of those

who develop an ATE can suffer a cerebral embolism which can leave patients with varying degrees of disability [11]. Conversely, patients who do not have the effects of these medications adequately reversed are left at an increased risk of post-operative hemorrhage leading to higher rates of infection and possible compartment syndrome [11].

Warfarin is one of the oldest anticoagulation agents on the market and works by inhibiting the reduction of vitamin K into vitamin K epoxide, which is required for gamma carboxylation of many clotting factors including II, V, VII, and X. The advantage of warfarin is that it can be easily measured via international normalized ratio (INR) and has many reversal agents. Troublesome aspects of warfarin include difficulty maintaining proper therapeutic levels which requires frequent testing as well as cross reactivity with many other medications, foods, and supplements. Studies have shown that an INR > 1.8 is an independent risk factor for post-operative hemorrhage, and an INR of >1.4 is a contra-indication to spinal anesthesia as it places the patient at risk for epidural hematoma [12, 13].

The mode of reversal for warfarin can be dictated by the timeframe of surgery. Urgent surgeries (within 24 h) require more aggressive measures than semi-urgent surgeries (24–72 h) and elective surgeries. For cases that require urgent intervention, prothrombin concentrate complex (PCC) and fresh frozen plasma (FFP) are agents that may be utilized. PCC is a balanced mixture of coagulation factors II, V, VII, and X. PCC has the advantage of being administered in small volumes over the course of several minutes and can reverse INR within 3–4 h. Disadvantages of PCC include a lack of intrinsic pathway coagulation factors and increased risk of patient developing thrombosis due to rapid reversal of anticoagulant. FFP contains all coagulation factors except for IX. It is administered in larger volumes over the course of hours. While it does provide a more gradual correction than PCC, the effects can be transient leaving the patient under-corrected at the time of surgery. Furthermore, FFP has a risk of disease transmission and the larger transfusion volumes can contribute to CHF and fluid overload. Key to FFP administration is monitoring INR just prior to surgery [11, 14, 15].

In the case of semi-urgent surgery, vitamin K has the safest side-effect profile. This method of anticoagulant reversal works by providing more vitamin K substrate for reduction by vitamin K epoxide and eventual gamma carboxylation of factors II, V, VII, and X. Though studies have shown intravenous (IV), intramuscular (IM), and per-oral (PO) vitamin K to be effective, each has its advantages. IV and IM vitamin K effects are more rapid when compared to oral administration, but are associated with higher rates of anaphylaxis in IV forms and cutaneous reactions with IM administration. For oral dosing, 2.5–5 mg of vitamin K is given and INR is measured until the goal is reached. Depending on the formulation, 73–93% of patients with presenting INR > 4.0 can achieve an INR < 2 within 24 h of PO vitamin K administration [16].

In elective surgery, patients can be allowed to drift down to a safe INR. Over 90% of patients with INR levels >2.0 can fall below 1.5 after 5 days [17]. It is recommended that patients undergoing major orthopedic surgery should have an INR of <1.3. Patients at high risk for thrombosis may be transitioned to bridging therapy with unfractionated heparin or low molecular weight heparin. **Table 1** outlines recommendations for bridging therapy based on thrombosis risk. Pneumatic compression stockings should be employed whenever possible [11].

Perioperative management of direct oral antocoaculants (DOAC), formerly known as novel anticoagulants, varies by agent. While they provide an advantage over warfarin with dosing consistency, they lack a means of reliable point-of-care measurement. While no standard protocol exists for the management of DOACs in urgent orthopedic surgery, some studies suggest that surgery is safe to perform

within 24 h as long as the treating teams remain vigilant of blood loss and transfusion requirements [18–20]. In the semi-urgent or elective setting, patients may be allowed to safely drift to subtherapeutic levels according to the medication half-life. Pre-operative recommendations for DOAC management as well as availability of reversal agents are listed in **Table 2**.

Lastly, in reference to anti-platelet agents, no standardized protocol has been developed. Aspirin has been heavily studied in the pre-operative setting, but evidence has been conflicting in relation to intra-operative bleeding or post-operative complications. Newer agents, such as clopidogrel or prasugrel, have limited high-quality, randomized controlled trial (RCT) data in non-cardiac surgery. A Cochrane review article in 2018 evaluated evidence available in the form of RCT for continuing antiplatelet therapy in non-cardiac surgery. They found no evidence of increased mortality or ischemic events (Grade: Low certainty) post-operatively and no evidence of increased bleeding requiring a transfusion (Grade: Moderate certainty) [21]. Historically, pooled platelets, desmopressin, and recombinant factor VII have been used to acutely counteract the effects of irreversible antiplatelet agents, though no prospective studies have been

Thrombosis risk	Stop WF	Begin LMWH bridge	Restart WF	Stop LMWH bridge
High	5 days pre-op	Once INR <1.8 until 24 h prior to surgery	Evening s/p Surgery	Once INR is therapeutic
Intermediate	Individualized, multidisciplinary approach		Evening s/p Surgery	Once INR is therapeutic
Low	5 days pre-op	No need for bridging Tx	Evening s/p Surgery	N/A

WF—warfarin; INR—international normalized ratio; LMWH—low molecular weight heparin.

Table 1.
Bridging therapy recommendations for patients on warfarin therapy.

Agent	Duration of pre-op ATI	CrCl correction	Reversal agent
Dabigatran (Pradaxa)	2 days	4 days w/CrCl <50 mL/min	idarucizumab (Praxbind)
Rivaroxaban (Xeralto)	2 days	3 days w/CrCl <30 mL/min	Recombinanat factor Xa (Andexxa)
Apixaban (Eliquis)	2 days	3 days w/CrCl <30 mL/min	Recombinanat factor Xa (Andexxa)
Endoxaban (Savaysa)	2 days	3 days w/ CrCl <30 mL/min	None
Aspirin	7–10 days	N/A	Pooled platelets
Clopidogrel (Plavix)	7–10 days	N/A	Pooled platelets
Duel antiplatelet Tx	Clopidogrel 7-10d Aspirin 5d	N/A	Pooled platelets

ATI—antithrombotic interruption; CrCl—creatine clearance

Table 2.
Pre-operative management of direct oral anticoagulants (DOAC) and antiplatelet agents.

conducted to evaluate effectiveness in orthopedic surgery [11]. When possible, surgery should be avoided in patients within 6 months of cardiac stent placement with an ideal delay of 1 year. **Table 2** contains recommendations for management of antiplatelet agents in elective orthopedic surgery.

2. Hemostasis in total hip and knee arthroplasty

Hip and knee arthroplasty are among the most commonly performed orthopedic procedures in the United States and they carry a unique set of challenges related to hemostasis. When cutting bony surfaces, surgeons are left with a bleeding bone edge which is recalcitrant to many soft tissue hemostatic techniques such as direct electrocautery. These bleeding edges, if not addressed, can contribute to both total measured blood loss as well as hidden blood loss. Below will outline biosurgical, mechanical, and technical methods for controlling blood loss during arthroplasty.

2.1 Tranexamic acid (TXA)

Perhaps, the most heavily studied agents for reducing blood loss is tranexamic acid (TXA). TXA is a synthetically derived analog of the amino acid lysine, and works by competitively binding the lysine binding site of plasminogen. This prevents plasmin from cleaving fibrin, thereby decreasing fibrinolysis and allowing for stable clot formation [22, 23]. The primary advantage of TXA is the minimal side-effect profile and plurality dosing routes including topical, intravenous, and oral.

2.1.1 Topical

Topical TXA is an unconventional mode of administration but carries several advantages including direct application to the source of bleeding, very little systemic absorption, and the ability to deliver the agent in higher concentrations. While no standard protocol exists for topical TXA in joint arthroplasty, the method used by Konig et al. has been replicated in several RCTs. For THA, 3 g of TXA is diluted in saline to make 150 mL of TXA concentrate. First, a 25 × 25 cm gauze is soaked in 50 mL of concentrate and packed into the acetabulum after reaming where it is left for 3 min. A second gauze soaked with 50 mL of TXA is packed into the femoral canal after broaching ×3 min. The final 50 mL of TXA concentrate is injected into the hip joint after fascial closure [24]. The results by Konig et al. were supported in a double-blind RCT by Yue et al. showing that topical TXA significantly decreases intra-operative blood loss, drainage rates, transfusions and hemoglobin drop on post-operative days 1 and 3 [25]. In a meta-analysis including over 2500 patients, Chen et al. found similar results without a reciprocal increase in the rate of DVT [26].

Konig et al. also developed a protocol for topical TXA in TKA, which involves diluting 3 g of TXA in 100 mL of saline and injecting it into the knee after closure [24]. The drain remains clamped for 1 h, after which it is placed to suction. This protocol was supported in a prospective RCT by Hamlin et al. who showed lower rates of transfusion and blood loss compared to IV TXA [27]. An alternative method described in a prospective RCT by Abdel et al. dilutes 3 g TXA in 45 mL of saline. The wound is irrigated with this solution after cementation and allowed to sit for 5 min before being suctioned away. This study found equivalence of topical TXA to IV TXA [28].

2.1.2 Intravenous

Intravenous TXA is the most common route of administration and also the most studied. Notwithstanding, there are a number of dosing protocols with no studies showing superiority of one dosing regimen over another. Low-dose TXA studies may use a weight-based protocol of 10–20 mg/kg pre-operatively, while higher dose protocols use up to 20 mg/kg administered pre-, intra-, and post-operatively. Other institutions use a standard 1 g of TXA IV pre-operatively before tourniquet deflation. As of yet, there has been no significant difference between protocols in relation to blood loss, transfusion rates of drain output. Some evidence does exist showing that TXA administered 10 min prior to incision is more effective than TXA given 10 min prior to tourniquet deflation in TKA [29, 30]. Fillingham et al. has published two large meta-analyses evaluating IV TXA in TKA and THA. In TKA, evidence does support use, but could not come to a conclusion regarding formulation, dose, or re-dosing. It did suggest that TXA should be administered pre-incision [31]. For THA, TXA was clearly effective in improving blood loss, transfusion rates, and hemoglobin drops, but no conclusion could be reached in regard to formulation, dosing, re-dosing, or timing [32].

2.1.3 Oral

The last route of administration for TXA is PO. The primary advantage of oral TXA over IV formulations is cost. Several studies have shown equivalence between intravenous and oral TXA in both THA and TKA [33–35]. The most commonly studied dose is 1.95 g, which is commercially available and is taken 2 h prior to incision. It is unclear whether multiple PO doses of TXA offer any advantage over a single dose. A full list of protocols and recommendations regarding TXA can be found in **Table 3**.

While TXA is generally deemed safe for a vast majority of patients, those with a history of pulmonary embolism, venous thromboembolism, stroke, cardiac stents, cardiac bypass, or pro-coagulation disorders have been historically contra-indicated for TXA. These recommendations have been precautionary in nature, but several studies have found that even in these "high risk" patients, TXA has not been associated with increased thromboembolic (TE) complications. In a small retrospective study, 240 patients with one of the seven comorbidities listed above were given IV TXA and found to have no increased risk for TE event compared to controls [36]. In a larger retrospective cohort study, Madsen et al. compared 2766 patients receiving TXA treatment to 393 patients who did not. Among patients with ASA scores III/IV, type II diabetes mellitus, or cardiovascular disease, there was no increased rate of TE events [37]. Further large-scale, prospective studies need to be performed to define risks of TXA.

2.2 Aprotinin

Aprotinin is a nonspecific serine protease inhibitor which decreases concentrations of fibrinolytic proteases such as cathepsins, kallikrein, protein C, plasmin, and thrombin. Inhibiting these serine proteases promotes clot formation. It is excreted renally and has a biphasic half-life. The rapid phase half-life is 40 min and the slow phase half-life is 7 h. A biphasic half-life lowers the risk of unwanted thrombosis and DVT formation [38].

No standardized protocol exists, but a double-blind prospective RCT performed by Colwell et al. in THA gave patients a loading dose of 2 million kallikrein inhibiting units (KIU) followed by a continuous infusion of 0.5 million KIU until the conclusion

	Dose	Timing
Arthroplasty		
THA		
IV	10–20 mg/kg	10 min pre-incision
Oral	1.95 g	2 h pre-incision
Topical	3 g in 150 mL saline	50 mL w/acetabular ream 50 mL w/femoral broach 50 mL s/p fascial closure
TKA		
IV	10–20 mg/kg	10 min pre-incision
Oral	1.95 g	2 h pre-incision
Topical	3 g in 45–100 mL saline	After cement polymerization or after closure
Spine		
IV	10–20 mg/kg bolus 10–20 mg/kg/h infusion	10 min prior to incision through closure
Oral	1.95 g	2 h pre-incision
Topical	1 g in 100 mL saline	Irrigate wound for 2–5 min prior to closure
Trauma		
IV	1 g bolus 1 g infusion	Bolus w/i 8 hours of injury over 10 min Infusion over 8 h
Oral	No current literature	
Topical	3 g in 30 mL saline	Injected after fascial closure
Oncology		
IV	15 mg/kg/h bolus 15 mg/kg/h infusion	Bolus at induction Infusion over 8 h
Oral	No current literature	
Topical	1 g in 10 mL saline	Sprayed over wound bed before closure

Table 3.
Tranexamic acid recommendations by subspecialty.

of surgery. They found that this significantly reduced blood transfusion rates [39]. In a study of bilateral TKA, Kinzel et al. employed a weight-based protocol infused over 30 min during the closing stages of the first knee arthroplasty. Patients weighing <75 kg were administered 1million KIU, 75–100 kg were given 1.5 million KIU, and those weighing >100 kg were given 2 million KIU. Patients had significantly lower transfusion rates and drain outputs compared to controls with no complications [40]. These results have been repeated in a small series of patients undergoing revision THA, TKA, or sarcoma resection [41]. Unfortunately, aprotinin was removed from the US market in 2007 for concerns for renal toxicity, though it does remain an active ingredient in some of the topical compounds listed below [42]. Further RCT may be needed to explore the risks of aprotinin.

2.3 Topical thrombin-based gels

Thrombin (also known as clotting factor IIa) is converted from the inactive pro-enzyme, prothrombin, by factor Xa. Thrombin then cleaves fibrinogen into fibrin to cross link platelets in a sort of brick-and-mortar structure. Topical thrombin-based

agents combine a high viscosity gel, often composed of engineered collagen granules, mixed with bovine derived thrombin. These agents are more commonly used in arenas of soft tissue procedures, but questions have been raised about their utility in arthroplasty. Again, no standardized protocol exists for use of thrombin-based gels in orthopedics, but two high-quality prospective RCTs used similar methods in TKA. The protocol involves applying 10 cc of gel to the exposed bone edges after the components have been placed and cement has polymerized. One study also applied gel to the surrounding soft tissues. The thrombin gel is allowed to sit for 2 min and is irrigated away [43, 44]. The most recent meta-analysis to date, Wang et al. found that these agents can significantly decrease mean calculated total blood loss, drain output, and drops in hemoglobin with minimal risk of side effects. Unfortunately, this meta-analysis only included five studies and further work must be done to support this practice as standard [45]. To date, no studies have evaluated the effectiveness of thrombin-based agents in THA.

2.4 Fibrin sealants

As described above, fibrin is a coagulation cascade end product necessary for stable clot formation. Topical fibrin sealants seek to reproduce this final step of the coagulation cascade by providing exogenous clotting reagents to induce clot formation. While there are many proprietary fibrin sealants on the market, most are a combination of fibrinogen, thrombin, factor XIII, and an antifibrinolytic such as aprotinin or TXA. Early iterations of fibrin sealants were animal derived, but modern preparations are obtained via donated autologous platelet-poor plasma or pooled human plasma [46]. These preparations are stored as separate mixtures in a two chamber (or syringe) system. One chamber typically contains thrombin

Agent	Mechanism	Risks
Passive		
Bone Wax	Intercalation within bony trabeculae	Impeds bone fusion, anaphylaxis, pro-inflammatory
Gelatin Sponge/Powders	Local tamponade	Mass effect near neural elements, DIC (powders)
Oxidized Regenerated Cellulose	Local tamponade	Mass effect near neural elements
Chitosan	Ion based muco-adherent activation of RBCs	None reported
Zeolite	Clot scaffold, H_2O sieve	Exothermic reaction can cause burns
Active		
Fibrin sealants	Coaguation lattice for clot formation	Hypersensitivity reaction for brands containing aprotinin
Topical thrombin-based agents	Coaguation lattice for clot formation	None reported
Aprotinin	Antifibrinolytic serine protease inhibitor	Renal toxicity
Microfibrillar collagen agents	Collagen scaffold for fibrin	Inhibits PMMAC interdigitation, possible hypersensitivity

DIC—diffuse intravascular coagulation; PMMAC—polymethylmethacrylate cement; RBCs—red blood cells.

Table 4.
List of topical hemostatic agents used in orthopedic surgery and their mechanism.

activated with calcium chloride, and the second chamber contains fibrinogen and an antifibrinolytic. The contents of these two chambers are sprayed in a fine mist allowing for the reagents to mix and commence the clotting cascade.

Two high-quality randomized controlled trials have evaluated the effects of fibrin sealants in total knee arthroplasty. These studies concluded that fibrin sealants significantly reduce perioperative blood loss, transfusion requirements, hemoglobin drop, and drain output [47, 48]. The protocol for the use of fibrin sealant in TKA is as follows: after final components have been placed and cement polymerized, the joint is thoroughly irrigated. About 10–20 mL of sealant (1–2 kits) is then sprayed into the wound bed evenly coating exposed boney edges, muscle, tendon and "hidden pouches." A drain is placed as per institutional protocol and layered closure was performed [47, 48].

Evidence for the use of fibrin sealants in total hip arthroplasty is also strongly supported in the literature. Crawford et al., in a retrospective case-control study, found that fibrin sealants in THA can reduce perioperative blood loss and transfusion rates. These results were later echoed by the work of Wang et al. in a prospective controlled trial [49, 50]. In these studies, cemented components were used and 10 mL of sealant was sprayed over the tissues after cement polymerization [49].

Please refer to **Table 4** for the complete list of topical hemostatic agents used in hip and knee arthroplasty.

3. Hemostasis in major spine surgery

Hemostasis in major spine surgery presents many unique challenges. As with arthroplasty, bone bleeding composes a significant portion of blood loss; but unlike arthroplasty, the surgeon must be continuously aware of the proximity of neural elements in the surgical field. Post-operative hematomas may also lead to neurologic complications. The presence of neural elements often precludes use of certain technologies such as bipolar sealers, but these challenges have also spurred innovation. Some of the more specific methods of hemostasis in spine surgery are outlined below.

3.1 TXA

As with lower extremity arthroplasty, tranexamic acid is one of the most heavily researched adjuncts for hemostasis in spine surgery. All three modes of administration have been studied and are outlined below:

3.1.1 Intravenous

IV TXA remains the most common route of TXA administration in spine surgery. To date, the most comprehensive meta-analysis outlining the effectiveness of IV TXA in spine surgery includes 18 RCTs and 18 non-RCTs. This analysis included cervical, thoracic, and lumbar spine surgery regardless of anterior or posterior approach. The type of surgery (discectomy, laminectomy, fusion, deformity correction, etc.) was not specified, but the authors did stratify studies by low-dose or high-dose administration of TXA. Low dose was considered a bolus of ≤10 mg/kg followed by ≤10 mg/kg/h infusion, and high dose was defined as a bolus ranging from >10 to 100 mg/kg followed by a maintenance infusion of >10 mg/kg/h thereafter. All studies had control groups receiving either a placebo of saline or no TXA at all. Pooled data was able to demonstrate that IV TXA reduced blood loss at every point of the operative cycle compared to controls regardless of dose. Interestingly,

there was a dose-dependent response of IV TXA in decreasing intra-operative and perioperative allogenic blood transfusions as well as operative times. Furthermore, there was no increase in the rate of post-operative complications or thromboembolic complications compared to control groups regardless of dose [51].

While a definitive statement on IV dosing protocol in spine surgery cannot be made, the data would suggest that patients may benefit from higher dose regimens in respects to transfusion rates and operative times. This comes with the caveat that more studies need to be performed to add context.

3.1.2 Oral

Overall, there is a paucity of data evaluating the efficacy of oral TXA in major spine surgery. Thus far, a singular prospective RCT has been conducted comparing PO administration of TXA to IV TXA in thoracolumbar spinal surgery. Patients randomized to the oral TXA group were given 1.95 g 2 h prior to surgery. The IV TXA arm was administered 1 g IV TXA as a bolus prior to incision and 1 g IV TXA before wound closure. The authors were able to establish equivalency of PO TXA to IV TXA according to calculated bloods loss, transfusion rates, post-operative hemoglobin drops, and rates of thromboembolic events [52]. While preliminary data regarding PO TXA in spine surgery is promising, more high qualities need to be performed to establish efficacy compared to placebo controls and established IV TXA protocols.

3.1.3 Topical

The best evidence outlining the efficacy of topical TXA in spine surgery compared to placebo controls has been published in two meta-analyses by Yerneni et al. and Luo et al. They were able to conclude that topical TXA can decrease total blood loss, post-operative hemoglobin drops, and drain outputs compared to placebo controls. Several protocols for the use of topical TXA were outlined, but the most common method was 1 g of TXA diluted in 100 mL of saline. The surgical wound was irrigated with this solution prior to closure and was allowed to sit for 2–5 min before being suctioned away [53, 54].

In an effort to compare topical TXA in spine surgery to the more commonly used IV TXA, Xiong et al. conducted a meta-analysis including eight Chinese RCTs. A compilation of 333 patients received IV TXA while 327 had topical TXA. They demonstrated no significant differences in blood loss, hemoglobin, hematocrit, fibrinogen concentrations, post-operative PT or APTT, drainage volume, and blood transfusions. Of note, this meta-analysis was limited to non-deformity correction surgeries, primarily lumbar and thoracolumbar decompression and fusions.

While more high-quality data needs to be obtained to confirm the efficacy of topical TXA in major spine surgery, the current body of evidence suggests that PO TXA is effective in decreasing blood loss, transfusion requirements, and drain outputs when compared to placebo and preliminary evidence shows that this route of administration may be equivalent to the more costly IV TXA.

To see a complete list of the protocols and recommendations for TXA in major spine surgery, please refer to **Table 3**.

3.2 Recombinant factor VIIa

Not uncommonly in major spine surgery, patients can lose the equivalent of one entire blood volume or more. This situation can lead to difficulty in clot formation

secondary to consumptive and dilutional coagulopathies. A consumptive coagulopathy exists as a result of coagulation factors and platelets appropriately being consumed at the surgical site, while a dilutional coagulopathy results from replacement of blood volume with non-plasma fluids. Traditional methods of addressing the relative shortage of coagulation factors and platelets is replacement therapy with allogenic pooled platelets or fresh frozen plasma, but these methods can be fairly nonspecific in their mechanism [55].

Recombinant clotting factor VIIa (rFVIIa) was originally developed to address intra-operative bleeding in patients with disorders of coagulation such as congenital hemophilia, acquired hemophilia, or antibodies to clotting factors VIII or IX. The theory behind using rFVIIa in patients with excessive blood loss is as follows: FVIIa normally works by combining with tissue factor (TF) to create FVIIa-TF complex which activates downstream clotting factors II, IX, and X eventually resulting in a thrombin burst. This thrombin burst is essential for creating a stable fibrin plug resistant to fibrinolysis. In situations of excessive blood loss, exogenously administering rFVIIa will selectively complex with TF at the site of injury, activating the clotting cascade, and leading a thrombin burst with local hemostasis [55, 56].

Thus far, limited data exists for the use of rFVIIa in major spine surgery. The studies available suggest that rFVIIa effectively reduces intra-operative blood loss, intra-operative transfusion requirements and has a sustained effect on reducing PT and INR [56, 57]. No standard protocol exists for dosing or timing given the limited patient data. One study randomized patients undergoing deformity correction surgery to a treatment arm receiving 23 μg/kg beginning 30 min prior to incision, while another study randomized patients undergoing major spine surgery to treatment arms of 30, 60, or 120 μg/kg given in three separate doses only after an estimated 10% of blood volume had been lost [56, 57]. Of these studies, no increased complications were observed in the treatment groups compared to control groups suggesting that this treatment is safe. Further prospective studies are needed to determine efficacy, dosing, and timing of rFVIIa but preliminary results are promising for use in spine surgery where major blood loss is expected.

3.3 Topical hemostatic agents

The category of topical hemostatic agents in spine surgery is vast and can be split into passive and active agents. Both classes are discussed below. See **Table 4** for a complete list of topical hemostatic agents used in spine surgery and their mechanism.

3.3.1 Passive hemostatic agents

3.3.1.1 Bone wax

Perhaps the oldest topical hemostatic agent in orthopedic surgery is bone wax. In modern times, it is employed less frequently, but it remains a mainstay in spine surgery and during certain approaches of the pelvis where bone bleeding is encountered frequently. Bone wax is derived from a combination of bees wax and petroleum jelly and works via mechanical intercalation within bony trabeculae to tamponade bleeding. Currently, no RCT has been performed to tests the overall effects of bone wax on blood loss in spine surgery, yet it remains a staple for many surgeons. One caveat of bone wax is that it can be a physical impediment to bone healing leading to possible pseudoarthrosis of fusion segments if used in excess. Bone wax can also illicit an allergic reaction in patients allergic to bee venom and has a local pro-inflammatory effect [58].

3.3.1.2 Gelatin sponge/powders

Gelatin sponges are hydrophilic compounds that, when exposed to moisture, will expand several times their size. In the context of surgery, these sponges can be placed into a cavity or can be rubbed vigorously onto the surface of a bleeding bone while powder is simply applied topically to a site of bleeding. Once deployed, the gelatin expands creating a tamponade effect. The effect of these sponges can be augmented with the addition of thrombin to encourage clot formation [59]. One benefit of gelatin-derived agents is that they do not serve as a physical impediment to bone healing like bone waxes. Currently, there are no RCTs exploring gelatin sponges/powders as they relate to blood loss in spine surgery. One important caveat to the use of gelatin sponges, especially in the arena of spine surgery, is that their expansion can cause a mass effect resulting in compression of neural elements. While mass effect has not been demonstrated by powdered gelatin agents, there has been a case report of powdered gelatin being inadvertently introduced intravascularly causing DIC. Given the possible complications, it is recommended that gelatin sponges be removed, and powders irrigated away [58].

3.3.1.3 Oxidized regenerated cellulose

Oxidized regenerated cellulose (ORC) is produced in a sponge-like form and works in a similar mechanism to gelatin sponges. No RCTs exploring the effect of ORC agents on blood loss in spine surgery has been performed. Similar cautions should be applied to these compounds as gelatin sponges [58, 59].

3.3.2 Active hemostatic agents

3.3.2.1 Fibrin sealants

Section 2.4 outlines the mechanism of action for fibrin sealants. While the primary use of fibrin sealants in spine surgery is aimed at augmenting dural repairs, these compounds have also been shown to promote hemostasis. In a 2008 study of 3+ level anterior cervical decompression and fusion, 2 mL of fibrin sealant was sprayed as a fine mist over the surgical bed before closure and a drain was placed as per institutional protocol. This study found that fibrin sealants significantly reduced post-operative drain output and length of stay [60].

3.3.2.2 Thrombin-based agents

The mechanism for topical thrombin-based agents is outlined above in the section on arthroplasty. Thus far, only one landmark study has been performed as it relates to topical thrombin-based agents and hemostasis in spine surgery. The multicenter, randomized controlled trial compared a novel thrombin-based agent to gelatin sponges soaked in thrombin. Compared to the gelatin sponge group, the novel thrombin-based agent was able to control bleeding within 10 min in a greater proportion of patients, and time to hemostasis was significantly shorter [61]. While this data is promising, further exploration of thrombin-based topical agents should be performed to determine effects on intra-operative and post-operative blood loss, drops in hemoglobin, etc.

Please refer to **Table 4** for the complete list of topical hemostatic agents used in major spine surgery.

4. Hemostasis in orthopedic trauma

The surgical timeframe in orthopedic trauma varies greatly ranging from emergent to elective. As a result, hemostatic principles must also reflect this level of plasticity as the mangled extremity is managed much differently in the emergent setting than an ankle fracture is in the elective setting. Often, the task of achieving hemostatis has started in the pre-hospital setting and it is the responsibility of the surgeon and the acute trauma medical colleagues to swiftly enact some of the methods described below to avoid downstream complications.

4.1 Topical hemostatic agents

While previously discussed topical hemostatic agent can be utilized in the trauma setting, this section will focus on novel agents specifically designed for major extremity trauma. These agents have primarily been used in battlefield settings and are not currently FDA approved, but may translate to civilian first responders in the future.

Chitosan is a freeze-dried, deacetylated form of chitin which is applied as a bandage to an exsanguinating wound. The positive surface charge of the chitin bandage attracts negatively charged red blood cells causing muco-adherent activation. The original formulation of this product was stiff and did not lend itself to being easily packed into wounds, but newer, more flexible iterations are now in use [62].

Zeolite is composed of biologically inert mineral granules, which act at local water sieves and exerts its mechanism of action in three different ways. First, by decreasing local concentrations of water, relative concentrations of platelets, and clotting factors increases. Second, the granular surface of the mineral serves as a medium for clot formation. Lastly, the hydration reaction of the granules is exothermic creating a thermal environment ideal for clot formation. The exothermic properties of these agents can be exuberant and cause chemical burns. They should therefore be used with irrigation [62].

Please refer to **Table 4** for the complete list of topical hemostatic agents used in orthopedic trauma surgery.

4.2 Tranexamic acid

TXA has much less robust utilization in orthopedic trauma than it does in arthroplasty or major spine surgery. Nonetheless, high-quality evidence exist showing efficacy of TXA in trauma. The 2010 Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) study was a placebo-controlled trial, which enrolled over 20,000 trauma patients from 40 different trauma facilities around the world. The study included patients who presented with, or had significant risk of, major hemorrhage. Those randomized to the treatment arm were administered 1 g of intravenous TXA over 10 min within 8 h of the initial injury and an additional 1 g of IV TXA was infused over 8 h. The authors found this IV TXA protocol significantly decreased all-cause mortality secondary to bleeding [63]. While this data is not specific to extremity trauma, it does show efficacy in critically ill patients.

Several RCTs have translated the exploration of TXA in general trauma to the world of lower extremity trauma. Two recent meta-analyses have demonstrated that TXA can decrease perioperative blood loss, transfusions, and drops in hemoglobin without reciprocal increased in thromboembolic events. All patients in these studies had suffered femoral neck fractures, intertrochanteic femur fractures, and

one study included calcaneus fractures. As with the data presented previously, several routes of administration were utilized with some studies included combination therapies (e.g., IV and topical TXA) [64, 65]. Interestingly, while these meta-analyses found TXA to be effective in lowering transfusion rates and blood loss in lower energy trauma, a recent prospective trial by Spitler et al. found minimal effect of TXA in higher energy trauma including pelvic, acetabular, and femur fractures in younger patients [66].

Superiority of one method over another has not been demonstrated, but a complete list of suggested TXA protocols can be referred to in **Table 3**.

5. Hemostasis in orthopedic oncology

Orthopedic intervention in the world of oncology covers a vast array of procedures which have a significant degree of overlap with the subspecialties listed above. Often, the goal of the orthopedic surgeon is to decrease or eliminate tumor burden through marginal resection, wide resection, and even amputation. These surgeries can be stand-alone, definitive treatments in the algorithm of patient care, or they can serve as adjuvant treatments to be used in addition to chemotherapy or radiation. Orthopedic oncology also extends to the world of palliative medicine, where patients with metastatic disease may present with lesions of impending fracture that benefit from surgical stabilization.

While many of the strategies above may be employed during orthopedic tumor surgery, some have limited evidence. The sections below focus on techniques, technologies, or biosurgical applications that have not been addressed in the sections above, and that are specific to tumor surgery or have a preponderance of evidence in orthopedic oncology literature.

5.1 Tranexamic acid

As outlined above, TXA is a heavily studied compound that has demonstrated efficacy in decreasing blood loss across nearly all orthopedic subspecialties. Unfortunately, far fewer studies have explored the effects of TXA in major tumor surgery. One of the primary reasons for the lag in supporting data is that oncologic patients are often hypercoagulable at baseline and may have other secondary comorbidities induced by tumor burden or chemotherapeutic agents.

Endoprosthetic reconstruction is one arena of orthopedic oncology which has some supporting data. In a recent study by Haase et al., patients undergoing proximal femoral replacement, distal femoral replacement, or proximal tibial replacement were given topical TXA intra-operatively. Compared to patients undergoing endoprothetic reconstruction without TXA, the TXA treatment group had lower perioperative blood loss, transfusion rates, and overall length of stay without increasing overall VTE rates. The authors cited a theoretical increased risk of thromboembolic complications as the reason for using topical TXA as opposed to IV or oral. The protocol involved diluting 1 g of TXA in 10 mL of normal saline which was then sprayed as a fine mist over the wound bed [67].

Only one study has evaluated the effects of intravenous TXA in orthopedic tumor resection. Damade et al. performed a retrospective case series on patients undergoing posterior laminectomy and fusion for metastatic spine disease. A 15 mg/kg dose of TXA was infused at induction and 15 mg/kg/h was continuously infused for the next 8 h. Patients undergoing this treatment did have significantly lower transfusion rates compared to controls and, once adjusted for the number of fusion levels, also had lower perioperative blood loss [68].

A summary of the TXA protocols in orthopedic oncology can be found in **Table 3**. While the preliminary data is promising, there is a significant gap in the literature supporting safety and efficacy of TXA in this patient population.

5.2 Microfibrillar collagen agents

Not uncommonly, orthopedic tumor surgery requires the use of bone graft to fill defects left behind from local or marginal resections. Autograft harvested from the iliac crest has many advantages over allograft counterparts, but can be associated with donor site morbidity including bleeding. Microfibrillar collagens (MFC) are bovine collagen derivatives that have used primarily to provide hemostasis at iliac crest donor sites. Though the exact mechanism of MFC agents is not fully understood, at least two theories have been supported by the literature. First, MFCs enhance platelet activity in a way similar to that of natural collagen, facilitating platelet adhesion to fibrin, platelet aggregation, and degranulation. Second, MFC agents complex with fibrin via the clot stabilizing factor XIIIa. It has been shown that even in thrombocytopenic environments, MFC agents can increase clot formation over controls [69].

Use of MFC agents in orthopedics is extremely limited and most of the data hails from spine literature where iliac crest autograft was formally the gold standard before modern grafting methods were developed. Craig et al. have the first reported human study of MFC agents in the orthopedic literature. Here, MFC agents were found to be equivalent to thrombin-soaked gel-foam in reducing hemovac output in the post-operative setting with no clinical evidence of immune reaction [70]. Intra-operatively, MFC agents have been shown to be better at reducing bone bleeding than control groups receiving no hemostatic agents, but does not reach the same level of effectiveness as gelatin paste of thrombin-soaked gel-foam [71]. More modern formulations combine MFCs, bovine-derived thrombin, and patient plasma into a composite gel applied to sites of bony bleeding. The patient's plasma provides fibrinogen which is cleaved by the bovine thrombin into fibrin. This fibrin is then able to complex with the MFC's creating a collagen-fibrin matrix. This self-contained mixture has been shown to significantly reduce total intra-operative blood loss compared to controls and may also decrease operative time [72].

Though several small, prospective case-control studies support the use of MFC agents for topical hemostasis, no large-scale RCT has evaluated its efficacy.

Please refer to **Table 4** for the complete list of topical hemostatic agents used in orthopedic tumor surgery.

5.3 Pre-operative embolization

On occasion, surgeons can take advantage of tumor composition prior to operative intervention. For tumors which are highly vascular in nature, interventional radiologists may be able to ablate the blood supply, thus shrinking the tumor and decreasing the risk of hemorrhage in regions which are difficult to reach operatively. The most common embolizing agents are polyvinyl alcohol (PVA) and microcoils, and the most common metastatic lesions susceptible to embolization are renal cell carcinoma, thyroid carcinoma, and multiple myeloma. In extremity tumors, definitive orthopedic intervention performed within 48 h of embolization can decrease transfusion requirements as well as perioperative blood loss in direct correlation to tumor size [73].

IR embolization can be especially helpful prior to decompressive spine surgery, but reliable data is difficult to decipher. Two RCTs with similar methodological criteria came to differing conclusions on the effects of embolization on intra-operative

blood loss, transfusion requirements, and blood loss [74, 75]. A separate study found that decreases in blood loss only became significant if arterial supply was completely embolized versus partial or subtotal embolization [76].

Given that most evidence exploring pre-operative embolization of tumors prior to orthopedic intervention is level III or IV, no definitive conclusions can be made regarding efficacy. Despite this, there are certain circumstances where embolization is likely beneficial including large tumors, highly vascular tumors, and tumors requiring large areas of resection. If the surgeon decides to pursue pre-operative embolization, it should be done within 24–72 h of planned orthopedic intervention and the surgeon should have a discussion with the interventional radiologist to determine if complete arterial occlusion can be achieved [77].

6. Conclusion

The topic of hemostasis in orthopedic surgery is immense, and the evidence behind certain principles is frequently limited. The sections above take a subspecialized approach to hemostasis encompassing technological breakthroughs, evolutions in surgical techniques, and novel biosurgical agents which can be used synergistically. Each subspecialty presents specific challenges when it comes to hemostasis, and even specific procedures may lend themselves to a high potential for blood loss. By remaining up to date with the most recent tools and techniques, as well as the evidence behind them, surgeons can continue to make informed decisions to minimize the risk of perioperative blood loss and thereby limit risk of post-operative complications.

Conflicts

None of the authors listed have financial conflicts to disclose.

Author details

Andrew Konopitski* and Chinenye Nwachuku
Department of Orthopaedic Surgery, St. Luke's University Medical Center, Bethlehem, PA, USA

*Address all correspondence to: andrew.konopitski@gmail.com

References

[1] Yoshihara H, Yoneoka D. National trends in the utilization of blood transfusions in total hip and knee arthroplasty. The Journal of Arthroplasty. 2014;**29**(10):1932-1937

[2] Yoshihara H, Yoneoka D. Trends in the utilization of blood transfusions in spinal fusion in the United States from 2000 to 2009. Spine (Phila Pa 1976). 2014;**39**(4):297-303

[3] Yoshihara H, Yoneoka D. National trends in spinal fusion for pediatric patients with idiopathic scoliosis: Demographics, blood transfusions, and in-hospital outcomes. Spine (Phila Pa 1976). 2014;**39**(14):1144-1150

[4] Lasocki S, Krauspe RR, Von Heymann C, Mezzacasa A, Chainey S, Spahn DR, et al. PREPARE: The prevalence of perioperative anaemia and need for patient blood management in elective orthopaedic surgery: A multicentre, observational study. European Journal of Anaesthesiology. 2015;**32**(3):160-167

[5] Arvinius C, Parra JLC, Mateo LS, Maroto RG, Borrego AF, Stern LLD. Benefits of early intramedullary nailing in femoral metastases. International Orthopaedics. 2014;**38**(1):129-132

[6] Wertheimer A, Olaussen A, Perera S, Liew S, Mitra B. Fractures of the femur and blood transfusions. Injury. 2018;**49**(4):846-851

[7] Sherrod BA, Baker DK, Gilbert SR. Blood transfusion incidence, risk factors, and associated complications in surgical treatment of hip dysplasia. Journal of Pediatric Orthopedics. 2018;**38**(4):208-216

[8] Smeets SJM, Verbruggen JPAM, Poeze M. Effect of blood transfusion on survival after hip fracture surgery. European Journal of Orthopaedic Surgery and Traumatology. 2018;**28**(7):1297-1303

[9] Basques BA, Anandasivam NS, Webb ML, Samuel AM, Lukasiewicz AM, Bohl DD, et al. Risk factors for blood transfusion with primary posterior lumbar fusion. Spine (Phila Pa 1976). 2015;**40**(22):1792-1797

[10] Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty-day complication rates. The Journal of Bone and Joint Surgery. American Volume. 2014;**96**(23):1945-1951

[11] Thakur NA, Czerwein JK, Butera JN, Palumbo MA. Perioperative management of chronic anticoagulation in orthopaedic surgery. Journal of the American Academy of Orthopaedic Surgeons. 2010;**18**:729-738

[12] Agnelli G, Becattini C. Treatment of DVT: How long is enough and how do you predict recurrence. Journal of Thrombosis and Thrombolysis. 2008;**25**(1):37-44

[13] Horlocker TT, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, et al. Regional anesthesia in the anticoagulated patient: Defining the risks (THE Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Regional Anesthesia and Pain Medicine. 2003;**28**(3):172-197

[14] Barlow BT, Hannon MT, Waldron JE. Preoperative management of antithrombotics in arthroplasty. The Journal of the American Academy of Orthopaedic Surgeons. 2019;**27**(23):878-886

[15] Vitale MA, Vanbeek C, Spivack JH, Cheng B, Geller JA. Pharmacologic

reversal of warfarin-associated coagulopathy in geriatric patients with hip fractures: A retrospective study of thromboembolic events, postoperative complications, and time to surgery. Geriatric Orthopaedic Surgery & Rehabilitation. 2011;**2**(4):128-134

[16] Watson HG, Baglin T, Laidlaw SL, Makris M, Preston FE. A comparison of the efficacy and rate of response to oral and intravenous vitamin K in reversal of over-anticoagulation with warfarin. British Journal of Haematology. 2001;**115**(1):145-149

[17] Schulman S, Elbazi R, Zondag M, O'Donnell M. Clinical factors influencing normalization of prothrombin time after stopping warfarin: A retrospective cohort study. Thrombosis Journal. 2008;**6**:1-7

[18] Schuetze K, Eickhoff A, Dehner C, Gebhard F, Richter PH. Impact of oral anticoagulation on proximal femur fractures treated within 24 h—A retrospective chart review. Injury. 2019;**50**(11):2040-2044

[19] Meinig R, Jarvis S, Orlando A, Nwafo N, Banerjee R, McNair P, et al. Is anticoagulation reversal necessary prior to surgical treatment of geriatric hip fractures? Journal of Clinical Orthopaedics and Trauma [Internet]. 2020;**11**:S93–S99. DOI: 10.1016/j.jcot.2019.10.004

[20] Hoerlyck C, Ong T, Gregersen M, Damsgaard EM, Borris L, Chia JK, et al. Do anticoagulants affect outcomes of hip fracture surgery? A cross-sectional analysis. Archives of Orthopaedic and Trauma Surgery. 2020;**140**(2):171-176

[21] Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF. Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery. Cochrane Database of Systematic Reviews. 2018:1-43

[22] Lin ZX, Woolf SK. Safety, efficacy, and cost-effectiveness of tranexamic acid in orthopedic surgery. Orthopedics. 2016;**39**(2):119-130

[23] Melvin JS, Stryker LS, Sierra RJ. Tranexamic acid in hip and knee. The Journal of the American Academy of Orthopaedic Surgeons. 2015;**23**(12):732-740

[24] Konig G, Hamlin BR, Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. The Journal of Arthroplasty [Internet]. 2013;**28**(9):1473-1476. DOI: 10.1016/j.arth.2013.06.011

[25] Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: A randomized double-blind controlled trial. The Journal of Arthroplasty [Internet]. 2014;**29**(12):2452-2456. DOI: 10.1016/j.arth.2014.03.032

[26] Chen S, Wu K, Kong G, Feng W, Deng Z, Wang H. The efficacy of topical tranexamic acid in total hip arthroplasty: A meta-analysis. BMC Musculoskeletal Disorders. 2016;**17**:81

[27] Hamlin BR, DiGioia AM, Plakseychuk AY, Levison TJ. Topical versus intravenous tranexamic acid in total knee arthroplasty. The Journal of Arthroplasty [Internet]. 2015;**30**(3):384-386. DOI: 10.1016/j.arth.2014.10.007

[28] Abdel MP, Chalmers BP, Taunton MJ, Pagnano MW, Trousdale RT, Sierra RJ, et al. Intravenous versus topical tranexamic acid in total knee arthroplasty: Both effective in a randomized clinical trial of 640 patients. The Journal of Bone and Joint Surgery. American Volume. 2018;**100**(12):1023-1029

[29] Imai N, Dohmae Y, Suda K, Miyasaka D, Ito T, Endo N. Tranexamic acid for reduction of blood loss during total hip Arthroplasty. The Journal of Arthroplasty [Internet]. 2012;**27**(10):1838-1843. DOI: 10.1016/j.arth.2012.04.024

[30] Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. Journal of Bone and Joint Surgery. British Volume (London). 2001;**83**(5):702-705

[31] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. THE efficacy of tranexamic acid in total knee arthroplasty: A network meta-analysis. The Journal of Arthroplasty [Internet]. 2018;**33**(10):3090-3098. DOI: 10.1016/j.arth.2018.04.043

[32] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The efficacy of tranexamic acid in total hip arthroplasty: A network meta-analysis. The Journal of Arthroplasty [Internet]. 2018;**33**(10):3083-3089. DOI: 10.1016/j.arth.2018.06.023

[33] Alshryda S, Mason JM, Sarda P, Lou T, Stanley M, Wu J, et al. The effect of tranexamic acid on artificial joint materials: A biomechanical study (the bioTRANX study). Journal of Orthopaedics and Traumatology. 2015;**16**(1):27-34

[34] Kayupov E, Fillingham YA, Okroj K, Plummer DR, Moric M, Gerlinger TL, et al. Oral and intravenous tranexamic acid are equivalent at reducing blood loss following total hip arthroplasty: A randomized controlled trial. The Journal of Bone and Joint Surgery. American Volume. 2017;**99**(5):373-378

[35] Perreault RE, Fournier CA, Mattingly DA, Junghans RP, Talmo CT. Oral tranexamic acid reduces transfusions in total knee arthroplasty. The Journal of Arthroplasty [Internet]. 2017;**32**(10):2990-2994. DOI: 10.1016/j.arth.2017.03.063

[36] Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities knee. Clinical Orthopaedics and Related Research. 2014;**472**(1):66-72

[37] Madsen RV, Nielsen CS, Kallemose T, Husted H, Troelsen A. Low risk of thromboembolic events after routine administration of tranexamic acid in hip and knee arthroplasty. The Journal of Arthroplasty [Internet]. 2017;**32**(4):1298-1303. DOI: 10.1016/j.arth.2016.10.015

[38] van Oeveren W, Jansen NJ, Bidstrup BP, Royston D, Westaby S, Neuhof H, et al. Effects of aprotinin on hemostatic mechanisms during cardiopulmonary bypass. The Annals of Thoracic Surgery. 1987;**44**(6):640-645

[39] Colwell CW, Chelly JE, Murkin JM, Stevens D, O'Keefe TJ, Hall R, et al. Randomized study of aprotinin effect on transfusions and blood loss in primary THA. Clinical Orthopaedics and Related Research. 2007;**465**:189-195

[40] Kinzel V, Shakespeare D, Derbyshire D. The effect of aprotinin on blood loss in bilateral total knee arthroplasty. The Knee. 2005;**12**(2):107-111

[41] Jeserschek R, Clar H, Aigner C, Rehak P, Primus B, Windhager R. Reduction of blood loss using high-dose aprotinin in major orthopaedic surgery: A prospective, double-blind, randomised and placebo-controlled study. Journal of Bone and Joint

Surgery. British Volume (London). 2003;**85**(2):174-177

[42] Hooper J, Schwarzkopf R. Additional tools to prevent blood loss in total joint arthroplasty. Techniques in Orthopaedics. 2017;**32**(1):34-40

[43] Kim HJ, Fraser MR, Kahn B, Lyman S, Figgie MP. The efficacy of a thrombin-based hemostatic agent in unilateral total knee arthroplasty. The Journal of Bone and Joint Surgery. American Volume. 2012;**94**(13):1160-1165

[44] Suarez JC, Slotkin EM, Alvarez AM, Szubski CR, Barsoum WK, Patel PD. Prospective, randomized trial to evaluate efficacy of a thrombin-based hemostatic agent in total knee arthroplasty. The Journal of Arthroplasty [Internet]. 2014;**29**(10):1950-1955. DOI: 10.1016/j.arth.2014.05.025

[45] Wang C, Han Z, Zhang T, Ma J, Jiang X, Wang Y, et al. The efficacy of a thrombin-based hemostatic agent in primary total knee arthroplasty: A meta-analysis. Journal of Orthopaedic Surgery and Research. 2014;**9**:90

[46] Thoms RJ, Marwin SE. The role of fibrin sealants in orthopaedic surgery. The Journal of the American Academy of Orthopaedic Surgeons. 2009;**17**(12):727-736

[47] Levy O, Martinowitz B, Oran A, Hashomer T, Tauber C, Horoszowski R, et al. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. JBJS. 1999;**81-1**(11):1580-1588

[48] Wang GJ, Hungerford DS, Savory CG, Rosenberg AG, Mont MA, Burks SG, et al. Use of fibrin sealant to reduce bloody drainage and hemoglobin loss after total knee arthroplasty. Journal of Bone and Joint Surgery. American Volume. 2001;**83**(10):1503-1505

[49] Crawford RW, Giangrande P, Murray D. Fibrin sealant reduces blood loss in total hip arthroplasty. Hip International. 1999;**9**(3):127-132

[50] Wang G-J, Goldthwaite CA Jr, Burks S, Crawford R, Spotnitz WD. Fibrin sealant reduces perioperative blood loss in total hip replacement. Journal of Long-Term Effects of Medical Implants. 2003;**13**(5):399

[51] Hui S, Xu D, Ren Z, Chen X, Sheng L, Zhuang Q, et al. Can tranexamic acid conserve blood and save operative time in spinal surgeries? A meta-analysis. The Spine Journal [Internet]. 2018;**18**(8):1325-1337. DOI: 10.1016/j.spinee.2017.11.017

[52] Yu CC, Kadri O, Kadado A, Buraimoh M, Pawloski J, Bartol S, et al. Intravenous and oral tranexamic acid are equivalent at reducing blood loss in thoracolumbar spinal fusion: A prospective randomized trial. Spine (Phila Pa 1976). 2019;**44**(11):755-761

[53] Yerneni K, Burke JF, Tuchman A, Li XJ, Metz LN, Lehman RA, et al. Topical tranexamic acid in spinal surgery: A systematic review and meta-analysis. Journal of Clinical Neuroscience [Internet]. 2019;**61**(2019):114-119. DOI: 10.1016/j.jocn.2018.10.121

[54] Luo W, Xin SR, Jiang H, Long MX. The efficacy and safety of topical administration of tranexamic acid in spine surgery: A meta-analysis. Journal of Orthopaedic Surgery and Research. 2018;**13**(1):1-6

[55] Weiskopf RB. The use of recombinant activated coagulation factor VII for spine surgery. European Spine Journal. 2004;**13**:83-88

[56] Kolban M, Balachowska-Kosciolek I, Chmielnicki M. Recombinant coagulation factor VIIa—A novel haemostatic agent in scoliosis

surgery? European Spine Journal. 2006;**15**(6):944-952

[57] Sachs B, Delacy D, Green J, Graham RS, Ramsay J, Kreisler N, et al. Recombinant activated factor VII in spinal surgery. Spine (Phila Pa 1976). 2007;**32**(21):2285-2293

[58] Baird EO, McAnany SJ, Lu Y, Overley SC, Qureshi SA. Hemostatic agents in spine surgery: A critical analysis review. JBJS Reviews. 2015;**3**:1-8

[59] Mikhail C, Pennington Z, Arnold PM, Brodke DS, Chapman JR, Chutkan N, et al. Minimizing blood loss in spine surgery. Global Spine Journal. 2020;**10**(1_suppl):71S–83S

[60] Yeom JS, Buchowski JM, Shen HX, Liu G, Bunmaprasert T, Riew KD. Effect of fibrin sealant on drain output and duration of hospitalization after multilevel anterior cervical fusion: A retrospective matched pair analysis. Spine (Phila Pa 1976). 2008;**33**(16):543-547

[61] Renkens KLJ, Payner TD, Leipzig TJ, Feuer H, Morone MA, Koers JM, et al. A multicenter, prospective, randomized trial evaluating a new hemostatic agent for spinal surgery. Spine (Phila Pa 1976). 2001;**26**(15):1645-1650

[62] Cox ED, Schreiber MA, McManus J, Wade CE, Holcomb JB. New hemostatic agents in the combat setting. Transfusion. 2009;**49**(Suppl. 5):248S-255S

[63] Olldashi F, Kerçi M, Zhurda T, Ruçi K, Banushi A, Traverso MS, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Lancet [Internet]. 2010;**376**(9734):23-32. DOI: 10.1016/S0140-6736(10)60835-5

[64] Gausden EB, Qudsi R, Boone MD, O'Gara B, Ruzbarsky JJ, Lorich DG. Tranexamic acid in orthopaedic trauma surgery: A meta-analysis. Journal of Orthopaedic Trauma. 2017;**31**(10):513-519

[65] Amer KM, Rehman S, Amer K, Haydel C. Efficacy and safety of tranexamic acid in orthopaedic fracture surgery: A meta-analysis and systematic literature review. Journal of Orthopaedic Trauma. 2017;**31**:520-525

[66] Spitler CA, Row ER, Ii WEG, Swafford RE, Hankins MJ, Nowotarski PJ, et al. Tranexamic acid use in open reduction and internal fixation of fractures of the pelvis, acetabulum, and proximal femur: A randomized controlled trial. Journal of Orthopaedic Trauma. 2019;**33**(8):371-376

[67] Haase DR, Templeton KJ, Rosenthal HG, Sweeney KR. Tranexamic acid in patients with cancer undergoing endoprosthetic reconstruction. The Journal of the American Academy of Orthopaedic Surgeons. 2019;**28**(6):248-255

[68] Damade C, Tesson G, Gilard V, Vigny S, Foulongne E, Gauthé R, et al. Blood loss and perioperative transfusions related to surgery for spinal tumors. Relevance of tranexamic acid. Neurochirurgie [Internet]. 2019;**65**(6):377-381. DOI: 10.1016/j.neuchi.2019.05.003

[69] Hatsuoka M, Seiki M, Sasaki K, Kashii A. Hemostatic effects of microfibrillar collagen hemostat (MCH) in experimental coagulopathy model and its mechanism of hemostasis. Thrombosis Research. 1986;**42**(9):407-412

[70] Craig C, Asher M. Hemostasis in human iliac crest donor sites with microfibrillar collagen. Spine (Phila Pa 1976). 1976;**2**(4):313-317

[71] Harris W, Crothers O, Moyen B, Bourne R. Topical hemostatic agents

for bone bleeding in humans. JBJS. 1978;**60**(4):454-456

[72] Thibodeaux KT, Lorio MP, Block JE. Intraoperative hemostasis during spinal reconstructive procedures. Orthopedics. 2003;**26**(4):413-414

[73] Pazionis TJC, Papanastassiou ID, Maybody M, Healey JH. Embolization of hypervascular bone metastases reduces intraoperative blood loss: A case-control study. Clinical Orthopaedics and Related Research. 2014;**472**(10):3179-3187

[74] Kato S, Murakami H, Minami T, Demura S, Yoshioka K, Matsui O, et al. Preoperative embolization significantly decreases intraoperative blood loss during palliative surgery for spinal metastasis. Orthopedics. 2012;**35**(9):1389-1395

[75] Clausen C, Dahl B, Frevert SC, Hansen LV, Nielsen MB, Lönn L. Preoperative embolization in surgical treatment of spinal metastases: Single-blind, randomized controlled clinical trial of efficacy in decreasing intraoperative blood loss. Journal of Vascular and Interventional Radiology [Internet]. 2015;**26**(3):402-412. DOI: 10.1016/j.jvir.2014.11.014

[76] Tan BWL, Zaw AS, Rajendran PC, Ruiz JN, Kumar N, Anil G. Preoperative embolization in spinal tumour surgery: Enhancing its effectiveness. Journal of Clinical Neuroscience. 2017;**43**:108-114

[77] Griessenauer CJ, Salem M, Hendrix P, Foreman PM, Ogilvy CS, Thomas AJ. Preoperative embolization of spinal tumors: A systematic review and meta-analysis [Internet]. World Neurosurgery. 2016;**87**:362-371. DOI: 10.1016/j.wneu.2015.11.064