Minimizing Blood Loss and Transfusions in Total Knee Arthroplasty

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Abstract

Blood loss management is critical to positive outcomes in patients undergoing total knee arthroplasty (TKA). Transfusions are associated with an increased risk of major and minor adverse events, length of hospitalization, and overall cost associated with surgery. Many techniques have been investigated and compared. Tranexamic acid (TXA), an antifibrinolytic drug widely known to reduce blood loss, may be a bridge to the goal of eliminating blood transfusions from TKA. Administration of TXA can be performed intravenously, topically at the knee joint, orally, or in combination. A single bolus or multiple doses have reduced total blood loss and transfusion rates consistently, safely, and cost-effectively. The uptake in use of TXA by surgeons has been slow due to concerns in patients deemed high risk for thromboembolic events. Newer evidence from studies specifically involving high-risk patients demonstrates that TXA is indeed safe in this cohort and provides benefits that greatly outweigh potential risks. Incorporation of TXA as a routine part of TKA is in the best interest of patients, health care teams, and medical institutions. TXA can be employed seamlessly with other blood saving techniques and has the capacity to increase productivity and decrease overall cost. This can be achieved by reducing the incidence of transfusion and length of stay, and the need for practices such as preoperative anemia treatment and suction drainage.

Keywords
► total knee arthroplasty
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► blood management
► transfusion

Total knee arthroplasty (TKA) is widely known to provide significant benefits to patients with end-stage arthritis by alleviating pain and restoring function. These benefits do not come without the risks of surgery, which are elevated further by comorbidities that are common in patients who typically undergo TKA. The 2009 National Inpatient Sample database indicated that 85% of TKA patients had at least one comorbidity and 32.5% had three or more.1 While patient comorbidities are often unavoidable, the reduction in perioperative and postoperative blood loss and thus the need for allogeneic blood transfusion is critical to ensure successful outcomes for all TKA patients.

Postoperative anemia is the primary indication for blood transfusion in TKA.2 The current guidelines put forth by the American Association of Blood Banks (AABB) include a good clinical practice statement that emphasizes the analysis of symptoms and the overall clinical situation when deciding when to transfuse. Their guidelines suggest adherence to a strict transfusion trigger for stable, hospitalized patients at 7 g/dL or lower and 8 g/dL or lower in patients with known cardiovascular disease (CVD).3 An assessment of volume status is always warranted as well as the patient’s response to volume resuscitation. Volume resuscitation is often indicated before transfusing blood in patients who are symptomatic and volume depleted.
Blood transfusions are associated with increased length of hospitalization (LOH), hemolytic transfusion reactions, pathogen transmission, immunological reactions, transfusion induced coagulopathy, renal failure, and death. These risks plus the associated costs of transfusions provide sufficient reason for clinicians to strive to eliminate the use of blood products in TKA.

Historically, many strategies have been employed to combat excessive blood loss, postoperative anemia, and ultimately blood transfusions. Preoperative strategies have included iron supplementation, erythropoietin (EPO), and autologous blood donation. Perioperative strategies include pneumatic tourniquets, use of electrocautery, blood salvage, hypotensive anesthesia, and regional anesthesia. Postoperative strategies include reinfusion drains and lower transfusion triggers. A method gaining momentum, the administration of tranexamic acid (TXA), may finally offer a more definitive solution.

This article presents current evidence and guidelines on techniques employed to minimize overall blood loss and transfusions following TKA and offers analysis of these practices.

**Autologous Blood Donation**

Preoperative blood donation of patients set to undergo TKA is a largely abandoned strategy to limit the need for postoperative allogenic blood transfusion. This practice involves donation of one to two units of blood at least 3 to 4 weeks prior to surgery. Autologous donation is associated with a > 1 g/dL drop in hemoglobin (Hgb), precipitating an iatrogenic anemia in many patients. Not surprisingly, studies have shown that patients who choose to utilize autologous donation have an increased risk of all transfusions (auto- logous or allogenic). It has also been reported that a considerable amount of preoperative donations is ultimately wasted. Rates of unused blood in primary unilateral TKA and revision were 55 and 47%, respectively, in a study of 2696 primaries and 223 revisions. Donation criteria and infectious disease testing are not on par with allogenic donation, and therefore, these wasted units cannot be transferred to the allogenic supply. The logistics and cost associated with donation, processing, and storage combined with the potential risks of infection, volume overload, coagulopathy, and clerical error leading to life-threatening transfusion reactions have greatly limited the value of preoperative blood donation and autologous transfusions.

**Erythropoietin**

Recombinant erythropoietin α (EPO) has been shown to decrease the risk of postoperative transfusion in multiple studies. It has also demonstrated reductions in allogenic blood usage in conjunction with preoperative autologous blood donation. Iron supplementation is necessary with EPO administration for full efficacy, and both intravenous (IV) and oral preparations have been associated with an increased risk of infection as well as gastrointestinal complications and headaches that limit patient compliance. Treatment with EPO alone can cost anywhere from $1200 to $2000 per patient, which, combined with insurance company reluctance to cover it, has proven to be a deterrent in its usage. Bedair et al determined that in order for EPO to be considered a cost-effective method of preventing transfusion, a single dose would need to cost $225 or less. In addition to cost, dosing regimens of once per week for 3 to 4 weeks leading up to surgery are cumbersome for patients. EPO can be considered for patients with low body weight (<50 kg), preoperative anemia (Hgb <13 g/dL), or in the context of complicated revision or simultaneous bilateral TKA. The emergence of TXA will likely render EPO obsolete in even these scenarios.

**Tranexamic Acid**

A lysine analog antifibrinolytic called TXA competitively blocks the binding of fibrin to plasminogen and thus the breakdown of the fibrin clot matrices. Intravenous TXA diffuses rapidly into the soft tissues and reaches concentrations equivalent to plasma. The half-life of a single IV dose is 2 to 3 hours. Following administration of 1 g, the drug is > 95% eliminated from circulation by the kidneys in 72 hours. Also notable is the fact that TXA must reach a concentration of 10 mg/mL in the blood before any change in coagulation markers can be observed. Tissue injury induces the coagulation cascade to seal damaged vessels while also activating the fibrinolytic system to ensure continued blood flow through vessels undergoing repair; together hemostasis is eventually achieved. Hyperfibrinolysis, the excessive breakdown of the fibrin clot matrix, can occur with excessive injury. It can often occur in the case of surgery, resulting in increased intraoperative and postoperative bleeding. TXA can be delivered IV, intra-articular (IA) via injection or irrigation, or in pill form, and all methods have been proven to stabilize the fibrin clot matrix, thereby reducing total blood loss (TBL) and ultimately, transfusion rates (TR).

The use of TXA in orthopaedic surgery, particularly in total joint arthroplasty and spine surgery, to reduce blood loss is currently an off-label application of the drug. On-label uses include the oral form as a treatment of heavy menstrual bleeding and IV use for dental extractions in patients with bleeding disorders such as hemophilia. To date there have only been rare reports of minor side effects which include nausea, diarrhea, and orthostatic reactions. There are no contraindications other than severe renal insufficiency, which may allow TXA to accumulate. A lower dose may be warranted for those with decreased creatinine clearance. Patients with impaired liver function have no restrictions of use.

The safety and efficacy of TXA in the reduction in blood TR following TKA are well documented. Hallstrom et al studied 23,236 TKA procedures and 11,489 total hip arthroplasties (THA) with 48 and 51% TXA use, respectively. This powerful study confirmed many earlier findings of a significantly reduced TBL, risk of transfusion, and reduced Hgb drop with no increase in adverse events. This study also concluded that TXA was not associated with an increased risk of myocardial infarction, stroke, or transient ischemic attacks. Unlike studies
in the past, this large patient cohort included patients with what they described as TXA-related contraindications.13

An interesting finding in their study was a significant decrease in the incidence of venous thromboembolic events (VTE) within 90 days of TKA.13 This is a new finding as many previous trials found a significant decrease in TR with no increase in VTE risk with TXA administration. In numerous meta-analyses, TXA proved to be successful in reducing TBL and TR without increasing the risk of VTE in primary TKA, revision TKA, and bilateral TKA.14,15 In addition, Waddell et al found IA TXA safe and effective for TKA revision of periprosthetic joint infections.16

The debate concerning the safety of TXA in high-risk patients has had a direct result on the slow uptake of TXA as a routine part of TKA. Patients with a prior history of VTE or CVD have been excluded from many studies due to their apparent contraindications.13 Physicians have been reluctant to administer TXA in this cohort due to lack of data. Some newer studies further demonstrate the safety of TXA by showing the intraoperative and postoperative benefits similar to those of the average patient without the increased risk of complications. Sabbag et al reviewed 1,262 TKA and THA patients (1,620 cases) with a prior history of VTE. They found a 2% risk of VTE recurrence and no significant increase in this percentage with IV TXA administration.17 Whiting et al identified 402 out of 1,002 primary THA and TKA patients with an American Society of Anesthesiologists (ASA) score of III or IV that had at least one of seven risk factors for VTE. Two-hundred forty out of the 402 “high risk” patients were administered TXA and compared with the remaining 762 patients. Their findings indicated no significant difference in 30-day VTE occurrence and a highly significant difference in TR favoring the TXA group.18

High-risk patients can also benefit from a nonsystemic dose of TXA.18,19 Topical or IA TXA has proven to be equally effective as IV TXA in the reduction in TBL, TR, and Hgb drop while maintaining the same safety profile.19,20 Delanois et al found that IA TXA in high-risk patients had no significant differences in TBL, TR, or adverse events when compared with patients receiving IV TXA.21 The benefits of TXA provide compelling evidence for its usage with patients deemed to be at high risk of VTE or cardiovascular complications.

In addition to its safety and efficacy, another attractive feature of TXA is its potential for cost reduction on a large scale. Studies have demonstrated sizeable institutional savings from substantially lower TR and shorter LOH in total joint arthroplasty patients after adopting TXA as standard protocol.22,23 Other studies have shown significant per patient cost reduction in TKA due to a decreased TR and decreased man-hours associated with transfusions.24 When comparing IV and IA TXA administration in TKA and THA, IV TXA proved to be less expensive.25

Savings have also been demonstrated in the context of workups for preoperative anemia. Styron et al found that preoperative treatment with EPO or IV Iron supplementation was costly, labor intensive, and not a predictor of transfusion.26 The same study also demonstrated that receiving TXA significantly decreased the odds of transfusion and that preoperative anemia treatment may not be necessary with TXA administration.26

An alternative method of use is oral TXA, the subject of newer studies, which appears to provide equal efficacy and safety while costing much less than IV and IA in TKA.27 Perreault et al demonstrated in TKA the efficacy and cost-effectiveness of oral TXA in the reduction in TR.28 The oral dose, however, must be taken approximately 2 to 3 hours before surgery to have the greatest effect and percent bioavailability at the time of incision and may differ from patient to patient.11 Oral administration requires further investigation to determine optimal application to benefit from the potential savings. Fillingham et al suggest that the implementation of oral TXA in place of IV with the increasing prevalence of TKA could save our health care system $23 to $67 million dollars annually, which supports further investigation into oral TXA.29

Other antifibrinolytics include aprotinin and e-aminoacproic acid. Aprotinin was discontinued after preliminary findings that it caused increased risk of death during the BART (Blood conservation using antifibrinolytics) trial.30 Amicar has been noted to have similar efficacy and safety to TXA with the addition of being more cost-effective.31 However, it has not been as widely studied as TXA, which has a 6- to 10-fold increased affinity for plasminogen.32 Larger, head-to-head studies are needed to determine if there is a clear indication for the use of one over the other.

Administration of TXA, the exact dosage of TXA, and timing in all three forms of use are currently under debate. Preliminary consensus in the literature for IV TXA is 20 mg/kg 15 minutes prior to tourniquet deflation or at skin prep with no tourniquet.32 A single bolus of 30 mg/kg TXA was shown to be as effective as continuous infusion over a 20-hour period.33 Administration of 10 mg/kg of TXA prior to inflation of the tourniquet and another 10 mg/kg prior to deflation has also proven to be safe and effective.19 Combined use of IV and IA proved to be superior to IV alone in the reduction in blood loss with no difference in safety.34 Multiple doses with a combination of preoperative, intraoperative, and postoperative regimens were found to have increasing effectiveness in reducing TBL with no difference in safety profile, but are not practical and difficult to implement.34,35 A combination of oral and IA TXA was compared with IA only and proved to be significantly better with regard to TR, TBL, and Hgb levels.27 It appears from the large number of studies that TXA is safe and effective in many different regimens of use. IV usage looks to be the easiest to administer and is less expensive than IA, while oral TXA currently has unanswered questions about dose and timing. Current administration protocols for TXA are up to surgeon preference.

**Pneumatic Tourniquets**

Tourniquets are employed frequently in TKA to reduce perioperative blood loss and increase visibility. The usage and overall efficacy of tourniquets have been a topic of the discussion for decades due to their potential for complications. Some of the risks associated with tourniquet application include neurovascular insult, muscle injury, deep vein thrombosis, and...
wound complications. These potential complications are widely known, but the risk is generally considered to be low with tourniquet times at or below 2 hours.

Multiple studies have investigated tourniquet release before wound closure with hemostasis compared with tourniquet release after wound closure. Results have shown that preclosure release may lead to higher perioperative blood loss and longer operative time compared with postclosure release; however, the risk of complications was significantly decreased. Rama et al found that tourniquet release after wound closure was associated with an increased rate of early postoperative complications requiring surgical intervention. To date, neither method has been proven superior to the other with regard to TBL and major adverse events.

While tourniquets can provide the benefits of reduced intraoperative blood loss, shorter operation times, and increased visibility at the operative site, their use is associated with increased fibrinolytic activity following release, which can lead to increased postoperative blood loss. Current recommendations suggest administering a dose of TXA 15 minutes prior to tourniquet deflation or at the start of wound closure to minimize the fibrinolytic effects of tourniquet release.

The effect of tourniquet usage on cementation and prosthesis fixation is a topic currently under debate. Tourniquets can aid in providing a bloodless operative site, which is considered by many to be necessary for successful implantation of components. Multiple studies have investigated postoperative implant migration using radiostereometric analysis in patients who underwent TKA with and without a tourniquet. Results demonstrated no difference in postoperative implant motion between the two groups. Larger studies are needed, however, to look at the association of component fixation and tourniquet use before any definitive conclusions can be made. The practical benefits of a dry operative site, especially during cementation and fixation, seem to outweigh the risk of complications from tourniquets, but this must be decided individually by surgeons.

A technique that has provided favorable initial results is the use of TXA supplemented by tourniquet use during the cementation phase of TKA as described by Rosenstein et al. They studied the combination of IV TXA and very limited tourniquet use and found no differences in operative time, adverse events, and had an average perioperative blood loss of 100 mL. This method appears to minimize the risks of long tourniquet times while also limiting TBL. A similar study recently investigated the difference in calculated blood loss in three different cohorts: tourniquet use during cementation only, IV TXA at incision and wound closure, and both tourniquet usage and TXA administration. TBL was lowest in the TXA only group and highest in the tourniquet only group. Larger studies comparing TXA use directly with tourniquet usage are needed to investigate these results further.

**Fibrin Sealants**

Topical fibrin glues and sprays are used perioperatively to establish hemostatic control. These compounds contain human coagulation proteins that induce local coagulation at the site of application. Conflicting evidence in the literature exists concerning their true efficacy with regard to TR, but the majority of these studies agree that there is a considerable cost associated with these products which can exceed $450 per patient. When compared directly to IV TXA in patients with preoperative Hgb levels of 13 g/dL or lower, TXA lowered TR by 52.9%, while topical fibrin reduced TR by 35%. This result was not statistically significant, but the cost associated with TXA per patient was < 5% of the cost of the fibrin spray. The authors also mentioned that they did not spray the cut surfaces of the femur and tibia for fear of interference with the ingrowth of press-fit components. Based on current knowledge, use of fibrin sealants is not recommended for routine TKA due to excessive cost. Future research is needed to investigate if these products have any influence on functional outcomes or implant fixation.

**Postoperative Suction Drains**

The use of closed suction drainage for postoperative blood management in TKA has been documented for decades. Their effectiveness has been questioned by many, even before the use of antifibrinolytics. Studies have shown no clear benefits or difference in complications when comparing closed drainage to nondondrainage in unilateral and bilateral TKA. Drains increase total cost and man-hours with no significant benefit to the patient. Parker et al demonstrated in their meta-analysis of 5, 464 patients that those who received closed suction drainage had a significantly higher TR than the nondondrainage cohort.

Newer studies have evaluated the use of postoperative drains in the presence of IA and IV TXA. Decreases in drainage volume of 200 to 300 mL in unilateral and 345 mL in simultaneous bilateral TKA have been exhibited. Furthermore, significant decreases in TBL and TR with no significant difference in adverse events were reported. These findings demonstrate once again that suction drains are not indicated in TKA, with or without with the use of TXA.

Intraoperative blood salvage and postoperative reinfusion systems, other applications of drains, have been employed to reduce TR. Their use has been noted as burdensome with regard to cost and ease of execution. Various studies have provided mixed results in the reduction in blood transfusions with reinfusion drains, but risk of transfusion reactions and similar adverse events still exists, particularly with unwashed red blood cell reinfusion. Guzel et al compared IA TXA to closed suction drainage alone and to postoperative reinfusion drainage demonstrating significantly lower TR, drainage volume, and overall cost with TXA. The substantial cost savings and favorable safety profile of TXA relative to reinfusion drains have helped in rendering them obsolete in TKA.

**Conclusion**

TXA should be considered a routine part of TKA. The data are overwhelmingly consistent with the fact that patients undergoing TKA can benefit substantially from TXA. With the large number of TKA being performed today and the projected...
growth over the next 15 years, institutions that implement TXA into their blood management protocol can expect to see significant savings and improved patient outcomes. Studies aimed at finding the optimal route of administration, dosage, and timing of TXA are warranted in addition to further studies of TXA’s potential for improving functional outcomes.

A successful course for a patient undergoing TKA relies heavily on intraoperative and postoperative blood management. Reducing a patient’s risk of transfusion is crucial to positive outcomes. Many techniques have been investigated over the past 25 years and to date, TXA has consistently lowered TR and outperformed others in studies of efficacy, cost-effectiveness, ease of administration, and coordination with workflow. Eliminating the use of blood products may finally be possible with the implementation of TXA as a routine component of TKA.

References
29. Fillingham YA, Kayuopov E, Plummer DR, Moric M, Gerlinger TL, Delta Valley CJ. The James A. Rand Young Investigator’s Award: A randomized controlled trial of oral and intravenous tranexamic acid in total knee arthroplasty: The same efficacy at lower cost? J Arthroplasty 2016;31(09, Suppl.):26–30
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Si HB, Yang TM, Zeng Y, Shen B. No clear benefit or drawback to the use of closed drainage after primary total knee arthroplasty: a systematic review and meta-analysis. BMC Musculoskelet Disord 2016;17:183