Relative efficacy of tranexamic acid and preoperative anemia treatment for reducing transfusions in total joint arthroplasty

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BACKGROUND: This study aimed to evaluate the efficacy of a perioperative blood management (PBM) protocol at a large, tertiary hospital at reducing blood transfusions after total hip or knee arthroplasty (THA or TKA).

STUDY DESIGN AND METHODS: A retrospective review of the PBM for patients undergoing THA or TKA was performed. Adjusted multiple logistic and Poisson regression models examined the effect of patient characteristics and preoperative, intraoperative, and postoperative factors on the likelihood of transfusion and units transfused.

RESULTS: Of 883 study patients, 330 (37.4%) had surgery before PBM protocol implementation and served as the control population while 553 (62.6%) were eligible for the protocol. Having a higher preoperative hemoglobin (Hb) was independently associated with a decreased odds of transfusion (odds ratio [OR], 0.480; \( p < 0.001 \)). Preoperative treatment for anemia (88 [15.9%] patients) did result in a significant, yet modest, increase in preoperative Hb (11.92 g/dL to 12.35 g/dL; \( p < 0.001 \)) but treatment was not a significant predictor of transfusion. Receiving intraoperative tranexamic acid (TXA; 204 [36.9%] patients) had the greatest effect in reducing the odds of transfusion (OR, 0.289; \( p < 0.001 \)) and the number of units transfused (−0.6; \( p = 0.008 \)).

CONCLUSION: Having a decreased Hb was shown to be an independent risk factor both for requiring a perioperative blood transfusion and for the volume of transfusion. The very modest increase in Hb achieved by the costly and time-consuming preoperative anemia optimization program, however, may not be justified when the use of intraoperative TXA led to drastic reductions in both transfusions and transfusion volumes.

ABBREVIATIONS: BMI = body mass index; DVT = deep venous thromboembolism; PBM = perioperative blood management; THA = total hip arthroplasty; TKA = total knee arthroplasty; TXA = tranexamic acid.
and decrease perioperative anemia. These interventions can be divided into preoperative interventions, including intravenous (IV) iron and/or epoetin alfa administration; intraoperative measures such as the use of cell saver, tranexamic acid (TXA), hemostatic gels, and/or cautery devices; and postoperative interventions, including the administration of IV iron, modified anemia tolerance, and/or lower transfusion criteria thresholds. TXA is a synthetic analog of the amino acid lysine, which inhibits plasminogen activation, thereby reducing fibrinolysis of existing thrombi. Antifibrinolytic medications, such as TXA, have effectively been used to minimize perioperative blood loss in other surgical specialties including obstetrics, trauma surgery, and cardiac surgery.16–18 TXA is typically administered IV in two doses, one before incision, and a second dose during closure. Its antifibrinolytic properties cause many surgeons to avoid its IV use in patients predisposed to form blood clots such as those with a history of pulmonary embolus, stroke, myocardial infarction, coronary artery disease with stents, or a patient on hemodialysis, in which case the TXA may be administered topically with similar efficacy.19,20

Perfecting the workflow for perioperative interventions can be challenging. Additionally, high-volume total joint surgery hospitals often face other challenges when trying to optimize patients before surgery, such as physician variation in practice, a limited time period for interventions before the scheduled surgery date, complex patient comorbidities, and distant geographical locations of patients. In an effort to reduce transfusions among the total joint arthroplasty patients at a large tertiary care hospital, a comprehensive perioperative blood management (PBM) workflow was established and incorporated into the clinical practice of four high-volume lower-extremity arthroplasty surgeons from preoperative Hb optimization, to intraoperative management and postoperative monitoring of the patients. This workflow was based on the blood management programs in use by other departments in the acute care hospital and was staffed by two full-time nurses to screen THA and TKA patients for preoperative Hb optimization.

The primary goal of this study was to evaluate the effectiveness of the PBM workflow, especially the preoperative Hb optimization, at reducing perioperative (both intra- and postoperative) blood transfusions in primary THA and TKA procedures. A secondary aim of the study was to evaluate the utilization of TXA specifically as a component of the PBM in reducing the perioperative transfusion rates among primary THA and TKA patients. Our hypothesis for the primary study aim was that patients managed with the PBM workflow (treated with and without TXA) would have lower overall transfusion rates and blood utilization per patient than a cohort of historical controls. The hypothesis of the secondary aim of the study was that TXA would have a greater effect on perioperative blood product transfusions than any other single predictor.

MATERIALS AND METHODS
A comprehensive PBM workflow was established and incorporated on April 9, 2012, into the clinical practice of a pilot group of four high-volume THA and TKA surgeons at a large academic tertiary care hospital. This workflow was based on other blood management programs in use by other departments at the hospital (e.g., spine, general, and cardiothoracic surgery). The workflow involves the active diagnosis and treatment of preoperative anemia and other transfusion risk factors before undergoing THA or TKA. Coordinated by two full-time nurses, the preoperative workflow targeted all patients scheduled to undergo a primary THA or TKA with any of the four surgeons. Additionally, the operating room schedule was screened by the blood management team to minimize missing eligible patients. All patients undergoing a primary THA or TKA by one of the four study surgeons between October 1, 2011, and October 31, 2013, were eligible for inclusion in the study (Fig. 1). Exclusion criteria for the study were the patient undergoing surgery during the pilot portion of the workflow program while the protocol was still being refined (surgery between April 9, 2012, and December 31, 2012), undergoing bilateral TKA, or undergoing a THA for a hip fracture rather than being electively scheduled. Patients scheduled during the period of protocol refinement were excluded due to the lack of consistency in screening and treating these patients until the process was optimized. Patients during the study period were identified as either being during the workflow protocol period or being historical controls but all patients, either controls or protocol patients, were obtained in a consecutive manner from the scheduled surgeries of the same four surgeons.

The workflow process began with patients receiving a complete blood count. Preoperative anemia (defined as a Hb concentration ≤ 13 g/dL) triggered the patient undergoing iron studies (i.e., ferritin, iron, total iron-binding capacity) and a thorough review of his/her medical history to identify any possible causes for anemia. Patients with any of the following characteristics were not treated by the PBM workflow (Fig. 1): 1) Hb concentration of less than 10 g/dL with an unknown source of anemia; 2) history of hematologic disease (e.g., thalassemia, a myeloproliferative disorder; regardless of Hb concentration); 3) history of chronic kidney disease under the care of nephrology (i.e., end-stage renal disease, regardless of Hb concentration); or 4) history of recent cancer (within 6 months). Instead these patients (11 in total) were referred to the appropriate specialist(s) for evaluation and treatment. The majority of patients treated by the PBM team had Hb concentrations between 10 and 13 g/dL.
Preoperative treatment included administration of IV iron, epoetin alfa, or both before surgery. Dosages of IV iron and epoetin alfa were assigned based on a set of criteria including Hb concentration, ferritin level, and transferrin saturation. Preoperative treatment duration varied by patient but typically lasted between 14 and 21 days. Patients were monitored throughout their hospital stay and transfused per the normal assessment by the orthopedic team. There were not specific criteria for triggering a blood transfusion, but transfusions were not typically given unless the patient had a Hb level below 8.0 g/dL and was symptomatic (e.g., tachycardic, light-headed).

Patient demographics, comorbidities, preoperative Hb, protocol compliance, preoperative treatment, and operative time were all recorded as potential factors affecting the rate of blood product transfusion. In addition, the administration of TXA intraoperatively, either IV (more common) or topically, was recorded. Intraoperative TXA was typically administered IV as one or two doses of 1 g (before incision and/or at closing); however, if the patient had a contraindication to IV TXA (i.e., history of myocardial infarction, cerebrovascular accident, cardiac stents, pulmonary embolus, or on hemodialysis), then it was administered topically.

The intraoperative and postoperative transfusion rates were manually recorded as the primary outcome of interest. The transfusion was included if it occurred at any time during the patient’s intraoperative or postoperative stay in the acute care hospital. These rates were then combined into a single transfusion variable because it was difficult to discern at times whether a patient was ordered a transfusion intraoperatively, which was only administered postoperatively or if the order was placed postoperatively.

The effect of the PBM protocol with concomitant treatment and TXA administration were evaluated by utilizing multiple logistic (whether transfused or not during the acute care hospital stay) and Poisson (number of units transfused) regression models (Stata 10, StataCorp). The most parsimonious models were obtained through a backward elimination stepwise process in which all of the clinically relevant variables were initially included in the models with the least significant variable being excluded in each step until all of the variables remaining had a p value of 0.10 or less with the exception that specific, biologically plausible relevant predictors were still retained regardless of p value. Thus all models were adjusted for the patient’s age, BMI, preoperative pretreatment Hb level (as a continuous variable), whether the patient underwent a TKA versus a THA, the length of the surgery (in minutes), and whether the patient received TXA.

RESULTS

Among the 1392 patients who underwent a primary THA or TKA during the study period, 509 were excluded due to...
undergoing surgery while the workflow protocol was still being finalized, undergoing bilateral simultaneous TKA surgery, or undergoing a primary THA for a hip fracture. This left 883 cases for inclusion in the study. This was divided among 330 patients who underwent surgery before the implementation of the PBM protocol who were included as historical controls and 553 patients who were eligible for screening under the PBM protocol. Of the 553 patients eligible for screening, 101 were not screened for various reasons (18.3%); most commonly this was due to their surgery being scheduled too quickly to allow appropriate screening by the two full-time nurses assigned to the program. Among those 101 not screened, 23 would have been eligible for preoperative treatment. There were 88 (19.5%) patients, among the 452 patients who were screened, who underwent treatment per the blood management protocol (Fig. 1). Twenty-nine (33.0%) of the 88 patients treated preoperatively also received intraoperative TXA, whereas 177 patients (85.9% of TXA patients) received intraoperative TXA but were not treated preoperatively. Preoperative treatment duration predominantly ranged from 14 to 21 days.

Patient characteristics did not differ significantly between the historical controls and those who underwent surgery during the PBM protocol (Table 1). Among the 553 protocol-eligible patients, 88 (15.9%) of the patients underwent some form of preoperative anemia treatment, most commonly this was IV-administered iron (94.3%; Table 2). There were a few patients prescribed a combination of vitamins and oral iron and this was labeled as “other” in Table 2. Patients receiving preoperative treatment did have a significant, although modest, increase in their Hb level (11.9 g/dL before treatment vs. 12.4 g/dL after treatment; p < 0.0001).

Significant differences in the treatment of patients before the protocol and during the PBM protocol did exist that were not a planned component of the protocol, specifically with the administration of aspirin with increasing frequency postoperatively. The rate of TXA utilization increased dramatically after implementation of the PBM, going from 0.6% of all patients receiving intraoperative TXA to 36.9% (p < 0.001; Table 3) due to the coincidental publication of papers at the same time indicating the effectiveness of TXA in reducing blood loss.22-24 In addition, there was a significant trend away from using Lovenox (enoxaparin) for deep venous thromboembolism (DVT) prophylaxis postoperatively (83.0% vs. 66.2%, p < 0.001) in favor of increased utilization of aspirin (34.6% vs. 55.3%, p < 0.001). Neither the use of TXA nor the use of aspirin were planned components of the PBM but occurred independently and their effects were adjusted for within the models.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before protocol (n = 330)</th>
<th>After protocol (n = 553)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>193 (58.5)</td>
<td>333 (60.2)</td>
<td>0.612</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 (±13)</td>
<td>64 (±12)</td>
<td>0.176</td>
</tr>
<tr>
<td>BMI</td>
<td>31.4 (±7.3)</td>
<td>31.2 (±7.0)</td>
<td>0.655</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1 (0-3)</td>
<td>1 (0-2)</td>
<td>0.056</td>
</tr>
<tr>
<td>Number of medications being taken</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>0.724</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>13.6 (±1.6)</td>
<td>13.5 (±1.4)</td>
<td>0.154</td>
</tr>
<tr>
<td>Postoperative (lowest)</td>
<td>9.28 (±1.4)</td>
<td>9.6 (±1.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Type of anesthesia</td>
<td></td>
<td></td>
<td>0.288</td>
</tr>
<tr>
<td>Spinal</td>
<td>225 (68.2)</td>
<td>369 (66.7)</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>105 (31.8)</td>
<td>180 (32.6)</td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td>0 (0.0)</td>
<td>4 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td>0.646</td>
</tr>
<tr>
<td>THA</td>
<td>137 (41.8)</td>
<td>240 (43.4)</td>
<td></td>
</tr>
<tr>
<td>TKA</td>
<td>192 (58.2)</td>
<td>313 (56.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Data are reported as number (%), mean (±SD), or median (interquartile range).

### Table 2. Preoperative treatments received and rates of transfusion

<table>
<thead>
<tr>
<th>Type of preoperative treatment</th>
<th>Number treated (n = 88 of 553 enrolled during the protocol period)*</th>
<th>OR for receiving a transfusion versus untreated protocol patients (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment intervention</td>
<td>88 (15.9% of 553 under the protocol)</td>
<td>3.13 (1.83-5.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Iron</td>
<td>83 (94.3% of the 88 treated)</td>
<td>3.22 (1.83-5.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EPO</td>
<td>24 (27.3% of the 88 treated)</td>
<td>1.78 (0.64-4.94)</td>
<td>0.230</td>
</tr>
<tr>
<td>B12</td>
<td>4 (4.5% of the 88 treated)</td>
<td>2.21 (0.23-21.52)</td>
<td>0.433</td>
</tr>
<tr>
<td>Other</td>
<td>10 (11.4% of the 88 treated)</td>
<td>1.66 (0.35-7.96)</td>
<td>0.628</td>
</tr>
</tbody>
</table>

* Data are reported as number (%).
The overall rate of blood product transfusion during the perioperative period did decrease after the implementation of the PBM protocol, from 17.6% to 13.2% (p = 0.077; Table 4). The mean number of units transfused to each patient also decreased after the implementation of the PBM protocol (p = 0.0332).

Patients who received a transfusion had a significantly lower lowest postoperative Hb (before receiving a transfusion) than those who did not receive a transfusion in the perioperative period (7.6 g/dL vs. 9.8 g/dL, p < 0.0001). In addition, there was a significant difference in the postoperative Hb level of patients who received intraoperative
TXA compared to those not treated with TXA (10.1 g/dL vs. 9.3 g/dL, p < 0.0001). There was no difference though between the preoperative Hb levels of patients who were and those who were not treated with TXA (13.5 g/dL vs. 13.6 g/dL, p = 0.4843).

In multiple logistic regression analyses, the same variables consistently were significant predictors of a patient receiving a transfusion. Increasing age and prolonged operative times were both associated with an increased risk of transfusion (p = 0.002 and p < 0.001, respectively; Table 5). A greater preoperative Hb, higher BMI, undergoing a TKA (instead of a THA), and TXA administration were all associated with decreased odds of receiving a blood transfusion. In univariate analyses, undergoing preoperative treatment for anemia was associated with an increased risk of having a transfusion postoperatively. Being eligible for protocol screening or actually receiving preoperative treatment for anemia, however, was not associated with any increased or decreased odds for undergoing a transfusion in the adjusted models. When evaluating only patients with preoperative Hb values of less than 13 g/dL, the patient's preoperative Hb level, undergoing a TKA, and having TXA administered were the only variables associated with significantly reducing the odds of receiving a blood transfusion (subset analysis results not shown).

In evaluating factors associated with the number of units transfused, the same factors were significantly associated with the number of units transfused, whether evaluating the entire cohort or only those patients with preoperative Hb values of less than 13 g/dL (subset analysis results not shown). Having a higher BMI, increased preoperative Hb, undergoing a TKA (again compared to a THA), and receiving TXA intraoperatively were all significantly associated with receiving fewer units of blood. Having a longer operative time was associated with requiring slightly more units of blood products.

CONCLUSION

Total joint arthroplasty patients tend to have significant blood loss intraoperatively and postoperatively, with patients frequently losing between 500 to 1500 mL in the perioperative period.1-3,25 Tremendous resources have been allocated to effectively screen patients preoperatively and medically optimize anemic patients in an effort to reduce the transfusion of blood products following a total joint arthroplasty.13,26-28 A study evaluating the use of preoperative epoetin alfa preoperatively did result in THA and TKA patients being less likely to receive a transfusion; however, this strategy was found not to be cost-effective.28 The use of preoperative autologous blood donation has been demonstrated to reduce the use of allogenic blood transfusions;3 however autologous blood donations are now infrequently performed due to a variety of reasons including time required, cost, labor issues, and blood storage expenses along with a reported 45% discard rate of autologous blood donations.11,29 Other PBM interventions that were used as models for this study protocol, such as the use of iron or erythropoietin and hard transfusion triggers, have been demonstrated to reduce the use of allogenic blood transfusions.30 Efforts to reduce transfusion rates are motivated by both patient safety and financial concerns. Blood transfusions in surgical patients have been associated with an increased risk of postoperative infection, poor physical function, longer acute care hospital stays, increased utilization of rehabilitation facilities, and increased mortality.8-11,13,32 Several recent randomized control trials have questioned the association between transfusions and adverse patient outcomes.33-35 There is also a financial cost associated with a transfusion. Shander and coworkers4 found that each unit of blood transfused could cost between $522 and $1183 in direct and indirect costs, which at the aggregate hospital level for all surgical patients results in an annual financial burden of blood and transfusion-related activities ranging from $1.62 to $6.03 million per hospital. This study found that preoperative Hb optimization of patients may not be as effective at reducing the need for a blood transfusion after a primary THA or TKA when compared to intraoperative utilization of TXA.

Other researchers have found TXA to be a cost-effective method for reducing transfusion rates.36,37 While in our study, TXA was primarily administered IV, there is evidence that topical administration may be as effective, or even more effective, at reducing transfusion rates.38,39 Critics of widespread use of TXA cite the potential increased risk for thromboembolism in a patient population already predisposed to the formation of DVTs. There has not been a single study adequately powered to identify any associated risk for the development of rare complications such as DVTs in orthopedic patients treated with TXA, however, and meta-analyses of THA and TKA studies have failed to identify any realization of the theoretical risk.40,41 Not a single patient in our study experienced a TXA-related thromboembolic event; however, it must be noted that our study was not powered to determine a difference in thromboembolic events among the patients.

Limitations in this study include its retrospective nature with historical controls. The difficulty in using historical controls was complicated by the implementation of additional changes in the perioperative management of THA and TKA patients independent of the PBM protocol. The utilization of the historical controls was more appropriate than using other patients undergoing surgery at the same time because using a different control group would have required using patients treated by surgeons other than those in the protocol pilot group. There likely would have been greater variations in the perioperative management of patients from other surgeons' practices than...
using the historic controls, thus the patients in the intervention and historical cohorts were derived from the practices of the same four surgeons to minimize confounding variables. The preoperative treatment received typically only lasted 14 to 21 days, which may not have provided enough time for the treatment to achieve maximum efficacy. In addition, iron administered preoperatively was typically iron sucrose rather than iron dextran, which also may be less efficacious. Another limitation of the study was the inability to distinguish whether the TXA was administered topically or IV. Early in its use, TXA was used nearly exclusively IV and only topically when the anesthesiologist felt it was too high of a risk to the patient to use IV (e.g., history of thromboembolism, stroke, myocardial infarction, pulmonary embolus, cardiac stents, or hemodialysis grafts/fistulas). Thus very few patients had TXA administered topically, limiting any potential subgroup analysis. This may not really affect the results of the study, however, given recent literature demonstrating a lack of difference in outcomes between TXA administered IV versus topically.20 Another significant limitation of the study was that despite having two full-time nurses managing the protocol, a substantial number of patients were missed for screening. This inability to obtain a complete capture of eligible patients also illustrates the challenges in treating these patients preoperatively.

The blood management protocol has been successful at correctly identifying which patients are at increased risk for requiring a blood product transfusion perioperatively. In addition, preoperative screening for anemia with concomitant medical intervention does succeed in increasing a patient’s preoperative Hb level. The tremendous resources employed to screen and treat patients preoperatively though do not significantly alter the patient’s requirement of a transfusion after a primary lower-extremity total joint arthroplasty. The utilization of TXA intraoperatively helps prevent the patient’s Hb from dropping to a level postoperatively that would necessitate a blood transfusion. The use of TXA was more effective at avoiding a blood transfusion than preoperatively attempting to optimize the patient’s Hb.

Preoperative Hb screening is still an important component of preoperative optimization of the lower-extremity total joint arthroplasty patient in identifying patients at increased risk for perioperative transfusions. The value in continuing to screen patients preoperatively is to identify patients with severe preoperative anemia (Hb values < 10 g/dL) who may require further medical optimization by specialists, from those patients who were the focus of this study, specifically patients with moderate anemia (Hb values of 10-13 g/dL). For patients with moderate preoperative anemia, preoperative treatments were ineffective in reducing the patient’s perioperative transfusion rate, in stark contrast to the utilization of intraoperative TXA, which did significantly reduce the transfusion rate of patients despite having preoperative anemia.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES


