10.5005/jp-journals-10017-1094

RETROSPECTIVE REVIEW

# Tranexamic Acid results in Less Blood Loss in Total Joint Arthroplasty: A Retrospective Study

[1]Kendall E Bradley, [2]Taylor R McClellan, [3]David Attarian, [4]Rhett Hallows, [5]Samuel S Wellman, [6]Michael P Bolognesi


## ABSTRACT

**Introduction:** Hemostasis is an essential component of surgical procedures and tranexamic acid (TXA), an antifibrinolytic, is widely used empirically in orthopedic patients. We hypothesized that TXA would significantly decrease intraoperative blood loss, the need for blood transfusion, and would decrease patient length of stay (LOS).

**Materials and methods:** We performed a retrospective review of 496 primary total joint arthroplasties (TJAs). We recorded clinical outcomes of those given TXA since the drug was first available at our hospital in November 2012. As a control group, we reviewed all total hip arthroscopies (THAs) or total knee arthroscopies (TKAs) during the 3 months just prior to availability of TXA.

**Results:** A total of 306 consecutive TKAs and 190 THAs were included. There were no differences in age or preoperative hemoglobin between groups. For TKAs, the difference between the preoperative hemoglobin to the first postoperative day (POD1) was 2.74 gm/dL for the "No TXA" cohort, compared with 2.07 gm/dL for the TXA cohort. Total blood loss was 571.1 *vs* 387.3 mL ($p < 0.01$). For THAs, the difference between the hemoglobin values from preoperative levels to POD1 was 3.16 gm/dL compared with 2.36 gm/dL. Total blood loss was greater for the "No TXA" group, 649.4 *vs* 464.1 mL ($p < 0.01$). Only the "No TXA" group underwent transfusion, 13.83%. Hospital LOS was longer in the "No TXA" group, 4.24 *vs* 3.57 days ($p < 0.01$). More "No TXA" were discharged to a skilled nursing or rehab compared with "home," 35.1 *vs* 13.7% ($p < 0.01$).

**Conclusion:** Patients with TXA had statistically significant differences in intraoperative, postoperative, and total blood loss. No patient given TXA required a transfusion. The THA patients given TXA had statistically significant shorter LOS and were more likely to be discharged to home. Therefore, TXA has the potential to improve clinical outcomes following TJA and possibly also reduce cost.


**Keywords:** Arthroplasty, Blood loss, Tranexamic acid, Transfusion.

Bradley KE, McClellan TR, Attarian D, Hallows R, Wellman SS, Bolognesi MP. Tranexamic Acid results in Less Blood Loss in Total Joint Arthroplasty: A Retrospective Study. The Duke Orthop J 2018;8(1):43-48.

[1,2]Resident, [3-6]Attending Surgeon

[1,3,4]Department of Orthopaedics, Duke University, Durham North Carolina, USA

[2]Department of Radiology, Duke University, Durham, North Carolina, USA

[5,6]Department of Orthopaedic Surgery, Duke University Medical Center, Durham, North Carolina, USA

**Corresponding Author:** Kendall E Bradley, Resident, Department of Orthopaedics, Duke University, Durham, North Carolina, USA e-mail: Kendall.bradley@duke.edu

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

Total joint arthroplasty is a procedure that continues to have grown rapidly in popularity in the US.[1] From 1993 to 2005, TKA procedures increased from 200,216 to 497,419 and total hip arthroscopy (THA) procedures from 135,992 to 237,647.[2] Hemostasis is an essential component of any surgical procedure, especially in the case of total joint surgical procedures. Hemostasis is achieved through the steps of vasospasm, platelet adhesion, contact phase, and then fibrinolysis. Increased fibrinolysis can lead to increased intraoperative blood loss.[3] Tourniquets applied during surgical procedures, such as the ones used during TKA, have been shown to increase fibrinolysis during deflation, despite no change in circulating clotting factors.[4] Medications that either retard or stop fibrinolysis would potentially decrease the breakdown of a clot leading to decreased operative blood loss, while not impacting the risk of systemic thrombosis.[5]

Tranexamic acid, an antifibrinolytic, is currently Food and Drug Administration approved as an oral agent for menorrhagia and intravenously for postdental bleeding in hemophiliacs. Tranexamic acid is a reversible competitive inhibitor of plasminogen/plasmin, currently empirically used widely in orthopedics, cardiothoracic surgery, and transplantation to reduce blood loss. Tranexamic acid can be administered by oral, topical, or intravenous routes. A Cochrane Review in 2011 reported TXA was associated with a 15% reduction in mortality from bleeding in trauma patients in one trial of over 20,000 patients.[6] A randomized controlled clinical trial of topical administration of TXA after cementing the implants resulted in higher postoperative hemoglobin and lower total blood loss compared with placebo.[7] Studies comparing intravenous TXA *vs* placebo also initially demonstrated decreased blood loss and fewer transfusions of blood products. However, there has been concern that there were too few patients in these studies to have adequate power to be able to detect if there was any increase in thromboembolism.[8] A meta-analysis of 15 randomized trials of TXA use in TKA demonstrated an average perioperative blood loss of 504 mL less than the placebo group,

used fewer units of blood, and were about six times less likely to need transfusion. There were no differences in the rate of thromboembolic events.[9] Similarly, a meta-analysis of THA indicated that TXA may reduce blood loss, without increasing complications.[10] There are limited data regarding its use in patients with THA.

Tranexamic acid became available to the orthopedic total joints team at the investigating institution in November of 2012. We sought to determine if in our patient population TXA (1) will significantly decrease intraoperative blood loss, (2) will decrease the need for blood transfusion postoperatively, and (3) will decrease LOS.

## MATERIALS AND METHODS

We performed a retrospective review of 496 patients undergoing primary TJA. All data collection was performed on a secure network protected by institutional firewalls. We identified and reviewed the charts from all primary arthroplasty patients in our institution beginning in July 3, 2012 through February 11, 2014. Primary total hip or knee surgery was performed as per the standard of care by a single attending surgeon.

Data were gathered from clinic notes, operative notes, perioperative progress notes, and discharge summaries. These included preoperative hemoglobin and hematocrit values; surgical data (operative time, blood loss based on surgeon's estimate as recorded in operative report and intraoperative complications, such as fracture or nerve injury); and perioperative data (postoperative hemoglobin and hematocrit, number of transfusions administered, blood loss collected via drains, in-hospital complications, adverse clotting events, LOS, and discharge status). Drain were placed at the discretion of the surgeon, as per the normal surgical protocol.

We compared data for patients who had received TXA with patients undergoing the same procedures in the 4 months prior to its availability. During this time period, no antifibrinolytics were used for TJA prior to November 2012. Analyses were performed in JMP Pro version 10.0.2 statistical software (SAS Institute, Cary, North Carolina, USA). We used an independent t-test when conditions of equal variances were met. When equal variance assumption was not met using a two-sided F-test for unequal variances, a Wilcoxon–Mann–Whitney test was used. Fisher's exact test-two tail was used for rates of transfusion and discharge status to a skilled nursing facility (SNF) or rehabilitation facility.

The Institutional Review Board reviewed the study proposal and approved it following expedited review (Protocol 00052773).

## RESULTS

In this study, 306 consecutive patients with TKA and 190 consecutive patients with THA were included. Of these, 10 patients had bilateral TKA (20 operations) and 9 patients had charts that were inaccessible to review. These were excluded from the sample. The final sample size was 278 TKA and 189 THA for a total of 467 patients (Table 1); 229 of these patients received TXA: 134 TKA and 95 THA.

The average age of the patients with TKA was 61.6 years for the "No TXA" group and 63.9 years for the TXA group. The average age of the patients with THA was 61.6 years for the "No TXA" group and 59.9 years for the TXA group. The difference in these ages was not statistically significant. Our patients' preoperative hemoglobin levels were essentially the same. The preoperative hemoglobin was 13.85 gm/dL for the "No TXA" group patients compared with 13.78 gm/dL for TXA patients. For the THA patients, the preoperative hemoglobin was 13.42 gm/dL for the "No TXA" group as compared with 14.01 for the TXA group (Table 2).

For the TKA patients, the difference between hemoglobin from preoperative levels to the first POD1 was 2.74 gm/dL for the "No TXA" group compared with 2.07 gm/dL for the TXA group. The difference between hemoglobin from preoperative levels to POD2 was 3.70 gm/dL for the "No TXA" group and 2.58 gm/dL for the TXA group (Graph 1). These differences were statistically significant ($p < 0.01$) (Graph 1). Only 7 TKA patients did not

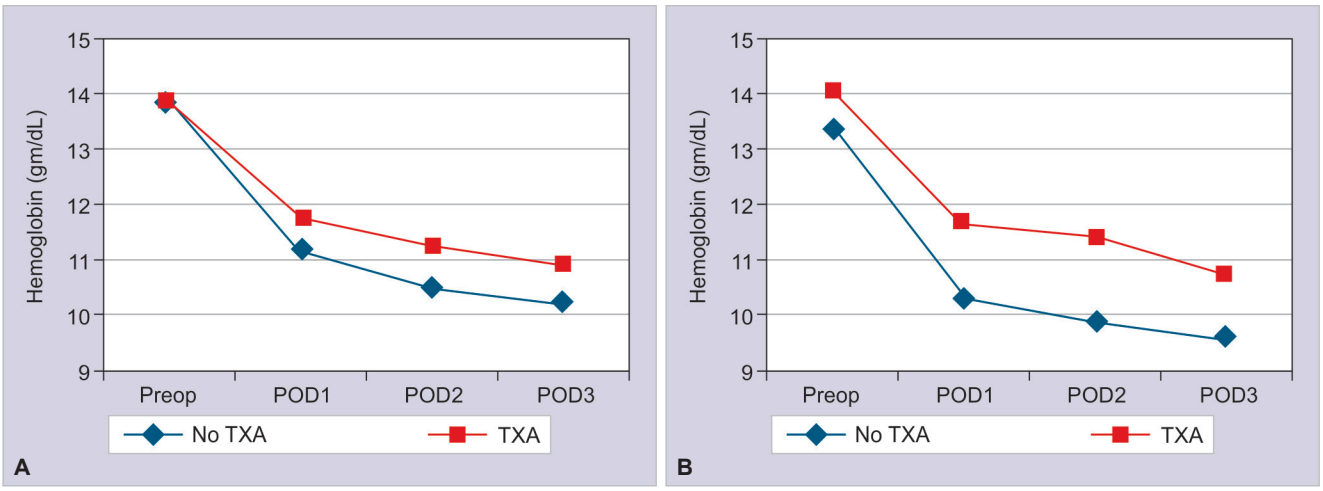
**Table 1:** Summary of inclusion and exclusion criteria

| | *TKA* | | *THA* | |
|---|---|---|---|---|
| | *No TXA* | *TXA* | *No TXA* | *TXA* |
| Total number of patients | 153 | 153 | 95 | 95 |
| Excluded due to bilateral operations | 4 | 16 | 0 | 0 |
| Excluded due to inaccessible charts | 5 | 3 | 1 | 0 |
| Patients included in the study | 144 | 134 | 94 | 95 |

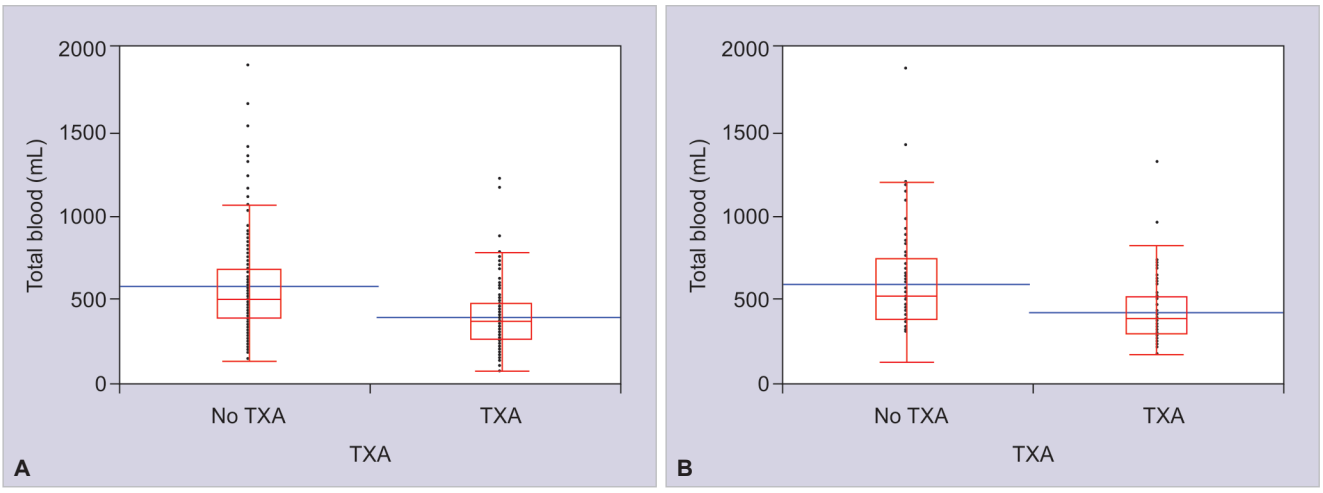
**Table 2:** Description of study population's age and preoperative hemoglobin (gm/dL)

| | *TKA* | | | *THA* | | |
|---|---|---|---|---|---|---|
| | *No TXA* | *TXA* | *p-value* | *No TXA* | *TXA* | *p-value* |
| Age (years) | 66.4 (n = 144) | 63.9 (n = 131) | 0.0316* | 61.6 (n = 94) | 59.9 (n = 95) | 0.4019* |
| Starting hemoglobin (gm/dL) | 13.85 (n = 142) | 13.78 (n = 133) | 0.6669* | 13.42 (n = 94) | 14.01 (n = 93) | 0.0126** |

There was no statistically significant difference between those given TXA and those not given TXA ($p < 0.01$). *Pooled independent t-test; **Mann–Whitney U test




**Graphs 1A and B:** Trend of average hemoglobin (gm/dL) throughout preoperative and postoperative course. TKA (*left*); THA (*right*)




**Graphs 2A and B:** Total blood loss during hospitalization (mL) for TKA (*left*) and THA (*right*) patients not given TXA *vs* patients given TXA. Total blood loss was less in patients given TXA ($p < 0.01$). Means (*blue line*) and quantiles (*red box* and whiskers) both represented

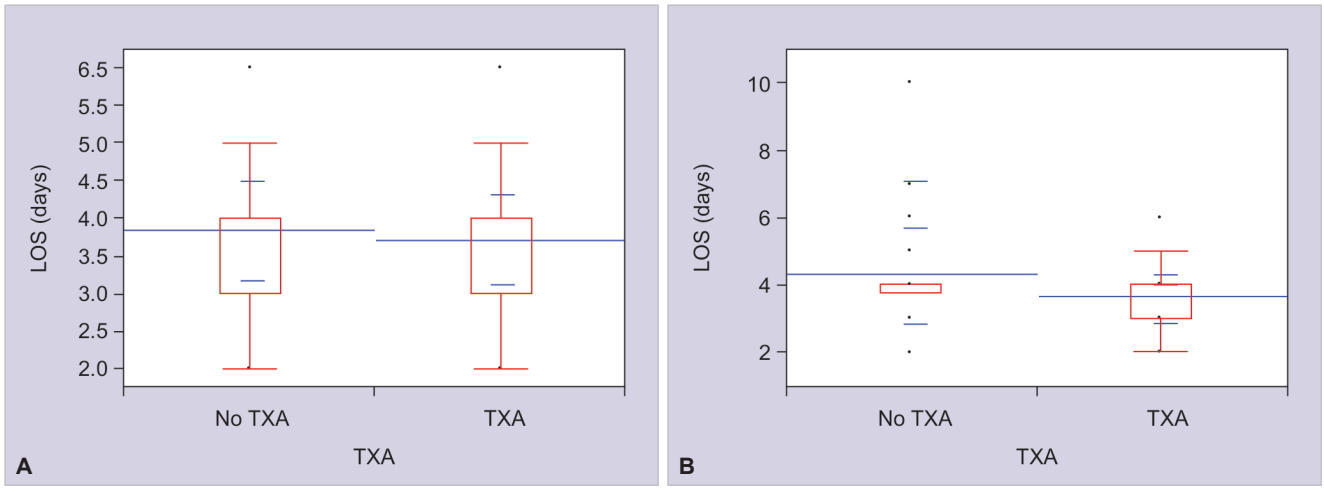
have drains placed, while 15 THA patients did not have drains placed.

The intraoperative blood loss was greater for the "No TXA" group: 227.7 *vs* 176.8 mL for the TXA group ($p < 0.01$) (Graph 2). Total blood loss (which included intraoperative blood loss and that recorded from postoperative drains) was also greater for the "No TXA" group: 571.1 *vs* 387.3 mL ($p < 0.01$). There was also a greater likelihood of transfusion for the "No TXA" group. 5.56% (n = 8) of the "No TXA" group transfused blood, while none of the TXA patients were transfused during their hospitalization ($p < 0.01$) (Graph 3). There was no statistically significant difference in LOS or discharge to a SNF or rehabilitation facility between the groups.

For the THA patients, the difference between the hemoglobin values from preoperative levels to POD1 was 3.16 gm/dL for the "No TXA" group compared with 2.36 gm/dL for the TXA group. The difference in hemoglobin from preoperative levels to POD2 was 3.47 gm/dL for the "No TXA" group and 2.63 gm/dL for the TXA group. Graph 1 shows the change in hemoglobin postoperatively for TKA (A) and THA (B) patients. All of these values were statistically significant ($p < 0.01$). Graph 1 shows the change in hemoglobin postoperatively for TKA (A) and THA (B) patients..

Intraoperative blood loss was greater for the "No TXA" group, 436.0 *vs* 280.9 mL ($p < 0.01$). Total blood loss was also greater for the "No TXA" group, 649.4 *vs* 464.1 mL ($p < 0.01$) (Graph 2). A higher percentage of patients in the "No TXA" group were transfused (13.83% [n = 13] *vs* 0%) ($p < 0.01$). Hospital LOS was longer in the "No TXA" group: 4.24 days compared with 3.57 days for the TXA group ($p < 0.001$) (Graph 3). More patients were discharged to a SNF/rehabilitation facility in the "No TXA" group as compared with TXA, 35.1 *vs* 13.7% ($p < 0.01$) (Table 3).

Thromboembolic complications were infrequent in both groups. Only one thromboembolic complication




**Graphs 3A and B:** Length of stay (days) for TKA (*left*) and THA (*right*) patients not given TXA *vs* patients given TXA. Length of stay was less in THA patients given TXA ($p < 0.01$). Means (*blue line*) and quantiles (*red box* and whiskers) both represented

**Table 3:** Summary of results including p-values

| | *TKA* | | | *THA* | | |
|---|---|---|---|---|---|---|
| | *No TXA* | *TXA* | *p-value* | *No TXA* | *TXA* | *p-value* |
| LOS (days) | 3.83 (n = 135) | 3.70 (n = 131) | 0.0906* | 4.24 (n = 94) | 3.57 (n = 95) | <0.0001** |
| Difference in Hgb pre-op to POD1 (gm/dL) | 2.74 (n = 142) | 2.07 (n = 132) | <0.0001* | 3.16 (n = 94) | 2.36 (n = 93) | <0.0001** |
| Difference in Hgb pre-op to POD2 (gm/dL) | 3.70 (n = 141) | 2.58 (n = 119) | <0.0001* | 3.47 (n = 91) | 2.63 (n = 83) | <0.0001* |
| Intraoperative blood loss (mL) | 227.69 (n = 143) | 176.83 (n = 134) | <0.0001** | 435.96 (n = 94) | 280.90 (n = 95) | <0.0001** |
| Total blood loss (mL) | 571.18 (n = 140) | 387.33 (n = 131) | <.0001** | 649.44 (n = 87) | 464.09 (n = 90) | <0.0001** |
| Transfusion % | 5.56 (n = 144) | 0 (n = 135) | 0.0073† | 13.83 (n = 94) | 0 (n = 95) | <0.0001† |
| Discharge SNF or rehab % | 36.84 (n = 133) | 27.41 (n = 135) | 0.1165† | 35.11 (n = 94) | 13.68 (n = 95) | 0.0007† |

*Pooled independent *t* test; **Mann–Whitney U test; †Fisher's exact test two-tailed; Hgb: Hemoglobin

occurred in the TXA group (in a TKA patient) and one occurred in the "No TXA" group (in a THA patient).

## DISCUSSION

The majority of studies on TXA in TJA have been limited by small sample size and have primarily been done in other countries where TXA is widely used. As adoption of antifibrinolytics become the standard of care in hospitals across the US, it is important to consider whether its use is effective, improves quality of care, and is cost effective. Two of our three hypotheses were confirmed. TXA did in fact reduce blood loss following joint replacement (Graph 2). Intraoperatively, there was more blood loss in both hip and knee patients including postoperative blood loss that was measured by drain output. Though statistically significant, the question becomes whether this quantity of blood loss is clinically significant. Human blood volume is estimated to be between 4 and 6 L, depending on a number of factors. As we age, absolute blood volume decreases by almost 25% in men, as does plasma volume, and erythrocyte volume.[11] In an elderly population, a loss of 0.5 to 1 L of blood may be extremely significant. The need for transfusions due to symptomatic anemia is an important marker. In our study, no patients who were given TXA required blood transfusions for either primary operation.

Blood transfusion is an expensive intervention and is not benign. As hospitals look to contain costs and improve quality, reducing transfusions can accomplish both. Though the risk of serious adverse outcomes is exceedingly rare, it is not zero and includes allergic reactions, bacterial contamination, viral infections (including hepatitis C and prion-associated conditions, fever, lung injury, hemolytic reaction, and graft *vs* host disease. One study reported 0.4% of 29,720 patients who received transfusions suffered adverse events.[12,13]

Despite the clinical advantages to using TXA *vs* placebo, it is frequently felt to be financially prohibitive. Tranexamic acid currently costs between $100 and $200 per each intravenous dose. A unit of RBC costs between $500 and $1,000.[14,15] Transfusion cost is not limited to the cost of the blood product but also to the overhead labor costs, leading to the actual total cost of a transfusion approaching $1,500.[16] While it may be argued that the criteria for transfusion are getting stricter, this study was performed in a condensed time period. The fact that none of the over 200 patients who received TXA in this study

received transfusions is not only statistically significant but also clinically and economically significant.

Hospital LOS is another economic cost under scrutiny. The number of days spent in the hospital for TJA is trending down and there are aggressive efforts to reduce them further. Age, sex, marital status, American Society of Anesthesiologists physical status classification prior to surgery, and need for transfusion all may be factors in a patient's probability of staying in the hospital longer.[17] In our review, we found that the LOS for THA patients was on average shorter by 0.67 day. In NC, the average cost for a hospital bed day is $1,698.[18] On average in NC this could represent $1,137.66 in cost savings. To our knowledge, decreased LOS with the use of TXA has not been previously reported in the literature. This has potential economic implications and warrants further study. In addition, patients were more likely to be discharged to home, rather than to a SNF or rehabilitation facility, further reducing costs and perhaps improving patients' quality of life.

A final question becomes the safety of TXA, especially as there is already a risk of thromboembolic complications in TJA, and adding an agent that potentially inhibits clot degradation theoretically could increase symptomatic thromboembolic complications. As with previous studies, this did not appear to be the case.[19] There were only two cases of symptomatic deep venous thrombosis or pulmonary embolism in this chart review in the immediate postoperative period. One was in the TXA cohort, and one was in the "No TXA" cohort. Patients are typically quoted that there is less than a 1% risk of these complications.

As with any retrospective study, our study has limitations. The lack of randomization in a retrospective trial means that not all factors can be controlled. In addition, while it can be a strength to only have one surgeon's data, minimizing practice differences that may influence outcomes, this can also be a weakness due to potential lack of generalizability. The selection of a control group to the few months before adopting TXA likely minimized any changes that would have been due to changed operative or institutional processes. The patients in the "No TXA" cohort were slightly older than the TXA cohort, although the difference in age was not statistically. Measurement of blood loss, both intraoperative and postoperative, is not always precisely measured and there may be "hidden blood loss."[20]

As TXA is more widely accepted in the US and becomes the standard of care, it may be beneficial to test different routes of delivery, such as an oral or intra-articular route compared with intravenous administration. It will also be interesting to compare TXA to a similar product, aminocaproic acid (Amicar). Amicar is significantly less expensive than TXA and has a similar mechanism of action. There are limited data comparing the clinical efficacy and cost-effectiveness of these two anti-fibrinolytics. Given the increased potency of TXA, it may be more efficacious and ultimately more cost-effective than the more widely used Amicar. Future research should focus on the clinical efficacy of these agents.

## CONCLUSION

In this high-volume retrospective study, primary total joint patients who were administered TXA experienced decreased blood loss during and following TJA and reduced transfusion rates. The TXA may also decrease LOS as well as impact discharge home, although further studies are needed to replicate this finding.

## REFERENCES

1. Losina E, Thornhill TS, Rome BN, Wright J, Katz JN. The dramatic increase in total knee replacement utilization rates in the United States cannot be fully explained by growth in population size and the obesity epidemic. J Bone Joint Surg Am 2012 Feb;94(3):201-207.
2. Tian W, DeJong G, Brown M, Hsieh CH, Zamfirov ZP, Horn SD. Looking upstream: factors shaping the demand for postacute joint replacement rehabilitation. Arch Phys Med Rehabil 2009 Aug;90(8):1260-1268.
3. Hardy JF, Desroches J. Natural and synthetic antifibrinolytics in cardiac surgery. Can J Anaesth 1992 Apr;39(4):353-365.
4. Klenerman L, Chakrabarti R, Mackie I, Brozovic M, Stirling Y. Changes in haemostatic system after application of a tourniquet. Lancet 1977 May;309(8019):970-972.
5. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. J Am Acad Orthop Surg 2010 Mar;18(3):132-138.
6. Roberts, I.; Shakur, H.; Ker, K.; Coats, TJ. Blood-clot promoting drugs for acute traumatic injury. London: John Wiley & Sons, Ltd; 2011.
7. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Davey JR, Gandhi R, Syed KA, Muhammad Ovais Hasan S, De Silva Y, Chung F. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty—a randomized, controlled trial. J Bone Joint Surg Am 2010 Nov;92(15):2503-2513.
8. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela J, Niemelä HM, Mäntylä SK, Kuisma RP, Ylinen JE. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg 1997 Apr;84(4):839-844.
9. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am 2012 Jul;94(13):1153-1159.
10. Zhou XD, Tao LJ, Li J, Wu LD. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. Arch Orthop Trauma Surg 2013 Jul;133(7):1017-1027.
11. Davy KP, Seals DR. Total blood volume in healthy young and older men. J Appl Physiol (1985) 1994 May;76(5):2059-2062.
12. Bhattacharya P, Marwaha N, Dhawan HK, Roy P, Sharma RR. Transfusion-related adverse events at the tertiary care center in North India: An institutional hemovigilance effort. Asian J Transfus Sci 2011 Jul;5(2):164-170.
13. Boucher BA, Hannon TJ. Blood management: a primer for clinicians. Pharmacotherapy 2007 Oct;27(10):1394-1411.

14. Gillette, BP.; DeSimone, L.; Kremers, HM.; Smith, H.; Duncan, C.; Trousdale, R.; Pagnano, MW.; Sierra, RJ.; editors. Economic impact of tranexamic acid in healthy patients undergoing primary hip and knee arthroplasty. AAHKS annual meeting, Rochester, Minnesota. 2012.
15. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 2010 Apr;50(4):753-765.
16. Blumberg N, Kirkley SA, Heal JM. A cost analysis of autologous and allogeneic transfusions in hip-replacement surgery. Am J Surg 1996 Mar;171(3):324-330.
17. Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. Acta Orthop 2008 Apr;79(2):168-173.
18. The Kaiser Family Foundation State Health Facts. Hospital adjusted expenses per inpatient day 2011. San Francisco (CA): AHA Annual Surveys; 2013. [cited 2014 Jun 4]. Available from: http://kff.org/other/state-indicator/expenses-per-inpatient-day/.
19. Ho KM, Ismail H. Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. Anaesth Intensive Care 2003 Oct;31(5):529-537.
20. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth 2003 May;90(5):596-599.