SAGE Open Medicine
Volume 4: 1–6
© The Author(s) 2016
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/2050312116637024
smo.sagepub.com

Perioperative blood loss in total hip and knee arthroplasty: Outcomes associated with intravenous tranexamic acid use in an academic medical center

Craig A Hogan[1,2], Larry K Golightly[1,3,4], Suzanne Phong[1,4], Michael R Dayton[1,2], Clark Lyda[1,4] and Gerard R Barber[1,4]

Abstract

Objectives: Clinical trials have reported decreased blood loss with the use of tranexamic acid during joint reconstruction. The purpose of this study was to assess the individual practice implications of tranexamic acid use in joint replacement surgery.

Methods: Health records of adults undergoing total knee arthroplasty and total hip arthroplasty over a 12-month period were retrospectively reviewed. The treatment group comprised patients who received intravenous tranexamic acid perioperatively. The control group comprised patients who did not receive tranexamic acid.

Results: Patients in the treatment group (n = 64) and the control group (n = 99) were well matched for demographics, orthopedic diagnosis, and comorbidities. In-hospital postsurgical mean decreases in hemoglobin concentrations were −4.05 g/dL and −4.94 g/dL in the treatment and control groups, respectively ($p < 0.001$). Postsurgical mean decreases in hematocrit levels were −11.2% and −14.2% in the treatment and control groups, respectively ($p < 0.001$). Three patients in the treatment group (5%) and 21 patients in the control group (21%) received red blood cell transfusions ($p = 0.006$). As compared to control, the relative risk of transfusion in the treatment group was 0.23 (95% confidence interval = 0.07–0.76) and the number needed to treat to avoid one transfusion was 7.0 (95% confidence interval = 3.8–14.4). No evidence of thromboembolism or other serious complications were observed in either group.

Conclusions: In patients undergoing joint replacement surgery, perioperative administration of tranexamic acid was associated with diminished blood loss and lesser resource utilization.

Keywords
Knee, hip, arthroplasty, transfusion, tranexamic acid

Date received: 27 October 2015; accepted: 10 February 2016

Background

Blood loss associated with joint replacement surgery has long been recognized as a substantive issue. Investigations performed in the 1980s revealed that intraoperative blood losses in total knee arthroplasty (TKA) averaged more than 1000 mL per procedure.[1] More recent studies have shown that non-visible blood loss such as bleeding into tissues and hemolysis with reinfusion typically accounts for volume losses equivalent to an additional 500 mL.[2]

Blood loss of this magnitude is often associated with postoperative anemia requiring transfusion. A systematic review of controlled studies comprising more than 29,000 patients undergoing knee or hip reconstruction revealed that

[1]University of Colorado Hospital, Aurora, CO, USA
[2]Department of Orthopedics, University of Colorado School of Medicine, Aurora, CO, USA
[3]Center for Drug Information, Education, and Evaluation, University of Colorado Health Sciences Library, Aurora, CO, USA
[4]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO, USA

Corresponding author:
Larry K Golightly, Center for Drug Information, Education, and Evaluation, University of Colorado Health Sciences Library, Anschutz Medical Campus, Box A-003, 12950 East Montview Boulevard, Aurora, CO 80045-2515, USA.
Email: larry.golightly@uchealth.org

Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

postoperative blood transfusions were administered in 45% of these cases.[3] In this review, postoperative anemia and allogeneic blood transfusion were associated with statistically significant increases in rates of postoperative infection, poor physical functioning and recovery, longer lengths of hospital stay, and greater mortality. Transfusions are also associated with substantial increases in resource utilization and cost.[4] Accordingly, efforts to minimize transfusion requirements have led to widespread implementation of blood conservation programs as well as utilization of various surgical, anesthetic, and pharmacological methods aimed at decreasing blood loss and improving outcomes in patients undergoing TKA and total hip arthroplasty (THA).

Orthopedic treatment guidelines[5–7] are equivocal regarding preferred pharmacologic blood management strategies for TKA and THA. For this reason, drug product selection is generally based on the knowledge, familiarity, and preferences of individual providers. Possible choices among available hemostatic agents include fibrin, thrombin, lavage with epinephrine or norepinephrine, and the antifibrinolytic drugs ε-aminocaproic acid and tranexamic acid (TXA). Although no definitive data on the comparative efficacy and cost-effectiveness of these agents are available, most current literature on pharmacological blood conservation centers on TXA. This is the focus of our investigation.

Objective

The purpose of this report is to recount experience with implementation of TXA use in orthopedics at an academic medical center. We sought to not only assess the potential clinical benefit, relative safety, and cost implications of TXA administration in joint reconstruction surgery, but also to gauge the overall impact of decisions to use or not to use TXA on the practice of individual orthopedic surgeons.

Methods

This study was approved by our local ethics committee (Colorado Multiple Institutional Review Board (COMIRB), protocol no. 13-3210) and the hospital's Research Support Service.

Patients greater than 18 years of age who underwent joint reconstruction at the University of Colorado Hospital between 1 November 2012 and 31 October 2013 were identified by review of computerized inpatient data (Epic Willow, Epic Systems Corporation, Verona Wisconsin USA) and their medical records were retrospectively examined. Patients were included if they received primary, revision, or bilateral TKA or THA performed by either of two participating orthopedic surgeons.

With the exception of insertion of drains in TKAs, both participating reconstructive orthopedic subspecialist surgeons used identical operative techniques for joint reconstruction. Both surgeons used similar postoperative pain management techniques, antithrombotic therapy (subcutaneous enoxaparin 40 mg daily beginning on postoperative day 1), and rehabilitation strategies and both employed a standardized protocol for daily laboratory monitoring. Both surgeons routinely followed identical criteria for decisions regarding blood transfusion (hemoglobin < 7.0 g/dL, unless anemic symptoms are present).

Subsequent to a request for formulary addition of TXA for the express purpose of use during joint replacement surgery, one surgeon adopted the use of this agent in all patients without contraindications. A standardized prescribing regimen was established in which patients received TXA 10 mg/kg as a direct intravenous (IV) injection immediately prior to skin incision and once again 3 h later. Patients who received TXA according to the above regimen were allocated to the treatment group.

Contrastingly, one participating surgeon elected not to use TXA. Contemporary patients undergoing joint reconstruction performed by this surgeon were allocated to the primary control group (control group 1).

An additional cohort of patients was evaluated. Patients who underwent joint replacement prior to formulary addition of TXA whose surgery was performed by the surgeon who subsequently adopted the use of TXA were allocated to a secondary control group (control group 2). Although patients in this group did not differ from others in terms of clinical characteristics, they did not receive TXA. These patients were evaluated for the primary outcome only.

The primary outcome was objective measures of perioperative blood loss and prevalence of blood transfusion among patients undergoing total joint arthroplasty. Accordingly, preoperative and nadir postoperative (usually postoperative day 2) hemoglobin and hematocrit levels were recorded and differences were determined. Blood product administrations were identified and recorded, including volumes or amounts and types of transfusion according to allogeneic or autologous blood. Secondary outcomes of interest included length of stay, relative health condition as described in the hospital discharge summary, and in-hospital occurrence rates for thrombotic, hemorrhagic, and other serious complications.

Cost implications of TXA treatment and blood transfusions were evaluated. We conservatively calculated costs with use of the average wholesale price for TXA (US$50.40 per 1000 mg/10 mL ampoule of Cyklokapron® injection; Red Book Online, Truven Health Analytics, http://sites.truvenhealth.com/redbook/index.html; accessed 23 February 2015) and the published mean cost for packed red blood cell (pRBC) transfusions in surgical patients with accounting for acquisition, processing, testing, and direct and indirect overhead expense (US$761 per unit in 2010 US dollars).[8]

Results are expressed as the mean ± standard deviation. Incidence rates were compared by construction of 2 × 2 contingency tables and statistical testing with chi-squared or Fisher's exact probability test. Continuous variables were tested as discrete populations with Student's *t* test. Analyses

Table 1. Patient demographics and clinical characteristics.

Patients	Control 1 (n = 99)	Treatment (n = 64)	p-value
Age (years)	59.9 ± 10.2	62.0 ± 11.4	0.157
Male gender	31 (31%)	29 (45%)	0.287
Height (inches)	65.6 ± 4.3	66.5 ± 3.9	0.349
Weight (kg)	86.7 ± 21.0	84.0 ± 18.9	0.349
ASA classification	2.33 ± 0.61	2.27 ± 0.59	0.865
Comorbidities			
Endocrine disorder	28 (28%)	16 (25%)	0.721
Cardiopulmonary disorder	68 (68%)	43 (67%)	0.920
Neuropsychiatric disorder	33 (33%)	18 (28%)	0.605
Genitourinary disorder	12 (12%)	13 (20%)	0.183
Musculoskeletal disorder	12 (12%)	10 (16%)	0.639
Hematological disorder	9 (9%)	1 (2%)	0.091
Malignant disorder	16 (16%)	4 (6%)	0.086
Diagnosis			
Osteoarthritis	84 (84%)	52 (81%)	0.675
Orthopedic device complication	9 (9%)	8 (12%)	0.601
Fracture	0 (0%)	1 (2%)	0.390
Other	6 (6%)	3 (5%)	0.990
Arthroplasty			
Primary TKA	45 (45%)	23 (36%)	0.261
Primary THA	43 (43%)	32 (50%)	0.509
Revision TKA	4 (4%)	4 (6%)	0.713
Revision THA	7 (7%)	5 (8%)	1.000
Operative variables			
Time, incision-closure (min)	83.9 ± 21.5	99.3 ± 27.5	<0.001
Tranexamic acid (mg/kg)	0	10.1 ± 0.50	<0.001
Admin $time_1$/incision (min)	–	−13.2 ± 11.1	–
Admin $time_2$/incision (min)	–	184.2 ± 50.9	–

Admin $time_1$/incision: time from first drug administration to skin incision; Admin $time_2$/incision: time from skin incision to second drug administration; ASA: American Society of Anesthesiologists; THA: total hip arthroplasty; TKA: total knee arthroplasty.

were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

During the period of observation, 173 patients underwent total joint arthroplasty performed by participating surgeons. Among these, 64 patients received perioperative TXA (treatment group). In all, 109 patients did not receive TXA, of whom 99 comprised control group 1 and 10 comprised control group 2.

Clinical characteristics of patients in the two primary analysis groups (treatment and control group 1) are displayed in Table 1. As shown, patients in both groups were generally well matched and no significant differences were observed between groups with regard to demographics, comorbidities, preoperative medications, orthopedic diagnosis, or type of reconstructive surgery. Differences were noted in duration of surgery, with operations in the treatment group averaging approximately 14 min longer than in control group 1 ($p < 0.001$).

Distinguishing group differences in regard to receipt of TXA were noted. Whereas patients in control group 1 did not receive TXA, patients in the treatment group received weight-based IV TXA in amounts equivalent to a mean of 10.1 mg/kg per dose. On average, TXA was administered approximately 13 min prior to skin incision and again at approximately 184 min after skin incision. Among patients in the treatment group, 61 received two doses of IV TXA and three patients inadvertently received only a single preoperative dose of IV TXA.

Hemoglobin concentrations declined following surgery. In the treatment group, the mean hemoglobin concentration decreased from 14.38 ± 1.68 g/dL preoperatively to a postoperative nadir of 10.33 ± 1.50 g/dL. In control group 1, the mean hemoglobin concentration fell from a preoperative value of 14.44 ± 1.38 g/dL to a postoperative nadir of 9.50 ± 1.60 g/dL. As illustrated in Figure 1, the magnitude of the mean operative decrease in hemoglobin concentration was less in the treatment group than in control group 1 (−4.05 g/dL and −4.94 g/dL, respectively; $p < 0.001$). In control group 2, mean operative hemoglobin concentrations

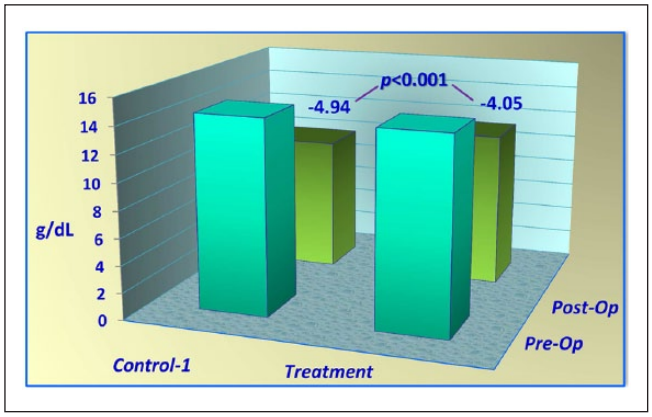

Figure 1. Mean preoperative and postoperative hemoglobin concentrations in the control group 1 and treatment group.

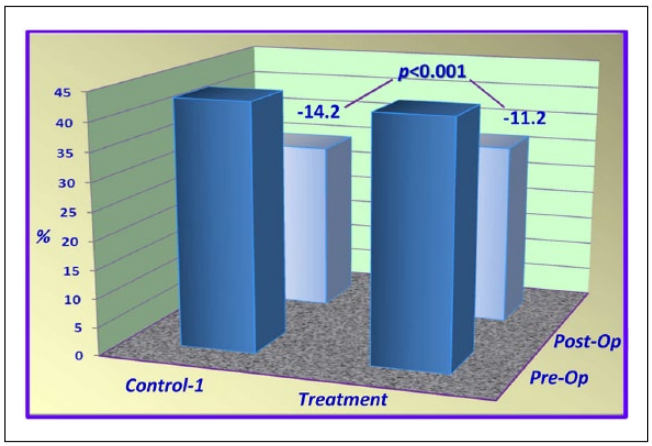

Figure 2. Mean preoperative and postoperative hematocrit levels in the control group 1 and treatment group.

decreased from 12.98±2.69 to 8.31±1.81 g/dL. The mean decrease in hemoglobin concentrations among patients in control group 2 (−4.67 g/dL) was not significantly different from that in the treatment group (−4.05 g/dL, p=0.179).

Hematocrit levels declined after surgery. In the treatment group, mean hematocrit decreased from 42.6%±4.3% preoperatively to a postoperative nadir of 31.4%±4.4%. In control group 1, hematocrit fell from a preoperative mean value of 43.0%±3.4% to a postoperative nadir of 28.9%±4.5%. As shown in Figure 2, the magnitude of mean operative decrease in hematocrit level was less in the treatment group than in control group 1 (−11.2% and −14.2%, respectively; p<0.001). In control group 2, mean operative hematocrit levels decreased from 40.1%±7.8% to 26.1%±5.0%. The decrease in hematocrit in control group 2 (−14.0%) was greater than that observed in the treatment group (−11.2%, p=0.008).

Consistent with changes in objective measures of operative blood loss, blood transfusion was indicated in selected patients (Figure 3). pRBC transfusions were administered to

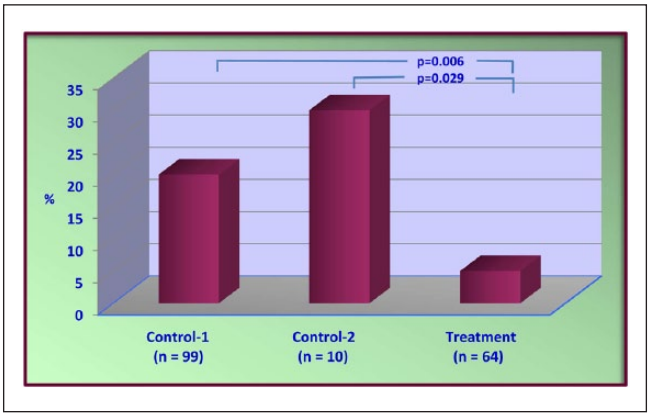

Figure 3. Percentages of patients requiring blood transfusions in the control and treatment groups.

21 patients (21.2%) in control group 1 and 3 patients (30.0%) in control group 2 as compared with 3 patients (4.7%) in the treatment group (p=0.006 and p=0.029, respectively). Further analysis of the proportions of patients receiving blood revealed that the relative risk for transfusion among patients in the treatment group was 0.23 (95% confidence interval (CI)=0.07–0.76) and the number needed to treat (NNT) to avoid one transfusion was 7.0 (95% CI=3.8–14.4).

By employing the NNT derived above, the cost implications of drug use and blood transfusion services in joint reconstruction were investigated. Using standardized cost figures for acquisition and administration, the cost for treatment of seven patients with two doses of TXA is US$705.60 as compared with US$1522 for one 2-unit pRBC transfusion. Thus, for every seven patients treated, a cost differential of approximately US$817 in favor of TXA is realized.

Overall, patient outcomes were positive in both the control group 1 and the treatment group. Discharge condition was described as good in all patients in both groups (100%). Length of stay did not differ between groups (3.96±0.89 days and 3.88±1.27 days in control group 1 and the treatment group, respectively; p=0.349). Neither thromboembolism nor infection or any other serious adverse effect was reported in any patient in either group (0%).

Discussion

Our evaluation of joint reconstruction surgery revealed that intraoperative TXA administration was associated with decreased blood loss and diminished transfusion requirements. These patient safety considerations are consistent with previous experience reported by others.

The first controlled trial of TXA administration in orthopedics was conducted in the early 1990s.[9] In this report, 29 patients undergoing TKA were randomly assigned to receive a direct IV injection of TXA 15 mg/kg or an identical volume of normal saline placebo a few minutes before tourniquet

deflation. Measured total postoperative blood loss was 1549 ± 574 mL in the placebo group and 847 ± 356 mL in the TXA group ($p < 0.001$). During hospitalization, patients in the placebo group received a mean 3.3 ± 1.8 units of pRBCs as compared with 1.5 ± 1.3 units in the TXA group ($p < 0.005$). Two patients in the placebo group experienced a thrombotic complication as compared with none in the TXA group.[9]

This initial experience in which operative blood loss and requisite blood replacement were approximately halved with use of TXA was replicated by others in successive years.[10,11] Since then, nationwide surveys[12] and numerous additional controlled trials have confirmed these findings in both TKA and THA. These trial results have been systematically reviewed in at least six meta-analyses.[13–18] Findings of these analyses of pooled data from 15 to as many as 46 clinical trials are congruent with regard to conclusions that TXA is effective and safe in reducing blood loss and transfusions in TKA and other major orthopedic procedures. Directed studies have shown TXA to be cost-effective in these procedures.[19,20] Further investigations have shown that TXA is effective in minimizing blood loss in concurrent[21] and staged bilateral TKAs[22] as well as revision TKA.[23] Finally, clinical trials have evaluated the comparative effectiveness of differing numbers of intraoperative doses of IV TXA and differing routes of administration including IV injection, IV infusion, intra-articular or topical application, oral ingestion, and various combinations of these.[24–26] Although some trials present data favoring multiple-dose regimens, the overall clinical effects of TXA in orthopedics appear favorable. In total, evidence concerning perioperative TXA in orthopedics has been categorized by the American Society of Anesthesiologists as A1 for strength and quality of research design and, due to this high regard, worthy of consideration as a means to prevent excessive bleeding in essentially all patients.[27]

TXA is a lysine analog procoagulant that acts by inhibiting fibrinolysis. Prominent adverse effects of procoagulants include thrombotic complications associated with excessive blood coagulation. However, when used as a blood conservation modality during primary TKA in conjunction with postoperative antithrombotic medications including aspirin, warfarin, or parenteral low-molecular-weight heparin, TXA has been associated with occurrence rates of symptomatic deep vein thrombosis of 0.5% and non-fatal pulmonary embolism (PE) of less than 0.4%.[28] Odds ratios for venous thromboembolism and mortality were shown to be equal in large cohorts of patients undergoing TKA or THA with and without TXA.[29] These reassuring incidence rates for serious thrombotic complications are juxtaposed by a recent report describing a 65-year-old male with a previously undiagnosed patent foramen ovale who suffered bilateral PE and an acute symptomatic cerebrovascular infarct following synchronous bilateral TKA in which IV TXA was administered.[30]

Among patients undergoing arthroplasty, our analysis revealed that treatment-related reductions in transfusion requirements were associated with a resource cost differential of approximately US$117 per patient in favor of use of TXA. When applied to the current annual case load of 350 joint reconstruction operations performed by the surgeon in our study who formerly did not use TXA, this correlates with institutional savings of more than US$40,000 per year. Group purchasing arrangements for medications available in many hospitals may lessen drug acquisition costs and facilitate additional cost advantages. Although not quantifiable with our data, the lesser transfusion requirement demonstrated with the use of TXA may lead to avoidance of transfusion-related complications with corresponding improvement in both economic and clinical outcomes.

Our study has several important limitations. It was performed with a retrospective, non-randomized design, and an assessment of care provided at the discretion of autonomous physicians. This study had relatively small sample sizes and it was performed at a single institution. The medical records used to identify signs and symptoms of venous thromboembolism, hemorrhage, or other complications did not always address specific clinical criteria required for systematic evaluation of these issues. Nonetheless, this assessment of case findings offers a clinical perspective taken from typical contemporary acute patient care and, as such, it is representative of a broad spectrum of orthopedics practice in hospitals. To our knowledge, this is the first evaluation that assessed the impact of TXA on the practice of individual orthopedic surgeons.

In conclusion, perioperative administration of IV TXA was associated with diminished perioperative blood loss and lesser transfusion requirements in patients undergoing joint replacement surgery. No serious treatment-related adverse effects were identified.

Acknowledgements

This work was presented in part as a poster at the American Society of Health System Pharmacists 50th Annual Midyear Clinical Meeting, New Orleans, Louisiania, December 2015.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from Colorado Multiple Institutional Review Board (COMIRB), protocol no. 13-3210.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Informed consent was not sought for this study because it was a retrospective study and granted full waiver of consent by the Colorado Multiple Institutional Review Board.

References

1. Berman AT, Geissele AE and Basacco SJ. Blood loss with total knee arthroplasty. *Clin Orthop Relat Res* 1988; 234: 137–138.
2. Sehat KR, Evans R and Newman JH. How much blood is really lost in total knee arthroplasty? Correct blood loss management should take hidden loss into account. *Knee* 2000; 7: 151–155.
3. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. *Anesthesiology* 2010; 113: 182–195.
4. Shander A, Hofmann A, Gombotz H, et al. Estimating the cost of blood: past, present, and future directions. *Best Pract Res Clin Anaesthesiol* 2007; 21: 271–289.
5. Banerjee S, Issa K, Pivec R, et al. Intraoperative pharmacotherapeutic blood management strategies in total knee arthroplasty. *J Knee Surg* 2013; 34: 566–585.
6. Mak JCS, Fransen M, Jennings M, et al. Evidence-based review for patients undergoing elective hip and knee replacement. *ANZ J Surg* 2014; 84: 17–24.
7. Memtsoudis SG, Hargett M, Russell LA, et al. Consensus statement from the consensus conference on bilateral total knee arthroplasty group. *Clin Orthop Relat Res* 2013; 471: 2649–2657.
8. Shander A, Hofmann A, Ozawa S, et al. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010; 50: 753–765.
9. Hiippala S, Strid L, Wennerstrand M, et al. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. *Br J Anaesth* 1995; 74: 535–537.
10. Benon G and Fredin H. Fibrinolytic induction with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomized, double-blind study of 86 patients. *J Bone Joint Surg Br* 1996; 78: 434–440.
11. Hiippala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg* 1997; 84: 839–844.
12. Poeran J, Rasul R, Suźuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 2014; 349: g4829.
13. Kagoma YK, Crowther MA, Douketis J, et al. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. *Thromb Res* 2009; 123: 687–696.
14. Yang Z-G, Chen W-P and Wu L-D. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am* 2012; 94: 1153–1159.
15. Gandhi R, Evans HMK, Mahomed SR, et al. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. *BMC Res Notes* 2013; 6: 184.
16. Zhou X-D, Tao L-J and Wu L-D. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Arch Orthop Trauma Surg* 2013; 133: 1017–1027.
17. Huang F, Wu D, Ma G, et al. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: a meta-analysis. *J Surg Res* 2014; 186: 318–327.
18. Wu Q, Zhang H-A, Liu S-L, et al. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol* 2015; 25: 525–541.
19. Moskal JT, Harris RN and Capps SG. Transfusion cost savings with tranexamic acid in primary total knee arthroplasty from 2009 to 2012. *J Arthroplasty* 2015; 30: 365–368.
20. Harris RN, Moskal JT and Capps SG. Does tranexamic acid reduce blood transfusion cost for primary total hip arthroplasty? A case-control study. *J Arthroplasty* 2015; 30: 192–195.
21. McGillivray RG, Tarabichi SB, Hawari MF, et al. Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. *J Arthroplasty* 2011; 26: 24–28.
22. Kelly TC, Tucker KK, Adams MJ, et al. Use of tranexamic acid results in decreased blood loss and decreased transfusions in patients undergoing staged bilateral total knee arthroplasty. *Transfusion* 2014; 54: 26–30.
23. Smit KM, Naudie DDR, Ralley FE, et al. One dose of tranexamic acid is safe and effective in revision knee arthroplasty. *J Arthroplasty* 2013; 28(Suppl. 1): 112–115.
24. Maniar RN, Kumar G, Singhi T, et al. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. *Clin Orthop Relat Res* 2012; 470: 2605–2612.
25. Zohar E, Ellis M, Ifrach N, et al. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. *Anesth Analg* 2004; 99: 1679–1683.
26. Lin S-Y, Chen C-H, Fu Y-C, et al. The efficacy of combined use of intraarticular and intravenous tranexamic acid on reducing blood loss and transfusion rate in total knee arthroplasty. *J Arthroplasty* 2015; 30: 776–780.
27. Apfelbaum JL, Nuttall GA, Connis RT, et al. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology* 2015; 122: 241–275.
28. Gillette BP, DeSimone LJ, Trousdale RT, et al. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. *Clin Orthop Relat Res* 2013; 471: 150–154.
29. Duncan CM, Gillette BP, Jacob AK, et al. Venous thromboembolism and mortality associated with tranexamic acid use during total hip and knee arthroplasty. *J Arthroplasty* 2015; 30: 272–276.
30. Bruce-Brand R, Dragomir R, Baker J, et al. Cerebrovascular infarction following bilateral total knee arthroplasty and tranexamic acid administration. *Acta Orthop Belg* 2013; 79: 351–354.