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Topical Application of Tranexamic Acid Reduces Postoperative Blood Loss in Total Knee Arthroplasty

A Randomized, Controlled Trial

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Background: Topical application of tranexamic acid to bleeding wound surfaces reduces blood loss in patients undergoing some major surgeries, without systemic complications. The objective of the present trial was to assess the efficacy and safety of the topical application of tranexamic acid on postoperative blood loss in patients undergoing primary unilateral total knee arthroplasty with cement.

Methods: In a prospective, double-blind, placebo-controlled trial, 124 patients were randomized to receive 1.5 or 3.0 g of tranexamic acid in 100 mL of normal saline solution or an equivalent volume of placebo (normal saline solution) applied into the joint for five minutes at the end of surgery. The primary outcome was blood loss calculated from the difference between the preoperative hemoglobin level and the corresponding lowest postoperative value or hemoglobin level prior to transfusion. The safety outcomes included Doppler ultrasound in all patients and measurement of plasma levels of tranexamic acid one hour after release of the tourniquet.

Results: Twenty-five patients were withdrawn for various reasons; therefore, ninety-nine patients were included in the intention-to-treat analysis. The postoperative blood loss was reduced in the 1.5 and 3-g tranexamic acid groups (1295 mL [95% confidence interval, 1167 to 1422 mL] and 1208 mL [95% confidence interval, 1078 to 1339 mL], respectively) in comparison with the placebo group (1610 mL [95% confidence interval, 1480 to 1738 mL]) ($p < 0.017$). The postoperative hemoglobin levels were higher in the 1.5 and 3.0-g tranexamic acid groups (10.0 g/dL [95% confidence interval, 9.5 to 10.4 g/dL] and 10.1 g/dL [95% confidence interval, 9.8 to 10.5 g/dL], respectively) in comparison with the placebo group (8.6 g/dL [95% confidence interval, 8.2 to 9 g/dL]) ($p < 0.017$). With the numbers studied, there was no difference in the rates of deep-vein thrombosis or pulmonary embolism between the three groups. Minimal systemic absorption of tranexamic acid was observed.

Conclusions: At the conclusion of a total knee arthroplasty with cement, topical application of tranexamic acid directly into the surgical wound reduced postoperative bleeding by 20% to 25%, or 300 to 400 mL, resulting in 16% to 17% higher postoperative hemoglobin levels compared with placebo, with no clinically important increase in complications being identified in the treatment groups.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

In the United States, >350,000 patients underwent total knee arthroplasty in 2007[1]. Total knee arthroplasty is associated with postoperative blood loss necessitating allogeneic blood transfusion in 10% to 38% of patients[2-5]. The reported amounts of blood loss have ranged from 1450 to 1790 mL[6-10], leading to anemia in many patients. About 12% of adults older than sixty

Disclosure: In support of their research for or preparation of this work, one or more of the authors received, in any one year, outside funding or grants in excess of $10,000 from Physicians' Services Incorporated Foundation. Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity.

years of age have symptomatic knee osteoarthritis[11]. It is expected that the number of total knee arthroplasty procedures will increase exponentially over the next two decades[12]; therefore, more patients will be at risk for anemia and blood transfusion with its associated morbidity and costs.

The major causes of postoperative blood loss following total knee arthroplasty can be attributed to surgical trauma that induces a considerable activation of both the coagulation cascade and local fibrinolysis[13]; the latter is further enhanced by tourniquet release at the end of the surgical procedure[14]. Several meta-analyses have shown that intravenous administration of the antifibrinolytic agent tranexamic acid reduced postoperative bleeding and the need for transfusion[15-17]. However, concerns about the safety of systemic administration of tranexamic acid and the risk of thromboembolic events such as deep-vein thrombosis or pulmonary embolism in this high-risk patient population have hindered the wide adoption of this medication in the setting of total knee arthroplasty[18].

In view of these safety concerns, topical application of tranexamic acid to the knee joint before closure at the time of total knee arthroplasty may be a safer route of administration that will reduce postoperative bleeding yet will not increase the hypercoagulable state associated with total knee arthroplasty. In fact, topical application of tranexamic acid in the surgical field is a cost-effective and simple route of administration that has been shown to reduce bleeding associated with dental[19], cardiac[20,21], and spine procedures[22]. Therefore, the objective of this prospective, randomized, double-blind, placebo-controlled trial was to assess the efficacy and safety of direct application of tranexamic acid on postoperative blood loss, the transfusion of blood products, and complications in patients undergoing a primary unilateral total knee arthroplasty with cement. We hypothesized that topical application of tranexamic acid before closure reduces postoperative bleeding as reflected by the maximum drop in hemoglobin level during the postoperative period.

Materials and Methods

The present study was registered in the public registry ClinicalTrials.gov (number NCT00985920). Approval was obtained from Health Canada, the Research Ethics Board of University Health Network, Toronto, Ontario, Canada, and written informed consent was obtained from all participants.

All adult patients (patients over the age of eighteen years) who were scheduled for a primary unilateral total knee arthroplasty with cement at Toronto Western Hospital, Toronto, Ontario, Canada were eligible for inclusion in the study. The exclusion criteria included allergy to tranexamic acid, acquired disturbances of color vision, preoperative anemia (a hemoglobin value of <11 g/dL in females and <12 g/dL in males), refusal of blood products, preoperative use of anticoagulant therapy within five days before surgery, fibrinolytic disorders requiring intraoperative antifibrinolytic treatment, coagulopathy (as identified by a preoperative platelet count of <150,000/mm^3, an international normalized ratio of >1.4, or a prolonged partial thromboplastin time [>1.4 times normal]), a history of arterial or venous thromboembolic disease (such as a cerebrovascular accident, deep-vein thrombosis, or pulmonary embolus), pregnancy, breastfeeding, major comorbidities (such as severe ischemic heart disease [New York Heart Association Class III or IV], previous myocardial infarction, severe pulmonary disease [forced expiratory volume <50% of normal], plasma creatinine of >115 μmol/L in males and >100 μmol/L in females, or hepatic failure), and participation in another clinical trial.

If intraoperative surgical, medical, or anesthetic complications occurred, such as myocardial infarction, intraoperative fracture, or neurovascular injury, the study medication was not administered and the patient was excluded from the study. However, if one of these problems occurred after the application of the study medication, the patient was excluded from outcome measurements and analysis but was followed for the occurrence of complications.

Patients participating in the study were still offered the usual standard of care for blood conservation at our institution. According to a blood-conservation protocol at the University Health Network, preoperative erythropoietin (40,000 to 80,000 IU) was offered to all patients with a hemoglobin level of <13 g/dL and autologous blood donation of two units was allowed two to three weeks before the proposed surgery. Patients who were taking acetylsalicylic acid, anti-platelet agents, or nonselective cyclooxygenase inhibitors were advised to discontinue these medications seven to ten days prior to the scheduled surgery.

The doses of tranexamic acid chosen for the current investigation were based on previous studies of intravenous tranexamic acid in patients undergoing total knee arthroplasty showing efficacy with doses of 15 to 20 mg/kg (i.e., 1.5 g) and a meta-analysis suggesting that doses of >30 mg/kg (i.e., 3 g) were more effective for reducing bleeding[15]. Therefore, patients undergoing an elective primary unilateral total knee arthroplasty with cement were randomized with use of a computer-generated randomization table with block sizes of 4 to receive a solution containing either (1) 1.5 g (100 mg/mL) of tranexamic acid (Cyklokapron; Sandoz, Boucherville, Quebec, Canada) in 100 mL of normal saline solution, (2) 3 g of tranexamic acid in 100 mL of normal saline solution, or (3) an equivalent volume of placebo (normal saline solution). A stratified randomization for surgeons was used to account for differences in surgical practice. The randomization schedule was kept inaccessible throughout the study period. Patient assignments were placed into sequentially numbered opaque sealed envelopes and were kept by a research pharmacist. On the day of surgery, the envelope was opened and the study medication was prepared under sterile conditions by a research pharmacist who was not involved in the care of the patients. The study medications were identical in appearance. The patients, surgeons, anesthesiologists, health-care providers, research personnel, and outcome assessors were blinded to the randomization.

All patients received a femoral nerve catheter and a sciatic nerve block with ropivacaine (0.2%) for postoperative analgesia. Patients received either a spinal anesthetic with 3 mL of 0.5% bupivacaine and 100 μg of morphine or general anesthesia with propofol, fentanyl, rocuronium, and a volatile agent (i.e., sevoflurane or desflurane with air/oxygen), depending on patient preference for regional or general anesthesia. Standard monitoring was used for all patients. Maintenance fluid requirements and third-space losses were replaced with balanced crystalloid solutions or pentastarch (Pentaspan; Bristol-Myers Squibb, Montreal, Canada) or hydroxyethyl starch (Voluven; Fresenius Kabi, Mississauga, Ontario, Canada). The goal of fluid replacement was to maintain an adequate intravascular volume as indicated by a mean arterial pressure ≥70 mm Hg or within 20% of normal.

Four orthopaedic surgeons (N.N.M., J.R.D., R.G., and K.A.S.) participated in this study. The surgical procedures were performed as per each surgeon's routine practice. After elevation of the limb and exsanguination of the extremity, a pneumatic tourniquet around the upper part of the thigh was inflated to a pressure of 350 mm Hg. A midline skin and medial parapatellar capsular incision was made to expose the knee joint. Standard surgical techniques for intraoperative hemostasis were used. An appropriate type and size of knee prosthesis (Triathlon [Stryker, Mahwah, New Jersey] or Genesis II [Smith & Nephew, Memphis, Tennessee]) was used. After all components were cemented into place, the joint was thoroughly irrigated and the study medication was applied to the open joint surfaces with use of a bulb syringe and was left in contact with the tissues for five minutes. The surgeon subsequently suctioned away excess study solution by placing the suction tip on the cemented component without touching the joint or the surrounding tissue surfaces. The wound was then closed without any irrigation or manipulation. No surgical drains were used. The tourniquet was released after the application of dressings.

Prophylaxis against venous thromboembolism was administered as per standard practice at our institution with low molecular weight heparin for ten days after surgery. While in the hospital, patients were examined daily for any clinical symptoms of deep-vein thrombosis. A diagnostic Doppler ultrasound examination of both legs was performed on Postoperative Day 2 or 3 for all patients, or earlier if a patient was symptomatic. All surgical and medical adverse events and any thromboembolic events occurring during the six weeks after surgery were recorded at the time of the six-week follow-up visit with the surgeon and/or by means of a telephone interview.

Daily postoperative hemoglobin levels were measured for five days. All patients remained in the hospital for a minimum of three days.

Outcome Measures

The primary outcome was blood loss as calculated from the difference between the preoperative hemoglobin and the lowest postoperative hemoglobin during the hospital stay or the lowest postoperative hemoglobin prior to blood transfusion. Based on hemoglobin balance, the estimated blood loss was calculated according to the formula described by Good et al.[7] and Nadler et al.[23] (see Appendix).

The secondary outcomes were the rate of perioperative blood transfusion, the number of blood units transfused, the rate of surgical infections, the length of hospital stay, the time until the start of a rehabilitation program, the postoperative changes in joint function (i.e., the range of motion and the severity of pain at rest as determined with use of a visual analog scale [possible range, 0 to 10] on Postoperative Day 2) and the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) score at six weeks after surgery. The active range of motion of the knee with the patient supine was determined with use of a standard 60-cm clinical goniometer before the operation and on Postoperative Day 2. The patient was told to bend the knee as much as possible while lying in a supine position.

All of the end-point measurements were collected by the research assistants, with the exception of range of motion, which required a clinical examination and therefore was measured by the orthopaedic surgeons.

To evaluate systemic absorption of the drug, the plasma tranexamic acid level was measured, one hour after tourniquet release, with use of Tandem Mass Spectrometry at The Hospital for Sick Children (Toronto, Ontario, Canada).

The criterion for the transfusion of blood products was a hemoglobin level of <8.0 g/dL or a hemoglobin level of <10.0 g/dL if the patient developed intolerable symptoms of anemia or any organ dysfunction that may have been related to anemia and was not attributable to another cause (such as myocardial ischemia or hypoxemia) or if ongoing blood loss was occurring. If transfusion was necessary, one unit of packed red blood cells was transfused at a time to increase the hemoglobin level to ≥8.0 g/dL. The transfusion guidelines were consistent with the guidelines of the American Society of Anesthesiologists[24] and the ONTraC study[5].

Venous thromboembolism prophylaxis was begun on the morning after surgery with a standard subcutaneous injection of dalteparin (5000 U) once daily. In November 2008, the Pharmacy and Therapeutics Committee at our institution switched from dalteparin to rivaroxaban because of studies indicating superiority of the latter for prophylaxis against thromboembolism[25]. Rivaroxaban (10 mg, administered orally) was started on the day after surgery and was continued for ten days. However, in March 2009, the Pharmacy and Therapeutics Committee switched to enoxaparin (40 mg daily for ten days) because of concerns about excessive postoperative bleeding in some patients (not study subjects). The time window of the change in prophylaxis against thromboembolism was examined for the primary outcome.

Statistical Methods

An intention-to-treat analysis was used to compare the study groups. The distribution of potential confounders between the study groups (such as demographic data, baseline data, and surgical and functional characteristics) and the primary and secondary outcomes was assessed with use of summary

statistics, including means and weighted means (to adjust for stratification) and standard deviations and 95% confidence intervals for quantitative data and frequencies and percentages for qualitative data. Continuous variables were compared with use of one-way analysis of variance, and categorical variables were compared with use of the chi-square test with the Yates correction factor as necessary. For the one-way analysis of variance and 2×3 chi-square analysis, a p value of <0.05 was considered significant. For the pairwise comparisons, the p value was adjusted according to the Bonferroni correction.

Sample Size Calculation

The sample-size estimate was based on the difference in the primary outcome (i.e., postoperative decrease in hemoglobin) among the three study groups. A review of eighty patients who had undergone a primary unilateral total knee arthroplasty at our institution from January to April 2006 showed that the mean reduction in postoperative hemoglobin (and standard deviation) was 4.6 ± 1.7 g/dL, which represented a 32.1% ± 10.6% change in comparison with preoperative levels. In fact, the hemoglobin level dropped from 13.9 ± 2.3 to 9.4 ± 1.3 g/dL, consistent with the published literature[26]. We performed a

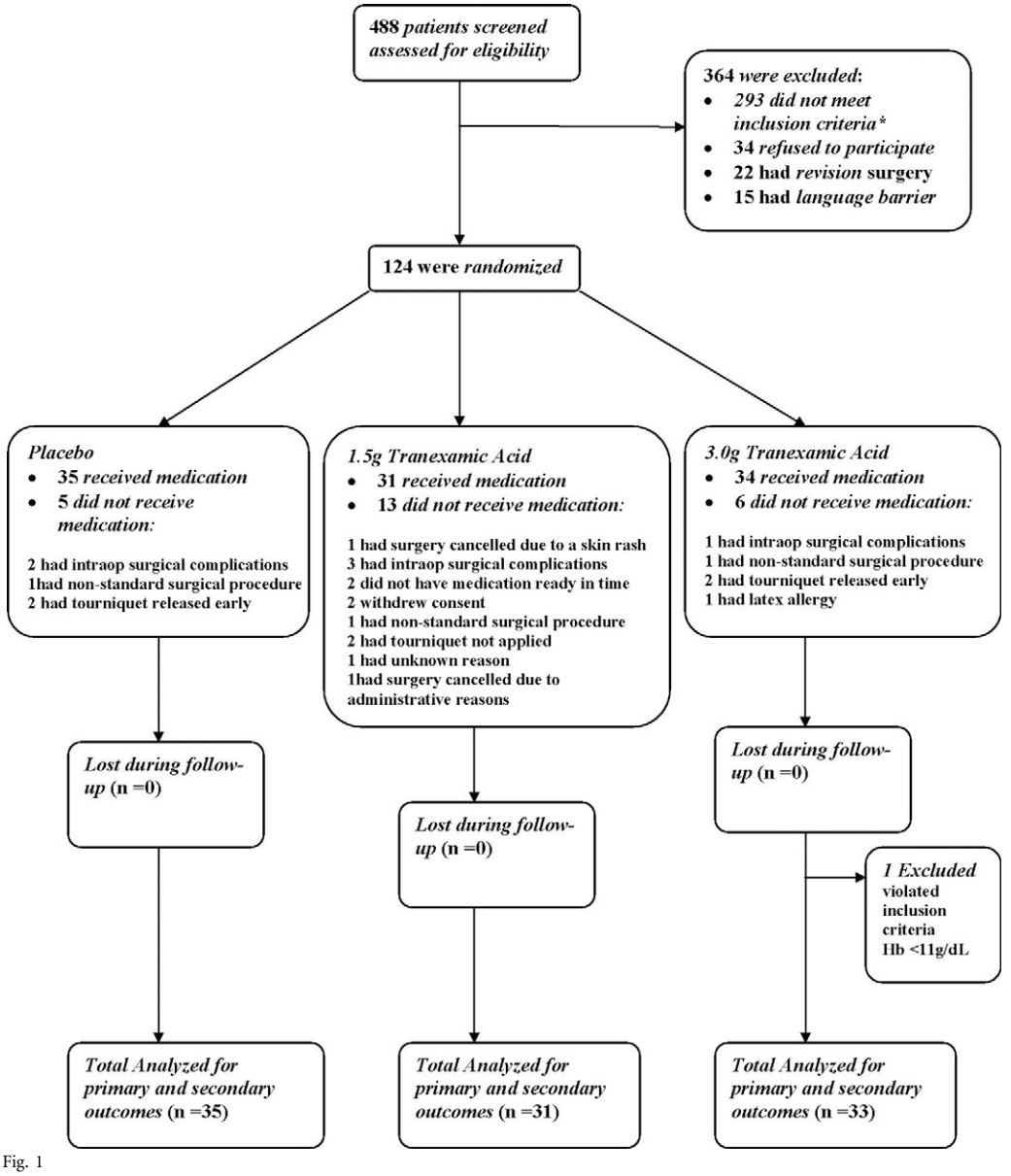

Fig. 1

Flow diagram indicating the number of patients assessed and included at each stage of the trial. *Of the 293 patients who did not meet the inclusion criteria, 159 were enrolled in other studies, eighty-three had a history of arterial or thromboembolic events, thirty-three had low preoperative hemoglobin levels (<11 g/dL in females or <12 g/dL in males), three were receiving preoperative anticoagulant medication, and fifteen had renal disease.

meta-analysis (RevMan 4.2; Cochrane Collaboration) of two randomized controlled trials that showed that intravenous tranexamic acid (20 mg/kg) produces a saving of 1 g/dL in the decrease of hemoglobin after total knee arthroplasty as compared with placebo (weighted mean difference, –0.98 g/dL; 95% confidence interval, –1.30 to –0.67 g/dL)[27,28]. Based on this information and our own review, to prevent a fall of 1 g/dL in postoperative hemoglobin, the sample size required for each arm of the study was twenty-six patients. This sample size was calculated for a fixed effects one-way analysis of variance design. It was assumed that the standard effect size (δ) = 0.36, the level of alpha (two-tailed) = 0.05, and power = 0.8. In addition, we assumed the standard deviation within each group to be 14 g/dL. The sample size was increased by 20% to compensate for expected dropouts, resulting in thirty-three patients per group (i.e., the total number of patients was ninety-nine).

Source of Funding
The Physicians' Services Incorporated Foundation did not play a role in the investigation.

Results

From April 2008 to May 2009, 488 patients undergoing a primary unilateral total knee arthroplasty with cement were assessed for eligibility for the present study. Three hundred and sixty-four patients were excluded for various reasons, including failure to meet inclusion criteria (293 patients), refusal to participate (thirty-four), revision surgery (twenty-two), or a language barrier (fifteen) (Fig. 1). A total of 124 patients were randomized to receive study medication in order to achieve our calculated sample size because after randomization, twenty-four patients were excluded for various reasons (Fig. 1). Therefore, the study group consisted of 100 patients, including thirty-five in the placebo group, thirty-one in the 1.5-g tranexamic acid group, and thirty-four in the 3-g tranexamic acid group (Fig. 1). One patient in the 3-g tranexamic acid group was excluded from the primary and secondary outcome analyses because of ineligibility (a preoperative hemoglobin level of <11 g/dL); however, this patient was included for the safety outcome analysis.

There were no differences in the age, weight, height, body mass index, American Society of Anesthesiologists sta-

TABLE I Baseline Demographic and Clinical Characteristics*

	Placebo (N = 35)	1.5 g Tranexamic Acid (N = 31)	3 g Tranexamic Acid (N = 33)
Demographic characteristics			
Age† *(yr)*	68.4 ± 10.4	67 ± 11.9	63.9 ± 10.6
Sex (female/male) *(no. of patients)*	22/13	25/6	19/14
Weight† *(kg)*	87.9 ± 19.2	82.9 ± 15.6	81.8 ± 14.7
Height† *(cm)*	163.5 ± 12	162.8 ± 10.4	163.2 ± 10.7
Body mass index† *(kg/m^2)*	32.7 ± 5.5	31.3 ± 5.4	30.6 ± 4.1
ASA status II/III *(no. of patients)*	22/13	21/10	28/5
Preoperative laboratory values			
Hemoglobin† *(g/dL)*	13.8 ± 1.3	13.9 ± 1.1	13.9 ± 1.3
Platelet count† *(×10^9/L)*	259 ± 67.0	260 ± 57.8	238 ± 57.5
International normalized ratio†	0.97 ± 0.06	0.95 ± 0.06	0.97 ± 0.06
Partial thromboplastin time† *(sec)*	29 ± 2.1	30 ± 10.5	29 ± 1.6
Surgical characteristics			
General/regional anesthesia *(no. of patients)*	2/33	3/28	3/30
Site (right/left) *(no. of patients)*	23/12	11/20‡	19/14
Preoperative knee flexion† *(deg)*	114 ± 9.6	111 ± 12.1	111 ± 13.9
Prosthesis (Genesis II/Triathlon) *(no. of patients)*	1/34	1/30	0/33
Surgical duration§ *(min)*	78.6 ± 14.2	76.0 ± 14.6 (70.8 to 81.1)	75.6 ± 17.1 (69.7 to 81.4)
Tourniquet time§ *(min)*	80.8 ± 14.4	78.5 ± 14.9 (73.2 to 83.7)	77.5 ± 17.5 (71.5 to 83.4)
Functional characteristics			
Preoperative VAS score§	3.6 ± 3.4	3.3 ± 3.0 (2.2 to 4.3)	3.4 ± 3.2 (2.3 to 4.5)
Preoperative WOMAC score§	45 ± 25	46 ± 18 (39 to 52)	45 ± 21 (38 to 52)

*ASA = American Society of Anesthesiologists, VAS = visual analog scale, and WOMAC = Western Ontario and McMaster Universities Osteoarthritis index. †The values are presented as the mean and the standard deviation. ‡Significantly different from the placebo group with use of the Bonferroni correction ($p < 0.017$). §The values are presented as the mean and the standard deviation, with or without the 95% confidence interval in parentheses.

TABLE II Blood Loss, Packed Red Blood-Cell Transfusion, and Intravenous Fluid Administration

	Placebo (N = 35)	1.5 g Tranexamic Acid (N = 31)	3 g Tranexamic Acid (N = 33)	P Value*
Blood loss				
Preoperative hemoglobin† *(g/dL)*	13.8 ± 1.3	13.9 ± 1.1	13.9 ± 1.3	0.873
Lowest postoperative hemoglobin† *(g/dL)*	8.6 (8.2 to 9.0)	10.0§ (9.5 to 10.4)	10.1§ (9.8 to 10.5)	0.008
Total blood loss† *(mL)*	1610 (1480 to 1738)	1295§ (1167 to 1422)	1208§ (1078 to 1339)	0.0001
Packed red blood-cell transfusion				
No. of patients given packed red blood-cell transfusion	5 (14.3%)	4 (12.9%)	0 (0%)	0.083
Number of units of packed red blood cells transfused	9	5	0	
Perioperative fluids† *(mL)*	5191 (4895 to 5487)	4967 (4477 to 5457)	5122 (4730 to 5514)	0.726

*The p value represents the result of one-way analysis of variance for independent means for continuous variables or the chi-square test for independent proportions that included the three groups. †The values are presented as the mean and the standard deviation. ‡The values are presented as the mean, with the 95% confidence interval in parentheses. §Significantly different from the placebo group with use of the Bonferroni correction ($p < 0.017$).

tus, preoperative hemoglobin level, platelet count, international normalized ratio, or partial thromboplastin time among the three groups (Table I). Patients in the three groups were also similar with regard to their surgical and functional characteristics. However, more patients had left total knee arthroplasty in the 1.5-g tranexamic acid group as compared with the

TABLE III Postoperative Recovery Characteristics

	Placebo (N = 35)	1.5 g Tranexamic Acid (N = 31)	3 g Tranexamic Acid (N = 33)
Visual analog scale pain score at rest *(cm)*			
Preoperative*	3.6 ± 3.4	3.3 ± 3.0	3.4 ± 3.2
Postoperative Day 2†	2.7 (1.9 to 3.5)	3.8 (2.9 to 4.7)	3.9 (3.1 to 4.7)
Postoperative Week 6†	0.8 (0.3 to 1.4)	1.6 (0.8 to 2.3)	1.6 (1.0 to 2.3)
WOMAC score‡			
Preoperative*	45 ± 25	46 ± 18	45 ± 20
Postoperative Week 6†	13 (6 to 15)	17 (9 to 24)	18 (7 to 26)
Knee flexion *(deg)*			
Preoperative*	114 ± 9.6	111 ± 12.1	111 ± 13.9
Postoperative Day 2†	84 (79 to 89)	80 (74 to 85)	80 (75 to 84)
Postoperative Week 6†	104 (100 to 109)	105 (101 to 109)	103 (97 to 109)
Thromboembolic manifestation§			
No. of patients with deep-vein thrombosis	1 (2.9%)	2 (6.5%)	1 (3.0%)
No. of patients with pulmonary embolism	1 (2.9%)	1 (3.2%)	0 (0%)
Time to rehabilitation* *(day)*	1	1	1
No. of patients with infection	0 (0%)	1 (3.2%)	0 (0%)
Length of hospital stay† *(day)*	4.3 (4.0 to 4.7)	4.7 (4.0 to 5.3)	4.5 (4.2 to 4.7)
No. of patients discharged to rehabilitation facility	8 (22.9%)	8 (25.8%)	4 (12.1%)
No. of patients readmitted	1 (2.9%)	0 (0%)	0 (0%)

*The values are presented as the mean and the standard deviation. †The values are given as the mean, with the 95% confidence interval in parentheses. ‡WOMAC = Western Ontario and McMaster Universities Osteoarthritis index. §Includes the patient who was excluded from the primary and secondary analyses because of violation of the inclusion criteria for safety outcome.

placebo and 3.0-g tranexamic acid groups ($p < 0.017$). Most patients had osteoarthritis, although one patient in the placebo group had rheumatoid arthritis. There were no differences among the three groups with regard to the types of prosthesis, surgical duration, or tourniquet time (Table I). The majority of patients received spinal rather than general anesthesia, and there was no difference among the groups ($p = 0.812$) (Table I). Three patients received preoperative erythropoietin, including one patient in the 1.5-g tranexamic acid group and two patients in the 3-g tranexamic acid group. None of the patients in the three groups predonated autologous blood.

The mean calculated postoperative blood loss was significantly reduced in the 1.5-g and 3-g tranexamic acid groups (1295 mL [95% confidence interval, 1167 to 1422 mL] and 1208 mL [95% confidence interval, 1078 to 1339 mL], respectively) in comparison with the placebo group (1610 mL [95% confidence interval, 1480 to 1738 mL]) ($p < 0.017$) (Table II). The lowest hemoglobin levels were recorded on Postoperative Day 2 or 3. There was no difference in calculated blood loss among the three groups when the type of thromboembolism prophylaxis was compared ($p = 0.2$). Moreover, the 1.5-g and 3.0-g tranexamic acid groups had higher postoperative hemoglobin levels (10.0 g/dL [95% confidence interval, 9.5 to 10.4 g/dL] and 10.1 g/dL [95% confidence interval, 9.8 to 10.5 g/dL], respectively) than the placebo group (8.6 g/dL [95% confidence interval, 8.2 to 9 g/dL]) ($p < 0.017$) (Table II). There was no difference between the low-dose (1.5-g) and high-dose (3-g) tranexamic acid groups with regard to the decrease in hemoglobin level or the lowest hemoglobin level determined in the postoperative period. Intraoperative blood loss was minimal in all patients. There was a trend toward a reduced number of red blood-cell transfusions in the tranexamic acid groups as compared with the placebo group (Table II). The amount of perioperative fluids administered intraoperatively and over the first forty-eight hours postoperatively was similar among the three groups ($p = 0.726$) (Table II). Three patients received allogeneic blood transfusion because of hemoglobin values above the transfusion trigger, including two patients in the placebo group (hemoglobin values, 8.2 and 8.4 g/dL) and one patient in the 1.5-g tranexamic acid group (hemoglobin value, 8.2 g/dL).

There was no difference among the groups in terms of postoperative visual analog scale pain scores at rest or in terms of range of motion (knee flexion) as measured preoperatively, two days after surgery, and six weeks after surgery (Table III). In addition, the time to the start of rehabilitation, the length of hospital stay, and the number of patients discharged to a rehabilitation facility were similar in all three groups (Table III).

The frequency of thromboembolic manifestations was rare and was similar in the three groups. One patient in the placebo group had unilateral calf edema that was suggestive of a deep-vein thrombosis; however, the Doppler evaluation was negative. Doppler studies were ordered but were not performed for one patient in the placebo group and three patients in each of the tranexamic acid groups. Four patients had detection of deep-vein thrombosis on Doppler ultrasonography, including one patient in the placebo group, two in the 1.5-g tranexamic acid group, and one in the 3-g tranexamic acid group (Table III). None of these patients had clinical symptoms suggestive of deep-vein thrombosis. Two patients had distal, posterior tibial thrombi and were discharged and were managed according to our institution's usual thromboembolism prophylaxis protocol. The other two patients were discharged and were managed with warfarin for three months. Two patients (one in the placebo group and one in the 1.5-g tranexamic acid group) had symptomatic pulmonary emboli confirmed with spiral computed tomography. Both of these patients had negative Doppler studies, were discharged, and were managed with warfarin for three months. One patient in the 1.5-g tranexamic acid group had postoperative chest pain; however, cardiac investigations were negative, and the symptoms resolved without intervention. One patient in the placebo group was readmitted to the emergency department with pain and swelling of the knee after discharge, and one patient in the 1.5-g tranexamic acid group returned to the hospital with redness around the incision site and was managed with antibiotics for one week. No deaths or any other adverse events were recorded in either group during the six-week follow-up period.

TABLE IV Tranexamic Acid Levels

	Placebo (N = 35)	1.5 g Tranexamic Acid (N = 31)	3 g Tranexamic Acid (N = 33)
Tranexamic acid level* *(mg/L)*	<0.50 (below detection limit)	4.5 (3.5 to 5.4)	8.5† (7.2 to 9.9)
Time from application to sample collection‡ *(min)*	80.3 ± 7.9	78.6 ± 12.3	82.4 ± 8.2
Time from tourniquet release to sample collection‡ *(min)*	60.9 ± 7.0	61.0 ± 6.1	62.8 ± 6.6

*The values are presented as the mean, with or without the 95% confidence interval in parentheses. †Significantly different from the 1.5-g tranexamic acid group with use of the Bonferroni correction ($p < 0.017$). ‡The values are presented as the mean and the standard deviation.

The plasma levels of tranexamic acid were minimal in the two tranexamic acid groups (Table IV).

Discussion

In the present study, topical administration of tranexamic acid to the knee joint before wound closure significantly reduced postoperative blood loss in patients having a primary unilateral total knee arthroplasty. The calculated blood loss was about 20% to 25% lower in patients who were managed with tranexamic acid as compared with placebo, with a mean difference of approximately 300 to 400 mL for the 1.5 and 3-g tranexamic acid groups, respectively. However, no difference in efficacy was seen between the low-dose (1.5-g) and the high-dose (3-g) groups. The patients in the low-dose and high-dose tranexamic acid groups had 16% and 17% higher mean postoperative hemoglobin levels, respectively, compared with the placebo group. With the numbers studied, we did not find a reduction in the frequency of allogeneic blood transfusion between the 1.5-g tranexamic acid group and the placebo group. However, none of the patients in the 3-g tranexamic acid group required transfusion.

The potential mechanism and advantage of topical application of tranexamic acid into the surgical field is to directly target the site of bleeding just before wound closure, but after surgical hemostasis has been achieved, thus attenuating the marked increase in local fibrinolysis associated with release of the tourniquet[29]. Such inhibited local fibrinolytic activity will help to prevent fibrin clot dissolution and increase its volume and strength at the raw surgical surfaces, thus enhancing microvascular hemostasis[30].

Our findings of reduced postoperative bleeding are consistent and comparable with the findings of previous meta-analyses of individual studies of intravenous tranexamic acid administration in patients undergoing total knee arthroplasty, which demonstrated a reduction of blood loss of about 400 mL per case[15,17,31]. When tranexamic acid is given intravenously, it is widely distributed throughout the extracellular and intracellular compartments[32]. Tranexamic acid rapidly diffuses into the synovial fluid and synovial membranes, reaching the same concentration in the joint fluid as in the serum[33]. The biological half-life in the joint fluid is about three hours[33]. Tranexamic acid is eliminated by glomerular filtration, with excretion being about 30% at one hour, 55% at three hours, and 90% at twenty-four hours after an intravenous dose of 10 mg/kg[32]. The advantage of topical application of tranexamic acid is minimal systemic absorption. In fact, the plasma levels of tranexamic acid detected in our patients were significantly (~70%) less than an equivalent dose of intravenously administered tranexamic acid. The plasma concentration one hour after intravenous injection of 10 mg/kg of tranexamic acid is 18 mg/L[32], whereas the low and high topical tranexamic acid doses used in the present study led to mean plasma levels of 4.5 and 8.5 mg/L, respectively. The minimum therapeutic concentration of tranexamic acid is 5 to 10 mg/L[34]; therefore, it is possible that the therapeutic effect of topical tranexamic acid in our study may be secondary to some, albeit minimal, systemic absorption.

Our findings are consistent with topical application of tranexamic acid in patients undergoing oral[19,34] and cardiac surgery[35], in whom the levels of tranexamic acid have been found to be minimal in the systemic circulation and not associated with clinically important thromboembolic manifestations. Therefore, the topical administration of tranexamic acid into the surgical wound in patients undergoing total knee arthroplasty can reduce the risks of a general prothrombotic state.

Topical application of tranexamic acid is simple and inexpensive compared with topical fibrin sealants, which also have been shown to reduce bleeding after total knee arthroplasty[36-38]. Another disadvantage of fibrin sealants is that they are derived from human plasma; therefore, the risk of transmission of infective agents cannot be completely excluded[37,39]. The reduction in bleeding in our study is comparable with that in previous studies of fibrin tissue adhesive[37,38]. A randomized study of topical fibrin spray as compared with intravenous tranexamic acid demonstrated a comparable reduction in blood loss; however, the cost of the topical fibrin group compared with the tranexamic acid group was $585.00 as compared with $6.00[37].

Our study is one of the few to examine the safety of tranexamic acid in total knee arthroplasty by systemically screening all study patients with diagnostic imaging to detect deep-vein thrombosis. The rate of detection of pulmonary emboli and asymptomatic deep-vein thromboses with use of Doppler ultrasonography was comparable among all three study groups. Orpen et al.[40] reported that no deep-vein thromboses were detected with duplex ultrasound scanning, and Tanaka et al.[41] also found there was no increase in deep-vein thromboses or pulmonary emboli on the basis of radioisotope venography and lung scanning in patients receiving intravenous tranexamic acid. Recent findings of increased mortality associated with the use of another antifibrinolytic, aprotinin[42], and an advisory issued by the United States Food and Drug Administration about erythropoiesis-stimulating agents because of an increased risk of deep-vein thrombosis in patients following orthopaedic surgery[43] emphasize that blood-conservation techniques need to be shown to be both safe and effective before their wide adoption into clinical practice.

Topical administration of tranexamic acid provides a novel therapeutic approach for decreasing bloodshed from the surgical wound after total knee arthroplasty that may be safer than other blood-conservation strategies, such as the preoperative administration of erythropoietin, and more cost-effective than preoperative autologous blood donation[44-47]. Moreover, several studies of patients undergoing total knee arthroplasty have demonstrated that blood transfusion, even after leukocyte filtration, is associated with an increased prevalence of postoperative surgical infections (noted in 10% to 20% of patients[5,48-51]).

Postoperative anemia can be an important problem that is associated with adverse effects, including increased mortality

and morbidity[52,53] and a longer hospital stay due to the associated need for blood transfusion[5,46,54]. Indeed, in one study, hemoglobin levels on admission to rehabilitation facilities after total knee arthroplasty were inversely correlated with the length of the hospital stay, and higher hemoglobin levels correlated with faster functional recovery at inpatient rehabilitation facilities[55]. These adverse effects are particularly important in elderly total knee arthroplasty patients, who already have a higher prevalence of anemia[56] and comorbid medical conditions. The effect of postoperative anemia on this patient population also may be of greater importance because of diminished hematopoietic reserve[57]. Recovery from profound postoperative anemia is slow; consequently, many of these patients can experience the adverse effects of postoperative anemia for as long as several weeks after surgery[58].

In the present study, the topical application of tranexamic acid to the exposed knee joint did not affect postoperative joint or patient function. This is inferred from the lack of a significant difference between the placebo and tranexamic acid groups with regard to postoperative knee flexion, visual analog scale pain scores, length of stay in the hospital, time to the start of rehabilitation, and the amount of improvement in WOMAC scores at six weeks after surgery.

The present study had several limitations. The study was not powered to examine the assumption that tranexamic acid can decrease the frequency of transfusion, although none of the patients in the 3-g tranexamic acid group required a transfusion. Another limitation of the study is that the type of prophylaxis against thromboembolism was changed partway through the study by our institutional Pharmacy and Therapeutics Committee because of the apparent superiority of rivaroxaban[25]. However, there was no difference in terms of calculated blood loss between the groups when the type of thromboembolism prophylaxis was compared. In addition, the Doppler ultrasound studies were performed prior to discharge (two to three days after surgery), rather than at the peak of clinically evident thrombosis[59] (six to seven days after surgery). Additionally, we did not perform routine screening for pulmonary emboli; however, no other thromboembolic complications were reported during the six-week follow-up period. Finally, we did not specifically assess postoperative functional recovery to investigate the relationship between hemoglobin levels and the outcome of rehabilitation.

In conclusion, topical application of tranexamic acid into the surgical wound of patients undergoing total knee arthroplasty reduces postoperative bleeding by 20% to 25% in comparison with the values in untreated controls, resulting in 16% to 17% higher postoperative hemoglobin values. No increase in thromboembolic or other complications was identified in patients managed with tranexamic acid. Larger trials are needed to further assess whether this promising strategy to reduce bleeding and the need for blood transfusion in patients undergoing total knee arthroplasty is safe with regard to thromboembolic complications.

Appendix

eA The formula used to calculate estimated blood loss is available with the electronic version of this article on our web site at jbjs.org (go to the article citation and click on "Supporting Data"). ■

NOTE: The authors thank Warren Walsh, BSc, ART, Department of Pediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada, for developing the assay for tranexamic acid analysis.

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References

1. Agency for Healthcare Research and Quality. HCUPnet. National and regional estimates on hospital use for all patients from the HCUP Nationwide Inpatient sample (NIS). 2007 National statistics –principle procedure only 81.54 total knee replacement. http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed 2009 Oct 29.

2. Bong MR, Patel V, Chang E, Issack PS, Hebert R, Di Cesare PE. Risks associated with blood transfusion after total knee arthroplasty. J Arthroplasty. 2004;19:281-7.

3. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am. 1999;81:2-10.

4. Goodnough LT, Verbrugge D, Marcus RE. The relationship between hematocrit, blood lost, and blood transfused in total knee replacement. Implications for postoperative blood salvage and reinfusion. Am J Knee Surg. 1995;8:83-7.

5. Freedman J, Luke K, Monga N, Lincoln S, Koen R, Escobar M, Chiavetta J. A provincial program of blood conservation: The Ontario Transfusion Coordinators (ONTraC). Transfus Apher Sci. 2005;33:343-9.

6. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemelä HM, Mäntylä SK, Kuisma RP, Ylinen JE. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg. 1997;84:839-44.

7. 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;90:596-9.

8. Biarnés Suñé A, Ciércoles Jiménez E, Márquez Martínez E, Medel Rebollo J, Godet Gimeno C, Roigé Solé J. [Risk factors for transfusion in primary knee arthroplasty]. Rev Esp Anestesiol Reanim. 2006;53:18-24. Spanish.

9. Kalairajah Y, Simpson D, Cossey AJ, Verrall GM, Spriggins AJ. Blood loss after total knee replacement: effects of computer-assisted surgery. J Bone Joint Surg Br. 2005;87:1480-2.

10. Sehat KR, Evans RL, Newman JH. Hidden blood loss following hip and knee arthroplasty. Correct management of blood loss should take hidden loss into account. J Bone Joint Surg Br. 2004;86:561-5.

11. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol. 2006;33:2271-9.

12. Lanes SF, Lanza LL, Radensky PW, Yood RA, Meenan RF, Walker AM, Dreyer NA. Resource utilization and cost of care for rheumatoid arthritis and osteoarthritis in a managed care setting: the importance of drug and surgery costs. Arthritis Rheum. 1997;40:1475-81.

13. Risberg B. The response of the fibrinolytic system in trauma. Acta Chir Scand Suppl. 1985;522:245-71.

14. Benoni G, Lethagen S, Fredin H. The effect of tranexamic acid on local and plasma fibrinolysis during total knee arthroplasty. Thromb Res. 1997;85: 195-206.

15. Zufferey P, Merquiol F, Laporte S, Decousus H, Mismetti P, Auboyer C, Samama CM, Molliex S. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? Anesthesiology. 2006;105:1034-46.

16. Cid J, Lozano M. Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. Transfusion. 2005;45:1302-7.

17. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. Thromb Res. 2009;123: 687-96.

18. Graham ID, Alvarez G, Tetroe J, McAuley L, Laupacis A. Factors influencing the adoption of blood alternatives to minimize allogeneic transfusion: the perspective of eight Ontario hospitals. Can J Surg. 2002;45:132-40.

19. Sindet-Pedersen S, Ramström G, Bernvil S, Blombäck M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med. 1989;320:840-3.

20. Fawzy H, Elmistekawy E, Bonneau D, Latter D, Erret L. Can local application of Tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. J Cardiothoracic Surg. 2009;4:25.

21. Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. Can J Anesth. 2009;56:202-12.

22. Krohn CD, Sørensen R, Lange JE, Riise R, Bjørnsen S, Brosstad F. Tranexamic acid given into the wound reduces postoperative blood loss by half in major orthopaedic surgery. Eur J Surg Suppl. 2003;588:57-61.

23. Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51:224-32.

24. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006;105: 198-208.

25. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358: 2776-86.

26. Feagan BG, Wong CJ, Johnston WC, Arellano R, Colterjohn N, Karkouti K, Turner K. Transfusion practices for elective orthopedic surgery. CMAJ. 2002;166: 310-4.

27. Camarasa MA, Ollé G, Serra-Prat M, Martín A, Sánchez M, Ricós P, Pérez A, Opisso L. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. Br J Anaesth. 2006;96: 576-82.

28. Hynes M, Calder P, Scott G. The use of tranexamic acid to reduce blood loss during total knee arthroplasty. Knee. 2003;10:375-7.

29. Aglietti P, Baldini A, Vena LM, Abbate R, Fedi S, Falciani M. Effect of tourniquet use on activation of coagulation in total knee replacement. Clin Orthop Relat Res. 2000;371:169-77.

30. Katsumata S, Nagashima M, Kato K, Tachihara A, Wauke K, Saito S, Jin E, Kawanami O, Ogawa R, Yoshino S. Changes in coagulation-fibrinolysis marker and neutrophil elastase following the use of tourniquet during total knee arthroplasty and the influence of neutrophil elastase on thromboembolism. Acta Anaesthesiol Scand. 2005;49:510-6.

31. 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;31:529-37.

32. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol). 1980;14:41-7.

33. Ahlberg A, Eriksson O, Kjellman H. Diffusion of tranexamic acid to the joint. Acta Orthop Scand. 1976;47:486-8.

34. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999;57:1005-32.

35. De Bonis M, Cavaliere F, Alessandrini F, Lapenna E, Santarelli F, Moscato U, Schiavello R, Possati GF. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. J Thorac Cardiovasc Surg. 2000;119:575-80.

36. Wang GJ, Hungerford DS, Savory CG, Rosenberg AG, Mont MA, Burks SG, Mayers SL, Spotnitz WD. Use of fibrin sealant to reduce bloody drainage and hemoglobin loss after total knee arthroplasty: a brief note on a randomized prospective trial. J Bone Joint Surg Am. 2001;83:1503-5.

37. Molloy DO, Archbold HA, Ogonda L, McConway J, Wilson RK, Beverland DE. Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: a prospective, randomised controlled trial. J Bone Joint Surg Br. 2007;89:306-9.

38. Levy O, Martinowitz U, Oran A, Tauber C, Horoszowski H. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. J Bone Joint Surg Am. 1999;81:1580-8.

39. Radosevich M, Goubran HI, Burnouf T. Fibrin sealant: scientific rationale, production methods, properties, and current clinical use. Vox Sang. 1997;72: 133-43.

40. Orpen NM, Little C, Walker G, Crawford EJ. Tranexamic acid reduces early postoperative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. Knee. 2006;13:106-10.

41. Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br. 2001;83:702-5.

42. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R; BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008;358:2319-31.

43. FDA. FDA Strengthens safety information for erythropoiesis-stimulating agents (ESAs). http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108864.htm. Accessed 2009 April 16.

44. Birkmeyer JD, Goodnough LT, AuBuchon JP, Noordsij PG, Littenberg B. The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. Transfusion. 1993;33:544-51.

45. Alvarez JC, Santiveri FX, Ramos I, Vela E, Puig L, Escolano F. Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. Transfusion. 2008;48:519-25.

46. Bierbaum BE, Callaghan JJ, Galante JO, Rubash HE, Tooms RE, Welch RB. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am. 1999;81:2-10.

47. Hatzidakis AM, Mendlick RM, McKillip T, Reddy RL, Garvin KL. Preoperative autologous donation for total joint arthroplasty. An analysis of risk factors for allogenic transfusion. J Bone Joint Surg Am. 2000;82:89-100.

48. Sitges-Serra A, Insenser JJ, Membrilla E. Blood transfusions and postoperative infections in patients undergoing elective surgery. Surg Infect (Larchmt). 2006;7 Suppl 2:S33-5.

49. Innerhofer P, Klingler A, Klimmer C, Fries D, Nussbaumer W. Risk for postoperative infection after transfusion of white blood cell-filtered allogeneic or autologous blood components in orthopedic patients undergoing primary arthroplasty. Transfusion. 2005;45:103-10.

50. Gharehbaghian A, Haque KM, Truman C, Evans R, Morse R, Newman J, Bannister G, Rogers C, Bradley BA. Effect of autologous salvaged blood on postoperative natural killer cell precursor frequency. Lancet. 2004;363: 1025-30.

51. Llewelyn CA, Taylor RS, Todd AA, Stevens W, Murphy MF, Williamson LM; Leucodepletion Study Group. The effect of universal leukoreduction on postoperative infections and length of hospital stay in elective orthopedic and cardiac surgery. Transfusion. 2004;44:489-500.

52. Kuriyan M, Carson JL. Anemia and clinical outcomes. Anesthesiol Clin North America. 2005;23:315-25, vii.

53. Carson JL, Terrin ML, Jay M. Anemia and postoperative rehabilitation. Can J Anaesth. 2003;50(6 Suppl):S60-4.

54. Triulzi DJ, Vanek K, Ryan DH, Blumberg N. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. Transfusion. 1992;32:517-24.

55. Diamond PT, Conaway MR, Mody SH, Bhirangi K. Influence of hemoglobin levels on inpatient rehabilitation outcomes after total knee arthroplasty. J Arthroplasty. 2006;21:636-41.

56. Beghé C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. Am J Med. 2004;116 Suppl 7A: 3S-10S.

57. Carmel R. Anemia and aging: an overview of clinical, diagnostic and biological issues. Blood Rev. 2001;15:9-18.

58. Biesma DH, Van de Wiel A, Beguin Y, Kraaijenhagen RJ, Marx JJ. Post-operative erythropoiesis is limited by the inflammatory effect of surgery on iron metabolism. Eur J Clin Invest. 1995;25:383-9.

59. Schiff RL, Kahn SR, Shrier I, Strulovitch C, Hammouda W, Cohen E, Zukor D. Identifying orthopedic patients at high risk for venous thromboembolism despite thromboprophylaxis. Chest. 2005;128:3364-71.