International Journal of Orthopaedics Sciences

ISSN: 2395-1958
IJOS 2019; 5(2): 328-333

www.orthopaper.com
Received: 04-02-2019
Accepted: 08-03-2019

Dr. GVS Ravibabu
Fellow in Arthroplasty, Fellow in Arthroscopy, Tutor, Department of Orthopedics, Government Medical College and Hospital, Ananthapuram, Andhra Pradesh, India

Dr. Dayal Chavan
Consultant Orthopedic Trauma, Joint replacement and sports medicine surgeon, Fatima Mata Hospital, Kalpetta, Kerala, India

Correspondence
Dr. Dayal Chavan
Consultant Orthopedic Trauma, Joint replacement and sports medicine surgeon, Fatima Mata Hospital, Kalpetta, Kerala, India

A study on use of tranexamic acid during total knee arthroplasty surgery

Dr. GVS Ravibabu and Dr. Dayal Chavan

DOI: https://doi.org/10.22271/ortho.2019.v5.i2g.42

Abstract
Purpose: Our aim was to determine whether the administration of intravenous tranexamic acid is a safe and effective means of reducing blood loss associated with unilateral total knee replacement surgery.
Method: Sequential cohort study analyzing hemoglobin titers, transfusion rates, and the occurrence of venous thromboembolism in patients undergoing unilateral knee replacements with and without the administration of tranexamic acid at the time of induction.
Results: One hundred patients were included in our study after the exclusion. We demonstrated that 10-15 mg/kg of tranexamic acid administered intravenously at the time of induction and two post operative doses significantly reduces operative blood loss and transfusion rates ($p < 0.05$). Moreover, the use of tranexamic acid reduces the costs associated with surgery.
Conclusions: The administration of 10-15 mg/kg of intravenous tranexamic acid is a safe and effective means of reducing operative blood loss and blood transfusion rates in patients undergoing unilateral knee replacements.

Keywords: tranexamic acid, blood loss, unilateral total knee replacement surgery

Introduction
Total knee arthroplasty (TKA) is one of the most commonly performed elective orthopaedic procedures in most parts of the world (1). By 2030, the number is estimated to grow up to 3.48 million Total Knee replacements performed a year [1]. Total Knee Arthroplasty provides significant pain relief and improvement in quality of life [2]. However TKA surgery is not without complications. Of note is the risk of bleeding and requirement for transfusion along with Venous thromboembolism. Total Knee Arthroplasty surgery has been shown to have significant blood loss that sometimes requires blood transfusions [3-5]. Bleeding during total knee arthroplasty can be from different factors such as patient characteristics (hemophiliac, anticoagulation, cirrhosis, etc.,) and surgical technique (bone cuts, soft tissues dissection, blood vessel injury). In some studies, transfusion rate after Total Knee Arthroplasty has been as high as 30% [4]. Transfusion of blood products is not a benign procedure and is associated with many possible risks such as infection, acute systemic reactions, and death [6]. Transfusions also increase rehabilitation time and lengthen hospital stay and cost for the patient and their insurers [7, 8]. Intraoperative blood loss can culminate in anemia. In the case of total knee replacements, hemoglobin on average falls by 3 g/dL perioperatively.
Therefore, controlling blood loss during and after surgery is an important goal in order to achieve good results in Total Knee Arthroplasty. One such method is to use tranexamic acid during Total Knee Arthroplasty surgery. Preoperative measures aimed at preventing postoperative anemia include the use of iron supplementation and recombinant human erythropoietin in patients with preexisting anemia. Intraoperative measures include the use of a tourniquet and the use of tranexamic acid. Postoperative measures include closely monitoring the use of anticoagulation and allogenic blood transfusion.
Tranexamic acid has been available for more than 20 years, with its medical uses ranging from dental extractions, tonsillectomy, cardiac surgery, prostate surgery, menstrual bleeding control, and treatment for patients with hemophilia [9, 10, 11]. The US Food and Drug Administration (FDA) first approved intravenous tranexamic acid in 1986 for the short-term use in hemophiliac patients undergoing tooth extraction. Recently, the FDA approved the oral form

of tranexamic acid for the treatment of menorrhagia [9, 10, 11]. There is now a growing corpus of evidence supporting the use of tranexamic acid in patients undergoing a total knee or total hip replacement. Primary fibrinolysis occurs in many trauma patients and is integral in the pathogenesis of the acute coagulopathy of trauma (ACOT) [12, 13]. Presence of hyperfibrinolysis is associated with high mortality rates [12, 13]. Use of antifibrinolytic agents such as tranexamic acid (TXA) has been shown to improve mortality rate in trauma patients with hyperfibrinolysis [12]. Furthermore tranexamic acid (TXA) has been extensively studied in trauma patients and other major surgical sub-specialties (such as thoracic surgery) to decrease blood loss and mortality. In orthopaedics, tranexamic acid has recently been gaining favor due to its efficacy and ease of use, both in IV and topical usage. Cost, bioavailability, efficacy and low complications have helped to increase the common use of tranexamic acid in Total Knee Arthroplasty [14, 15].

Methodology

A total of 163 patients were included for this study. We excluded patients who underwent bilateral simultaneous TKAs and Patients who received blood transfusions either before or during the surgery were also excluded. In total 63 patients were excluded from the final analysis. The excluded patients were followed for the occurrence of complications including infection or venous thromboembolic events.

A retrospective study was conducted at Hosmat hospital from March 2009 to March 2012, 50 patients 411 undergoing unilateral TKAs were treated without intravenous tranexamic acid during surgery and this was the Control group.

Between AUG 2016- JANUARY 2017 we enrolled 50 patients with osteoarthritis who were undergoing cemented TKAs with the use of tranexamic acid (TXA group) who received intravenous administration of TXA 10-15 mg/kg 10 min prior to tourniquet inflation, 10 min before tourniquet deflation and 3 h after the operation.

In all patients, TKA was performed by one surgeon (ST).

Exclusion criteria were preoperative hepatic or renal dysfunction, an allergy to tranexamic acid, thrombophilia, serious cardiac or respiratory disease, congenital or acquired coagulopathy and history of thromboembolic disease and patients undergoing bilateral Total Knee replacement. All patients followed the same clinical pathway, including standard postoperative care and a protocol of blood transfusion.

No other blood conservation strategies were implemented during the study period. After Hosmat hospital review board approval, clinical records were retrieved from the electronic and medical records database. The following data points were collected : age, sex, diagnosis, American Society of Anesthesiology (ASA) status, operation time, preoperative hemoglobin (Hb), hematocrit (Hct) and platelet counts, intraoperative blood loss, intraoperative blood transfusion, the lowest postoperative Hb and Hct, length of hospital stay and any intraoperative or postoperative complications.

A tourniquet was placed around the upper thigh and inflated to a pressure of 280 – 300 mmHg after exsanguination. An anteromedial skin incision was made, and the medial parapatellar approach was used in all patients. Patellar replacement was performed in all patients, and all components were fixed using cement. The medullary cavity of femur was plugged using an autologous bone.

At the end of the procedure, the tourniquet was deflated, and major bleeding was controlled by diathermy before closure. An intra-articular drain was used. On the first postoperative day, the drain was removed and physiotherapy was initiated. Haemoglobin (Hb) and PCV levels were measured prior to operation and on day 1 post operation.

The need for intraoperative transfusion of blood products was not standardized and was determined by the surgeon and the anesthesiologist based on the physiologic conditions to maintain a mean arterial pressure of 70 mmHg.

Fluid requirements and third-space losses were replaced with balanced crystalloid solutions. The amount of crystalloid solutions was not recorded. In all groups, A transfusion protocol was utilized to standardize the use of blood transfusions. According to the protocol, blood transfusion was not indicated when the hemoglobin concentration was >10 g/dL; was indicated when the hemoglobin concentration was <7 g/dL; was indicated when the hemoglobin concentration was <8 g/dL in a patient who tolerated anemia poorly; and was indicated when the hemoglobin concentration was between 7 and 10 g/dL in a patient who developed fatigue, palpitation, pallor, tachycardia, and tachypnea due to anemia.

On postoperative day 1, Hb and Hct were measured. Transfusion of allogeneic red blood cells was performed in patients based on the clinical pathway as mentioned above. Chemical prophylaxis for thromboembolism was administered during the study period using Enoxaparin 12 hours after surgery and continuing every 24 hr for 4 days. No systematic screening for thromboembolic disease was performed; however, patients with symptoms or signs of thromboembolism of legs (such as swelling, ecchymosis, and pain) were screened using venous duplux scan or venous angiography.

Estimated blood loss was calculated using the following formula

Eestimated blood loss = Estimated blood volume (final Hct reduction/mean Hct).

Results

The final analysis 100 patients divided into the control group and the tranexamic acid group consisted of similar number (50 in each group). There were no statistically significant differences in the patient demographics, weight, ASA status, and diagnosis between the two groups (Table 1).

Table 1: Baseline demographic and clinical data

Demographic and clinical data	Control group	Tranexamic group	Significance*
Number	50	50	
Age (years)*	56.7 ± 14.6	57.2 ± 14.3	0.747
Sex (Female/Male)	38/12	35/15	
Weight (Kg)*	64.1 ± 10.6	64.7 ± 12.6	0.573
ASA status (I/II/III)	7/33/10	4/35/11	
Diagnosis Osteoarthritis	50	48	
Rheumatoid arthritis	0	2	

*Student's t-test; ° mean± SD; ASA-American Society of Anaesthesiologists

The surgical results, including total operating time, wound length and the length of hospital stay, were not significantly different between the two groups (Table 2). The preoperative Hb and Hct levels were not statistically different between the two groups (Table 3).

A Student's t-test, analysis of variance, and chi-square test were used to analyze the data. A `p' value of less than 0.05 was considered statistically significant.

Table 2: Surgical results and hospital course

Surgical result	Control group (N = 50)	Tranexamic acid group (N = 50)
Operation time	125 ± 30	136 ± 34
Wound length (cm)	8.9 ± 2.0	9.5±1.7
Length of Hospital stay (days)	5.2±1.9	5.7±1.9

Values are mean ± SD

Table 3: Blood loss, hematologic data and allogeneic blood transfusion

	Hb> 12 g/dL (n=44)	Hb<12 g/dL (n=6)	Hb> 12 g/dL (n=27)	Hb<12 g/dL (n=23)	
Preoperative Hb (g/dL)	13.5±1.6		13.3±1.4		0.229
Preoperative hematocrit (%)	40.5±4.8		40.0±4.1		0.229
Hb reduction (g/dL)	2.34±1.37	1.37±0.93	2.00±1.10	1.07±0.68	0.010*
Hematocrit reduction (%)	7.02±4.10	4.11±2.80	6.01±3.30	3.22±2.04	0.010*
Estimated Blood Loss (mL)	819±695	561±402	736±507	448±371	0.041*

Preop Hb Sub grouping Control group (n = 50) TXA group (n = 50) Significance
Values are mean ± SD; * Student's t-test; Hb = hemoglobin;

The final Hemoglobin and Hematocrit reduction in the tranexamic acid group was less than that in the control group (p = 0.01). The intraoperative blood loss and early Hb and Hct level reduction were similar between the control and tranexamic acid groups (Table.3). Further analysis showed that the reduction in final Hb and Hct levels was less in cases with preoperative Hb levels of <12 g/dL than in those with preoperative Hb g/dL (Table.3). The reduction in final Hb and Hct levels was the least in the subgroup that had preoperative Hb levels of <12 g/dL and received tranexamic acid. The estimated blood loss was 695 ± 499 mL in the tranexamic acid group; this was less than that of the control group (819 ± 695 mL). Subgroup analysis of the group that did not receive tranexamic acid revealed that the estimated blood loss was lower in patients with preoperative Hb <12 g/dL than in those with preoperative Hb <12 g/dL. The amount of blood was the lowest in the subgroup that had preoperative Hb <12 g/dL and received tranexamic acid. The intraoperative estimated blood loss in the control group was not different from the tranexamic acid group (409 ± 198 mL and 388 ± 163 mL, respectively; Table 3). Each group was further divided into two subgroups using a preoperative Hb level of 12 g/dL as the cutoff value. There were no differences in intraoperative blood loss among the four subgroups.

The blood transfusion rate was lower in the tranexamic acid group (25%) than in the control group (35%) (p 0.05). The highest blood transfusion rate (60%) was found in the subgroup that had preoperative Hb <12 g/dL and did not receive tranexamic acid. The lowest blood transfusion rate (15%) was found in the subgroup that had preoperative Hb g/dL and received tranexamic acid. There was no evidence of Deep vein thrombosis or pulmonary embolism noted in either group.

Discussion

From the multitude of studies and reviews on tranexamic acid use in trauma, orthopaedics, and total joint surgeries, we can assume that tranexamic acid is safe and efficacious for decreasing blood loss. Intravenous use in total knee arthroplasty has been extensively studied and has shown good results [27-31, 42-50]. Reported uses in min-incision, bilateral and revision total knee arthroplasty are few, but are also promising [51-53].

Tranexamic acid has gained popularity in reducing perioperative blood loss, particularly after the publication of a trial in high-risk cardiac surgery. Tranexamic acid is cheaper and safer than aprotinin, much more potent than aminocaproic acid and has overall good penetration into the major joints. In our study, administration of Tranexamic acid reduced postoperative blood loss and eliminated the need of blood transfusion. Blood levels of Tranexamic acid are reduced by half from 2 to 3 h after intravenous administration. Therefore, administration of Tranexamic acid 3 hours after the operation reduced blood loss from 6-9 hours after the operation.

Total Knee Arthroplasty surgery may cause considerable blood loss. Postoperative anemia can lead to increased mortality and morbidity [8, 22], a longer hospital stay [47], and delayed rehabilitation [12], especially in patients with vascular disease [7] Blood transfusion is associated with several well-recognized risks and complications, including transfusion-related acute lung injury, hemolytic transfusion reactions, transfusion-associated sepsis [49], and transmission of infectious agents [4, 27]. Many studies report that intravenous use of tranexamic acid can reduce blood loss and blood transfusion in patients undergoing primary arthroplasty [9, 17-19, 28, 35, 40, 41, 43, 46, 48].

Several studies have shown that preoperative autologous blood donation, perioperative transfusion, an aesthetic technique and nonmonomeric hemodilution are useful methods for avoiding allogeneic blood transfusion. Preoperative autologous blood donation followed by autotransfusion is an expensive procedure with logistic problems in many hospitals. Furthermore, about 45% of personated units may be discarded for of different reasons [19].

Although the use of air tourniquet decreases intraoperative blood loss in Total Knee Arthroplasty, postoperative blood loss occurs because of increased fibrinolysis in response to exsanguination [20]. Because hyperfibrinolysis is considered to be the major cause of postoperative bleeding after Total Knee arthroplasty, antifibrinolytic drugs, including aprotinin, aminocaproic acid and Tranexamic acid have been proposed.

The dosage of tranexamic acid used in our study was lower than that used in other studies in which the systemic dosage ranged from 2-3 g [9, 17-19, 28-30, 35, 41, 43, 46]. Although the dosage

of tranexamic acid was low, we may effectively reduce the amount of total blood loss and the need for blood transfusion in our patients by using the intravenous route.

The present study had several limitations. First, this was not a randomized study but a sequential series study. However, we did not preselect the patients for this study, which might decrease the selection bias. Second, the case number was made equal between the two groups. Third, the blood loss was estimated by a validated method [15, 32]; although it was not accurate, it was simple and practicable. We also excluded the patients who had received blood transfusion before or during surgery to avoid the confounding effect. Fourth, the need for blood transfusion was arbitrarily determined based on the clinical pathway. Fifth, venography or CT scan was not routinely performed to screen for pulmonary embolism or thromboembolic complications.

Some asymptomatic venous thromboembolism might be overlooked.

The use of antifibrinolytics has increased anxiety about increased thrombotic tendency. However, only case reports for cerebral thrombosis, arterial thrombosis, acute renal failure and coronary graft occlusion exist for Tranexamic acid administration [23]. Furthermore, several dose-ranging studies have recommended Tranexamic acid dose of up to 100 mg/kg in patients undergoing cardiac surgery [24]. Murkin *et al*. reported that a high dose of Tranexamic acid ranging from 61 to 259 mg/kg had no adverse events [25]. In the case of our patients, we found no differences between the control and the two Tranexamic acid groups regarding VTE rate, including asymptomatic Deep vein thrombosis and Pulmonary embolism.

Administration of Tranexamic acid twice reduced postoperative blood loss after Total Knee Arthroplasty, and Tranexamic acid was not associated with the risk of Deep vein thrombosis and Pulmonary embolism. Further, administration of Tranexamic acid twice may eliminate the need for blood transfusion during Total Knee Arthroplasty.

We were not aware of any drug-drug interaction of the tranexamic acid with the antibiotic although it is conceivable that there might be such an interaction. However, we did observe that the addition of low-dose tranexamic acid was effective in decreasing blood loss after Total Knee Arthroplasty without an apparent increase in symptomatic thromboembolic events.

When tranexamic acid is administered intravenously, it is widely distributed through the extracellular and intracellular compartments [34]. When a high dose of systemic tranexamic acid is administered, the drug rapidly diffuses into the joint and has a biological half-life of approximately 3 hours [2]. To address the potential risk of thromboembolism with high doses of tranexamic acid, low-dose tranexamic acid has been topically used in dental surgery [42], cardiac surgery [1, 13], and spine surgery [21]. Similar to our 1 findings, the results of these studies have demonstrated that use of tranexamic acid significantly decreases the amount of blood loss. One other study that we know of in Total Knee Arthroplasty has evaluated topical tranexamic acid [3]. In this small, randomized trial, the authors found-much as we did-less bleeding, fewer transfusions, and no increase in postoperative complications.

Although topical tranexamic acid has shown good results, further studies are needed to find the optimal application dose, timing, and frequency of administration. Furthermore, since intra-articular tranexamic acid directly bathes polyethylene, its effects on wear needs further investigation. On a systemic level, high dose tranexamic acid (61-259 mg/kg) has been shown to be associated with seizures during cardiac procedures [40]. It is unlikely for orthopaedic surgeons to use such high dosages; however further studies need to determine optimal dosing to minimize potential risks.

Conclusion

In conclusion, the use of low-dose topical tranexamic acid in patients undergoing Total Knee Arthroplasty effectively reduced postoperative bleeding and blood transfusion rates. Although the study was retrospective, it is worth noting that the surgical procedures and perioperative care were similar in both groups and that the number of patients included was reasonable.

References

1. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am. 2007; 89:780-785.
2. Kirwan JR, Currey HL, Freeman MA, Snow S, Young PJ. Overall long-term impact of total hip and knee joint replacement surgery on patients with osteoarthritis and rheumatoid arthritis. Br J Rheumatol. 1994; 33:357-360.
3. Prasad N, Padmanabhan V, Mullaji A. Blood loss in total knee arthroplasty: an analysis of risk factors. Int Orthop. 2007; 31:39-44.
4. Banerjee S, Issa K, Kapadia BH, Khanuja HS, Harwin SF, McInerney VK *et al.* Intraoperative No pharmacotherapeutic Bloo G Management Strategies in Total Knee Arthroplasty. J Knee Surg, 2013.
5. Cushner FD, Friedman RJ. Blood loss in total knee arthroplasty. Clin Orthop Relat Res. 1991, 98-101.
6. Maxwell 1M, Wilson MM. Complications of blood transfusion. CEACCP. 2006 6:225-229.
7. Bower WF, Jin L, Underwood MJ, Lam YH, Lai PB. Peri-operative blood transfusion increases length of hospital stay and number of postoperative complications in non-cardiac surgical patients. Hong Kong Med J. 2010; 16:116-120.
8. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010; 113:482-495.
9. Wellington K, Wagstaff Aj. Tranexamic acid: a review of its use in the management of menorrhagia. Drugs. 2003; 63:1417-1433.
10. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999; 57:1005-1032.
11. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs. 2012; 72:585-617.
12. Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC *et al.* Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma. 2008; 64:1211-1217.
13. Gando S, Sawamura A, Hayakawa M. Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature. Ann Surg. 2011; 254:10-19.
14. Ipema HJ, Tanzi MG. Use of topical tranexamic acid or aminocaproic acid to prevent bleeding after major surgical procedures. Ann Pharmacother. 2012; 46:97-107.
15. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. J Am Acad Orthop Surg. 2010; 18:132-138.

16. Green D. Coagulation cascade. Hemodial Int 2006; 10(2):2-4.
17. Zorio E, Gilabert-Estelles J, Esparta F, Ramon LA, Cosin R, Estelles A. Fibrinolysis: the key to new pathogenetic mechanisms. Curr Med Chem. 2008; 15:923-929.
18. Hardy JF, Desroches J. Natural and synthetic antifibrinolytics in cardiac surgery. Can J Anaesth. 1992; 39:353-365.
19. Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation. 2007; 115:2801-2813.
20. Henry DA, Moxey AJ, Carless PA, O'Connell D, McClelland B, Henderson KM *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2007; CD001886.
21. Gybel M, Kristensen K, Roseva-Nielsen N. (Cardiac arrest caused by massive pulmonary embolism during treatment with tranexamic acid). Ugeskr Laeger. 2013; 175:1426-1427.
22. Taparia M, Cordingley FT, Leahy MF. Pulmonary embolism associated with tranexamic acid in severe acquired haemophilia. Eur J N-Jit Haematol. 2002; 68:307-309.
23. Krivokuca I, Lammers JW. Recurrent pulmonary embolism associated with a hemostatic drug: tranexamic acid. Clin Appl,Thromb Hemost. 2011; 17:106-107.
24. Bruce-Brand R, Dragomir R, Baker J, Harty J. Cerebrovascular infarction following bilateral total knee arthroplasty and tranexamic acid administration. Acta Orthop Belg. 2013; 79:351-354.
25. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes Bj, McClelland B *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011; CD001886.
26. CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, *et al.* Effects of tranexamic acid on death, vascular Ask occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010; 376:23-32.
27. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM. Tranexamic acid in total knee replacement: a systematic review and meta-analysis. J Bone Joint Surg Br. 2011; 93:1577-1585.
28. 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; 94:1153-1159.
29. Gandhi R, Evans HM, Mahomed SR, Mahomed NN. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. BMC Res Notes. 2013; 6:184.
30. Karam JA, Bloomfield MR, Diiorio TM, Irizarry AM, Sharkey PF. Evaluation of the Efficacy and Safety of Tranexamic Acid for Reducing Blood Loss in Bilateral Total Knee Arthroplasty. J Arthroplasty, 2013.
31. Gillette BP, DeSimone LJ, Trousdale RT, Pagnano MW, Sierra RJ. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. Clin Orthop Relat Res. 2013; 471:150-154.
32. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi P *et al.* Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am. 2010; 92:2503-2513.
33. Onodera T, Majima T, Sawaguchi N, Kasahara Y, Ishigaki T, Minami A. Risk of deep venous thrombosis in drain clamping with tranexamic acid and carbazochrome sodium sulfonate hydrate in total knee arthroplasty. J Arthroplasty. 2012; 27:105-108.
34. Wind TC, Barfield WR, Moskal JT. The effect of tranexamic acid on blood loss and transfusion rate in primary total knee arthroplasty. J Arthroplasty. 2013; 28:1080-1083.
35. Mutsuzaki H, Ikeda K. Intra-articular injection of tranexamic acid via a drain plus drain-clamping to reduce blood loss in cementless total knee arthroplasty. J Orthop Surg Res. 2012; 7:32.
36. Georgiadis AG, Muh SJ, Silverton CD, Weir RM, Laker MW. A prospective double-blind placebo controlled trial of topical tranexamic Acid in total knee arthroplasty. J Arthroplasty. 2013; 28:78-82.
37. Panteli M, Papakostidis C, Dahabreh Z, Giannoudis PV. Topical tranexamic acid in total knee replacement: A systematic review and meta-analysis. Knee. 2013; 20:300-309.
38. Seo jG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2013; 21:1869-1874.
39. Mohseni K, Jafari A, Nobahar MR, Arami A. Polymyoclonus seizure resulting from accidental injection of tranexamic acid in spinal anesthesia. Anesth Analg. 2009; 108:1984-1986.
40. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M *et al.* High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg. 2010; 110:350-353.
41. Furtmuller R, Schlag MG, Berger M, Hopf R, Huck S, Sieghart W *et al.* Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid (A) receptor antagonistic effect. J Pharmacol Exp Ther. 2002; 301:168-173.
42. Capdevila X, Calvet Y, Biboulet P, Biron C, Rubenovitch J, d'Athis F. Aprotinin decreases blood loss and homologous transfusions in patients undergoing major orthopedic surgery. Anesthesiology. 1998; 88:50-57.
43. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemela HM, Mantyla SK *et al.* Tranexami,: acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg. 1997; 84:839-844.
44. 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; 48:519-525.
45. 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; 45:1302-1307.
46. Camarasa MA, 011e G, Serra-Prat M, Martin A, Sanchez M, Ricos P *et al.* Efficacy of aminocaproic, tranexamic acids in the control of Nay bleeding during total knee replacement: a randomized clinical trial. Br I Anaesth. 2006; 96:576-582.
47. Zhang H, Chen J, Chen F, Que W. The effect of tranexamic acid on blood loss and use of blood products

in total knee arthroplasty: a meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2012; 20:1742-1752.
48. Tan J, Chen H, Liu Q, Chen C, Huang W. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. J Surg Res. 2013; 184:880-887.
49. Lwai T, Tsuji S, Tomita T, Sugamoto K, Hideki Y, Hamada M *et al.* Repeat-dose intravenous tranexamic acid further decreases blood loss in total knee arthroplasty. Int Orthop. 2013; 37:441-445.
50. Maniar RN, Kumar G, Singhi T, Nayak RM, Maniar PR. 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.
51. Lin PC, Hsu CH, Huang CC, Chen WS, Wang JW. The blood-saving effect of tranexamic acid in minimally invasive total knee Air replacement: is an additional pre-operative injection effective? J Bone Joint Surg Br. 2012; 94:932-936.
52. Aguilera X, Videla S, Almenara M, Fernandez JA, Gich I, Celaya F. Effectiveness of tranexamic acid in revision total knee arthroplasty. Acta Orthop Belg. 2012; 78:68-74.
53. MacGillivray RG, Tarabichi SB, Hawari MF, Raoof NT. Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. J Arthroplasty. 2011; 26:24-28.
54. Sa-Ngasoongsong P, Channoom T, Kawinwonggowit V, Woratanarat P, Chanplakorn P, Wibulpolprasert B *et al.* Postoperative blood loss reduction in computer-assisted surgery total knee replacement by low dose intra-articular tranexamic acid injection together with 2-hour clamp drain: a prospective triple-blinded randomized controlled trial. Orthop Rev (Pavia). 2011; 3:12.
55. Roy SP, Tanki UF, Dutta A, Jain SK, Nagi ON. Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2012; 20:2494-2501.
56. Ishida K, Tsumura N, Kitagawa A, Hamamura 5, Fukuda K, Dogaki Y *et al.* Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. Int Orthop. 2011; 35:1639-1645.