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Original research

A prospective, randomized, comparative study of intravenous alone and combined intravenous and intraarticular administration of tranexamic acid in primary total knee replacement

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ABSTRACT

Background: Studies on the use of tranexamic acid (TXA) to improve clinical outcomes after joint arthroplasty have reported contrasting results between intravenous (IV) TXA alone and combined IV and intraarticular (IA) administration. We compared the effectiveness of the 2 methods in providing higher postoperative hemoglobin (Hb) levels in patients undergoing primary total knee arthroplasty (TKA).
Methods: A total of 100 TKA patients were randomly assigned to receive either IV TXA alone (group 1) or combined IV and topical IA TXA (group 2). Hb and hematocrit levels were measured before and after surgery. The amount of drained blood and transfused blood for the 2 groups was compared.
Results: The Hb level was significantly higher at postoperative day 4, together with a positive, albeit not significant, trend toward less postoperative blood loss in the group that received combined IV and IA TXA. No postoperative infections or deep venous thrombosis events occurred.
Conclusions: This study reinforces evidence that, as compared to IV TXA alone, combined IV and IA administration of TXA has a synergic effect, leading to higher postoperative Hb levels without influencing drug safety in TKA patients.

Introduction

Intra- and postoperative bleeding in total knee arthroplasty (TKA) is associated with a higher risk of developing painful intraarticular (IA) hematoma and subsequent infection, as well as increased healthcare costs due to longer hospital stay [1,2]. Currently available strategies for bleeding management include reinfusion of intra- and postoperative drainage volume, which is more expensive and less effective in controlling blood loss than the use of tranexamic acid (TXA) [3]. Fibrin sealants have also been shown to be effective in reducing intraoperative blood loss, but because of their cost, their use is not suggested in standard knee arthroplasty [4]. Postoperative blood loss can also be controlled by placing the knee in flexion for 6 hours immediately after surgery [5].

TXA, being both inexpensive and effective, has become the method of choice for controlling blood loss [6]. TXA, a synthetic antifibrinolytic that inhibits lysine from attaching to the plasminogen-binding site, blocks plasminogen from binding to the fibrin surface. In this way, plasminogen activation is inhibited and fibrinolysis is blocked [7]. Although the effectiveness of TXA in controlling blood loss has been widely demonstrated, debate continues over the potential benefit of local IA vs systemic administration. We compared the effectiveness of intravenous (IV) administration of TXA alone vs combined IV and IA administration in providing higher postoperative hemoglobin (Hb) in TKA.

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Material and methods

Between September 2015 and February 2016, a total of 100 patients underwent TKA (75 women and 25 men; age range, 48-91 years) for primary knee osteoarthritis (n = 85), post-traumatic knee osteoarthritis (n = 9), or knee osteoarthritis secondary to rheumatoid arthritis (n = 6). Inclusion criteria were primary TKA and age between 18 and 95 years. Local institutional review board approval (CdCP71498-2015) and patients' consent were obtained. Exclusion criteria were knee flexion deformity >20°; varus and valgus deformity >20°; revision unicompartmental or total knee replacement; pregnancy; known allergy to TXA, low-molecular-weight heparin, and local anesthetics; congenital or acquired coagulopathy; history of thromboembolism; use of anticoagulants or contraceptive pills 5 days before surgery; anemia; severe cardiovascular and respiratory disorders; ischemic heart disease; renal and/hepatic insufficiency; and refusal of blood transfusion for religious reasons.

Preoperative assessment included blood tests and clinical examinations to rule out severe cardiovascular and respiratory disorders. The patients were randomly assigned in a 1:1 ratio to 2 groups. Blind randomization was performed with the use of sealed envelopes opened at the time of surgery: group 1 (n = 50) received 1 g TXA IV 30 minutes before induction of anesthesia and then at 3 and 9 hours after surgery; group 2 (n = 50) received 1 g TXA IV 30 minutes before induction of anesthesia, then at 3 and 9 hours after surgery plus 3 g topical TXA, which was injected into the joint after closure of the capsule. The IA TXA was prepared intraoperatively, and 3 g of TXA was diluted in 100 mL of saline solution (0.9%) [8]. Blood loss parameters were assessed postoperatively: Hb levels and platelet count on postoperative days (POD) 1, 2, and 4; number of transfusion units; and amount of drained blood in the first 24 hours after surgery.

Surgical technique

Spinal anesthesia was used in all patients (Chirocaine 10-20 mL) together with intraoperative sedation with IV propofol if needed; all patients received antibiotic prophylaxis with 2 g of IV cefazolin 30 minutes before surgery, followed with 1 g every 8 hours after surgery. Patients with a known allergy to cephalosporins received an alternative antibiotics for prophylaxis. A midline skin incision with a medial parapatellar approach was used; the tourniquet was insufflated before skin incision and deflated to obtain accurate hemostasis after the cuts were completed. Local anesthetic (150 mL of ropivacaine [0.2%]) was injected around the soft tissues (Hoffa's body, capsule, subcutaneous fat tissue), and the femoral canal was closed with a press-fit bone plug obtained from the patient's bone cuts. The tourniquet was then again insufflated before cementing and implanting the definitive components and released for hemostasis before closing the capsule. An IA drain was placed and kept clamped for the first 3 postoperative hours. Postoperative blood transfusion was given to patients with anemia (Hb <8 g/dL) or ischemic heart disease (Hb 10 g/dL).

Outcome assessment

The main outcome measure was the Hb value at POD 4. According to previously published studies, and in line with our clinical experience, the Hb level is usually lowest on POD 4 [9]. Secondary outcome measures were amount of drained blood (mL) in the first 24 hours after surgery, number of blood transfusion units, and total postoperative blood loss. Patients were monitored for deep vein thrombosis (DVT) events or other postoperative complications; patients with clinically suspected DVT would be further investigated by ultrasound examination.

Postoperative program

Low-molecular-weight heparin was given according to patient's weight the day before surgery and then repeated every 24 hours. All patients were mobilized with the assistance of a physiotherapist and 2 crutches on the evening of the operative day.

Sample size

Sample size was calculated based on previous studies. As reported by Nielsen et al. [8] in a study comparing combined IV and IA administration of TXA with IV-only administration of TXA in TKA, the combined administration of IV and IA TXA resulted in a clinically relevant reduction in Hb compared with IV TXA alone. Mean values and standard deviations (SD) in the 2 groups at day 2 are as follows: 12.2 ± 1.1 g/dL and 11.1 ± 1.3 g/dL in IV+IA TXA vs IV TXA alone, respectively. On the other hand, Chen et al. [9] observed that Hb reaches its nadir at fourth POD. Our hypothesis was that Hb difference between groups (IV+IA TXA vs IV TXA alone) turns to be significant at the fourth POD. The achievements from the study by Nielsen et al. [8] were used to test the sample size required to obtain a significant difference between groups. Thus, 43 patients per group achieved a 80.530% power to reject the null hypothesis of equal means when the population mean difference is $\mu 1 - \mu 2 = 12.6 - 11.8 = 0.8$ with a SD for both groups of 1.3 and with a significance level (alpha) set at 0.050 using a 2-sided 2-sample equal-variance *t*-test.

Statistical analysis

Descriptive statistical analysis (number, mean ± SD) was applied to continuous variables. Hb levels (g/dL) before and after surgery and the amount of drained blood were defined as continuous variables and analyzed using descriptive statistics. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Statistical analysis was performed using a heteroskedastic 2-tailed Student *t*-test for unpaired data. The statistical power of the study was analyzed and a *P* value of .5 was set to determine statistical significance with a confidence interval of 95%. Analyses were performed using the Number Cruncher Statistical System (NCSS version 2007) and Power Analysis and Sample Size Software (PASS version 2008), (NCSS LLC, Kaysville, UT).

Results

There were no significant differences in age ($P > .05$), height ($P > .05$), weight ($P > .05$), and preoperative Hb levels ($P > .05$) between the 2 groups The Hb levels were comparable between the groups at POD 1 and 2; at POD 4, significantly higher Hb levels were noted in group 2 ($P = .0075$), with a trend, albeit not statistically significant, for a lower amount of drained blood in the first 24 hours and total blood loss in this group ($P > .05$). Two patients in group 1 received a blood transfusion (Table 1). No postoperative infections or thromboembolic events occurred. All patients were discharged on POD 5.

Discussion

We compared the effectiveness and safety of combined systemic and topical administration (IV and IA) of TXA vs topical (IA) TXA alone. The main findings were a significantly higher Hb level at POD 4 and a positive, albeit not statistically significant, trend toward less

Table 1
Demographic and clinical characteristics of TKA patients who received either IV TXA alone or combined IV and IA TXA administration.

Variables	IV TXA group	IV+IA TXA group	*P* value
Age (y)	70.9 ± 9.6	69.5 ± 8.3	NS
Weight (kg)	82 ± 17	79 ± 15	NS
Height (cm)	1.63 ± 0.06	1.65 ± 0.09	NS
Hb (g/dL) preoperative	13.8 ± 1.3	14.1 ± 1.0	NS
Hb (g/dL) POD 1	11.2 ± 1.3	11.5 ± 1.2	NS
Hb (g/dL) POD 2	11.0 ± 1.3	11.4 ± 1.1	NS
Hb (g/dL) POD 4	10.4 ± 1.3	11.1 ± 1.2	.0075
Ht preoperative (%)	41.4 ± 3.3	42.2 ± 2.9	NS
Ht POD 1 (%)	34.0 ± 3.6	34.9 ± 3.6	NS
First 24-h drained blood (cc)	323.8 ± 151.3	277.6 ± 90.9	NS
Blood bags transfused (patients)	2	0	NS
Volemia (L)	3.55 ± 0.62	3.48 ± 0.57	NS
PLT preoperative ($10^3/\mu L$)	241 ± 56	231 ± 50	NS
PLT POD 1 ($10^3/\mu L$)	199 ± 47	188 ± 41	NS
Postoperative blood loss (mL)	853.9 ± 294.2	746.2 ± 291.5	NS

Ht, hematocrit; PLT, platelet count; NS, not significant.
Plus-minus values are the means ± SD.

postoperative blood loss in the group that had received combined IV and IA administration of TXA. No complications or DVT events occurred in either group.

The expected blood loss for a TKA surgery is about 1500 mL on average, with a subsequent loss of Hb of 3 g/dL [10,11]. While the replacement of blood losses by conventional allogeneic blood transfusion has been the mainstay of management of major surgery and trauma, it carries considerable risk of transmission of infection and of immunological reactions [12]. As an alternative to allogeneic blood transfusion, antifibrinolytic agents such as TXA have been widely studied to improve perioperative blood management. TXA has proven effective in reducing blood loss, cost, and risk burden [13]. There is an increasing body of evidence supporting the efficacy of IV administration of TXA in reducing perioperative bleeding [14-25]; nonetheless, concerns about the efficacy of IV administration stem from the belief that only a relatively small amount of the drug reaches the targeted joint, while the major part enters the extravascular space of tissues other than the targeted site of action [26]. Moreover, the blood TXA concentration is reportedly 18 mg/L 1 hour after IV administration of 10 mg/kg, whereas the blood TXA concentration is about half that after IA administration of 3 g TXA, with a lower risk of side effects [27]. Also, because TXA acts directly on the bleeding site, IA administration achieves partial microvascular hemostasis by attenuating local fibrinolysis after tourniquet release [20,21,28].

Local IA administration of TXA has become well established and has been extensively investigated in diverse surgical settings showing promising results [29]. A recent meta-analysis showed that IA TXA in patients undergoing TKA is both effective and reliable in reducing blood loss and avoiding the need for blood transfusion without increasing the rate of DVT [30]. More recently, the combined use of IA (topical) and IV TXA has been studied as a viable alternative to obtain a synergic effect. The authors are aware of 4 randomized controlled trials (RCTs) comparing combined IV and IA TXA vs IV TXA alone. Huang et al. [31] randomized 184 TKA patients into 2 groups: in the group that had received combined IA and IV TXA, there was a smaller maximum decline in Hb, less drainage volume, less postoperative knee pain, less knee swelling, shorter length of hospital stay, and higher short-term satisfaction. As no significant difference in total blood loss or hidden blood loss was observed between the groups, the authors concluded that combined IA and IV TXA does not add meaningful advantages to administration of IV TXA alone The study results could have been influenced by the use of general anesthesia, which is associated with higher blood loss [32], and the use of an insufflated tourniquet from skin incision to wound closure.

In contrast, in their study involving a total of 119 patients undergoing unilateral TKA and randomized to 2 treatment groups, Jain et al. [33] found statistically significant differences in calculated total blood loss, blood transfusion rate, and Hb loss in favor of the group that had received combined IV and IA TXA. Although the authors did not apply a tourniquet or place drainages, as we did in our study, they administered IV TXA with a mg/kg scheme, 30 minutes before skin incision, and at 3 and 6 hours postoperatively, which was closer to the dosage we followed.

Nielsen et al. [8], in a very recent RCT involving 60 unilateral TKA patients, found a marked reduction in blood loss of 37% as compared with IV TXA alone at both 24 hours postoperative and on POD 2. These observations differ from our finding of a significant reduction in Hb loss only at POD 4. The authors did not use a tourniquet based on evidence that it increases fibrinolysis [18,34]. This could explain the differences with respect to our findings. Another recent meta-analysis reported that releasing the tourniquet before wound closure is associated with a significantly higher blood loss [35]; however, there were several methodological limitations that the authors themselves mentioned in their discussion. In our study, we deflated the tourniquet twice to achieve tissue hemostasis. This is a technique that we have developed to get the benefits of using tourniquet without encountering the risk of tourniquet-related fibrinolysis, in case of prolonged insufflation [36]. The main advantages that the authors found with this technique are 2. The first one is to cement with a clean and dry bone bed. The second and in our opinion extremely useful is that of performing a very accurate and thorough hemostasis, especially at the posterior wall, having more room into the joint before implanting the definitive components. However, this novel method to control intraoperative bleeding could have influenced the outcomes of our study and therefore should be further investigated. No postoperative DVT events occurred in either group, and 2 patients in the IV TXA group required blood transfusion. No TXA-related adverse events occurred in either group, consistent with previous RCTs documenting the safety profile of TXA.

The latest RCT [37] compared 4 groups for a total of 200 patients undergoing primary navigated TKA: control, IV TXA, IA TXA, and combined. The authors found that TXA use decreased blood loss. However, contrary to the previously quoted RCTs, no differences among the single or combined administration routes were noticed, concluding that there are no added advantages in combining multiple TXA administrations.

In the study by Huang et al. [31] and in the one by Camarasa et al. [38], the authors used 1 postoperative IV administration, because the authors advanced that the major bleeding in replacement surgery occurs in the first hours after surgery, therefore they chose a regimen with 2 doses, 3 hours apart, for the effect to last over the first 6 hours. Because we have experienced that bleeding can last for longer than the first 6 postoperative hours, we chose to follow a 3-dose regimen, 3 hours apart as previously used by Jain et al. [33]. In our study, that specific regimen could be responsible for nonstatistically significant differences between the groups.

One of the limitations of the present study is the use of drainage. It has been reported that drains can increase blood loss [39] and that they may not be accurate for calculating postoperative blood loss owing to the progressive reduction in hematocrit over time [40]. There is, however, evidence that the combined use of TXA and clamped drains is more effective in reducing blood loss compared to TXA or drain to clamping alone [41]. The choice of clamping the drainage for 3 hours was based on the evidence that this timing optimizes the action of IA TXA [42] and follows the evidence that

the half-life of IA TXA has been shown to be 3 hours [43], avoiding, at the same time, the risk of clots formation that could obstruct the drain, in case of prolonged clamping (it is the authors' experience that this happen when drainage is kept clamped for more than 3 hours). In addition, we insufflated the tourniquet for a short time, because there is evidence that the combined use of tourniquet application and TXA administration provides advantages in terms of operative time and bleeding control [44,45]. Finally, our choice of administering a uniform dose of IV TXA was based on evidence from a previous study that found no difference in TXA efficacy between weighted (20 mg/kg) and uniform (1 g) dosage in TKA patients [46].

Conclusions

This study reinforces evidence that, as compared to IV TXA alone, administration of combined IV and IA TXA has a synergic effect, leading to reduced blood loss without affecting drug safety in TKA patients. This effect was noticed at POD 4, with a positive trend for less drained blood in the first 24 hours and less total blood loss in the group that received combined IV and IA administration of TXA.

References

[1] Galat DD, McGovern SC, Hanssen AD, et al. Early return to surgery for evacuation of a postoperative hematoma after primary total knee arthroplasty. J Bone Joint Surg Am 2008;90(11):2331.
[2] Whiting DR, Duncan CM, Sierra RJ, Smith HM. Tranexamic acid benefits total joint arthroplasty patients regardless of preoperative hemoglobin value. J Arthroplasty 2015;30(12):2098.
[3] Liu D, Dan M, Martinez Martos S, Beller E. Blood management strategies in total knee arthroplasty. Knee Surg Relat Res 2016;28(3):179.
[4] Kluba T, Fiedler K, Kunze B, Ipach I, Suckel A. Fibrin sealants in orthopaedic surgery: practical experiences derived from use of QUIXIL(R) in total knee arthroplasty. Arch Orthop Trauma Surg 2012;132(8):1147.
[5] Napier RJ, Bennett D, McConway J, et al. The influence of immediate knee flexion on blood loss and other parameters following total knee replacement. Bone Joint J 2014;96-B(2):201.
[6] Danninger T, Memtsoudis SG. Tranexamic acid and orthopedic surgery-the search for the holy grail of blood conservation. Ann Transl Med 2015;3(6):77.
[7] Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. Biochim Biophys Acta 1981;673(1):75.
[8] Nielsen CS, Jans O, Orsnes T, et al. Combined intra-articular and intravenous tranexamic acid reduces blood loss in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. J Bone Joint Surg Am 2016;98(10):835.
[9] Chen ZY, Wu HZ, Zhu P, Feng XB. Postoperative changes in hemoglobin and hematocrit in patients undergoing primary total hip and knee arthroplasty. Chin Med J (Engl) 2015;128(14):1977.
[10] Voorn VM, Marang-van de Mheen PJ, So-Osman C, et al. Designing a strategy to implement cost-effective blood transfusion management in elective hip and knee arthroplasties: a study protocol. Implement Sci 2012;7:58.
[11] Park JH, Rasouli MR, Mortazavi SM, et al. Predictors of perioperative blood loss in total joint arthroplasty. J Bone Joint Surg Am 2013;95(19):1777.
[12] Vielpeau C. Perioperative bleeding and early mortality in hip and knee surgery. Orthop Traumatol Surg Res 2012;98(5):475.
[13] Kim TKC, Chang CB, Koh IJ. Practical issues for the use of tranexamic acid in total knee arthroplasty: a systematic review. Knee Surg Sports Traumatol Arthrosc 1849;22:2014.
[14] Ekback G, Axelsson K, Ryttberg L, et al. Tranexamic acid reduces blood loss in total hip replacement surgery. Anesth Analg 2000;91(5):1124.
[15] Orpen NM, Little C, Walker G, Crawfurd EJ. Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. Knee 2006;13(2):106.
[16] Rajesparan K, Biant LC, Ahmad M, Field RE. The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. J Bone Joint Surg Br 2009;91(6):776.
[17] Ross J, Al-Shahi Salman R. The frequency of thrombotic events among adults given antifibrinolytic drugs for spontaneous bleeding: systematic review and meta-analysis of observational studies and randomized trials. Curr Drug Saf 2012;7(1):44.
[18] 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(12):2494.
[19] Sa-Ngasoongsong P, Channoom T, Kawinwonggowit V, 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(2):e12.
[20] 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(8):1869.
[21] Wong J, Abrishami A, El Beheiry H, 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(15):2503.
[22] Zanasi S. Innovations in total knee replacement: new trends in operative treatment and changes in peri-operative management. Eur Orthop Traumatol 2011;2(1-2):21.
[23] 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(9):1742.
[24] Li ZJ, Fu X, Xing D, et al. Is tranexamic acid effective and safe in spinal surgery? A meta-analysis of randomized controlled trials. Eur Spine J 2013;22(9):1950.
[25] Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? Anesthesiology 2006;105(5):1034.
[26] Mannucci PM. Hemostatic drugs. N Engl J Med 1998;339(4):245.
[27] Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol) 1980;14:41.
[28] Ishida K, Tsumura N, Kitagawa A, 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(11):1639.
[29] Shemshaki H, Nourian SM, Nourian N, et al. One step closer to sparing total blood loss and transfusion rate in total knee arthroplasty: a meta-analysis of different methods of tranexamic acid administration. Arch Orthop Trauma Surg 2015;135(4):573.
[30] Zhao-Yu C, Yan G, Wei C, Yuejv L, Ying-Ze Z. Reduced blood loss after intra-articular tranexamic acid injection during total knee arthroplasty: a meta-analysis of the literature. Knee Surg Sports Traumatol Arthrosc 2014;22(12):3181.
[31] Huang Z, Ma J, Shen B, Pei F. Combination of intravenous and topical application of tranexamic acid in primary total knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 2014;29(12):2342.
[32] Hu S, Zhang ZY, Hua YQ, Li J, Cai ZD. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. J Bone Joint Surg Br 2009;91(7):935.
[33] Jain NP, Nisthane PP, Shah NA. Combined administration of systemic and topical tranexamic acid for total knee arthroplasty: can it be a better regimen and yet safe? A randomized controlled trial. J Arthroplasty 2016;31(2):542.
[34] Petaja J, Myllynen P, Myllyla G, Vahtera E. Fibrinolysis after application of a pneumatic tourniquet. Acta Chir Scand 1987;153(11-12):647.
[35] Zan PF, Yang Y, Fu D, Yu X, Li GD. Releasing of tourniquet before wound closure or not in total knee arthroplasty: a meta-analysis of randomized controlled trials. J Arthroplasty 2015;30(1):31.
[36] Watanabe H, Kikkawa I, Madoiwa S, et al. Changes in blood coagulation-fibrinolysis markers by pneumatic tourniquet during total knee joint arthroplasty with venous thromboembolism. J Arthroplasty 2014;29(3):569.
[37] Song EK, Seon JK, Prakash J, et al. Combined administration of IV and topical tranexamic acid is not superior to either individually in primary navigated TKA. J Arthroplasty 2017;32(1):37.
[38] Camarasa MA, Olle G, Serra-Prat M, et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. Br J Anaesth 2006;96(5):576.
[39] Husted H, Gromov K, Malchau H, et al. Traditions and myths in hip and knee arthroplasty. Acta Orthop 2014;85(6):548.
[40] Harrap RS, Whyte GS, Farrugia A, Jones C. Some characteristics of blood shed into the Solcotrans postoperative orthopaedic drainage/reinfusion system. Med J Aust 1992;157(2):95.
[41] Chareancholvanich K, Siriwattanasakul P, Narkbunnam R, Pornrattanamaneewong C. Temporary clamping of drain combined with tranexamic acid reduce blood loss after total knee arthroplasty: a prospective randomized controlled trial. BMC Musculoskeletal Disorders 2012;13:124.
[42] Sa-ngasoongsong P, Chanplakorn P, Wongsak S, et al. An in vivo study of low-dose intra-articular tranexamic acid application with prolonged clamping drain method in total knee replacement: clinical efficacy and safety. Biomed Res Int 2015;2015:164206.
[43] Ahlberg A, Eriksson O, Kjellman H. Diffusion of tranexamic acid to the joint. Acta Orthop Scand 1976;47(5):486.
[44] Rosenstein AD, Michelov YA, Thompson S, Kaye AD. Benefits of limited use of a tourniquet combined with intravenous tranexamic acid during total knee arthroplasty. Ochsner J 2016;16(4):443.
[45] Tarwala R, Dorr LD, Gilbert PK, Wan Z, Long WT. Tourniquet use during cementation only during total knee arthroplasty: a randomized trial. Clin Orthop Relat Res 2014;472(1):169.
[46] Levine BR, Haughom BD, Belkin MN, Goldstein ZH. Weighted versus uniform dose of tranexamic acid in patients undergoing primary, elective knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 2014;29(9 Suppl):186.