Original Article

Additional Dose of Intravenous Tranexamic Acid after Primary Total Knee Arthroplasty Further Reduces Hidden Blood Loss

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Abstract

Background: Total knee arthroplasty (TKA) is the most frequently performed procedure in treating advanced knee osteoarthritis. Excessive perioperative blood loss can sometimes lead to postoperative anemia. Tranexamic acid (TXA) is a potent fibrinolysis inhibitor which has been extensively used at the surgical incision and closure to lower overall blood loss in adult reconstruction surgery. Our previous study suggested that about two-thirds of the total blood loss (TBL) came from hidden blood loss (HBL) on postoperative days 1 and 2. The role of reducing HBL with TXA administration in postoperative TKA patients is unknown. The current study was designed to evaluate the efficiency and safety of supplemental intravenous (IV) TXA in further reducing HBL after primary TKA.

Methods: A prospective pilot study was conducted at a single institution on 43 consecutive patients who underwent unilateral TKA from September 2014 to February 2015. All patients were given 1 g of IV TXA 10–15 min before operation and another 1 g of IV TXA at the time of wound closure on the day of surgery. On postoperative days 1 and 2, the supplemental group ($n = 21$) was given additional 1 g of TXA intravenously twice a day, whereas the control group ($n = 22$) received an equal volume of saline. Drain output, hemoglobin (Hb), and hematocrit (HCT) were recorded preoperatively and 5 consecutive days postoperatively in both groups. HBL was calculated with the Gross formula. Pre- and post-operative lower extremity Doppler venous ultrasound was performed in all patients to detect deep vein thrombosis (DVT). The indexes were compared using the Mann-Whitney test, whereas the results of Hb and HCT were analyzed by repeated-measures analysis of variance. The difference was considered statistically significant if $P < 0.05$.

Results: The demographics and surgical characteristics of the two groups were comparable. Supplemental group had higher Hb level on postoperative days 1–5 compared to the control; however, the difference was not significant ($F = 2.732$, $P = 0.106$). The HCT of the supplemental group was significantly higher than that of the control group on postoperative day 5 ($F = 5.254$, $P = 0.027$). No significant difference was found in drainage volume and TBL, but the HBL was reduced in the supplemental group (supplemental 133.1 [71.8, 287.3] ml and control 296.0 [185.3, 421.4] ml, $Z = 2.478$, $P = 0.013$, median [interquartile range]). There was one DVT in the control group and none in the supplemental group. All patients were followed at 1 year after surgery, and no further complications were reported.

Conclusion: Based on the current study, additional doses of IV TXA could potentially further reduce HBL after primary TKA without increasing the risk of venous thromboembolism.

Key words: Hidden Blood Loss; Total Knee Arthroplasty; Tranexamic Acid

Introduction

Total knee arthroplasty (TKA) is a commonly performed procedure treating advanced knee osteoarthritis. Perioperative blood loss could sometimes lead to postoperative anemia, which might require occasional transfusion. Based on our previous study, nearly two-thirds of the total blood loss (TBL) comes from the hidden blood loss (HBL).[1] HBL is defined as the volume of blood that diffuses into tissue spaces and the articular cavity after TKA and contributes to 66% of the TBL. To reduce the TBL, we should think of the cause of the HBL and how to reduce it.[1,2] Recent studies suggested that prolonged fibrinolytic activity from delayed activation of plasmin

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beyond the initial surgical trauma might be a potential cause for HBL.[3-5]

Tranexamic acid (TXA) has been recently used to reduce the blood loss after TKA. As a synthetic antifibrinolytic agent, it can competitively inhibit the activation of plasminogen and noncompetitively inhibit the plasmin activity at high concentrations.[6] Consequently, TXA can reduce the blood loss by decreasing the conversion of plasminogen into plasmin, an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins including procoagulant factors 5 and 8.[7] TXA has been proven to be effective in reducing TBL and transfusions after TKA by different methods without risk of complications.[6,8-11] The most commonly reported administration methods included intravenous (IV) and topical administration.[12] Moreover, there is no difference in efficiency and safety between IV or topical administration.

Administration of two additional doses of IV TXA at 3 and 6 h postoperatively was demonstrated effective and safe on reducing the HBL.[13] As mentioned before, the HBL peaked around postoperative days 2–3 after TKA. The purpose of the current study was to investigate whether supplemental doses of TXA up to postoperative day 3 could further reduce HBL in primary TKA without major complications.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local Ethics Committee of the Peking University Third Hospital (No. 2014120-2). Informed written consent was obtained from all patients or their guardians for all study participants before their enrollment in this study.

Study subject

A prospective pilot study on 51 consecutive patients was conducted at Peking University Third Hospital from September 2014 to February 2015. The inclusion criteria were (1) patients with advanced knee osteoarthritis and (2) patients with primary unilateral TKA. The exclusion criteria were (1) patients with hemorrhagic disease; (2) patients undergoing anticoagulation therapy; (3) patients with preoperative hemoglobin (Hb) lower than 100 g/L; (4) patients with a history of infection of the lower limbs; (5) patients with a history of malignant tumor, peripheral vascular disease, or thrombosis; (6) patients with comorbidity unacceptable for TXA administration including renal insufficiency (creatinine [Cr] >133 μmol/L), hepatic insufficiency, severe respiratory or cardiovascular disease (patients who had undergone coronary stent implantation in the past 12 months), coagulopathy, high risks of thrombosis (congenital/acquired thrombotic diseases), history of venous thromboembolism, or history of stroke; and (7) patients who were unwilling to participate in the study. Eight patients refused to take part in the study were excluded from the study, and 43 patients included in this study finally.

Surgical technique and perioperative management

All procedures were performed by senior surgeon (Zi-Jian Li). Patients underwent TKA with medial parapatellar approach under spinal anesthesia. The tourniquet was inflated 300 mmHg (1 mmHg = 0.133 kPa) until wound closure. A pulsed lavage irrigator was used to prepare cement surface and wound irrigation. The GENESIS II (Smith and Nephew, Memphis, TN, USA), an open condylar prosthesis, was implanted in all cases. None of the patients received patella resurfacing.

Postoperatively, every patient received a routine intra-articular drain connected to an anti-reflux bag, and the operative lower extremity was wrapped with an elastic compression bandage for 24 h after surgery. A femoral nerve block (FNB) was administered to control postoperative pain in all patients for 48 h. To avoid hypovolemia, all patients received fluid therapy routinely on the day of surgery and the 1st postoperative day. Patients were instructed to begin muscle contraction of the lower extremity and ankle pump exercises, as soon as they recovered from anesthesia. Quadriceps muscle training was also recommended from the 1st postoperative day. Patients were encouraged to resume their normal diet on the 1st postoperative day. Ambulation with a walker was encouraged from the 3rd postoperative day after removal of FNB. All patients received deep vein thrombosis (DVT) prophylaxis using oral rivaroxaban (10 mg daily) for 2 weeks after surgery. Bilateral lower extremity venous ultrasound examinations were routinely performed in all patients 5 days and 3 months after surgery to detect DVT.

The indications for blood transfusion in this study were as followed: (1) Hb ≤80 g/L; (2) hematocrit (HCT) ≤20%; and (3) patients who did not meet 1st or 2nd criteria but presented with severe anemic symptoms (e.g., dizziness and syncope).

Tranexamic acid use

On the day of surgery, all patients were given 1 g of IV TXA (Guangzhou Pharmaceutical Group, Guangzhou, China; batch number: H20056987, Specification: 10 ml: 1.0 g) 15 min before tourniquet inflation and 1g postoperatively after tourniquet release at the time of wound closure. Patients in the supplemental TXA group received four additional IV TXA doses, which were 1 g given twice a day with 100 ml of physiological saline on the 1st and 2nd postoperative days.

Data collection

Patients' demographic data (age and gender), as well as general health information (body mass index [BMI] and American Society of Anesthesiologists [ASA] physical status score), were collected. Preoperative Hb, HCT, and Cr clearance rate were also collected. Tourniquet time was recorded for every patient.

Postoperative data included Hb and HCT on postoperative days 1–5, drain output, volume of allogeneic blood transfusion, and venous ultrasound of the lower extremity on the 5th day after surgery. The volume of dominant blood loss was equal to intraoperative blood loss plus postoperative

drain output. The volume of HBL was calculated using the Gross formula as follows:[14,15]

TBL (ml) = Preoperative blood volume × (preoperative HCT level – postoperative HCT level).

Preoperative blood volume (BV) was calculated by the Nadler method as follows:

$BV = k_1 \times H^3 + k_2 \times W + k_3$

For males, $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.1833$; for females, $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$; H = height (m) and W = weight (kg).

HBL (ml) = TBL + volume of autologous blood transfusion + volume of allogeneic blood transfusion − dominant blood loss.

Data analysis

SPSS version 19.0 (IBM, Chicago, IL, USA) software was used for data analysis. If the data complied had a normal distribution (age and BMI), the results were expressed in the form of mean ± standard deviation (SD). For data with nonnormal distribution (HBL, TBL, and drain output volume), median and 25th and 75th percentiles were used. The indexes were compared using the Mann-Whitney test, whereas the results of Hb and HCT were analyzed by repeated-measures analysis of variance. The difference was considered statistically significant if $P < 0.05$.

Results

Forty-three patients met the inclusion criteria, including 9 males and 34 females, with an average age of 65.8 years (50–81 years).The supplemental TXA group included 21 patients (male:female = 5:16) and the control group included 22 patients (male:female = 4:18). No difference was found in age, BMI, preoperative condition (including Hb, HCT, and Cr), tourniquet time, and ASA status (Table 1, $P > 0.05$).

The Hb levels on postoperative days 1–5 were higher in the supplemental TXA group than those in the control group, but the difference was not significant ($F = 2.732$, $P = 0.106$, Figure 1). However, HCT on postoperative day 5 was significantly higher in the supplemental TXA group ($F = 5.254$, $P = 0.027$, Figure 2), and the HBL was significantly reduced in the supplemental TXA group compared to the control group (133.1 ml vs. 296.0 ml, $Z = 2.478$, $P = 0.013$, Table 2). There was no significant difference in the drain output and TBL between the groups [Table 2]. No one required blood transfusion for any reason in both groups.

One patient in the control group was diagnosed with calf DVT 5 days after surgery but none in the supplemental TXA group. All patients were followed for other potential complications 1 year after surgery. No further complications such as pulmonary embolism (PE), seizure, or cardiovascular events were reported.

Discussion

Perioperative IV TXA administration has been proven to be not only safe but also effective in reducing postoperative blood loss in TKA. HBL comprises nearly two-thirds of TBL in TKA and usually continues till postoperative day 2–3. The effect of TXA on HBL has not been extensively studied previously.

Nielsen *et al.*[16] demonstrated that additional intra-articular TXA could reduce blood loss of 37% compared with one dose IV TXA alone both at 24 h postoperatively and on postoperative day 2. Xie *et al.*[17] demonstrated that administration of TXA at 3 and 6 h after surgery was safe and effective in HBL reduction, as well as reducing postoperative inflammatory response. A recent meta-analysis confirmed that IV administration of TXA could significantly reduce HBL after TKA.[18] Jansen *et al.*[19] reported that the repeated use of TXA for 3 days after TKA, with an equivalent volume of saline as a placebo, resulted in improved coagulation profile, decreased TBL, and decreased transfusions. In a study on 99 total joint arthroplasty patients, those who were treated with TXA had significantly lower levels of D-dimer and tissue plasminogen activator.[20] Since TXA has the ability to decrease fibrinolytic activity postoperation by inhibiting plasmin-induced platelet activation, additional doses might lead to increased clotting by preserving platelets and reducing blood loss.

In this study, the HBL was significantly lower compared to the control group when IV TXA was continued to postoperative day 2. The TXA doses were chosen with

Table 1: Comparison of the general characteristics of the study

Items	Supplemental TXA group ($n = 21$)	Control group ($n = 22$)	t	P
Gender (male/female)	5/16	4/18	–	0.721*
Age (years)	66.5 ± 6.3	64.6 ± 5.9	1.062	0.295
BMI (kg/m^2)	27.6 ± 3.6	27.8 ± 3.8	−0.144	0.886
ASA	1.8 ± 0.4	2.0 ± 0.4	−1.549	0.129
Preoperation creatinine (μmol/L)	67.1 ± 14.5	68.8 ± 8.8	−0.456	0.652
Preoperation Hb (g/L)	134.0 ± 10.2	131.6 ± 13.7	0.652	0.518
Preoperation HCT (%)	40.9 ± 3.3	40.3 ± 4.2	0.473	0.639
Tourniquet time (min)	79.7 ± 19.3	72.5 ± 15.9	1.361	0.181

Data are presented as n or mean ± SD. *When comparing the gender of two groups, the expectations of two cells are <5, so Fisher's exact test was used. ASA: American Society of Anesthesiologists; BMI: Body mass index; Hb: Hemoglobin; HCT: Hematocrit; SD: Standard deviation; TXA: Tranexamic acid.

Table 2: Comparison of the results after TKA of the study

Items	Supplemental TXA group (n = 21)	Control group (n = 22)	Z	P
Drainage (ml)	250.0 (150.0–325.0)	195.0 (107.5–305.0)	1.398	0.163
TBL (ml)	428.0 (356.6–575.9)	481.9 (408.0–522.6)	0.972	0.331
HBL (ml)	133.1 (71.8–287.3)	296.0 (185.3–421.4)	2.478	0.013

Data are presented as median (IQR). TKA: Total knee arthroplasty; IQR: Interquartile range; HBL: Hidden blood loss; TBL: Total blood loss; TXA: Tranexamic acid.

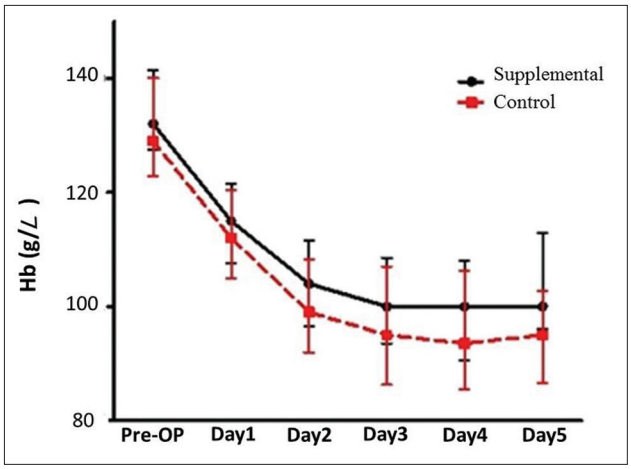

Figure 1: Drop in hemoglobin level from the 1st to 5th days postoperation in the supplemental group and control group. No statistical difference was observed between the two groups by repeated-measures analysis of variance (F = 2.732, P = 0.106). Data are presented as median (interquartile range). Pre-OP: Preoperation; Hb: Hemoglobin.

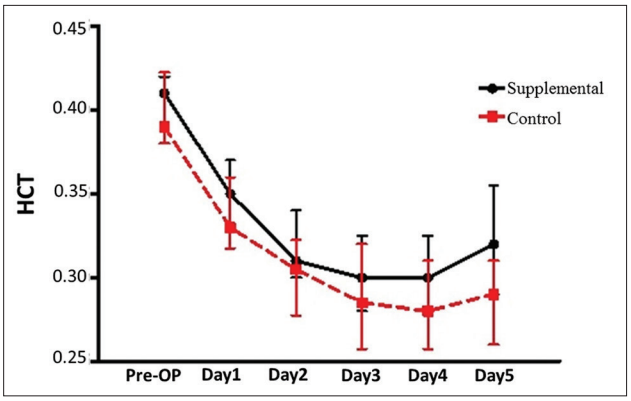

Figure 2: Drop in HCT level from the 1st to 5th days postoperation in the supplemental group and control group. The HCT level in 5 days after surgery was significantly higher in the supplemental group than that in the control group by repeated-measures analysis of variance (F = 5.254, P = 0.027). Data are presented as median (interquartile range). Pre-OP: Preoperation; HCT: Hematocrit.

extra caution, as these levels had not been previously tested. The supplemental dose was very low, and the time interval between the two additional doses in a day was much longer than the half-life of TXA, which is approximately 2–3 h,[8] and 90% of TXA would be excreted in urine in an IV dose of 10 mg/kg in a healthy patient.[17] Two additional days of supplemental TXA administration were selected based on a retrospective study of 422 consecutive patients that demonstrated that the lowest HCT level occurred on the 3rd postoperative day after TKA.[18]

The Hb was higher in the supplemental TXA group compared to the control group on all postoperative days with less TBL, although there was no statistical difference with this small cohort of patients. The results might be different given a larger cohort. However, HCT on postoperative day 5 was significantly higher in the supplemental TXA group ($P < 0.05$). Seo *et al.*[21] reported a mean blood loss of 528 ± 227 ml and a decrease of preoperative Hb values by 0.16 ± 0.08 mg/L in the IV TXA patients after TKA, which are both higher compared with the results in the supplemental group. The study evaluated the efficiency of additional TXA doses for maintaining Hb and HCT, and the positive result confirmed the hypothesis that HBL can be further decreased by adding additional doses of TXA.

Although numerous studies have confirmed the safety of using TXA with routine methods,[22] the safety of supplemental dosages of TXA is still a matter of debate, as studies have reported that there was an increased risk of DVT for higher doses of TXA or prolonged use.[23-25] In this study, however, no DVT was reported at 3-month follow-up after surgery in the supplemental TXA group, and no PE or cardiovascular complications were found in the supplemental TXA group at 1-year follow-up.

The present study had several limitations. First, the mechanism of supplemental TXA application was not investigated in detail. Second, the threshold of additional dose still remains to be determined. Finally, admitting this was a fairly small cohort of patients, further large-scale study is needed to test the safety of the medication in this population.

In conclusion, supplemental doses of IV TXA on the 1st and 2nd postoperative days appear to be safe in reducing HBL in primary TKA without major complications. Further studies including prospective randomized controlled trials should be considered to validate the findings.

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Conflicts of interest

There are no conflicts of interest.

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初次膝关节置换术后额外静脉追加氨甲环酸可以进一步减少术后隐性失血量

摘要

背景：全膝关节置换术是治疗膝关节终末期骨性关节炎最常采用的手术方式。大量的围手术期失血经常会造成手术后贫血的发生。氨甲环酸作为纤溶抑制剂，常规是在手术开始前和伤口闭合时使用来减少手术的总体失血。我们既往的研究证实膝关节置换术后总失血量的三分之二是隐性失血，而在隐性失血阶段使用氨甲环酸的作用并不清楚。本研究旨在评价初次膝关节置换术后隐性失血阶段静脉追加使用氨甲环酸对于减少隐性失血的有效性和安全性。

方法：2014年9月至2015年2月期间，单一中心对43例单侧膝关节置换患者进行前瞻性序列研究。所有病人在手术开始前15分钟静脉给予氨甲环酸1g，在关闭伤口时静脉给予氨甲环酸1g。手术后第一天和第二天，额外追加组（n=21）静脉追加氨甲环酸每天两次，一次1g；对照组（n=22）接受等量的生理盐水。记录两组病人术后引流量以及术前和术后连续5天的血色素和红细胞压积。采用Gross方程计算隐性失血量。所有病人术前和术后接受多谱勒静脉超声检查明确有无下肢深静脉血栓形成。采用重复测量方差分析比较两组病人在血色素和红细胞压积变化趋势的差异，如果p<0.05，认为具有统计学上显著性差异。

结果：两组病人在一般资料和手术相关因素上具有可比性。额外追加组相比对照组在术后1-5天具有更高的血色素水平，尽管差异不具有统计学意义上的显著性 (F=2.732,p=0.106)。额外追加组的红细胞压积明显高于对照组(F=5.254,p=0.027)。两组间的引流量和总失血量未见显著差异，但额外追加组但隐性失血量更低[额外追加组133.1（71.8,287.3）ml，对照组296.0（185.3,421.4）ml，Z=2.478,p=0.013]。所有病人术后随访1年，未发现相关并发症。

结论：基于本研究，在初次膝关节置换术后额外静脉追加使用氨甲环酸具有进一步减少隐性失血的潜力，并不增加静脉血栓疾病的风险。