Tranexamic acid use and risk of thrombosis in regular users of antithrombotics undergoing primary total knee arthroplasty: a prospective cohort study

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Background. The effect of tranexamic acid has not been examined in patients who are regular users of antithrombotics before undergoing total knee arthroplasty. The aim of this study was to determine the impact of tranexamic acid on bleeding and the risk of transfusion and thrombosis in patients taking an antithrombotic treatment before primary unilateral total knee arthroplasty.

Material and methods. A prospective observational study was conducted in a series of 385 consecutive primary total knee arthroplasties performed with and without the administration of tranexamic acid. We compared post-operative bleeding, as determined by a bleeding index, and postoperative haemoglobin and haematocrit between patients taking an antithrombotic treatment before the operation (ATT+ group) and those naïve or non-regular users of antithrombotics (ATT− group). Post-operatively, rivaroxaban was prescribed for deep vein thrombosis prophylaxis, unless contraindicated. Antiplatelet therapy and vitamin K antagonist anticoagulants were not resumed during the early post-operative period.

Results. The prevalence of total knee arthroplasty performed in patients who are regular users of antithrombotics was 33%. Tranexamic acid was administered during 62% of the arthroplasties in the ATT+ group and to 90% in the ATT− group. In both study groups, the bleeding index was significantly lower in patients who received tranexamic acid, both in the ATT+ ($p<0.001$) and in the ATT− group ($p=0.001$). No patients in the ATT+ group received a blood transfusion during the first post-operative week. No thrombotic complications were identified for up to 2 months in the ATT+ group.

Discussion. Tranexamic acid use after the induction of general anaesthesia in total knee arthroplasty represents a fast, inexpensive, and effective opportunity to reduce peri-operative blood loss in patients on chronic antithrombotic treatment undergoing total knee arthroplasty.

Keywords: tranexamic acid, total knee arthroplasty, blood transfusion, rivaroxaban.

Introduction

The growing number of patients in the ageing population who wish to preserve their autonomy correlates with the growing number of primary total knee arthroplasties (TKA)[1-3]. Antithrombotic treatment is among the fastest growing treatments used in medicine for primary or secondary prevention[4,5], and orthopaedic surgeons are frequently confronted with the challenge of performing TKA in patients who regularly use blood-thinning agents before their operation. TKA is a procedure with a high risk of bleeding and thrombosis[6]. Both risks are increased in patients taking an antithrombotic treatment prior to the operation.

One potentially successful and inexpensive means to minimise the blood loss, blood transfusion needs, and risk of bleeding complications following TKA is the use of tranexamic acid (TXA). TXA is a synthetic antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin[7]. TXA has been shown to decrease blood loss and the need for transfusion following TKA and total hip arthroplasty in highly selected populations, and it has been reported as safe without known risk factors for thromboembolic events[8-15].

To date, limited evidence is available regarding the safety and effectiveness of TXA in joint replacement surgery performed in patients receiving antiplatelet therapy and/or anticoagulants before the surgery. Hence, the majority of the clinical trials investigating the use of TXA in total joint arthroplasty have excluded patients under antithrombotic treatment prior to the operation because of methodological concerns or contraindications. Studies on the use of TXA in patients under antithrombotic treatment undergoing TKA surgery are lacking.

The current prospective study was performed to evaluate the effectiveness of TXA on reducing blood loss and morbidity following TKA surgery in patients under chronic antithrombotic treatment prior to surgery. This study was prompted by the patient blood management programme implemented in our clinic in 2005, which instituted the use of TXA instead of blood salvage systems (autologous blood transfusion) during primary total hip arthroplasty and TKA[16]. The impact of this clinical policy was reported in a prospective observational study including (not excluding) patients who were regular users of antithrombotic agents since: (i) they represent, in routine clinical practice, a non-negligible part of the elderly population undergoing total joint arthroplasty, and (ii) they should benefit most from the haemostatic properties of TXA because antithrombotic treatment is a major risk factor for bleeding. We hypothesised that the use of TXA would decrease the blood loss and morbidity in patients on long-term antithrombotic treatment undergoing TKA. We also wanted to determine the demographics of the population of patients under antithrombotic treatment undergoing TKA in our unit.

Table I - Baseline characteristics of the ATT+ and ATT− groups.

	ATT− group (n=256)	ATT+ group (n=129)	p-value
Age at surgery (years)[a]	70.8 (8.7)	75.6 (6.9)	<0.001
Female (%)	180 (70.3)	71 (55.0)	0.003
Weight (kg)[a]	84.3 (15.5)	85.3 (17.1)	0.551
Body mass index (kg/m^2)[a]	31.7 (5.9)	32.0 (6.2)	0.648
ASA score[a]	2.0 (0.4)	2.4 (0.5)	<0.001
Pre-operative Hb (g/dL)[a]	13.7 (1.2)	13.8 (1.2)	0.427
Pre-operative Hct (vol %)[a]	41.2 (3.3)	41.9 (3.4)	0.077
Pre-operative EPO (n)[b]	28 (10.9)	16 (12.4)	0.670
Duration of surgery (minutes)[a]	67.0 (10.6)	65.5 (11.3)	0.198
TXA administered[b]	234 (91.4)	80 (62.0)	< 0.001

[a]Presented as mean (standard deviation); [b]Presented as a number (percentage). ATT: antithrombotic therapy; ASA: American Society of Anesthesiologists; Hb: haemoglobin; Hct: haematocrit; EPO: erythropoietin; TXA: tranexamic acid.

Material and methods

An observational, non-interventional prospective study was performed in consecutive patients undergoing elective TKA under general anaesthesia. From June 2009 until March 2014, 385 TKA were performed in our centre by a single surgeon (HH). All patients received posterior stabilised TKA with either fixed or mobile surface bearings through a standardised medial parapatellar approach and with the use of a patient blood management programme. Revision TKA, partial knee arthroplasty, hinge prostheses, and bilateral one-stage TKA and TKA performed in the context of a recent trauma (e.g., fracture around the knee) were excluded. The cohort of TKA was divided into two groups in relation to whether the patients were regularly taking oral antithrombotic treatment, including antiplatelet agents and/or anticoagulant agents taken in the 2 months prior to the operation (ATT+ group) or were not taking such drugs (ATT− group). Table I lists the patients' baseline characteristics.

TXA IV (Exacyl, Sanofi, Paris, France; 500 mg/5 mL) was administered to 234 patients (91.4%) in the ATT− group and to 80 patients (62.0%) in the ATT+ group. TXA administration was routine clinical practice after the induction of general anaesthesia with an individual dose of 30 mg/kg based on patient body weight[17]. The venous solution was administered slowly over 5 to 10 minutes via a minibag of 0.9% saline prepared in the operating theatre by a nurse or by the anaesthetist in charge of the operation. The decision not to administer intravenous TXA was made by the anaesthetist on the basis of the presence of any contraindications to TXA. TXA was given to patients deemed at risk of requiring post-operative blood transfusion. Contraindications were a venous or arterial thromboembolic event in the preceding 3 months, a history of epilepsy, and severe renal insufficiency defined as an estimated urinary glomerular filtration rate <30 mL/minute, using the Modification of Diet in Renal Disease formula[18].

Study population

The series comprised 385 unilateral TKA operations in 364 patients. Primary osteoarthritis was the reason for TKA in most patients in this study. There were no cases of TKA performed due to sequelae of pyogenic arthritis of the knee.

Peri-operative protocols

Peri-procedural protocols included the detection and management of pre-operative anaemia, standard antibiotic regimens, and multimodal pain management. The peri-procedural strategy for antithrombotic management was as follows:

- patients taking antithrombotic agents were instructed to suspend their antithrombotic treatment throughout the pre-procedural period of 3 to 7 days. A specific time was designated for each drug (rivaroxaban, 3 days; vitamin K antagonist [VKA], dabigatran or aspirin, 5 days; clopidogrel, 7 days);
- continued anticoagulant therapy with parenteral heparins in 10 patients who had been taking VKA.

In all of these patients with a pre-operative bridge of VKA to low molecular weight heparin (LMWH), the last injection of LMWH was administered approximately 24 hours before the procedure.

Pharmacological venous thromboprophylaxis was initiated 6 to 10 hours after the wound closure. Most patients received 10 mg of rivaroxaban once daily. In patients with non-valvular atrial fibrillation aged <80 years with an estimated glomerular filtration rate >50 mL/minute and a body weight ≥60 kg, the dose was increased to 15 or 20 mg once daily after 1 week. In patients with a mechanical heart valve, LMWH was re-initiated post-operatively at an intermediate therapeutic dose. Antiplatelet therapy and VKA anticoagulants were not resumed during the early post-operative period.

Anaesthesia, surgical procedures and patients' care

All patients were seen in the clinic 3 to 6 weeks before their operation, when intra-operative and blood conservation information was shared with the patient, and the patient's consent was acquired. Anaemic patients with Hb levels <12 g/dL for females and <13 g/dL for males were prescribed oral elemental iron supplementation (Tardyferon, Pierre Fabre Pharma, Paris, France) at a dose of 240 mg once daily for 2 weeks along with two injections of epoetin alpha 40,000 IU (EPREX, Janssen-Cilag, Issy-les-Moulineaux, France) once a week for 2 weeks before surgery. Patients using non-steroidal anti-inflammatory drugs were instructed to switch to acetaminophen and/or tramadol if analgesia was needed within 10 days prior to surgery. Patients were admitted to the clinic 1 day before surgery. Blood samples were collected on admission to the clinic to check the Hb levels and international normalised ratio in patients on pre-operative anticoagulant treatment prior to the operation. In addition, an arterial Doppler examination of the lower limbs was performed 1 day before the operation to evaluate the peripheral arterial status of the lower limbs, to exclude the presence of popliteal aneurysms, and to anticipate safety regarding the use of a tourniquet.

Procedures were performed under general anaesthesia with standardised techniques and monitoring. Hypotensive anaesthesia was not used. Before anaesthesia, a single-shot ultrasound-guided sciatic nerve block was performed and a catheter was inserted in the inguinal region along the femoral nerve for post-operative analgesia. All the operations were performed by an experienced, high-volume orthopaedic surgeon using a standardised surgical technique consisting of standard open procedures with excision of both cruciate ligaments.

TKA was performed in a bloodless field provided by a tourniquet inflated at 250 mmHg after limb elevation following skin preparation and surgical draping. Exsanguination by elastic bandaging was not used. The tourniquet was released after the cementing of prosthesis components had been completed. A posterior-stabilized cemented knee design was used in all cases. Patellar resurfacing was performed at the surgeon's discretion. After deflation of the tourniquet, surgical haemostasis was achieved by standard electrocautery of the bleeding points and vessels prior to closure of the wound. A lateral retinacular release was completed whenever continuous symmetric patellar facet contact with the trochlear groove from 0° to 90° of flexion was not obtained using the rule of no thumb technique. No blood salvage system was used and only one superficial drain was inserted and removed on the morning of the first day after the operation.

Post-operative anaemia was investigated on days 1 and 7 by measuring Hb levels from blood samples. Transfusion protocols were standardised. The local transfusion protocol stipulated that patients with a post-operative Hb level <8.0 g/dL received transfusion. Patients with a post-operative Hb level between 8 and 10 g/dL were only given a transfusion if they had relevant symptoms and a history of ischaemic heart disease, and those with a Hb level >10 g/dL were not given a transfusion.

Non-steroidal anti-inflammatory drugs were stopped 1 week before surgery and used sparingly with a proton pump inhibitor for gastric protection during the post-operative period. No mechanical pumps were used for the prevention of venous thromboembolism. All patients underwent Doppler ultrasound of both lower limbs 7 days after surgery, or sooner if there was any clinical suspicion of deep vein thrombosis. All patients at risk of cardiovascular complications were post-operatively monitored for troponin elevation. Computed tomography scans were performed in the case of suspicion of pulmonary embolism. International Knee Society scores[19] were calculated pre-operatively and at the 6-week and 12-month follow-ups.

Complications were defined as haematoma formation requiring specific measures (such as reduced passive motion exercises, prolonged duration of hospitalisation and evacuation), repeat surgery, delayed wound healing (defined as persistent wound draining beyond the third week after surgery), infection, and stiffness with <70° of flexion more than 4 weeks after the operation requiring manipulation under general anaesthesia.

The primary efficacy outcome was bleeding as evaluated by a bleeding index (BI), calculated for each patient by measuring the drop in Hb level (g/dL) between post-operative days 1 and 7, and adding the number of packed red blood cells transfused within the same period, assuming that transfusion of one packed red blood cell unit raises the level of Hb by 1 g/dL[17,20].

The primary safety outcome was the incidence of death, perioperative myocardial infarction, cerebrovascular accident, symptomatic pulmonary embolism and proximal deep vein thrombosis up to day 60 after surgery.

All patients provided inform consent. In accordance with French law, ethics committee approval was not obtained, as the study was purely observational, with no changes to standard clinical practice.

Statistical analysis

Baseline data are presented as mean ± standard deviation for continuous variables and as counts and percentages for categorical variables. Univariate analysis was performed using the chi-squared test or Fisher's exact test for categorical variables, and the Student's *t*-test for continuous variables. Multiple linear regression was used to compare groups with regards to the BI outcome, with the potentially confounding baseline variables of age, sex, and American Society of Anesthesiologists (ASA) scores which were added as control variables in the model. Treatment comparisons for longitudinal data were analysed using mixed linear models. We included time as a linear spline in the model and estimated separate intercepts and time terms for each group. Random effects were included for each technique and the time term. Wald tests were used to evaluate differences in outcome for each single time point. Two-tailed tests were used throughout the analysis. The level of statistical significance was set at $p<0.05$. All statistical analyses were carried out using Stata 12.1 (StataCorp, College Station, TX, USA).

Results

One hundred and twenty-nine patients (33.5%) were regular users of antithrombotic treatment prior to surgery. Patients under antithrombotic treatment before undergoing TKA were older and had more comorbidities than patients not regularly using antithrombotic agents, as reflected by the mean ASA score. No other differences were found in terms of baseline characteristics. Among patients receiving antithrombotic treatment, the most common therapy was antiplatelet treatment alone (aspirin only, n=79; clopidogrel only, n=13), followed by VKA (fluidione, n=25; warfarin, n=3), dual antiplatelet therapy (aspirin + clopidogrel, n=6), and novel oral anticoagulants (dabigatran, n=2; rivaroxaban, n=1). Seven patients were receiving a combined regimen of antithrombotic drugs.

The overall mean BI was 3.0 (95% CI, 2.9 to 3.1). TXA was associated with a significantly lower BI among ATT− patients (p=0.001) and among ATT+ patients (p<0.001; Table II). TXA was equally effective in ATT− and ATT+ patients (difference, 0.5; 95% CI, −0.1 to 1.1, p=0.101). Among patients who received pre-

Table II - Comparison of BI, thromboembolic events, complications, and additional procedures following primary TKA in the ATT+ and ATT− groups.

	ATT− group (n=256)	ATT+ group (n=129)	p-value
Bleeding Index (adjusted)[a]			
TXA+	2.8 (2.7-3.0)	2.6 (2.4-2.8)	0.126
TXA−	3.6 (3.2-4.1)	3.9 (3.6-4.3)	0.291
p-value	0.001	<0.001	
Complications[b]			
TXA+			
Total	14	7	0.392
Wound healing disturbance	4	4	
Transient ischaemic attack	1	0	
Haematoma	5	2	
Insert luxation	1	0	
Mobilisation	2	0	
Sepsis	1	1	
TXA−			
Total	5	4	0.124
Proximal DVT/PE	1/0	0/0	
Haematoma	3	4	
Wound healing disturbance	1	0	

[a]Presented as mean (standard deviation); [b]presented as a number. ATT: antithrombotic therapy; DVT: deep vein thrombosis; PE: pulmonary embolism; TXA: tranexamic acid.

operative bridging therapy, univariate analysis revealed differences in BI between patients who received TXA (n=6; mean, 2.6; 95% CI, 1.3 to 3.8) and those who did not receive TXA (n=4; mean, 4.4; 95% CI, 3.2 to 5.6; p=0.032).

In the overall study population, two patients in the ATT− group and one patient in the ATT+ group required transfusion (p=1.00).

No significant differences in Hb concentrations were observed and there were no consistent differences in haematocrit between the ATT+ and ATT− groups (Table III). Significantly higher Hb and haematocrit values were found in the TXA+ groups 7 days after surgery.

No patients in the ATT+ group were lost to follow-up, and only one patient in the ATT− group was lost to follow-up before 2 months postoperatively. Complications in the ATT+ group consisted of haematomas (n=6), delayed wound healing (n=4), and sepsis (n=1), whereas complications in the ATT− group consisted of haematoma (n=8), delayed wound healing (n=5), stiffness (n=2), sepsis (n=1), asymptomatic proximal deep vein thrombosis (n=1), and a transient ischaemic attack occurring 4 days after surgery. No additional procedures were performed in the ATT+ group, whereas four additional procedures were performed in the ATT− group (2 wound leakages related to early post-operative falls and 2 knee manipulations under anaesthesia). In total, three patients (1 in the ATT+ group, 2 in the ATT− group) died within 1 year after surgery. One death of an 86-year old male patient can be linked to sepsis, the two other deaths were unrelated to the surgical intervention. TXA was well tolerated in both study groups. No adverse events due to the administration of TXA were identified. No incident thromboembolic complications were identified in the subgroup of patients under preoperative antithrombotic treatment who received intraoperative tranexamic acid. No consistent significant differences in International Knee Society score over time were found (Table IV).

Discussion

The present study found that TXA reduces blood loss in patients who are regular users of antithrombotics. No increase in complication rate, including incident

Table III - Comparison of haemoglobin and haematocrit values.

	Time point	ATT− group (n=256)	ATT+ group (n=129)	p-value
Haemoglobin	*Pre-operative*			
	TXA+	13.8 (13.7-14.0)	13.7 (13.5-14.0)	0.427
	TXA−	13.9 (13.4-14.3)	14.3 (14.0-14.6)	0.086
	p-value	0.966	0.003	
	1 day			
	TXA+	12.2 (12.0-12.3)	12.2 (11.9-12.4)	0.871
	TXA−	11.6 (11.2-12.0)	12.0 (11.7-12.3)	0.189
	p-value	0.015	0.387	
	7 days			
	TXA+	11.0 (10.9-11.2)	11.1 (10.9-11.4)	0.495
	TXA−	10.3 (9.8-10.8)	10.3 (10.0-10.7)	0.864
	p-value	0.004	<0.001	
Haematocrit	*Pre-operative*			
	TXA+	41.2 (40.8-41.7)	41.2 (40.5-41.9)	0.884
	TXA−	41.1 (39.8-42.4)	43.0 (42.0-33.0)	0.026
	p-value	0.917	0.002	
	1 day			
	TXA+	36.3 (35.9-36.7)	36.2 (35.6-36.9)	0.874
	TXA−	34.5 (33.2-35.8)	36.2 (35.1-37.2)	0.048
	p-value	0.008	0.907	
	7 days			
	TXA+	33.0 (32.5-33.5)	33.2 (32.3-34.0)	0.720
	TXA−	30.5 (28.9-32.1)	31.3 (30.2-32.5)	0.396
	p-value	0.003	0.012	

ATT: antithrombotic therapy; TXA: tranexamic acid.

Table IV - Clinical outcome.

	Time point	ATT− group (n=256)	ATT+ group (n=129)	p-value
Knee score	*Pre-operative*			
	TXA+	26.7 (24.9-28.6)	24.5 (21.3-27.6)	0.234
	TXA−	28.5 (22.6-34.4)	26.8 (22.5-31.2)	0.662
	p-value	0.575	0.376	
	6 weeks			
	TXA+	83.2 (81.4-85.1)	78.2 (75.0-81.4)	0.008
	TXA−	81.7 (75.8-87.6)	78.8 (74.5-83.2)	0.450
	p-value	0.620	0.815	
	1 year			
	TXA+	93.0 (90.4-95.7)	90.5 (85.7-95.2)	0.351
	TXA−	93.8 (86.1-101.5)	86.2 (79.1-93.4)	0.159
	p-value	0.855	0.332	
Function score	*Pre-operative*			
	TXA+	45.8 (43.8-47.9)	42.2 (38.0-46.3)	0.126
	TXA−	41.8 (35.6-48.0)	38.0 (32.7-43.2)	0.361
	p-value	0.223	0.208	
	6 weeks			
	TXA+	65.6 (63.5-67.8)	65.0 (60.8-69.2)	0.819
	TXA−	65.9 (59.7-72.1)	62.6 (57.4-67.8)	0.439
	p-value	0.932	0.476	
	1 year			
	TXA+	78.0 (75.2-80.8)	76.3 (70.0-82.7)	0.645
	TXA−	73.5 (65.6-81.4)	73.9 (67.5-80.4)	0.938
	p-value	0.296	0.596	

ATT: antithrombotic therapy; TXA: tranexamic acid.

thrombotic events and haematomas, was identified in patients under antithrombotic treatment who received TXA during TKA surgery. Although the decrease in BI among patients who received TXA during surgery was greater than in those who did not in the ATT+ group (1.3 *vs* 0.8), the difference was not statistically significant (p=0.101), and the data do not, therefore, support the claim that ATT− patients benefit more from the haemostatic properties of TXA than do ATT+ patients.

Others have already reported that TXA is safe for use in patients with severe comorbidities and at risk of thrombosis during total joint arthroplasty[21,22]. To the best of our knowledge, this is the first prospective study to compare the efficacy and safety of TXA during primary total knee replacement in regular users of antithrombotic agents and patients who have never taken antithrombotic therapy or have used antithrombotics irregularly.

TKA *per se* is considered a procedure at high risk of bleeding[6]. Both risks are increased in patients on chronic antithrombotic treatment because of inherent impairment of coagulation/haemostasis, medical comorbidities, and older age. Elderly patients have multi-organ changes, increased risks of bleeding and ischaemic events, frequent comorbidities and are very often taking multiple medications.

Since antithrombotic treatment is a major risk factor for bleeding, patients who regularly use antithrombotic treatment should benefit more from the use of TXA during TKA to reduce bleeding complications and transfusion requirements.

In the present study, no study participant who received TXA in the ATT+ group required a blood transfusion during the first post-operative week. This result can be explained by the blood management programme applied, which included identification and management of pre-operative anaemia, pre-operative optimisation of Hb levels using erythropoietin plus iron supplementation if baseline Hb levels were ≤12 g/dL in women and ≤13 g/dL in men; the use of a tourniquet; surgical haemostasis consisting of electrocoagulation of all possible bleeding points and vessels after deflation of the tourniquet; limited synovectomy; and limited

use of a drain. The result can also be explained by the peri-procedural management strategy of antithrombotic drugs applied, including the interruption of antiplatelet therapy and oral anticoagulation before the operation and forgoing the use of heparin at an intermediate or high dose in the early post-operative course (in patients with non-valvular atrial fibrillation), the use of anticoagulation with rivaroxaban, given at a prophylactic dose of 10 mg once daily during the early post-operative course, and also by the demographic characteristics of the study participants who had an elevated baseline erythrocyte mass (reflected by baseline Hb concentration) in association with an elevated estimated blood volume (reflected by the mean body mass index). A third explanation could be the surgical technique performed by an expert surgeon, since blood loss varies between surgeons.

Our study showed that post-operative Hb and haematocrit levels were significantly higher when TXA was used. So far, we believe that reducing blood loss lowers the risk of reaching the transfusion triggers and, therefore, of being transfused following TKA.

Besides the risk of bleeding, TKA is a procedure that carries a high risk of venous thrombosis. The use of a prophylactic dose of parenteral or oral anticoagulant for a period of 14 days is recommended following surgery in patients at risk of thrombosis[23,24]. Patients on continuous anticoagulation therapy undergoing TKA are *a priori* at a high risk of thrombosis following TKA. The use of continuous anticoagulation in the post-operative period is, therefore, a foremost standard of care. However, the ideal anticoagulant drug, dose, and time of initiation/re-initiation for post-operative immediate anticoagulation is debatable because of the risk of bleeding complications.

The administration of heparin and LMWH at a therapeutic or intermediate dose has long been the standard of care for the peri-operative management of patients receiving VKA as anticoagulation treatment, but its usefulness and safety has been questioned in total joint arthroplasties since previous studies reported an alarmingly high rate of bleeding complications when heparin is used at intermediate or therapeutic doses following TKA[25-27].

A premature re-initiation of heparin is an avoidable provider-specific variable for bleeding complications[28]. The 2012 American College of Chest Physicians Antithrombotic Guidelines for the peri-operative management of anticoagulation recommended re-initiating heparin 48 to 72 hours after closure of the wound[23]. A previous single-centre study found that, compared to bridging therapy, the continuation of warfarin represents a reliable strategy in patients on continuous anticoagulation therapy undergoing TKA[29].

In the current series, ten patients on VKA anticoagulant therapy before the operation were pre-operatively given bridging treatment with LMWH, following the instructions of either the general practitioner, cardiologist or anaesthesiologist. However, we did not re-initiate heparin or LMWH at therapeutic or intermediate doses in the early post-operative period, unless patients had mechanical cardiac valve disorders or a contraindication to the use of factor Xa inhibitors.

The anticoagulant that most patients in both study groups received was a direct-acting factor Xa inhibitor, rivaroxaban 10 mg/kg, initiated 6 to 10 hours after the end of the operation. We believe that the peri-operative management of antithrombotic treatment may be improved by oral direct-acting agents with fewer side effects and off-target effects and reduced burden of administration. Rivaroxaban is the first drug in the class of direct inhibitors of factor Xa to reach the market. It is designed to be administered orally at a fixed dose of 10 mg, once a day for the prevention of venous thromboembolism following elective knee or hip replacement surgery and at a dose of 15 to 20 mg once a day for a reduction in the risk of stroke or systemic embolism in patients with non-valvular atrial fibrillation. The preliminary results of this independent prospective study support the use of rivaroxaban as a stand-alone post-operative chemoprophylactic antithrombotic treatment in the peri-procedural management of patients undergoing TKA.

In this study, aspirin or clopidrogel was stopped 5 or 7 days, respectively, before the operation. It has been suggested that pre-operative discontinuation of aspirin results in an increased risk of thrombosis. However, among the 4,382 patients undergoing non-cardiac surgery in the continuation stratum arm of the POISE 2 randomised clinical trial, no increase in thrombotic events was found as a result of withholding aspirin throughout the entire post-operative period of 7 days[30].

In the present series, aspirin and clopidogrel were not resumed during the immediate post-operative period to prevent the risk of bleeding complications. We considered the concomitant use of aspirin with rivaroxaban could increase the risk of bleeding complications because such an association increases the bleeding time considerably.

In this study, TXA was given as a single 30-mg/kg bodyweight dose, injected intravenously. This regimen has some clinical advantages as it is simpler to administer, rapid, less cumbersome to manage for the nurses, cheaper than a continuous or repeat bolus regimen, and avoids TXA accumulation in the case of post-operative renal dysfunction with a low glomerular filtration rate[17,31].

This study has some limitations. Firstly, a selection bias may have affected which patients received TXA and which patients did not. TXA was used at the discretion of the anaesthetist in charge of each operation. Second, anaesthesia was given by a team of three independent anaesthesiologists not solely dedicated to orthopaedic surgery. The team created variability in the use of TXA because of different opinions regarding the indications and contraindications for the use of TXA. Thirdly, the bridging group was too small to allow for meaningful comparisons. Another limitation of this study is that it is underpowered to yield and accurate assessment of the effect of TXA on thromboembolic events. However, we were able to carry out a sensible study, which is useful even on a small scale given the clinical importance of the topic. Importantly, this study adds incremental evidence for the safety of prophylactic intravenous use of TXA in patients who are regular users of antithrombotic agents before surgery. Finally, all observational studies have some unmeasured, unknown, and confounding factors, and multivariable analyses may, perversely, confound other unmeasured factors. Multivariable analysis cannot, therefore, completely overcome the limitations of observational studies. The results of the present study must, therefore, be interpreted with caution.

Conclusions

Prophylactic administration of TXA is a fast, inexpensive, effective, and safe means to improve the outcomes following TKA surgery in patients who regularly use antithrombotic agents.

In the context of a patient blood management programme implemented with routine anticoagulation with rivaroxaban for the prevention of thromboembolism, a single, intravenously administered, loading-dose of TXA provides the desirable reduction in the risk of reaching the transfusion trigger without an increased risk of thromboembolic complications. Larger scale studies are, however, necessary to substantiate or refute these findings.

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Authorship contributions

HH designed the study and performed the measurements. HH and PF analysed the data. HH and PF and wrote the paper. Both Authors approved the final version of the manuscript.

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