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Duration of Postoperative Fibrinolysis after Total Hip or Knee Replacement: A Laboratory Follow-up Study

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ABSTRACT

Introduction: Hyperfibrinolysis is observed during and immediately after major orthopedic surgery. The kinetics and duration of this phase should be defined to adjust the duration of antifibrinolytic treatment with tranexamic acid (TXA).
Objective: We aimed to quantify the duration of postoperative fibrinolysis and to assess the biological impact of TXA administration.
Materials and Methods: Fourteen patients undergoing total hip replacement (THR) and 10 patients undergoing total knee replacement (TKR) with tourniquet were included in an observational, prospective, single-center study. Among these patients, 7 THR patients and 5 TKR patients received TXA (15 mg/kg IV intraoperatively, followed by continuous infusion of 15 mg/kg/h until end of surgery, then every 4 hours until 16±2 hours after surgery). D-dimers, euglobulin lysis time (ELT), and thrombin generation time (TGT) were measured prior to surgery as well as 6, 18 and 24 hours (H) after.
Results: No significant difference in ELT was observed between the groups. In contrast, D-dimers significantly increased postoperatively in patients not treated with TXA ($p<0.001$), while such an increase was prevented in patients receiving TXA, as measured at H0, H6, H18 and H24 after THR, and at H6 and H18 after TKR ($p<0.001$). No significant between-group change in TGT, was observed (peak thrombin and endogenous thrombin potential) all along the study.
Conclusion: This study shows that fibrinolysis peaked 6 hours after end of surgery and maintained about 18 hours after surgery, as evidenced by an increase in D-dimers. When administered for up to 16±2 hours after surgery, TXA reduced postoperative fibrinolysis.

Introduction

A hyperfibrinolytic phase, leading to increase bleeding is observed during and immediately after major orthopedic surgery. In the wake of stimuli such as vascular hypoxia, hypotension, or cytokine circulation, the endothelium releases tissue plasminogen activator, which in turn catalyzes the conversion of plasminogen to plasmin, resulting in the breakdown of fibrin and the destruction of blood clots [1]. Postoperative fibrinolysis may vary in duration and intensity depending on surgery type and whether a tourniquet is applied. Eriksson *et al.* showed that in 10 cases of total hip replacement (THR), fibrinolysis activation began at implantation [2,3]. After total knee replacement (TKR), the rate of fibrinolysis was higher with tourniquet and peaked after tourniquet release [4,5]. Fibrinolysis in THR and TKR appears to decrease after day (D) 2 following surgery [2,5–8]. The exact kinetics of fibrinolysis in such interventions nonetheless requires further investigation.

Tranexamic acid (TXA) is a synthetic lysine analog and acts as an antifibrinolytic agent. It binds reversibly to the lysine binding site of plasminogen, inhibiting the binding to fibrin and the activation to plasmin. Its efficacy in limiting blood loss and transfusion after THR and TKR has been thoroughly demonstrated by several meta-analyses [9–13]. However, at this time, current guidelines do not recommend using TXA during THR and TKR, even if it is widely used because, optimal dosage and duration of treatment remain unknown. A bolus of 15 mg/kg appears to be sufficient and is most commonly used [10]. The few studies that have addressed postoperative fibrinolysis and the very short half-life of TXA (about 2 hours) stated that prolonged administration of TXA might further decrease blood loss after major orthopedic surgery [14]. Blood loss has been shown to be essentially postoperative, with 2/3 occurring postoperatively after THR and 4/5 after TKR with tourniquet [13,15]. Single intraoperative administration of TXA has demonstrated less efficacy in limiting blood loss and transfusion than prolonged

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administration (10 mg/kg intraoperatively, then at hour (H) 3 after surgery) [15,16]. Therefore, it seems appropriate to prolong TXA administration postoperatively in this type of surgery.

Notwithstanding the above, venous thromboembolic events have also been observed immediately after major orthopedic surgery [6,8], and TXA might increase this risk. Some studies have sought to measure biomarkers of fibrinolysis and coagulation perioperatively in major orthopedic surgery. Reduced fibrinolytic marker activity may be associated with increased thrombotic risk [2,17], but studies of TKR with tourniquet show conflicting results as to the effects of TXA on coagulation markers [18–20]. In clinical practice, various meta-analyses of TXA in orthopedic surgery have shown no increase in thrombotic or thromboembolic risk [10,11,21,22].

Intraoperative TXA infusion sustained for up to 16 hours postoperatively may help limit blood loss and transfusion needs, as shown by preliminary studies [14–16]. Before the initiation of any randomized trials, the exact kinetics of postoperative fibrinolysis had to be further explored so as to determine the appropriate duration of antifibrinolytic TXA treatment without increasing the risk of thrombotic events. The objectives of this investigation were to quantify the duration of postoperative fibrinolysis and assess the impact of TXA administration after THR and TKR through a follow-up pilot laboratory study.

Materials and Methods

Patients and Study Design

This prospective observational study was performed in the orthopedic surgery unit of Cochin-Hôtel Dieu Hospital. Following the National regulations for this kind of observational study, Internal Review Board approval was not necessary. However, patients were informed during preoperative visits, and a signed informed consent was obtained.

A total of 14 patients undergoing THR and 10 patients undergoing TKR with tourniquet were included. The exclusion criteria were refusal to participate, arterial or venous thrombotic history, anticoagulant therapy, aspirin or clopidogrel intake, coagulopathy, preoperative bed rest >24 h, acute sepsis, renal failure (creatinine clearance <50 ml/min) and history of seizures.

TXA is a validated therapeutic agent for the limitation of blood loss and transfusion needs following THR or TKR [10], but at this time, it is not systematically recommended. For this reason, the decision to administer TXA was left up to the attending anesthesiologist. When used, TXA was administered as an intravenous bolus of 15 mg/kg (over a period of 30 minutes) intraoperatively, followed by a continuous infusion of 15 mg/kg/h until end of surgery, then every 4 hours until 16±2 hours after surgery. The initial intraoperative infusion was begun at induction in THR and 30 minutes prior to tourniquet release (during cementing of the prosthesis) in TKR.

Patients undergoing THR were assigned to either the *THR* group (THR without TXA) or the *THR-TXA* group (THR with TXA). Patients undergoing TKR with tourniquet were assigned to either the *TKR* group (TKR without TXA) or the *TKR-TXA* group (TKR with TXA).

Laboratory Haemostasis Testing

Haemostasis testing was performed as part of systematic laboratory assessments for haemoglobin monitoring, preoperatively and postoperatively, as necessary in all patients undergoing major orthopedic surgery. Venous samples were collected from patients' upper limbs into 5 ml citrated tubes (trisodium citrate, 0.129 mM).

Euglobulin lysis time (ELT) was analyzed over a 6-hour period (normal >180 min). D-dimers (DDE) were analyzed using the ELISA method (miniVIDAS, BioMérieux, normal <500 ng/mL). Thrombin generation time measurements in the presence of 5 nM tissue factor and w/o thrombomodulin (CAT technique, Diagnostica Stago) included peak thrombin (nM of thrombin) and endogenous thrombin potential (nM of thrombin.min). So as to overcome inter-individual variability in this small patient population, delta values for peak thrombin were defined by taking the H6 or H18 values minus preoperative values (yielding Delta peak H6-preop and Delta peak H18-preop, respectively).

Measurements were performed prior to surgery, during surgery (10 minutes after hip reduction or tourniquet release) and 6, 18 and 24 hours after surgery (respectively: *preop, H0, H6, H18* and *H24*).

Data Collection

The following data were recorded for all patients: age, body mass index (BMI, kg/cm^2), gender, medical history, preoperative erythropoietin administration, duration of surgery, limb ischemia time (duration of tourniquet use or hip luxation in min), preoperative and postoperative administration of volume expanders (mL/kg), transfusion, preoperative and postoperative hemoglobin levels (g/dL), intra- and postoperative total TXA dosage (g), non-steroidal anti-inflammatory agents, postoperative anticoagulation, temperature at end of surgery (°C), arterial or venous complications, and infectious complications.

This observational study entailed no modifications to treatment. No additional invasive interventions were required because all measurements were performed during systematic preoperative and postoperative laboratory analyses.

Statistical Analysis

Continuous variables were reported as medians with 25%-75% interquartile ranges (IQR), and categorical variables as percentages (95% confidence interval).

Table 1
Clinical or laboratory data between *THR* (n=7) and *THR-TXA* (n=7) and between *TKR* (n=5) and *TKR-TXA* (n=5) preoperatively.

	THR n=7	THR-TXA n=7	*p*	TKR n=5	TKR-TXA n=5	*p*
Age, (years)	57 [52-65]	59 [51-66]	0.751	72 [65-82.5]	64 [63-67]	0.054
Women (n)	3	4	1	5	4	1
BMI (kg/cm^2)	25 [20-28]	26 [24-28]	0.903	28 [22.5-30]	27 [23-30]	0.754
Creatinin clearance (mL/min)	98 [71-106]	80 [70-94]	0.312	70 [54.5-91]	101 [79.5-113]	0.173
Medical history						
Arterial hypertension (n)	1	3		3	3	1
Diabetes (n)	0	2		1	0	1
Rheumatoid arthritis (n)	1	0		0	0	
Sleep apnoea syndrome (n)	1	0		0	0	
Preoperative non-steroid anti-inflammatory (n)	0	1	1	0	1	1
Preoperative erythropoietin administration (n)	2	2	1	1	2	1
Preoperative hemoglobin level (g/dL)	14.1 [12.9-15.7]	14,3 [13.4-15.8]	0.949	12.7 [12.5-13.6]	12.1 [10.9-14.6]	0.465

The continuous variables were described by median [interquartile range] and the categorical variables by number or percentage [confidence interval at 95%].