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Bleeding Kinetics after Total Hip or Knee Replacement: A Prospective Observational Study

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Abstract

Background and objectives: The objective was to assess the kinetics of postoperative bleeding after total hip or knee replacement, with or without administration of tranexamic acid, in order to anticipate red blood cell transfusion thresholds in the recovery room.

Materials and methods: This was a prospective, observational, single-center study. All patients undergoing primary or revision total hip or knee replacement were enrolled for two months. Patients were managed using a multimodal strategy designed to reduce the need for red blood cell transfusion. Postoperative bleeding kinetics was assessed according to the drop of hemoglobin levels between the arrival in the recovery room and day one after surgery.

Results: A total of 106 patients were included. The mean transfusion rate was 18%. Nadir hemoglobin levels were observed on day + 2, and about 60% of bleeding occurred during the postoperative period, with a drop of 1.2 ± 0.2 g/dL between the recovery room and day one for patients receiving tranexamic acid, and 1.9 ± 0.2 g/dL for those not receiving tranexamic acid (p=0.018).

Discussion: In our center, the hemoglobin transfusion threshold in recovery room might be raised by 1 or 2 g/dL depending on whether tranexamic acid is used.

Keywords: Bleeding; Total hip replacement; Total knee replacement; Hemoglobin; Tranexamic acid

Introduction

A prior French survey [1] has shown that unappropriate perioperative time interval to transfusion was responsible for 88 deaths per year in France among a total of 419 deaths totally or partially related to anesthesia. This was mainly related to the management of transfusion, leading to myocardial ischemia or cardiovascular events. Orthopedic prosthetic surgery is known to entail some risk of hemorrhage during the intraoperative period as well as for the few first postoperative days. Such interventions use up to 8% of transfused red cell concentrates, and major orthopedic surgery is the main reason of transfusion after surgery [2]. Once back in the ward, patients no longer benefit from the same human and logistical resources available in the operating and recovery areas. Knowledge of postoperative bleeding kinetics is crucial for our ability to anticipate a drop in Hemoglobin (Hb) levels during the first few hours after surgery, and thus to decrease the morbidity and mortality rates associated with acute anemia.

It is necessary to keep in mind that perioperative homologous transfusion is independently associated with increased mortality [3,4], acute pulmonary oedemas [5], hospital-acquired infection [3], Acute Respiratory Distress Syndrome (ARDS) [6,7], and important additional costs [8]. As a result, strategies have been developed to reduce the need for red cell transfusion. Such measures include the implementation of "restrictive" transfusion thresholds, preoperative blood mass optimization (Iron and Erythropoietin use), perioperative blood salvage, and pharmacological interventions to reduce bleeding.

Restrictive transfusion strategies, which have been recommended in official guidelines [9], are those involving Hb thresholds between 7 g/dL (healthy subjects) and 8-9 g/dL (patients with cardiovascular history and no clinical or electrocardiographic signs of anemia). One key sentence nonetheless stands out: "transfusion should be adapted to bleeding flow so as to maintain Hb levels above the transfusion threshold". This means that either frequent Hb level monitoring or immediate Red Blood Cell (RBC) transfusion, therefore staff availability, is required, or bleeding kinetics must be known to anticipate a drop in Hb. All these parameters are essential to the establishment of appropriate transfusion thresholds for the first few days after surgery.

Therefore, a prospective observational study was conducted with the objective of assessing postoperative bleeding kinetics after primary or revision hip or knee replacement with or without Tranexamic Acid (TXA).

Materials and Methods

An observational prospective study was conducted in the orthopedics department of Cochin Hospital, Paris, over the course of a two-month period (October and November 2011). The objective was to include every patient operated for Total Hip Replacement (THR), Total Knee Replacement (TKR) and Revision Total Hip Replacement (RTHR). There was no need of approval of ethical committee in this only observational study without any modification of treatment. Patients were informed of the aim of the study.

Patients were managed using a multimodal strategy designed to reduce the need for RBC transfusion; preoperative blood mass optimization (iron and erythropoietin use), and pharmacological interventions to reduce bleeding. A resident and a senior physician

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sheet. Hb levels were recorded in the recovery room (estimated from two capillary Hb), and between D+1 and D+5 postoperatively (laboratory measures). Capillary Hb was measured using a HemoCue® Hb 201+ instrument (HemoCue AB, Angelholm, Sweden). In the ward, blood samples were collected in a EDTA (EthyleneDiamineTetraacetic Acid) tube, which were sent immediately to the haematology laboratory for Hb measurement by the ADVIA® 2120 (Siemens Medical Solutions Diagnostics, Zurich, Switzerland).

The primary endpoint was the mean variation in Hb levels between RR and D+1, typically used to assess postoperative bleeding depending on surgery type and treatment with TXA. Secondary endpoints included Hb level variation and bleeding, with comparison between one day prior to surgery (D-1) and nadir Hb levels, between D-1 and recovery room (RR), and between D+1 and nadir Hb levels, depending on surgery type and treatment with TXA. Blood loss was calculated using Mercuriali's formula [10], for a 35% haematocrit, based on total uncompensated RBC loss calculated according to changes in haematocrit level between D-1 and D+5, added with compensated RBC volume calculated, based on RBC received between D-1 and D+5. Estimated Blood Volume was calculated in relation to gender and body surface area.

Tranexamic acid (Exacyl®, Sanofi-Aventis, Paris, France) was administered systematically, except when contraindicated, namely in arteritis of the lower limbs, stroke, myocardial infarction, recent or unstable ischemic heart disease, unstable hypertension, and epilepsy or history of seizures. Knee surgery did not use any tourniquet. TXA (15 mg/kg) was administered at incision. For revision arthroplasty, TXA (15 mg/kg/h) was given intravenously from the second hour of surgery until end of surgery. In both cases, TXA was administered for 12 hours (h) after surgery at a dose of 1 g every 4 or 6 hours depending on creatinine clearance.

Fluid administration and perioperative blood salvage were left to the anesthesiologist's discretion.

Statistical tests were conducted using Excel® 2007 (Microsoft, Redmond, WA, USA) and JMP9® (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as mean ± standard deviation for patient characteristics; mean ± standard error for results, or median (interquartile range). Error bars represent standard error. Qualitative variable results are expressed as proportions. The sample is intended to be representative of the population of orthopedic prosthetic patients operated at Cochin Hospital. Observations are assumed to be independent, and data distribution in the population is assumed to be Gaussian. The standard deviation of the main endpoint is assumed constant across the different groups. Two parametric tests were used to analyze the main endpoint: one-way analysis of variance to compare Hb levels between RR and D+1 depending on surgery type, and an unpaired one-sided Student t-test to assess the effect of TXA. The null hypothesis was that Hb level variations between RR and D+1 were random, and that their means were the same across the whole study population. Given that there were two independent null hypotheses, the significance threshold was lowered to 0.025 so as to keep risk α to 0.05. Secondary endpoints were also analyzed with tests of variance and unpaired two-sided t-tests.

Results

One hundred and six patients were included in the study, accounting for 98% of patients operated for total hip or knee replacement during the enrollment period. Characteristics of patients are described, broken down by surgery type (Table 1) and by TXA administration (Table 2).

	Total	THR	TKR	RTHR
Number (n)	106	57	30	19
Gender (proportion of female %)	58	58	57	56
Age (years)	68 ± 12	67 ± 13	71 ± 9	70 ± 13
Comorbidities				
Body mass index (kg/m²)	27 ± 4	24 ± 4	28 ± 5	26 ± 4
Median ASA score (Q1;Q3)	2 (2;3)	2 (2;3)	2 (2;3)	2 (2;3)
Cardio-vascular disease history (%)	29	28	37	22
Antiplatelet agents at D-30 (%)	25	25	33	17
Anticoagulant agents at D-30 (%)	8	9	7	11
Hemoglobin level at D-1 (g/dL)	13.7 ± 1.2	13.9 ± 1.1	13.3 ± 1.0	13.6± 1.6
Perioperative period				
Tranexamic acid (%)	76	74	73	89
Intraoperative dose (mg/kg)	16 ± 15	15 ± 10	14 ± 9	47 ± 18
Dose per 24h (mg/kg/24h)	75 ± 25	71 ± 19	69 ± 20	102 ± 36
Fluids (intraoperative and RR, in mL)	2094 ± 747	2079 ± 646	1683 ± 549	2861± 782
Postoperative intravenous iron (%)	86	86	83	94
Transfusion				
Autologous transfusion (%)	0	0	0	0
Transfusion (between D0 et D+5, in %)	18	14	10	44
Number of transfused patients (n)	19	8	3	8
Median number of RBC units (Q1,Q3)	2 (2;2.5)	2 (1;2)	3 (2,5;4)	2 (2;2,75)
Mean Hb transfusional threshold (g/dL)	8.7 ± 1.1	8.8 ± 1.4	8.2 ± 1.0	8.8 ± 1.0

THR: Total Hip Replacement; TKR: Total Knee Replacement; RTHR: Revision Total Hip Replacement; ASA: American Society of Anesthesiology; RR: Recovery Room; RBC: Red Blood Cell; Hb: Hemoglobin

Table 1: Patient characteristics broken down by surgery type

For the main outcome variable (change in Hb level between RR and D+1), data from the whole study population indicates that there was a change of - 1.4 ± 0.2 g/dL (42% of their total perioperative Hb variation) (Figure 1A). TKR patients exhibited a change of -1.2 ± 0.2 g/dL (43% of their total perioperative Hb variation) (Figure 1B). THR patients exhibited a change of -1.5 ± 0.2 g/dL (47% of their total perioperative Hb variation) (Figure 1B). RTHR patients showed a change of -1.2 ± 0.6 g/dL, which amounted to 30% of their perioperative Hb variation (Figure 1B). The difference between the three groups was not significant (p=0.98).

The change in Hb level was -1.9 ± 0.2 g/dL for patients not receiving TXA, i.e. 48% of their perioperative Hb variation (Figure 1C). Patients receiving TXA showed a change of -1.2 ± 0.2 g/dL, representing 40% of their total perioperative Hb variation (Figure 1C). The difference between the two groups was significant (p=0.018).

Mean nadir Hb levels occurred at D+2 for TKR and THR, and at D+3 for RTHR (Figure 1B). Median total calculated bleeding (Figure 2) was 1099 mL (815; 1451) for TKR, 1219 mL (953; 1565) for THR, and 1771 mL (1536; 2520) for revision procedures. Between D-1 and nadir, Hb varied by -2.9 ± 0.2 g/dL in primary knee replacement, -3.2 ± 0.2 g/

	Without TXA	With TXA
Number (n)	25	81
Gender (proportion of female %)	60	57
Age (years)	73 ± 10	67 ± 12
Comorbidities		
Body mass index (kg/m²)	26 ± 4	27 ± 5
Median ASA score (Q1;Q3)	3 (3;3)	2 (2;2)
Cardio-vascular history (%)	80	14
Antiplatelet agents at D-30 (%)	44	20
Anticoagulant agents D-30 (%)	28	2
Hb D-1 (g/dL)	13.3 ± 1.1	13.4 ± 1.1
Type of surgery		
THR (%)	60	50
TKR (%)	32	29
RTHR (%)	8	21
Perioperative period		
Tranexamic acid		
Intraoperative dose (mg/kg)	0	17 ± 15
Dose per 24h (mg/kg/24h)	0	75 ± 25
Fluids (intraoperative and RR, in mL)	2140 ± 700	2080 ± 764
Postoperative intravenous iron (%)	80	87
Transfusion		
Allogeneic transfusion (between D0 et D+5, in %)	40	11
Number of transfused patients (n)	10	9
THR (%)	40	5
TKR (%)	25	5
RTHR (%)	100	38
Median number of RBC unit (Q1,Q3)	2 (2;3)	2 (2;2)
Mean Hb transfusional threshold (g/dL)	8.4 ± 1.3	9.1 ± 0.6

TXA: Tranexamic Acid; ASA: American Society of Anesthesiology; Hb: Hemoglobin; THR: Total Hip Replacement; TKR: Total Knee Replacement; RTHR: Revision Total Hip Replacement; RBC: Red Blood Cell

Table 2: Patient characteristics broken down by TXA vs. no TXA administration

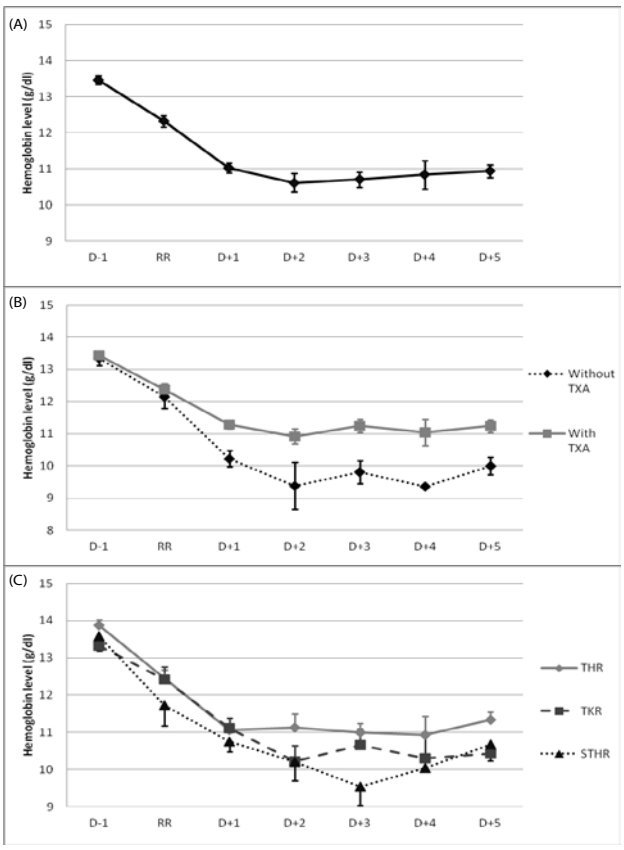

Figure 1: Changes in the Hb level between D-1 and D+5 for the entire sample, depending on intake of TXA and surgery type. Error bars represent standard error.

dL in primary hip replacement, and -3.9 ± 0.5 g/dL in secondary knee replacement.

Median total calculated bleeding was greater ($p < 0.001$) in patients without TXA (1513 mL [1151; 2518]) than with TXA (1219 mL [882; 1582]). Similarly, variations in Hb level between D-1 and nadir were greater (p=0.004) in patients who did not receive TXA (-4.0 ± 0.3 g/dL) than in those who did receive TXA (-3.1 ± 0.1 g/dL).

The difference in median calculated bleeding (Figure 3) depending on the use of TXA, was significant during the postoperative period, between RR and D+1 (506 mL *vs.* 824 mL; p=0.003) and between D+1 and nadir Hb levels (84 mL *vs.* 214 mL; p=0.002), but not during surgery (529 mL *vs.* 484 mL; p=0.81). Variations in Hb level depending on the use of TXA were significant between RR and D+1 (main endpoint), but not intraoperative (-1.1 g/dL *vs.* - 1.2 g/dL; p=0.59) or between D+1 and nadir (-0.4 g/dL *vs.* - 0.8 g/dL; p=0.15).

Aspirin was never discontinued (n=27) and there was no significant difference in term of median total calculated bleeding (1080 *vs.* 1083 mL, p=0.84) or transfusion need (26% *vs.* 15%, p=0.21) in these patients.

The mean Hb level used to justify homologous transfusion was 8.7 ±1.1 g/dL. 60% of patients were transfused at a threshold higher than 8 g/dL. The mean threshold value during surgery was 9.1 ± 0.3 g/dL, in the RR 9.5 ± 0.7 g/dL, and during post-recovery hospitalization 7.6 ± 1.1 g/dL.

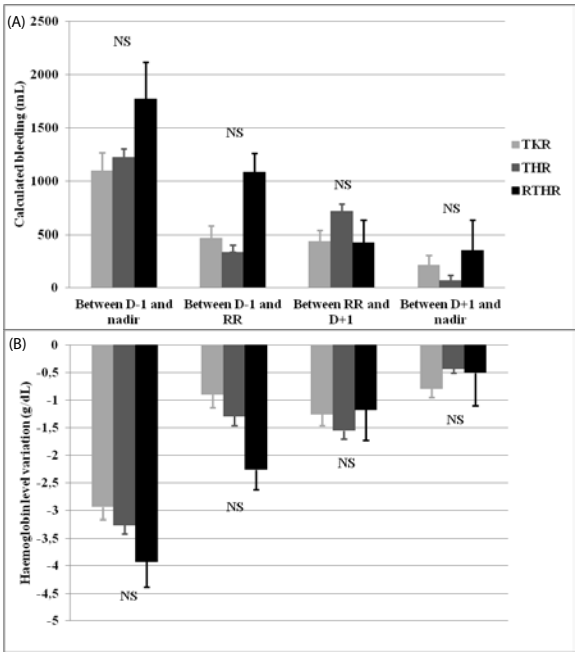

Figure 2: Calculated bleeding and Hb level variation depending on type of surgery between D-1 and nadir, D-1 and RR, RR and D+1, and D+1 and nadir. Error bars represent standard error.

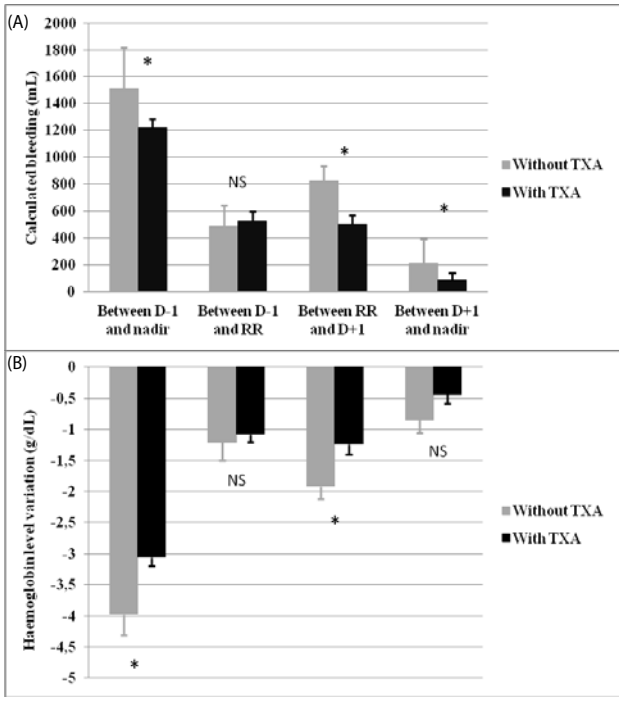

Figure 3: Calculated bleeding and Hb level variation depending on intake of TXA or not, between D-1 and nadir, D-1 and RR, RR and D+1, and D+1 and nadir. Error bars represent standard error.

Discussion

The goal of this study was to streamline transfusion thresholds based on the foreseeable kinetics of bleeding after primary and revision hip or knee replacement patients. More specifically, this study described the critical time period during which blood loss and Hb level monitoring should be increased. Blood loss occurred essentially after surgery. Mean Hb loss between RR and D+1 was 1.4 g/dL, with no difference between primary and revision procedures, with a gap of 1.2 g/dL in patients receiving TXA versus 1.9 g/dL in those who were not treated.

Initial observations addressed the correspondence between baseline and the patient characteristics reported in the European multicenter study entitled OSTHEO [11], published in 2003. Patients were representative of a standard population for hip and knee replacement surgery. In total, 13% of patients operated for primary replacement received transfusions. In our study, this rate was lower than those published (36% for primary hip replacement and 35% for primary knee replacement) [11]. Median total calculated blood loss (1099 mL [815; 1451] for primary knee replacement, 1219 mL [953; 1565] for primary hip replacement, and 1771 mL [1536; 2520] for revision procedures), for a 35% haematocrit, was lower than that found in the OSTHEO study [11] (respectively 1934 mL, 1944 mL, and 2875 mL), which translates into a 40-45% reduction in bleeding. In recent meta-analyses [12], median bleeding for THR and TKR was 1004 mL, close to our results. The reduced need for transfusions was probably linked to a broader use of erythropoietin and iron during the preoperative period as it is recommended [13], the establishment of a widely followed procedure for TXA administration, and harmonization of postoperative RBC prescription based on lower transfusion thresholds.

There was still a high transfusion rate for RTHR, although this population was not older, did not exhibit more comorbidities, and received as much iron, erythropoietin, and TXA as the population undergoing primary surgery (Tables 1 and 2). It was surprising to note that no perioperative blood salvage was implemented, while the ¾ of RBC were administered intraoperatively. Although it is contraindicated in suspected prosthesis infection, some patients could benefit from this technique. Moreover, it is very difficult to properly assess bleeding kinetics during operations, which may be abruptly indicated or unpredictable in length. It is quite possible that, on such occasions, blood products were sometimes over-ordered as compared to actual patient needs. This overestimation would have been based not on Hb threshold, but on fear of some undesirable clinical evolution.

According to Hb level variations between RR and D+1, it might be advantageous to anticipate Hb loss and establish higher transfusion thresholds in the RR. Such measures would help avoid falling below the transfusion threshold at D+1 and risking acute anemic complications. It is also fundamental to properly monitor Hb levels between RR and D+2, when the human and logistical resources available are not the same as those in the operating and recovery rooms.

As far as transfusion thresholds are concerned, the recent FOCUS study [14] showed that, in patients operated for hip fractures and at cardiovascular risk (but with no anemia symptoms), a threshold of 8 g/dL had no adverse effect on morbidity and mortality as compared to a liberal strategy with a transfusion threshold of 10 g/dL. In our study, the mean threshold value at which patients were transfused was 8.7 g/dL. This could appear as excessive, but the corresponding value during post-recovery hospital stays was 7.6 g/dL. During this period, patients with cardiovascular history exhibited Hb levels down by 1 g/dL (TXA) and 2 g/dL (no TXA) between D0 and D+1 following implementation of a restrictive 8 g/dL transfusion threshold. Patients with no cardiovascular history had a threshold of 7 g/dL. Given these results, it might be advantageous to offer, respectively, thresholds of at least 10 g/dL and 9 g/dL in RR for patients not receiving TXA, and 9 g/dL and 8 g/dL for patients receiving TXA. In the FOCUS study [15], the transfusion threshold was 9.2 g/dL for the liberal group, and 7.9 g/dL for the restrictive group. The mean threshold in our study was thus intermediate between these two values, but applied to less fragile patients. In the restrictive group, there are a significant higher number of patients who required transfusion related to clinical symptoms. It should be noted that all patients in the restrictive group that had a sign of intolerance of anemia were transfused, thus reducing the mortality in this group. Do we have, in real life, the medical manpower in each ward to see the patients many times a day for diagnosis of EKG or tachycardia early enough before Myocardial Infarction (MI) occurs?... This happens only in randomized studies. What is the real life delay to obtain one RBC unit and then to transfuse it? If the blood sample is collected at 8:00 am, results are seen at 11:00 am and transfusion starts at 2:00 pm and therefore, what happens if the patient is still bleeding? Should we wait for clinical signs of intolerance to anemia before starting transfusion? The answer is controversial for many reasons. According to the POISE study [15], 5% of patients undergoing non-cardiac surgery had a perioperative MI within 30 days of randomization. Most of these MI (74.1%) occurred within 48 hours of surgery. Moreover, 65.3% of patients did not experience any ischemic symptom. The 30-day mortality rate was 11.6% of patients who had a perioperative MI (48 of 415 patients) and only 2.2% (178 out of 7936 patients) among those who did not ($P<0.001$). It is important to emphasize that mortality rates were high and quite similar between those with (9.7%) and without ischemic symptoms (12.5%).

Endpoint analysis poses several problems. First, caution must be

taken in interpreting Hb level variations, which reflect uncompensated bleeding rather than bleeding compensated by RBC transfusion, thus providing only fragmentary information about bleeding. This endpoint was chosen for its simplicity and ease of use in clinical practice, both criteria which are not met by Mercuriali's formula [10]. In addition; it would seem that Hb level decreases and median calculated bleeding were greater intraoperatively in RTHR than in primary arthroplasty, although the difference was not significant in our study. This non-significance was certainly due to a lack of power, with only 19 patients operated for RTHR and important variations in term of kind of surgery (replacing femur and acetabulum or only femur). On the other hand, such a difference was not found postoperatively, which suggests that the most critical period for RTHR is intraoperative. This may justify more frequent intraoperative blood salvage whenever possible.

Moreover, our results surprisingly suggest that TXA was more efficient in reducing bleeding between RR and D+1, and between D+1 and D+2, than intraoperatively. It is difficult to draw any conclusions on these secondary endpoints, but one possible explanation is that the effect of prolonged TXA administration within the first 12 hours postoperatively may have limited the prolonged hyper fibrinolysis that occurs after such procedures [16,17]. Lastly, this study tended to underestimate the effect of TXA because the proportion of patients operated for RTHR was greater in the group receiving TXA than in that not receiving TXA (21% *vs*. 8%). This type of surgery probably involved increased haemorrhagic risk as well.

One of the limits is that our study was a single-center observational study with a small sample size and many confounding factors, and therefore a very low level of evidence. Nonetheless, it included all available patients undergoing hip and knee replacement for a period of two months. The lack of power precludes any interpretation of secondary outcomes. One important confounding factor emerges from the fact that patients not receiving TXA were those in which it was contra-indicated, and therefore those with a definite cardio-vascular personal history, more co-morbidities, and more antiplatelet therapy.

It should be emphasized that transfusion strategies require rigorous implementation. Transfusion is an independent factor in morbidity and mortality, as is non-transfusion and delayed transfusion. It is therefore reasonable to consider anticipating RR transfusion thresholds based on bleeding kinetics and, according to the use of TXA. This strategy may help avoid postoperative anemia and cardiovascular consequences with respecting recommended transfusion thresholds.

We should not manage anemia in the RR and at postoperative day 5 in the same way. Indeed, according to the kinetics of bleeding, transfusion trigger should be different in the RR and in the ward. Recommend these thresholds, leads to assume perfect logistical coordination of blood product delivery and administration. Today, point-of-care devices for Hb measurement must find their place even in the surgical wards in addition to clinical monitoring. Optimization of these strategies may lead to better timing of transfusions and may have an impact on morbidity and mortality in orthopedic prosthetic surgery with respecting transfusion trigger.

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