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Single tranexamic acid dose to reduce perioperative morbidity in primary total hip replacement: a randomised clinical trial

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Introduction: *Although prophylactic tranexamic acid (TXA) is a safe, low-cost option to reduce bleeding in patients undergoing total hip replacement (THR), its optimal dose and duration is unknown. We compared the safety and effectiveness of TXA given as either a single injection or continuous infusion in THR patients, hypothesising that a second TXA dose would not offer any clinical advantages over the single injection.*

Materials and methods: *One hundred and sixty-four patients undergoing unilateral THR were randomised. Exclusion criteria were history of thromboembolic events (TE), epilepsy, thrombophilia, and severe chronic renal failure. Patients received either a single dose of 30 mg/kg TXA on induction of surgery (one shot [OS] group), or a loading dose of 10 mg/kg TXA followed two hours later by a continuous infusion of 2 mg/kg per hour for 20 hours (one day [OD] group). The primary outcome was blood loss (BL) calculated from haematocrit levels. Secondary outcomes were mortality and TE events within 90 days postoperatively.*

Results: *All patients completed treatment, with none lost to follow-up. Mean BL was 1107 ± 508 ml in Group OS and 1047 ± 442 ml in Group OD (p = 0.43). No patients were transfused prior to Day 10 postoperatively. At final follow-up, no patients had died, and there were no occurrences of major TE.*

Conclusion: *The 30 mg/kg TXA single shot was as safe as continuous infusion. As it is also less cumbersome, we recommend it as part of routine care in THR patients.*

Keywords: *Tranexamic acid, Total hip replacement, Blood transfusion, Randomised controlled trial*

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INTRODUCTION

Blood loss during total hip replacement surgery (THR) can lead to acute anaemia, placing patients at risk of perioperative noxious cardiovascular complications. Red blood cell (RBC) transfusion prevents these complications, but confers inherent risks (1, 2), such as infection and immunological reaction (3) and escalating associated costs.

The antifibrinolytic tranexamic acid (TXA) has been shown to reduce bleeding and mortality during cardiac surgery and liver transplantation, as well as in trauma patients (4). Evidence gathered over the decade since the introduction of TXA supports the notion that it can be safely and efficaciously employed to decrease blood loss and transfusion requirements after THR (5-9). However, the ideal dosing and timing schedule to obtain the maximal benefit from TXA in THR is unknown. Most commonly, TXA is initiated intraoperatively at a dose of 15 mg/kg (5, 8). This loading dose is followed by a continuous infusion or repeated boluses, typically of 10 mg/kg. In most cases, the second bolus is given at three, six or eight hours, with repeat doses at regular intervals for 24 hours (8).

To be effective, the intravenous prophylactic administration of TXA in THR must be made at the beginning of, and not after, the surgical procedure (10, 11), but the wide variability in administration regimens in terms of both dose and duration is a source of concern among orthopaedic surgeons. Nevertheless, a meta-analysis indicated that multiple-dose regimens and total dose ≥30 mg/kg are more effective than a single shot regimen of 10-15 mg/kg, and a total dose ≥30 mg/kg is required to reduce allogenic blood transfusions after THR (12).

In 2006, our institution initiated a protocol in which one intraoperative single dose of TXA 30 mg/kg was administered to all THR patients without contraindications (13). The purpose of the current study was to investigate the safety and effectiveness of TXA when given to THR patients, either as a single injection of 30 mg/kg or as a continuous infusion. We hypothesised that a second dose of TXA would not lead to any clinical advantages over the single-injection dose.

PATIENTS AND METHODS

Study design

In 2009, 181 adult patients undergoing unilateral primary THR gave informed consent to participate in a double-blind randomised clinical trial. Exclusion criteria were revision THR, recent fracture of the femoral neck, a history of venous or arterial thromboembolism (TE), thrombophilia, a history of epilepsy and severe chronic renal insufficiency, defined as an estimated glomerular filtration rate >30 mg albumin per gram creatinine in the urine using the Modification of Diet in Renal Disease formula. Prior to randomisation, a further 17 patients were excluded by the anaesthetist at the time of surgery due to relative contraindications, such as a history of venous thrombosis, renal insufficiency, epilepsy or atrial fibrillation, and current epilepsy treatment.

The remaining patients were randomly allocated to either a single 30 mg/kg intravenous TXA (Exacyl; Sanofi, Paris, France) infusion at the start of surgery (one shot [OS] group; n = 85) or to a control group initially given a loading 10 mg/kg TXA dose at the start of surgery followed two hours later by a continuous infusion of 2 mg/kg per hour for 20 hours by electric syringe (one day [OD] group; n = 79). A simple randomisation schedule using random numbers generated by Microsoft Excel (Microsoft Corp, Redmond, WA) was employed. After patient eligibility had been confirmed by the anaesthetist, the patient was allocated to a group randomised via envelopes opened at anaesthesia induction. The anesthetist was blinded to treatment allocation, as he received the medication from a study nurse, who had prepared the medication before the operation. The surgeon was also blinded to the type of TXA treatment. Patients in the control (OD) group received 10 mg/kg of TXA intraoperatively and 40 mg/kg postoperatively, while patients in the treatment (OS) group received 30 mg/kg TXA intraoperatively and a placebo saline treatment (infusion with saline) postoperatively. At the time of postoperative evaluation, neither the patients nor the authors were aware of the group assignments.

The primary outcome was blood loss (BL) up to postoperative Day 7, calculated from haematocrit collected one day before and seven days after surgery, taking into account compensated blood loss and the number of red blood cells units transfused during the same period. The primary safety outcome measures were any major TE events in the 90-day postoperative period, including death related to TE events, proximal deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), or cerebrovascular accident (CVA).

Surgical procedure

All surgeries were performed in 2009 by one senior surgeon in a single operating room with horizontal laminar airflow. All patients received prophylactic antibiotics, begun approximately half an hour before skin incision. The procedures followed a standardised technique, including a modified anterolateral approach to the hip (14), capsule repair and no drain.

In all cases, a tapered uncemented stem was implanted after femoral preparation using a broach-only system motorised by a pneumatic hammer. On the acetabular side, a curved hemispherical reamer was used to prepare the bed and subsequently to insert a cementless modular acetabular component.

Anaesthesia was managed by a team of three anaesthesiologists using standardised modern perioperative medical care protocols. All but one patient received general anaesthesia. A femoral block nerve was routinely performed using Doppler imaging before the induction of general anaesthesia, which was induced by propofol, sufentanyl and atracurium. The patients were intubated, and ventilation was

controlled with a nitrous oxide/oxygen mixture. Anaesthesia was maintained with sufentanyl re-injections and sevoflurane inhalation. A warming blanket set at 37°C was applied on the upper body throughout the procedure. Mean body temperature was recorded at entry into the recovery room.

Blood plan

The same blood-conserving procedures were used throughout the patient series. Patients were not included in a pre-deposit autologous blood donation program before THR. Non-steroidal anti-inflammatory drugs (NSAIDs) were discontinued at least 48 hours before surgery. Surgical haemostasis was achieved in situ with standard electro-coagulation. Vessel ligature was not executed during the surgical procedure, as the anatomical approach to the hip was non-vascular. Oral iron (Tardyferon 80 mg; Laboratoires Pierre Fabre, Castres, France) was prescribed twice daily for 20 days prior to the operation, unless contraindicated. Patients undergoing THR with preoperative anaemia, defined as a haemoglobin (Hb) level lower than 13 g/dL in males and 12 g/dl in females, received one preoperative weekly subcutaneous dose of 40,000 IU epoetin-alpha (EPO, Eprex; Janssen, Issy-les-Moulinaux, France) for three weeks before surgery.

Postoperative protocols

Postoperative care incorporated a multimodal pain control programme. Urinary retention was systematically detected by bladder scan during the immediate postoperative period. Transfusion triggers were 8 g/dL Hb in patients with irrelevant cardiovascular comorbidities and 10 g/dL of Hb in patients with coronary artery disease. The rehabilitation protocol consisted of immediate hip mobilisation. Full weight-bearing was allowed postoperatively with the protection of crutches for one month.

Pharmacological venous thromboembolism (VTE) prophylaxis was started on the day of surgery, 6–10 hours after the closure of the skin. Two different anticoagulant molecules were used through successive periods for the immediate postoperative period: fondaparinux (Arixtra; GlaxoSmithKline, Marly-le-Roi, France) 2.5 mg once daily for nine days followed by subcutaneous pharmacologic VTE prophylaxis with 4,500 IU tinzaparine (Innohep, Leo Pharma, St-Quentin-en-Yvelines, France) once daily. Oral rivaroxaban (Xarelto; Bayer, Lille, France) was continued at 10 mg once daily for 35 days without platelet monitoring. NSAIDs were not used for prevention of heterotopic ossification. All patients underwent Doppler ultrasound of both lower limbs on postoperative Day 7, or earlier if there was any clinical suspicion of DVT.

Assessment of blood loss and complications

Total blood loss was calculated from haematocrit levels using Gross's formula (15): TBL = estimated blood volume X (Ht reduction/mean Ht), where the Ht reduction is the difference between preoperative and postoperative Day 8 values. Gilcher's criteria (16) were used to estimate each patient's blood volume (Tab. I). Compensated blood loss was determined by taking into account that one unit packed of homologous blood contains 150 ml of red blood cells. Laboratory measurements, including haematocrit and Hb levels, were determined from venous blood samples collected at admission (Day 1) and postoperative Day 7 (±1 day).

Major complications were defined as death within 90 days of the procedure, perioperative MI, CVA, proximal DVT and symptomatic PE.

Statistical analysis

For continuous data, Shapiro-Wilk tests were used to test for major violations of the normality assumption. Mann-Whitney tests were used in case a normal distribution could not be assumed; data are presented as a median and interquartile range (IQR). For normally distributed data, we used unpaired Student *t* tests for comparison between groups and continuous data, and are presented as a mean and standard deviation. Categorical variables are presented as frequencies and percentages and tested using Fisher's exact test. Two-sided tests were used throughout. $P<0.05$ was considered statistically significant. All analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX, USA).

TABLE I - ESTIMATED BLOOD VOLUME OF AN ADULT (16)

BMI	Female	Male
<18.5	65 ml/kg	70 ml/kg
18.5 – 29.9	70 ml/kg	75 ml/kg
≥30	60 ml/kg	65 ml/kg

RESULTS

One hundred and sixty-four patients were included in the study: 85 in the OS group and 79 in the OD group. As shown in Table II, demographic data and operative variables were comparable between the groups with regards to sex, age, weight, BMI, length of incision and median duration of operation. The proportion of patients who received preoperative EPO was 11% in both groups and the mean quantity of epoetin delivered preoperatively was similar in both groups (116,000 vs 115,000).

No patient was lost to follow-up. We did not observe any serious adverse events directly related to TXA administration. Mean blood loss up to Day 7 was 1107 ± 508 ml in group OS and 1047 ± 442 ml in group OD (p = 0.43). No patients were blood transfused prior to Day 8. No major bleeding complications emerged in the immediate postoperative period. Hb levels at postoperative Day 1 were significantly higher in the OS group (p = 0.02). At postoperative Day 7, there was no significant difference between the two groups (p = 0.72) (Tab. III).

The lowest Hb levels recorded during the postoperative period were 9.1 g/dL in group OS and 9.6 g/dL in group OD. No patient returned to the operating room for evacuation and debridement of haematoma. In the 90-day postoperative period, no patients died and there were no occurrences of major TE, including proximal DVT, PE, MI and CVA, in either group. No deep periprosthetic infections had been identified by one-year follow-up. No patient had reported blood transfusion at one-year follow-up.

TABLE II - DEMOGRAPHIC AND MEDICAL CHARACTERISTICS BY TREATMENT GROUP

	Group OS (n = 85)	**Group OD (n = 79)**
Sex (female) (%)	46 (54)	41 (52)
Age at THR (years)	68.7 ± 9.5	68.4 ± 11.1
Body weight (kg)	81.8 ± 16.5	79.1 ± 14.3
Height (cm)	166 ± 8	165 ± 9
Incision length (cm)*	10.3 (9–11)	10.3 (9–11)
Operative time (min)	59 ± 10	60 ± 9
Preoperative EPO (n, %)	10 (11)	9 (11)
Preoperative Hb (g/dl)	14.2 ± 1.1	14.1 ± 1.2
Mean epoetin-alpha dose (UI)	116,000	115,000
Fondaparinux/rivaroxaban (n)	37/48	28/51

Presented as frequency (percentage) or mean ± standard deviation, except * as median (interquartile range).

TABLE III - OUTCOME VARIABLES UP TO DAY 7 BY TXA TREATMENT GROUP

	Group OS (85 hips)	**Group OD (79 hips)**	**P value**
Mean total blood loss over perioperative period (ml)	1107 ± 508	1047 ± 442	0.43
Red blood cell transfusions	0	0	1.0
Hb at postoperative day 1 (g/dl)*	12.3 (11.5–13.2)	11.8 (11.8–11.8)	0.02
Hb at postoperative day 7 (g/dl)*	11.7 (10.7–12.3)	11.4 (10.8–12.3)	0.72

Presented as mean ± standard deviation, except * as median (interquartile range).

DISCUSSION

For the current randomised controlled clinical trial, we compared the impact of one shot of 30 mg/kg TXA with that of an overall fractioned total dose of 50 mg/kg on perioperative blood loss, packed cell transfusion requirements and the postoperative incidence of major thrombotic events after primary THR.

The most important finding of this present study was that there were no differences in efficacy and safety between the single 30 mg/kg shot and the multiple-dose regimen. Our finding conflicts with the traditional view that a single dose application of TXA is not as effective as a multiple dose regime to reduce allogenic transfusions in THR (12). However, it should be noted that the analysis by Zufferey et al was constructed from clinical trials using a single bolus of TXA 10–15 mg/kg dose, since which the effect of TXA has been found to be dose-dependent, with a threshold dose of 30 mg/kg (12).

Our study also revealed a significant difference in Hb levels between the two groups at postoperative Day 1, favouring the single dose application. The lack of significant

difference at postoperative Day 7 can be explained by the differences in duration of the TXA therapy.

The most commonly prescribed regimen of TXA for inhibition of fibrinolysis during the phase of maximum bleeding after THR is a 10–15 mg/kg initial bolus dose, followed by a second similar dose injection at 3, 6 or 8 hours, with repeat doses at regular intervals for 24 hours (5-8, 12). In the current study, we compared two regimens both dosed ≥30 mg/kg and, to our knowledge, it is the first report comparing a single shot 30 mg/kg dose with a fractioned regimen in THR. We believe that a single shot of 30 mg/kg is sufficient to inhibit fibrinolysis after THR, and found that a second dose is not required owing to prolonged extravascular effectiveness.

The single-shot application of 30 mg/kg on induction of surgery has been the preferred protocol at our unit since 2006. This protocol was defined in 2005 on the basis of TXA pharmacokinetics and post-arthroplasty fibrinolysis. Our TXA protocol has a number of advantageous clinical implications, as it is technically simpler to institute and less cumbersome to manage for the nurses than a fractioned regimen administered partly in the recovery ward. Even though TXA is a relatively inexpensive drug, the total dose delivered is smaller and cheaper than a continuous infusion or repeat bolus regimen. To date, TXA prophylaxis has already been recommended by the Australian Therapeutic Goods Administration to prevent the risk of blood transfusion in THR, with the second dose modulated in cases of chronic renal failure in order to avoid TXA accumulation (17).

While TXA has a historically safe profile stretching back for more than 50 years, the potential prothrombotic effect of TXA is a source of concern among orthopaedic surgeons. Nevertheless, the use of TXA in hip arthroplasty does not appear to increase the risk of thrombosis. Several meta-analyses indicated no increase in venous TE associated with TXA (18, 19). Our experience of giving one routine intraoperative dose of 30 mg/kg TXA alone has revealed no troubling incidents of venous and arterial TE events in a population of more than 1000 patients, all examined with ultrasound before their discharge from the clinic.

However, it should be observed that our patients were: 1) selected to receive TXA; and 2) treated with a combined potent anticoagulant pharmacologic therapy to prevent VTE after THR, with a first dose of anticoagulant given 6–10 hours after the end of the operation. Nevertheless, a recent publication regarding the use of routine TXA as a blood conservation modality during primary THA and TKA reported a low complication rate of TE events using thromboembolic pharmacologic regimens considered less aggressive, such as aspirin alone and dose-adjusted warfarin (20).

The strength of our study is the randomisation and the use of a pragmatic methodology. The homogeneity of the study groups is also extremely strong: all surgeries were performed by the same surgeon using one approach, similar implants, analogous perioperative medical care procedures and analogous postoperative measurements, as well as comparable preoperative criteria and demographic and operative variables. Moreover, the measurement of blood loss was computed from haematological parameters analysed at the same laboratory from blood samples collected at precise times during the perioperative period, and the measurement of blood loss was not biased by blood transfusion.

Our study does have some limitations. Firstly, the results may potentially be confounded by the use of two different molecules to prevent VTE during the immediate postoperative period. However, both drugs have the same target. They are inhibitors of factor Xa and considered both effective drugs for the prevention of venous thromboembolism after total joint arthroplasty. Moreover, the fondaparinux/rivaroxaban ratio did not differ substantially between the two groups. Secondly, we have prospectively investigated only proximal (and not distal) DVT, as the detection of asymptomatic DVT by ultrasound is not recommended by French health agencies following THR. Thirdly, we did not conduct a prior power analysis. Instead, a pragmatic choice was made to recruit patients during one year. The results presented in the paper must therefore be interpreted with caution. However, the sample size was probably large enough to rule out the possibility of any large and clinically relevant differences in transfusion rates.

In conclusion, the present study demonstrated, with a high level of evidence, that a second dose of TXA did not lead to any clinical advantage over a single-injection regimen at doses considered effective in primary THR. Therefore, we continue to give one 30 mg/kg TXA dose as part of routine care in THR patients. A prophylactic dose of TXA should be considered as part of any comprehensive strategy to avoid transfusion and reduce postoperative bleeding in primary THR surgery with the potential for significant blood loss.

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Conflict of Interest: The authors declare that they have no competing interests.

Ethics committee approval was obtained.

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