Tranexamic acid reduces blood loss and financial cost in primary total hip and knee replacement surgery

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Summary

Background: Blood conservation strategies have been developed to diminish blood transfusion requirements in patients undergoing hip or knee replacement surgery. Tranexamic acid (TA) is an inexpensive antifibrinolytic agent that is little used in orthopaedic surgery due to the absence of standardised optimal administration regimens.

Hypothesis: Blood transfusion requirements and induced costs can be diminished by using TA according to a standardised administration protocol in a large cohort of patients.

Materials and methods: A retrospective study in patients who underwent joint replacement surgery by a single surgeon compared two periods, 2007–2008 without TA and 2008–2009 with TA. The 451 included patients underwent primary unilateral hip (n = 261) or knee (n = 190) replacement for osteoarthritis. Standardised protocols were used for surgery and anaesthesia. TA was given intravenously in a dose of 1 g (i.e., 15 mg/kg) at incision and wound closure then at 6-hour intervals for 24 hours. Blood losses were estimated using the Mercuriali formula. Haemoglobin on D−1 and D8 and the number and volume of autologous (from intra-operative blood salvage) and homologous blood transfusions were collected. The costs of TA, blood salvage systems, and homologous blood units were recorded. The two groups were compared using Student’s t, Wilcoxon’s test, and the Khi² test, and multivariate analyses were performed. Values of p less than 0.05 were considered significant.

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**Introduction**

Osteoarthritis causes functional and quality-of-life impairments and is the main cause of morbidity in industrialised countries [1]. Surgery is reserved for patients with primary or secondary failure of conservative management. Total hip arthroplasty (THA) and total knee arthroplasty (TKA) carry a risk of bleeding. The incidence of major bleeding events (requiring more than two red-blood-cell (RBC) packs or reoperation or causing death) is 1.4% [2]. Overall, the mean mortality rate in orthopaedic surgery is less than 1% [3]. Importantly, mortality is increased 5-fold in patients with anaemia [4]. Half the deaths ascribable entirely or in part to inadequate blood management during anaesthesia occur in orthopaedic surgery [5]. RBC transfusion is the only currently available treatment for poorly tolerated acute anaemia. However, blood transfusion is an independent risk factor for death [4]. The risks and costs associated with blood transfusion, together with challenges in obtaining sufficient labile blood products, have generated interest in blood-sparing strategies.

Tranexamic acid (TA) is an inexpensive synthetic antifibrinolytic agent. TA prevents the degradation of fibrin and delays the breakdown of haemostasis clots. A 30% reduction in blood transfusion requirements due to a decrease by one-third in blood losses has been demonstrated with TA in orthopaedic surgery [6]. However, TA is used in only 17% of patients meeting theoretical criteria for this treatment, due to the wide variability in administration regimens (dose, duration, and route) [7,8]. Furthermore, the potential prothrombotic effect of TA is a source of concern among orthopaedic surgeons and has not been investigated in specifically designed studies providing a high-level of evidence. In our centre, intravenous TA is given intraoperatively and postoperatively according to a protocol based on TA pharmacokinetics and knowledge of postoperative fibrinolysis.

The primary objective of this study was to confirm that our TA therapy protocol diminished the need for homologous blood transfusions and for autologous transfusion of blood salvaged intra-operatively in a large cohort of patients undergoing scheduled primary lower-limb joint replacement surgery by a single surgeon. The secondary objective was to determine whether our blood-sparing strategy was associated with a reduction in the financial cost of surgery.

**Material and methods**

**Inclusion and exclusion criteria**

We conducted a single-centre retrospective study to compare two groups of consecutive patients with osteoarthritis who underwent scheduled primary unilateral THA or TKA by a single surgeon. The first group consisted of the patients whose joint replacement procedure was done between January 2007 and October 2008, none of whom received TA (TA- group). In the second group, surgery was performed between November 2008 and December 2009 and TA was administered perioperatively (TA+ group). Exclusion criteria in both groups were as follows:

- medical contraindication to TA, i.e., history of seizures, severe renal failure (creatinine clearance < 30 mL/min), bleeding disorders, history of venous thromboembolism (deep vein thrombosis and/or pulmonary embolism) and/or of arterial thromboembolism (angina, myocardial infarction, stroke, acute lower-limb ischaemia);
- perioperative anaemia defined as a haemoglobin (Hb) level lower than 13 g/dL in males and 12 g/dL in females.

Of the 800 eligible patients over the two periods, 203 did not have all the inclusion criteria and 146 had one or more exclusion criteria, leaving 451 patients for the study.

**Surgical technique**

The surgical technique was standardised and all procedures were done by the same surgeon (JNA). For THA, the Watson-Jones anterolateral approach was used and a cementless anatomic prosthesis was implanted. TKA was performed via the minimally invasive peripatellar approach without patellar eversion, using modern instrumentation to allow bone preparation in the coronal plane [9]. A three-compartment cemented posterior-stabilised prosthesis with a mobile plateau was implanted. No tourniquet was used. Pulsed lavage was performed to optimise recipient bone preparation. An intraarticular drain was inserted then removed routinely 36 hours after surgery.
Anaesthetic technique

All patients were evaluated by an anaesthetist one month before surgery. Antiplatelet agents were interrupted five days before surgery, after discussion with the patient’s usual cardiologist. In the absence of medical contraindications, either general anaesthesia or spinal anaesthesia was used, with or without sedation was used. The patient was in the supine position. A standardised intravenous fluid regimen was used: 500 mL of 6% hydroxethyl starch colloid (HES [130 kDa]) at anaesthesia induction followed by 1000 mL of Ringer Lactate® until the patient was returned to the surgical ward.

In the TA+ treated group, TA was given as a 30-minute intravenous infusion. The total TA dose was 6 g (i.e., 15 mg/kg) before the incision, at wound closure, and every 6 hours for 24 hours thereafter. In both groups, a multimodal regimen was used after postoperative analgesia, first intravenously then orally starting on the first postoperative day: paracetamol combined with tramadol or nefopam, plus ketoprofen (50 mg every 6 hours) for three to five days in the absence of contraindications. An analgesic nerve block was performed routinely in the recovery room, either a fascia iliaca compartment block in THA patients or a continuous sciatic nerve block with a femoral catheter for 72 hours in TKA patients. A patient-controlled morphine pump was used for rescue analgesia if needed. The prevention of venous thromboembolism relied on enoxaparin 40 mg or fondaparinux sodium 2.5 mg subcutaneously starting on D1, in the absence of contraindications (creatinine clearance < 30 mL/min and active bleeding).

Blood transfusion protocol

An intra-operative blood salvage device was used routinely. The blood was processed prior to infusion by automatic sequential washing using a Cell Saver 5+® (Haemonetics, Plaisir, France) when the volume recovered by aspiration (blood and rinsing solution) exceeded 1000 mL. The recirculated autologous blood was routinely transfused to the patient in the recovery room. The cut-offs used to perform homologous blood transfusion were those recommended by the French Healthcare Product Safety Agency (Agence française de sécurité sanitaire des produits de santé) in 2002 [10]:

- 7 g/dL of Hb in patients free of cardiovascular disease;
- 8 to 9 g/dL of Hb in patients with established cardiovascular disease (coronary artery disease, cerebrovascular events, peripheral vascular disease, or heart failure) or multiple cardiovascular risk factors (age > 45 years in males and > 55 years in females, family history of premature cardiovascular disease [> 55 years in males and < 65 years in females], hypertension, diabetes, smoking, dyslipidaemia, obesity);
- 10 g/dL of Hb in patients with poor clinical tolerance of lower values.

Intravenous iron supplementation was given postoperatively (200 mg on D—1 and D3) if the preoperatively predicted blood transfusion risk was high in the TA+ group and routinely in the TA+ group except when the blood transfusion risk was low.

Data collection

The study data were obtained from a computerised database in which data were entered prospectively at the end of each arthroplasty procedure. For all patients, we collected the physical, medical, anaesthesiological, and surgical characteristics. Total blood volume (TBV) was estimated using Glcher’s formula [11]. To estimate the blood transfusion risk, we computed the difference between estimated blood losses (evaluated at 10% of the TBV at our centre) and the blood loss needed to reach the blood transfusion cut-off (TBV [Haematocrit (Ht) D1—Ht cut-off]) [12,13]. We analysed the following variables: blood loss estimated using Mercuriali’s formula (TBV [Ht D1—Ht D8] + autologous and homologous RBCs transfused), the Hb levels on D—1 and D8, the homologous transfusion rate, and the autologous transfusion rate and volume [14]. Patients were evaluated clinically for side effects of TA therapy (thromboembolic events, coronary artery events, seizures, vascular events), which were recorded in each group.

Simultaneously, a pharmacoeconomic study was conducted. We took into account the cost of blood transfusions based on the cost of one RBC pack (190 €), of cell salvage consumables (50 €), and of the salvaged blood processing system (100 €). Each TA treatment (6 g/patient) cost 12 €. The overall cost was then converted to the costs per patient and per group.

Statistical analysis

The two groups were compared using the Student and Wilcoxon tests for quantitative variables and the Khi² test for qualitative variables. Values of p less than 0.05 were considered significant. Two multivariate analyses were conducted to simultaneously assess the influence on the blood transfusion rate of TA, non-steroidal anti-inflammatory drugs (NSAIDs), and intravenous iron given postoperatively (logistic regression analysis) and of estimated blood losses (ANOVA).

Results

Of the 451 study patients, 241 did not receive TA and 210 received TA (Table 1). All demographic characteristics were similar in the two groups (P, NS). Mean patient age was 70 years (39–89 years) in the TA— group and 69 years (33–90 years) in the TA+ group. The male-to-female ratio was 1. The two types of surgical procedures were evenly distributed between the two groups: in the TA— group, 140 (58%) patients underwent THA and 101 (42%) TKA, and the corresponding values in the TA+ group were 121 (58%) and 89 (42%), respectively. Mean operative time was 75 min (40–145 min) in the AT— group and 78 min (45–160 min) in the AT+ group. General anaesthesia was used in 187 (78%) of the 241 TA— patients and 161 (77%) of the 210 AT+ patients and spinal anaesthesia in 54 (22%) TA— patients and 49 (23%) TA+ patients. For thromboembolism prevention,
fondaparinux was used in 58 (24%) TA− patients and 57 (27%) TA+ patients and enoxaparin in 183 (76%) TA− patients and 153 (73%) TA+ patients. NSAID therapy was prescribed in a significantly larger proportion of TA− than TA+ patients (226/241, 94% versus 164/210, 78%, respectively; \( P < 0.001 \)) and intravenous iron in a significantly smaller proportion of TA− than TA+ patients (73/241, 30% and 190/210, 90%, respectively; \( P < 0.001 \)).

Blood losses estimated using Mercuriali’s formula were lower by 34% in the TA+ group compared to the TA− group (1260 ± 620 mL versus 1900 ± 690 mL, \( P < 0.001 \)). The Hb level on D-1 was 14 ± 1 g/dL in the TA− group and 14.2 ± 1 g/dL in the TA+ group (\( P = 0.21 \)). On D8, the Hb level was significantly higher in the TA+ group than in the TA− group (11.8 ± 2.0 g/dL versus 10.7 ± 2.0 g/dL, \( P < 0.001 \)) (Fig. 1). The difference between the initial and final Hb levels was -3.3 ± 1.2 g/dL in the TA− group and -2.4 ± 1.1 g/dL in the TA+ group (\( P < 0.001 \)). In keeping with the reduction in blood losses, the TA+ group required significantly fewer homologous blood transfusions compared to the TA− group (0/210 versus 10/241, 4%, \( P = 0.003 \)) (Table 2). Most of the reduction in homologous blood transfusions was ascribable to the TA+ group (0 versus 7%, \( P = 0.03 \)). The number of autologous blood transfusions of recirculated blood was 38% lower in the TA+ group (123/210, 59% versus 234/241, 97% in the TA− group, \( P < 0.001 \)). Again, the reduction in homologous blood transfusions was greater in theTKA patients (18% with TA vs 96% without TA, \( P < 0.001 \)). The volume of autologous blood transfusions was 68% lower in the TA+ group compared to the TA− group (110 ± 125 mL versus 350 ± 190 mL, \( P < 0.001 \)). After adjustment for the use of intravenous iron and NSAIDs, TA+ therapy remained significantly associated with reductions in the overall blood transfusion rate (\( z = -6.6; P < 0.001 \)) and estimated blood losses (\( F = 35.3; P < 0.001 \)).

During the postoperative period, one patient in the TA− group experienced pulmonary embolism and 1 patient in the TA+ group had an episode of angina pectoris. No seizures were recorded during the hospital stay.

The total cost of blood transfusions was 38,870 € in the TA− group and 22,800 € in the TA+ group. When taking the cost of TA treatment into account (2520 € for the entire group), the overall cost savings in the TA+ group were 13,350 €. Mean cost of blood transfusions and TA therapy per patient was estimated at 162 € in the TA− group and 121 € in the TA+ group, indicating a 25% reduction in the cost of anaesthesiological management.

**Discussion**

In our clinical study, perioperative treatment with TA significantly decreased the blood transfusion rates and the cost of anaesthesiological management. For surgical procedures carrying a high risk of bleeding, the morbidity and mortality associated with anaemia must be weighed against the risks associated with blood transfusions [4]. On the one hand, postoperative anaemia — found in 90% of patients after arthroplasty — increases the risk of myocardial infarction due to a mismatch between oxygen supply and requirements.
Table 2: Effect of tranexamic acid therapy in decreasing blood losses and blood transfusion requirements. The data are mean ± SD, number, or percentage.

<table>
<thead>
<tr>
<th></th>
<th>TA− (n = 241)</th>
<th>TA+ (n = 210)</th>
</tr>
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<tbody>
<tr>
<td>Hb D1 (g/dL)</td>
<td>14.0 ± 1</td>
<td>14.2 ± 1</td>
</tr>
<tr>
<td>Hb D8 (g/dL)</td>
<td>10.7 ± 1.2</td>
<td>11.8 ± 1.2*</td>
</tr>
<tr>
<td>Total blood losses (mL)</td>
<td>1900 ± 690</td>
<td>1260 ± 620*</td>
</tr>
<tr>
<td>Homologous blood transfusions, n of patients</td>
<td>10</td>
<td>0*</td>
</tr>
<tr>
<td>N (1, 2, or 3) of RBC packs in homologous blood transfusions, n of patients</td>
<td>3/6/1</td>
<td>0</td>
</tr>
<tr>
<td>Autologous blood transfusion rate (%)</td>
<td>97</td>
<td>59*</td>
</tr>
<tr>
<td>Volume of autologous blood transfusions (mL)</td>
<td>350 ± 190</td>
<td>110 ± 125*</td>
</tr>
</tbody>
</table>

TA−: group managed without tranexamic acid; TA+: group managed with tranexamic acid; Hb: haemoglobin; D: day; RBC: red blood cell. *P<0.001 versus the group managed without tranexamic acid.

during the perioperative period, and myocardial infarction is the leading cause of death after major orthopaedic procedures [15,16]. However, the use of restrictive blood transfusion strategies does not increase mortality [17]. On the other hand, transfusion of labile blood products carries potentially life-threatening risks (e.g., incompatibility and pulmonary oedema) [18]. TA therapy is among the available blood-sparing strategies. Studies have provided high-level evidence that TA therapy is effective. In addition, no side effects have been reported, and the cost of TA is low. Nevertheless, TA is rarely used in everyday practice [6–8], in large part because no consensus exists about the best administration regimen.

Our clinical study designed to confirm the beneficial effects of TA given during and after joint replacement surgery compared two populations of patients who underwent scheduled unilateral THA or TKA. The retrospective design is an inherent limitation. However, our cohort is large, whereas most of the meTA–analyses on TA therapy in orthopaedic surgery rest on studies of fewer than 150 patients [19,20]. Importantly, all procedures were performed by the same surgeon and the TA treatment protocol was standardised. Patients with contraindications to TA therapy were excluded from both groups. Confounding may have occurred, due to the differences in the proportions of patients given NSAIDs and intravenous iron between the two groups. NSAIDs are used to minimise the risk of peri prosthetic ossification, but they inhibit platelet activation and cause a slight increase in the incidence of abnormal operative site bleeding (of about 1%) [21,22]. Intravenous iron supplementation accelerates recovery from postoperative anaemia. However, the effect of iron supplementation on the Hb level takes more than 1 week to develop, as the inflammatory state seen during the first 15 postoperative days is associated with relative deficiency and inefficiency of the endogenous erythropoietin needed for erythropoiesis to occur [23,24].

We computed blood losses in our patients, because measuring blood losses during surgery underestimates actual blood losses by about 50% [25]. Preoperative anaemia was an exclusion criterion, as erythropoietin therapy is required in this situation [26] and may bias the Hb level evaluation on D8, resulting in underestimation of blood losses computed based on this parameter. The TA treatment protocol used at our centre is based on knowledge of TA pharmacokinetics and of postarthroplasty fibrinolysis. Peak serum TA levels are reached immediately upon intravenous administration. The elimination half-life is 3 hours. The effect of TA seems to be dose-dependent (>30 mg/kg in all) [6]. No additional benefits are obtained by increasing the bolus dose above 10 to 20 mg/kg [27]. The cumulative dose used at our centre is higher than in most of the reported TA treatment regimens [28]. However, fibrinolysis activation persists for 12 to 24 hours after surgery, supporting the prolonged use of TA during the postoperative period, which has been reported to increase efficacy [29].

Blood losses were diminished by 34% in our TA+ group [8,30]. The result was a smaller overall Hb decrease with a higher final Hb level [31]. Our results also confirm the efficacy of TA therapy in diminishing homologous and autologous blood transfusion requirements in patients undergoing major orthopaedic surgery [6,19,32]. The decreased rate and volume of autologous blood transfusions directly reflected the ability of TA therapy to diminish bleeding and showed that the yield of intra-operative blood salvage in terms of blood transfusions was poor. Earlier studies showed that intra-operative blood salvage systems were used on average in 46% of THAs and 40% of TKAs [6]. Intra-operative blood salvage adds to the cost of surgery and carries specific risks such as bacterial contamination, gas embolism, and haemolysis [33]. The present study served as an evaluation of professional practices study at our centre and, based on its results, intra-operative blood salvage is no longer used routinely. The effect of TA therapy was larger in the TKA group, in keeping with earlier data, as fibrinolysis activation in the postoperative period is more marked than after THA, particularly when a tourniquet is used [6,34].

The cost of blood salvage was decreased by 25% when TA was used. The simple cost evaluation performed for our study underestimated total costs, as we did not consider the cost of purchasing and maintaining the Cell Saver™ machine or the costs related to the personnel in charge of setting up this technique. The cost savings associated with TA treatment are further increased by the savings related to decreased use of the intra-operative blood salvage system. An earlier study suggested a cost-saving effect of TA therapy related to a decrease in hospital stay length [35].

Conclusion

Minimising blood transfusion requirements in orthopaedic surgery rests on the development of protocols that are...
specific of each department and can be adjusted to each individual patient. These protocols should rely on multiple blood-sparing techniques. The present study in a large patient cohort confirms that TA therapy decreases homologous and autologous blood transfusion requirements and diminishes blood losses. TA therapy decreases the risk of blood transfusion without increasing the risk of postoperative anaemia. A rational regimen of TA therapy given intra-operatively and postoperatively seems effective and devoid of notable side effects. TA therapy was directly associated with a reduction in the costs of treatment in our study. In addition, this study served as an evaluation of professional practices, and its results led to intra-operative blood salvage no longer being routinely used at our centre, given its limited impact in patients treated with TA.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

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