



Effectiveness of Tranexamic Acid in revision total knee arthroplasty

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The effectiveness of Tranexamic Acid (TXA, antifibrinolytic drug) in reducing allogeneic blood transfusion requirements has not been tested in revision total knee arthroplasty. The aim of this study was to assess the effectiveness of TXA after two intravenous doses of 1 g each. Between April 2006 and February 2010, 68 consecutive patients (19 male, 49 female) of 74 ± 6 [m \pm SD] years of age were included and divided into three groups: control (28 patients), in which TXA was not administered but was not contraindicated; TXA (19 patients) who received TXA, and NO-TXA (21 patients), who were not administered TXA because of a contraindication. The proportions of patients transfused were 54%, 32% and 62% respectively in the control, TXA and NO-TXA group; the median numbers of RBC units transfused were respectively 2 [range: 1-4], 2 [range: 2-2] and 2.5 [range: 1-5], ($p = 0.057$). Mean total estimated blood loss was 1693 mL (SD: 689) in the control group, 1196 mL (SD: 665) in the TXA group and 2454 mL (SD: 2166) in the NO-TXA group, ($p = 0.015$). No adverse events were reported. TXA administration appeared as an effective and safe means of reducing blood transfusion requirements and blood loss in revision total knee arthroplasty.

Keywords: tranexamic acid; antifibrinolytic; blood loss; revision total knee arthroplasty.

INTRODUCTION

The number of primary total knee arthroplasties (TKA) performed around the world in recent years in developed countries has increased (14).

Consequently, the number of revision total knee arthroplasty (revision TKA) has also risen. This rise is associated with the longer life expectancy of the population, implant longevity, patient selection, and the increased number of TKA's performed on younger people (21). Moreover, the demand for revision TKA procedures is expected to increase substantially over the next decades (14).

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Revision TKA, as a major orthopaedic surgery, is associated with major blood loss. This blood loss is of significant concern to orthopaedic surgeons and anaesthetists. In fact, blood loss after a revision TKA is greater than in a primary TKA due to the extensive nature of the surgery. Revision TKA is a more aggressive surgery, implies bone loss, and a blood transfusion is generally required in those patients (10). On the other hand, several techniques have been used to reduce the need for allogeneic blood transfusions: intraoperative blood saving, hypotensive anaesthesia, postoperative salvage devices or autologous blood transfusions.

Antifibrinolytic agents improve haemostasis and reduce blood loss in orthopaedic surgery. Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine. It inhibits fibrinolysis by blocking the lysine binding sites on plasminogen (18). A randomized placebo-controlled trial was recently published which concluded that TXA reduced the risk of death in bleeding trauma patients, and its use was recommended (23). Previously and in line with the aforementioned trial, three systematic reviews of patients who had undergone total knee and hip arthroplasties concluded that TXA reduced allogeneic red cell transfusions (3,7,9). However, there is still limited information available on the effect of TXA on blood loss in revision TKA. The aim of this descriptive retrospective study was to assess the effectiveness of the early administration of a short course of tranexamic acid on blood loss in patients undergoing revision total knee arthroplasty.

PATIENTS AND METHODS

Study design

This was a single-centre, retrospective cohort study. The protocol was approved by the hospital's independent ethics committee.

Study population

Between April 2006 and February 2010, all consecutive revision TKA patients with aseptic loosening requir-

ing revision of femur and tibia components, and on whom the surgical procedure was performed in one stage, were identified and included in this study. Patients with a revision TKA for infection, those on whom a pneumatic tourniquet was not applied as per the surgeon's decision or when the surgical procedure was performed in two-stages were not included. It is worth mentioning that in April 2006 revision TKA and blood transfusion protocols were established in our centre; this was considered the starting point of this cohort. The TXA utilization protocol was available from 2008.

The following data was collected: date of birth, gender, weight, height, date of surgery, discharge date, blood haemoglobin (Hb) concentrations (baseline and 24, 48, 72 and 120 hours after the operation), blood transfusion (yes/no), red blood cell (RBC) units transfused, volume (mL) of bleeding in the vacuum drains at 24 and 48 hours, adverse events (including death).

Procedure in clinical practice

Revision total knee arthroplasty protocol

Senior orthopaedic surgeons with extensive experience in revision TKA performed all surgical procedures. The anaesthesia used was a combined spinal/epidural block with an epidural analgesic catheter.

A pneumatic tourniquet was placed around the upper thigh and inflated to 350 mmHg; it was deflated after wound closure, when the compression dressing was applied. A midline incision and anteromedial approach was used. Only one prosthetic model was implanted (Genesis cemented prosthesis, Smith & Nephew, Memphis, USA). Accurate electro-coagulation was applied to all bleeding soft tissue during surgery. An intravenous prophylactic antibiotic was administered during induction and for 24 hours after surgery. Both components, the femoral and tibial, were revised. Preoperative studies detected no infection. Furthermore, intra-operative microbiological studies of the bone-prosthesis membranes were performed. Before closing the wound, two number 8 vacuum drains were inserted. These drains were removed between 36 to 48 hours after surgery. Starting the day after surgery, all patients received low molecular weight heparin for 30 days in order to prevent thromboembolic complications. A post-operative rehabilitation protocol with active and passive movement of the knee joint was also started by a physiotherapist on the day after surgery. Weight bearing was allowed depending on the bone status and quality and after checking the post-operative radiographs.

At discharge, the patient received an out-patient appointment to have the sutures removed 15 days after surgery. A visit at home by a physiotherapist was also set up for 3 days a week over the first 2 months.

Blood transfusion protocol

Transfusion of red blood cells was indicated if Hb was < 8 g/dL in the general population, < 8.5 g/dL in patients with heart disease or older than 70 years old ; between 8.5-9 g/dL in patients who did not tolerate sitting. The decision to transfuse allogeneic blood during surgery was taken by the anaesthesiologist or during the post-operative period by the ward doctor. The total number of allogeneic blood transfusion units was recorded.

Tranexamic acid utilization protocol

In revision TKA, two 1g bolus doses of TXA (Amchafibrin®, Rottafarm SL, Valencia, Spain) were administered over a period of 30 minutes. The first dose was administered 15 to 30 minutes before the pneumatic tourniquet was inflated. The second dose was administered as follows : if the surgery time was less than 60 minutes, it was given between 60 to 90 minutes after the first dose ; or in the case of a surgery that lasted more than 60 minutes, the second dose was given when the tourniquet was deflated.

TXA was contraindicated in cases of allergy to TXA, a previous history of coagulopathy or a thromboembolic event, patients under anticoagulant or contraceptive treatment, a previous by-pass surgery and carriers of a cardiovascular prosthesis.

Statistical analysis

This cohort study was planned as an exploratory study. Thus, no formal calculation of the sample size, required in studies with a previous hypothesis, was performed. The final sample size was defined by the total number of patients who fulfilled the inclusion criteria in our center. Statistical analysis was carried out according to the complete sample analysis (full analysis set).

Statistical Comparisons

The final cohort of revision TKA patients was divided into 3 groups depending on whether they had been treated with TXA. The control group corresponded to patients not treated with TXA because the TXA protocol was not applied (TXA not administered although it was not contraindicated) ; the TXA group included patients

who followed the TA protocol ; and the NO-TXA group incorporated patients who did not fulfill the TXA protocol (TXA not administered because of contraindication).

The main variable was the percentage of patients transfused. The secondary variables included the number of RBC units transfused, the change in the Hb concentration between the pre- and postoperative periods, the volume of bleeding in the vacuum drains, and hidden blood loss calculated according to the formula described previously (17). The safety variables were the incidences of adverse events related to study treatment, medical complications, and vascular complications (pulmonary embolism, PE ; myocardial infarction, MI ; cerebral vascular accident, CVA ; transient ischaemic attacks, TIA ; deep vein thrombosis ; DVT) and the mortality of patients.

A descriptive analysis was performed for baseline patients' characteristics. Continuous data was summarized as a median (range) or mean (standard deviation), and categorical data was summarized as percentages and the number of cases. Differences between diagnostic groups were evaluated with the Fisher test for qualitative variables and with an analysis of variance (ANOVA) for quantitative variables when they followed a normal distribution or with a Kruskal-Wallis test when normality tests failed. A p value of ≤ 0.05 was considered statistically significant.

Data analysis was performed using the statistical software programs SPSS version 18.0 (SPSS Inc (IBM), Chicago, IL).

RESULTS

Patient characteristics

A total of 68 patients were included. Table I shows the baseline characteristics of the patients included in the study stratified by TXA treatment groups : control (28 patients), TXA (19 patients) and NO-TXA (21 patients). The ratio male/female was 1:3.

Revision total knee arthroplasty procedure

All surgical procedures were performed by senior orthopaedic surgeons with extensive revision TKA experience. An epidural anaesthesia with an analgesic catheter was performed in all cases. All patients received the same prosthesis model. The

Table I. — Baseline characteristics (control group : tranexamic acid not-administered although it was not contraindicated ; TA group : tranexamic acid administered ; and NO-TA group : tranexamic acid not administered because it was contraindicated)

Characteristics		Whole population N = 68	Control group N = 28 (41%)	TA group N = 19 (28%)	NO-TA group N = 21 (31%)
Age (years)	Mean [sd]	74 (6)	74 (5)	75 (5)	74 (8)
Male/female	n / n	19 / 49	9 / 19	2 / 17	8 / 13
Weight (kg)	Mean [sd]	79 (12)	80 (12)	77 (14)	79 (10)
Height (cm)	Mean [sd]	159 (8)	158 (9)	158 (7)	161 (7)
Body Mass Index	Median [range]	30 [23-48]	31 [23-48]	29 [25-43]	30 [23-39]
Time of ischaemia ¹ (min)	Mean [sd]	123 (13)	125 (13)	120 (16)	124 (8)
Antiplatelets ²	n (%)	7 (10%)	0 (0%)	0 (0%)	7 (34%)
Dicoumarinics	n (%)	3 (5%)	0 (0%)	0 (0%)	3 (14%)
Thromboembolic disease	n (%)	6 (42%)	0 (0%)	0 (0%)	6 (29%)
Respiratory insufficiency	n (%)	8 (12%)	3 (11%)	1 (5%)	4 (19%)
Hypertension	n (%)	44 (65%)	13 (46%)	16 (84%)	15 (71%)
Diabetes mellitus	n (%)	4 (6%)	1 (4%)	0 (0%)	3 (14%)
Cardiovascular disease ³	n (%)	10 (15%)	0 (0%)	0 (0%)	10 (48%)
Valve prosthesis	n (%)	1 (1%)	0 (0%)	0 (0%)	1 (5%)
Deep Vein Thrombosis	n (%)	2 (3%)	0 (0%)	0 (0%)	2 (10%)
Pulmonary embolism	n (%)	1 (1%)	0 (0%)	0 (0%)	1 (5%)
Peripheral vascular pathology	n (%)	5 (7%)	0 (0%)	0 (0%)	5 (24%)

¹ Time of ischemia or time of tourniquet.

² Antiplatelets includes : AAS and clopidogrel.

³ Cardiovascular disease : CVA, TIA, MI.

mean hospital stay was 11 (SD 4) days in the control group, 10 (SD 3) days in the TXA group and 12 (SD 5) days in the NO-TXA group.

No complications were recorded during the surgical procedure or in the post-operative period.

Effectiveness of tranexamic acid

Table II shows the variables related to blood loss (percentage of patients transfused, RBC units transfused, Hb concentration, estimated blood loss : drainage and hidden blood loss) in the 3 groups studied. Although the pre-operative Hb concentration was similar in all groups, the group treated with TA was less often transfused, required a lower number of transfused units (Kruskall-Wallis, $p = 0.057$), had favourable Hb evolution during the study period and a lower estimated blood loss.

Safety of tranexamic acid

No adverse events were recorded. No patients developed thromboembolic episodes.

DISCUSSION

To our knowledge, this retrospective cohort study is the first one done to evaluate the effectiveness of tranexamic acid in revision TKA that provides evidence that early administration of a short course of TXA decreases the number of patients transfused and the number of transfused blood units required. In fact, TXA reduced the total blood loss in revision TKA, reduced hidden blood loss and the total drained blood collected in comparison to patients not treated with TXA.

Table II. — Variables related to blood loss (control group : tranexamic acid not administered although it was not contraindicated ; TA group : tranexamic acid administered ; and NO-TA group : tranexamic acid not administered because it was contraindicated)

		Control group N = 28	TA group N = 19	NO-TA group N = 21
Patients transfused	n (% , [95%CI])	15 (54% , [34%-72%])	6 (32% , [13%-57%])*	13 (62% , [38%-82%])
RBC units transfused	Median [range]	2.0 [1-4]	2.0 [2-2]	2.5 [1-5]
Hb concentration (g/L)				
Pre-operative	Median [range]	134 [109-167]	132 [118-150]	130 [101-162]
24 hours (day 1)	Median [range]	104 [75-128]	109 [90-137]	96 [63-124]
48 hours (day 2)	Median [range]	99 [74-112]	108 [82-126]	96 [82-112]
72 hours (day 3)	Median [range]	99 [88-117]	104 [78-110]	102 [85-115]
120 hours (day 5)	Median [range]	104 [90-129]	113 [93-131]	102 [90-139]
Estimated blood loss (mL)	Mean [sd]	1693 (689)	1196 (665)**	2454 (2166)
Drainage ¹ (mL)	Mean [sd]	783 (468)	501 (326)***	859 (715)
Hidden blood loss (mL)	Mean [sd]	884 (731)	694 (832)	1594 (2241)

¹total volume of bleeding recollected in the vacuum drains.

Patients transfused : *TA versus control : p = 0.137 and TA NO-TA : p = 0.055.

Estimated blood loss (mL) : **TA versus control : p = 0.018 and TA versus NO-TA : p = 0.020 ; ***TA versus control : p = 0.028.

Revision TKA in comparison to primary TKA implies a major loss of bone stock and the inadequacy of soft-tissue constraints even if it is performed by a skilled, experienced surgeon. Moreover, all of the risks associated with primary TKA are increased in revision TKA, especially infection, nerve damage, blood clot formation and bleeding. Among these, postoperative blood loss associated with allogenic blood transfusion is one of the major problems in primary TKA. Although blood loss may be predictable in a primary unilateral TKA (13), it is less predictable in revision TKA (4). Presumably, postoperative blood loss should be higher. Our findings suggest that TXA administered as a short course during the surgical procedure decreased total blood loss in revision TKA. It is worth noting that a standard protocol for the use of TXA is not available. TXA has been tested in different doses and schedules, as a single bolus dose, repeated doses, continuous infusion and during and/or after surgery (2,8,11,24,25). The aforementioned variability among studies makes it difficult to determine the efficacy of TA in reducing diffuse micro-vascular bleeding. Regardless of that, the reduction in total blood loss observed in revision

TKA in our study, following a TXA schedule used for primary TKA (24), is in concordance with other studies of primary TKA (1,6,15), in bilateral TKA (16) as well as in revision total hip replacement (5). Likewise, similar results have recently been published on topical application of TXA directly onto the open joint surfaces (26). In contrast and as expected, the patients not treated with TXA presented a percentage of transfusion as usually reported in this type of surgery (4). The evaluation of the cost-effectiveness of TXA in revision TKA was not within the scope of this study. Nevertheless, an important topic in health policy is allogenic blood transfusion requirements. Our results suggest that the implementation of a TXA protocol reduces the percentage of patients with a need for a blood transfusion and reduces the number of blood units needed to be transfused per patient.

Hidden blood loss in orthopaedic surgery is a major concern as it may be another risk factor that leads to severe complications after surgery ; it is difficult to measure. Its quantification by ultrasonographic methods (20) or by measuring the joint circumference (2) may underestimate it. We calculated it by means of a formula (17) and the hidden

blood loss was higher than the volume of drained blood collected in all groups studied. This result differs from that reported in primary TKA (6), where the authors suggested that concealed loss was only marginally influenced by TXA and was at least as great as the drainage volume. One reason for this difference between studies may be the extended period of time the drains remained in place, which was longer in our study. In contrast and as expected in the group of patients not treated with TXA because of a contraindication, hidden blood loss was higher than in the other groups. Likewise, the findings in terms of hidden blood loss were in accordance with the volume of blood collected in the vacuum drains.

The prevalence of preoperative anaemia has to be taken into account among patients admitted for major elective orthopaedic arthroplasty. Approximately 20% of these patients were relatively anaemic (21). In our study, only 15% of the patients were considered anaemic on admission. In addition, those patients with a preoperative Hb level < 13 g/L reportedly had four times more risk of having a transfusion than those with an Hb level between 13 and 15 g/L (22). In fact, the overall mean preoperative Hb level (13.3 g/L) in our patients was close to the boundary of this risk factor of having a transfusion.

On the other hand, the use of TXA in primary knee arthroplasty does not appear to increase the risk of thrombosis despite different dosing regimens among varying studies (1,2,6,9,12,15,19,25). No clinical thromboembolic complications were observed in our study, but a systematic ultrasonographic examination was not performed on these patients.

Some limitations of this study should be acknowledged. The retrospective design and the small sample size may cause the results obtained to be underestimated or overestimated. The quantitative variables analyzed (number of transfused patients, volume of bleeding in the vacuum drains, Hb concentrations...), and the blinded conditions to carry out the statistical analysis and interpretation of the results minimize these limitations. Likewise, the Hb level at baseline may have caused the results obtained to be overestimated. Despite these limita-

tions, this study reflects the clinical practice of our unit and provides important information about the effectiveness of TXA in revision TKA.

In summary, in this retrospective study, TXA appeared as an effective, safe, easy to use and cost-efficient means to reduce blood loss and blood transfusion requirements in revision TKA. Further research based on prospective randomised clinical trials will be necessary to confirm these findings.

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