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ORIGINAL STUDY

Tranexamic acid in joint replacement : a randomized trial comparing intravenous oral and topical routes

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Our purpose is to compare intravenous, oral and topical routes of tranexamic acid in terms of reducing perioperative blood loss and blood transfusion rates in total knee and hip arthroplasty. In this prospective randomized comparative study, 57 patients undergoing primary knee or hip arthroplasty were assigned to receive intravenous, oral or topical tranexamic acid. Primary outcomes were blood loss at day 1 and day 3. The mean blood loss at day 1 was 954 ±356 mL in the intravenous group, 880 ±506 mL in the oral group and 754 ±382 mL in topical group with no statistically significant difference (p=0.15). The mean blood loss at day 3 was 1659 ±637 mL in the intravenous group, 1530 ±686 mL in the oral group and 1296 ±588 mL in topical group. With no statistically significant difference (p=0.22). None of the 3 routes was found to be superior in terms of reducing perioperative blood loss in joint replacement.

Keywords : tranexamic acid ; knee arthroplasty ; hip arthroplasty ; drug administration routes.

INTRODUCTION

Reducing perioperative blood loss is a major current concern in total knee and hip arthroplasty. Excessive blood loss and subsequent allogenic blood transfusion are associated to increased postoperative pain and swelling, higher rates of anemia and infection and longer hospital stay *(24)*. Numerous procedures have been used in order to reduce this loss including antifibrinolytic agents *(15,22,38)*. Tranexamic acid (TXA) is increasingly implemented in blood management protocols in total knee and hip arthroplasty *(4,14,25,8)*. Abundant recent high quality data confirmed the effectiveness and the safety of use of TXA in total knee arthroplasty (TKA) and total hip arthroplasty (THA) to reduce perioperative blood loss and transfusion rate *(1-3,5,8,9,16,21,30-36,40)*. However, there is a considerable disparity in terms of TXA administration protocols concerning mainly the minimal effective dose and the administration route *(11)*. Initially, the intravenous (IV) route has been widely preferred for years. At present, oral and topical routes use is progressively merging. Their effectiveness and safety are now confirmed by good quality studies either for single or combined use *(1,5,6,21,37)*.

Our prospective randomized trial aimed to compare IV, oral and topical routes in terms of

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reducing perioperative blood loss in TKA and THA patients.

MATERIALS AND METHODS

Our study is a single-center, randomized, comparative trial. It included patients who underwent either primary TKA or THA. The study was conducted between February 1st, 2017 and August 31st, 2017. The trial intervention was explained to patients and consent to participate in the study was obtained.

All patients scheduled within the study period for primary TKA or THA were evaluated for inclusion to the trial according to the following criteria :

- 18 years of age and more
- indication for surgery : patients with osteoarthritis (TKA and THA patients) or aseptic femoral head osteonecrosis(THA patients) were exclusively included
- scheduled for spinal anesthesia
- ability to give a free informed consent.

Before randomization, the following patients were excluded from the trial :

- patients with history of renal failure, seizures, thrombophilia and/or major thromboembolic accidents (deep venous thrombosis and/or pulmonary embolism)
- patients with active cancer
- patients allergic to TXA
- patients with chronic alcoholism
- women under oral contraceptive drugs
- patients under adenosine diphosphate antagonists, under vitamin K antagonists, Xa factor inhibitors or thrombin inhibitors
- patients refusing to participate in the trial

Moreover, after the surgery, patients who underwent conversion to general anesthesia during the surgery were excluded.

Included patients were randomized to one of three protocols :

- IV group : patients received a 30 minutes IV perfusion of 1g of TXA, 30 minutes prior to incision. After surgery, patients received 30 minutes IV perfusion of TXA every 8 hours during the first postoperative 24 hours.
- oral group : patients received 2 tablets of 500mg of TXA, 2 hours prior to surgery. After surgery, patients received 2 tablets of 500mg of TXA every 8 hours during the first postoperative 24 hours.
- topical group : for patients undergoing TKA, the surgeon injected 3g of TXA in the joint right after joint capsule closure. For patients undergoing THA, the surgeon injected 3g of TXA in the operative site right after the closure of the iliotibial band.

Both TKA and THA patients underwent a spinal anesthesia. Prophylactic antibiotic treatment protocol was applied according to the French Anesthesiology and Intensive Care Society Guidelines *(29)*. Interventions were performed by one senior knee and hip specialized surgeon.

TKA surgery and postoperative care

Peroperative bleeding was prevented with tourniquet for all patients. A medial para-patellar trans-vastus approach was performed. Bone cuts and ligament balance were computer-navigated. Thus, no drilling of the femoral and tibial canals was made. A single brand of cementless posterior crutiate-retaining prosthesis with mobile insert was implanted. Patellar resurfacing with a cemented implant was performed for all patients. Synovial membrane and subcutaneous tissue were infiltrated with 100 ml of a 2mg/mL ropivacain solution just prior to closure. No postoperative drain was put. Tourniquet was deflated right after dressing.

Local postoperative analgesia was provided by a 6ml/hour ropivacain 2mg/mL infiltration using an intra-articular catheter kept for the first 24 hours. A patient-monitored IV morphine analgesia was also applied. Pharmacologic thromboprophylaxis consisted of daily 10mg single oral dose of rivaroxaban for the first 15 days. In case of contraindication, rivaroxaban was replaced by a daily single subcutaneous injection of 10mg/10kg of enoxaparin. Physic thromboprophylaxis methods were also applied (pneumatic compression, elastic socks, limb elevation). Icing and early motorized passive mobilization of the knee was started 2 hours after of the surgery. First standing and progressive walking program were started at day 1.

Hemoglobin level (Hb) was assessed at day 1 and day 3. A blood transfusion was indicated in

case of Hb drop under 7.5g/dL for non-coronary patients or under 10g/dL for coronary patients or in case of Hb decrease ≥2g/dL with objective clinic signs of anemia. In-hospital thromboembolic accidents were screened by clinical examination twice a day. During the first 3 months, out-hospital thromboembolic accidents were screened by clinical examination at every scheduled control and whenever the complication is suspected by patients and physiotherapy care providers. Based on clinical assessment, imaging exams were performed whenever indicated.

THA surgery and postoperative care

Patients were installed in lateral position. A posterolateral approach was made. Joint posterior capsule was incised and not removed. Acetabular preparation, femoral neck cut and femoral shaft preparation were made in a classic fashion. A single brand of cementless implants with dual mobility cups were used. No postoperative drain was put.

A patient-monitored IV morphine analgesia was applied. Thromboprophylaxis protocol was the same as TKA patients. First standing and progressive walking program were started at day 1.Transfusion indications and thromboembolic accidents screening were similar to those applied for TKA patients.

Prior to intervention, demographic data, medical history, physical examination findings and preoperative Hb were collected for each patient eligible for randomization.

Primary outcomes were blood loss in the first 24 and in the first 48 hours after surgery. Secondary outcomes were : the need for blood transfusion during the hospital stay and the occurrence of major thromboembolic accidents in the first 3 months after surgery.

Blood loss was calculated using Gross formula method *(13)*. Preoperative Hb (Hb pre), Postoperative Hb (Hb post) at postoperative day 1 and day 3, weight (Wt) and estimated total blood volume (BV) were used for calculation :

$$\text{Blood Loss (ml)} = \frac{\text{BV(mL/Kg) x Wt(Kg) x 2 x (Hb pre-HB post}}{\text{(Hb pre + Hb post)}}$$

Nadler's formula method was used to assess BV *(23)*.

Preoperative data, primary and secondary outcomes were described as the mean ± standard deviation (SD) for quantitative variables and in frequencies and proportions for qualitative variables. To compare the 3 groups, a univariate analysis was used for continuous variables and a chi^2test was used for categorical variables. A p value <0.05 was retained as a statistical significance threshold.

RESULTS

Between February 2017 and August 2017, 74 patients met the inclusion criteria and were screened for participation in the study, of which 16 were excluded prior to intervention. One more patient was excluded after the intervention because he required a conversion to general anesthesia. Eventually, 57 patients were included, randomized and assessed

Figure 1. — Study flow diagram.

Table I. — Preoperative characteristics

	IV group	*Oral group*	*Topical group*	*p value*
Age	70,51 (±11,46)	67,67 (±10,57)	71,4 (±8,41)	0,5
Sex (male/female)	4/15	8/10	4/16	0,17
Weight (Kg)	80,84 (±6,71)	80,88 (±20,74)	80,2 (±20.20)	0,99
Preoperative Hb (g/dL)	14,36 (±1,16)	14,47 (±1,30)	13,87 (±1,30)	0,29

Table II. — Mean blood loss at postoperative day 1 and day 3

TXA administration route	*n at day 1*	*Mean blood loss (mL)*	*n at day 3*	*Mean blood loss (mL)*
IV	19	954 (±356)	18*	1659 (±637)
Oral	18	880 (±506)	18	1530 (±686)
Topic	20	754 (±382)	19**	1296 (±588)
p value		p=0,32		p=0,22

* blood loss at day 3 was not assessed for one patient in the IV group because he left the hospital at day 2. ** blood loss at day 3 was not assessed for one patient in the topical group because he received a blood transfusion at day 2.

Table III. — Mean blood loss at postoperative day 1 and day 3 for TKA and THA subgroups

Administration route		*n at day 1*	*Mean blood loss (mL)*	*n at day 3*	*Mean blood loss (mL)*
TKA subgroup	*IV*	12	995(±374)	12	1708(±725)
	Oral	9	684(±430)	9	1338(±669)
	Topical	15	751(±398)	14**	1401(±398)
	p value		p=0,15		p=0,37
THA subgroup	*IV*	7	484(±338)	6*	1562(±453)
	Oral	9	1074(±554)	9	1722(±732)
	Topical	5	763(±421)	5	1003(±500)
	p value		p=0,44		p=0,11

* blood loss at day 3 was not assessed for one patient in the IV group because he left the hospital at day 2. ** blood loss at day 3 was not assessed for one patient in the topical group because received a blood transfusion at day 2.

for study outcomes (figure 1). Preoperative characteristics were similar in the 3 groups (table I).

Mean blood loss at postoperative day 1 and day 3 are represented in table II. Blood loss at day 3 was not evaluated in 2 patients. Reasons are detailed in table II. The difference between the 3 groups was not statistically significant.

The difference between the 3 administration protocols in the TKA and THA subgroups was not statistically significant for perioperative blood loss in the first 24 and in the first 48 hours. Mean blood loss for the 3 groups and corresponding p values in each subgroup are represented in table III.

Table IV: details of patients that required blood transfusion

	Group	*Sex*	*Age*	*Comorbidities*	*Surgery*	*Hb pre (g/dL)*	*Hb post day 1 (g/dL)*	*Hb post day 3 (g/dL)*
Patient 1	topical	Female	72	Hypertension	TKA	10,2	8	10,1*
Patient 2	oral	Female	81	Hypertension	THA	13,4	10,2	8,2

* Hb level after transfusion, this patient was not assessed for blood loss at day 3.

Two patients required blood transfusions for a Hb drop more than 2g/dL with objective clinical intolerance signs. The details of the two patients are represented in table IV. No major thromboembolic accident occurred in the first 3 months after surgery.

DISCUSSION

TXA is a synthetic competitive analogue of lysine. It forbids fibrinogen to activate plasminogen by occupying the lysine binding sites. Therefore, it inhibits plasmin formation. As a result, fibrinolysis process is not triggered and blood clots remain stable *(22)*. Interest to TXA in orthopaedic centers is relatively recent. Its use was first generalized in trauma patient based on the large CRASH-2 trial in 2011*(26)*. Its use was progressively generalized for most of the major orthopaedic procedures with blood loss concerns including arthroplasy. Compared to placebo, TXA reduces as much as 30% of perioperative blood loss and transfusion requirements for patients undergoing major joint replacement *(11)*. The effectiveness and the safety of this molecule in this indication has been confirmed for each of IV, oral and topical routes by good quality studies either for single or combined administration *(1,5,6,21,37)*.

Our prospective trial was conducted in order to compare these 3 administration routes in terms of reducing perioperative blood loss in TKA and THA patients. Our results showed that calculated blood loss was slightly lower with topical TXA but the difference was not statistically significant. Thus, topical TXA was found as effective as IV and oral TXA in terms of reducing perioperative blood loss in primary TKA and THA. One transfusion was recorded in each of topical and oral groups and no major thrombotic accident occurred. Because of this small number, no conclusion could be made concerning secondary outcomes.

Best to our knowledge, no prior study reported a direct comparison of the 3 administration routes of TXA used in TKA and THA. Our findings are consistent with prior studies comparing 2 administration routes that generally do not confirm the superiority of any protocol in terms of effectiveness and safety. Recent meta-analyses demonstrated the superiority of combining topical TXA to the classic single IV protocols *(19,28,34,39)*. Comparable results were observed with topical TXA used alone. Chen and al. reported a meta-analysis including 20 randomized controlled trials (RCT) with 1800 patients comparing IV TXA to single use of topical TXA for patients undergoing TKA and THA. The main findings were that topical TXA used on its own was as effective and safe as IV TXA in reducing blood loss and transfusion rate*(6)*. Later, an updated meta-analysis including 22 RCT (among whom 14 were included in the meta-analysis of Chen and al.) showed no difference in terms of blood transfusion rate and safety but found a significant difference in terms of maximum Hb drop in favor of IV route. However this difference was not higher than 0.25 g/dl per patient *(32)*. Furthermore, Hb drop seems inadequate to evaluate the effect of TXA on preventing peroperative blood loss since it do not take into consideration disparity in terms of anthropometric parameters and preoperative Hb *(20)*. Lee and al. compared 3 TXA administration regimens (IV, topical and combined topical and IV) in terms of reducing blood loss and transfusion rates in TKA patients. This study found that topical TXA protocol was the most effective and that no additional effect was obtained with the combination of IV route *(18)*. DiBlasi and al. found a significant difference in favor of topical TXA compared to IV

TXA in reducing postoperative drop of Hb levels in THA and TKA and calculated blood loss in TKA with no difference in terms of blood transfusion rate *(7)*.

Few studies compared IV to oral routes. A recent meta-analysis including 5 RCT with 3474 patients found a similar effect of IV and oral TXA in terms of blood loss sparing and blood transfusion rate in TKA and THA *(37)*.Our results showed a little superiority of oral route with no statistical significance for TKA patients sub-group. A RCT reported the superiority of combined oral and topical TXA compared to single topical injection in TKA patients *(5)*. In that study, a dose of 1.5g for topical route protocol and a maximum dose of 2g for oral route protocol were used compared to 3g and 1g respectively in the present study. Furthermore, authors reported the use of a suction drain in contrast with the technique described in the present study. Thus, topical TXA could have been partially eliminated with drainage. Thirdly, in opposition to that trial, a computer-navigated TKA technique was used in our patients with no need for intra-medullary drilling. TXA injected in the joint space would have poor effect on the intra-medullary bleeding in the other study. These technical disparities between the 2 studies keep us from retaining a clear conclusion about the benefit of combining oral and topical routes.

Our findings could call into question the usefulness of systemic TXA administration routes (IV and oral) in the indication being addressed. The use of systemic routes is associated with poor drug concentration in the joint site, increase of nursing workload, and the contested effect on hidden blood loss *(10,12)*. A pharmacokinetic study conducted in rabbits showed that topical route is associated with reduced peak plasma TXA concentration and prolonged therapeutic drug level compared with IV route *(27)*. Other studies confirmed that no additional blood loss saving effect is obtained by maintaining therapeutic plasmatic TXA level more than 16 hours after surgery *(17,41)*.Therefore, one could presume that topical route being as effective and safe as the systemic routes, and having comparable plasma TXA concentration profile in the earlier postoperative hours, would be simpler to apply. However, DiBlasi and al. found that the use of topical TXA is associated with increased cost compared with IV route.The study gives few details about the methodology of assessing cost-effectiveness. In particular, authors did not mention if the cost of blood transfusions for each group has been took into consideration knowing that topical TXA reduced blood transfusion requirements in this study in a significant way (6 patients versus 10 for IV route) *(7)*. Further higher quality studies with larger groups and longer follow-up are needed to assess the relevance and the cost-effectiveness of abandoning systematic administration routes in favor of topical TXA in TKA and THA blood saving protocols.

Our study has some limits. First, it is a mono-centric study including only 57 patients. A statistically significant difference in favor of one of the 3 administration routes could appear with larger patient samples. No conclusion was retained concerning the difference in terms of blood transfusion rate and thrombo-embolic complications because of the restricted number of patients. The sample size was limited because patients of one single surgeon in our department were screened in order to avoid interferences of blood loss disparities related to different operative techniques adopted by other colleagues (no computer navigation, tourniquet deflating timing, use of suction drain, cemented implants and surgery duration). Second, our trial was not blinded for both patients and surgeon. We assumed that the awareness of the surgeon about the TXA administration route would not modify the operative technique. Finally, our study was not controlled with a placebo group. We considered that it would be unethical to deprive patients from the TXA well established benefits and expose them to the potential risks of excessive blood loss and blood transfusion complications. Currently, the design of a multi-centric larger study including patients undergoing TKA with a similar operative technique (computer-assisted, no suction drain and cementless implants) is being set up.

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