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Analysis of the Results on Perioperative Blood Loss after a Total Knee Arthroplasty Employing Tranexamic Acid Before or After Inflating the Tourniquet

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Abstract

Introduction: Tranexamic acid has showed its good results reducing blood loss in total knee arthroplasties. It has also probed being cost-effective (red cell concentrate: 350 euros/ TXA vial 3, 05 euros) but it remains not being clear at what time during the surgery we have to administrate it. In this prospective, randomized study, we have investigated the effects of the use of tranexamic acid before or after inflating the tourniquet on blood loss, transfusion needs and thromboembolic complications after implanting a total knee arthroplasty. 120 patients were selected and assigned randomly in two groups: tranexamic acid employed before inflating (Group 1) or just before deflating the tourniquet (Group 2).

Methods and materials: From May 2011 to May 2012, 80 patients (38 males, 42 females; aged 64-81 years, mean age 69, 2 years) underwent to a total knee replacement. All of them had moderate-severe knee osteoarthritis. They were randomized divided into Group 1 and Group 2 of 40 patients each. The patients in Group 1 received Tranexamic Acid (TXA) before inflating the tourniquet and TXA was administered on the patients in Group 2 5 minutes before deflating the tourniquet. TXA was used in both groups every 8 hours during the first three days postop. Variables under comparison included haemoglobin determinations (pre, postop and fifth days after surgery), drainage blood volume, transfusion requirements and appearance of thromboembolic complications.

Results: The drainage blood loss was 364 +/- 186 ml (Group 1) and 413 +/- 175 ml (Group 2). The total blood loss was 573 +/- 159 ml (Group 1) and 608 +/- 132 (Group 2). No statistical significant differences were found in the amount of blood at the drain and on the total blood loss. The haemoglobin values did not showed statistical significant differences between groups before surgery on the postop or 5 days after the surgery. No significant difference in haemoglobin determinations (pre, postop and fifth days after surgery), drainage blood volume, transfusion requirements, deep-vein thrombosis, and pulmonary embolism was detected between the groups. One patient in group 1 received 1 unit of allogenic blood and one patient in group 2 received 3 units. No statistical significant difference was seen. Two patients in group 1 and three patients in group 2 had clinical symptoms of deep vein thrombosis. Only one patient in group 2 presented an eco-Doppler study positive for a lower limb thrombosis

Conclusions: We conclude that there is no significant difference on blood loss, transfusion requirements and thromboembolic complications after performing a total knee arthroplastywhen thetranexamic acid is employed before inflating or just before releasing the tourniquet.

Keywords

Tranexamic acid, TKA, Administrate, Effectiveness

Introduction

Performing a total knee replacement (TKR) supposes the loosening of 1500 to 1900 cc of blood (drainage volume + haematoma formation) [1-3].

Some factors have being related to the TKR bleeding as: patients co-morbidities (cardiovascular, respiratory, hepatic and coagulation diseases), drugs (NSAIDs, salicilates, LMWH, antiagregants), anaesthetic technique (spinal or general), postoperative blood pressure (systolic under 150 mmHg) and surgical technique (use of cement, size of the incision, tourniquet time, haemostasia, tissue damage).

Nearly fifty present of the patients operated of a TKR need postoperative blood transfusion. Blood transfusion presents of disease transmission [4-6], ABO group incompatibility [7], infection due to inmunosupression [8,9] and high costs.

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Some solutions, as the administration of antifibrinolytic drugs (tranexamic acid), have been proposed to reduce the bleeding on a TKR surgery and to decrease the number of transfusions. Hyperfibrinolysisis considered being the major cause of postoperative bleeding after TKA surgery [10-14], the fibrinolytic system is activated in the first hours after surgery increasing the postoperative bleeding after remove the pneumatic tourniquet [15-17]. Tranexamic Acid (TXA, trnas-4-aminomethyl cyclohexane carboxylic acid), is a synthetic reversible inhibitor of fibrinolysis, that competitively blocks a lysine binding site of plasminogen [18]. It has been used during more than 20 years in cardiac surgery, urology, genecology, liver transplants, etc. This medication reduces blood loss but it can also increase the risk of thromboembolic complications [19].

Multiple studies have been done to verify the efficacy of tranexamic acid and find the correct dose and the duration of treatment [1,2,20-24].

The first publishedstudies established the correct therapeutic dose of tranexamic acid at 10 mg /kg [25,26]. But this dose maintains a correct plasma concentration of TXA just for only 3 hours [27] and this fact has been the argument to use higher doses of TXA.

More recent studies demonstrated that a tranexamic acid dose of 15 mg/kg every 8 hours during 24 hours would be appropriate to reduce blood loss [16,28].

Hiippala et al. [24] proposed to maintain TXA for several days taking into account that the tourniquet application may affect haemostasis for a considerably longer time than the surgical procedure. Jansen 1999 et al. [15], employed TXA before and 72 hours after surgery demonstrating that the degree of blood loss correlated significantly with both fibrinogen and plasminogen concentrations during the first 24 hours. Research on tranexamic acid and thrombosis failed to show any thrombogenic effect [22,23,29] but thrombotic complications were reported with therapy exceeding 24 hours [30,31].

Frequently, TXA was administered before the deflating of the tourniquet [20,22-24]. Knowing that tourniquet inflation stimulates the fibrinolytic system [32,33] Jansen et al. [15] employed TXA before inflating the tourniquet having good results and without increasing the number of thrombotic complications.

As no consensus has been reached on when starting to use the TXA and for how long we performed this study to analyse the results (blood loss, transfusion requirements and thromboembolic complications) employing TXA before inflating the tourniquet or just before deflating it and maintaining the TXA in both groups during 24 hours.

Methods and Materials

A randomized clinical trial approved by the Hospital Ethics Committee was carried out with two groups: group 1 administrating Tranexamic Acid (TXA) before inflating the tourniquet and group 2 were the acid was given 5 minutes before deflating the tourniquet.

Patients with a coagulopathy, a thromboembolic event, treated with aspirin or non –steroidal agents the week before the surgery, a plasma creatinine greater than 115 micromol litre in men and 100 micromol litre in women, allergic to tranexamic acid, a hepatic or renal dysfunction, aserious cardiac or respiratory disease, an acute infection, a malignant disease or being treated with drugs affecting the coagulation system were excluded.

The patients included presented an anaesthetic risk (ASA) I or II, signed the informed consent and presented and osteoarthritic knee.

Patients were operated performing a unilateral total knee replacement between May 2011 and May 2012 by two senior surgeons following a standardized procedure in the same Hospital.

The sample size was calculated on the basis of the mean difference in the visible blood loss greater or equal to 300 ml between the two study groups with a standard deviation of 500ml, an alpha error of 0, 05 and 90% statistical power: 30 patients were needed in each group. Estimating 10 % losses on the follow up, 80 patients were included in our study.

Anumber was assigned to each patient following the order of inclusion in the study. The patients were randomized in two groups: one received tranexamic acid before inflating the tourniquet and the other, five minutes before the release of the tourniquet.

Twelve hours before the surgery a subcutaneous injection with 40 mg of enoxaparin (Clexane, Sanofi-Aventis, S.A., Barcelona, Spain) was administrated. The antithrombotic prophylaxis with 40 mg of enoxaparin per day was maintained during one month. Isobaric bupivacaine was employed to perform the subarachnoid spinal anaesthesia.

The antibiotic prophylaxis consisted in 2 g of cefazoline administrated 30 minutes before starting the surgery and 1 gr every 6 hours during the first day postop. In patients allergic to penicillin we employed 1g of vancomicin one hour before surgery followed by 1 g every 12 hours during 24 hours.

Before inflating the pneumatic tourniquet to 300mmHg, the patient leg was elevated during 5 minutes to allow a partial exanguination.

Posterior stabilized cemented (Palacoscement, HeraeusMedical, Hanau, Germany) knee prostheses Genesis II (Smith & Nephew; Memphis, Tenn) were implanted. The wound was closed, one intraarticular drain at atmospheric pressure opened 30 minutes after the end of the surgical procedure was inserted and maintained for 24 hours and a compressive bandage was applied before release of the tourniquet.

Tranexamic acid at a dose of 15 mg/kg (Amchafibrin, Rottapharm, S.A., Barcelona, Spain) was infused intravenous in 100 cc saline 30 minutes before surgery in group one and five minutes before deflate the tourniquet in group 2. Then tranexamic acid was used in both groups every 8 hours for 1 day with the same dose.

During the surgical intervention patients received a Ringer's solution at a rate of 4ml/kg/h for compensation of insensible fluid losses and crystalloids in equal volumes to compensate measured blood losses.

Patients were transfused an allogenic red blood concentrate of 250ml if they reached a haemoglobin level of less than 8 g/dl or they present signs or symptons of hypoxia (tachycardia, dyspnoea or syncope) with a haemoglobin level of less than 10g/dl.

Physiotherapy has started on the first postoperative day after removing the drainage.

Blood tests were performed the night before the surgery, 5 hours after the operation and 5 days after the surgical procedure.

Variables under comparison included haemoglobin determinations (pre, postop and fifth days after surgery), drainage blood volume, transfusion requirements and appearance of thromboembolic complications.

To estimate the blood loss wecalculated first the loss of Hb (grams) assuming that the blood volume on the fifth day after surgery was the same as before surgery [34] and employing the following formula [35]:

Hb_{loss}= BV x (Hb_{B}-Hb_{5}) x 0,001+Hb_{t}

Hb_{p}= Haemoglobin preop

Hb_{5}= Haemoglobin fifth day after surgery

Hb_{t}= Haemoglobin transfused (every unit of banked blood is considered to contain 52 g of haemoglobin)

The blood loss (ml) was related to the patient's preoperative Hb value (Hb_{p}) following this formula:

Table 1: Demographics parameters.

	Group 1	Group 2	P Value
Sex (M/F)	22/18	16/24	0,416
age	68 (64-81)	70.5 (64-81)	0,124
weight	74,3	77,8	0,386
height	158,7	162,5	0,374
ASA (I/II)	12/28	9/31	0,569

Table 2: Operative time and duration of tourniquet inflation.

	Group 1	Group 2	P Value
Duration of surgery (min)	92,1	86,5	0,436
Tourniquet time (min)	97,4	91,7	0,320

Table 3: Blood values before surgery, postop and 5 days after the surgery.

	Group 1	Group 2	P-value
Hb concentration preop	13,2 (12,4-15,8)	12,9 (11,8-15,2)	0,735
Hb concentration postop	10,8 (8,0-12,3)	10,4 (7,8-12,6)	0,379
Hb concentration 5 days postsurgery	11,6 (10,1-12,7)	11,2 (10,2-12,3)	0,553
Drainage (ml)	364 +/- 186	413 +/- 175	0,274
Blood loss	573 +/- 159ml	608 +/- 132	0,341
Red cells transfused (units)	1	3	0,413
Number of patients transfused	1	1	0,586
Thromboembolic complications	2 DVP	3 DVP (1 Doppler +)	0,163

Blood loss=1000 x Hb_{loss}/Hb_{p}

Patients were seen at the out-patient clinic 2 weeks after the surgery to check the presence of possible complications, particularly thrombosis and thromboembolisms.

All results were recorded and an Excel chart was done. A statistical analysis was performed describing the variables first. Then a Student'st - test was used to assess the homogeneity and to compare the main results between the two groups for continuous variables. When the distribution was not normal, the Mann -Whitney U test was used to compare means. ANOVA test (analysis of variance) was used to compare means between different parameters. The chi square test was used to compare percentages. In all cases, the level of statistical significance was 0, 05. Comparisons were made employing the SPSS v.18.0.

Results

The groups studied had similar characteristics before surgery with no statistically significant differences in demographics parameters (Table 1).

The two groups were statistically comparable in operative time and duration of tourniquet inflation (Table 2).

The drainage blood loss was364 +/- 186 ml (Group 1) and 413 +/- 175 ml (Group 2)

The total blood loss was 573 +/- 159 ml (Group 1) and 608 +/- 132(Group 2)

No statistical significant differences were found in the amount of blood at the drain and on the total blood loss.

The haemoglobin values did not showed statistical significant differences between groups before surgery on the postop or 5 days after the surgery (Table 3).

One patient in group 1 received 1 unit of allogenicblood (Haemoglobine postop=8) and one patient in group 2 received 3 units (Haemoglobine postop=7,8). No statistical significant difference was seen.

Two patients in group 1 and three patients in group 2 had clinical symptoms of deep vein thrombosis (oedema and painful calf). Only one patient in group 2 presented an eco-Doppler study positive for a lower limb thrombosis. All of them received one month treatment of low-molecular weight heparin at therapeutic dosage. 2 weeks after the surgery, at the out patient's clinic, only this patient continued with oedema and pain on his leg. The rest were asymptomatic.

No pulmonary embolism was detected in our series.

Discussion

There are meta-analysis published studying the results of employing TXA against placebo in TKR concluding that is an effective drug degreasing blood loss and the needs of transfusion without increasing thromboembolic complications [1,2,36,37].

Our results obtained in drainage blood loss and total blood loss is similar to the ones obtained in those meta-analysis.

What is clear is that more than one dose of TXA is needed to be effective [37] and no differences have seen on the good results obtained with the TXA maintaining its administration for more than 24 hours [15].

In our experience, multimodal protocol with TXA administrated in dose of 15 mg/kg reduces the total bleeding and the drainage blood comparing our results with the obtained in other series where TXA results were measured against placebo [1,2,36-38].

It is use reduces transfusion requirements if we compare our results to the studies published comparing TXA against placebo. TXA reduces the cost of transfusion and avoids its risks.

Treatment with TXA before inflation of the tourniquet did not seem to augment the risk of DVT.

The results obtained in our study allow us to continue using TXA in unilateral TKR procedures to reduce blood total loss, the need of transfusion and knowing that there is no higher risk of thromboembolic complications. We have showed that there is no statistical significant difference in administrating the TXA before inflating or just before deflating the tourniquet so we can continue using it in a dose of 15mg/kg during 24 hours postop.

Conclusion

We conclude that there is no significant difference on blood loss, transfusion requirements and thromboembolic complications after performing a total knee arthroplasty when the tranexamic acid is employed before inflating or just before releasing the tourniquet.

As fibrynolitic activation is a cascade process that is most easily inhibited in its earlier phase, and tranexamic acid has little effect when given after heavy blood loss [39,40] we recommend to star administrating it before inflating the tourniquet.

Conflict of Interest

The authors received no financial support for the research and/or authorship of this article. The authors declare that they have no conflict of interest to the publication of this article.

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