Topical administration of tranexamic acid in primary total knee replacement

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Abstract

Introduction: Total knee replacement is a procedure potentially involved in major postoperative blood loss. Tranexamic acid is a synthetic antifibrinolytic agent which over the past years has been i.v. administered with good results by reducing the bleeding associated with total knee replacement. However, doctors are hardly experienced in the topic use of tranexamic acid.

Materials and Methods: We conducted a retrospective study with 117 primary total knee replacements so as to compare results between 63 surgeries with topic tranexamic acid and 54 surgeries without it. We compared rates of blood transfusion, haemoglobin concentrations and HCTs 24 and 48 h after the surgery, as well as required dressing changes, comorbidities and complications.

Results: In the tranexamic acid-group there was a 43.9%-decrease in blood transfusion rates as compared to the other group. Moreover, we registered a 0.2-1.3 g/dl-decrease in haemoglobin fall 24 h after the surgery. We did not detect any complication.

Conclusions: Topic use of tranexamic acid in primary total knee replacement decreases the requirement of blood transfusion without increasing the risk of complications.

Key words: Tranexamic acid; total knee replacement; blood transfusion.
Level of evidence: III

Uso tópico de ácido tranexámico en el reemplazo total de rodilla primario

Resumen

Introducción: El reemplazo total de rodilla es un procedimiento que puede generar una gran pérdida de sangre durante el período posoperatorio. El ácido tranexámico es un agente sintético antifbrinolítico que, en los últimos años, se ha administrado por vía intravenosa, con buenos resultados, al reducir el sangrado asociado al reemplazo total de rodilla. Sin embargo, existe escasa experiencia con su uso tópico.

Materiales y Métodos: Se llevó a cabo un estudio comparativo retrospectivo de 117 reemplazos totales de rodilla primarios, para comparar los resultados obtenidos en 63 cirugías con el uso tópico de ácido tranexámico y en 54 reemplazos sin ácido tranexámico. Se compararon la tasa de transfusión, las concentraciones de hemoglobina y hematocrito a las 24 y 48 h, las curaciones requeridas, las comorbilidades y las complicaciones.

Resultados: En el grupo con ácido tranexámico tópico, se redujo un 43,9% la tasa de transfusiones cuando se lo comparó con el otro grupo. Además, se registró una disminución de 0,2-1,3 g/dl en la caída de la hemoglobina a las 24 h de la cirugía. No se detectaron complicaciones.

Conclusiones: El uso tópico de ácido tranexámico en reemplazos totales primarios de rodilla disminuye los requerimientos de transfusiones, sin incrementar el riesgo de complicaciones.

Palabras clave: Ácido tranexámico; reemplazo total de rodilla; transfusiones sanguíneas.
Nivel de Evidencia: III

Conflict of interests: The authors have reported none.

Introduction

One of the most frequent complications to be seen in association with total knee replacement (TKR) is the excessive blood loss that this procedure involves.[1] Surgical traumatism and the use of the haemostatic cuff cause a fibrinolytic response[2] which increases bleeding during the surgery and immediately afterwards.

Over the past years different methods have been incorporated with the aim of decreasing such blood loss—among them, tranexamic acid. This is a synthetic antifibrinolytic agent which acts blocking lysine receptors in plasminogen molecules, thus inhibiting its adhesion to fibrin.[3] Therefore, tranexamic acid can decrease perioperative bleeding altering the fibrinolytic system and contributing to decreasing the requirement of blood transfusión,[4-7] postoperative morbidity and hospital stay.[8]

Nowadays there are numerous publications describing the effectiveness of i.v. tranexamic acid; however, doctors' scarce experience with the topic use of this agent has showed in the difficulties to find studies that support this practice.

At the time of comparing it with i.v. administration, the topic use of tranexamic acid offers doctors the advantage of easy administration and brings bleeding spots maximal concentration, with scarce or null systemic absortion.[7]

This study describes a protocol of topic use of tranexamic acid in TKR and its effects on the amount of blood loss and the rate of perioperative blood transfusion.

Materials and Methods

We included all the patients subject to TKR between January 2009 and December 2015. We excluded the patients with acknowledged history of hypersensitivity to tranexamic acid, altered coagulation tests (KPTT, PT, bleeding time, >1.2 INR, <130,000 platelets), revision knee arthroplasty, and also those who had received treatment with anticoagulant or antiaggregant agents 15 days prior to the surgery.

The analysis included 108 patients with 117 TKRs; 115 of them had been diagnosed knee osteoarthritis, whereas two patients suffered osteonecrosis of the knee.

The first 63 consecutive TKRs, operated on between January 2009 and December 2013, were the "control group" which did not receive tranexamic acid. The remaining 54 TKRs, which were carried out between January 2013 and December 2015, made up the "study group".

Every surgery was carried out by the same surgeon (senior surgeon) and the prosthetic design that was used was the same too (ColumbusR, Aesculap AG, Tuttlingen, Germany; Genesis IITM, Smith & Nephew, Memphis, US.; OptetrakR, ExactechR, Gainesville, US.).

Analyzed variables

We registered patients' statistical variables such as age, sex, comorbidities, TKR aetiology, and previous surgery in the affected knee. We determined HCT and haemoglobin before surgery and during hospital stay (24 h and 48 h after the surgery). Moreover, we quantified the RBCs transfusion units per patient and the necessary number of wound dressing changes.

We conducted blood transfusion in those patients with ≤9 g/dl haemoglobin levels.

Wound dressing changes were carried out in aseptic and sterile conditions, the necessary number to keep bandages dry and white as seen from the outside.

Surgical technique

We administered spinal anaesthesia in all cases but those with contraindications or difficulties to carry out such procedure; in these cases, we opted for general anaesthesia. We applied haemostatic cuff within a 400-450 mmHg-pressure range. We used a knee anterior approach with medial parapatellar arthrotomy. Tibial and femoral cuts were carried out using guiding devices suitable for the surgical technique, extramedullary and intramedullary guides, respectively. All prosthetic components were cemented, and we performed patellar replacement in no case.

Once the prosthetic components had been implanted, we administered 1 gram of non-dissolved tranexamic acid (Arotran, Química Ariston, Buenos Aires, Argentina) within the joint cavity. We deflated the haemostatic cuff generating pressure with bandages. Upon 3 minutes-waiting, we took bandages out and sucked the solution up. We conducted haemostasis with electrocautery pen and carried out layered tissues closure: arthrotomy, soft tissues, and skin. Once wound closure was over, we administered 500 mg of tranexamic acid in intra-articular depot fashion. We did not use drainage. Patients in the control group received the same protocol without the tranexamic acid.

During the first 48 postoperative hours, we gave patients NSAIDs to relieve pain. Antithrombotic prophylaxis consisted of early mobilization, ankle antithrombotic exercises, high compression socks and enoxaparin-40 mg per day during hospital stay. At the time of hospital discharge, we classified patients according to their risk of developing thrombotic episodes—low or high-risk patients. Consequently, low-risk patients received p.o. aspirin-325 mg every 12 h during 15 days, whereas high-risk patients continued getting enoxaparin-40 mg per day during 10 more days.

Statistical analysis

Quantitative variables are conveyed as +/- standard deviation, and qualitative variables as absolute and relative percentage frequencies. Comparison between groups in

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terms of quantitative variables was made using the t-Student test and the Mann- Whitney's U test, as suitable; on the other hand, we used the Pearson's chi-squared test for qualitative variables. <0.05 p values were considered to be statistically significant.

Results

Sixty-four out of the 117 TKRs were conducted in females (54.7%) and 53, in males (45.3%). At the time of the procedure, patients averaged 70.2 +/- 9.6 years old (being minimally 35 and maximally 89 years old); 40% of the patients were between 61 and 70 years old (Table 1).

The aetiologies underlying the surgeries were osteoarthritic knee varum deformity (79%, 92 patients), osteoarthritic knee valgum deformity (20%, 23 patients) and osteonecrosis of the knee (2%, 2 patients).

Among comorbidities, the most frequent one was high blood pressure (61% of the sample), followed by diabetes mellitus (23%), overweight (>25-BMI) and obesity (>30-BMI) (23%). The remaining comorbidities represented 6% of the patients at most (Figure 1).

Twelve percent of the patients had got antiaggregant or anticoagulant treatment prior to the surgery: acetylsalicylic acid (77%), and other antiaggregant (15%) or anticoagulant (8%) agents (Figure 2).

Five percent of the patients operated on had history of surgery in the affected knee.

Table 1. Descriptive figures of the variables age and sex

Variable	Descriptive figure
Age (average ± SD)	70.2 ± 9.6
Sex (female)	64 (54.7%)

SD= Standard deviation

With respect to the procedure and the type of implant that was used in each patient, we registered 78 TKRs with no stem (67%), 37 TKRs with tibial stem (31%) and two TKRs with both tibial and femoral stems (2%).

Regarding the variables being compared between both groups, patients' average age did not show significant statistical differences between patients with and without tranexamic acid (p= 0.126). Sex distribution between groups did not show significant statistical differences either (p=0.359). Therefore, we can affirm that both groups are similar regarding sex and age (Table 2).

We compared both groups in terms of tranexamic acid use on the basis of the average values of haemoglobin and HCT that patients showed 24 and 48 h after the surgery. Average haemoglobin at postoperative hour 24 resulted to be higher in patients with tranexamic acid as compared to those without it (11.3 +/- 1.8 vs. 10.6 +/- 1.3; p=0.011; Table 3). However, average haemoglobin differences at

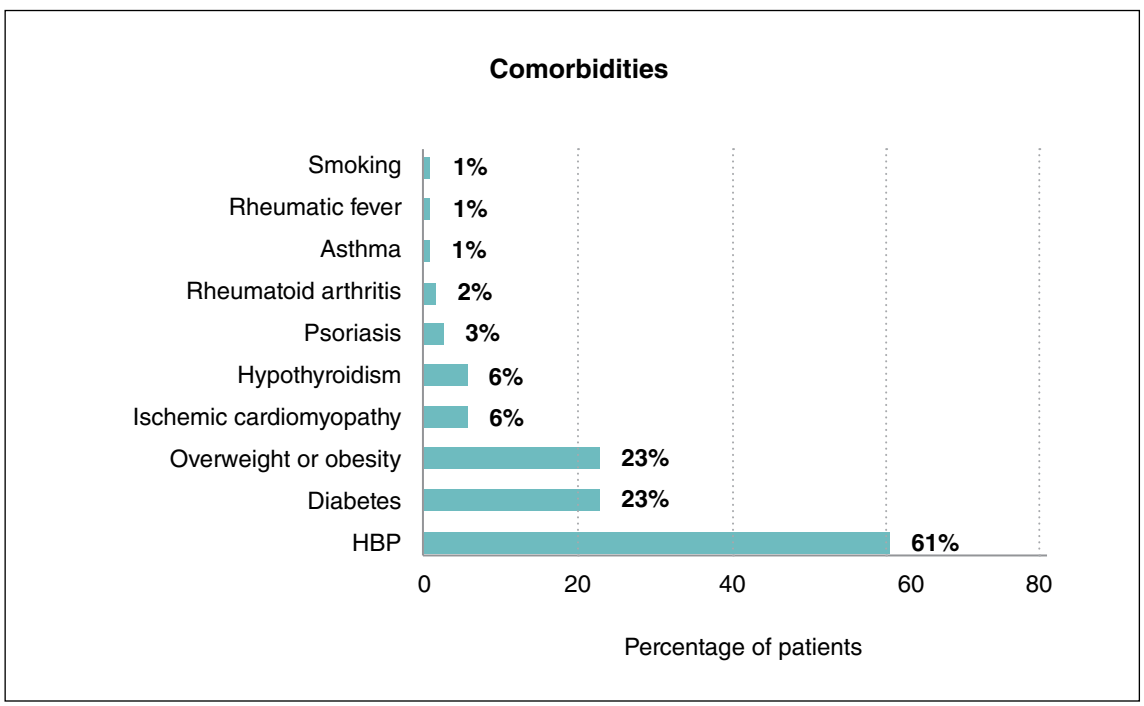

Figure 1. Comorbidities.

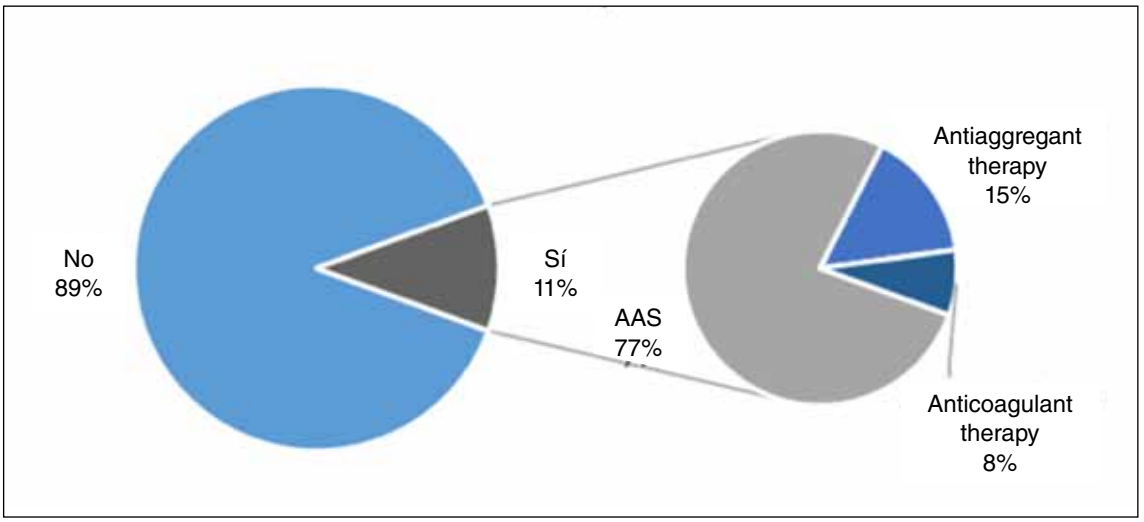

Figure 2. Previous antiaggregant or anticoagulant treatment.

Table 2. Comparison of the variables age and sex between both groups with and without tranexamic acid

Variable	With tranexamic acid (n = 54)	Without tranexamic acid (n = 63)	p
Age (average ± SD)	71.7 ± 9.0	69.0 ± 10.0	0.126
Sex (female)	32 (59.3%)	22 (49.2%)	0.359

SD= Standard deviation

postoperative hour 48 did not result to be statistically significant (p=0.082). We can affirm with 95%-confidence interval that average haemoglobin at postoperative hour 24 is between 1.3 and 0.2 units lower in the group without tranexamic acid as compared to the tranexamic acid-group (Figure 3).

Likewise, average HCT at postoperative hour 24 resulted to be higher among the patients with tranexamic acid as compared to those without it (34.4 +/-3.9 vs. 32.9 +/-3.8; p= 0.033; Table 3). However, average HCT differences at postoperative hour 48 were not statistically significant (p=0.123). With 95%-confidence interval we can affirm that average HCT at postoperative hour 24 is between 3.0 and 0.1 higher in the group with tranexamic acid as compared to the group without it (Figure 3).

In the tranexamic acid-group, the number of wound dressing changes varied between two and five, with a 3.6 +/- 0.6-average, whereas in the group without tranexamic acid, this number varied between three and five, with a 3.6 +/- 0.6-average too. This difference did not result to be statistically significant (p=0.623; Table 4). On the other hand, the number of blood transfusions per patient amongst those who received tranexamic acid varied between 0 and 2, with a 0.2 +/- 0.4-average, whereas in the group without tranexamic acid, this number also varied between 0 and 2 but with a 0.8 +/- 0.8-average. This difference did result to be statistically significant (p=0.001; Table 4). Therefore, we can affirm that the average number of blood transfusions that patients without tranexamic acid required is higher than that among the patients who received tranexamic acid.

With respect to the type of implant that was used, average haemoglobin and HCT decreases after the surgery did not show significant statistical differences between the groups with and without stem (p=0.052 and 0.092, respectively; Table 5). Likewise, the average number of patients' wound dressing changes and blood transfusions did not show significant statistical differences between the groups being compared (p=0.320 and 0.778, respectively; Table 5).

We did not register thrombotic episodes in any of the 117 TKRs, nor were there patients with signs and symptoms of hypersensitivity to tranexamic acid or adverse effects associated with it.

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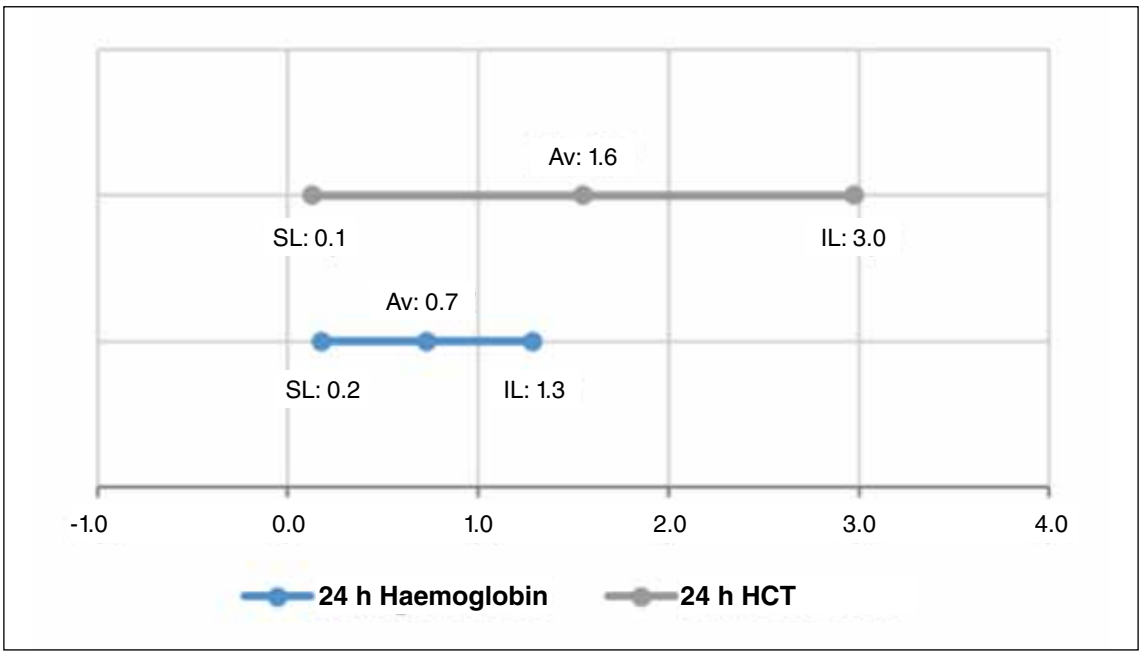

▲ **Figure 3.** Average (Av) and inferior (IL) and superior (SL) limits of the 95%-confidence interval for the difference in haemoglobin and HCT 24 h after the surgery between the patients with and without tranexamic acid.

Table 3. Comparison of haemoglobin and HCT figures 24 and 48 h after the surgery between both groups with and without tranexamic acid

Variable	With tranexamic acid (n = 54)	Without tranexamic acid (n = 63)	p
24 h haemoglobin	11.3 ± 1.8	10.6 ± 1.3	0.011
48 h haemoglobin	10.4 ± 1.3	10.0 ± 1.5	0.082
24 h HCT	34.4 ± 3.9	32.9 ± 3.8	0.033
48 h HCT	32.6 ± 3.9	31.6 ± 3.3	0.123

Table 4. Comparision of the number of dressing changes and blood transfusions between both groups with and without tranexamic acid

Variable	With tranexamic acid (n = 54)	Without tranexamic acid (n = 63)	p
Dressing changes	3.6 ± 0.6	3.6 ± 0.6	0.623
Blood transfusions	0.2 ± 0.4	0.8 ± 0.8	0.001

Table 5. Comparison of the type of implant between both groups with and without tranexamic acid

Variable	With stem (n = 78)	Without stem (n = 39)	p
Haemoglobin decrease	2.1 ±1.6	2.7 ± 1.0	0.052
HCT decrease	6.5 ± 4.0	7.8 ± 3.5	0.092
Dressing changes	3.6 ± 0.6	3.5± 0.6	0.320
Blood transfusions	0.5 ± 0.7	0.5 ± 0.8	0.778

Discussion

Over the past years, there have been numerous publications about the use of i.v. tranexamic acid in orthopaedic surgery. However, the effectiveness and the safety associated with its topic use are currently unknown.

The most important data derived from our study was that tranexamic acid reduced the postoperative hour 24-haemoglobin fall (0.2-1.3 g/dl on average). We found a smaller decrease in the postoperative hour 48-haemoglobin fall, and in HCT figures. All things considered, we got a 43.9%-reduction in patients' blood transfusion using tranexamic acid (average 0.2 blood transfusion per patient; p=001).

These results are similar to those got in other comparable studies. Serrano Mateo et al.[9], using a protocol of 3 g of intraarticular tranexamic acid in 179 TKRs, reported 5%- blood transfusions and a 17%-decrease as compared to the control group.

Martin et al.[10] got a 38.8%-reduction in blood transfusions in 50 TKRs using a protocol of 2 g of tranexamic acid.

The Georgiadis et al.'s study[11] reports a haemoglobin 3.3 g/dl-decrease at postoperative hour 24 using a protocol of 2 g of tranexamic acid before deflating the haemostatic cuff.

As this study shows, tranexamic acid may act decreasing haemoglobin and HCT falls within the first 24-48 postoperative hours and, therefore, decreasing the requirement of blood transfusions and, perhaps, the risks associated with them such as adverse reactions, hemodynamic overload, infections[12] and hospital stay.[7,13,14] Moreover, the topic use of tranexamic acid has been associated with improvement in the mid-term TKR's functional results.[9] On top of that, the use of tranexamic acid may have an economic impact.[1,10,15] In our country, one unit of blood transfusion costs between 1500 and 2000 *pesos*, whereas 1 g of tranexamic acid costs 146.2 *pesos*; this may result in benefits for health institutions with the possibility of reallocating resources.

As it has already been stated, the use of stems in the analyzed TKRs did not alter the good results that we found in association with tranexamic acid; perhaps one weakness of our study is the fact of not having included revision TKRs, about which there are not many publications and where benefits may be much more.[16,17]

None of our patients suffered thrombotic episodes. This info is important because it improves even more the low rates of thombotic episodes that other authors got while using topic tranexamic acid. Alshryda et al.[7] registered two patients in 157 TKRs who had been diagnosed deep venous thromobisis (0.010%). Chimento et al.[14] had six patients in 310 TKRs with deep venous thrombosis (0.010%).

A very important limitation that our study has is that of being retrospective. However, it is worth highlighting that it includes groups of consecutive patients who were operated on by the same surgeon and under the same protocol of postoperative, intraoperative and postoperative care.

Conclusions

The topic use of tranexamic acid in TKR reduces the requirement of blood transfusion with no increase in the risk of thrombotic episodes. In this context, we got good results by using low doses of tranexamic acid (1 g before wound closure + 500 mg afterwards); however, nowadays there is little information about recommendable doses and this will surely be worked on in future pieces of research.

All in all, topic tranexamic acid might improve TKR postoperative history, avoiding the complications associated with blood transfusion and contributing to the patient's well being in safe and effective fashion.

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