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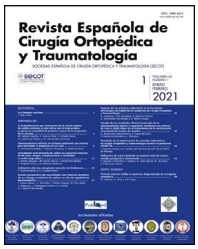

ORIGINAL PAPER

[Translated article] Randomized, placebo-controlled, double-blind clinical trial to evaluate efficacy and safety of topical tranexamic acid in saving blood loss in patients undergoing prosthetic knee surgery

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KEYWORDS
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Abstract
Background and objective: Knee arthroplasty is a major surgery with potential significant blood loss. Assess the efficacy and safety of topical administration of 3 g of tranexamic acid (TXA) in terms of reducing blood loss in knee arthroplasty.
Material and method: A randomized, phase III, double-blind, placebo-controlled clinical trial has been conducted. We included 150 patients in 2 parallel treatment groups (75 per arm). The solution was administered topically intra-articular after cementation and prior to capsular closure. Analytical determinations were made before and after surgery to quantify blood loss.
Results: Total blood loss for the placebo group was 831.5 ml and 662.3 ml for the TXA group. The difference between the 2 groups was 169.2 ml; which means a save of 20.4%; this difference being statistically significant ($p < .001$). There were no differences in terms of the onset of ambulation, days of admission or visual analogue scale at one month of surgery. Ten patients were rejected for presurgical urinary tract infection, metal allergy, selection failure, patellar weakening, prosthetic instability, intrasurgical tibial fracture, change of indication to unicompartimental prosthesis and a loss of follow-up. There was only one complication unrelated to the investigational drug (bladder balloon).
Conclusion: The administration of TXA topically after cementation of the prosthetic components in total knee arthroplasty in a single dose has demonstrated being safe and effective.

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PALABRAS CLAVE
Ácido tranexámico;
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Tranexámico tópico

Ensayo clínico aleatorizado, controlado con placebo y doble ciego para evaluar la eficacia y la seguridad del ácido tranexámico tópico en el ahorro de pérdidas sanguíneas en pacientes tratados mediante cirugía protésica de rodilla

Resumen
Antecedentes y objetivo: Durante la artroplastia de rodilla se produce una pérdida sanguínea importante. El objetivo de nuestro estudio es valorar la eficacia y la seguridad de la administración tópica de 3 g de ácido tranexámico (TXA) en cuanto a la reducción de pérdidas sanguíneas en artroplastia de rodilla.
Material y método: Se ha realizado un ensayo clínico aleatorizado, fase III, doble ciego, controlado con placebo. Se incluyó a 150 pacientes en 2 grupos paralelos de tratamiento (75 por brazo). La solución se administró de forma tópica intraarticular tras la cementación y previo al cierre capsular. Se realizaron determinaciones analíticas antes y después de la cirugía.
Resultados: La pérdida total de sangre media para el grupo placebo fue de 831,5 ml, y de 662,3 ml para el grupo TXA, con una diferencia entre ambos de 169,2 ml, lo que supone un ahorro del 20,4%, siendo estadísticamente significativa ($p < 0,001$). No se obtuvieron diferencias en el inicio de la deambulación, días de ingreso o escala visual analógica al mes de la cirugía. Se retiró a 10 pacientes por infección del tracto urinario prequirúrgico, alergia a metales, fallo de selección, debilitamiento rotuliano, inestabilidad protésica, fractura tibial intraquirúrgica, cambio de indicación a prótesis unicompartimental y una pérdida de seguimiento. Hubo una única complicación no relacionada con el fármaco (globos vesicales de repetición).
Conclusión: La administración de TXA de forma tópica tras la cementación de los componentes protésicos en artroplastia de rodilla en una única dosis demuestra que es segura y eficaz.

Introduction

Total knee replacement is a major surgical procedure that involves an array of complications, including blood loss and the consequent need for blood transfusion.[1–3] In recent years, published studies have been focused on patient fast recovery and decreasing postoperative complications, in particular, those that have to do with blood transfusions, such as: higher costs, bacterial contamination, the transmission of viral infections, and reactions to the transfusion.[2]

One of the drugs that has garnered interest recently is tranexamic acid (TXA). It is an anti-fibrinolytic agent that has been used for many years to control active bleeding and as a preventive measure in specialties such as ENT and gynaecology.[4] In the field of orthopaedic surgery, studies can be found on the use of intravenously administered TXA that evidence a reduction in post-surgical bleeding, as well as in the need for transfusion. Nevertheless, given the potential adverse effects of intravenous administration, the use of topical TXA was contemplated as an alternative.[5] The various studies published have shown that topical administration of TXA achieves high dose concentrations at the joint with low systemic distribution, thereby reducing adverse effects and achieving equal outcomes in terms of blood loss savings compared to intravenous administration.[6–9]

However, most of these studies are observational or reviews, and no experimental study based on a clinical trial of the topical administration of TXA in total knee arthroplasty surgery has been found in our setting.

The main objective of our study is to compare both the efficacy and safety of topical TXA in terms of blood loss savings compared to placebo in individuals diagnosed with severe osteoarthritis who had been treated with prosthetic knee surgery.

Materials and methods

An independent, phase III, randomised, double-blind, placebo-controlled clinical trial was carried out from January 2018 to April 2019 at Hospital Puerta del Mar, Cádiz. This trial was authorised by the Spanish Agency of Medicines and Medical Devices and the Hospital Ethics Committee. The sample size was calculated for a power of 90%, beta 0.1, and alpha 0.05, resulting in the need for 66 patients per treatment group and an expected loss to follow-up rate of 5%. It was determined that 150 patients needed to be recruited, with 75 patients allocated to each treatment arm, in 15 blocks of 10 patients. Allocation was randomised using the free software application www.randomization.com. Study medication was masked by the hospital's Pharmacy Service, where 30 ml pre-filled syringes with an odourless, transparent solution were prepared, containing either the study medication (3 g of TXA) or placebo, with similar labelling. In this way, both patient and surgeon remain double-blinded.

Inclusion criteria for participation in the study were: age between 18 and 80 years, with a visual analogue scale (VAS) score of seven or more, with a Kellgren's grade equal to or greater than II, and signed informed consent. Exclusion criteria were: severe heart disease, thromboembolic disease, prior hypersensitivity to TXA, severe systemic disease, history of seizures, severe mental disorder, taking anticoagulants, pregnancy or breastfeeding.

The primary endpoint of the study was estimated total blood loss (TBL) according to the formula of Nadler et al.[10] Socio-demographic variables, anthropometric variables, need for blood transfusion, ambulation time, and time to hospital discharge were also examined. Safety variables were also analysed: adverse events of any kind, infection rate, need for haematoma evacuation, or surgical wound dehiscence. Patients were followed up for one month after the procedure in all cases.

To estimate blood loss during surgery, two analytical determinations were performed: the first, 1 h prior to surgery, and the second, 24 h after surgery.

All surgeries were performed by members of the Knee Unit of this hospital, using the internal parapatellar approach. Two prosthetic models were used: Sigma® by DePuy Synthes (DePuy-Synhes®, Johnson & Johnson®) and Triathlon® by Stryker (Stryker®). > [*sic*] After cemented placement of the prosthetic components and prior to closure of the capsule, the following drug protocol was followed: the knee was placed in extension, the contents of the syringes were administered and distributed over the entire joint. Subsequently, the edges of the surgical wound were approximated, covered with compresses, and a compressive bandage was applied. The ischaemia cuff was removed and the bandage was kept in place for 3 min to allow the medication to take effect. After 3 min, the compressive bandage was removed and the aqueous solution was aspirated. Finally, thorough local haemostasis was performed, closure by planes, and a cotton inguinopedic elastic bandage was applied. Drainage was not used in any case.

SPSS v.21 for Macintosh (IBM Corp., Armonk, NY, USA) was used for data collection and processing. An intention-to-treat analysis was performed from the time of patient randomisation (following signature of informed consent). The normality of the distribution of all variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. To analyse baseline intergroup differences in quantitative variables, the Student's *t*-test and the chi-squared test for qualitative variables were used.

Results

Of the total of 150 patients recruited, 10 were excluded from the trial for the following reasons: three were over 80 years of age at the time of surgery; one patient had symptoms of urinary tract infection; another two patients were excluded for reasons related to the surgical technique (weakness of the patellar tendon and placement of a single compartment prosthesis), and, finally, the results of the post-operative analysis were lost in another of the patients. This left 69 patients in the TXA group and 71 in the placebo group.

The descriptive demographic analysis of the sample is summarised in Table 1, with the percentage of males and females being 29.3% ($n = 44$) and 70.7% ($n = 106$), respectively, and adhering to a normal distribution.

The type of prosthesis used was Sigma® (Depuy-Synthes) in 44.2% ($n = 65$) and Triathlon® (Stryker) in 55.8% ($n = 82$) of the cases, displaying similar distribution in both groups; 33 Sigma® and 40 Triathlon® prostheses for the TXA group, and 32 Sigma® and 42 Triathlon® prostheses for the placebo group. No statistically significant differences (p-value = 0.94) were detected between the two groups.

Table 1 Descriptive analysis of demographic variables.

	Mean	SD
Age (years)	69.17	6.45
Weight (kg)	82.88	12.05
Height (m)	1.59	.09
BMI (kg/m^2)	32.73	4.23

Regarding clinical and functional variables, no statistically significant differences were observed in both groups at the time when the patient began to stand upright (p value = NS), or for the total days of hospitalisation (p value = NS) or for the pain assessment based on the VAS score one month after surgery (p value = NS) (Table 2).

As regards efficacy variables, haemoglobin (Hb) and haematocrit (HCT) were measured and the data presented a normal distribution for Hb prior to surgery. In the case of prior HCT, the data followed a normal distribution for the TXA group, although not for the placebo group. No statistically significant differences were discovered between the two groups for either Hb or HCT. On the other hand, statistically significant differences were found in the differences between Hb and HCT pre- and post-surgery, the difference being greater for the placebo group (Table 3).

The primary endpoint, TBL, had a mean of 662.30 ml (95% confidence interval (CI), 600.8–723.7) for the TXA group and 831.5 ml (5% CI, 752.8–910.2) for the placebo group; the difference between the two were 167.78 ml in favour of the TXA group and was statistically significant, with a p value of 0.001, which corresponds to a savings of 20% with respect to the placebo group.

In terms of safety analysis, there were no complications with the surgical wound; no patient required a repeat operation; there were no infections, and no blood transfusions were necessary in any case. The only adverse event unrelated to the use of TXA was one case of recurrent bladder ballooning.

Discussion

In the present study, a 20% decrease (an average of 167.78 ml) in total blood loss was achieved by administering TXA in prosthetic knee surgery. In the literature, we found several studies with a methodology similar to ours. In 2010, Wong et al. analysed 3 treatment arms (in the first arm, 1.5 g of TXA was administered; in the second, 3 g, and in the third group, placebo) and observed a reduction of 315 ml of blood loss on average in the first arm and 402 ml in the second arm, compared to the control group.[11] Subsequently, Konig et al.[12] and Georgiadis et al.[13] reported a reduction in blood loss of 353 and 231 ml on average, respectively. We believe that these results that are quantitatively greater compared to our study may be due to the methodology used in terms of surgical manoeuvres, which, given that they are not standardised, may lead to differences that are unrelated to the administration of the drug.[14]

As for savings in blood loss, the main effect of administering TXA is that it reduces the rate of transfusion. Different

Table 2 Descriptive analysis of functional variables: similar distribution in both groups.

	TXA group	Placebo group	
Beginning of ambulation: days (RF)			*p* value .55
First	41 (.28)	39 (0.27)	
Second	25 (.17)	24 (0.17)	
Third	5 (.08)	8 (0.6)	
Fourth	0 (.0)	2 (0.01)	
Days of hospitalisation (RF)			*p* value .14
2	1 (.01)	5 (0.03)	
3	48 (.33)	38 (0.26)	
4	14 (.10)	23 (0.16)	
5	7 (.05)	5 (0.03)	
6	1 (.01)	1 (0.01)	
11	0 (.00)	1 (0.01)	
VAS at one month: score (RF)			*p* value .82
0	20 (.14)	20 (0.14)	
1–3	13 (.09)	16 (0.11)	
4–6	25 (.17)	21 (0.15)	
7–9	13 (.09)	16 (0.11)	

RF: relative frequency.

Table 3 Statistical analysis of efficacy variables.

	TXA group	Placebo group	*p* value
Previous haemoglobin (g/dl)	13.74 (95% CI 13.41–14.07)	13.59 (95% CI 13.29–13.90)	.526
Previous haematocrit (%)	41.52 (95% CI 40.64–42.79)	40.65 (95% CI 39.52–41.79)	.333
Difference Hb pre-Hb post-surgery (g/dl)	1.785 (95% CI 1.593–1.976)	2.319 (95% CI 2.046–2.591)	.004
Difference HCT pre-HCT post-surgery (%)	5.603 (95% CI 5.012–6.194)	6.683 (95% CI 5.565–7.801)	.012

The pre-Hb and pre-HCT variables are similar in both groups. The variables pre-post-surgery Hb difference and pre-post-surgery HTC show statistically significant intergroup differences, being higher in patients who did not receive tranexamic acid.

studies indicate that patients undergoing knee arthroplasty who receive this drug do not require blood transfusion after surgery.[15–17] In our case, the transfusion rate was zero for both TXA-treated patients and the control group.

Regarding the analysis of functionality, the interest lies in the fact that, by decreasing blood loss-related complications, rehabilitation does not have to be delayed because of said complications. Therefore, in 2018, Grosso et al.[18] proposed to analyse functional outcomes and early recovery among the participants who received intravenous TXA. To do so, 560 patients were randomised into two treatment arms; the first group received TXA and the second group received placebo. The result was that the subjects who were given TXA were able to walk more from the second day on. However, there was no difference on the VAS score. On the other hand, Serrano et al.[19] analysed post-surgical functional outcomes with the Knee Society Score (KSS) and differences were observed at six weeks after drug administration, but not at four months. In 2019, Hirose et al.[20] conducted an analysis of joint balance (JB) after intra-articular TXA administration following surgical wound closure. They achieved an improvement in JB on the fourth, tenth, and fourteenth day. However, there was no difference in the 10 m ambulation test, VAS, or muscle strength.

Similar to Guerreiro et al.,[21] we found no significant differences in our study between the two groups with respect to time to onset of standing following surgery, VAS at one month postoperatively, and days of hospitalisation.

In our opinion, these differences between the various studies in terms of functional outcomes are likely to be due to the analysis of multiple secondary variables. Therefore, a pre-study protocol is deemed fundamental to clearly define the primary endpoint, as well as the sample size.

As for the possible adverse reactions of TXA administration, thromboembolic events are particularly relevant, as described in its technical data sheet.[22] However, in this clinical trial, no cases of thromboembolic events were reported in either of the two treatment arms. Other events related to the surgical technique, such as surgical wound dehiscence, haematoma requiring drainage, or bleeding that could not be controlled with conservative measures, were also not reported. Similar results were reached in studies by Konig

et al.,[12] Wong et al.,[11] and Geordiadis et al.,[13] in which no increased incidence of thromboembolism or any other complication was observed when TXA was topically administered.

A meta-analysis conducted in 2018[23] that included 73 clinical trials with a total of 6953 patients undergoing prosthetic knee surgery concluded that the overall incidence of venous thromboembolism was 2.1% in individuals who were given TXA versus 2% in the control group. However, these results should be taken with caution, inasmuch as clinical trials often select patients with strict inclusion criteria that do not reflect standard clinical practice, and exclude those who are at high surgical risk, as is the case in our study; this implies a lack of external validity. For this reason, Poeran et al.[24] conducted a retrospective analysis comparing the safety profile of TXA in 872,416 patients who underwent knee and hip replacement surgery in 510 hospitals in the United States. The study concluded that those who received TXA had a lower rate of thromboembolic complications (0.6% vs. 0.8%), as well as a decrease in acute renal failure (1.2% vs. 1.6%); the difference was significant. A similar result was obtained by Sabbag et al.[25] in their study, in which they observed that the administration of TXA in patients who had experienced an episode of thromboembolism did not increase the risk of recurrence of a new episode when they were treated with prosthetic knee surgery. In 2020, Porter et al.[26] also analysed the safety profile of the drug in 22,491 prosthetic knee surgery recipients. Of the total number of patients, 5501 were at high thromboembolic risk (deep vein thrombosis, pulmonary thromboembolism, myocardial infarction, stroke, atrial fibrillation, coronary artery bypass grafting, cardiac stents). TXA was administered to approximately 50% of these patients without finding an increased incidence of thromboembolic events. The importance of the latter article is greater, given that it reflects the results of routine clinical practice, thereby increasing its external validity.

Among the limitations of our study, we found that the sample may not be representative of the general population as it was conducted under ideal conditions, which decreases its external validity. On the other hand, the participation of up to four surgeons may have affected the blood loss results. Finally, it is worth mentioning that subjects have benefited from closer monitoring, which may have had a bearing on initiation of standing and length of hospitalisation.

Conclusions

Topical administration of 3 g TXA in a single dose has proven to be safe and effective in our population.

We believe that the rate of blood transfusion depends more on refined technique than on drug administration.

Future lines of research could focus on clinical trials with greater external validity as more information becomes available about the safety profile of TXA. We also consider that future comparative studies could focus on functional variables as their primary endpoint.

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Level of evidence

Level of evidence I.

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Conflict of interests

Each author certified that they have no commercial associations that might constitute a conflict of interest with respect to the document submitted.

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