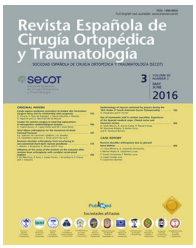
Rev Esp Cir Ortop Traumatol. 2019;63(2):138–145

Revista Española de Cirugía Ortopédica y Traumatología

www.elsevier.es/rot



ORIGINAL ARTICLE

Which route of administration of acid tranexamic, intravenous or intra-articular, is more effective in the control of post-surgical bleeding after a total hip arthroplasty? A prospective, controlled and randomized study☆

P. Gómez Barbero[a,*], M.S. Gómez Aparicio[a], J.A. Blas Dobón[a], J.M. Pelayo de Tomás[a], M. Morales Suárez-Varela[b], J.L. Rodrigo Pérez[a]

[a] *Servicio de Cirugía Ortopédica y Traumatología, Hospital Universitario Doctor Peset, Valencia, Spain*
[b] *Área de Medicina Preventiva y Salud Pública, Epidemiología, Universidad de Valencia, Valencia, Spain*

Received 12 March 2018; accepted 3 May 2018

KEYWORDS
Tranexamic acid;
Intravenous administration;
Intra-articular administration;
Total hip arthroplasty;
Transfusion

Abstract
Introduction: One of the most frequent complications after a total hip arthroplasty (THA) is bleeding, intravenous tranexamic acid (TXA) is used to reduce it. We considered it necessary to carry out a study to clarify which administration route is superior.
Material and method: Prospective, controlled and randomized study in 2 arms carried out between February 2017 and February 2018. 15 mg/kg of intravenous TXA were administered in group A and 2 g of intra-articular TXA in group B. The values of haemoglobin and haematocrit were evaluated at 24 h-72 h, blood loss volume, drained blood volume, transfusions and complications.
Results: 78 patients were included, 31 with intravenous treatment and 47 with intra-articular. The decrease of haemoglobin in the intravenous group was 3.15 ± 1.64 g/dl in 24 h and 3.75 ± 1.56 g/dl in 72 h, the haematocrit decreased by 10.4 ± 4.17% in 24 h and 11.85 ± 4.15% in 72 h. In the intra-articular group there was a haemoglobin fall of 3.03 ± 1.30 g/dl in 24 h and 3.22 ± 1.2 g/dl in 72 h and the haematocrit fell by 10.66 ± 3.6% and 12.11 ± 3.29% in 24 and 72 h ($p > .05$). The mean drainage in 24 h was 195.80 ml in group A versus 253.93 ml in group B ($p > .05$) and in 48 h it was 225.33 ml in group A and 328.19 ml in group B ($p = .009$). The intravenous group lost an average of 1505 ml of blood compared to the 11,280 ml of the intra-articular group. In 5.1% of the cases, transfusions were necessary. We had no secondary complications.

☆ Please cite this article as: Gómez Barbero P, Gómez Aparicio MS, Blas Dobón JA, Pelayo de Tomás JM, Morales Suárez-Varela M, Rodrigo Pérez JL. Aplicación del tranexámico intravenoso o intraarticular en el control del sangrado posquirúrgico tras una artroplastia total de cadera. Estudio prospectivo, controlado y aleatorizado. Rev Esp Cir Ortop Traumatol. 2019;63:138–145.
* Corresponding author.
E-mail address: gomez.barbero.patricia@gmail.com (P. Gómez Barbero).

1988-8856/Published by Elsevier España, S.L.U. on behalf of SECOT.

Conclusions: The different routes of administration of TXA in THA have a similar effect in the reduction of postoperative bleeding. There was no evidence of an increase in complications.
Published by Elsevier España, S.L.U. on behalf of SECOT.

PALABRAS CLAVE
Ácido tranexámico;
Vía intravenosa;
Vía intraarticular;
Artroplasia total de cadera;
Transfusión

Aplicación del tranexámico intravenoso o intraarticular en el control del sangrado posquirúrgico tras una artroplastia total de cadera. Estudio prospectivo, controlado y aleatorizado

Resumen
Introducción: Una complicación frecuente tras una artroplastia total de cadera es el sangrado, y para reducirlo se utiliza el ácido tranexámico (TXA) intravenoso. Recientemente se han publicado los beneficios de su aplicación tópica. Consideramos necesario realizar un estudio que justifique qué vía de administración resulta superior.
Material y método: Estudio prospectivo, controlado, aleatorizado en 2 brazos realizado entre febrero de 2017 a febrero de 2018. En el grupo A se administró 15 mg/kg TXA intravenoso y en el B 2 g TXA intraarticular. Se evaluó los valores de hemoglobina y hematocrito a las 24-72 horas, volumen de sangre drenado, volumen de sangre perdida, transfusiones y complicaciones.
Resultados: Fueron incluidos 78 pacientes, 31 con tratamiento intravenoso y 47 intraarticular. La hemoglobina descendió 3,15 ± 1,64 g/dl en 24 horas y 3,75 ± 1,56 g/dl en 72 horas en el grupo intravenoso, el hematocrito descendió un 10,4% ± 4,17% en 24 horas y 11,85% ± 4,15% en 72 horas. En el intraarticular se observó una caída de hemoglobina de 3,03 ± 1,30 g/dl en 24 horas y de 3,22 ± 1,2 g/dl en 72 horas y el hematocrito descendió 10,66% ± 3,6% y 12,11% ± 3,29% en 24 y 72 horas ($p > 0,05$). El drenaje medio en 24 horas fue 195,80 ml en el grupo A frente a 253,93 ml en el grupo B ($p > 0,05$) y a las 48 horas 225,33 ml en el grupo A y de 328,19 ml en el grupo-B ($p = 0,009$). En el grupo intravenoso perdieron una media de 1.505 ml de sangre frente a 1.280 ml del grupo intraarticular. Fueron necesarias un 5,1% de transfusiones. No tuvimos complicaciones secundarias.
Conclusiones: Las diferentes vías de administración del TXA en la artroplastia total de cadera tienen un efecto similar en la reducción del sangrado postoperatorio sin evidenciar un incremento de complicaciones.
Publicado por Elsevier España, S.L.U. en nombre de SECOT.

Introduction

Total hip arthroscopy is one of the most common interventions in the treatment of osteoarticular hip pain secondary to arthrosis or avascular necrosis of the femoral head. One of the most frequent complications of surgery is large-scale intraoperative bleeding that will continue postoperatively. Previous studies have shown ranges of blood loss from 1.188 ml to 1.651 ml.[1,2] Furthermore, it has been observed that between 10% and 38% of patients undergoing arthroplasty require an average 2 units of packed erythrocytes to minimise the haemoglobin and haematocrit drop.[3,4] No allogenic blood transfusion is risk-free, and in addition to adding to costs, it significantly increases complications: postoperative infections, hospital stay, mortality or delayed physical recovery, for example.[5]

Many strategies have been deployed to reduce postoperative bleeding and the number of transfusions after prosthetic surgery, including autologous donation, intraoperative controlled hypotension, regional anaesthesia, blood saving measures, erythropoietin and antifibrinolytic agents. Tranexamic acid (TXA), marketed as Amchafibrin® is the most powerful and has the fewest complications of the antifibrinolytic agents. Its administration inhibits the activation of plasminogen to plasmin, through blocking the lysine binding site, and prevents fibrin degradation.[6,7]

Previous orthopaedic and cardiovascular surgery studies have demonstrated that TXA reduces postoperative bleeding and the amount of allogenic transfusions compared to a control group using routine haemostasis.[7,8] Moreover, it did not increase the number of thromboembolic events, or surgical infections.[4,9] However, most of these prospective, randomized or meta-analysis studies have focussed on the effectiveness, efficacy and safety of tranexamic acid without specifying the optimal administration route.[10–12] Recently the benefits of topical administration of TXA have been published, delivering a maximum concentration to the surgical site with low systemic effect.[10] Therefore, we consider it necessary to undertake a study to clarify which administration route, topical or intravenous, is superior and equally safe in reducing postoperative bleeding after a primary hip arthroplasty. To that end we evaluated two independent parameters, the volume of blood drained and total blood loss, taking into account the need for transfusions.

We presumed that the topical application (intra-articular) of TXA after closure would reduce postoperative bleeding and help maintain haemodynamic stability as well as its intravenous use. Our secondary aim was to analyse whether either of the administration routes reduced the number of allogenic blood transfusions and the incidence of possible thromboembolic events more than the other.

Material and method

Design

We undertook a prospective and randomized, two-arm, phase IV clinical trial in the Doctor Peset University Hospital of Valencia after approval from the clinical research ethics committee. Group A (arm A) were given 15 mg/kg of TXA intravenously 15–20 min before the end of the surgical intervention. Group B (arm B) received 2 grams of intra-articular TXA in 100 ml of saline via the Redon drain, once the wound had been closed; the Redon drain was then clamped for 2 h.

The dose of TXA we used was based on previous studies according to routine clinical practice.[13,14]

We did not require a control group, because there is already sufficient published literature demonstrating the usefulness and safety of TXA as an antifibrinolytic agent to reduce postoperative bleeding, which is already marketed as Amchafibrin®.

Study population and sample size

The study was performed on patients who underwent elective total hip arthroplasty due to coxarthrosis or avascular necrosis in the period between February 2017 and February 2018.

Given that at the time of starting the study there were no publications describing differences in the use of intravenous or intra-articular TXA after a total hip prosthesis, we used a time criterion to calculate the sample size.

All the patients who met the inclusion criteria were consecutively randomized by intervention demand into 2 groups or arms, group A, who received intravenous treatment with TXA plus routine haemostasis, and group B, who received intra-articular treatment plus routine haemostatis. During the study the orthopaedic surgeon and the anaesthetist were not blinded due to the different tranexamic acid administration routes. However, the entire subsequent follow-up was undertaken homogeneously and in a standardised way for the 2 groups.

Selection criteria

Inclusion criteria

All patients aged between 18 and 85 who had undergone a total hip replacement due to primary coxarthrosis or avascular necrosis were included in the study. The patients had to have signed their informed consent for the surgical intervention and to take part in the study, and have a recent lab test result confirming normality of platelet count, INR and prothrombin time.

Exclusion criteria

All patients who were allergic to tranexamic acid, those who refused to participate in the study, those with a secondary arthropathy (rheumatoid arthritis, post-traumatic arthritis, psoriatic arthritis), cardiovascular disease (acute myocardial infarction, atrial fibrillation, angina, grade 3–4 heart failure, prior heart surgery), cerebrovascular disease (stroke, transient ischaemic attack and vascular surgery, thromboembolic disease (deep vein thrombosis [DVT], fibrinolysis disorders and coagulopathies (if INR > 1.4, platelets < 150,000 $\times$ 10^9/l, prothrombin time > 1.4), liver and/or kidney failure, treatment with anticoagulants 7 days prior to the surgical intervention, blood product rejection, intraoperative complications (anaesthetic or surgical), those participating in another clinical trial, and with preoperative haemoglobin levels < 12 g/dl were excluded from the study.

Variables studied

The patients' sociodemographic variables were collected (age at the time of the intervention, sex, weight, height and body mass index), medical history, preanaesthetic assessment and variables relative to the intervention (such as the type of anaesthesia used, approach, surgical time, days of hospital stay and laterality). The main clinical variables collected were preoperative and postoperative haemoglobin and haematocrit (at 24 h and 72 h), the lowest haemoglobin recorded during the hospital stay, the patient's blood volume (Annex 1), total blood loss (Annex 2), hidden blood loss (Annex 3), and the drainage volume at 24 and 48 h (ml). In addition, the number of blood units transfused and the complications from the intervention (the wound developing infection or necrosis, DVT, PTE or death) were gathered as secondary variables.

The centre's surgical protocol

All the interventions were performed by a team of orthopaedic surgeons with experience in primary hip arthroplasty. All the patients received cementless models.

In the anaesthetic induction intravenous antibiotic prophylaxis was administered according to the hospital's infections committee. During the entire operation haemostatis was undertaken using electrocoagulation of the blood vessels. After the intervention we placed a number 12 vacuum drain, which was removed after 48 h. The topical TXA (group B) was inserted via the Redon drain, once the wound had been closed, which was then clamped for 2 h. The Redon drains of the patients receiving intravenous TXA (group A) were opened after placing the compression bandage. Six hours after the surgical intervention the patients received venous thromboembolism prophylaxis with low molecular weight bemiparin, which was maintained for 30 days.

All the patients who were admitted followed the same blood transfusion protocol based on the perioperative transfusion guidelines of the National Institutes of Health Consensus Conference.[15] Red blood cell transfusion was indicated should the patient's haemoglobin levels fall below 8 g/dl, or below 10 g/dl if they had associated cardiopulmonary disease and symptoms of anaemia, defined as syncope, fatigue, palpitations or dizziness.

Any complications such as thromboembolic events were noted and collected throughout the patients' hospital stay. On discharge, all the patients were given outpatient appointments 3 weeks after the intervention, when any possible complications were assessed.

Data collection

The patient data collection was undertaken homogeneously and in a standardised way for the 2 groups. The data were collectively postoperatively by a different team of surgeons. The haemoglobin levels and haematocrit at 24 and 72 h following the surgery, the daily drained blood volumes, whether or not a blood transfusion had been given, and a series of the abovementioned demographic variables were recorded. In this assessment phase the analysis was blinded. In addition, confusion bias was avoided since these were objective results.

Statistical analysis

Firstly a descriptive analysis was undertaken where normally distributed continuous variables were described as mean ± standard deviation (SD), and those that were not normally distributed, or non-Gaussian, were described as median (maximum–minimum). The qualitative variables were described in frequencies and percentages. The Kolmogorov–Smirnov test was used to check the variables' normality distribution. The χ^2 test was used to study the association between qualitative variables. The Student's *t*-test, Mann–Whitney *U* test or ANOVA were used to study the differences between means according to the application conditions. Differences with $p < .05$ were considered statistically significant in all the tests. The computer analysis was performed using SPSS 22.0.

Ethical aspects

This paper was completed after the approval of the Doctor Peset University Hospital's ethics committee, in compliance with the recommendations of the 1964 Declaration of Helsinki. All the patients included in the study signed their informed consent.

Results

Between February 2017 and February 2018, 90 patients scheduled for primary hip arthroscopy were included in the study. Of this initial group, 12 patients were excluded from the study, 8 because they did not meet the inclusion criteria, 3 because they did not want to participate, and one case was excluded during the follow-up when an iatrogenic fracture was confirmed that required intraoperative transfusions. The final analysis was undertaken on 78 patients, of whom 31 were randomized to group A and received the intravenous treatment, and 47 patients to group B who received intra-articular TXA (Fig. 1).

No significant differences were found in terms of age, sex, body mass index or American Society of Anesthesiologists' classification[16] (Table 1). The comorbidity associated with the surgical intervention was gathered and assessed; chronic diseases such as arterial hypertension, diabetes mel-

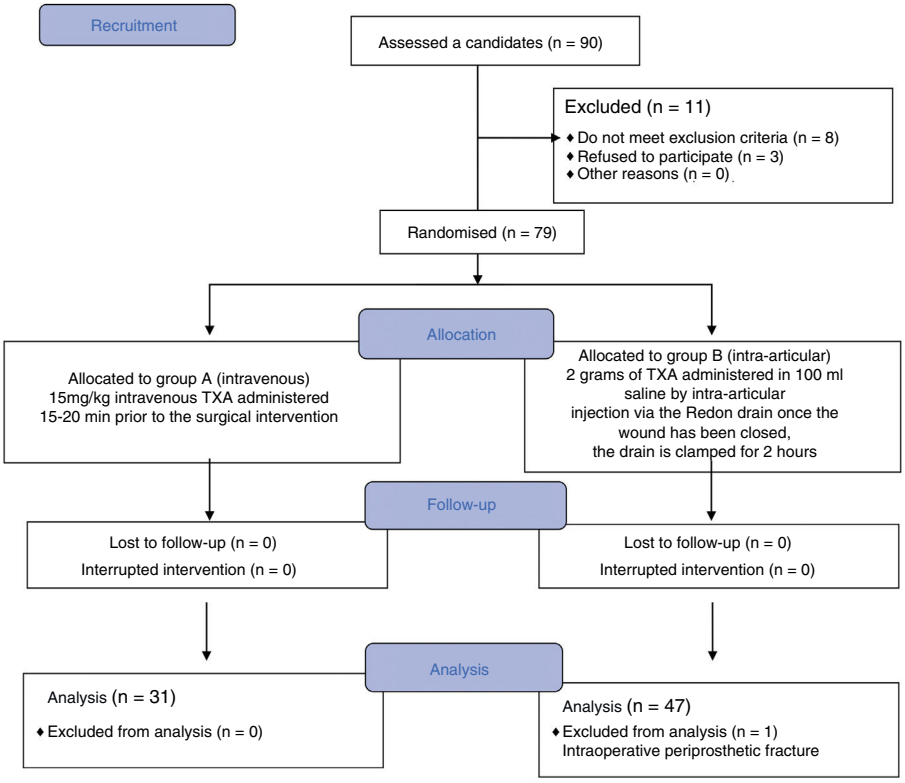


Figure 1 Consolidated Standards of Reporting Trials (CONSORT). Diagram for the study.

Table 1 Description of the sample according to the TXA administration route.

	Overall ($n = 78$)	Group TXA_IV ($n = 31$)	Group TXA_IA ($n = 47$)	p value[a,b]
Age (mean + SD)	63.14 ± 12.22	62.74 ± 11.95	63.40 ± 12.51	.817
Female sex, n (%)	35 (44.9)	13 (41.9)	22 (46.8)	.672
BMI	28.47 ± 3.91	28.52 ± 3.98	28.44 ± 3.91	.925
ASA n (%)				
1	11 (14.1)	3 (9.7)	8 (17.0)	
2	59 (75.6)	24 (77.4)	35 (74.5)	
3	8 (10.3)	4 (12.9)	4 (8.5)	.581

ASA: American Society of Anesthesiologists; SD: standard deviation, BMI: body mass index; n: number.
[a] p-Value: Student's t-test for independent samples.
[b] χ^2 test.

litus and dyslipaemia under treatment were found in 66.66% of the patients (52 cases).

The preoperative haemoglobin levels and haematocrit were similar in both groups. The fall in haemoglobin and mean haematocrit after the intervention was also similar. In group A, who received intravenous TXA, we started with a mean preoperative Hb of 14.28 g/dl, with a mean fall at 24 h of 3.15 ± 1.64 g/dl, and of 3.75 ± 1.56 g/dl at 72 h. The haematocrit suffered a mean drop of 10.4 ± 4.17% at 24 h, and of 11.85 ± 4.15% at 72 h. In group B, with the intra-articular administration, we started with a mean Hb of 14.23 g/dl, and a mean fall of 3.03 ± 1.30 g/dl was observed at 24 h, and of 3.22 ± 1.2 g/dl at 72 h. The haematocrit dropped 10.66 ± 3.6% and 12.11 ± 3.29% at 24 and 72 h respectively. The lowest recorded mean haemoglobin levels were 10.3 g/dl for group A, and 10.8 g/dl for group B. We found no significant differences between either group in any of the values studied (Table 2).

The mean drainage values in the first 24 h were 195.80 ml in group A with intravenous administration compared to 253.93 ml collected from group B, with the intra-articular administration. At 48 h, prior to removing the drain, a mean drainage of 225.33 ml was recorded for group A compared to the 328.19 ml of group B; there was a statistically significant association ($p = .009$) in the values collected at 48 h. If we analyse the patient's blood volume and calculate the total blood loss after the surgery we see that the intravenous group lost 1505.42 ± 499.32 ml, while the intra-articular group lost 1280.00 ± 352.89 ml, showing a statistically significant association ($p = .022$).

The proportion of patients who required a transfusion was 9.7% in group A, whereas in group B 2.1% of the cases received a transfusion.

The surgery time and mean hospital stay were similar in both groups, with no statistically significant association (Table 3).

Table 2 Drainage levels and haemoglobin (HB) levels and haematocrit (Htc) pre and post surgery. Median (minimum and maximum).

	Overall ($n = 78$)	Iv_TXA group ($n = 31$)	Ia_TXA group ($n = 47$)	p value [*]
Preoperative Hb, g/dl (mean + SD)	14.253 ± 1.261	14.284 ± 1.483	14.232 ± 1.107	.861
Preoperative Hto (mean + SD)	43.11 ± 3.82	42.95 ± 4.32	43.21 ± 3.47	.768
Hb 24h postop. (g/dl)	11.177 ± 1.441	11.132 ± 1.649	11.206 ± 1.303	.826
Hto 24h postop.	33.08 ± 3.87	32.55 ± 4.17	33.43 ± 3.65	.331
Hb (72h postop.)	10.827 ± 1.362	10.538 ± 1.568	11.017 ± 1.187	.13
Hto 72h postop.	32.04 ± 3.71	31.10 ± 4.15	32.66 ± 3.29	.069
Lowest Hb (g/dl)	10.663 ± 1.285	10.370 ± 1.359	10.855 ± 1.201	.104
Patient's blood volume (ml)	4641.5 (3.380–6.045)	4537.0 (3.380–5.954)	4757 (3.403–6.045)	.698 [*]
Total blood loss (ml)	1.369.59 ± 428.79	1.505.42 ± 499.32	1.280.00 ± 352.89	.022
Hidden blood loss (ml)	1.084.53 ± 444.34	1.285.74 ± 492.88	951.81 ± 356.07	.001
Drainage 24h (ml)	230.83 ± 147.44	195.80 ± 176.49	253.93 ± 121.26	.088
Median (minimum–maximum)	245.00 (0–850)	200.00 (0–850)	250.00 (0–500)	
Drainage 48h (ml)	288.12 ± 170.69	225.33 ± 184.62	328.19 ± 149.78	.009
Median (minimum-maximum)	300.00 (0–900)	200.00 (0–900)	300.00 (0–650)	
Days of hospital stay	5.05 ± 1.06	5.13 ± .91	5.0 ± 1.16	.595
Transfusion, n (%)				
No	74 (94.9)	28 (90.3)	46 (97.9)	
Yes	4 (5.1)	3 (9.7)	1 (2.1)	.139

SD: standard deviation; n: number.
[*] Mann–Whitney U test. Descriptive analysis mean ± standard deviation and p value Student's t-test for independent samples.

Table 3 Description of the sample in relation to the characteristics of the intervention and according to the administration of tranexamic acid (TXA).

	Overall ($n = 78$)	Iv_TXA group ($n = 31$)	Ia_TXA group ($n = 47$)	p value[a,b]
Anaesthesia				
General, *n* (%)	33 (42.3)	10 (32.3)	23 (48.9)	
Spinal, *n* (%)	44 (56.4)	20 (64.5)	24 (51.1)	
Spinal + general, *n* (%)	1 (1.3)	1 (3.2)	0	.188
Laterality				
Right, *n* (%)	43 (55.1)	19 (61.3)	24 (51.1)	
Left, *n* (%)	35 (44.9)	12 (38.7)	23 (48.9)	.374
Approach				
Anterolateral, *n* (%)	17 (21.8)	3 (9.7)	14 (29.8)	
Posterolateral, *n* (%)	61 (78.2)	28 (90.3)	33 (70.2)	.031
Complications				
No complications, *n* (%)	74 (94.9)	30 (96.8)	44 (93.6)	
Fissure, *n* (%)	1 (1.3)	0	1 (2.1)	
Calcar fracture, *n* (%)	1 (1.3)	0	1 (2.1)	
ADR bemiparin	1 (1.3)	1 (3.2)	0	
Seroma, *n* (%)	1 (1.3)	0	1 (2.1)	.476
Surgery time (min)	105.91 ± 21.60	109.35 ± 25.01	103.6 ± 18.93	.255

SD: standard deviation; n: number; ADR: adverse drug reaction.
[a] p value: Student's t-test for independent samples.
[b] χ^2 test.

In terms of complications, of a total 78 operated patients, we only had 4 cases with complications (2 calcar fractures, one case of symptoms of allergic reaction to bemiparin and one surgical infection). No thromboembolic complications or complications secondary to the TXA administration route were found in the immediate postoperative period or in the follow-up (Table 3).

Discussion

Total hip arthroplasty involves significant intra- and postoperative blood loss. The onset of postsurgical anaemia can increase mortality and morbidity, increase length of hospital stay and delay rehabilitation.[17] Different processes have been developed over many years in order to minimise blood loss, and thus prevent allogenic blood transfusion, an invasive technique associated with major complications.[2] Many studies report the benefits of tranexamic acid in reducing postoperative bleeding.[8,18,19] There has been increasing interest in the topical administration of TXA in recent years due to its direct application to the surgical site with local action which minimises systemic side effects.[10,20,21] When tranexamic acid is given intravenously it distributes intracellularly and extracellularly until it reaches its maximum concentration after 5–15 min, increasing its risk of causing thromboembolic complications.[10,22,23] In our randomized clinical trial we demonstrated that there are no statistically significant differences in the topical administration of 2 g of tranexamic acid compared to the standard treatment of 15 mg/kg intravenously, in terms of falls in haemoglobin and haematocrit, blood loss and the need for transfusions. In a recently published meta-analysis similar results to ours were obtained in terms of reduced bleeding and minimising transfusions.[23] However, unlike our results, they observed less of a fall in haemoglobin in the intravenous group, without being able to ensure the superiority of this route; probably due to insufficient data.

Many studies have demonstrated that the intra-articular route is not inferior to the standard intravenous administration after a total knee arthroplasty,[4,12–14] some authors even recommend intra-articular administration as more effective, since it is a direct and simple route that can be used for patients for whom the systemic use of TXA is contraindicated, since its absorption from the joint is not very clinically significant.[24] We found few publications on the hip that refer to statistically significant differences in decreased bleeding according to the administration route, and the few we did find defend the intravenous route.[25,26] Our study found very similar results, but always with less total blood loss and lower falls in haemoglobin in the intra-articular group, and there was a statistically significant association in some values. Likewise, the patients in the intra-articular administration group received fewer transfusions compared to the intravenous group, and although we did not obtain a statistically significant result and we cannot confirm the superiority of one route over the other, this constant tendency towards better results using the intra-articular route has encouraged us to use it in our clinical practice.

The administration of tranexamic acid has proved a safe technique, since we have had no increase in complications (PTE, DVT or deep infections). Only one patient in group B developed a seroma that required surgical cleaning and intravenous antibiotic therapy for 7 days. However, most authors recommend the topical route for patients with a potential risk of thromboembolic events.[23]

Most publications make no mention of surgery time,[18] therefore they consider that it might influence blood loss. In our study we assessed the surgery time of the intravenous group (109.35 ± 25.01 min) compared to the topical group (103.6 ± 18.9 min), and found no statistically significant differences.

This study has some limitations. Firstly, we used sequential randomisation excluding patients with major cardiovascular comorbidities, i.e., potentially thromboembolic patients. Furthermore, the number of cases allocated to each group was not equal, and was too small to be able to demonstrate a statistically significant association. Different surgeons participated which might have led to unequal intraoperative bleeding. We excluded patients who required intraoperative blood transfusions to prevent potential biases in monitoring a population with no intraoperative complications. And finally, in our hospital we do not perform routine screening for PTE or DVT, and therefore only Doppler ultrasonography was indicated in the event of clinical suspicion. Any complications might have been underestimated if there had been any asymptomatic thromboembolic events. The strengths of this paper are that it was a prospective, randomized study with team of doctors, surgical nurses and operating theatre that follow a rigorous protocol of action and data collection.

The doses of tranexamic acid that should be prescribed are still a matter of controversy. Studies on the dose regimens are very heterogeneous, and probably require larger samples to obtain valid results. Our study used 15 mg/kg intravenously and 2 g via the intra-articular route; our doses were based on similar regimens recommended in Ref.[17]

Conclusion

The different administration routes for tranexamic acid that we studied for primary total hip arthroplasty (topical intra-articular versus intravenous) have a similar effect in reducing postoperative bleeding. We found no increase in complications with either of the 2 established regimens. However, we prefer the intra-articular route for patients with a thromboembolic risk. Further studies are required with a larger number of cases to establish the optimal dose of tranexamic acid.

Level of evidence

Level of evidence II.

Conflict of interests

The authors have no conflict of interest to declare.

Appendix A. Annex 1[27]

Patient's blood volume = ($k1 \times$ height [m^3]) + ($k2 \times$ weight [kg]) + $k3$

- Males: $K1 = .3699 / K2 = .3219 / K3 = .6041$
- Females: $K1 = .3561 / K2 = .03308 / K3 = .1833$

Appendix B. Annex 2[28]

Total blood loss = patient's blood volume $\times$ (Hct(pre) − Hct(post)/mean Hct)

Appendix C. Annex 3[29]

Hidden blood loss = total blood loss − drained volume at 72 h.

References

1. Chen Y, Chen Z, Cui S, Li Z, Yuan Z. Topical versus systemic tranexamic acid after total knee and hip arthroplasty: a meta-analysis of randomized controlled trials. Medicine (Baltimore). 2016;95:e4656.
2. Levine BR, Haughom B, Strong B, Hellman M, Frank RM. Blood management strategies for total knee arthroplasty [abstract]. J Am Acad Orthop Surg. 2014;22:361–71.
3. Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty-day complication rates. J Bone Joint Surg Am. 2014;96:1945–51.
4. Sarzaeem MM, Razi M, Kazemian G, Moghaddam ME, Rasi AM, Karimi M. Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. J Arthroplasty. 2014;29:1521–4.
5. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010;113:482–95.
6. Canillas F, Gomez-Ramirez S, Garcia-Erce JA, Pavia-Molina J, Gomez-Luque A, Munoz M. Patient blood management in orthopaedic surgery. Rev Esp Cir Ortop Traumatol. 2015;59:137–49.
7. Muñoz M, Páramo JA. Antifibrinolytic agents in current anaesthetic practice: use of tranexamic acid in lower limb arthroplasty. Br J Anaesth. 2014;112:766–7.
8. Ngichabe S, Obura T, Stones W. Intravenous tranexamic acid as an adjunct haemostat to ornipressin during open myomectomy. A randomized double blind placebo controlled trial. Ann Surg Innov Res. 2015;9:10.
9. Gillette BP, DeSimone LJ, Trousdale RT, Pagnano MW, Sierra RJ. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. Clin Orthop Relat Res. 2013;471:150–4.
10. Chang C-H, Chang Y, Chen DW, Ueng SWN, Lee MS. Topical tranexamic acid reduces blood loss and transfusion rates associated with primary total hip arthroplasty. Clin Orthop Relat Res. 2014;472:1552–7.
11. Liu X, Liu J, Sun G. A comparison of combined intravenous and topical administration of tranexamic acid with intravenous tranexamic acid alone for blood loss reduction after total hip arthroplasty: a meta-analysis. Int J Surg. 2017;41:34–43.
12. Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. J Arthroplasty. 2014;29:2452–6.
13. Soni A, Saini R, Gulati A, Paul R, Bhatty S, Rajoli SR. Comparison between intravenous and intra-articular regimens of tranexamic acid in reducing blood loss during total knee arthroplasty. J Arthroplasty. 2014;29:1525–7.
14. Patel JN, Spanyer J, Smith LS, Huang J, Yakkanti MR, Malkani AL. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. J Arthroplasty. 2014;29:1528–31.
15. De Leon EM, Szallasi A. Transfusion indication RBC (PBM-02): gap analysis of a Joint Commission Patient Blood Management

Performance Measure at a community hospital. Blood Transfus. 2014;12 Suppl. 1:s187–90.
16. American Society of Anesthesiologists. American Society of Anesthesiologists: ASA physical status classification system. Available at: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system. Published October 15, 2014.
17. Aguilera-Roig X, Jordán-Sales M, Natera-Cisneros L, Monllau-García JC, Martínez-Zapata MJ. Ácido tranexámico en cirugía ortopédica. Rev Esp Cir Ortop Traumatol. 2014;58:52–6.
18. Fernández-Cortiñas AB, Quintáns-Vázquez JM, Gómez-Suárez F, Murillo OS, Sánchez-López BR, Pena-Gracía JM. Efecto de dosis única intravenosa de ácido tranexámico sobre el sangrado en artroplastia total de cadera. Estudio prospectivo, controlado y aleatorizado. Rev Esp Cir Ortop Traumatol. 2017;61:289–95.
19. Castro-Menéndez M, Pena-Paz S, Rocha-García F, Rodríguez-Casas N, Huici-Izco R, Montero-Viéites A. Eficacia de 2 gramos intravenosos de ácido tranexámico en la reducción del sangrado postoperatorio de la artroplastia total de cadera y rodilla. Rev Esp Cir Ortop Traumatol. 2016;60:315–24.
20. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am. 2010;92:2503–10.
21. Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. Can J Anaesth. 2009;56:202–12.
22. Sun X, Dong Q, Zhang Y-G. Intravenous versus topical tranexamic acid in primary total hip replacement: a systemic review and meta-analysis. Int J Surg. 2016;32:10–8.
23. Zhang P, Liang Y, Chen P, Fang Y, He J, Wang J. Intravenous versus topical tranexamic acid in primary total hip replacement: a meta-analysis. Medicine (Baltimore). 2016;95:e5573.
24. Digas G, Koutsogiannis I, Meletiadis G, Antonopoulou E, Karamoulas V, Bikos C. Intra-articular injection of tranexamic acid reduce blood loss in cemented total knee arthroplasty. Eur J Orthop Surg Traumatol. 2015;25:1181–8.
25. North WT, Mehran N, Davis JJ, Silverton CD, Weir RM, Laker MW. Topical vs intravenous tranexamic acid in primary total hip arthroplasty: a double-blind randomized controlled trial. J Arthroplasty. 2016;31:1022–6.
26. Wind TC, Barfield WR, Moskal JT. The effect of tranexamic acid on transfusion rate in primary total hip arthroplasty. J Arthroplasty. 2014;29:387–9.
27. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51:224–32.
28. Gross JB. Estimating allowable blood loss: corrected for dilution. Anesthesiology. 1983;58:277–80.
29. Aguilera X, Martínez-Zapata MJ, Hinarejos P, Jordán M, Leal J, González JC, et al. Topical and intravenous tranexamic acid reduce blood loss compared to routine hemostasis in total knee arthroplasty: a multicenter, randomized, controlled trial. Arch Orthop Trauma Surg. 2015;135:1017–25.