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Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial

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Background. Risks and costs of allogeneic blood transfusions mandate strategies to reduce blood loss in surgery. The objective of this study was to assess the efficacy of antifibrinolytic treatment in reducing perioperative blood loss during total knee replacement.

Methods. A double-blind, randomized and placebo-controlled clinical trial was carried out on 127 patients undergoing total knee replacement. Patients in the study group received tranexamic acid 10 mg kg^{-1} i.v. just before the tourniquet was deflated and 3 h later, or epsilon-aminocaproic acid 100 mg kg^{-1} before tourniquet deflation followed by continuous perfusion (1 g h^{-1}) during 3 h. External perioperative blood loss was measured and total blood loss was calculated. The number of patients transfused and number of packed red cell (PRC) units transfused was recorded and possible postoperative thromboembolic complications were investigated.

Results. Total blood loss [mean (SD)] was 1099 ml (535) in the group that received antifibrinolytic agents and 1784 ml (660) in the control group ($P<0.001$). Five patients (7.5%) in the study group and 23 (38.3%) in the control group ($P<0.001$) received blood transfusions; the first group received a mean of 0.10 PRC unit per patient and the second, 0.58 ($P<0.001$). Mean reduction in haemoglobin levels (g dl^{-1}) between preoperative and fifth day postoperative readings was 2.5 (0.9) in the study group and 3.4 (1.2) in the control group ($P<0.001$). Clinical assessment did not reveal any thromboembolic complications.

Conclusions. Antifibrinolytic agents produce a significant decrease in blood loss in patients undergoing total knee replacement, reflected in a reduction in the number of blood transfusions required.

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Keywords: agents, antifibrinolytic, 6-aminocaproic acid; agents, antifibrinolytic, tranexamic acid; blood, loss, surgical; surgery, arthroplasty, knee replacement

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An increase in postoperative bleeding on removal of the pneumatic tourniquet has been described in total knee replacements (TKR) and is attributed to an activation of the fibrinolytic system in the first hours after surgery.[1–3] The effect is positive in so far as it reduces the risk of thromboembolism in orthopaedic surgery but it can also increase postoperative bleeding which in turn frequently causes the need for blood transfusions. Medication that reduces hyperfibrinolysis could be administered to reduce blood loss[4] but the increased risk of thromboembolic complications must be taken into account. Tranexamic acid (TXA),[5–7] epsilon-aminocaproic acid (EACA),[8–10] and aprotinin are three such agents that can be used to decrease perioperative bleeding in TKR[11] and other surgical procedures.[10 12–16] Some studies have shown that aprotinin may be slightly more efficacious than other antifibrinolytics but with poorer cost-effectiveness and with a potential risk of anaphylaxis.[8 9 17 18] In a study of 55 patients undergoing total hip replacement, Harley and colleagues[19] found that EACA greatly reduced postoperative bleeding and the need for transfusions but there are no studies on TKR. Moreover, EACA is cheap, does not carry any risk of anaphylaxis

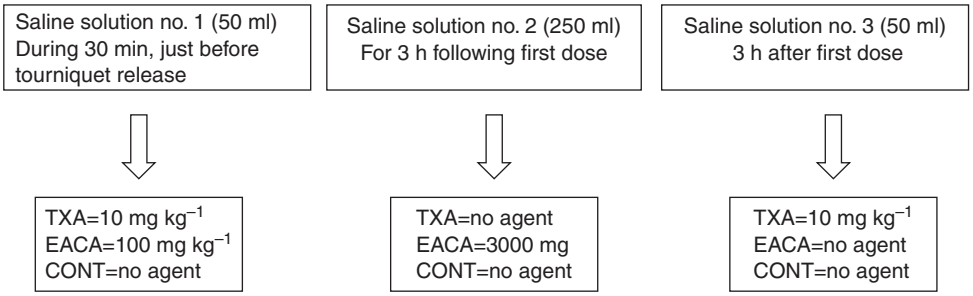


Fig 1 Algorithm used to guarantee masking of study treatment agents. TXA, tranexamic acid; EACA, epsilon-aminocaproic acid; CONT, control group.

and is available in many countries. The objective of the present study was to assess the efficacy of antifibrinolytic treatment with TXA or EACA in reducing perioperative bleeding in TKR surgery.

Material and methods

A randomized, double-blind, clinical trial was carried out with two parallel surgical groups: the study group (ANTIF) underwent surgery with antifibrinolytics and the control group (CONT), with placebo. From March 2004 to March 2005, all patients who needed unilateral, bicompartmental, primary, cemented TKR because of osteoarthritis or rheumatoid arthritis and were in the anaesthetic risk groups ASA I–III were invited to participate in the study. Patients were excluded if they had a history of coagulopathy or thrombosis, embolism, or both or had received acenocoumarol, aspirin or platelet antiaggregant treatment in the week before surgery, or nonsteroidal antiinflammatory agents in the 2 days before surgery. Patients were also excluded if their preoperative plasma creatinine were greater than 130 μmol litre^{-1}, they had a history of myocardial infarction or chronic arteriopathy, had had unstable angina in the previous 12 months, or their mental states prevented them from understanding the study proposal. Eligible patients were informed of the objectives and procedure of the study and signed their written, informed consent before being enrolled. The study design was approved by the Clinical Research Ethics Committee and by the Agencia Española de Medicamentos y Productos Sanitarios (Spanish Medicines and Healthcare Products Agency).

The study sample size was estimated on the basis of the mean difference in the visible blood loss greater or equal to 300 ml between the two study groups. Assuming a standard deviation of 500 ml, an alpha error of 0.05, and 90% statistical power, 59 patients were needed in each group, or a total of 118. Assuming a 10% loss to follow up, 130 patients were finally enrolled.

A correlative identification number, strictly after order of enrolment, was given to each patient when they gave their written consent to participate. Patients were assigned to groups using statistical software which provided a series of random numbers. Two groups, CONT and ANTIF, were considered for the randomization procedure. Within the study group patients were randomized again into two groups: the first received TXA and the second EACA. The randomized assignment was sealed in an opaque, numbered envelope which was opened only by the nurse who prepared the endovenous solutions. This nurse was the only person who knew the patients' study groups and did not participate in any other phase of the trial. Masking was ensured by the administration of three apparently identical saline drips to each patient: the first, 50 ml; the second, 250 ml for 3 h continuous perfusion, and the third, 50 ml. Medication or placebo was added to the saline drip according to the protocol, as shown in Figure 1. Neither the patient nor the anaesthetist who assessed the results knew the patient's study group. Earlier trials of TXA have used from 15 to 150 mg kg^{-1}, administered in one or several doses,[2 20 21] obtaining similar effects with these different doses.[22] Moreover, major bleeding in this type of surgery occurs in the first hours so a regimen of two doses, 3 h apart, was chosen for the effect to last over the first 6 h. With regard to EACA, the dose chosen (100 mg kg^{-1}) was midway between doses used in other studies[8 10 19] and the dose recommended by the laboratory (Fides Ecopharma) and was followed by a perfusion of 1 g h^{-1} for 3 h, similar to doses used in the studies mentioned. The first dose of antifibrinolytics was administered over 30 min immediately before releasing the tourniquet which prevented the agent from reaching the lower limb.

In order to avoid exposure to allogeneic blood, patients without contraindications followed the predeposit autologous donation programme normally used at the centre, with preoperative donation of a mean volume of 400 ml. A unit of packed red cell (PRC) was reserved for patients who could not follow this procedure and cell salvage system for blood recovery was used for the first 5 h after surgery. Antithrombotic prophylaxis was started the night before surgery with s.c. dalteparin sodium 5000 iu and was continued daily for 40 days. Where possible, patients were given intradural anaesthesia for the operation and an epidural catheter was inserted and maintained for 48 h for postoperative pain control. The operations were performed by a team of five surgeons. Cemented knee prostheses (Legacy®, Zimmer,

$$\text{TBL (ml)} = \frac{\text{TRCL (ml)}}{\text{mean Hi–Hf}}$$

TRCL=ARCL (ml)+VTRC (ml)

ARCL=Vth×(Hi–Hf) ; Vth in men=weight (kg)×70 ; Vth in women=weight (kg)×65.

VTRC=1 iu packed homologous blood=170 ml of red cells
1 iu packed autologous blood=140 ml of red cells
Every 100 ml of concentrated blood from the blood recovery system corresponded to 54 ml red cells.

Fig 2 Formulae used to calculate total blood loss. TBL, total blood loss; TRCL, total red cell loss; Hi, haematocrit the night before surgery; Hf, haematocrit fifth day after surgery; ARCL, accepted red cell loss; Vth, estimated volaemia (ml); VTRC, volume of transfused red blood cells.

USA) were inserted in bloodless conditions and the lumen of the femur was plugged with autologous bone. After tourniquet release, haemostasis was performed and two intraarticular drains were inserted and maintained for 48 h. A haemoglobin level of less than 8 g dl^{-1} was considered a transfusion trigger except in patients who could have poor tolerance to these levels because of associated conditions such as myocardial ischaemia chronic obstructive pulmonary disease (COPD), cerebral arterial insufficiency, or patients who presented signs, symptoms, or both of hypoxia such as tachycardia, dyspnoea, or syncope. The transfusion trigger was placed at less than 10 g dl^{-1} for these patients.

In order to assess the antihaemorrhage efficacy of the antifibrinolytics, external intra- and postoperative blood loss was estimated by measuring the differential weight of all the surgical swabs and dressings used during the operation and the quantity of blood recovered in the suction bottles, in the blood recovery system (subtracting the volume of saline solution used), and the blood in the drain collectors on removal after 48 h. The quantity of blood recovered and reinfused by the blood recovery system was also registered for those patients who used it. Total blood loss was calculated by the changes in haematocrit levels between the day before the operation and the fifth day after, according to the formulae[23] shown in Figure 2. Haematological analysis was performed (i) approximately 4 weeks before, (ii) on admission, the night before, (iii) 5 h after, (iv) 1 day after and (v) 5 days after the operation. The difference between estimated total loss and external loss is considered to be hidden blood loss, from bleeding into the tissues and haemolysis. Other parameters considered were the number of patients who received transfusions and the number of units of PRC administered. All relevant inhospital complications were recorded. A systematic clinical screening for thrombosis was undertaken in which calf and supramalleolar circumferences were measured before and 5 days after surgery, and compared. Thrombosis was suspected with increases greater than 3 cm and, with this or other clinical signs or symptoms (pain, oedema or swelling of the limb), vascular specialists were consulted over whether venous echo-Doppler was indicated to confirm this complication. Three months after hospital release, patients were given a telephonic survey on the presence of possible complications, particularly thrombosis and thromboembolisms.

All results were recorded in a computer data base for subsequent cleansing and statistical analysis. An initial description of the main characteristics was performed with continuous variables expressed as means with SDs, and categorical variables as percentages. The Student's *t*-test was used both to assess 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 was used to compare means between three groups (TXA, EACA and CONT). The χ^2-test was used to compare percentages and to assess the categorical variables associated with blood transfusion. Variables associated with blood transfusion in the univariate analysis with *P*-values less than 0.10 were included in the multivariate logistic regression model using the forward conditional method. In all cases, the level of statistical significance was 0.05.

Results

A total of 128 patients were enrolled in the study and randomized into one of the two groups: 68 in the ANTIF group (35 with TXA and 33 with EACA) and 60 in the CONT group. One patient in the ANTIF group could not be analysed as the data were misplaced, and finally 127 patients were analysed. Figure 3 is a flow graph of the patients at the various stages of the clinical trial. Intradural anaesthesia using 12 mg bupivacaine 0.5% and insertion of an epidural catheter for postoperative pain control was performed on all patients except two, in the CONT group, for whom it was technically impossible. Table 1 compares the main characteristics of the study sample for each of the study groups. No significant differences were found between groups for any of the variables considered.

The ANTIF group presented significantly lower external and total blood losses than the control group (Table 2). External bleeding in the ANTIF and the CONT group were 273 (SD 224) ml *vs* 329 (248) ml (P=0.191) in the operating theatre, 192 (168) ml *vs* 613 (467) ml (P<0.001) in recovery, and 281 (138) ml *vs* 239 (201) ml (P=0.171) in the

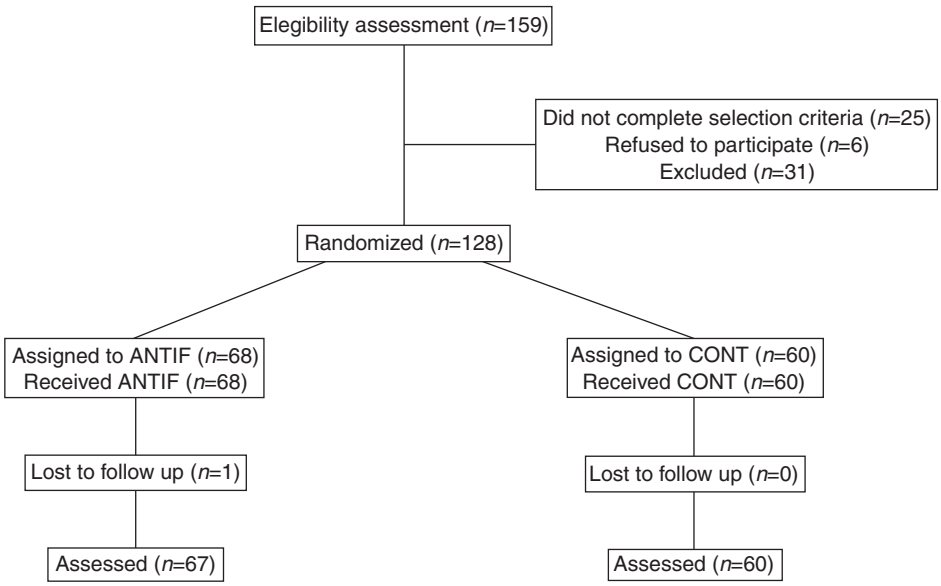


Fig 3 Flow chart of patient progression through trial phases.

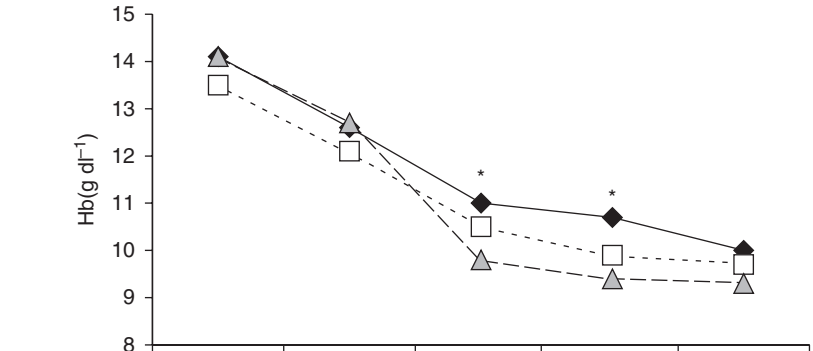
Table 1 Main characteristics of the study groups, a comparison. **P*, statistical significance corresponding to the comparison between two groups: ANTIF and CONT. *†*P*, statistical significance corresponding to the comparison between two groups: TXA and EACA

	CONT (*n*=60)	ANTIF (*n*=67)	*P*-value*	TXA (*n*=35)	EACA (*n*=32)	*P*-value*†
Age (yr)	72 (52–85)	73 (59–84)	0.500	73 (61–84)	73 (59–80)	0.994
% Women	80.0	80.6	0.933	74.3	87.5	0.223
% Right knee	51.7	60.6	0.312	54.3	67.7	0.264
ASA risk (%)						
ASA-I	5.0	3.0		5.7	0	
ASA-II	73.3	77.6	0.786	68.6	87.5	0.128
ASA-III	21.7	19.4		25.7	12.5	
Preoperative blood reserve type (%)						
Autologous	8.3	6.1		6.5	5.7	
Homologous	38.3	45.5	0.687	41.9	48.6	0.864
Autologous + homologous	53.3	48.5		51.6	45.7	
Haemoglobin on admission (g dl^{-1})	12.6 (1.2)	12.4 (1.0)	0.147	12.6 (0.9)	12.1 (1.1)	0.190
Haematocrit on admission	36.9 (3.2)	36.2 (2.7)	0.145	36.8 (2.5)	35.5 (2.8)	0.169
Perioperative use of Cell Saver (%)	23.3	27.3	0.612	28.6	25.8	0.801
Duration of surgery (min)	102 (19)	99.4 (21)	0.511	97 (22)	102 (20)	0.574
Duration of ischaemia (min)	89 (16)	87 (18)	0.424	88 (16)	85 (20)	0.864

ward, respectively. Moreover, the ANTIF group required transfusions in a significantly smaller percentage of patients (Table 2). No significant differences were found between the EACA and TXA groups for any of the outcome measures considered. The ANTIF group received seven units of PRC compared with 35 in the CONT group. Five patients in the ANTIF group (7.5%) and 23 in the CONT group (38.3%) received transfusions ($P<0.001$) (Table 2). The reduction in the haemoglobin levels between admission and the fifth day after surgery were significantly less in the ANTIF group than the CONT group as shown in Figure 4. The results of the multivariate logistics regression analysis showed that antifibrinolytic treatment acted as a protective factor against blood transfusion while systolic arterial pressure values greater than 150 mm Hg and preoperative haemoglobin levels lower than 12.5 g dl^{-1} favoured blood transfusion (Table 3).

Seventy-three patients in the study sample (57.5%) were included in the autotransfusion programme and 18 (24.7%) received transfusions of their own blood. A reduction of 1.8 g (0.7) dl^{-1} haemoglobin between the preoperative visit and admission was observed in patients who donated their own blood for possible autologous transfusion, compared with 0.9 (0.7) g dl^{-1} ($P<0.001$) in patients who did not donate blood. The percentage of patients who received transfusions was 44.4% of those who had given two units of autologous blood, 21.9% of those who had given 1, and 17% of those who had not given any preoperative blood ($P=0.177$). Four patients in the preoperative autologous donation programme received allogeneic blood transfusions.

There were no postoperative complications and follow-up of possible thromboembolisms revealed eight patients with suspected deep vein thrombosis attributable to an increase in circumference and major oedema: 6 (8.9%) ANTIF and



	Preoperative	Admission	5 h after surgery	First day after surgery	Fifth day after surgery
TXA	14.1	12.6	11	10.7	10
EACA	13.5	12.1	10.5	9.9	9.7
CONT	14.1	12.7	9.8	9.4	9.3

Fig 4 Reduction of haemoglobin levels (g dl^{-1}) between preoperative visit and fifth day after surgery. *P<0.05 between the TXA and EACA groups with respect to the CONT group.

Table 2 Comparison of the main results between the groups. *P, statistical significance corresponding to the comparison between two groups: ANTIF and CONT. *†P, statistical significance corresponding to the comparison between two groups: TXA and EACA

	CONT (n=60)	ANTIF (n=67)	P-value*	TXA (n=35)	EACA (n=32)	P-value*†
External blood loss (ml)	1.270 (625)	798 (406)	<0.001	787 (281)	810 (512)	0.984
Total blood loss (ml)	1.784 (660)	1.099 (535)	<0.002	1095 (473)	1104 (603)	0.998
% Patients given transfusions	38.3	7.5	<0.001	2.8	12.5	0.185
Transfusion units per patient (%)						
0	61.7	92.5		97.1	87.5	
1	20.0	4.5	0.001	2.9	6.3	0.248
2	16.7	3.0		0	6.3	
3	1.7	0		0	0	
Transfusion units per patient	0.58 (0.8)	0.10 (0.4)	<0.001	0.03 (0.2)	0.19 (0.5)	0.566
Reduction in haemoglobin between admission and fifth day after surgery (g dl^{-1})	3.4 (1.2)	2.5 (1.0)	<0.001	2.6 (1.0)	2.4 (1.0)	0.704
Reduction in haematocrit between admission and fifth day after surgery	9.2 (3.5)	6.8 (3.0)	<0.001	7 (3.0)	6.6 (2.9)	0.819

Table 3 Factors associated with blood transfusion. Multivariate logistic regression

	OR	95% CI	P-value
Antifibrinolytic treatment (TXA and EACA)	0.08	0.27–0.02	<0.001
Preoperative systolic blood pressure >150 mm Hg	4.59	1.54–13.69	0.006
Preoperative haemoglobin levels <12.5 g dl^{-1}	4.21	1.44–12.34	0.009

2 (3.3%) CONT (P=0.175). Venous echo-Doppler was performed on four of these patients and the results were negative in all cases. In the telephone survey 3 months after the operation, six patients were not located, one had died from aggravation of a prior condition of pulmonary fibrosis, and five suspected episodes of thrombosis were resolved by examining clinical records. No lower limb, pulmonary, cardiac or cerebral thromboembolic episodes were found.

Discussion

The results of the present study indicate that antifibrinolytic treatment with EACA and TXA greatly reduces blood loss in TKR which in turn reduces the number of blood transfusions required. The externally visible blood losses and the estimated total losses, the reduction in haemoglobin and haematocrit levels, the number of patients who received transfusions, and the number of units transfused were significantly lower in the study group compared with the control group. These results are similar to those observed in other clinical trials[1 15 20] in which external blood losses were also measured. Differences of around 700 ml of blood, such as those observed in the present study, have clinical relevance as they may indicate the need for blood transfusion. Some studies have observed lesser blood losses than our control group[12 21] and others have measured greater blood losses than our study.[24] Unlike Good and colleagues,[20] a relevant reduction in hidden blood loss was found in the ANTIF group in the present study. These differences are

probably because of different methods of measuring blood loss, underlying the need for standardization. The decrease in haemoglobin and haematocrit levels between the day before and the fifth day after the operation was slight although significantly greater in the control group than the study group. The greater number of transfusions received by the control group would have had the effect of making even the results of the two groups by the fifth day. The reduction in bleeding in the ANTIF group occurred in the recovery room during approximately the first 6 h after surgery but not in the ward afterwards, effect which is related to the minimum effective concentration in plasma, each dose lasting for 3 h.[24] Given that bleeding persists at a lower but not negligible rate for 48 h after surgery, administering an additional dose of ANTIF should be considered. Further studies should assess the efficacy and safety of prolonging the treatment.

The multivariate analysis of factors associated with blood transfusion also showed that antifibrinolytic treatment greatly reduced the requirement for blood transfusion. Preoperative systolic blood pressure levels greater than 150 mm Hg and haemoglobin levels lower than 12.5 g dl^{-1} were also shown to be risk factors for blood transfusion. These results suggest that greater preoperative control of haemoglobin levels is necessary, and stricter pre- and perioperative guidelines for the control and treatment of blood pressure, particularly among patients with a known history of hypertension.

The present study has contributed new evidence on the efficacy of EACA in major orthopaedic surgery[19] particularly in TKR for which no studies have been published to our knowledge. The present study compares the effects of EACA and TXA on the reduction of perioperative bleeding and on the number of transfusions needed, without significant differences between the two antifibrinolytic agents being found. Nevertheless, one patient from the TXA group and four from the EACA group received transfusions. The limited number of patients studied could have impeded statistically significant differences being found between the groups.

Regarding dosage and length of TXA treatment, Harrow and colleagues[12] found that 10 mg kg^{-1} was the minimum dosage needed to obtain the desired antihaemorrhagic effect. Given that the mean duration of effect of TXA is around 3 h, a second dose was administered after this period to prolong the effect over the first 6 h, when most bleeding occurs. Regarding EACA, a weaker loading dose than that used in other studies but stronger than the dose recommended by the laboratory was used, followed by 3 h continuous perfusion at similar doses to those used in other studies,[8 10 19] because of the agent's brief half-life. In all patients, antifibrinolytic treatment was given before releasing the tourniquet. Although there are clinical trials that have administered antifibrinolytic treatment before inflating the tourniquet without increasing thromboembolic complications,[25 26] administering procoagulant drugs to a limb in prolonged stasis could increase the risk of thrombosis. No relevant complications were observed in any study patient, suggesting that the treatment is safe when applied under the conditions mentioned. Not performing echo-Doppler systematically on all patients enrolled in the trial is a limitation of the present study. Nevertheless, no clinically relevant thromboembolic episode was identified. These results also coincide with the literature which has not described a significant increase in side-effects attributable to the study intervention.[5 11 21 24] Clinicians should exercise caution in interpreting these results when considering the safety of TXA and EACA.

In the present study, 73 patients entered the autotransfusion programme (61.7% in the control group *vs* 53.7% in the ANTIF group) of which only 18 received autologous transfusions; for every four bags extracted, three were wasted. Autotransfusion is justified when the probability of transfusion is greater than 50%.[23] Moreover, reduction in haemoglobin levels between the preoperative visit and the day of admission of patients in the autotransfusion programme was significantly greater than for patients who did not enter the programme, suggesting the autologous programme has an iatrogenous effect which increases when the closer, in time, the extraction is to surgery. In the light of these points and the evidence obtained, the autotransfusion programme was not justified under the conditions of the present study. Every medical centre must design blood saving strategies taking into account their specific circumstances. The sharp reduction in transfusions in the ANTIF group also meant a reduction in homologous transfusions, making comparison of the efficacy of the autotransfusion programme between the ANTIF and CONT groups difficult.

In conclusion, EACA and TXA reduce perioperative bleeding by almost a third in patients undergoing TKR, and reducing blood transfusion requirement in these patients by almost 80%. Moreover, treatment cost is low, and safety has proved to be high, there being no increased risk of thromboembolic complications. According to the efficacy, safety, and efficiency criteria, these antifibrinolytic agents should be indicated in patients undergoing TKR.

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