Acta Orthop. Belg., 2020, **86 e-SUPPLEMENT** 2, 58-65

ORIGINAL STUDY

Efficacy of IV tranexamic acid versus autologous blood salvage systems in controlling blood loss following knee arthroplasty

Carlos JIMÉNEZ-GARRIDO, Maximiano LOMBARDO-TORRE, Ines RODRÍGUEZ-DELOURME, Elvira MONTAÑEZ-HEREDIA

From the Hospital Universitario Virgen de la Victoria, Campus Teatinos s/n. Málaga, Spain

The purpose of this study is evaluate and compare efficacy of tranexamic acid (TXA) versus autologous blood salvage systems in blood loss management following primary total knee arthroplasty (TKA). Observational, prospective, randomized study performed between April 2016 and June 2017. 120 consecutive patients who underwent TKA were divided into three 40-patient groups: Group A, with one drain and a blood salvage system; Group B, with two drains and a blood salvage system; and Group C, with IV TXA and one drain without a blood salvage system. Principal outcomes included hemoglobin (Hb) and hematocrit (Htc) decreases 24 hours after surgery and need for transfusion. The mean decrease in Hb levels was 2.96±1.17 g/dL in A, 3.05±0.99 g/dL in B, and 1.79±0.77 g/dL in C. The mean decrease in Htc levels was 9.19±3.7% in A, 9.49±3.2% in B, and 5.57±2.1% in C. We found statistically-significant differences between Group C versus A and B (P=0.002, P=0.004) and among the groups individually: C vs A (P=0.012) and C vs B (P=0.003) in hemoglobin levels; C vs A (P=0.022) and C vs B (P=0.007) in hematocrit levels. There were no significant differences between A and B. Three patients in A (50%) and 3 in B (50%) needed transfusions. No patients in C required transfusion, but this was not statistically significant with respect to the other groups (P=0.206). As conclussions, TXA significantly reduces decreases in hemoglobin and hematocrit levels following TKA compared to blood salvage drains. For blood salvage systems, there is no difference between using one or two drains.

Keywords : Knee Arthroplasty ; Tranexamic Acid ; Drains ; Blood transfussions.

INTRODUCTION

Total knee arthroplasty (TKA) can cause considerable perioperative blood loss. Mean blood loss ranges from 800 mL to 1800 mL *(3,4,20)* and may make blood transfusions, which are not free of risk, necessary in 20% of patients approximately *(8)*. In addition to posing a clinical risk to the patient such as a substantial risk of hemolytic and non-hemolytic transfusion reactions, transmission of infectious diseases and a increase of prosthesis joint infection. Greater perioperative blood loss is associated with a longer hospital stay and an increase in healthcare costs *(15)*.

To limit blood loss and reduce the need for blood transfusions, numerous strategies are available: strict control of surgical hemostasis, intraoperative

■ Carlos Jiménez-Garrido[1].
■ Maximiano Lombardo-Torre[1].
■ Ines Rodríguez-Delourme[2].
■ Elvira Montañez-Heredia[1,2]
[1]*Department of Orthopedic Surgery and Traumatology.*
[2]*Instituto de Investigación Biomédica de Málaga (IBIMA).*
Correspondence : Hospital Universitario Virgen de la Victoria, Campus Teatinos s/n. Málaga, Spain.
E-mail : Cjgmedicina@gmail.com

Conflicts of interest: The authors declare that there are no conflicts of interest in the execution of this work.

hypotension, local and regional anesthetic techniques or an autologous blood salvage system with drains, or anti-fibrinolytic agents such as tranexamic acid (TXA). TXA is a synthetic derivative of lysine that acts by binding to the lysine binding sites on plasminogen, impeding fibrin from binding to the tissue plasminogen activator-plasmin compound, and inhibiting fibrin degradation *(7)*. It also plays a role in protecting platelets due to its antiplasmin effect and inhibition of platelet-activating factor *(17)*.

The efficacy and safety of locally- or systemically-administered TXA in the decrease of perioperative blood loss and the need for transfusions following TKA has been demonstrated in numerous works. However, there is no consensus in the literature on the best protocol for administering TXA or the most appropriate dosage *(1,3,4,7,9,11,15,17,18,19,20,21,27,28)*.

On the other hand, the use of autologous blood salvage systems with drains in TKA is another very popular method for salvaging perioperative blood. These systems have been shown to be a safe method for autologous blood transfusion, avoiding the majority of the risks of allogenic transfusion while being equally effective in decreasing perioperative blood loss in TKA *(14,26)*. Nevertheless, there is no clear consensus in the literature regarding its efficacy in decreasing the need for blood transfusion in the post-operative period or its advantages in cost-benefit terms *(2,23)*.

Due to the upward trend in the number of TKAs performed each year, complications related to blood transfusions have also increased. These complications currently pose a significant problem and may jeopardize the results of patients who undergo TKA.

The principal aim of this study is to evaluate and compare the efficacy of using TXA versus autologous blood salvage systems with one or two intra-articular drains in patients who have undergone primary TKA. Assessment is based on reducing decreases in hemoglobin and hematocrit levels 24 hours following surgery and the need for blood transfusions.

MATERIALS AND METHODS

This study included 120 consecutive patients who underwent TKA between April 2016 and June 2017 and who met the following inclusion criteria: patients who underwent TKA without posterior stabilization and with cementing of the tibial component only; no prior procedures on the knee to be operated on except for simple knee arthroscopy; pre-operative hemoglobin (Hb) levels >10 g/dL; and International Normalized Ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT) levels within normal ranges. Patients who took antiplatelet drugs and anticoagulants stopped their treatment seven days prior to scheduled surgery. For anticoagulated patients, anticoagulant treatment was substituted with low-molecular-weight heparin until 24 hours prior to surgery.

Exclusion criteria were: allergy to tranexamic acid, known coagulopathy, a documented prior medical history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within the year before to surgery, ischemic stroke, intermittent claudication, coronary stent, epilepsy, severe kidney failure, or hormone replacement therapy.

Randomization was carried out externally by means of a simple 1:1:1 randomization by computer generated random card into three groups: Group A, which had one intra-articular closed suction drain connected to a blood salvage system; Group B, which had two intra-articular closed suction drains connected to a blood salvage system; and Group C, with one closed suction drain and IV TXA in two boli according to weight: an initial IV bolus of 10 mg/kg of the patient's weight administered 10 minutes prior to beginning ischemia of the limb to be operated on and a second IV bolus of 10 mg/kg of weight administered 10 minutes after removing the tourniquet from the limb operated on *(12)*.

To calculate sample size, according to the results found in the literature, it was estimated that the mean decrease in Hb following TKA without the use of intravenous tranexamic acid is approximately 151.76 ± 51.26 g/mL. Considering that decreasing this loss of Hb in the TXA group to 28.83 ± 9.73 g/mL would be clinically significant, the study would

have a power of 80% in order to detect this decrease with a significance of 5%. In accordance with these premises, it was determined that at least 39 patients per group are needed.

General socio-demographic variables and specific variables regarding treatment received were collected from all patients and analyzed. They were considered secondary outcomes. They included, among others, sex; age; laterality; treatment with antiplatelet drugs or anticoagulants prior to surgery; transfusion from the autologous blood salvage system; volume of blood collected in the drains; procedure-related complications such as infection, deep vein thrombosis (DVT), or hemarthrosis that occur during the first month after surgery; and, lastly, length of hospital stay in days.

Primary outcomes included presurgical hemoglobin and hematocrit levels, hemoglobin and hematocrit levels 24 hours after surgery, and transfusion of packed red blood cells in the first 72 hours following surgery.

Absolute and relative frequency were calculated for each qualitative variable. In regards to quantitative variables, the mean, median, mode, and standard deviation were calculated and compared by means of the Chi-squared test, ANOVA, and the Bonferroni correction, in accordance with whether they met the Kolmogorov-Smirnov normality criteria. Statistical significance was set at $p < 0.05$ bilateral. All data were analyzed using the SPSS v23.0 (SPSS Inc., Chicago, IL, USA) statistical program.

Ethical considerations

All procedures were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients included in the study. This work was authorized by the Provincial Research Ethics Committee of Málaga.

Surgical protocol

The operations were performed by four surgeons from our center's Knee Unit. The same prosthesis model was used for all patients: Triathlon CR (Stryker Orthopedics, Mahwah, NJ) with cement only on the tibial component and without patellar substitution. All surgeons used the same surgical technique: elevation of the limb and application of the tourniquet for ischemia between 300 and 350 mmHg, incision along the midline, and internal parapatellar arthrotomy. The ischemia was stopped once the wound had been closed. The mean duration of the surgery was 80 minutes (50 - 90 minutes). Group C patients were administered a bolus of 10 mg/kg of weight 10 minutes prior to inflating the tourniquet. For Group A and Group B patients, one or two intra-articular closed suction drains, respectively, were placed and linked to an autologous blood salvage system. Autologous transfusion was carried out in the first six hours following surgery only if blood drainage greater than 400 ml was obtained. For Group C patients, a standard intra-articular closed suction drain was placed and a second bolus of TXA was administered 10 minutes after removing the tourniquet. For all three groups, the drains were removed 24 hours after surgery.

According to the postoperative protocol, the patient was allowed to sit 24 hours following the intervention and walk 48 hours following the intervention.

Blood transfusion was performed according to the following criteria: patients who are hemodynamically stable and who have Hb levels <8 g/dL 24 hours following surgery (5). All transfused patients received 2 units of packed red blood cells within 72 hours following surgery.

RESULTS

Of the 120 patients, 47 were male (39.8%) and 73 were women (60.2%). 59 had TKA of the right knee (49.2%) and 61 had TKA of the left knee (50.8%). Six patients had preoperative antiplatelet drugs (5%), 9 patients had anticoagulants (7.5%), and 105 patients did not use either of them (87.5%). The mean age was 68.9 ± 7.07 years (51-85). Upon analyzing length of hospital stay, we found a mean of 4.57 ± 1.89 days, with a minimum stay of 3 days and a maximum stay of 20 days. The latter corresponds to a patient who developed acute pancreatitis that was unrelated to the surgical procedure. We found no significant differences between the different groups in regards to length of hospital stay in days (P=0.092).

In terms of incidents during the immediate postoperative period, there were four suspected DVTs due to postoperative swelling of the limb operated on. DVT was ruled out by means of a Doppler ultrasound of the popliteal-femoral region. There was one referred case of acute pancreatitis. No hemorrhagic complications or acute postsurgical infections were found in any of the patients in the study. Therefore, there were no statistically-significant differences between the different groups in regards to incidences of complications (P=0.812).

A total of 30 patients were autotransfused by means of the blood salvage system out of the 80 patients who used the system (37.5%). Mean volume transfused was 428.76 ± 150.76 ml.

Mean presurgical hemoglobin in the entire study sample was 13.76 ± 1.53 g/dL. Mean presurgical hematocrit was 42.19 ± 4.5 %. Hemoglobin 24 hours after surgery was 11.16 ± 1.58 g/dL and hematocrit 24 hours after surgery was 34.1 ± 4.54%.

In Group A (n=40), there were 20 patients of each sex (50%) and mean age was 70.15 ± 6.17 years (58-80). Seventeen TKAs of the right knee (42.5%) and 23 TKAs of the left knee (57.5%) were performed. Thirty-three patients did not take antiplatelet drugs or anticoagulants (82.5%), four patients took antiplatelet drugs (10%), and three patients took anticoagulants (7.5%). Three transfusions of allogenic packed red blood cells were performed (7.5%) and there were 15 autologous transfusions from the blood salvage system (37.5%). Prior to performing the TKA, hemoglobin was 13.84 ± 1.63 g/dL (10.6-16.9) and hematocrit was 42.53 ± 4.97% (32.10-52). Twenty-four hours after the TKA, mean hemoglobin was 10.88 ± 1.61 g/dL (7.5-14) and hematocrit was 33.34 ± 4.93% (23.4-43.8). Mean blood volume collected by the drain following the TKA was 347.73 ± 203.72 mL (<25-900). There were two suspected DVTs that were ruled out following a Doppler ultrasound. Mean length of hospital stay was 4.32 days (3-9).

In Group B (n=40), there were 13 men (32.5%) and 17 women (67.5%) and mean age was 68 ± 7.74 years (51-79). Seventeen TKAs of the right knee (42.5%), and 23 TKAs of the left knee (57.5%) were performed. 33 patients did not take antiplatelet drugs or anticoagulants (87.5%), two patients took antiplatelet drugs (5%), and three patients took anticoagulants (7.5%). Allogeneic transfusions of packed red blood cells were performed in three patients (7.5%) and there were 15 autotransfusions from the blood salvage system (37.5%). Mean preoperative hemoglobin was 13.78 ± 1.64 g/dL (11.1-16.1) and hematocrit was 42.46 ± 4.08% (34.6-52). Twenty-four hours after the TKA, mean hemoglobin was 10.73 ± 1.31 g/dL (7.9-13.5) and hematocrit was 32.97 ± 3.75% (24.7-40). Mean blood volume collected by the drain was 380 ± 176.23 mL (<25-700). There were two suspected DVTs that were ruled out following a Doppler ultrasound. Mean length of hospital stay was 4.27 days (3-7).

In Group C (n=40), there were 14 men (35%) and 16 women (65%) and mean age was 68.45 ± 7.27 years (56-85). Twenty-five TKAs of the right knee (62.5%) and 15 TKAs of the left knee (37.5%) were performed. Thirty-seven patients did not take antiplatelet drugs or anticoagulants (92.5%), no patients took antiplatelet drugs, and three patients took anticoagulants (7.5%). No patients in this group needed transfusions. Mean preoperative hemoglobin was 13.67 ± 1.64 g/dL (10.4-16.9) and hematocrit was 41.6 ± 4.27% (32.9-51.5). Twenty-four hours after the TKA, mean hemoglobin was 11.88 ± 1.52 g/dL (8.6-14.2) and hematocrit was 36.03 ± 4.45% (27.5-43.4). Mean blood volume collected by the drain following the TKA was 127.5 ± 125.52 mL (<25-400). One patient in this group had acute pancreatitis following the surgery. This complication was not related to the surgery. Mean length of hospital stay was 5.1 ± 2.62 days (3-20).

The remaining results obtained can be seen in Table I.

We found statistically-significant differences in hemoglobin and hematocrit levels 24 hours following surgery, with a smaller decrease in these levels in Group C with respect to Groups A and B (P=0.002 and P=0.004). The mean decrease in hemoglobin levels 24 hours following the operation was 2.96 ± 1.17 g/dL in Group A, 3.05 ± 0.99 g/dL in Group B, and 1.79 ± 0.77 g/dL in Group C (Fig 1). The mean decrease in hematocrit levels 24 hours following the operation was 9.19 ± 3.7% in Group A, 9.49 ±

Table I. – Summary of results. (Ag e: years. Presurgical hemoglobin : g/dL. Presurgical hematocrit : %. Hemoglobin 24 hours after surgery : g/dL. Hematocrit 24 hours after surgery : %. Volume of blood loss : mL)

	N= 120	Group A (n=40)	Group B (n=40)	Group C (n=40)
Age	68.9 ± 7.07 (51-85)	70.15 ± 6.17 (58-80)	68.03 ± 7.74 (51-79)	68.45 ± 7.27 (56-85)
Sex Male Female	 47 (39.8%) 73 (60.2%)	 20 (50%) 20 (50%)	 13 (32.5%) 27 (67.5%)	 14 (35%) 26 (65%)
Laterality Right Left	 59 (49.2%) 61 (50.8%)	 17 (42.5%) 23 (57.5%)	 17 (42.5%) 23 (57.5%)	 25 (62.5%) 15 (37.5%)
Antithrombotic drugs None Antiplatelet drugs Anticoagulants	 105 (87.5%) 6 (5%) 9 (7.5%)	 33 (82.5%) 4 (10%) 3 (7.5%)	 35 (87.5%) 2 (5%) 3 (7.5%)	 37 (92.5%) 0 (0%) 3 (7.5%)
Transfusion	6 (5%)	3 (7.5%)	3 (7.5%)	0 (0%)
Autologous transfusion	30 (25%)	15 (37.5%)	15 (37.5%)	0 (0%)
Complications	5 (4.2%)	2 (5%)	2 (5%)	1 (2.5%)
Presurgical Hemoglobin	13.76 ± 1.53 (10.4-16.9)	13.84 ± 1.63 (10.6-16.9)	13.78 ± 1.64 (11.1-16.1)	13.67 ± 1.64 (10.4-16.9)
Presurgical Hematocrit	42.19 ± 4.5 (32.1-52)	42.53 ± 4.97 (32.10-52)	42.46 ± 4.08 (34.6-52)	41.6 ± 4.27 (32.9-51.5)
Hemoglobin 24 hours after surgery	11.16 ± 1.58 (7.5-14.2)	10.88 ± 1.61 (7.5-14)	10.73 ± 1.31 (7.9-13.5)	11.88 ± 1.58 (8.6-14.2)
Hematocrit 24 hours after surgery	31.4 ± 4.54 (23.4-43.8)	33.34 ± 4.83 (23.4-43.8)	32.97 ± 3.75 (24.7-40.2)	36.03 ± 4.45 (27.5-43.4)
Hospital stay in days	4.57 ± 1.89 (3-20)	4.32 ± 1.36 (3-9)	4.27 ± 1.32 (3-7)	5.1 ± 2.62 (3-20)
Volume of blood loss	334 ± 198.45 (25-900)	347.73 ± 203.72 (<25-900)	380 ± 176.23 (<25-700)	127.5 ± 125.52 (<25-400)

3.2% in Group B, and 5.57 ± 2.1% in Group C (Fig 2). There were also significant differences among the groups when analyzed individually: Group C vs Group A (P=0.012) and Group C vs Group B (P=0.003) for hemoglobin levels 24 hours following the intervention and Group C vs Group A (P=0.022) and Group C vs Group B (P=0.007) for hematocrit levels 24 hours following the intervention. There were no significant differences in any of these variables between Groups A and B (P=1.00) (Table II).

In regards to the need for transfusion, despite the fact that there was a greater number of patients who needed allogeneic transfusion in the autologous blood salvage system groups than in the TXA group — in which no patients needed transfusion — this finding was not significant (P=0.206) (Table III).

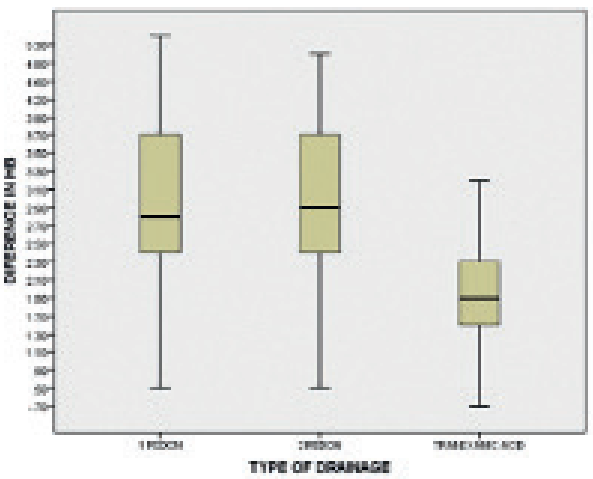

Figure 1. – Difference in the decrease of Hb levels following surgery in the study groups.

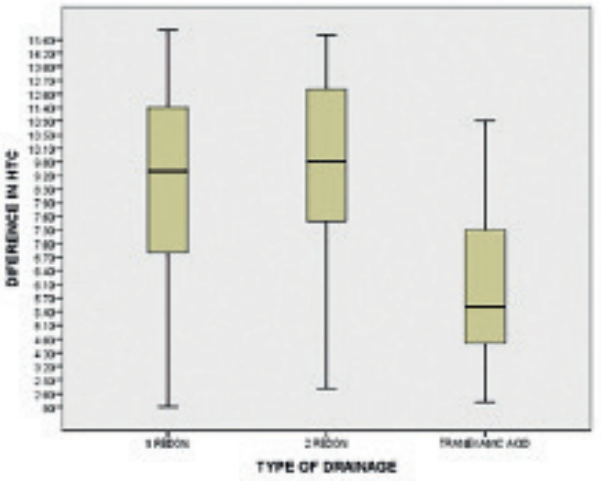

Figure 2. – Difference in the decrease of hematocrit levels following surgery in the study groups.

Table II. – Differences between mean hemoglobin and mean hematocrit caused by the arthroplasty 24 hours after surgery according to the different study groups. Hb = g/dL. HTC %

	Group A	Group B	Group C	P
Difference in Hb	Δ 2.96 ± 1.17	Δ 3.05 ± 0.99	Δ 1.79 ± 0.77	0.002
Difference in Htc.	Δ 9.19 ± 3.7	Δ 9.49 ± 3.2	Δ 5.57 ± 2.1	0.004

Table III. – Allogenic transfusions performed in the different groups.

	Allogenic transfusions (P=0.206)	
	NO	YES
Group A	37 (92.5%)	3 (7.5%)
Group B	37 (92.5%)	3 (7.5%)
Group C	40 (100%)	0 (0%)

DISCUSSION

There are numerous strategies for managing blood loss in TKA whose objectives are to control this blood loss following surgery and decrease the need for blood transfusions. Transfusions are not without risk and entail an increase in the cost of the procedure that is not insignificant *(1,3,4,9,11,15,20,21,27,28)*. Tranexamic acid and autologous blood salvage drainage systems have been established as two of the most popular methods for managing perioperative blood loss in TKA in recent years *(25)*.

The use of TXA for controlling blood loss in primary arthroplasty, mainly in the knee and the hip, has gained great popularity in recent years. Despite the fact that our study did not include a control group or a placebo group, there are a large number of works that have already shown a significant reduction in the decrease in Hb figures and the number of transfusions in the postoperative period with the use of TXA with respect to patients in which it was not used. What's more, there was no increase in thromboembolic events or other complications of interest *(1,9,18,20,27,28)*. A recent meta-analysis *(28)* evaluated all recent prospective works on the use of TXA in TKA. It showed a significant decrease in the need for blood transfusion (P <0.001) and in Hb loss (P <0.0002) with no significant differences in regards to complications between TXA and a placebo.

On the other hand, the efficacy of managing blood loss using autologous blood transfusion systems with drains is an area of conflict in the literature, without consensus between one or two drains. Though there are works that find no significant differences in the decrease in blood loss with their use *(20,22)*, other prospective studies do indeed show a significant reduction in blood loss and in the need for allogeneic blood transfusion with their use *(2,13,14,25)*. There is a meta-analysis *(24)* that has found less blood-loss when using a reinfusion drain in older studies, but not in more recent studies with contemporary blood management protocols. Thus, the latter recommend them as a valid strategy for controlling perioperative blood loss. Our data show that those systems are significantly inferior to TXA in controlling blood loss. Even so, in those cases for which use of TXA is contraindicated, we believe that it continues to be a very useful tool. Furthermore, given that no significant differences were observed in any of the variables studied between the groups with one or two drains, we can conclude that use of two drains connected to an autologous blood salvage system does not provide any additional benefit.

In regards to length of hospital stay in days, our results do not show significant differences between the three groups, though this may be due to the extreme values: one of the Group C patients (TXA)

had acute pancreatitis that was unrelated to TKA during his stay which made it necessary to prolong hospitalization to 20 days.

The comparison between TXA and autologous blood salvage systems with drains in TKA carried out in this work has not been previously studied in depth. Despite the wealth of literature on each separate method, we have only found one prospective work that compares the efficacy, safety, and costs of TXA versus blood salvage systems with drains in the management of blood loss in patients who undergo primary arthroplasty *(22)*. In that work, Springer et al. compared the use of a standard drain, a blood salvage drain, and TXA (in a single dose of 20 mg/kg) in 186 patients who underwent primary knee or hip arthroplasty. They observed significant differences in the decrease in hemoglobin in the TXA group with respect to the standard drain group ($P<0.0001$) and the blood salvage drain group ($P<0.0061$). However, just as in our study, no significant differences were observed in regards to the ratio of postoperative transfusions. In large part, the data from that work are in accordance with the data we obtained, though the Springer et al. work also included hip arthroplasties and the TXA guidelines followed were different. They used a single intravenous dose of 20 mg/kg prior to surgery compared with the double dose of 10 mg/kg administered pre- and post-surgery that our protocol stipulated.

With respect to costs, different works show that the mean savings of using TXA with respect to a standard drain varies between $83.70 and $128.00 per patient. This can be explained by a decrease in the need for blood transfusions *(6,22)*. Although we did not carry out a cost analysis for the different study groups in our work, substantial savings in the costs of the TKA procedure in the TXA group can be adduced. This is due to both the lower price of a vial of TXA with respect to the blood salvage system as well as to the reduced need for allogeneic transfusions. Furthermore, the average price of reinfusion drains is about €400, so they are not cost-effective *(16)*.

Among this study's limitations, we firstly highlight the limited sample size of 120 patients, calculated for a confidence interval of 95%. With this sample size, we were able to obtain significant differences in hemoglobin and hematocrit levels between the groups, but it was not sufficient to obtain statistically-significant results in regards to the decrease in the number of blood transfusions between the groups. Despite this, in the TXA group, a transfusion rate of 0% was observed versus the rate of 6.25% in the autologous blood salvage groups.

We believe that more prospective studies with greater sample sizes are necessary in order to evaluate the possible significant differences in the use of TXA in TKA.

We conclude that the use of TXA versus autologous blood salvage systems in TKA procedures leads to a smaller drop in Hb and Htc levels following surgery and decreases the need for transfusions, leading to lower costs for the health systems that pay for these procedures. In addition, a drain should not be used when there's a contemporary blood management protocol in place.

Protection of people and animals: The authors declare that no experiments were performed on humans or animals for this work.

Data confidentiality: The authors declare that they have followed their workplaces' protocols on the publication of patient data.

Right to privacy and informed consent: The authors declare that no patient data appears in this article and they all signed the informed consent.

Acknowledgements: The authors thank Manuel Jiménez Navarro for his collaboration in the creation of this article.

REFERENCES

1. **Alshryda S, Mason J, Vaghela M** *et al.* Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). *J Bone Joint Surg Am* 2013 ; 95 : 1961-68.
2. **Al-Zahid S, Davies AP.** Closed suction drains, reinfusion drains or no drains in primary total knee replacement? *Ann R Coll Surg Engl* 2012 ; 94(5) : 347.
3. **Benoni G, Fredin H.** Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion

after knee arthroplasty: a prospective, randomized, double-blind study of 86 patients. *J Bone Joint Surg Br.* 1996 ; 78 : 434-440.

4. **Browne JA, Adib F, Brown TE** *et al.* Transfusion rates are increasing following total hip arthroplasty: risk factors and outcomes. *J Arthroplasty* 2013 ; 28(8 Suppl) : 34-7.
5. **Carson JL, Guyatt G, Heddle NM** *et al.* Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. *JAMA* 2016 ; 316(19) : 2025-2035.
6. **Demos HA, Lin ZX, Barfield WR** *et al.* Process Improvement Project Using Tranexamic Acid Is Cost-Effective in Reducing Blood Loss and Transfusions After Total Hip and Total Knee Arthroplasty. *J Arthroplasty* 2017 ; 32(8) : 2375-2380.
7. **Drun CJ, Goa KL.** Tranexamic acid. A review of its use in surgery and other indications. *Drugs* 1999 ; 57 : 1005-32.
8. **Evangelista PJ, Aversano MW, Koli E** *et al.* Effect of tranexamic acid on transfusion rates following total joint arthroplasty: A cost and comparative effectiveness analysis. *Orthop Clin North Am* 2017 ; 48(2) : 119-115.
9. **Fu DJ, Chen C, Guo L** *et al.* Use of intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Chin J Traumatol* 2013 ; 16 : 67-76.
10. **Horstmann WG, Swierstra MJ, Ohanis D** *et al.* Reduction of blood loss with the use of a new combined intra-operative and post-operative autologous blood transfusion system compared with no drainage in primary total hip replacement. *Bone Joint J* 2013 ; 95-B(5) : 616.
11. **Kamath AF, Pagnano MW.** Blood management for patients undergoing total joint arthroplasty. *J Bone Joint Surg Rev* 2013 ; 1(2) : e1.
12. **Maniar RN, Kumar G, Singhi T** *et al.* Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. *Clin Orthop Relat Res* 2012 ; 470(9) : 2605-12.
13. **Martin A, von Strempel A.** Transfusion of autologous blood from reinfusion systems in total knee arthroplasty. *Int Orthop* 2006 ; 30(6) : 541.
14. **Moonen AF, Knoors NT, van Os JJ** *et al.* Retransfusion of filtered shed blood in primary total hip and knee arthroplasty: a prospective randomized clinical trial. *Transfusion* 2007 ; 47(3) : 379.
15. **Nichols CI, Vose JG.** Comparative risk of transfusion and incremental total hospitalization cost for primary unilateral, bilateral, and revision total knee arthroplasty procedures. *J Arthroplasty* 2016 ; 31 : 583-589.
16. **So-Osman C, Nelissen RG, Koopman-van Gemert AW** *et al.* Patient blood management in elective total hip- and knee-replacement surgery (part 2): a randomized controlled trial on blood salvage as transfusion alternative using a restrictive transfusion policy in patients with a preoperative hemoglobin above 13 g/dl. *Anesthesiology* 2014 ; 120(4) : 852-60.
17. **O'Brien JG, Batisttini B, Zaharia F** *et al.* Effects of tranexamic acid and aprotinin, two antifibrinolytic drugs, on PAF-induced plasma extravasation in unanesthetized rats. *Inflammation* 2000 ; 24 : 411-29.
18. **Patel JN, Spanyer JM, Smith LS** *et al.* Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. *J Arthroplasty* 2014 ; 29(8) : 1528-31.
19. **Saleh A, Small T, Chandran Pillai AL** *et al.* Allogenic blood transfusion following total hip arthroplasty: results from the Nationwide Inpatient Sample, 2000 to 2009. *J Bone Joint Surg Am* 2014 ; 96(18) : e1558.
20. **Sarzaeem MM, Razi M, Kazemian G** *et al.* Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. *J Arthroplasty* 2014 ; 29 : 1521-24.
21. **Sehat KR, Evans R, Newman JH.** How much blood is really lost in total knee arthroplasty? Correct blood loss management should take hidden loss into account. *Knee* 2000 ; 7 : 151-155.
22. **Springer BD, Odum SM, Fehring TK.** What Is the Benefit of Tranexamic Acid vs Reinfusion Drains in Total Joint Arthroplasty? *J Arthroplasty* 2016 ; 31(1) : 76-80.
23. **Thomassen B, den Hollander P, Kaptijn H** *et al.* Autologous wound drains have no effect on allogeneic blood transfusions in primary total hip and knee replacement a three-arm randomised trial. *Bone Joint J* 2014 ; 96(6) : 765.
24. **Van Bodegom-Vos L, Voorn VM, So-Osman C** *et al.* Cell Salvage in hip and knee arthroplasty: a meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2015; 17 ; 97(12) : 1012-21.
25. **Weber KL, Jevsevar** *et al.* AAOS Clinical Practice Guideline: Surgical Management of Osteoarthritis of the Knee Evidence-based Guideline. *JAAOS* 2016 ; 24 : 8 : 94-96.
26. **Woolson ST, Wall WW.** Autologous blood transfusion after total knee arthroplasty: a randomized, prospective study comparing predonated and postoperative salvage blood. *J Arthroplasty* 2003 ; 18(3) : 243.
27. **Yang ZG, Chen WP, Wu LD.** Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am* 2012; 94(13) : 1153.
28. **Zhang H, Chen J, Chen F** *et al.* The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 2012 ; 20 :1742- 52.