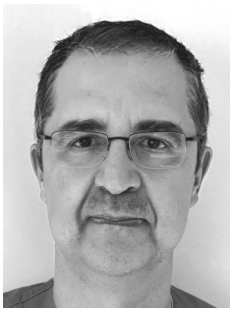
ARTYKUŁ ORYGINALNY / ORIGINAL PAPER
Otrzymano/Submitted: 12.09.2022 • Zaakceptowano/Accepted: 03.11.2022

Prophylactic tranexamic acid in major orthopedic surgery: our experience in 4921 patients



José R. Ortiz-Gómez[1], Marta Perepérez-Candel[1], Berta Torrón-Abad[1], Inocencia Fornet-Ruiz[2], Andrea Ortiz-Domínguez[3], Francisco J. Palacio-Abizanda[4]

[1] Department of Anesthesiology. University Hospital of Navarre, Pamplona, Spain
[2] Department of Anesthesiology, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain
[3] School of Medicine, University of Navarre, Pamplona, Spain
[4] Department of Anesthesiology, University Hospital Gregorio Marañón, Madrid, Spain

Abstract

Background. Tranexamic acid (TXA) is an antifibrinolytic used to reduce perioperative bleeding, one of the main complications in major orthopedic surgery ((MOS), knee, hip, shoulder arthroplasties and extensive tumor or spine surgeries). However, there is great heterogeneity in the existing studies with insufficient data to draw definitive conclusions on its usefulness. ***Study design and methods.*** This is an observational study with medications of retrospective follow-up (from 2018/03 to 2022/05) of 4921 patients undergoing MOS in a monographic orthopedic surgery center. ***Results.*** There were clinically favorable statistically significant differences (TXA *vs.* no TXA) in postoperative bleeding, both subjective (p=0.0001) or objective (>1 $mL \cdot kg^{-1} \cdot h^{-1}$, p=0.0001 or >0.5 $mL \cdot kg^{-1} \cdot h^{-1}$, p=0.0001), transfusion rate (p= 0.0001), volume of blood recovered postoperatively (p=0.0001), and the volume of total bleeding in the PACU (p=0.0001). There were no significant differences in the volume of intraoperative blood recovered (p=0.922). TXA was a safe drug in our series, with only one case report of adverse effect, a possible allergy episode (skin manifestations and patient discomfort) well controlled with corticosteroids and withdrawal of TXA administration. ***Conclusions.*** Our data suggest that TXA is a useful drug in MOS. However there is still a long way to go in matters that need to be investigated, such as its use in patients at thromboembolic risk or in the routes and guidelines of TXA administration. *Anestezjologia i Ratownictwo 2022; 16: 119-128. doi: 10.53139/AIR.20221615*

Keywords: Tranexamic acid / adverse effects, Orthopedic surgery, Perioperative care, Surgical blood loss, Blood transfusion

Introduction

The population susceptible to major orthopedic surgery (MOS) is increasingly numerous, older and more multipathological, and blood loss is a significant concern. The most common complications of perioperative bleeding are the appearance of hematomas, acute anemia, hemodynamic deterioration and the need for allogeneic transfusion that carries a risk of adverse reactions, higher rate of postoperative infections, intravascular hemolysis, post-transfusion coagulopathy, kidney failure, immune deterioration, and risk of recurrence in tumor surgery, with increased mortality. In addition, it is associated with a prolonged hospital stay and an increase in the final cost per process [1-3].

Utako Okamoto discovered tranexamic acid (TXA) in 1962, an antifibrinolytic synthetic analog of lysine that decreases the conversion of plasminogen to

plasmin, preventing fibrin degradation and preserving the framework of fibrin's matrix structure. TXA also inhibits plasmin at higher doses [4, 5] and could have an anti-inflammatory effect [6,7].

Prophylactic TXA has been widely used in different surgeries, mainly in obstetrics [8], cardiac [9] and trauma surgery [10-12] to reduce perioperative bleeding with good results. However, the data available in MOS are not so conclusive, which is why we present our experience in 4921 patients.

Materials and methods

William Thomson Kelvin said: "*If you cannot measure it, you cannot improve it*". In March 2018 we began to collect data related to the perioperative evolution of our patients, which has allowed us to improve their care, excluding subjectivity.

This is an observational study with medications of retrospective follow-up (from 2018/03 to 2022/05). Institutional Research Ethics Board approval (Drug Research Ethics Committee) was obtained at University Hospital of Navarre (Pamplona, Spain, registry reference number EO_2022/6, approval date 2022/05/24).

It is important to establish the context in which to place the results of this study, a monographic orthopedic surgery center, where only scheduled surgeries are performed.

This study included 4921 patients undergoing elective major orthopedic procedures from March 2018 to May 2022. Our protocol establishes that MOS patients (i.e., prosthetic lower limb or instrumented spinal surgery) remain under monitoring in the PACU until the following morning, whereas minor surgery patients (15730 in the same period) were discharged on the same day. This workflow allows us to have direct control of the immediate perioperative period and adopt advanced measures to control pain, nausea and vomiting or postoperative bleeding, for example.

There is no randomization in the groups. We have protocols of TXA use for different surgeries, its administration (or not) to a patient is entirely a decision of the anesthesiologists involved in the perioperative care considering all factors individually, including the potential risk of bleeding, the patient's medical history, renal function, active postoperative bleeding, and hemodynamic status, to obtain the most appropriate risk-benefit balance for the patient. Our standard protocol establishes an intravenous bolus dose of 10-20 $mg{\cdot}kg^{-1}$ administered over 10 minutes (maximum 1 g) before incision (in surgeries without ischemia such as total hip arthroplasty or spinal surgery, whereas in total knee arthroplasty the bolus is administered 10-20 min before the end of ischemia). In spinal instrumented surgery, an intraoperative IV infusion is also administered at 1 $mg{\cdot}kg^{-1}h^{-1}$. In the PACU, another 2 doses are administered every 6-8 h of 10-20 $mg{\cdot}kg^{-1}$ administered over 10 minutes (maximum 1 g) when the anesthesiologist considered necessary.

Data collected in this study included: age, sex, weight, height, ASA physical status, surgery, hemoglobin values at anesthesia consultation (preoperative) and at 18:00 PM the day of surgery and 8:00 AM the day after and the use of TXA (administration or not, doses number of doses and adverse effects). The bleeding data includes the volume of blood recovered intraoperatively and postoperatively, the total volume of bleeding, the subjective sensation of excessive bleeding by the anesthesiologist on call (responsible for the PACU) and the objective bleeding, calculated based on the weight and the time the patient remains in the PACU (bleeding greater than 0.5 or 1 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$). Transfusion data included number of red blood cells, plasma and platelets used and transfusion complications. In patients enrolled in self-donation programs, the initial and final (prior to surgery) hemoglobin values are collected, as well as the number of self-donation units.

Statistics

Data were analyzed using statistical software package IBM SPSS 26 (IBM, USA), Stata/MP v14. (StataCorp, USA) and gretl 2020e (GNU regression, http://gretl.sourceforge.net/).

Normality of variables was studied with the Kolmogorov-Smirnov test and homoscedasticity with the Levene test. The different groups were compared with one-way analysis of variance (ANOVA), followed by the Tukey-B multiple comparison test if normally distributed and using the Kruskal–Wallis test followed by the Mann–Whitney U-test with Finner's modification of Bonferroni's correction if not normally distributed. Qualitative data were analyzed using the chi square-test.

Results

Demographic data are exposed in Table I and age population pyramid in Figure I.

Table I. Demographic data

	TXA			p
	No (20.7%)	Yes (79.3%)	Total (100%) (n=4921)	
Age (years)	70.1±10.6 (69.4, 70.8)	60.4±12.8 (65.0, 65.8)	66.5±12.5 (66.1, 66.8)	0.0001
Weight (kg)	81.5±15.2 (80.5, 82.6)	78.6±15.4 (78.1, 79.2)	79.1±15.5 (78.7, 79.6)	0.0001
Height (cm)	164.7±9.5 (164.0, 165.3)	164.3±9.8 (163.9, 64.6)	164.3±9.7 (164.0, 164.6)	0.264
BMI (kg/m^2)	30.0±5.0 (29.7, 30.3)	29.1±5.3 (28.9, 29.3)	29.2±5.3 (29.1, 29.4)	0.0001
Sex				
Male	59.1%	51.6%	53.1%	0.0001
Female	40.9%	48.4%	46.9%	
ASA				
I	1.3%	8.5%	7.0%	
II	16.5%	53.2%	45.6%	0.0001
III	69.5%	36.4%	43.3%	
IV	12.7%	1.9%	4.1%	
Surgery				
Hip	33.1%	38.2%	37.2%	
Knee	47.9%	44.6%	45.3%	
Spine	17.0%	16.6%	16.7%	0.0001
Shoulder	0.7%	0.1%	0.2%	
Tumor	0.9%	0.4%	0.5%	
Other	0.2%	0.0%	0.1%	

Age, weight, height, BMI and times data are mean ± SD and 95% Confidence Interval.
Sex, ASA physical status and surgery data are percentages.

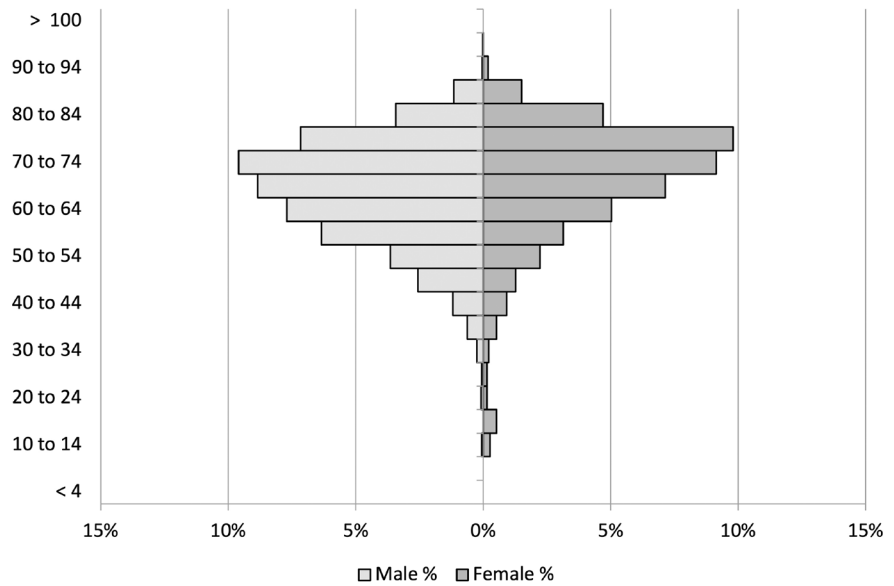


Figure I. Population pyramid of patients (age)

The most prevalent co-existing diseases (often associated) were arterial hypertension (up to 70%), dyslipidemia (28.5%), type II diabetes mellitus (11.9%), obesity (77.0% are overweight (48.4% obese and 10.9% obesity class II-III), hypothyroidism (9.5%), atrial fibrillation (9.1%), ischemic heart disease (7.0%),

chronic obstructive pulmonary disease (7.0%), type I diabetes mellitus (5.1%), obstructive sleep apnea syndrome (4.7%), cerebrovascular diseases (4.4%), asthma (3.9%), hyperuricemia (3.6%), chronic renal insufficiency (3.2%), peripheral venous disease (1.6%) and alcoholism (1.2%).

The most frequent surgeries were total knee arthroplasty 40.2%, total hip arthroplasty 30.4%, spinal arthrodesis 12.2%, total knee arthroplasty replacement 4.9%, total hip arthroplasty replacement 2.8%, scoliosis 1.6%, cervical spine 1.2%, tumors 0.5% and a 0.4% of surgical revisions (infections, hematoma drainage…). There were also surgeries in patients ASA IV or with intraoperative complications, such as vertebroplasties 0.2%, knee arthrodesis 0.2%, removal of osteosynthesis material 0.2%, shoulder arthroplasty 0.2% or laminectomies 0.1%, among others.

Hemoglobin, bleeding, and transfusion data are exposed by sex (Table II) and TXA use (Table III).

TXA was administered in 79.5% of patients, primarily IV in the OR (0.5±0.3 g, CI 95% (0.5, 0.6), (min 0 g, max 1.25 g)). In hip surgery we also apply it as part of a local infiltration analgesia (LIA) (2.0±0.3 g, CI 95% (2.0, 2.0), (min 0 g, max 2.5 g). The patients received 0.05±0.2 doses of 0.03±0.1 g of TXA in the PACU, with a total dose of 2.6±0.5 g, CI95% (2.5, 2.7), (min 0 g, and max 5 g). We have only one case report of adverse effect to TXA (0.02%), a possible allergy episode (skin manifestations and patient discomfort) well controlled with corticosteroids and withdrawal of TXA administration.

There were no significant differences in the volume of intraoperative blood recovered (*Ortho-Pat, Haemonetics*) (147.5±124.7 mL, p=0.922). However, there were statistically significant differences between patients who did not receive TXA and those who did in the volume of blood recovered postoperatively (*ConstaVac™ CBCII Blood Conservation System, 3T Medical*) (393.7±338.4 mL, CI 95% (361.4, 426.1), (min 0 – max 1440) vs. 87.1±141.8 mL, CI 95% (79.3, 94.4), (min 0 – max 1010), p=0.0001), and in the volume of total bleeding in the PACU 740.2±483.6 mL, CI 95% (696.9, 783,6), (min 0 – max 2850) vs. 356.9±253.9 mL, CI 95% (345.6, 368.2), (min 0 – max 2740), p=0.0001).

A blood self-donation program was carried out in 60 patients scheduled for scoliosis surgery, with-

Table II. Hemoglobin, bleeding and transfusion data by sex

		Sex		Total	p
		Male	Female		
Preoperative Hb (Anesthesia consultation)		14.8±1.3 (14.7, 14.9)	13.5±1.2 (13.4, 13.5)	14.2±1.4 (14.1, 14.2)	0.0001
Surgery day Hb (18:00 PM)		13.3±1.4 (13.2, 13.3)	12.0±1.3 (11.9, 12.1)	12.7±1.5 (12.6, 12.7)	0.0001
Surgery day + 1 Hb (08:00 AM)		11.8±1.4 (11.7, 11.9)	10.6±1.2 (10.5, 10.5)	11.2±1.4 (11.2, 11.3)	0.0001
Preoperative - Surgery day (Hb difference)		-1.5±0.9 (-1.6, -1.5)	-1.5±1.0 (-1.6, -1.5)	-1.5±0.9 (-1.6, -1.5)	0.636
Preoperative - Surgery day +1 (Hb difference)		-3.0±1.0 (-3.0, -2.9)	-2.9±1.0 (-2.9, -2.8)	-2.9±1.0 (-3.0, -2.9)	0.006
Hemoglobin <13		7.9%	29.9%	18.2%	0.0001
Hemoglobin intervals	***<10***	0.4%	1.3%	0.8%	0.0001
	10-11	0.6%	1.4%	1.0%	
	11-12	1.0%	5.9%	3.3%	
	12-13	5.2%	17.0%	10.7%	
	>13	92.9%	74.4%	84.2%	
Bleeding (subjective)	***No***	85.1%	90.8%	87.8%	0.0001
	Yes	14.9%	9.2%	12.2%	
Bleeding (> 1 mL·kg^{-1}·h^{-1})	***No***	97.0%	98.4%	97.7%	0.0001
	Yes	3.0%	1.6%	2.3%	
Bleeding (> 0.5 mL·kg^{-1}·h^{-1})	***No***	82.6%	90.5%	86.4%	0.0001
	Yes	17.4%	9.5%	13.6%	
Transfusion	***No***	96.6%	92.9%	94.9%	0.0001
	Yes	3.4%	7.1%	5.1%	

Hemoglobin (Hb) values (g·dL^{-1})) are mean ± SD and 955 Confidence Interval at Anesthesia Consultation (preoperative), at 18:00 PM the surgery day (Surgery day) and at 08:00 AM the first day after surgery (Surgery day + 1).
Hemoglobin intervals (g·dL^{-1}), bleeding and transfusion data are percentages.

Table III. Hemoglobin, bleeding and transfusion data by tranexamic acid use

		TXA		Total	p
		No	Yes		
Preoperative Hb (Anesthesia consultation)		14.1±1.4 (14.0, 14.2)	14.2±1.3 (14.2, 14.3)	14.2±1.3 (14.2, 14.3)	0.028
Surgery day Hb (18:00 PM)		12.5±1.6 (12.4, 12.6)	12.7±1.4 (12.7, 12.8)	12.7±1.4 (12.6, 12.8)	0.001
Surgery day + 1 Hb (08:00 AM)		11.0±1.5 (10.9, 11.1)	11.3±1.4 (11,3, 11.4)	11.2±1.4 (11.2, 11.3)	0.0001
Preoperative - Surgery day (Hb difference)		-1.6±0.9 (-1.7, -1.5)	-1.5±0.9 (-1.6, -1.5)	-1.5±0.9 (-1,6, -1.5)	0.015
Preoperative - Surgery day +1 (Hb difference)		-3.1±1.1 (-3.2, -3.0)	-2.9±1.0 (-2.9, -2.8)	-2.9±1.0 (-3.0, -2.9)	0.001
Hemoglobin <13		21.1%	16.9%	17.7%	0.002
Hemoglobin intervals	***<10***	0.7%	0.5%	0.5%	0.013
	10-11	1.2%	0.8%	0.9%	
	11-12	4.9%	2.8%	3.3%	
	12-13	11.3%	10.5%	10.6%	
	>13	81.9%	85.4%	84.7%	
Bleeding (subjective)	***No***	68.7%	92.8%	87.8%	0.0001
	Yes	31.3%	7.2%	12.2%	
Bleeding (> 1 mL·kg^{-1}·h^{-1})	***No***	93.6%	98.7%	97.7%	0.0001
	Yes	6.4%	1.3%	2.3%	
Bleeding (> 0.5 mL·kg^{-1}·h^{-1})	***No***	63.4%	92.2%	86.5%	0.0001
	Yes	36.6%	7.8%	13.5%	
Transfusion	***No***	91.9%	96.2%	95.3%	0.0001
	Yes	8.1%	3.8%	4.7%	

Hemoglobin (Hb) values (g·dL^{-1})) are mean ± SD and 95% Confidence Interval at Anesthesia Consultation (preoperative), at 18:00 PM the surgery day (Surgery day) and at 08:00 AM the first day after surgery (Surgery day + 1).
Hemoglobin intervals (g·dL^{-1}), bleeding and transfusion data are percentages.

out observing significant differences between those patients who received TXA and those who did not. An average of 1.48±0.5 autotransfusion units was obtained (p=0.967), using 1.28±0.6 and remaining without transfusing 0.53±0.6 units (p=0.919). The mean hemoglobin values after each unit extraction were 14.2±1.1 (p=0.778) and 12.4±1.6 g·dL^{-1} (p=0.154) respectively.

Table IV shows the transfusion rates in the most common surgeries by hemoglobin level and TXA use and Table V the Relative Risk, Odds Ratio and Number Needed to Treat of transfusion and bleeding with the TXA administration.

The overall incidence of transfusion was 4.7% (8.1% without TXA vs. 3.8% in TXA group, p=0.0001).

There were statistically significant differences (no TXA vs. TXA) in allogenic packed red blood cells used (1.4±0.6 units, CI 95% (1.2, 1.5), (min 1 – max 5) vs. 1.8±1.2, CI 95% (1.5, 2.0), (min 1 – max 8), p=0.017), but not in the fresh frozen plasma units (2.6±2.3, CI 95% (0.6, 4.5), (min 1 – max 8) vs. 2.2±1.2, CI 95% (1.4, 3.0)), (min 1 – max 6), p=0.647). Only 4 patients received platelets (one unit each).

Discussion

Patients who did not receive TXA were older, more obese and had more (and often coexisting) diseases than patients with prophylactic TXA. We must indicate a bias in our data because our daily routine "*normalizes*" the existence of certain diseases, with a tendency to classify as ASA II patients that are really ASA III. Precisely for the same reason, the ASA IV patients in this study were patients in very poor physical condition.

The drop in hemoglobin levels (Tables II and III) represents an average loss of 20.4% of the erythrocyte mass in one day (19.6% in men and 21.5% in women). Therefore, we have acute bleeding in elderly patients, very possibly hypertensive (in addition to other potential cardiovascular risk factors) where hypovolemia and the resulting hypotension can pose a serious risk to their health.

The three pillars of PBM (patient blood management) programs are: optimize RBC mass, minimize blood loss, and manage anemia [13]. The first pillar represents a problem for our activity, beyond our control, because the surgical schedule is not done with

Table IV. Transfusion rates in the most common surgeries by hemoglobin level and tranexamic acid use

Surgery	Hemoglobin	TXA	Transfusion rate	Total
Total hip arthroplasty (n=1496)	>13	No	4.6%	3.1%
		Yes	0.5%	
	<13	No	25.0%	
		Yes	12.8%	
Total hip arthroplasty replacement (n=117)	>13	No	8.3%	12.0%
		Yes	3.2%	
	<13	No	27.3%	
		Yes	35.0%	
Total knee arthroplasty (n=1738)	>13	No	1.3%	1.3%
		Yes	0.2%	
	<13	No	17,2%	
		Yes	3.3%	
Total knee arthroplasty replacement (n=221)	>13	No	15.9%	10.9%
		Yes	2.4%	
	<13	No	33.3%	
		Yes	21.2%	
Cervical arthrodesis (n=57)	>13	No	0.0%	0.0%
		Yes	0.0%	
	<13	No	0.0%	
		Yes	0.0%	
Scoliosis (n=57)	>13	No	100%	80.4%
		Yes	79.2%	
	<13	No	66.7%	
		Yes	82.1%	
Spinal arthrodesis (n=581)	>13	No	5.6%	6.9%
		Yes	3.4%	
	<13	No	21.4%%	
		Yes	17.0%%	
Tumor (n=22)	>13	No	0.0%	22.7%
		Yes	12.5%	
	<13	No	50%	
		Yes	50%	

Hemoglobin values are expressed in $g.dL^{-1}$ and transfusion rates in percentages.

enough time to allow effective preoperative hemoglobin optimization (a 29.9% of women had a hemoglobin lower than 13 $g{\cdot}dL^{-1}$, the critical point that most PBM studies agree on).

Regarding the second pillar of the PBM, the usual measures applied in our center have derived from preoperative blood self-donation (usually for scoliosis surgery) to intraoperative and postoperative blood recovery systems. In fact, we usually use nerve blocks instead of local infiltration analgesia (excepting hip surgery) to avoid unwanted absorption of local anesthetics.

TXA was our last measure introduced, and then a reduction in postoperative bleeding and the need for transfusion was observed subjectively. The optimization of preoperative hemoglobin values (>13 $g{\cdot}dL^{-1}$) with the administration of TXA reduced significantly transfusion rate in MOS (Table IV).

TXA has turned out to be a safe drug in our series, with only one episode of allergy, without observing other adverse effects described [14] such as allergic dermatitis, gastrointestinal disorders (diarrhea, nausea, vomiting), headache, malaise, hypotension, anaphylaxis, visual disturbances [15] or seizures, a rare adverse effect usually due to high doses of TXA [16, 17] (10% of the TXA dose crosses the blood-brain barrier, although this proportion is higher in trauma or coronary surgery [14]).

Table V. Transfusion, bleeding and tranexamic acid use: Relative Risk, Odds Ratio and Number Needed to Treat

		BT	Bl.Sub.	Bl >1	Bl >0.5
RR	Absolute Risk – TXA Group	0,04	0,07	0,01	0,08
	Absolute Risk – No TXA Group	0,08	0,31	0,06	0,37
	Absolute Risk Reduction	0,04	0,24	0,05	0,29
	Relative Risk (RR)	0,47	0,23	0,20	0,21
	Relative Risk Reduction	0,53	0,77	0,80	0,79
	Lower Limit of 95% CI for RR	0.36	0.20	0.12	0.18
	Upper Limit of 95% CI for RR	0.62	0.27	0.33	0.26
OR	Odds – TXA Group	0.03	0,08	0,01	0,08
	Odds – No TXA Group	0.08	0,46	0,07	0,58
	Odds Ratio (OR)	0.45	0,17	0,19	0,15
	Lower Limit of 95% CI for OR	0.34	0.14	0.11	0.11
	Upper Limit of 95% CI for OR	0.61	0.21	0.32	0.19
NNT	**Number Needed to Treat (NNT)**	23.26	4.16	19.39	3.48
	Lower Limit of 95% CI for NNT	16.20	3.67	13.50	3.01
	Upper Limit of 95% CI for NNT	41.87	4.78	34.40	4.11

RR: Relative Risk; OR: Odds Ratio; NNT: Number Needed to Treat; 95% CI: 95 percent Confidence Interval; BT: Blood transfusion; Bl.Sub.: Bleeding (subjective); Bl >1: Bleeding > 1 $mL \cdot kg^{-1} \cdot h^{-1}$; Bl >0.5: Bleeding > 0.5 $mL \cdot kg^{-1} \cdot h^{-1}$

Some adverse effects are due to the administration of excessive doses or to the very rapid intravenous infusion of the drug, so we do not exceed 10 $mg \cdot kg^{-1}$ IV in half an hour.

The great heterogeneity of published studies about TXA in MOS makes it difficult to adopt universal measures based on evidence. There are hardly any studies with enough patients to have good statistical power. There is also a wide variability of surgeries, physical status of patients and dose, timing, routes, and intervals of administration of TXA.

The available meta-analyses analyze studies with small numbers of patients, grouping surgeries with different bleeding risks to have a larger number of patients. In addition, we must indicate that the global term "*blood conservation*" has been evaluated in various ways that are not fully comparable. Thus, in the different studies, the authors can find data on total intraoperative or postoperative blood loss, the need for allogeneic transfusion, the number of packed red blood cells or other blood components transfused per patient, and even the volumes of blood products transfused. Sometimes there is no clear differentiation of these concepts, grouping the conclusions under the global heading of "*blood conservation*". The meta-analyses on TXA in MOS [3] have precisely this problem, so their conclusions must be carefully evaluated, and if possible, compared with the susceptible population of each hospital.

TXA has the potential to cause arterial and venous thromboembolic events. A meta-analysis [3] established that the incidence of deep vein thrombosis does not increase with prophylactic TXA. It is estimated that doses of 1-2 g IV do not increase the thromboembolic risk in the general population [10, 18]. TXA administration should be carefully evaluated in patients with history of thromboembolic diseases, higher incidence of thromboembolic events in their family history (i.e., thrombophilia) and prothrombotic treatments, such as oral contraceptives, due to a potential increased risk of thrombosis. A review of 1131 total joint arthroplasties concluded that TXA appeared to be safe and effective in ASA III-IV patients, although larger studies were needed [19].

A careful assessment should be made in patients with associated comorbidities (ASA III-IV), especially if several risk factors for the use of TXA coincide, including dose adjustment in patients with renal insufficiency [20]. Regarding the presence of cardiovascular risk factors, there are currently insufficient data available to demonstrate the safety of TXA [21,22]. It has been speculated that topical TXA could be more advantageous than intravenous TXA in patients at thromboembolic risk [21,22], reducing thrombotic events, but the reality is that there are no conclusive studies in this regard.

Concerning "*blood conservation*", the most recent data suggest that antifibrinolytics represent an

important adjunct to reduce bleeding and the need for allogeneic transfusions [23], as confirmed by our data.

A meta-analysis [3] from 24 randomized clinical trials (n=1696, 833 with TXA and 863 controls) estimated in 408.33 mL the weighted mean of total blood loss avoided with the prophylactic use of TXA in MOS (CI 95% (505.69, 310.97), p<0.00001). However, it should be noted the high heterogeneity of the reviewed data (I^2 = 89%).

Intraoperative blood loss in MOS prevented with TXA has been calculated [24] in 127 mL (p<0.002), a weighted mean of 125.65 mL (p<0.0001) [3], whereas avoided postoperative blood loss range from 95 mL (p<0.009) [24] to a weighted mean of 214.58 mL (p<0.0000) [3].

Prophylactic TXA reduces the probability of receiving a blood transfusion in MOS (OR 0.58 [24] and OR 0.17 [23]). It has been calculated at 49% (RR 0.51, CI95% (0.46, 0.56), p<0.00001) [3].

TXA also decreases the number of packed red blood cells transfused [24], (weighted mean of 0.78 units per patient; CI95% (0.19, 0.37 U), p=0.0002 [3] in data extracted from 11 studies, n=917) and the blood volumes transfused per patient (weighted mean of 205.33 mL, CI 95% (301.37, 109.28 mL), p<0.0001 in data from 7 studies, n=397) [3].

The difference in the number of packed RBCs in our results may be due exclusively to the magnitude of bleeding in a few patients.

Analyzing TXA in specific types of MOS, there are numerous references reviewing the use of TXA in hip and knee arthroplasties [25-28] and extensive spinal surgeries [29,30]. Spinal deformity corrective surgery is the example of MOS where all available PBM measures should be applied and where prophylactic TXA has greater importance. Different administration schedules have been used, the most frequent being a loading dose of 10-15 mg·kg^{-1} IV (some groups directly administer 1 g IV), followed by a maintenance infusion of 0.5-2 mg. kg^{-1}.h^{-1} (some groups eliminate continuous perfusion and repeat bolus doses at 3, 6 and/or 12 hours) [30]. Other authors had described the use of high doses of TXA has been described [31] (bolus of 50 mg·kg^{-1} followed by continuous infusion at 5 mg·kg^{-1}.h^{-1} until incision closure) concluding that its use may be safe, but described 1 case of pulmonary thromboembolism and 2 of deep vein thrombosis. As a result, there is an ongoing prospective randomized clinical trial (Tranexamic Acid Dosing in Adult Spinal Deformity Surgery, NCT02053363) comparing the two regimens, low-dose and high-dose [32].

TXA is gradually being applied to other orthopedic surgeries. Tumor surgery has the disadvantage of prothrombotic risk in cancer patients, in addition to the difficulty in analyzing homogenized series of large numbers of patients.

A meta-analysis [28] of 8 shoulder surgery trials (including open surgery and arthroscopy) demonstrated (TXA vs. controls) a significant reduction in estimated total and postoperative blood loss, but not in hemoglobin levels, although it is true that the latter result became significant with the sensitivity analysis excluding arthroscopic procedures. In shoulder arthroplasty [33] (n=54) TXA compared to placebo reduced mean perioperative blood drainage, estimated total blood volume loss, pain during the first postoperative day and hematoma formation without adverse effects. However, there is a case report of a coronary thrombosis in a patient who received TXA for a shoulder arthroplasty [34]. Therefore, we are in favor of individually assessing the risks and benefits of TXA in each patient, especially in certain surgeries.

Although many factors (such as method of cost calculation, market fluctuation, and regional or national variation in health care expenditures) can lead to discrepancies, most studies that report costs provide strong evidence that the use of TXA was cost-effective [26, 35-39], especially in hospitals with high transfusion rates (above 25%), since it was possible to reduce them by 12% [38]. We do not have data available to calculate hospital cost savings per avoided transfusion (macromanagement), but at the level of micromanagement, we can indicate that due to the significant reduction in postoperative bleeding and therefore also in recovered postoperative blood volume, we have begun to select patients candidate to wear postoperative blood recovery systems (instead of doing it routinely) with the resulting savings.

Conclusions

Tranexamic acid reduced significantly postoperative bleeding, the volume of total bleeding in the PACU and the transfusion rate, with almost no adverse effects in patients undergoing elective major orthopedic surgery.

However, we must remember that the prophylaxis of postoperative bleeding has more measures that must

be applied, highlighting a preoperative hemoglobin greater than 13 $g \cdot dL^{-1}$. In addition, we believe that it is necessary to investigate other aspects of the use of tranexamic acid, such as the minimum effective dose or alternative routes of administration to intravenous administration, especially in patients with thromboembolic risk.

Acknowledgments:

The authors wish to express our sincere thanks to the staff of our Anesthesiology Department for their collaboration.

Funding and resources:

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Authorship contributions:

All authors contributed equally to the manuscript, read and approved the final version of the manuscript. All authors meet the criteria for authorship established by the Uniform Requirements for Manuscripts Submitted to Biomedical Editors by the International Committee of Medical Journal Editors.

Konflikt interesów / Conflict of interest
Brak / None

Adres do korespondencji / Correspondence address
José R. Ortiz-Gómez
University Hospital of Navarre, Irunlarrea St. 3, 31008 Pamplona, Navarre, Spain
☎ +34 848422222
j.r.ortiz.gomez.md.phd@gmail.com

Piśmiennictwo/References

1. Lin ZX, Woolf SK. Safety, Efficacy, and Cost-effectiveness of Tranexamic Acid in Orthopedic Surgery. Orthopedics. 2016;39:119-30. doi: 10.3928/01477447-20160301-05.
2. Cardone D, Klein AA. Perioperative blood conservation. Eur J Anaesthesiol. 2009;26:722-9. doi: 10.1097/EJA.0b013e32832c5280.
3. Huang F, Wu D, Ma G, Yin Z, Wang Q. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: a meta-analysis. J Surg Res. 2014;186:318-27. doi: 10.1016/j.jss.2013.08.020.
4. Levi MM, Vink R, de Jonge E. Management of bleeding disorders by prohemostatic therapy. Int J Hematol. 2002;76 Suppl 2:139-44. doi: 10.1007/BF03165104.
5. Levy JH. Hemostatic agents. Transfusion. 2004;44(12 Suppl):58S-62S. doi: 10.1111/j.0041-1132.2004.04173.x.
6. Barrett CD, Moore HB, Kong YW, Chapman MP, Sriram G, Lim D, et al. Tranexamic acid mediates proinflammatory and anti-inflammatory signaling via complement C5a regulation in a plasminogen activator-dependent manner. J Trauma Acute Care Surg. 2019;86:101-7. doi: 10.1097/TA.0000000000002092.
7. Prudovsky I, Carter D, Kacer D, Palmeri M, Soul T, Kumpel C, et al. Tranexamic acid suppresses the release of mitochondrial DNA, protects the endothelial monolayer and enhances oxidative phosphorylation. J Cell Physiol. 2019;234:19121-9. doi: 10.1002/jcp.28603.
8. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389:2105-16. doi: 10.1016/S0140-6736(17)30638-4.
9. Henry D, Carless P, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ. 2009;180:183-93. doi: 10.1503/cmaj.081109.
10. CRASH-trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394:1713-23. doi: 10.1016/S0140-6736(19)32233-0.
11. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. 2012;147:113-9. doi: 10.1001/archsurg.2011.287.
12. Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. Cochrane Database Syst Rev. 2013 Jan 31;2013(1):CD010245. doi: 10.1002/14651858.CD010245.pub2.
13. Althoff FC, Neb H, Herrmann E, Trentino KM, Vernich L, Fullenbach C, et al. Multimodal Patient Blood Management Program Based on a Three-pillar Strategy: A Systematic Review and Meta-analysis. Ann Surg. 2019;269:794-804. doi: 10.1097/SLA.0000000000003095.
14. Taam J, Yang QJ, Pang KS, Karanicolas P, Choi S, Wasowicz M, et al. Current Evidence and Future Directions of Tranexamic Acid Use, Efficacy, and Dosing for Major Surgical Procedures. J Cardiothorac Vasc Anesth. 2020;34:782-90. doi: 10.1053/j.jvca.2019.06.042.
15. Cravens GT, Brown MJ, Brown DR, Wass CT. Antifibrinolytic therapy use to mitigate blood loss during staged complex major spine surgery: Postoperative visual color changes after tranexamic acid administration. Anesthesiology. 2006;105:1274-6. doi: 10.1097/00000542-

200612000-00029.

16. Furtmuller R, Schlag MG, Berger M, Hopf R, Huck S, Sieghart W, et al. Tranexamic acid, a widely used antifibrinolytic agent, causes convulsions by a gamma-aminobutyric acid(A) receptor antagonistic effect. J Pharmacol Exp Ther. 2002;301:168-73. doi: 10.1124/jpet.301.1.168.
17. Lecker I, Wang DS, Kaneshwaran K, Mazer CD, Orser BA. High Concentrations of Tranexamic Acid Inhibit Ionotropic Glutamate Receptors. Anesthesiology. 2017;127:89-97. doi: 10.1097/ALN.0000000000001665.
18. CRASH-2 Trial Collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23-32. doi: 10.1016/S0140-6736(10)60835-5.
19. Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. Clin Orthop Relat Res. 2014;472:66-72. doi: 10.1007/s11999-013-3134-0.
20. Wong J, George RB, Hanley CM, Saliba C, Yee DA, Jerath A. Tranexamic acid: current use in obstetrics, major orthopedic, and trauma surgery. Can J Anaesth. 2021;68:894-917. doi: 10.1007/s12630-021-01967-7.
21. Spanyer J, Patel J, Emberton E, Smith LS, Malkani AL. Topical Tranexamic Acid in Total Knee Arthroplasty Patients with Increased Thromboembolic Risk. J Knee Surg. 2017;30:474-8. doi: 10.1055/s-0036-1593371.
22. Yen SH, Lin PC, Wu CT, Wang JW. Comparison of Effects of a Thrombin-Based Hemostatic Agent and Topical Tranexamic Acid on Blood Loss in Patients with Preexisting Thromboembolic Risk Undergoing a Minimally Invasive Total Knee Arthroplasty. A Prospective Randomized Controlled Trial. Biomed Res Int. 2021;2021:2549521. doi: 10.1155/2021/2549521.
23. Zufferey P, Merquiol F, Laporte S, Decousus H, Mismetti P, Auboyer C, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? Anesthesiology. 2006;105:1034-46. doi: 10.1097/00000542-200611000-00026.
24. Lu VM, Ho YT, Nambiar M, Mobbs RJ, Phan K. The Perioperative Efficacy and Safety of Antifibrinolytics in Adult Spinal Fusion Surgery: A Systematic Review and Meta-analysis. Spine (Phila Pa 1976). 2018;43:E949-E58. doi: 10.1097/BRS.0000000000002580.
25. Goldstein M, Feldmann C, Wulf H, Wiesmann T. Tranexamic Acid Prophylaxis in Hip and Knee Joint Replacement. Dtsch Arztebl Int. 2017;114:824-30. doi: 10.3238/arztebl.2017.0824.
26. Wu Y, Zeng Y, Hu Q, Li M, Bao X, Zhong J, et al. Blood loss and cost-effectiveness of oral vs intravenous tranexamic acid in primary total hip arthroplasty: A randomized clinical trial. Thromb Res. 2018;171:143-8. doi: 10.1016/j.thromres.2018.10.006.
27. Allen G. A Meta-Analysis of Complications of Tranexamic Acid Use in Lower-Limb Orthopedic Surgery. AORN J. 2021;113:657-60. doi: 10.1002/aorn.13415.
28. National Guideline Centre (UK). Evidence review for tranexamic acid to minimise blood loss: Joint replacement (primary): hip, knee and shoulder: Evidence review G. London: National Institute for Health and Care Excellence (NICE); 2020 Jun. PMID: 32881462.
29. Cheriyan T, Maier SP, 2nd, Bianco K, Slobodyanyuk K, Rattenni RN, Lafage V, et al. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. Spine J. 2015;15:752-61. doi: 10.1016/j.spinee.2015.01.013.
30. Zhang Y, Liu H, He F, Chen A, Yang H, Pi B. Does Tranexamic Acid Improve Bleeding, Transfusion, and Hemoglobin Level in Patients Undergoing Multilevel Spine Surgery? A Systematic Review and Meta-Analysis. World Neurosurg. 2019;127:289-301. doi: 10.1016/j.wneu.2019.02.170.
31. Lin JD, Lenke LG, Shillingford JN, Laratta JL, Tan LA, Fischer CR, et al. Safety of a High-Dose Tranexamic Acid Protocol in Complex Adult Spinal Deformity: Analysis of 100 Consecutive Cases. Spine Deform. 2018;6:189-94. doi: 10.1016/j.jspd.2017.08.007.
32. Verma K, Kohan E, Ames CP, Cruz DL, Deviren V, Berven S, et al. A Comparison of Two Different Dosing Protocols for Tranexamic Acid in Posterior Spinal Fusion for Spinal Deformity: A Prospective, Randomized Trial. Int J Spine Surg. 2015;9:65. doi: 10.14444/2065.
33. Pauzenberger L, Domej MA, Heuberer PR, Hexel M, Grieb A, Laky B, et al. The effect of intravenous tranexamic acid on blood loss and early post-operative pain in total shoulder arthroplasty. Bone Joint J. 2017;99-B:1073-9. doi: 10.1302/0301-620X.99B8.BJJ-2016-1205.R1.
34. Bridges KH, Wilson SH. Acute Coronary Artery Thrombus After Tranexamic Acid During Total Shoulder Arthroplasty in a Patient With Coronary Stents: A Case Report. A A Pract. 2018;10:212-4. doi: 10.1213/XAA.0000000000000667.
35. Gillette BP, Maradit Kremers H, Duncan CM, Smith HM, Trousdale RT, Pagnano MW, et al. Economic impact of tranexamic acid in healthy patients undergoing primary total hip and knee arthroplasty. J Arthroplasty. 2013;28(8 Suppl):137-9. doi: 10.1016/j.arth.2013.04.054.
36. Kyriakopoulos G, Oikonomou L, Panagopoulos A, Kotsarinis G, Vlachou M, Anastopoulos G, et al. Transfusion rate, hospital stay and cost-effectiveness of intravenous or local administration of tranexamic acid in total hip and knee arthroplasty: A single-center randomized controlled clinical study. Orthop Rev (Pavia). 2019;11:7866. doi: 10.4081/or.2019.7866.
37. Chimento GF, Huff T, Ochsner JL, Jr., Meyer M, Brandner L, Babin S. An evaluation of the use of topical tranexamic acid in total knee arthroplasty. J Arthroplasty. 2013;28(8 Suppl):74-7. doi: 10.1016/j.arth.2013.06.037.
38. Slover J, Bosco J. Cost analysis of use of tranexamic Acid to prevent major bleeding complications in hip and knee arthroplasty surgery. Am J Orthop (Belle Mead NJ). 2014;43:E217-20. PMID: 25303447.
39. Smit KM, Naudie DD, Ralley FE, Berta DM, Howard JL. One dose of tranexamic acid is safe and effective in revision knee arthroplasty. J Arthroplasty. 2013;28(8 Suppl):112-5. doi: 10.1016/j.arth.2013.05.036.