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"Randomized double blind trial to evaluate blood loss reduction with three different bias of tranexamic acid administration in sarcoma surgery." Is it more effective in mixed bias?

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ABSTRACT

BACKGROUND: Operative blood loss and transfusions have different impairments as allergic reaction, disease transmission and immunologic dysfunction. Transfusions are also associate with wound and lung infection after surgery and systemic recurrence in oncologic patients. To decrease the blood loss and red blood cell transfusion (RBCT) is mandatory in orthopedic oncology patients. Tranexamic acid (TXA) is drug used to reduce the bleeding in non-oncologic orthopedic surgeries. **PURPOSE:** 1)To determine blood loss in drainage and total blood loss as postoperative decrease in hemoglobin and hematocrit levels in patients with administration of TXA.2)To compare the effectiveness of TXA administered by three different biases during surgery in primary limb sarcomas. 3)To evaluate the safeness of the TXA in oncology patients with sarcoma. **PATIENTS AND METHODS:** Randomized double blind trial phase III with 67 patients included in our center since 2017 to 2021. Sixty-five patients were suitable for analysis. We recalled blood loss in drainage 24 hours after surgery and we calculated the total blood loss through the difference between preoperative and postoperative hemoglobin and hematocrit levels in fifth day. We evaluate possible adverse effects of tranexamic use during the trial. **RESULTS:** 1.Postoperative bleeding in drainage in 24 hours was 326 +/- 186 cc. Perioperative blood loss related to 5th day was 1,52 g/dl RQ [(25-75) 0,64-2,95]. The drop of the hematocrit in 5th day was 2,940% RQ [(25-75)0,80-3,80] Blood red cell infusion were necessary in 36% of the patients intra-operatory and in 21% of the patients during the post-operatory.2.There were no significant differences in the blood loss between the three biases of administration.3.No patient had an allergic reaction or adverse effect during the trial with a follow up of 1 moth post operatory. **CONCLUSIONS:** We could not prove a difference in effectivity between the three biases od administration. We did not detect adverse events related to the drug in the patients included in the study.

Keywords: Sarcoma, Orthopedic Oncology, Blood loss, tranexamic acid, Transfusion

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BACKGROUND

The orthopedic oncology surgeries are often challenging procedures with long surgical time and large surgical exposures. The bleeding is a problem during the peri-operatory and the need of RBCT is frequent in these patients. Several studies have associated the transfusion and surgery bleeding directly with nosocomial lung and wound infection [1, 25, 13]. The red blood cells transfusion may cause evident problems as allergies and adverse reactions that nowadays are rare but also can affect the T cells immune system in randomized controlled trials (RCT) and metanalysis [3,12]. There are also reports that connect the RBCT with the systemic recurrences in hepatocellular carcinoma, prostate carcinoma, and sarcomas [5,14,18]. Although this relation is controversial [19], blood products administration is known to contribute to the suppression of immune system through an inflammatory and regulatory effect on cytotoxic cells and monocytes, an increase in prostaglandins levels, interlekine-2 inhibition, and high T cell activity [6]. Moreover, RBCT is associated, in selected patients, with an increase in infection, mortality, and days to discharge, as long as the direct and indirect costs [15].

Tranexamic acid (TXA) is an antifibrinolytic drug with a strong inhibition effect on the fibrolisine activation. There is a post-commercialization indication for orthopedic patients in knee, hip and recently shoulder arthroplasty. Its effectivity is also accepted for trauma and spine surgery patients. Latest years the use of this drug has increased in intravenous, topical, even oral bias in spine, trauma, and orthopedic surgery to diminish the perioperative blood loss with a safety profile like placebo [2,11,16,26]. Some paper proved that topical administration does not increase systemic levels of the drug and neither systemic, nor topical administration causes adverse thromboembolic events in published series [9,10,24].

The effect of tranexamic acid in patents with sarcoma has not been properly evaluated.

The main objective is to determine the effectivity to decrease the perioperative bleeding. This is measured through the visible bleeding in drainage and total bleeding through hematocrit and hemoglobin levels drop-in 5th day laboratory The secondary aims are:

- To detect adverse event related to the use of TXA in patients with sarcoma.
- To evaluate the effectivity of TXA in combined administration versus isolated conventional intravenous and local administration.

PATIENTS AND METHODS

We perform a randomized double blind phase III trial to determine the effectivity of TXA trough three different bias of administration to reduce the perioperative bleeding and transfusion of patients with sarcoma. We recall the patients in a Referal Orthopedic Oncology center since July 2017 to May 2021 after IRB and Spanish drug control agency (AEMPS) approval of the trial. Inclusion and exclusion criteria are shown in Figures 1a y 1b. We changed the inclusion criteria in 2018 with the addition of a new recruitment center and the inclusion of patients with more than 9 g/dl HB instead of 11 g/dl as was determine in the first approval. The amendments were evaluated and approved by AEPMS and IRB. Randomization is implemented by an informatic program by investigation Department in Hospital la Paz (Idipaz), Clinical trials Unit (UCICEC) and sealed in closed numbered envelopes. Each number is assigned to a patient once included in trial and it stay blinded for the investigator until the data analysis. The envelope was opened by the anesthesiologist and closed again inside the trial data chart. The variables were collected by one of the investigators and noted in the trial charts.

We randomized patients in three groups according to the administration of AMCHAFIBRIN® ampoules of 5 ml with 500 mg of TXA:

- Intravenous administration (IV): 1 g (2 ampoules) of TXA in 20 minutes infusion through intravenous peripherical vessel 10

minutes before the approach. In case of surgeries with high risk of bleeding as hemipelvectomy, sacrectomy or soft tissue sarcomas with volume over 500 cc we infuse another 1 gram of TXA 8 hours after the start of the intervention. We administer 50 cc of Ringer lactate through the drainage to blind the study.

- Local Administration (L): The local doses is 3 gram (6 ampoules) in 50 cc of Ringer lactate through 12mm drainage Drenofast (Drenofast®; IHT Innovation S.L.U) after closure of the wound.
- Mixed administration (M): Randomized patients in this group receive both local and intravenous administration of TXA.

The drainage is the same in all surgeries and it remain closed for 1 hour after the end of the operation.

The variables to evaluate in the study are:

- Visible blood loss through drainage in cubic centimeters (cc) 24 horas after the surgery.
- Red cell irradiated Unit transfusion 300cc intra (RBCT IO) and postoperative (RBCT PO)
- Total blood loss estimation with 5th day Hemoglobin (Hb g/dl) and hematocrit (Hcto %) drop.
- Adverse effects related to TXA
- Early Surgical complications

RBCT is indicated in asymptomatic patients without previous heart disease and younger than 70 years with Hemoglobin levels below 8 g/dl and in patients over 70 years, symptomatic or previous heart impairment and Hb levels below 9 g/dl.

Patients had clinical follow up for 1 month to detect adverse effects related to TXA: Deep vein thrombosis (DVT), Thromboembolic event (TEE), Pulmonary embolism (PE). We perform a Doppler Ultrasonography of the patients with symptoms compatibles with Thrombosis disease. This adverse effect together to the surgical complication are reported as a descriptive analysis and treatment and result are also recalled.

We use Nadler formula [22] to calculate total blood loss according to the body volume (VSP) with Hcto and Hb drop-in 5th day*. The RBCT are balanced adding 1 gram in patients with each red cell 300 cc transfusion and 2% in Hematocrit levels [8].

*VSP =k1*altura3 (metro) + K2*peso (kg) + K3

k1 = 0,3669, k2 = 0,03219, K3 = 0,6041 men

k1 = 0,3561, k2 = 0,03308, K3 = 0,1833 women

Hcto drop (TBL)= VSP X ((Hct preoperatory - Hct post operatory) +2xRCT)

Hb drop= VSP X ((HB preo peratory - HB post operatory) + 1xRCT)

Out of the 67 patients randomized, 64 patients were included in the main variable analysis. Three out of the 67 were excluded of the analysis because the patient did not accomplish the inclusion criteria after randomization. Twenty-two patients receive systemic administration of TXA (IV group), 21 had Local administration of TXA (group L) and 21 to mixed group. The figure 2 shows the evolution of the visits of the patients randomized.

Statistical analysis the description of the qualitative data is report as absolute frequency and percentage. The quantitative data as standard deviation, media, median and interquartile range (RQ). The normality of the variables is evaluated with the Kolmogorov-Smirnov proof. The association between the qualitative variables is determine with the chi-square test or Fisher exact test. If we compare quantitative variables we use as parametric test T Student for 2 groups and ANOVA for 2 or more groups. The U de Mann-Whitney test (comparation between 2 groups) and the Kruskal-Wallis test (more than 2 groups) are non-parametric.

All the statistics tests are considered bilateral, and we report as significant p values < 0.05. The data are analyzed with SAS 9.3 (SAS Institute, Cary, NC, USA).

INCLUSION CRITERIA	
1	Male or female > 12 yo
2	Primary bone or soft tissue sarcoma >10 cm in the greater diameter, appendicular skeleton, pelvis and scapula.
3	Limb sparing resection and reconstruction surgery performed in one of the centers included in the study
4	Pre-operatory Hemoglobin > 9 g/dL

Figure 1a: Inclusion Criteria

EXCLUSION CRITERIA	
1	Previous allergic reaction or contraindication of TXA
2	Surgical procedure different to wide resection: radical or intralesional planned surgery
4	Comorbidities:
	- Ischemic Cardiopathies (clase III y IV de la New Cork Heart Association)
	- Valvopathy
	- Obstructive sleep apnoea syndrome
	- Chronic obstructive pulmonary disease (COPD) severe
	- Epilepsy
	- Severe renal dysfunction (creatinine >2mg/dl male and > 1,8 g/dl female in pre-operatory blood test maximum 30 days before surgery
	- Severe hepatic dysfunction (grade C Child-Pugh)
5	Coagulopathies:
	- Platelets <40.000/mm^3
	- International normalized Reason (INR)>1,4
	- TPTa > x 1,4
6	Previously diagnose of thromboembolic artery or vein event
7	blood dyscrasias: hemorrhagic or thrombogenic
8	Retinopathies
9	Young women with pregnancy test positive performed in the last month
10	Women breast feeding
11	Patients must use anticonception methods highly effective for at least 7 days before the surgery

Figure 1b: Exclusion Criteria

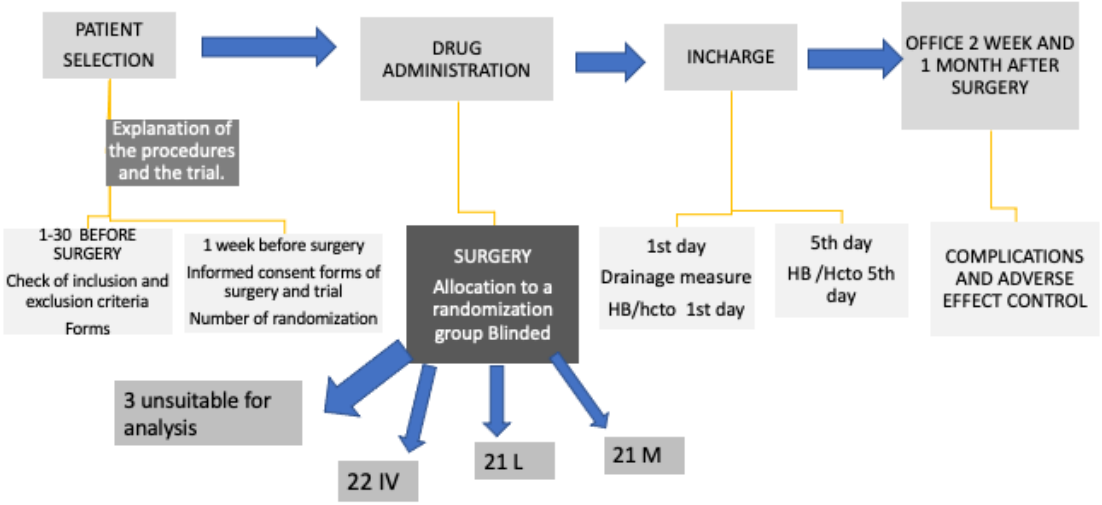

Figure 2: Diagram of visits in the study

Table 1: Descriptive study of epidemiologic variables. p>0.05, no statistical difference between randomization groups.

	Median (64)	IV (22/64)	L (21/64)	M (21/64)
Gender (M/F)	44/23	15/7	12/9	14/7
Age (years)	39 +/-19,5	39 (17-77)	40 (14-66)	40 (12-77)
BMI (RQ)	24 (21-27)	25(23-29)	21(20-27)	23 (22-27)
Bone sarcoma/ Soft Tissue Sarcoma	39/25	14/8	12/9	13/8
Surgical Time (minutes)	260 (190-320)	270 (197-322)	257 (197-324)	240(167-297)
Size cc (AP X CC X ML)	948	325 (176-952)	321 (67-678)	428 (96-740)

M: male; F: female; IV: intravenous group; L: Local group; M: mixed group; RQ: interquartile range; BMI: Body mass index; Cc: Cubic centimeters; AP: Antero posterior; CC: cephalic caudal; ML: medio lateral.

RESULTS

We randomized 67 patients. Three out of the 67 were excluded of the analysis because the patient did not accomplish the inclusion criteria after randomization. One case finally required a radical resection intraoperatively and in other 2 cases the reconstructive surgeon recommended avoiding the use of drainages. We included finally 64 patients since September 2017 until May 2021 The series have 40 bone sarcomas and 24 soft tissue sarcomas. The epidemiologic data are included in Table 1. No statistical difference in the epidemiologic data was observed between the randomization groups. The stage was IIIB in 69% of soft tissue sarcoma 5% were metastasis at diagnosis. Bone sarcomas were stage IIB 68% with a 12 % metastasis disease at diagnosis. Comorbidities were common disease as Hypertension (8) or diabetes (6); 2 patients suffer of neurofibromatosis type I and 6 had a previous carcinoma. The pathology of the cases includes 8 chondrosarcomas, 16 osteosarcomas, 3 vascular origin sarcoma, 10 Ewing sarcoma, 5 liposarcomas, 11 pleomorphic sarcoma, 3 synovial sarcoma, 3 malignant peripheral nerve sheath tumor (MPNST), 5 other histologic subtypes. The surgical margin was wide in 59 cases and marginal in 5, three of the 5 cases with marginal resection had a reoperation. Eleven cases were localized in upper limbs and 53 in lower limbs. The preoperatory embolization was necessary in 8 cases with pelvic resection and ischemia was used in 10 cases during the surgery for up to 120 minutes.

Table 2: Results in visible blood loss in drainages. Results of total blood loss corrected by body volume in the 5th day in hemoglobin and hematocrit levels.

	HB LOSS 5th day (g/dl) P=0.275	HCTO drop 5th day (%) P=0.345	RBCT IO P=0.490	RBCT PO P=0.561	RBCT	DRENAJE 24H (cc) P=0.551
IV	2,42 g/dl (RQ 1,15-3,31)	2,74 g/dl (RQ 1,23-4,52)	0 (RQ 0-2)	0 (RQ 0-2)	0,5 (RQ 0-2)	200 (RQ 200-505)
L	1,24 g/dl (RQ 0,5-3,1)	1,68 g/dl (RQ 0,47-4,20)	0,5 (RQ 0-2)	0 (RQ 0-0.75)	1 (RQ 0-2)	295 (RQ 212-475)
M	1,28 g/dl (RQ 0,55-2,76)	1,92 g/dl (RQ 0,49- 3,10)	0 (RQ 0-1,25)	0 (RQ 0-0)	0 (RQ 0-2)	285 (RQ 120-387)

Transfusions in each randomization group. RBCT *IO : intra-operatory red blood cell transfusion.* RBCT *PO: post-operatory red blood cell transfusion.* RBCT*: Total transfusions*

The visible blood loss in drainage was 326 +/- 186 cc. Hemoglobin drop-in 5th day corrected with the total blood volume (VPS) was 1,52 g/dl RQ [(25-75) 0,64-2,95]. The drop of the hematocrit corrected with VPS in 5th day was 2,940% RQ [(25-75)0,80-3,80]. The RBCT were required in 36% of the patients during the surgery (RBCT IO) and 21% during the post-operatory (RBCT PO) follow up. The median value of RBCT IO was 1 [(RQ (25-75) 2-3)] y RBCT PO de 2 (RQ 1-2,5).

We did not find statistical significative differences in total blood loss as adjusted hemoglobin drop or hematocrit in fifth day. Table 2. However, there is a trend towards a lower RBCT PO in patients who receive intravenous TXA (29% & 42%) and lower RBCT IO in patients 46% IV, 31% local y 23% in mixed TXA administration.

No patient had adverse reactions to the TXA. 1 patient had a deep vein thrombosis (DVT). This event was diagnosed clinically and with Ultrasonography doppler 48 days after the surgery. After discussing the case with internal medicine physicians and considering that the complication was more than a month after the drug administration TXA was not considered the cause of the DVT. No patients suffer from an EP during the follow up. One patient had a high digestive bleeding with progressive anemización that needed multiples red blood cell transfusion in the 10th post operatory day and finally required endoscopic sclerosis therapy. Twelve patients had a superficial wound infection and 10 needed additional surgery. One patient has wound dehiscence and need flap coverage and finally 2 patients had seromas that did not required additional procedures.

DISCUTION

Intra and post operative bleeding in major surgery is a problem difficult to manage. Moreover, the bleeding and transfusions can be the cause of system disturbance that can lead to an increment of nosocomial infections and poorer oncologic systemic prognosis. Surgeon can use hemoglobin optimization, surgery time, rational use of ischemic, intra-operatory hemostatic devices and embolization. However, the RBCT is a frequent measure to treat post-operatory anemia in sarcoma [1,3,5,6,12-14,18,19,24]. The TXA is used long time ago to decrease the bleeding in orthopedic surgeries. with evidence level [7,16,17]. The use of local TXA had proved a 20% - 25% decrease in hemoglobin loss in total knee arthroplasty, it was similar to the systemic intravenous infusion [11].

We cannot find in literature prospective studies considering the use of TXA in orthopedic oncology surgeries which have a higher thrombogenic risk. *Atalay et al* evaluate retrospectively the effectivity of systemic TXA to reduce the transfusions in 15 patients who had malignant proximal femur tumors [4]. They found a significant hemoglobin decrease in drainages and in 24 and 48 blood tests without an increase in thromboembolic events. The present study evaluates the effectiveness of TXA in three different biases. The local administration can be useful in cases with comorbidities that discourage the systemic bias. Other authors suggested the superiority of the mixed administration in orthopedic reconstruction compared to intravenous or local bias. Recently Lee et al, Lin et al and Mi et al proven the higher effectivity of mixed administration of TXA compared to the local or systemic bias alone. in total knee arthroplasty [20,21,23]. We could not find statistical differences in the total blood loss corrected or visible loss in drainage between local or systemic administration alone and the combinate administration of TXA

We detected a trend to lower RBCT IO in the cases with systemic administration and lower RBCT PO in cases with local administration. This difference does not reach statistical significance with the sample size.

This study had no safety adverse events related to the drug. Previous studies had described the safety profile of this drug for the local and systemic administration in major orthopedic surgeries as spine, hip and knee total

arthroplasty. [9,10,24]. TXA is not detected in blood test with local administration.

The limitations of the study are the short sample size that do not reach statistical significance to determine the possible difference between the three administration biases. There is also a heterogeneity in surgical procedures and diagnoses.

As a conclusion the study has the advantage of the prospective evaluation of the effectivity of the TXA to decrease the bleeding through the three administration biases without an increment in adverse events related to the drug.

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ABBREVIATIONS

XA: Tranexamic acid; TVP: Deep Vein trombosis: DVT: Pulmonary embolism PE; RQ: interquartile range: RBCT IO: intra-operatory red blood cell transfusion; RBCT PO: post-operatory red blood cell transfusion transfusions. RBCT:_ red blood cell transfusion

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