Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Tranexamic acid in total shoulder arthroplasty under regional anesthesia: a randomized, single blinded, controlled trial

Teresa Garcia[a], **Mariana Fragão-Marques**[b,*], **Pedro Pimentão**[a,c], **Martim Pinto**[a,c], **Inês Pedro**[a,c], **Carlos Martins**[a]

[a] *Hospital Lusíadas, Department of Anesthesiology, Lisboa, Portugal*
[b] *Centro Hospitalar Universitário de São João, Department of Clinical Pathology, Porto, Portugal*
[c] *Hospital Lusíadas, Lisboa, Portugal*

Received 6 April 2020; accepted 26 October 2020
Available online 6 February 2021

KEYWORDS
Total shoulder replacement;
Tranexamic acid;
Surgical blood loss;
Blood transfusion

Abstract
Purpose: The purpose of this study was to determine whether Tranexamic Acid (TXA) can significantly reduce perioperative blood loss in Total Shoulder Arthroplasty (TSA) performed under regional anesthesia.
Methods: We performed a randomized, single blinded, controlled study. Forty-five patients were submitted to TSA under regional anesthesia to treat cuff tear arthropathy, proximal humeral fractures, chronic instability, primary osteoarthrosis, and failures of previous prosthesis. Patients were randomized to either group TXA therapy (TXA), with 1 g intravenous (IV), or no Intervention (NTXA). Postoperative total drain output, hemoglobin variation, total blood loss, hemoglobin loss, and need for transfusion were measured. Pain-related variables were also assessed: postoperative pain assessment by visual analog scale, inpatient pain breakthrough, quality of recovery, length of stay, and coagulation function testing.
Results: Participants presented a mean age of 76 years, 15.6% were male, 82.2% were American Society of Anesthesiologists (ASA) physical status I or II. There were no differences between groups concerning transfusions, operative time, Post-Anesthesia Care Unit (PACU) length of stay and in-hospital stay, and QoR-15 or postoperative pain. Bleeding measured by drain output at 2, 24 and 48 hours was significantly less in the TXA group at each timepoint. There was a difference in Hb variation – TXA: median (IQR) -1.4 (1.3) $g.dL^{-1}$ vs. NTXA: -2.2 (1.3) $g.dL^{-1}$; median difference: 0.80 (0.00–1.20); $p = 0.047$. aPTT was lower in TXA administered patients – TXA: median (IQR) 29.6 (14.0)s vs. NTXA: 33 (5.8)s; difference in medians: -4.00 (-6.50–-1.00); $p = 0.012$.

* Corresponding author.
E-mail: marianaifrm@gmail.com (M. Fragão-Marques).

https://doi.org/10.1016/j.bjane.2021.02.011

Conclusion: TXA use significantly decreased blood loss measured by drain output and Hb drop in TSA under regional anesthesia.

Introduction

Total Shoulder Arthroplasty (TSA) is associated with the risk of significant perioperative blood loss, with a rate of blood transfusions reported to be 4.3% to 43%[1–3] with recent transfusion rates ranging from 2.4% to 11.3%[2,4,5] Although the amount of blood loss and number of necessary transfusions have been reported to be lower in TSA when compared to arthroplasties of the hip and knee, administration of erythrocyte concentrates is sometimes still indicated.[2,3,6] Complications of blood transfusions include allergic reactions, immunosuppression, infection and transfusion-related cardiopulmonary injury.[3,7,8] Moreover, perioperative blood transfusions increase the risk of medical complications such as myocardial infarction, pneumonia, sepsis and cerebrovascular accidents, as well as venous thromboembolic events and surgical complications, including periprosthetic infections, periprosthetic fractures, and mechanical complications.[7]

TXA is a synthetic antifibrinolytic agent which reversibly binds to plasminogen, preventing the normal cascade of fibrin clot dissolution.[1,9,10] The use of TXA results in less perioperative blood loss, fewer wound hematomas, and significantly lower transfusion rates.[11,12] TXA has demonstrated an excellent safety profile with minimal side effects and no increase in thromboembolic or cardiac events in the perioperative period, while being cost-effective in joint and hip arthroplasty, spine surgery and cardiac surgery.[11,12]

TXA has been validated to be effective in reducing blood transfusion requirements after hip and knee arthroplasty.[13,14] The efficiency of TXA in reducing blood loss following TSA has been demonstrated in small retrospective and controlled clinical trials;[5,7,11,15] however, their results are not consistent.[4] The influence of TXA in TSA due to humeral fracture was not studied. In all the papers TSA was performed under general anesthesia. We aimed to determine whether TXA can significantly reduce perioperative blood loss measured by drain output, drop in Hemoglobin (HG) and total blood loss in TSA performed under regional anesthesia.

Methods

Study design

We conducted a phase 3 randomized, single blinded (patient blinded), controlled trial in a tertiary hospital to assess whether TXA reduces blood loss and transfusion rate, intra- and postoperative, in patients undergoing TSA under regional anesthesia.

Patients undergoing TSA were recruited from February 2017 to May 2019. Eligibility criteria included patients with more than 18 years of age and with the following indications for surgery: cuff tear arthropathy, proximal humeral fractures, chronic instability, primary osteoarthrosis, and failures of previous prosthesis. Patients with known allergy to TXA, thromboembolic event in the previous year and refusal to be transfused, to perform regional anesthesia or give written informed consent were excluded from the study.

Sample size was calculated for a superiority trial in which hemoglobin variation differs 0.8 between groups, assuming a probability of a type II error of 0.20 and a critical alpha level of 0.05, with an expected standard deviation between groups of 1. A required sample of 20 subjects in each group was calculated. Thus, a total of 45 participants were enrolled and therefore randomized in two groups according to a computer-generated randomization list (parallel design, allocation ratio 1:1): TXA group (TXA, n = 23), where patients received an intravenous (IV) infusion of TXA 1 g immediately before surgery,[5] and a control group (NTXA, n = 22) where the same care was provided without the TXA infusion. The principal investigator was responsible for enrolling participants; the second and third authors generated the allocation sequence and assigned the intervention, respectively. Patients were blinded for the intervention as they were unaware of TXA administration. Moreover, participants were followed during their inpatient stay as well as 2 months postoperatively and defined primary and secondary outcomes were monitored and recorded.

Anesthesia and surgical procedures

All patients were evaluated on a preoperative anesthesia appointment and anticoagulation therapy was stopped according to the guidelines of the European Society of Anesthesiology.[16]

Regional anesthesia was performed under 0.05–0.1 mg of fentanil using an ultrasound-guided interscalene brachial block (20 mL) combined with a supraclavicular block (10 mL), in plane approach, with a mixture of ropivacaine 0.75% (135 mg), lidocaine 2% (200 mg) and dexamethasone 8 mg. Regional anesthesia was complemented with propofol sedation (1–3 $mg.kg^{-1}.h^{-1}$) in all cases.

All procedures were performed with the patient in a beach chair position, through a standard anterior deltopectoral approach. In 43 patients a reverse total shoulder arthroplasty was implanted (DePuy DELTA XTEND) and in 2 patients an anatomic arthroplasty (Depuy GLOBAL UNITE) was used. The same standard techniques and hemostasis were applied during all procedures. A medium Hemovac active drain was used in all cases placed deep into the joint space and was removed on postoperative day 2. Patients were transfused if Hemoglobin (Hb) level was < 7 $g.dL^{-1}$ or

if 7.1–9 g.dL^{-1} with symptoms of anemia (fatigue, hypotension, tachycardia, or tachypnea) orischaemic heart disease.[1]

Postoperative analgesia was performed with paracetamol 1 g 8/8 h, tramadol 300 mg and ketorolac 60 mg in 24 hours. In case of allergic or adverse reaction to any drugs, dipyrone 2 g 12/12 h was used in substitution. For rescue analgesia it was used morphine 2 g IV. In addition, all patients received Deep Venous Thrombosis (DVT) prophylaxis with Enoxaparin 40 mg SC once a day and compression stockings on both legs until discharge from the hospital. Antibiotics prophylaxis were also performed.

Data collection

Preoperative data regarding patient demographics and comorbidities was collected. Anemia was defined as less of 13 g.dL^{-1} for males and less of 12 g.dL^{-1} for females.[17] Chronic pulmonary disease included asthma, Chronic Obstructive Pulmonary Disease (COPD), and obstructive sleep apnea. Cerebrovascular disease was defined as transient ischemic attack or stroke. Postoperative platelet count and coagulation studies were performed in the first postoperative day. Hemoglobin was measured at three different timepoints – preoperatively and at 2 and 24 hours postoperatively. Hemoglobin variation, total blood loss, hemoglobin loss and total blood volume for males and females were defined as follows:

$$\text{Equation1 : Hbvariation} = (\text{Hbat24 h[g.L}^{-1}\text{]-preoperativeHb[g.L}^{-1}\text{]})$$

$$\text{Equation2 : Totalbloodlost(mL)} = (1000 \times \text{Hbloss[g]/Hbinitial[g]})$$

$$\text{Equation3 : Hbloss} = \text{bloodvolume}\ (\text{L} \times [\text{Hbinitialg.L}^{-1}\text{-Hbfinalg.L}^{-1}] + \text{Hbtransfused[52 gofHbperunit]})$$

$$\text{Equation4(males) : BloodVolume-}(0.3669 \times \text{heightinmeters}^3) + (0.03219 \times \text{weightinkg}) + 0.6041$$

$$\text{Equation5(females) : BloodVolume-}(0.3561 \times \text{heightinmeters}^3) + (0.03308 \times \text{weightinkg}) + 0.1833$$

Outcomes

Primary outcomes were blood loss-related:[1,5] total drain output measured at 2, 24 and 48 hours postoperatively; hemoglobin variation, using preoperative hemoglobin levels (Equation 1), total blood loss (Equation 2), hemoglobin loss (Equation 3) and need for transfusion. Total blood volume was calculated using Equations 4 and 5 by Nadler et al.[18] and Good et al.[19]

Secondary outcomes were postoperative pain assessment by Visual Analog Scale, (VAS) measured at rest and with movement at 2, 24, and 48 hours postoperatively; inpatient pain breakthrough, defined by extra morphine prescriptions when VAS > 3; quality of recovery, measured by the Portuguese adapted version of the Quality of Recovery 15 (QoR-15) questionnaire, a validated outcome measurement instrument in clinical trials;[20] PACU and in-hospital length of stay and coagulation function, assessed by International Normalized Ratio (INR) and activated Partial Thromboplastin Time (aPTT).

Patients were followed two months postoperatively and complications such as hematoma, transfusion reaction, infection and thromboembolic or other adverse events were recorded.

Statistical analysis

Intention-to-treat analysis was performed. Normally distributed continuous variables were represented as mean and Standard Deviation (SD), while non-parametric variables as median and Interquartile Range (IQR). Categorical variables were presented as number and respective percentages. Continuous variables were compared between groups using Mann-Whitney *U* or Student's *t*-test according to normality testing; effect size was reported either as differences between means or medians and respective 95% Confidence Intervals (95% CI). Chi-Squared or Fisher's exact test were used to compare categorical variables; corresponding effect size was presented as Odds Ratio (OR) and 95% CI. Statistical significance was considered when $p < 0.05$. Statistics Package for Social Sciences (SPSS) v.25.0 was used for all statistical analysis.

Ethical statement

This study was approved by the hospital's Ethics Committee – Institutional Review Board. All enrolled participants signed a written informed consent and were blinded for the intervention.

Results

Patient characteristics

A total of 48 patients were assessed for eligibility. Three patients were excluded from the study as they were submitted to general anesthesia. Thus, 45 patients were included, of which 23 were allocated to the intervention arm (TXA) and 22 to the no intervention arm. Enrolled participants had the following surgery indications: cuff tear arthropathy (n = 20), proximal humeral fractures (n = 18), chronic instability (n = 2), primary osteoarthrosis (n = 2) and failures of previous prosthesis (n = 3). There was no exclusion

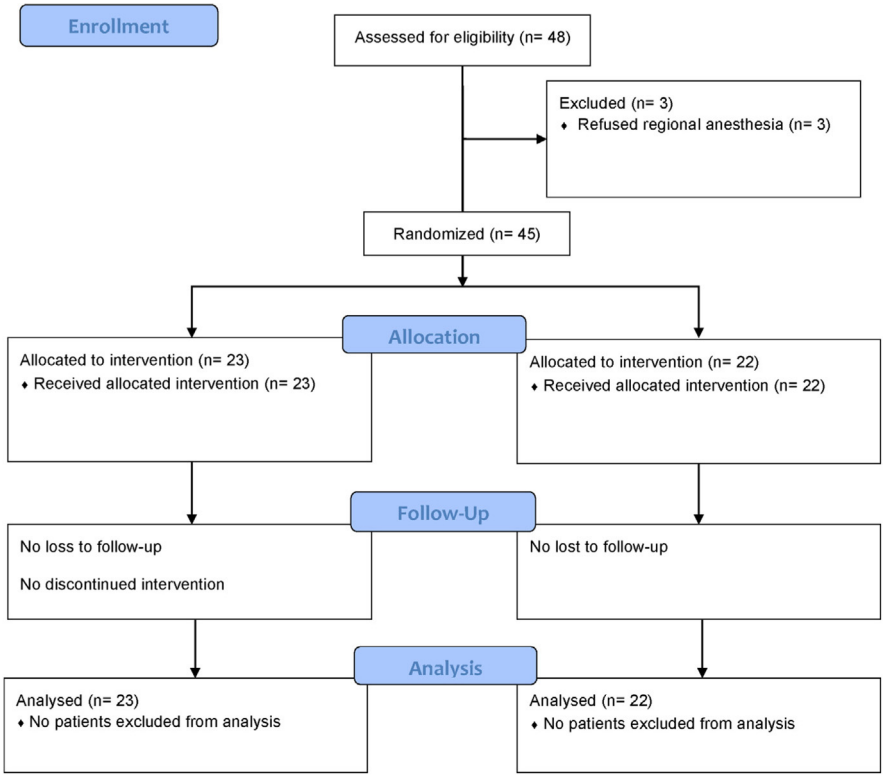

Figure 1 Patient recruitment, randomization, and follow-up.

after randomization, contamination, or loss to follow-up in this study (Figure 1).

Participants' mean age was 76.2 ± 6.4 years, and patients overall had excess weight (BMI 28.1 ± 4.0). In addition, 15.6% (n = 7) of participants were male, 82.2% (n = 37) were American Society of Anesthesiologists (ASA) physical status I or II, and 82.2% had a Revised Cardiac Index Risk (RCIR) of 0 (n = 37). The most common comorbidity was arterial hypertension (68.9%, n = 31), followed by dyslipidemia (51.1%, n = 23), anemia (33.3%, n = 15) and type 2 diabetes mellitus (20%, n = 9). Hematologic disorders (8.9%, n = 4) included thrombocytopenia (n = 1), antiphospholipid syndrome (n = 1), use of anticoagulants (n = 2). Other comorbidities such as rheumatoid arthritis and peripheral artery disease were documented in 2 control group patients. There were no baseline differences between groups, either in age (p = 0.602), gender (p = 0.365), body mass index (p = 0.784), ASA physical status (p = 0.358), or RCIR (p = 0.473). Likewise, distribution of comorbidities was similar between study arms. Patient characteristics are listed in Table 1.

Analgesia and anesthesia assessment

Results regarding analgesia and anesthesia are depicted in Table 2. There were no differences between groups concerning operative time (TXA: mean 113.7 ± SD 27.7 min; NTXA: 107.9 ± 35.2 min; p = 0.542), PACU length of stay (TXA: median 127.5 IQR (53.8) min; NTXA: 120 (60) min; p = 0.752) and in-hospital stay (TXA: 3 (1) days; NTXA: 3 (2) days; p = 0.429). Concerning patient postoperative recovery evaluated by QoR-15 questionnaire, no differences in score were observed between groups (TXA: 128.2 ± 22.3; NTXA: 121.4 ± 23.1; p = 0.357). Moreover, pain did not vary according to TXA administration – Numeric Pain Scale (NPS) at 2, 24, and 48 hours, at rest and with motion, and the inpatient pain breakthrough were similar between study arms (Table 2).

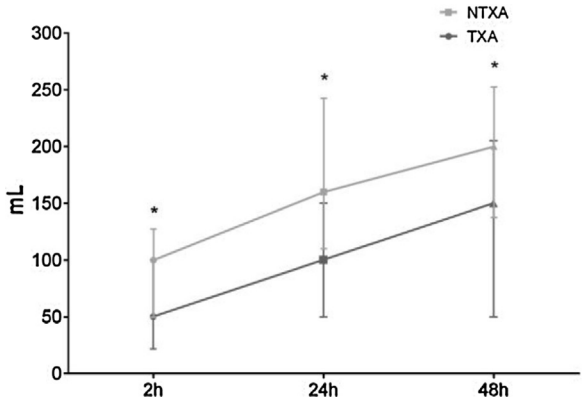

Figure 2 Cumulative drain output at 2 h, 24 h, and 48 h in TXA and NTXA patients.

Blood loss and coagulation function assessment

Concerning cumulative drain output at 2, 24, and 48 hours, bleeding was significantly less for the TXA treated group at each timepoint (Figure 2). At 2 hours postoperatively, drains presented a median (IQR) of 45 (93) mL in the TXA group vs. 100 (88) mL in the control group (difference in medians: -50.0 [-70.0–0.0]; p = 0.009). Drain output at 24 hours was 112.5 (108) mL in TXA vs. 200 (100) mL in controls (-60.0

Table 1 Patient characteristics.

	Total (n = 45)	TXA (n = 23)	NTXA (n = 22)	*p*-value
Age (years), mean ± SD	76.2 ± 6.4	76.7 ± 7.1	75.7 ± 5.7	0.602
Sex				
Male, n (%)	7 (15.6)	4 (17.4)	3 (13.6)	1.000
BMI, mean ± SD	28.1 ± 4.0	28.0 ± 4.1	28.3 ± 4.1	0.784
ASA classification, n (%)				0.699
I–II	37 (82.2)	18 (78.3)	19 (86.4)	
III	8 (17.8)	5 (21.7)	3 (13.6)	
RCRI, n (%)				1.000
0	37 (82.2)	19 (82.6)	18 (81.8)	
1–2	8 (17.8)	4 (17.4)	4 (18.2)	
Hypertension, n (%)	31 (68.9)	18 (81.8)	13 (56.5)	0.108
Dyslipidemia, n (%)	23 (51.1)	9 (40.9)	14 (60.9)	0.181
Obesity, n (%)	7 (15.6)	2 (8.7)	5 (22.7)	0.243
Diabetes mellitus, n (%)	9 (20)	5 (21.7)	4 (18.2)	1.000
Chronic kidney disease, n (%)	3 (6.7)	2 (8.7)	1 (4.5)	1.000
Cerebrovascular disease, n (%)	3 (6.7)	1 (4.3)	2 (9.1)	0.608
Congestive heart disease, n (%)	1 (2.2)	0 (0)	1 (4.5)	0.489
Ischemic heart disease, n (%)	1 (2.2)	1 (4.3)	0 (0)	1.000
Chronic pulmonary disease, n (%)	3 (6.7)	0 (0)	3 (13.6)	0.109
Anemia, n (%)	15 (33.3)	11 (47.8)	4 (18.2)	0.057
Other hematologic disorders, n (%)	4 (8.9)	1 (4.3)	3 (13.6)	0.346
Hypothyroidism, n (%)	4 (8.9)	2 (8.7)	2 (9.1)	1.000
Depression, n (%)	4 (8.9)	1 (4.3)	3 (13.6)	0.346
Parkinson, n (%)	2 (4.4)	2 (8.7)	0 (0)	0.489

ASA, American Society of Anesthesiologists physical status; RCRI, Revised Cardiac Risk Index; SD, Standard Deviation.

Table 2 Analgesia/anesthesia parameters between study groups.

	TXA	NTXA	95% CI	*p*-value
Operative time (min), mean ± SD	113.7 ± 27.7	107.9 ± 35.2	-5.84 (-25.02–13.34)[a]	0.542
Length of stay (days), median (IQR)	3 (1)	3 (2)	0.0 (-1.0–0.0)[b]	0.429
PACU length of stay (min), median (IQR)	127.5 (53.8)	120 (60)	0 (-20.0–45.0)[b]	0.752
QoR-15, mean ± SD	128.2 ± 22.3	121.4 ± 23.1	-6.78 (-21.48–7.93)[a]	0.357
Numeric pain scale (0–10), median (IQR)				
2 h				
Rest	0	0		
Motion	0	0		
24 h				
Rest	0 (3)	0 (1)	0.0 (0.0–0.0)[b]	0.296
Motion	2 (5)	0 (4)	2.0 (0.0–2.0)[b]	0.496
48 h				
Rest	0 (0)	0 (0)	0.0 (0.0–0.0)[b]	0.180
Motion	0 (2)	0 (4)	0.0 (0.0–0.0)[b]	0.713
Inpatient pain breakthrough, n (%)	5 (25)	6 (28.6)	1.12 (0.52–2.42)[c]	1.000

PACU, Post-Anesthesia Care Unit; QoR, Quality of Recovery; IQR, Interquartil Range.
[a] 95% Confidence Interval of the mean difference.
[b] 95% Confidence Interval of the median difference.
[c] 95% Confidence Interval of the Odds Ratio.

[-110.0–20.0]; p = 0.008). Total cumulative drainage at 48 hours was 150 (155) mL in patients with TXA comparing to 210 (95) mL in the no intervention group (-50.0 [-110–0.0]; p = 0.030) (Table 3).

Hemoglobin was measured preoperatively and at 2 and 24 hours postoperatively. Neither individual value was different between groups – TXA: median (IQR) 12.5 (1.5) vs. NTXA: 13.1 (1.3), p = 0.152; 11.2 (1.9) vs. 11.8 (1.5), p = 0.220 and 10.8 (1.5) vs. 10.8 (1.2), p = 0.993, respectively. However, there was a difference in Hb variation between intervention arms – TXA: median (IQR) -1.4 (1.3) $g.dL^{-1}$ vs. NTXA: -2.2 (1.3) $g.dL^{-1}$; difference in medians: 0.80 [0.00–1.20]; p = 0.047 (Figure 3, Table 3).

Table 3 Postoperative blood loss, platelets, and coagulation parameters between study groups.

	TXA	NTXA	95% CI	*p*-value
Drain output (mL), median (IQR)				
2 h	45 (93)	100 (88))	-50.0 (-70.0–0.0)[b]	0.009
24 h	112.5 (108)	200 (100)	-60.0 (-110.0–20.0)[b]	0.008
48 h	150 (155)	210 (95)	-50.0 (-110–0.0)[b]	0.030
Hb ($g.L^{-1}$), mean ± SD				
Preoperative	12.5 (1.5)	13.1 (1.3)	0.62 (-0.24–1.49)[b]	0.152
2 h	11.2 (1.9)	11.8 (1.5)	0.64 (-0.40–1.68)[a]	0.220
24 h	10.8 (1.5)	10.8 (1.2)	0.004 (-0.810–0.817)[a]	0.993
Hb variation, median (IQR)	-1.4 (1.3)	-2.2 (1.3)	0.80 (0.00–1.20)[b]	0.047
Hb loss (g), median (IQR)	54.2 (64.0)	91.7 (53.6)	-33.02 (-42.82–5.15)[b]	0.134
Total blood loss (mL), median (IQR)	458.1 (434.6)	672.3 (382.9)	-190.30 (-280.6–48.63)[b]	0.166
Need for transfusion, n (%)	3 (13.0)	2 (9.1)	1.50 (0.226–9.964)[c]	1.000
Platelets ($\times 10^9$/L), median (IQR)	243.5 (118.0)	205.0 (74.0)	17.50 (-40.00– -42.00)[b]	0.982
aPTT (s), median (IQR)	29.6 (14.0)	33.0 (5.8)	-4.00 (-6.50– -1.00)[b]	0.012
INR, median (IQR)	0.99 (0.50)	1.02 (0.08)	-0.04 (-0.07–0.04)[b]	0.526

Hb, hemoglobin; IQR, Interquartil Range.
[a] 95% Confidence Interval of the mean difference.
[b] 95% Confidence Interval of the median difference.
[c] 95% Confidence Interval of the Odds Ratio.

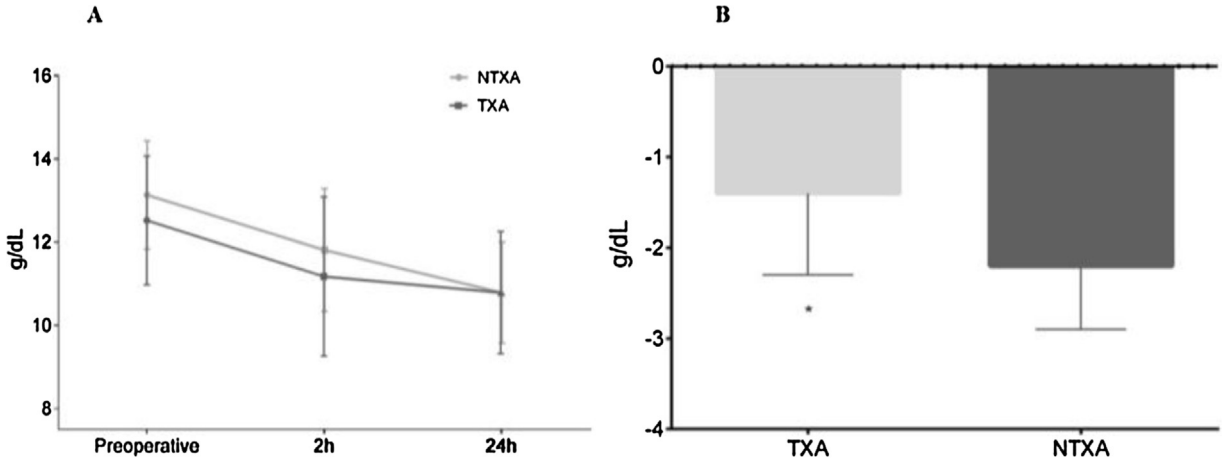

Figure 3 (A) Preoperative and postoperative (at 2 h and 24 h) hemoglobin in TXA and NTXA patients. (B) Hemoglobin variation in TXA and NTXA patients.

Additionally, hemoglobin loss and total blood loss were decreased in the TXA group when compared with controls, although non-significant – $p = 0.134$ and $p = 0.166$, respectively (Table 3). Regarding transfusion requirements, 3 patients (13%) were transfused in the TXA group and 2 (9.1%) in the control group ($p = 1.000$).

Postoperative platelet count was unaffected by TXA administration ($p = 0.982$). Regarding coagulation function assessment, aPTT was lower in TXA administered patients (TXA: median (IQR) 29.6 (14.0)s vs. NTXA: 33 (5.8)s; difference in medians: -4.00 [-6.50–1.00]; $p = 0.012$), despite INR not differing between study groups ($p = 0.526$).

Adverse events

Two complications were reported in the TXA group. One patient was readmitted at the hospital due to anemia (Hb: 6.1 $g.dL^{-1}$) with a shoulder hematoma and was transfused without further complications. The other patient had a postoperative delirium. In the no intervention group three complications were documented: stroke after discharge during the first postoperative week with the need for in-hospital care, a postoperative delirium, and a metabolic acidosis with admission in the intensive care unit. No other adverse events were registered during the follow-up period of 2 months (until July 31, 2019).

Discussion

This randomized study is the first to evaluate the effect of intravenous TXA in shoulder arthroplasty under regional anesthesia (ultrasound-guided combined interscalene and supraclavicular block). As far as we are concerned this is the only article including the use of TXA in TSA for treatment of fractures and revision surgeries.

We included 45 patients in our study, regardless of the comorbidities, which included anemia, other hematologic diseases, and cerebrovascular disease. Pauzenberger et al.[3] excluded patients with hematologic disorders. The inclusion of these diseases adds up to the relevance of our work. Although one patient in the control group had a stroke in the follow-up period, no other complications attributable to TXA occurred.

The most important findings were that intravenous TXA is effective in reducing postoperative blood loss by evaluating drain output and hemoglobin variation after TSA. An observed 0.8 $g.dL^{-1}$ median difference in Hbdrop between groups is clinically significant, even more so when it can determine transfusion in a population with 33% of preoperative anemia. Friedman's et al.[12] retrospective study reported a difference between groups regarding Hb variation similar to our results (TXA: 2.13 vs. NTXA: 2.63; p = 0,045). In the meta-analysis of Randomized Controlled Trials (RCTs) and Retrospective Cohort Studies (RCS) performed by Kuo L et al.[7] with 677 patients a less change in haemoglobin in the TXA group of 0.64 $g.dL^{-1}$ was also reported.

At 2, 24, and 48 hours postoperatively, there was a statistically significant difference in drain output between the two groups. The use of TXA decreased drain output in approximately 30% at the second postoperative day. Likewise, Abildgaard et al.[21] retrospectively reviewed the administration of 1 g intravenous TXA in 171 shoulder arthroplasties – TXA reduced postoperative drainage by 58%, with an overall blood-saving effect of 25% in TSA.

Although there is a decrease in Hb loss and total blood loss, the difference is not statistically significant. Total blood loss in our study was approximately half of what other studies found, including Vara el al.[1] Our study occurred at a private hospital without residents in training and surgeries were performed by a senior shoulder surgeon with a vast experience in shoulder prostheses. This might explain the low level of lost blood and the lack of a statistically significant difference in these parameters.

Several studies of TXA in TSA show less postoperative blood loss although the route of administration and dose of TXA vary among studies. We used intravenous TXA in a dose of 1 g, while Gillespie et al.[2] administered a topical application of 2 g of TXA. In addition, Vara et al.[1] infused two doses of TXA (10 $mg.kg^{-1}$ before surgery and 10 $mg.kg^{-1}$ by the end of the surgery) and Pauzenberger et al.[3] used two doses of TXA but in the dose of 1 g intravenously. Kim et al.[22] gave only a single dose of TXA 500 mg IV before surgery, whilst Abildgaard et al.[21] used 1 g of TXA. Thus, more studies are needed to elect TXA ideal dose, frequency, and route of administration.

Anemia was extremely prevalent and approximately 33%, which could be due to the older age of the population (76 years) and 40% of fractures.[15] Transfusion was necessary in 3 patients in the TXA group (13%) and 2 in the control group (9.1%), with four patients presenting preoperative anemia and two of the transfusions occurring intraoperatively. This percentage is supported by existing literature.[1] However, Gillespie et al.,[2] Pauzenberger et al.,[3] Kim et al.[22] and Cvetanovich et al.[5] reported no transfusions, while Kim et al.[22] excluded patients who received an intraoperative transfusion. Ameta-analysis of Randomized Controlled Trials (RCTs) by Kuo et al.[7] with 677 patients suggested TXA decreases transfusion rate,[23] which was not found in this study.

Furthermore, Pauzenberger et al.[3] concluded the use of TXA decreased early postoperative pain and hematoma formation in TSA. In our study, the mean in numeric pain scale at 24 and 48 hours postoperatively, inpatient pain breakthrough, QoR-15, and length of stay in PACU and at the hospital was no different between the TXA and the control group. Our negative results regarding pain could be explained by a low overall pain score during the first postoperative days, which could be related to a better pain control associated with regional anesthesia.

Few studies evaluate the impact of TXA in coagulation parameters.[24] Our results demonstrate a decrease in aPTT when TXA is administered. The latter helps explain the effect of TXA in bleeding control and presents biological plausibility, since TXA is an antifibrinolytic drug. Previous randomized controlled trials in TSA have not documented the effect of TXA in coagulation parameters, which might be clinically relevant when considering treatment criteria.

The current study presents slight differences in results regarding existing literature. We included in our study all performed prostheses regardless of the indication. Theoretically, revision surgery and fractures tend to have more bleeding than cuff tear.[12] Since we are not a teaching hospital and surgeons were experts in shoulder interventions, the outcomes might not be applicable to every center. Moreover, our study did not present contamination between trial arms, nor did it have attrition bias, since there was no loss to follow-up. One advantage of the primary outcome is its objectivity and ease of detection in both groups. Every researcher directly involved in patient care provided the same care regardless of study group, although this randomized trial is single blinded, which could be a source of bias. Despite the limited number of patients in the study, this is the first randomized clinical trial testing TXA in TSA with broader indications and under regional anesthesia. Nevertheless, more studies are needed to clarify the effect of TXA in postoperative outcomes.

Conclusions

TXA use (1 g IV) significantly diminished blood loss measured by drain output and Hb drop in TSA under regional anesthesia performed mainly due to cuff tear arthropathy and humeral fractures, although the number of transfusions remained similar between groups. Our results suggest the use of TXA IV does not improve the numeric analgesic scale and QoR-15, neither does it influence length of stay at the hospital or PACU. Notwithstanding, more studies are required to determine the ideal dose and route of administration of TXA in TSA and to evaluate the effectiveness of TXA in reducing transfusion requirements.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Vara AD, Koueiter DM, Pinkas DE, et al. Intravenous tranexamic acid reduces total blood loss in reverse total shoulder arthroplasty: a prospective, double-blinded, randomized, controlled trial. J Shoulder Elb Surg. 2017;26:1383–9.
2. Gillespie R, Shishani Y, Joseph S, et al. Neer Award 2015: A randomized, prospective evaluation on the effectiveness of tranexamic acid in reducing blood loss after total shoulder arthroplasty. J Shoulder Elb Surg. 2015;24:1679–84.
3. Pauzenberger L, Domej MA, Heuberer PR, et al. The effect of intravenous tranexamic acid on blood loss and early postoperative pain in total shoulder arthroplasty. Bone Joint J. 2017;99-B:1073–9.
4. Yu B-F, Yang G-J, Li Q, et al. Tranexamic acid decreases blood loss in shoulder arthroplasty: A meta-analysis. Medicine (Baltimore). 2017;96:e7762.
5. Cvetanovich GL, Fillingham YA, O'Brien M, et al. Tranexamic acid reduces blood loss after primary shoulder arthroplasty: a double-blind, placebo-controlled, prospective, randomized controlled trial. JSES Open Access. 2018;2:23–7.
6. Gilbody J, Dhotar HS, Perruccio AV, et al. Topical tranexamic acid reduces transfusion rates in total hip and knee arthroplasty. J Arthroplasty. 2014;29:681–4.
7. Kuo L-T, Hsu W-H, Chi C-C, et al. Tranexamic acid in total shoulder arthroplasty and reverse shoulder arthroplasty: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2018;19:60.
8. Gruson KI, Accousti KJ, Parsons BO, et al. Transfusion after shoulder arthroplasty: An analysis of rates and risk factors. J Shoulder Elb Surg. 2009;18:225–30.
9. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis, and meta-regression of the effect of tranexamic acid on surgical blood loss. Br J Surg. 2013;100:1271–9.
10. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999;57:1005–32.
11. Sun C-X, Zhang L, Mi L-D, et al. Efficiency and safety of tranexamic acid in reducing blood loss in total shoulder arthroplasty: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e7015.
12. Friedman RJ, Gordon E, Butler RB, et al. Tranexamic acid decreases blood loss after total shoulder arthroplasty. J Shoulder Elb Surg. 2016;25:614–8.
13. Chang C-H, Chang Y, Chen DW, et al. Topical tranexamic acid reduces blood loss and transfusion rates associated with primary total hip arthroplasty. Clin Orthop Relat Res. 2014;472:1552–7.
14. Kagoma YK, Crowther MA, Douketis J, et al. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: A systematic review of randomized trials. Thromb Res. 2009;123:687–96.
15. Kirsch JM, Bedi A, Horner N, et al. Tranexamic acid in shoulder arthroplasty. JBJS Rev. 2017;5:e3.
16. De Hert S, Staender S, Fritsch G, et al. Pre-operative evaluation of adults undergoing elective noncardiac surgery. Eur J Anaesthesiol. 2018;35:407–65.
17. WHO Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. WHO; 2018.
18. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51:224–32.
19. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth. 2003;90:596–9.
20. Kleif J, Waage J, Christensen KB, et al. Systematic review of the QoR-15 score, a patient reported outcome measure measuring quality of recovery after surgery and anaesthesia. Br J Anaesth [Internet]. 2018;120:28–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29397134. Jan 1 [cited 2019 Sep 28].
21. Abildgaard JT, McLemore R, Hattrup SJ. Tranexamic acid decreases blood loss in total shoulder arthroplasty and reverse total shoulder arthroplasty. J Shoulder Elb Surg. 2016;25:1643–8.
22. Kim SH, Jung WI, Kim YJ, et al. Effect of Tranexamic Acid on Hematologic Values and Blood Loss in Reverse Total Shoulder Arthroplasty. Biomed Res Int. 2017;2017:9590803.
23. He J, Wang X, Yuan G-H, et al. The efficacy of tranexamic acid in reducing blood loss in total shoulder arthroplasty. Medicine (Baltimore). 2017;96:e7880.
24. Liu F, Xu D, Zhang K, et al. Effects of tranexamic acid on coagulation indexes of patients undergoing heart valve replacement surgery under cardiopulmonary bypass. Int J Immunopathol Pharmacol. 2016;29:753–8.