The Efficacy of Tranexamic Acid in Primary Total Shoulder Arthroplasty: A Systematic Review and Meta-Analysis of Level I Randomized Controlled Trials

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INTRODUCTION: Tranexamic acid (TXA) is commonly used during hip and knee arthroplasty procedures to reduce perioperative blood loss, however its role in total shoulder arthroplasty is still being established. Although prior studies have attempted to synthesize the available data regarding the efficacy of TXA in total shoulder arthroplasty, all have incorporated level III studies, and none have exclusively analyzed high-quality randomized controlled trials (RCTs). Given the difficult and sensitive nature of obtaining data in the perioperative period, the inclusion of low-quality retrospective studies calls the accuracy and validity of this reported data into question. There is significant value in limiting meta-analysis to high quality studies appropriate for treatment recommendation, and therefore the purpose of this study was to systematically review and synthesize the available level I evidence regarding the impact of TXA on the reduction of blood loss, transfusion rate, and early postoperative outcomes in patients undergoing total shoulder arthroplasty.

METHODS: A systematic review of the PubMed Central, MEDLINE, Embase, and Scopus databases from inception through April 2023 was performed to identify level I RCTs examining the use of TXA at the time of primary reverse or anatomic total shoulder arthroplasty. Studies were included if they met the following inclusion criteria: 1) regarded clinical outcomes of TXA use in patients undergoing primary reverse or anatomic total shoulder arthroplasty, 2) were of level I evidence, 3) included a non-TXA control, and 4) had available text written in the English language. Studies were excluded if they 1) were systematic reviews/meta-analyses, letters to the editor, elemental analyses, or case reports, and 2) were of level II-V evidence. Dichotomous outcomes were pooled into risk ratios (RR) whereas continuous outcomes were pooled into weighted mean differences (MD) using random effects meta-analysis.

RESULTS: Database searching identified 397 studies, of which 5 were deemed eligible for inclusion in our study. All included studies were double-blinded, placebo-controlled, RCTs of level I evidence. Among included studies, a total of 435 patients (219 TXA, 216 control) were identified. The weighted mean age of the TXA cohort was 68 years (range, 67-72), and 122 of the patients were female (55.7%). The weighted mean age of the control cohort was 68 years (range, 65-73), and 116 of the patients (53.7%) were female. The total dose of TXA was 2g in three studies, 1g in one study, and weight-based (20 mg/kg total) in one study. The route of administration was intravenous in four studies, and topical in one. Control patients received a normal saline placebo in all studies. Hematologic outcomes were significantly better among the TXA cohort, including lower 24-hour drain output (MD [95% CI], -112.70 mL [-152.75, -72.66]; p < 0.001), lower pre- to postoperative change in hemoglobin (MD [95% CI], -0.68 g/dL [-0.97, -0.39]; p < 0.001), and less total blood loss (MD [95% CI], -249.56 mL [-347.60, -151.52]; p < 0.001) (Figure 1). Postoperative Visual Analog Scale for pain (VAS-Pain) scores were lower in the TXA group, but not significantly (MD [95% CI], -0.46 [-1.11, -0.19]; p = 0.17) (Figure 2). No difference in operative time (MD [95% CI], -2.90 [-8.13, 2.33]; p = 0.28) or hospital length of stay (MD [95% CI], -0.06 [-0.32, 0.20]; p = 0.65) was observed between cohorts. Postoperative blood transfusion was required in 3/219 TXA patients (1.4%) and 7/216 control patients (3.2%) (RR [95% CI], 0.40 [0.11, 1.45]; p = 0.16). Overall, 1 adverse event (0.46%), a syncopal fall treated with fluids, was reported in the TXA cohort. Among the control cohort, 3 adverse events (1.4%) including 1 skin hypersensitivity reaction, 1 non-ST segment elevation myocardial infarction, and 1 deep vein thrombosis were reported. No other thromboembolic events were reported in either cohort in any study. Pooled analysis revealed no difference in the risk of postoperative complications between groups (RR [95% CI], -0.01 [-0.03, 0.02]; $l^2 = 0\%$; p = 0.58). **DISCUSSION AND CONCLUSION:**

Among patients undergoing primary total shoulder arthroplasty, compared with placebo control, perioperative TXA reduces drain output, change in hemoglobin levels, and total blood loss without increasing the risk of adverse events or loss of operative time. TXA is safe, effective, and may be a useful adjunct in primary total shoulder arthroplasty procedures.

A) 24 hour/POD 1 Drain Output (mL)

		IXA		Co	ontrol			Mean Difference	M	ean Difference	
Study or Subgroup	Mean [mL]	SD [mL]	Total	Mean [mL]	SD [mL]	Total	Weight	IV, Random, 95% CI	IV,	Random, 95% CI	
Gillespie 2015	110	104	56	170	128	55	27.5%	+60.00 [+103.43, -16.57]	-		
Pauzenberger 2017	50	88	27	170	183	27	16.3%	-120.00 [-196.59, -43.41]			
Vara 2017	153	89	53	294	130	49	27.4%	-141.00 [-184.58, -97.42]			
Cunningham 2021	94	72	31	226	87	29	28.7%	-132.00 [-172.56, -91.44]			
Total (95% CI)			167			160	100.0%	-112.70 [-152.75, -72.66]	-		
Heterogeneity: Tau* =	1026.68; Chi	= 8.18, dt	= 3 (P	= 0.04); I* = 6	3%				1000 100	-	a
Test for overall effect.	Z= 5.52 (P <	0.00001)							-200 -100	TXA Control	0 200

B) Pre- to Postoperative Change in Hemoglobin (g/dL)

		TXA		Ce	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [p/dL]	SD [g/dL]	Total	Mean [g/dL]	SD [gidL]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Gillespie 2015	1.7	1.7	56	2.6	1.4	55	25.1%	-0.90 [-1.48, -0.32]	
Vara 2017	3.3	1.2	53	3.9	1.1	49	42.2%	-0.60 [-1.05, -0.15]	
Cunningham 2021	1.7	1	31	2.3	1	29	32.8%	-0.60 [-1.11, -0.09]	
Total (95% CI)			140			133	100.0%	-0.68 [-0.97, -0.39]	•
Heterogeneity: Tau*:	= 0.00; Chi# = 0	77, df = 2 (P = 0.6	B); I*= 0%					
Test for overall effect	Z= 4.57 (P < 0	0.00001)							-1 -0.5 0 0.5 1 TXA Control

C) Total Blood Loss (mL)

		TXA		C	ontrol			Mean Difference		Mea	n Differe	ence	
Study or Subgroup	Mean [ml.]	SD [mL]	Total	Mean [mL]	SD [mL]	Total	Weight	IV, Random, 95% CI		IV, Ra	ndom, 9	/5% CI	
Pauzenberger 2017	871	472.8	27	1,248.2	550.2	27	11.9%	-377.20[-650.83, -103.57]		•			
Vara 2017	1,122.4	411.6	53	1,472.6	475.4	49	26.5%	-350.20 [-523.40, -177.00]	_	•			
Cvetanovich 2018	1,100.9	367.4	52	1,274.5	460	56	31.3%	-173.60 [-330.08, -17.12]		-	_		
Cunningham 2021	550	340	31	740	290	29	30.3%	-190.00 [-349.58, -30.42]		-	-		
Total (95% CI)			163			161	100.0%	-249.56 [-347.60, -151.52]		٠			
Heterogeneity: Tau ^a = Test for overall effect	1621.55; ChP Z = 4.99 (P < 0	'= 3.57, df 0.00001)	= 3 (P =	0.31); I ^a = 16	36				-500	-250	XA Co	250 ntrol	500

A) Postoperative VAS-Pain Score

		TXA		Co	ontrol	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Pauzenberger 2017	1.3	0.7	27	2	1.4	27	65.5%	-0.70 [-1.29, -0.11]	
Cunningham 2021	4	1.8	31	4	2	29	34.5%	0.00 [-0.97, 0.97]	+
Total (95% CI)			58			56	100.0%	-0.46 [-1.11, 0.19]	
Heterogeneity: Tau* =	0.08; CI	hi ^z = 1	.47, df	= 1 (P =	0.23	3); F= 3	2%		
Test for overall effect:	Z=1.38	(P =	0.17)						TXA Control

B) Operative Time (min)

	1	TXA		Ce	ontrol			Mean Difference		1	Mean Differ	rence	
Study or Subgroup	Mean [min]	SD [min]	Total	Mean (min)	SD [min]	Total	Weight	IV, Random, 95% CI		D.	, Random,	95% CI	
Vara 2017	100	16	53	104	22	49	48.4%	-4.00 [-11.52, 3.52]				-	
Cvetanovich 2018	101.1	21.4	52	102.7	21.6	56	41.5%	-1.60 [-9.71, 6.51]		_	-		
Cunningham 2021	83	31	31	86	34	29	10.0%	-3.00 [-19.50, 13.50]	-		•		
Total (95% CI)			136			134	100.0%	-2.90 [-8.13, 2.33]		-	-		
Heterogeneity: Tau*: Test for overall effect	= 0.00; Chi# = 0 Z = 1.09 (P = 0	.18, df = 2 ().28)	P = 0.9	1); I ^a = 0%					-20	-10	TXA CI	10 ontrol	20

C) Hospital Length of Stay (days)

	and a second	TXA		Co	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [days]	SD [days]	Total	Mean [days]	SD [days]	Total	Weight	IV, Random, 95% CI	 IV, Random, 95% CI
Vara 2017	2.3	0.9	53	2.5	1	49	48.8%	-0.20 [-0.57, 0.17]	
Cvetanovich 2018	1.8	1	52	1.8	1.2	56	38.7%	0.00 [-0.42, 0.42]	· · · · · · · · · · · · · · · · · · ·
Cunningham 2021	5.1	1.8	31	4.8	1	29	12.5%	0.30 [-0.43, 1.03]	· · · ·
Total (95% CI)			136			134	100.0%	-0.06 [-0.32, 0.20]	-
Heterogeneity: Tau ² =	0.00; Chi# = 1.	56, df = 2 (P	= 0.46); I [#] = 0%					1 10 10 10
Test for overall effect	Z = 0.45 (P = 0	.65)							-1 -0.5 0 0.5 1