1 Hemostatic Effect and Safety of TXA: An Umbrella Review

- 3 Short Title: Hemostatic Effect and Safety of TXA
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22 Abstract

Aim: To evaluate the hemostatic effect and safety of TXA.

24 Methods: Meta-analyses were retrieved from databases. Risk ratios (RR), odds ratios

(OR), weighted mean difference (WMD), standard mean difference (SMD) and 95%
confidence intervals (CI) were extracted to compare the effeteness of TXA in
reducing TBL, transfusion rate, Hb drop, mortality, DVT, PE.

Results: In total, 136 trials (396 comparisons) including 17 kinds of surgeries were 28 retrieved. The evidence for TXA using in total knee arthroplasty (TKA), total hip 29 arthroplasty (THA), postpartum bleeding, intertrochanteric fractures, orthopaedic 30 surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, cardiac surgery, 31 menstrual bleeding, plastic surgery, myomectomy, nasal surgery was assessed as 32 possible for the association of reducing TBL. The evidence for TXA using in TKA, 33 34 THA, postpartum bleeding, orthopaedic surgery, shoulder arthroplasty was assessed as probable for the association of reducing transfusion rate. The evidence for TXA 35 using in liver surgery, spinal surgery, hip fracture surgery, cancer, cardiac surgery was 36 considered to be possible for the association of reducing transfusion rate. The 37 38 evidence for TXA using in intertrochanteric fractures, orthopaedic surgery, hip fracture surgery was assessed as probable for the association of reducing Hb drop. 39 The evidence for TXA using in TKA, THA, postpartum bleeding, shoulder 40 arthroplasty was considered to be possible for the association of reducing Hb drop. 41 The evidence for TXA using in trauma, gastrointestinal bleeding was assessed as 42 probable for the association of reducing mortality. 43

44 **Conclusion:** This umbrella review indicated that TXA was regarded as effective to 45 reduce TBL, transfusion rate, Hb drop, mortality, and did not increase the incidence of 46 DVT and PE. However, more convincing evidence should be provided to further 47 clarify the level of efficacy and safety of TXA.

49 Introduction

50 Antifibrinolytic drugs have been widely used in obstetrics and gynecology surgery, 51 cardiac surgery, trauma, hip and knee replacement and other fields to reduce 52 perioperative bleeding and blood transfusion.¹

Among them, tranexamic acid (TXA) is the most common type used in surgery, andits main mechanism has been deeply studied.

Fibrinolysis is related to the decomposition of fibrinolysis and the increase of vascular 55 permeability under physiological or pathological conditions, as well as the occurrence, 56 development and cure of fibrinolysis-induced reactions, bleeding symptoms and 57 allergic reactions.² TXA can inhibit the effect of fibrinolytic enzyme and show 58 hemostatic, anti-allergic and anti-inflammatory effects. (1) Anti-fibrinolytic enzyme 59 effect. Aminocycline can strongly adsorb (LBS), which is the lysine binding site of 60 61 fibrinolytic enzyme and plasminogen, and inhibit the binding of fibrinolytic enzyme and plasminogen to fibrin. Thus, the fibrinolysis induced by the fibrinolytic enzyme 62 was strongly inhibited. Also, in the presence of anti-fibrinolytic enzymes such as 63 macroglobulin 2 in serum, the anti-fibrinolytic effect of TXA was more obvious, and 64 the hemostatic effect was more significant.³ (2) Hemostatic effect. Abnormal 65 hyperactivity of the fibrinolytic enzyme will cause platelet agglutination inhibition 66 and coagulation factor decomposition. Mild hyperactivity first leads to the 67 decomposition of fibrin. Therefore, it is considered that in general bleeding, TXA can 68 inhibit fibrin decomposition and play a hemostatic role.⁴ (3) Anti-allergic and 69 anti-inflammatory effects. TXA can inhibit the production of kinin and other active 70 peptides (guinea pigs and rats) which cause vascular permeability enhancement, 71 allergy and inflammatory lesions.⁵Nowadays, there are many meta-analyses to study 72 the efficacy and safety of TXA in clinical events, such as trauma or surgical bleeding 73 in the brain, uterus and other organs rich in plasminogen activator. However, it is still 74 inconsistent whether TXA is effective and safe enough and whether it can be used in 75 all clinical applications. With the increase in the number of systematic reviews 76 available, a logical next step to provide decision-makers in healthcare with the 77 evidence they require has been the conduct of reviews of existing systematic reviews. 78 Syntheses of existing systematic reviews are referred to by many different names, one 79 of which is an umbrella review. An umbrella review allows the findings of reviews 80 relevant to a review question to be compared and contrasted. An umbrella review's 81 most characteristic feature is that this type of evidence synthesis only considers for 82 inclusion the highest level of evidence, namely other systematic reviews and 83 meta-analyses.⁶ Therefore, we summarized the results of existing meta-analyses and 84 comprehensively evaluated their quality. The purpose of this review is to explore the 85 efficacy and safety of TXA and to provide more options for the clinical application of 86 hemostatic drugs. 87

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89 Methods

90 Search strategy

91 This is an umbrella review (Systematic collection and evaluation of multiple 92 systematic reviews and meta-analysis of specific research topics). Two researchers 93 systematically searched published systematic reviews and meta-analyses evaluating 94 the hemostatic effect and safety of TXA from inception to Aug 17th, 2019. The 95 language was restricted to English. The databases we searched included Medline, 96 Embase, PubMed, The Cochrane Library and relative studies in referenceto retrieved 97 articles. We used the following keywords: "TXA" and "meta-analysis". Full text of 98 potentially qualified articles was screened by another two researchers respectively.

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100 Inclusion and exclusion criteria

Inclusion criteria: (1) meta-analyses of RCTs assessing hemostatic effect and safety of
 TXA; (2) meta-analyses of observational studies evaluating hemostatic effect and
 safety of TXA.

Exclusion criteria: (1) no meta-analysis; (2) studies on genetic polymorphisms related to TXA; (3) studies with incomplete or erroneous data; (4) meta-analyses in which endpoints of TXA was only a little part of the outcome; (5) the studies included in the meta-analysis were completely overlapping; (6) the endpoints of the meta-analysis were not of interest.

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110 Data extraction

Two authors reviewed the contents of the retrieved meta-analyses independently. Total 111 blood loss (TBL), Transfusion rate, Haemoglobin drop (Hb drop), deep venous 112 thrombosis (DVT), pulmonary embolism (PE) and mortality were extracted and 113 verified by a third author. The characteristics extracted were as follows: the first 114 author, year of publication, number of studies, intervention measures in experimental 115 group and control group, number of sample size, effect size (95%CI), meta-analyze 116 metric, heterogeneity and p-value. If a quantitative synthesis was done, we also 117 extracted the study-specific relative risk estimates (risk ratio, odds ratio, mean 118 difference, Std mean difference) together with the corresponding CI and the number 119 of cases and controls in each study for each risk factor. In the event of a dispute, a 120 121 third author would coordinate the settlement. In this umbrella review, all data were extracted from previously published studies, thus no patient consent and ethical 122 approval were required. 123

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125 Statistical analysis

126 For each meta-analysis, we estimated the effect size and its 95% CI with both fixed-effects and random-effects models. To compare the hemostatic effect and safety 127 of TXA more clearly, we unified the effect size as a forest plot. Between-study 128 heterogeneity was assessed by the I² metric. I² ranges between 0% and 100% and are 129 the ratio of between-study variance over the sum of the within-study and 130 between-study variances. Values exceeding 50% or 75% are usually judged to 131 represent large or very large heterogeneity, respectively. A p-value less than 0.05 was 132 judged to be significant evidence. The criteria used for evidence categorization were 133 134 showed in Table 1. Whenever more than one meta-analysis was conducted using the same endpoints, and the same study design and type of population, the most recent or 135 most exhaustive study was considered. Stata (version 13.0) was used for statistical 136

- 137 analysis and calculation.

Table 1

Convincing	Level 1a (high): concordance between meta-
	analyses of RCTs and meta-analyses of
	observational studies (any)
	Level 1b (low): meta-analyses of RCTs with
	results contrary to those from meta-analyses
	of observational studies (any)
Probable	Level 2a (high): meta-analyses of RCTs and
	prospective studies with no heterogeneity, no
	potential confounding factors identified, and
	agreement of results over time and among
	meta-analyses, including studies with
	different designs
	Level 2b (medium): meta-analyses of RCTs
	and prospective studies with no heterogeneity
	and no potential confounding factors
	identified
	Level 2c (low): meta-analyses of retrospective
	studies with no heterogeneity and no potential
	confounding factors identified
Possible	Level 3a (high): meta-analyses of RCTs and
	prospective studies lacking information on
	heterogeneity and potential confounding
	factors
	Level 3b (low): meta-analyses of retrospective
	studies or meta-analyses of any other study
	design with significant heterogeneity ($I2 >$
	50%) and potential confounding factors
Limited/contrasting	Level 4: Limited studies included in meta-
	analyses $(n = 3)$ or evident contrasting results
	from meta-analyses with the same level of
	evidence

Result

According to the retrieval strategy, 232 articles were initially obtained, of which 96 were excluded according to the type of articles by title evaluation. Through reviewing the abstract and full text, 136 studies (396 comparisons) ⁷⁻¹⁴² were finally included to compare the efficacy of TXA in the reduction of TBL, transfusion rate, Hb drop, mortality, DVT and PE as shown in Figure 1. The effect sizes of each meta-analysis and baseline characteristics for 136 meta-analyses of TXA related to TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, menstrual bleeding, plastic surgery, cardiac surgery, nasal surgery, gastrointestinal bleeding, trauma, liver surgery, cancer and myomectomy reported were shown in Table 2.

Table 2

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t el al	2014 27	Inflation TAA	Change - Cha	667-572		CMD	- 48.20(-199.24-00.00)	0' +L0'									
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First authors	Year	No. of studies	Experiment	Control	No. of cases/controls	Effect size(95%CI)	Meta-analyse metric	Effect size(95%CI)2	²	P Val
Hb drop										
Orthopedics										
TKA										
Nu et al	2014	12R	IV and topical TXA	Placebo	NA		SMD	-0.78(-1.070.50)	81,3	< 0.01
loseph et al		5R 4CC	Topical TXA	Placebo	748/657	181	SMD	-0.78(-0.95,-0.60)	NA	< 0.01
Guo et al	2018		Oral TXA	Placebo	260/255	181	SMD	-0.94(-1.12,-0.75)	80.3	<0.01
Zhang et al		2R,1RC	Oral TXA	Control	1169/981		WMD	-0.80(-0.88,-0.71)	0	<0.01
ietal	2018		Oral TXA	Placebo	307/301		WMD	-0.49(-0.70,-0.29)	55.9	NA
						1				
.ietala	2017	2R 4B 2RC	Oral TXA	Placebo	73/66 328/354		WMD	-1.14(-1.890.40)	37.5	<0.01
Veng et al			IV/topical TXA	Placebo				-0.74(-1.19,-0.29)	84.8	
Chen et al	2013		Topical TXA	Normal saline	NA		WMD	-0.63(-0.96,-0.31)	68.2	0.02
Panteli et al	2013		Topical TXA	Normal saline	99/99		WMD	-0.94(-1.24,-0.65)	0	<0.01
Zhang et al	2014		Topical TXA	Placebo	149/150	1	WMD	-0.71(-1.12,-0.30)	71	<0.01
Chen et al	2016	8R	Topical TXA	Placebo	419/319		WMD	-0.66(-0.81,-0.52)	41	< 0.01
Tian et al	2017	2RC	TXA	Placebo	290/221	1-8-1	WMD	-0.52(-0.79,-0.25)	62	<0.01
Zhang et al a	2017	4R	TXA and drain-clamping	Drain-clamping	179/179	141	WMD	-0.87(-1.040.70)	0	< 0.01
Liac et al a	2018	5R	TXA and drain-clamping	Drain-clamping	274/229		WMD	-0.99(-1.29,-0.69)	72.7	<0.01
Zhang et al b		1R,1RC	TXA and drain-clamping	Placebo	60/60	1- 1 -1	WMD	-1.50(-1.79,-1.21)	NA	<0.01
liac et al b	2018		TXA and drain-clamping	Placebo	60/60		WMD	-1.50(-1.791.21)	NA	<0.01
Tao et al p	2010	IR	TAA and drain-clamping	Placebo	60/60	100000	WIND	-1.50(-1.79,-1.21)	NA	<0.01
(iong et al	2018		IV and topical TXA	IV TXA	296/295	1	WMD	-0.56(-0.93,-0.19)	90	<0.01
Vang et al	2017		IV and topical TXA	IV/topical/placebo	542/638		WMD	-0.81(-1.91,-0.42)	89.7	< 0.05
Chen et al		4R,3P	IV TXA	Topical TXA	291/295	H-8-	WMD	-0.42(-0.89,0.05)	94	0.08
vleena et al	2017	7R	IV TXA	Topical TXA	301/305		WMD	-0.50(-0.96,-0.04)	94	0.03
Fu et al	2016	7R	IV TXA	Topical TXA	346/293		WMD	-0.35(-0.78.0.09)	93.6	0.12
Dai et al		9R	IV TXA	Topical TXA	NA	10.	WMD	-0.20(-0.54.0.14)	90	0.24
Wang et al	2014		IV TXA	Topical TXA	NA		WMD	-0.43(-1.11,0.25)	95	0.22
Chen et al a	2014		IV TXA		491/495		WMD		93	0.19
				Topical TXA			WMD	-0.18(-0.46,0.09)	93	0.19
Wang et al	2016	IDR	IV TXA	Topical TXA	692/679		UNIND	-0.15(-0.39,0.10)	86	0.24
THA										
Chen et al	2016	5R, 6P	Topical TXA	Placebo	822/774	H#1.	SMD	-0.66(-0.91,-0.41)	81	<0.01
Vang et al	2014	1R, 3P	Topical TXA	Placebo	388/413		WMD	-0.86(-1.32,-0.39)	89	<0.01
hu et al	2017		TXA	Placebo	224/175		WMD	-10.81(-14.03,-7.58)	48	<0.01
	LOTT	101	1501	Tideebo	LEGINO		TIME	10.01(14.00,11.00)	40	-0.01
Sun et al	0045	2R,1RC	IV TXA	Topical TXA	459/404	100	WMD	-0.29(-0.68,0.10)	87	0.14
ietal							WMD			
		2R, 2P	IV TXA	Topical TXA	697/540			-0.24(-0.34,-0.15)	91.7	<0.01
Chen et al b		3R	IV TXA	Topical TXA	241/241	+	WMD	-0.30(-0.68,0.08)	0	0.12
Zhang et al a		5R	IV and topical TXA	IV TXA	662/547		WMD	-0.56(-0.78,-0.34)	69	<0.01
Liu et al	2017	3R	IV and topical TXA	IV TXA	145/152	H.	WMD	-0.11(-0.40.0.17)	78.1	0.44
Zhang et al	2017	4R	IV and topical TXA	IV TXA	202/210	1	WMD	-0.43(-0.75,-0.10)	66	0.01
Zhang et al b	2017	4R	IV and topical TXA	Topical TXA	612/391		WMD	-1.06(-1.30,-0.82)	75	<0.01
THA/TKA										
Liu et al	2019	3R.1RC	IV TXA	IV aminocaproic acid	755/959	-	WMD	-0.18(-0.290.07)	0	< 0.01
							WMD			<0.01
(uo et al	2018	1P,3RC	IV TXA	Placebo	434/307		WMD	-0.88(-1.31,-0.44)	NA	<0.01
Han et al	2018		IV TXA	Oral TXA	340/334	-	SMD	0.03(-0.12,0.18)	0	0.67
Vang et al	2018	4R.2RC	IV TXA	Oral TXA	384/1650	-	WMD	-0.09(-0.20.0.02)	0	0.12
ietal b	2017		IV TXA	Oral TXA	80/74		WMD	-0.14(-0.47,0.19)	0	0.41
Chen et al		4R.2RC	IV TXA	Oral TXA	3083/741		WMD	-0.06(-0.13,0.01)	39	<0.01
Zhang et al		3R	IV TXA	Oral TXA	220/214		WMD	0.01(-0.09.0.10)	0	0.88
(ie et al	2017		IV TXA	Topical TXA	NA		WMD	-0.33(-0.58,-0.07)	92	0.01
	2017			IV TXA	221/222		WMD		92	0.01
Shang et al			IV and topical TXA					-0.41(-0.73,-0.08)		
Li et al	2017		IV and topical TXA	IV TXA	243/244		WMD	-0.51(-0.83,-0.18)	84	<0.01
rang et al	2017	3R	IV and topical TXA	IV/Topical TXA	261/262		WMD	-0.44(+0.79,+0.09)	88	0.01
Intertrochanteric fracture:	s									
Wang et al	2017	4R	IV/Topical TXA	Saline/none	254/260		WMD	-0.31(-0.430.18)	0	<0.01
Orthopaedic surgery										
Amer et al	2017	5R	TXA	Placebo	NA		WMD	-0.76(-1.02,-0.50)	32	<0.01
	2011					1 10779				-0.01
Ob and does and have 1										
Shoulder arthroplasty										
(uo et al		2R,3RC	IV TXA	Placebo	316/310	H H H	WMD	-0.64(-0.81,-0.46)	0	<0.01
Kirsch et al	2017		IV/Topical TXA	Placebo	319/313	3 -8 4 (WMD	-0.64(-0.84,-0.44)	0	< 0.01
le et al	2017	2R,2RC	IV/Topical TXA	Placebo	292/345	H#H	WMD	-0.53(-0.83,-0.23)	61.6	<0.01
ru et al		1R,1RC	TXA	Placebo	159/131		WMD	-0.43(-5.57,4.72)	39	0.87
	2011					1000				0.01
Hip fracture surgery										
	0045			Discussion in a second second	1001105		110.00	4.00/ 4.04 0.00		-0.0
Zhang et al	2017	зк	IV TXA	Placebo/normal saline	102/105		WMD	-1.36(-1.84,-0.88)	0	<0.01
Postpartum bleeding										
Vang et al	2015	6R	TXA	Placebo	707/720		WMD	-0.87(-1.300.45)	97	< 0.01
Simonazzi et al	2016	6R	IV TXA	Placebo/none	NA		WMD	-0.61(-1.040.18)	NA	<0.01
	20.0									-0.01

First authors	Year	No. of studies	Experiment	Control	No. of cases/controls	Effect size	(95%CI)	Meta-analyse metric	Effect size(95%CI)2	1 ²	P Value
Mortality											
Trauma						1					
El-Menyar et al	2018	2R	TXA	No TXA	NA	-		OR	0.49(0.28,0.85)	0	NA
Keret al	2015	2R	TXA	Placebo	10180/10187			RR	0.90(0.85,0.97)	0	< 0.01
Weng et al	2019	3R	IV TXA	Placebo	327/330	-		RR	0.64(0.41,1.00)	0	0.05
Liver surgery											
Molenaar et al	2007	3R	TXA	Placebo	83/78		4	OR	0.57(0.18,1.79)	NA	0.33
Gurusamy et al	2011	3R	ТХА	Placebo	83/56		-	RR	0.55(0.17,1.76)	14	0.31
Gastrointestinal bleeding											
Bennett et al	2014	8R	TXA	Placebo/no treatment	851/850	18-1		RR	0.60(0.42.0.87)	0	<0.01
Cardiac surgery											
Ngaage et al	2010	8R,1RC	IV/Topical TXA	Placebo	1473/2045	1		OR	0.80(0.48,1.34)	NA	0.4
Hutton et al	2012	NA	TXA	Aprotinin	NA	1.00		OR	0.71(0.50,0.98)	NA	NA
Howell et al	2012	23R	TXA	Placebo	3048/4887	-	+	RR	1.48(0.84,2.58)	NA	NA
Takagi et al	2009	9R	TXA	Aprotinin	1415/1419	-		RR	0.68(0.47,0.99)	0	0.05
Henry et al	2009	19R	TXA	Placebo	922/880			RR	0.55(0.24,1.25)	0	>0.05
Umscheid et al	2007	5R,1RC	TXA	Placebo	747/550	+		RR	0.55(0.26,1.18)	NA	0.85
Brown et al	2007	18R	TXA	Placebo	NA			RR	0.67(0.33,1.37)	NA	0.276

First authors	Year	No. of studies	Experiment	Control	No. of cases/controls	Effect size(95%CI)	Meta-analyse metric	Effect size(95%CI)2	12	P Value
DVT										
Orthopedics										
TKA										
Gandhi et al a	2013		IV TXA	Placebo	221/186		OR	1.03(0.44.2.42)	NA	0.95
He et al		3R,2RC,1P	IV TXA	Placebo	245/262	1	OR	1.02(0.25.4.16)	0	0.98
rang et al	2012		TXA	Placebo	361/361			0.75(0.34.1.67)	0	0.48
in et al c		7R	IV and topical TXA	Control	NA		RR	0.74(0.29.1.92)	0	>0.05
Shemshaki et al	2015	14R	IV and topical TXA	Normal saline	1088/968		RR	0.84(0.60.1.19)	0	0.33
Wu et al		29R	IV and topical TXA	Placebo	1057/1044		RR	0.95(0.67.1.44)	0	>0.05
Weng et al	2016	3R,1CC,1RC	IV/lopical TXA	Placebo	266/306		RR	0.68(0.24.1.90)	0	0.46
Vei et al a	2015	21R	ft/topicational TXA	Salineinone	779/808		RR	0.57(0.26.1.24)	0	0.15
Zhang et al	2014	NA	Topical TXA	Placebo	NA	+	RR	0.83(0.35,1.98)	NA	0.68
Chen et al	2015	78	Topical TXA	Placebo	652/557		RR	0.87(0.41.1.86)	D	0.73
Zhang et al	2017	39	TXA and drain-clamping	Drain-clemping	179/179	-	RR	2.33(0.35.15.46)	0	0.38
and a second			transfer and the second s	and a start prog				2100(01031101-03)		
Chen et al a	2016	60	IV TXA	Topical TXA	322/318		OR	0.91(0.37.2.22)	0	0.83
Mietal	2017	40	IV and topical TXA	IV TXA	231/232			0.33(0.03.3.22)	0	0.34
Kiong et al	2018	6R	IV and topical TXA	IV TXA	351/350		RR	1.01(0.14.7.12)	0	0.99
in et al a	2016		IV and topical TXA	IV TXA	NA			0.45(0.10.1.98)	0	>0.00
		18		Topical TXA	NA			0.45(0.10.1.36)	NA	>0.01
in et al b			IV and topical TXA		NA 591/588	-				
Chen et al		9R,6P	IV TXA	Topical TXA		(1 • ••)	RR	1.17(0.52.2.50)	0	0.68
Meena et al	2017	3R	IV TXA	Topical TXA	472/476		RR	0.44(0.12.1.69)	0	0.23
uli et al		16R	IV TXA	Topical TXA	627/659			2.00(0.67.5.25)	0	0.21
Wang et al	2016	7R	IV TXA	Topical TXA	310/309		RR	0.93(0.42.2.08)	0	0.86
THA										
Yoon et al a	2018	NA	IV TXA single	Placebo	NA	· · · ·	OR	1.57(0.64.3.83)	NA	NA
(pon et al b	2018	NA	IV TXA multiple	Placebo	NA		OR	0.91(0.34.2.46)	NA	NA
Sandhi et al b	2013		IV TXA	Placebo	187/157		OR	1.07(0.39.2.91)	NA	0.9
Zhou et al		198	IV TXA	Salineinone	539/535		OR	0.73(0.36.1.49)	NA	0.39
Xu et al	2015		Topical TXA	Placebo	351/294		OR	1.64(0.39.6.97)	0	0.5
			Topical TAA			-				
Yoon et al c	2018	NA	Topical TXA	Placebo	NA		OR	0.59(0.20.1.78)	NA	NA
2hu et al	2017		TXA	Placebo	685/680		OR	1.14(0.50.2.62)	0	0.75
Veietal b	2015	15R	IV/topical/oral TXA	Salineinone	413/415	-	RR	0.63(0.20.2.01)	0	0.43
Chen et al b	2016		IV TXA	Topical TXA	191/192			4.35(0.91.20.00)	0	0.07
Fu et al	2016	12R	IV TXA	Topical TXA	555/613		RR	1.16(0.57.2.38)	0	0.68
Chen et al	2015	3R, 3P	IV TXA	Topical TXA	1355/348	- 1 -	RR	0.84(0.28,2.50)	D	0.16
Lietal	2016	3R, 2P	IV TXA	Topical TXA	731/574		RR	0.92(0.33.2.50)	D	0.7
Llu et al	2017	65	IV and topical TXA	IV TXA	370/377	4.0	RR	1.23(0.38,4.00)	D	0.72
Zhang et al	2017		IV and topical TXA	IV TXA	471/479		RR	1.22(0.52.2.89)	D	0.65
cruing at an			Te and topped they		41.0419	-		The Contractory		0.00
THA/TKA										
Ho et al	2003		IV TXA	Placebo	317/269		OR	0.98(0.45.2.12)	NA	NA
no et al	2003	118	IV DAA	Placebo	31//269		UR	0.96(0.45.2.12)	NA	nos.
			1. martin						1.	
Han et al	2018		IV TXA	Oral TXA	3117/721		OR	1.72(0.57.5.26)	0	0.33
Xie et al	2017		IV TXA	Topical TXA	NA			0.50(0.24.1.01)	0	0.05
Shang et al	2016		IV and topical TXA	IV TXA	301/302	- H		0.84(0.26.2.70)	0	0.76
Zhang et al	2016	3R	IV and topical TXA	IV TXA	212/212		RR	1.00(0.28.3.63)	0	1
Intertrochanteric fractures										
Jiang et al	2019	48	IV/lopical TXA	Saline/placebo	245/255		RR	0.81(0.24.2.75)	D	NA
Zhu et el	2018		Topical TXA	Saline/none/placebo	317/329			0.94(0.41.2.19)	55	NA
			repiter thet	and a strategy access				ana deservation and		
Spinal surgery										
Yuan et al	2019		IV TXA	Placebo	NA		OR	0.61(0.20.1.81)	NA	NA
						1				
Hui et al		18R,12RC	IV TXA	Placebo	1075/1081			0.64(0.17.1.74)	9	0.3
Zhang et al	2014		TXA	Placebo	238/233	H 	OR	1.01(0.06.16.07)	0	0.99
Yang et al	2013	7R	IV TXA	Placebo	242/237		RR	0.34(0.01.8.16)	NA	0.5
Shoulder arthroplasty										
Sun et al	2017	2R.2RC	IV/Topical TXA	Placebo	250/234	-	OR	1.15(0.33.4.00)	0	0.83
Kup et al	2018	3R.3RC	IV TXA	Placebo	343/337		RR	0.31(0.01.7.40)	NA	0.47
and a second			10000		1000000		2010			1000
Trauma										
El-Menyar et al	2018	28	TXA	No TXA	NA	1.0	OR	0.74(0.27,2.07)	0	NA
er menyer et el	2010		From .	100 1001		1		(0.1 *(0.2 · (2.0 f))		1993
Other orthopaedic surgery										
other orthopaedic surgery	0005	100	White	Discourse						0.70
Zufferey et al	2006	18R	TXA	Placebo	524/451	1	OR	0.93(0.65.1.66)	NA	0.78
Amer et al	2017		TXA	Placebo	NA			2.55(0.94.7.00)	36	0.24
Franchini et al	2018		TXA	Placebo	NA	+	RR	1.07(0.76,1.50)	34	NA
Huang et al	2014	44R	TXA	Placebo	1376/1313	+	RR	1.11(0.69.1.79)	0	0.66
Postpartum bleeding										
Simonazzi et al	2016	9R	IV TXA	Placebo/none	1193/1172		RR	0.98(0.13.7.09)	NA	NA
Lietal	2017		IV TXA	Saline/none/glucose	2387/2360		RR	0.69(0.20.2.39)	0	0.55
leesen et al	2014		IV/lopical TXA	Placebo	781/797	and a second	RR	1.01(0.33.3.12)	0	0.98
icvikova et al	2014		TXA	Placebolno treatment	1517/1495	1		0.98(0.14.5.78)	NA	0.98
Novikova et al Mouse et al	2015		TXA	Placebo/no treatment	1517/1495	1			NA	0.98
								2.00(0.19,21.57)		
Topsoee et al	2016	10R	TXA	Placebo/no treatment	1162/1150	1	RR	0.99(0.14.7.01)	NA	NA
Liver surgery										
Molenaar et al	2007		TXA	Placebo	83/78			0.56(0.07.4.36)	NA	0.58
Surusamy et al	2011		TXA	Placebo	103/76		RR	2.20(0.38.12.64)	0	0.38
Keretal	2015		TXA	Placebo	10180/10187		RR	0.95(0.62, 1.47)	0	0.83
	20.0						100		Ť	
Gastrointestinal blasting			1000	I second a second second second second	522/526		RR	2.32(0.60.8.89)	0	0.22
Gastrointestinal bleeding	2014									
Gastrointestinal bleeding Bennett et al	2014	3R	TXA	Placebo/no treatment	022/028			2.32(0.00.0.03)	0	0.22
Sennett et al	2014	3R	TXA	Placebo/no treatment	022/028	-		2.32(0.00,0.03)		0.22
Gastrointestinal bleeding Sennett et al Cardiac surgery Jmscheid et al	2014		тха	Placebo/no treatment	263/231		RR	0.84(0.30.2.30)	NA	

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First authors	Year	No. of studies	Experiment	Control	No. of cases/controls	Effect size(95%CI)	Meta-analyse metric	Effect size(95%CI)2	1 ²	P Value
PE								-		
Orthopedics										
ТКА										
Yang et al	2012	5R	TXA	Placebo	174/175		OR	0.65(0.18,2.33)	0	0.5
Wu et al	2014	16R	IV and topical TXA	Placebo	705/706	-	RR	0.45(0.14,1.42)	0	>0.05
Weiet al a	2015	21R	IV/topical/oral TXA	Saline/none	779/808		RR	1.63(0.43,6.12)	0	0.47
Zhang et al	2014		Topical TXA	Placebo	NA	H	RR	0.54(0.10.2.89)	NA	0.46
Chen et al	2016	7R	Topical TXA	Placebo	677/582		RR	0.66(0.09,4.80)	0	0.68
Kiong et al	2018		IV and topical TXA	IV TXA	NA	1 1 .	RR	0.33(0.01,7.91)	NA	0.49
Wang et al	2016	1R	IV TXA	Topical TXA	69/62		RR	1.79(0.17,20.00)	NA	0.63
THA										
Zhou et al	2013	3R	IV TXA	Saline/None	539/535	-	OR	1.95(0.34,11.06)	NA	0.45
Yoon et al a	2018		IV single	Placebo	NA		OR	1.09(0.28.4.19)	NA	NA
Yoon et al b	2018		IV multiple	Placebo	NA		OR	1.23(0.25.6.07)	NA	NA
Yoon et al c	2018		Topical TXA	Placebo	NA	1	OR	0.84(0.18.3.99)	NA	NA
Wei et al b	2015		IV/Topical/Oral TXA	Saline/none	393/395	· •	RR	1.65(0.40,6.82)	0	0.49
Chen et al	2016	38	IV TXA	Topical TXA	241/241	•	OR	0.33(0.01,8.32)	0	0.5
Chen et al	2016		IV TXA	Topical TXA	1281/224	-	RR	0.90(0.09.9.09)	0	0.21
Trauma										
Ker et al	2015	2R	TXA	Placebo	10180/10187	+	RR	1.01(0.73,1.41)	NA	0.93
								1		
Intertrochanteric fractures										
Jiang et al	2019	4R	IV/topical TXA	Saline/placebo	245/256	1	RR	0.64(0.25,1.62)	0	NA
Cardiac surgery										
Umscheid et al	2007	2R.1RC	TXA	Placebo	396/260		RR	0.32(0.07.1.56)	NA	NA

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According to the largest studies, the meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, menstrual bleeding, plastic surgery and nasal surgery reported significantly reduced TBL; the meta-analyses of TXA using for liver surgery and myomectomyreported reported that there was no significant difference in TBL; the meta-analyses of TXA using for cardiac surgery reported

significantly increased TBL. The meta-analyses of TXA using for TKA, THA, 170 postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, shoulder 171 arthroplasty, hip fracture surgery reported significantly reduced Hb drop; the 172 meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric 173 fractures, liver surgery, orthopaedic surgery, spinal surgery, hip fracture surgery, 174 175 cancer and cardiac surgery reported significantly reduced transfusion rate; the meta-analyses of TXA using for trauma, shoulder arthroplasty, gastrointestinal 176 bleeding, plastic surgery and myomectomy reported there was no significant 177 difference in transfusion rate. The meta-analyses of TXA using for TKA, THA, 178 postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, 179 shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding and cardiac 180 surgery reported there was no significant difference in DVT. The meta-analyses of 181 182 TXA using for TKA, THA, trauma, intertrochanteric fractures and cardiac surgery reported there was no significant difference in PE. The meta-analyses of TXA using 183 for trauma and gastrointestinal bleeding reported significantly reduced mortality; the 184 meta-analyses of TXA using for liver surgery and cardiac surgery reported there was 185 no significant difference in mortality as shown in Table 3. 186

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188 **Table 3**

First authors	Year	No. of studies	Experiment	Control	No. of cases/controls	Effect size(95	%0) Meta-analyse metric	Effect size(95%C0)2	7	P Value
TKA	2015		N and Inginal TXA	Normal solina	931/777		9940	-373 75(-504 41 -243 10)		40.01
Chemshaki et st THA Chen et e		218							98	
Dhan at a THA/TKA	2016	\$9, \$P	Topical TXA	Placebo	635-842	5.8.	WWD	-297.65(-371.68,-118.08)	71	-0.01
	2018	JR.1RC	AVE TOOL	To' aminocaprolic acid	750-959	.(*)	WWD	-116.21(-158.2474.10)	0	-0.01
Postperturn blending List al	2017	107	N 7365	Salno/nons/gl.xoso	2040/2048		WWD	146.32(-172.47, 118.17)	55	-0.01
identrochanteric fractures	2017	45	Interior Kal TAA	Salaciaore	254/250		WND	-131,48(-163,63 -98,35)	45.9	<0.01
nterfrochanteric fractures Vang et al Jver surgery Sunsemy et al Prthopaedic surgery taeng et al						-				
Sundarny et al Stithonaudic sunnery	2011	28	734	Placebo	35/30		SMC	-1.88(-10.18,9.23)	9	0.05
turrg et al loinal surgery fai et el	2014	288	TX4	Placetro	833853	1-8-1	7990	-408 33(-505 68,-318.97)	89	40.01
ha et el	2017	8R.6RC	IV TXA	Placebolito treatment	494/499	1.0.1	WIND	-310.86(-418.20,-205.52)	92	<0.01
Shoulder arthroplasty	2017	18,250	MTookal TXA	Placebo	250.234		WWD	172.16(.303.87.30.46)	72.9	0.01
iun et al 4p frecture surgery 2hang et al Denties sungery 2n mile et al	-	45				1.00				
Diang of al Certified surgery	2017		AVET VI	Placeborhormal salihe	128/137		WWD	277.33(334.74, 219.92)	78.0	-10.01
Carless et al Aenatruel bleeding	2005	108	TXA	Aprotinin	330/399		WIND	106.46(35.57,175.26)	NA	+0.01
kyant-Smith et a Hastic surgery	2015	58	TXA	Piecebo	496/159		WIND	-53.26(42.7043.10)	8	<0.81
Hastic surgery Aughs et al.	2016	41	N TAA	Seine	57.85		7270	-18.21(-23.84(-10.55)	47	40.01
	2017	49	V DA	Salte-tore						0.02
Nerg et al Resel surgery Yog et al					183/163		SNO	-1.51(-2.75,-0.28)	95.4	
Pinglet al	2019	9R	TXA	Placebo	316/292	•	Ainto	-72.65(-102.42,-44.85)	92	<0.61
Hb										
RA	2017	2R.150	Oral TAA	Contro	1109-901		9940	0.00(0.00,0.71)		10.01
harg stal NA										40.01
lang et al HATKA	2014	17, 34	Topical TXA	Placebo	355-413		WMD	-0.00(+1.32-0.36)	63	
	2018	28.1805	IV TXX	19 aminocaprois acid	755-939		WWD	-0.101-0.280.07)	0	40.81
o stoartum blaading Neng et al Intertrochanteric fractures	2015	59	TXA	Placebo	797/796		WWD	-0.87(-1.30,-0.45)	\$7	40.01
	2017	49	MiTopical TAA	Satrehore	254/250		7740	-0.31(-0.43,-0.18)	2	<0.01
Orthopaedic surgery										
Orthopsedic surgery oner at al Drouider enthropienty Disch at al	2017	58	TX4	Placebo	NA		WPAD	-0.76(-1.02,-0.50)	32	<0.01
Orsch et al Gestrecture surgery	2017	58	MTopical TXA	Placebo	319/313		WIND	0.64(0.84, 0.44)	9	<0.01
tip mechanis surgery Dang et al	2017	35	IV TXA	Placebolhormal saline	102/100		WIND	1.30(-1.54, 0.50)	0	-0.01
					-44	n-mana a	o seaso seaso			
Transfusion rate										
nka Chargistia THA	2017	2R.180	Oral TRA	NA	1283/1101		85	0.40(0.30.0.02)		-0.01
HA	2016	58.70	Topical TXA	Placebo	1893-871		OR	0.26(0.17.0.40)	45	<0.01
Chen et s THA/TKA						1103				
iso et al Postpartum blaading	2018	1R.1P.cRC	77 TAA	Placebo	591-129	•	OR	0.20(0.11.0.34)	NA	<0.01
	2017	99	IV DA	Salmeinsneiglassee	2045/2048	•	RR	0.31(0.19,0.51)	. 0	40.01
Rauma Ger et cl	2015	29	TXA	Placebo	10180/10187		RR	0.08/0.06(1.01)		0.19
ntertrochanteric fractures Stu 41 al	2018	75	Topical TXA	Salinemenablesebo	267/379		RR.	9,79(9,50,1,11)	55	+0.01
aver surgery										
aver eurgery buresamy et al Dittoposedic eurgery	2010	18	7304	Placebo	108/106	•1	RR	0.08(0.00,0.45)	NA.	+0.01
	2014	368	TXA	Placebo	1371/1278	•	RR.	0.51(0.46,0.65)	43	10.01
tpinal surgary full et al Rhoulder arthroplasty	2017	4R NRC	IV TAS	Patebolio treatment	277.0 M		OR	0.33(0.17,0.65)	19	<0.01
shoulder arthroplasty	2017	51		Placebo	319313	1	MR.	0.4500.10,1.09)		0.05
Sinch et al. Hip fracture surgery			N/Topical TRA			-				
Ferrow et al Dancer Vortroy et al	2016	ER.1RC	IV TXA	Pacacono heatmen/Salme	321/429	-	RR	0.54(0.35,0.85)	79	40.81
vioritroy et el	2017	78	TXA	Placebo	478/477		RR	0.52(0.34,0.80)	87	<0.01
Asstrointestinal bleeding	2014	25	TXA	Placebolito treatment	4551453		88	1.02(0.94,1.11)		0.61
Denties eargery Anschold of al	2007	10 100	754	Elercho.	1127/778			0.60(0.00.0.75)	NA	-0.01
Mastic surgery Auchy et al										
Aurphy et al Avenactomy	2016	38	IV TXA	Saine	73/70	•	RR	0.40(0.17,1.40)	0	0.18
iongrysy et al	2014	12	IN TAK	Placebo	50/50		- OR	1.2198.08.4.201	NA:	0.25
OVT										
KA Nu scel	2014	218	Al and a sector of the	Plepetro	1087/1044		89			
			N eno topical TXA					0.95(0.67,1.44)		>0.05
Diantal MATKA Sciel al	2017	NA	784	Placebo	655-650	1	OR	1 14(0 50,2 82)	9	0.75
to et al.	2013	118	IV TXA	Placebo	317.299		OR	0.08(0.46,2.12)	NA.	10
ostpertum bleeding	2017	218	IV THA	SalnehoneoLcose	2397/2360		88	0.69(0.20.2.29)		0.65
intertrochasteric fractures	2017	78			317.025				5	
hu et al Inthopenduc surgery			Topical TXA	Bailhernena/placebo		-		0.94(0.41,2.19)		NA.
	2014	48	7354	Placebo	1376/1313	-	RR	1.11(0.59,1.79)	. 9	0.65
lpinal surgary III et al Rhoulder arthroplasty	2017	HR.IZRC	17.738	Placebo	1075/1081		OR	0.54(0.17.1.74)		0.3
shoulder arthroplasty	2018	SIK SIKG	17.738	Placebo	313037		BR	0.3160.01,7.40)	NA	0.67
luci et el Jiver surgery										
Sanakerry et el Traunna	2011	59	TXA	Plazatio	100-76		RR	2.20(0.58,12.84)	.9	0.38
Conservy et al Trauma Car al cl Restrointestinal bleeding	2015	29	TXA	Placebo	10180(10187		RR	0.99(0.62,1.47)	9	0.83
	2014	35	TIGA	Placebolho treatment	022/026		RR	2.32(0.60,8.89)	0	0.22
lenties surgery	2007	180	744	Birroho	263/231			0 540 30 2 201	NA	
	2007	SRU	1.04	Paccoo	283(231	T		0.54(0.50,2.20)	TRA.	M
PE KA										
Celefala HA	2015	ZIR	Mitapice/oral TXA	Seline/sone	779/808	•	RR	1.53(0.43.5.12)	0	0.47
HA hourd	2013	31	IN TAA	SeineNore	539535		Off	1,95(0.34,11.03)	NA	0.45
		28	TXA		10180/10187		88	1.01(0.73,1.41)		0.93
	2015			Planetro					NA	
	2019	48	Fritopical TXA	Salnajpiacebo	245-256		RR	0.64(0.25,1.62)	9	NA
		2R.1R0	TXA	Placebo	396-260		RR	0.32(0.07,1.05)	NA	NA
	2007									
Interfrochasteric fractures lang et e Dertino sungery Unscheld et al	2007									
ntertrochanteric fractures lang at a Sentine surgery Jinscheid at al Mortality Teams										
hauma ier et al	2015	28	TXA	Placebo	10180/10187		Rt	0.90(0.85.0.97)	0	< 0.01
nbortrochasteric fractures lang at a Dentied surgery Inschald of al Mortality hearing laret al Jone surgery Sciencer 41 al		2R 38	TX4 TX4	Placebo Placebo	10190/10187 83/78		RR	0.90(0.05.0.97)	ə NA	<.0.01 0.83
nterforchasteric fractures lang et e Berties surgery Inscheld et al Mortality heame ier et al John surgery	2015									

However, considering all the effect sizes of the included studies, the results were controversial.

A summary of evidence from the retrieved meta-analyses of TXA is shown in Table 4. 192 The evidence for TXA using in TKA (combine administration vs single administration; 193 TXA vs placebo), THA (combine administration vs single administration; TXA vs 194 195 placebo), TKA/THA (combine administration vs single administration; TXA vs placebo), postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal 196 surgery, shoulder arthroplasty, hip fracture surgery, cardiac surgery, menstrual 197 bleeding, plastic surgery, myomectomy, nasal surgery was assessed as possible for the 198 association of reducing TBL. There was probably no association between TXA and 199 TBL in TKA (IV TXA vs topical/oral TXA), THA (IV TXA vs topical/oral TXA), 200 201 TKA/THA (IV TXA vs topical/oral TXA) and liver surgery.

- 202
- 203 **Table 4**
- 204

Level of	End point	S				
evidence	TBL	Transfusion	Hb drop	Mortalit	DVT	PE
		rate		у		
Convincing	-	-	-	-	-	-
Probable	-	Reducing	Reducing	Reducin	-	-
		transfusion	Hb drop	g		
		rate of	of	mortalit		
		TKA (TXA	intertroch	y of		
		vs placebo),	anteric	trauma,		
		THA (TXA	fractures,	gastroint		
		vs placebo;	orthopaed	estinal		
		combine	ic	bleeding		
		administrati	surgery,			
		on vs single	hip			
		administrati	fracture			
		on),	surgery			
		TKA/THA(
		combine				
		administrati				
		on vs single				
		administrati				
		on),				
		postpartum				
		bleeding,				
		orthopaedic				
		surgery,				
		shoulder				
		arthroplasty				
Possible	Reducing	Reducing	Reducing	-	-	-

TBL of	TBL of	Uh dron		
		Hb drop		
TKA	TKA/THA(of TV A (TV		
(combine	TXA vs	TKA(TX		
administr	placebo),	A vs		
ation vs	liver	placebo;		
single	surgery,	combine		
administr	spinal	administr		
ation;	surgery, hip	ation vs		
TXA vs		single		
placebo),	surgery,	administr		
THA	cancer,	ation),		
(combine	cardiac	THA(TX		
administr	surgery	A vs		
ation vs		placebo;		
single		combine		
administr		administr		
ation;		ation vs		
TXA vs		single		
placebo),		administr		
TKA/TH		ation),		
А		TKA/TH		
(combine		A(TXA		
administr		VS		
ation vs		placebo;		
single		combine		
administr		administr		
ation;		ation vs		
TXA vs		single		
placebo),		administr		
postpartu		ation),		
m		postpartu		
bleeding,		m		
intertroch		bleeding,		
anteric		shoulder		
fractures,		arthroplas		
orthopae		-		
dic		ty		
surgery,				
spinal				
surgery,				
shoulder				
arthropla				
sty, hip				
fracture				

Image: constraint of the second sec	surgery, cardiac surgery, menstrua bleeding, plastic surgery, myomect omy, nasal surgery No associati on with FKA(IV FXA vs opical/or al TXA), FHA(IV FXA vs opical/or al TXA), FKA/TH A(IV FXA vs opical/or al TXA), FKA/TH A(IV FXA vs opical/or al TXA), FXA vs	No association with TKA(comb ine administrati on vs single administrati on; IV TXA vs topical/oral TXA), THA(IV TXA vs topical/oral TXA), THA(IV TXA vs topical/oral TXA), TKA/THA(IV TXA vs topical/oral	No associatio n with TKA(IV TXA vs topical TXA), THA(IV TXA vs topical TXA), TKA/TH A(IV TXA vs topical TXA)	No associati on with liver surgery, cardiac surgery	No associati on with TKA, THA, TKA/TH A, postpartu m bleeding, intertroch anteric fractures, orthopae dic surgery, spinal surgery,	No associati on with TKA, THA, trauma, intertroch anteric fractures, cardiac surgery
--	--	--	---	---	---	--

Contrasting

206 The evidence for TXA using in TKA (TXA vs placebo), THA (TXA vs placebo; combine administration vs single administration), TKA/THA (combine administration 207 vs single administration), postpartum bleeding, orthopaedic surgery, shoulder 208 arthroplasty was assessed as probable for the association of reducing transfusion rate. 209 The evidence for TXA using in TKA/THA (TXA vs placebo), liver surgery, spinal 210 surgery, hip fracture surgery, cancer, cardiac surgery was considered to be possible for 211 the association of reducing transfusion rate. There was probably no association 212 between TXA and transfusion rate in TKA (combine administration vs single 213 administration; IV TXA vs topical/oral TXA), THA (IV TXA vs topical/oral TXA), 214 TKA/THA (IV TXA vs topical/oral TXA), trauma, intertrochanteric fractures, 215 gastrointestinal bleeding, plastic surgery, myomectomy. 216

The evidence for TXA using in intertrochanteric fractures, orthopaedic surgery, hip 217 fracture surgery was assessed as probable for the association of reducing Hb drop. 218 The evidence for TXA using in TKA (TXA vs placebo; combine administration vs 219 single administration), THA (TXA vs placebo; combine administration vs single 220 administration), TKA/THA (TXA vs placebo; combine administration vs single 221 administration), postpartum bleeding, shoulder arthroplasty was considered to be 222 possible for the association of reducing Hb drop. There was probably no association 223 between TXA and Hb drop in TKA (IV TXA vs topical TXA), THA (IV TXA vs 224 225 topical TXA), TKA/THA (IV TXA vs topical TXA).

The evidence for TXA using in trauma, gastrointestinal bleeding was assessed as probable for the association of reducing mortality. There was probably no association between TXA and mortality in liver surgery, cardiac surgery.

229 There was probably no association between TXA and DVT in TKA, THA, TKA/THA,

230 postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery,

shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding, cardiac surgery.

There was probably no association between TXA and PE in TKA, THA, trauma,intertrochanteric fractures, cardiac surgery.

Several other associations were found but were often affected by heterogeneity orpotential confounding factors.

236

237 Discussion

Hemostatic drugs can accelerate blood coagulation or reduce capillary permeability 238 and stop bleeding.¹⁴³ The normal hemostatic mechanism depends on the integrity of 239 the structure and function of the vascular wall, platelet, coagulation system, 240 anticoagulation system, fibrinolysis (fibrinolysis) system and hemorheology, as well 241 as the physiological regulation and balance between them.¹⁴⁴ The hemostatic drugs 242 used in the clinic can either reduce the arteries and capillaries, or enhance the platelet 243 244 function, or accelerate or strengthen the blood coagulation process, or inhibit the clot dissolution process to achieve the purpose of hemostasis.¹⁴⁵ 245

246

247 The hemostatic drugs commonly used in the clinic are mainly divided into 4

categories: 1. Antifibrinolytic drugs: (1) aminocaproic acid acts by inhibiting the 248 fibrinolytic system. It is mainly used for bleeding caused by the increase of 249 fibrinolytic enzyme activity, such as obstetrics and gynecology, prostate, liver, 250 pancreas, lung and so on. Early or preoperative use of drugs during operation can 251 reduce blood leakage during operation and reduce the amount of blood transfusion. 252 253 Overdose can lead to thrombosis with a tendency to thrombosis or a history of thrombotic vascular disease. Renal insufficiency should be used with caution. Due to 254 the side effects of this drug, it has been less used at present.¹⁴⁶ (2) the mechanism of 255 aminomethylbenzoic acid (hemostatic aromatic acid) is the same as that of 256 aminocaproic acid, and its effect is 4-5 times stronger than that of aminohexanoic acid. 257 Suitable for lung, liver, pancreas, prostate, thyroid, adrenal gland surgery abnormal 258 bleeding, obstetrics and gynecology and postpartum hemorrhage and pulmonary 259 260 tuberculosis hemoptysis, sputum with blood, hematuria, prostate hypertrophy bleeding, upper gastrointestinal bleeding and so on. It has a significant effect on 261 chronic blood oozing.¹⁴⁷ (3) the mechanism of aminocycline (hemostatic cyclic acid, 262 thrombotic acid) is the same as TXA, and its effect is slightly stronger than that of 263 264 aminomethylbenzoic acid. The indication is similar to hemostatic aromatic acid. It is used for all kinds of hemorrhagic diseases, abnormal bleeding during the operation 265 and so on. Side effects can be headache, dizziness, nausea, vomiting and other 266 reactions.¹⁴⁸ 2. Drugs to reduce capillary permeability: (1) phenolsulfonethylamine 267 (hemostatic) works by promoting the process of coagulation. It can increase platelet 268 aggregation and adhesion in the blood, promote the release of clotting substances, 269 accelerate blood coagulation.¹⁴⁹ Clinically, it is used to prevent and treat bleeding 270 caused by surgical bleeding, thrombocytopenic purpura, or Henoch-Schonlein purpura 271 and other causes. This product can be used in combination with other types of 272 hemostatic drugs. Fewer side effects. (2) carbacarbital (Anluo blood) is a 273 274 semicarbazide of adrenaline oxidation product adrenaline, which is often used as sodium salicylate (carbacarbital) or sodium sulfonate (sodium caroesulfonate). This 275 product can promote capillary contraction. Reduce the permeability of capillaries, 276 increase the retraction of the broken end of broken capillaries, and play a hemostatic 277 role. Indications: This product is often used in idiopathic purpura, retinal hemorrhage, 278 chronic pulmonary hemorrhage, gastrointestinal hemorrhage, epistaxis, hemoptysis, 279 hematuria, hemorrhoid bleeding, uterine bleeding, cerebral hemorrhage and so on. 280 Side effects: this product is low toxicity, but not suitable for mass use, can induce 281 epilepsy and mental disorders. 3. Thrombin drugs: (1) the common name of batroxine 282 is snake venom hemagglutinin for injection, which is a kind of batroxobin extracted 283 from Brazilian spearhead. Clinically, it is used to treat bleeding caused by various 284 causes, especially in patients with bleeding whose traditional hemostatic drugs are 285 ineffective. Contraindication: bleeding caused by DIC and patients with a history of 286 thrombosis or embolism are prohibited. In addition to emergency bleeding, the first 3 287 months of pregnancy should not be used. (2) Thrombin can directly act on the 288 fibrinogen in the blood, promote the transformation into fibrin, accelerate the 289 coagulation of the blood and stop the bleeding. Clinical use for trauma, surgery and 290 oral hemostasis for gastrointestinal bleeding.¹⁵⁰ No injections. 4. Coagulation factors: 291

(1) Vitamin K1 is a natural vitamin used for injection. The effect was stronger than
that of K3 and K4. (2) Sodium bisulfite mono-naphthoquinone (vitamin K3) is a
synthetic vitamin, which is used in the treatment of vitamin K deficiency. (3)
methylnaphthalene hydroquinone (vitamin K4, acetylnaphthoquinone) is a synthetic
vitamin, which is used for oral administration.¹⁵¹

297

Fibrinolysis is related to the decomposition of fibrinolysis and the increase of vascular 298 permeability under physiological or pathological conditions, as well as the occurrence, 299 development and cure of fibrinolysis-induced reactions, bleeding symptoms and 300 allergic reactions.² TXA can inhibit the effect of fibrinolytic enzyme and show 301 hemostatic, anti-allergic and anti-inflammatory effects. (1) Anti-fibrinolytic enzyme 302 effect. Aminocycline can strongly adsorb (LBS), which is the lysine binding site of 303 304 fibrinolytic enzyme and plasminogen, and inhibit the binding of fibrinolytic enzyme and plasminogen to fibrin. Thus, the fibrinolysis induced by the fibrinolytic enzyme 305 was strongly inhibited. Besides, in the presence of anti-fibrinolytic enzymes such as 306 macroglobulin 2 in serum, the anti-fibrinolytic effect of TXA was more obvious, and 307 the hemostatic effect was more significant.³ (2) Hemostatic effect. Abnormal 308 hyperactivity of the fibrinolytic enzyme will cause platelet agglutination inhibition 309 and coagulation factor decomposition. Mild hyperactivity first leads to the 310 decomposition of fibrin. Therefore, it is considered that in general bleeding, TXA can 311 inhibit fibrin decomposition and play a hemostatic role.⁴ (3) Anti-allergic and 312 anti-inflammatory effects. TXA can inhibit the production of kinin and other active 313 peptides (guinea pigs and rats) which cause vascular permeability enhancement, 314 allergy and inflammatory lesions.⁵ 315

316

In the current controversial situation, researchers are trying to use different methods 317 to verify the safety of TXA. Because it is necessary to design a clinical trial with a 318 large enough sample to illustrate the differences between these low probability events, 319 the researchers turned to look for answers to questions from some population-based 320 databases in recent years. To answer our questions about the use of TXA in different 321 clinical situations. There are limitations, such as the fact that these studies are 322 retrospective, or that there is only limited clinical data and the risk of confusion. 323 Although these randomized trials do not comply with strict inclusion or exclusion 324 325 criteria but are artificially defined, the benefits are considerable, such as the provision of large samples and the true clinical results of hundreds of hospital cases. 326

327

Poeran et al.¹⁵² have recently found that the use of TXA in most joint operations can 328 be benefit. Their study found that TXA is safe and effective in total hip or knee 329 arthroplasty. In 872416 cases in 510 hospitals across the United States, the researchers 330 found that the use of TXA reduced the rate of blood transfusions by 60 percent or 331 more. The application of TXA could reduce the incidence of allogeneic or autologous 332 blood transfusion (7.7% vs. 20.1%, P < 0.001), thrombus-related complications (0.6%) 333 vs.0.8%, P < 0.0057). The overall complications (1.9% v.s.2.6%, P < 0.001), the need 334 for mechanical ventilation (0.1% vs.0.2%, P < 0.0003), and the need to enter ICU (3.1% 335

vs.7.5%, P < 0.001). Besides, the median hospitalization cost of patients treated with 336 TXA was relatively low (P<0.001). Very importantly, while showing significant 337 effectiveness, the use of TXA did not significantly increase the risk of complications, 338 such as thrombus-related events (probability ratio 0.85: 1.02), acute renal failure (0.70: 339 1.11, This is a hidden danger to the use of antifibrinolytic drugs since protease 340 inhibitors left the market), the overall complication (0.75: 0.98). The overall 341 complications also include acute myocardial infarction, which is important because 342 the pathogenesis of perioperative myocardial infarction is due to myocardial oxygen 343 deficiency, coronary plaque rupture and platelet activation. If intraoperative bleeding 344 is reduced as a result of the use of TXA, myocardial hypoxia caused by tachycardia 345 and reduced hemoglobin in the blood can be effectively reduced. In this regard, 346 preliminary data using the same data set may indicate no increased risk in cases with a 347 history of coronary artery disease, but there is a clear need for more research in this 348 area. In providing the data, the authors point out that although the use of TXA is 349 becoming more and more popular, only 11.2 percent of patients were found to be 350 using it in the 2012 year study. At the same time, they also stressed that although the 351 use of TXA is safe in the population as a whole, the safety of using TXA in different 352 subgroups needs to be further studied. 353

354

355 Another way to solve the safety problem of TXA is to reduce the amount of TXA in the whole body by local application of TXA in the surgical site. Gomez-Barrena et 356 al.¹⁵³ recently published an article in JBJS comparing the efficacy of local TXA and 357 intravenous TXA in patients with primary total knee arthroplasty. A phase III 358 single-center double-blind randomized controlled trial was conducted to demonstrate 359 that local administration of TXA (3 g TXA dissolved in 100 mL saline) was no worse 360 than twice intravenous administration of TXA (15 mg/kg TXA dissolved in 100 mL 361 saline, once before the tourniquet was loosened. It was used 3 hours after operation). 362 The main indicators were defined as the need for postoperative blood transfusions. 363 The secondary indicators included blood loss through drainage at 3 hours 24 hours, 364 hemoglobin levels 24 hours, 48 hours and 5 days after the operation, and estimated 365 total bleeding volume (calculated by the lowest hemoglobin level before and after the 366 operation). Besides, complications and serious adverse reactions, days of 367 hospitalization and active motion range of knee joint after operation were also within 368 the scope of their evaluation. The sample size was calculated by a maximum expected 369 transfusion rate of 5%, based on a 0 transfusion rate in previous studies of total knee 370 arthroplasty. In the preliminary results, the significance was set to unilateral 0.025, the 371 test efficiency was 99%, and the sample size of each group was 39 cases. There was 372 no statistically significant difference in the main results (the transfusion rate was 0 in 373 both groups), and there was no significant difference in the secondary results (blood 374 loss in 3-24 h drainage and the calculated amount of blood loss 48 h and 5 d after the 375 operation). The decline levels of hemoglobin at 24 h, 48 h and 5 d were similar 376 between the two groups (local use of TXA group was 2.3 g/L, 2.1 g/L and 2.0 g/L). 377 Intravenous use of TXA group was -2.5, -3.4, -2.6 g/dL). 378 379

On the other hand, the use of TXA in orthopedic patients is more economically 380 efficient. Its performance in reducing the hospitalization cost of patients with total hip 381 and total knee arthroplasty makes its application prospect more bright. TXA itself is 382 cheap (about \$6 per box on average), and studies by Poeran et al.¹⁵² have shown that it 383 can significantly reduce the average hospitalization costs of patients. Given that the 384 number of joint replacements is likely to continue to rise across the United States and 385 elsewhere over the next decade, an economical and effective treatment is 386 indispensable. 387

388

Overall, the evidence so far has irrefutably confirmed the role of TXA in joint 389 replacement: it can effectively reduce bleeding and transfusion rates. At present, the 390 data on its safety in the perioperative period is considerable. However, for those at 391 392 risk of thrombotic complications, the use of TXA still needs further research, as well as further research on the safe use of TXA and the minimum effective dose of TXA. 393 Local use of TXA, is a better method than intravenous administration, especially in 394 terms of reducing plasma concentrations. But strong enough evidence is still needed 395 to prove its safety. At the same time, because of its economy and clinical effectiveness, 396 397 the overall dosage of TXA is increasing. However, with the expansion of the use of TXA, there will be more new problems, so it is necessary to continue to assess the 398 risks and benefits of TXA, especially for those cases where there is a risk of adverse 399 events. To provide evidence-based evidence to ensure the reasonable clinical use of 400 TXA, an umbrella review that systematically assessing the hemostatic effect and 401 safety of TXA is crucial. 402

403

In our study, the results of 136 meta-analyses (396 comparisons) ⁷⁻¹⁴² including TXA 404 to reduce TBL, transfusion rate, Hb drop, mortality, DVT and PE were reviewed; 405 these meta-analyses included 15 kinds of surgeries. Most of the evidence comes from 406 a meta-analysis of RCTs; only a few meta-analyses include observational studies. 407 Based on these results, there may be evidence that TXA may help reduce TBL, 408 transfusion rate, Hb drop and mortality in different kinds of surgeries. In terms of 409 different ways of administration, intravenous combined topical application of TXA 410 significantly reduced TBL in TKA and THA compared with intravenous or topical 411 application of TXA alone; intravenous combined topical application of TXA 412 413 significantly reduced transfusion rate in THA compared with intravenous or topical application of TXA alone; intravenous combined topical application of TXA 414 significantly reduced Hb drop in TKA and THA compared with intravenous or topical 415 application of TXA alone. 416

The potential clinical implications of this study are as follows: (1) This is the first umbrella review to assess the hemostatic effect and safety of TXA. The study summarized all meta-analyses of TXA used in different surgeries from the inception to now and classified the endpoints according to the level of evidence. (2) 136 meta-analyses with 396 comparisons were retrieved which included a large sample size of participants compared to other studies. This was of great significance in the field of evidence-based medicine. (3) With the increase of RCT and meta-analysis, TXA is more and more widely used in reducing blood loss, but accompanied by great controversy. In this study, TXA used in surgeries reported by meta-analyses were systematically classified into three grade according to effect size, concordance of results, heterogeneity and potential confounding factors. Therefore, this study has better reference value for clinical drug use than other meta-analysis and general review.

The limitations of this study are as follows: (1) Baseline characteristics were not 430 considered and this may lead to mixed bias. (2) We used the effect sizes reported in 431 the retrieved studies. Therefore, it is difficult to assess the effect of these baseline 432 characteristics on the results. (3) The experimental group and the control group were 433 not unified. The comparison of different meta-analyses of the same surgery may be of 434 limited significance. (4) There is no internationally uniform standard for the level of 435 436 evidence. Therefore, we can only make a summary of the existing meta-analyses as a reference, but cannot give the exact quantitative conclusion. (5) Intervention measures 437 and medication doses were not uniform in different meta-analyses of the same surgery. 438 Since the results of all meta-analyses cannot be directly combined, there is no 439 accurate criterion for the effectiveness of different meta-analyses of the same 440 441 medication. (6) Some different meta-analyses may include the same RCT, so there may be some duplications among the participants included in this review. (7) There 442 are few studies on the use of TXA in some surgeries (such as Myomectomy, Cardiac 443 surgery), so the classification of these studies may not be accurate. (8) There may be 444 no meta-analysis report on the use of TXA in some areas, but only sporadic RCT 445 publication, we do not consider. 446

- 447
- 448 Summary points

This umbrella review indicated that TXA was regarded as effective to reduce TBL,
transfusion rate, Hb drops and mortality in different kinds of surgeries, and did not
increase the incidence of DVT and PE.

452

453 Future issues

(1) Future studies should include stratification by the dose of TXA to definitively 454 exclude mixed bias. (2) In the future meta-analyses, authors should pay attention to 455 unifying the intervention measures in the experimental group or the control group to 456 457 avoid the heterogeneity, and reduce the difficulty of the combined effect size of umbrella review. (3) Multicenter large sample size RCTs should be implemented to 458 promote more representative meta-analyses creation, to provide more convincing 459 evidence for assessing hemostatic effect and safety of TXA. (4) The international 460 criteria of the level of evidence for umbrella review should be identified as soon as 461 possible, to provide a reference for the development of umbrella review in the future. 462

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472	None.
473	Author Contributions
474	The authors confirm contribution to the paper as follows: study conception and design:
475	Mingyang JIANG. Author, Ke ZHANG. Author; data collection: Chuanliang CHEN.
476	Author; analysis and interpretation of results: Xiaochong ZOU. Author, Kaicheng LIU.
477	Author. Yongheng DAI. Author; draft manuscript preparation: Zhandong BO. Author.
478	Mingyang JIANG. Author. All authors reviewed the results and approved the final
479	version of the manuscript.
480	Availability of Data and Materials
481	The datasets generated during and/or analysed during the current study are available
482	from the corresponding author on reasonable request.
483	Ethnics Approval
484	None.
485	Conflict of interest
486	All authors declared that there was no conflict of interest.
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960	Figure Legends
961	Fig. 1 Flowchart
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963	Table 1 Criteria used to define the level of evidence for TXA
964	RCT= Randomized Controlled Trials
965	
966	Table 2 Results from 136 meta-analyses of association between TXA and TBL,
967	transfusion rate, Hb drop, mortality, DVT and PE.
968	OR=Odds Ratio; RR=Risk Ratio; CI=Confidence Interval; RC=retrospective cohort;
969	P=prospective cohort; R=randomized controlled trial
970	
971	Table 3 Results from the largest meta-analyses of TXA and TBL, transfusion rate, Hb
972	drop, mortality, DVT and PE.
973	OR=Odds Ratio; RR=Risk Ratio; CI=Confidence Interval; RC=retrospective cohort;
974	P=prospective cohort; R=randomized controlled trial
975	
976	Table 4 Evidence from meta-analyses of association between TXA and TBL,
977	transfusion rate, Hb drop, mortality, DVT and PE.
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