### Systematic review

# Tranexamic acid versus placebo for preventing postpartum hemorrhage after cesarean section: systematic review and meta-analysis

# Supplementary material

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after cesarean section

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SEARCH ENGINE	STRATEGY	#
PUBMED	("Cesarean Section" OR "Cesarean Sections" OR "Abdominal Delivery" OR "C-Section (OB)" OR "C Section (OB)" OR "C-Sections (OB)" OR "Caesarean Section" OR "Caesarean Sections" OR "Delivery, Abdominal" OR "Abdominal Deliveries" OR "Deliveries, Abdominal" OR "Postcesarean Section") AND ("Tranexamic Acid" OR "AMCA" OR "AMCHA" OR "t-AMCHA" OR "trans-4-(Aminomethyl)cyclohexanecarboxylic Acid" OR "Cyklokapron" OR "Ugurol" OR "Transamin" OR "KABI 2161" OR "Amchafibrin" OR "Anvitoff" OR "Spotof" OR "Exacyl") AND ("Postpartum Hemorrhage" OR "Hemorrhage, Postpartum" OR "Delayed Postpartum Hemorrhage" OR "Hemorrhage, Delayed Postpartum Hemorrhage" OR "Hemorrhage" OR "Hemorrhage, Immediate Postpartum Hemorrhage, Immediate Postpartum Hemorrhage, Immediate")	117
SCOPUS	(TITLE-ABS-KEY ("Cesarean Section" OR "Cesarean Sections" OR "Abdominal Delivery" OR "C-Section" OR "Caesarean Section" OR "Postcesarean Section")) AND (TITLE-ABS-KEY ("Tranexamic Acid" OR "AMCA" OR "Cyklokapron" OR "Transamin" OR "Exacyl")) AND (TITLE-ABS-KEY ("Postpartum Hemorrhage" OR "Delayed Postpartum Hemorrhage" OR "Immediate Postpartum Hemorrhage"))	494
WEB OF SCIENCE	TS=("Cesarean Section" OR "Cesarean Sections" OR "Abdominal Delivery" OR "C-Section" OR "Caesarean Section" OR "Postcesarean Section")  AND TS=("Tranexamic Acid" OR "amcf" OR "cyclokapron" OR "transamine" OR "exactly")  AND TS=("Postpartum Hemorrhage" OR "Delayed Postpartum Hemorrhage" OR "Immediate Postpartum Hemorrhage")	252
Embase	('cesarean section'/exp OR'cesarean section' OR 'abdominal delivery' OR'c-section' OR 'caesarean section'/exp OR 'caesarean section' OR 'postcesarean section'/exp OR 'postcesarean section') AND ('tranexamic acid'/exp OR'tranexamic acid' OR'amca' OR'amcha'/exp OR'amcha' OR'cyklokapron' OR'transamin' OR'transamin' OR'exacyl'/exp OR'exacyl') AND ('postpartum hemorrhage'/exp OR'postpartum hemorrhage' OR'hemorrhage, postpartum'/exp OR'hemorrhage, postpartum' OR'delayed postpartum hemorrhage'/exp OR'delayed postpartum hemorrhage' OR'immediate postpartum hemorrhage'/exp OR'immediate postpartum hemorrhage')	583
	TOTAL OF RECORDS	1446
	REMOVED DUPLICATES	736
	AFTER DUPLICATES REMOVED	710
	FULLTEXT	50
	FINAL SELECTION	23

SM2. GRADE. Tranexamic acid compared to placebo for the prevention of postpartum hemorrhage after cesarean section. Patient or population: the prevention of postpartum hemorrhage after cesarean section. Intervention: tranexamic acid. Comparison: placebo.

Outcomes	№ of participants (studies)	Certainty of the	Relative effect (95% CI)	Anticipated absolute effects		
	Follow-up	(GRADE)	(00700)	Risk with placebo	Risk difference with tranexamic acid	
Total blood loss assessed with: mL	6457 (11 RCTs)	⊕○○○ Very lowa,b,c	-	-	SMD 0.97 SD lower (1.64 lower to 0.3 lower)	
Total blood loss (EBL)	5378 (4 RCTs)	⊕⊕⊕○ Moderatec	-	The mean total blood loss (EBL) was 0	MD 104.91 lower (119.58 lower to 90.24 lower)	
Total blood loss (No Reported)	60 (1 RCT)	⊕⊕⊕○ Moderated	-	The mean total blood loss (No Reported) was 0	MD 131.67 lower (186.02 lower to 77.32 lower)	
Total blood loss (gravimetric method) assessed with: gr	998 (6 RCTs)	⊕○○○ Very lowb,c,d	-	The mean to- tal blood loss (Weigh) was 0	MD 195.71 lower (339.06 lower to 52.37 lower)	

<sup>\*</sup>The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence effect estimate limited: true be substantially effect. effect different from the estimate of the may Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

- Downgraded one level due to high risk in randomisation process, some concerns in desviations from the intended interventions and selection of the reported result.
- Downgraded one level due to high heterogeneity.
- Downgraded one level due to crosses the clinical decision threshold.
- d. Downgraded one level due to randomisation process, desviations from the intended interventions.

CI: confidence interval: MD: mean difference: SMD: standardised mean difference.

SM3. GRADE. Tranexamic acid compared to placebo for Total blood loss after and before of the cesarean section. Patient or population: Total blood loss after and before of the cesarean section. Intervention: tranexamic acid. Comparison: placebo.

Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect (95% CI)	Anticipated absolute effects		
	Follow-up	(GRADE)	<b>(</b>	Risk with placebo	Risk difference with tranexamic acid	
After	5016 (4 RCTs)	⊕○○○ Very lowa,b,c	-	The mean after was 0	MD 147.95 lower (399.65 lower to 103.75 higher)	
Before	1341 (6 RCTs)	⊕⊕○○ Lowb,d	-	The mean before was 0	MD 151.65 lower (227.9 lower to 75.4 lower)	
No reported	100 (1 RCT)	⊕⊕○○ Lowb,d	-	The mean no reported was 0	MD 269.05 lower (301.86 lower to 236.24 lower)	

<sup>\*</sup>The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. confidence limited: Low certainty: our in the effect estimate is the substantially different from estimate of **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

- Downgraded one level due to high risk in randomisation process.
- Downgraded one level due to high heterogeneity.
- Downgraded one level due to crosses the clinical decision threshold. C.
- Downgraded one level due to high risk in randomisation process, some concerns in desviations from the intended interventions and selection of the reported result.

CI: confidence interval: MD: mean difference.

**SM4. GRADE.** Tranexamic acid compared to placebo for total blood loss at two hours. Patient or population: total blood loss at two hours. Intervention: tranexamic acid. Comparison: placebo.

Outcomes	№ of participants (studies)	Certainty of the evidence	Relative effect (95% CI)	Anticipated absolute effects		
	Follow-up	(GRADE)	(22,72,27)	Risk with placebo	Risk difference with tranexamic acid	
Total blood loss at two hours	2202 (8 RCTs)	⊕⊕⊕○ Moderatea	-	-	SMD 1.25 SD lower (1.72 lower to 0.78 lower)	
Before	552 (6 RCTs)	⊕⊕○○ Lowa,b	-	The mean before was 0 SD	MD 177.23 SD lower (245.59 lower to 108.87 lower)	
After	1650 (2 RCTs)	⊕⊕○○ Lowb,c	-	The mean after was 0	MD 208.06 lower (983.71 lower to 567.59 higher)	
Total blood loss at two hours (sensibility)	1262 (6 RCTs)	⊕⊕⊕○ Moderatea	-	-	SMD 0.97 SD lower (1.18 lower to 0.77 lower)	
Postpartum hemorrhage	17863 (13 RCTs)	⊕⊕○○ Lowa,d	RR 0.84 (0.76 to 0.93)	128 per 1,000	20 fewer per 1,000 (31 fewer to 9 fewer)	

<sup>\*</sup>The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % Cl).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence the effect estimate is limited: effect substantially different from the estimate of the effect. may be Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

- a. Downgraded one level due to high risk in randomisation process, some concerns in desviations from the intended interventions and selection of the reported result
- b. Downgraded one level due to high heterogeneity
- c. Downgraded one level due to some concerns in selection of the reported result
- d. Downgraded one level due to crosses the clinical decision threshold

CI: confidence interval; MD: mean difference; RR: risk ratio; SMD: standardised mean difference.

SM5. GRADE. Tranexamic acid compared to placebo for total blood secondary outcomes. Patient or population: total blood secondary outcomes. Intervention: tranexamic acid. Comparison: placebo.

	№ of participants	Certainty of the	Relative effect	Anticipated absolute effects		
Outcomes	(studies) Follow-up	evidence (GRADE)	(95% CI)	Risk with pla- cebo	Risk difference with tranexamic acid	
Additional uterotonics	18685 (11 RCTs)	⊕⊕○○ Lowa,b	RR 0.67 (0.49 to 0.91)	120 per 1000	40 fewer per 1000 (61 fewer to 11 fewer)	
Need for blood transfusion	17723 (9 RCTs)	⊕⊕○○ Lowa,b	RR 0.57 (0.33 to 0.99)	35 per 1000	15 fewer per 1,000 (23 fewer to 0 fewer)	
Hospital stay	13499 (5 RCTs)	⊕○○○ Very lowb,c,d	-	-	SMD 0.14 SD lower (0.59 lower to 0.3 higher)	
Side effects	18788 (15 RCTs)	⊕○○○ Very lowa,b,d	RR 1.50 (1.01 to 2.24)	138 per 1000	69 more per 1000 (1 more to 172 more)	
Serious event	17706 (15 RCTs)	⊕⊕○○ Lowa,b	RR 1.16 (0.86 to 1.55)	2 per 1000	0 fewer per 1000 (0 fewer to 1 more)	

<sup>\*</sup>The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI).

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low confidence effect estimate limited: certainty: our in the is the of effect substantially different from the estimate effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

- a. Downgraded one level due to high risk in randomisation process, some concerns in desviations from the intended interventions and selection of the reported result.
- Downgraded one level due to crosses the clinical decision threshold.
- Downgraded one level due to some concerns in selection of the reported result.
- Downgraded one level due to high heterogeneity.

CI: confidence interval; RR: risk ratio; SMD: standardised mean difference.

#### **SM6.** Meta-regression results

Mixed-Effects Model (k = 11; tau^2 estimator: REML)

logLik deviance AIC. BIC AICc -0.3298 0.6596 22.6596 0.6596 286.6596

0.0996 (SE = 0.1601)tau^2 (estimated amount of residual heterogeneity):

tau (square root of estimated tau^2 value): 0.3155 87.93 % I^2 (residual heterogeneity / unaccounted variability): H^2 (unaccounted variability / sampling variability): 8.28 R^2 (amount of heterogeneity accounted for): 89.62 %

Variable	Estimate	Standard error	Z	p-value	95% CI	Significance
(Intercept)	-8.5767	2.8264	-3.0345	0.0024	-14.1163 to -3.0370	**
Administration15min before	-1.2242	0.7875	-1.5545	0.1201	-2.7678 to 0.3193	-
Administration no reported	-3.3408	1.0246	-3.2606	0.0011	-5.3489 to -1.3326	**
Blood loss calculation method: no reported	-2.7686	1.0600	-2.6118	0.0090	-4.8463 to -0.6910	**
Blood loss calculation method: weight	-0.7722	0.3231	-2.3898	0.0169	-1.4055 to -0.1389	*
Blinding: no available	0.8849	0.6730	1.3149	0.1885	-0.4341 to 2.2039	-
Blinding: open	0.9161	0.7709	1.1883	0.2347	-0.5948 to 2.4270	-
Blinding: unblinded	0.5164	0.9101	0.5675	0.5704	-1.2673 to 2.3001	-
Age (intervention group)	-5.1924	2.3062	-2.2515	0.0244	-9.7125 to -0.6724	*
Age (control group)	5.3668	2.3285	2.3049	0.0212	0.8031 to 9.9305	*

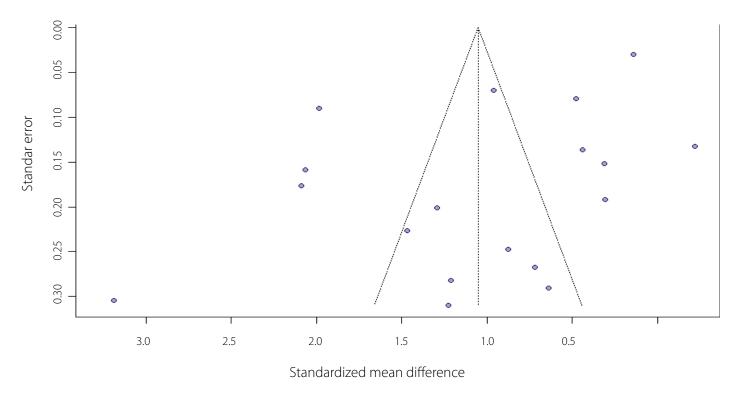
Significance Legend

p < 0.001: \*\*\*

p < 0.01: \*\*

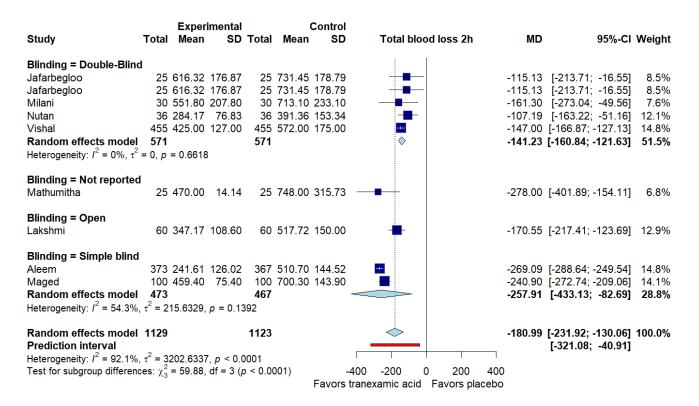
p < 0.05: \*

p < 0.1:

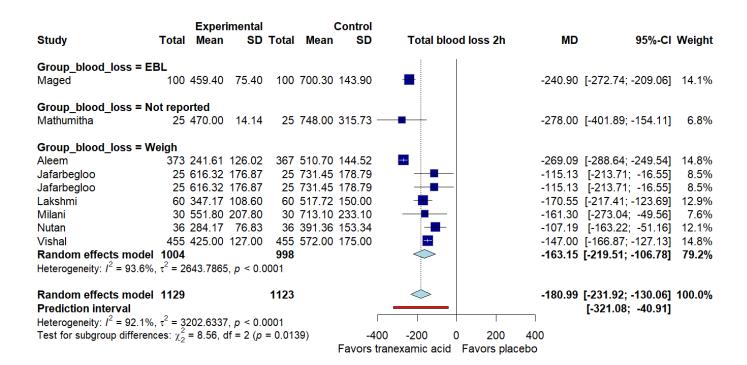


**SM8.** Total blood loss after and before of the cesarean section

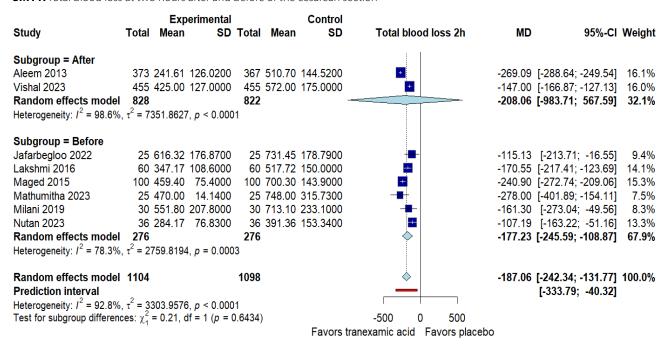
		Exp	erimental			Control				
Study	Total	Mean	SD	Total	Mean	SD	Total blood loss	MD	95%-CI	Weight
Subgroup = Before										
Gugorduk 2011	330	499.90	206.4000	330	600.70	215.7000	<b>=</b>	-100.80	[-133.01; -68.59]	9.9%
Lee 2023	86	620.60	405.7000	91	754.10	447.9000	<del></del>	-133.50	[-259.28; -7.72]	7.3%
Masood 2023	30	301.66	64.9700	30	433.33	137.2900	<del></del>	-131.67	[-186.02; -77.32]	9.4%
Rani 2021	50	559.70	113.8200	50	800.91	200.2600	— <del>—</del>	-241.21	[-305.06; -177.36]	9.2%
Ray 2016	50	559.68	113.8000	50	800.91	200.2600	<del>-                                      </del>	-241.23	[-305.07; -177.39]	9.2%
Sentürk 2013	122	272.05	143.2300	122	346.87	189.4900	-	-74.82	[-116.97; -32.67]	9.7%
Random effects mode				673				-151.65	[-227.90; -75.40]	54.6%
Heterogeneity: $I^2 = 84.9\%$ , $\tau$	<sup>2</sup> = 4214	.2741, p <	0.0001							
Subgroup = After										
Ogunkua 2022	55	2274.00	469.0000	55	2407.00	388.0000	<del> </del>	-133.00	[-293.87; 27.87]	6.2%
Oseni 2021	122	414.00	143.7000	122	773.80	199.2000		-359.80	[-403.38; -316.22]	9.7%
Ragusa 2024	104	405.64	35.4528	127	397.66	36.5468	p i	7.98	[ -1.34; 17.30]	10.1%
Sentilhes 2021	2222	680.00	748.0000	2209	787.00	750.0000	-	-107.00	[-151.11; -62.89]	9.6%
Random effects mode				2513				-147.95	[-399.65; 103.75]	35.6%
Heterogeneity: $I^2$ = 98.9%, $\tau$	<sup>2</sup> = 2335	1.7125, <i>p</i>	< 0.0001							
Subgroup = Not report	ed									
Rashid 2024	50	577.12	62.8400	50	846.17	100.3300	<b>=</b>	-269.05	[-301.86; -236.24]	9.9%
Random effects mode	3221			3236				-162.55	[-234.99; -90.10]	
Prediction interval	2								[-401.57; 76.47]	
Heterogeneity: $I^2$ = 98.4%, $\tau$ Test for subgroup difference	= 1045 2 = 1045	0.5397, p 3.21 df - 1	< 0.0001 2 (n = 0.001)	4)		_/	100 -200 0 200	400		
restror subgroup difference	3. λ <sub>2</sub> – 1.	J.Z 1, UI – 2	2 (p = 0.0014	+)			ranexamic acid Favors pl			
						1 47015	ranezaniic acid Favois pi	aceno		



SM10. Subgroup analysis of total blood loss at two hours by quantification method



**SM11.** Total blood loss at two hours after and before of the cesarean section



**SM12.** Metaregression of blood loss after two hours

Mixed-Effects Model (k = 9; tau^2 estimator: REML)

logLik deviance AIC BIC AICc 1.6384 -3.2767 8.7233 5.0410 92.7233

tau^2 (estimated amount of residual heterogeneity): 0 (SE = 0.0223)

tau (square root of estimated tau^2 value): 0

I^2 (residual heterogeneity / unaccounted variability): 0.00% H^2 (unaccounted variability / sampling variability): 1.00 R^2 (amount of heterogeneity accounted for): 100.00% Test for Residual Heterogeneity: QE(df = 4) = 1.4040, p-val = 0.8435

Test of Moderators (coefficients 2:5): QM(df = 4) = 77.3715, p-val < 0.0001

Variable	Estimate	SE	Z	p-value	95% CI	Significance
Intercept	-1.0005	0.2424	-4.1280	<.0001	-1.4755 to -0.5254	***
Administration15min before	0.2726	0.1919	1.4204	0.1555	-0.1036 to 0.6488	-
Blood loss calculation method: weight	0.0795	0.1594	0.4987	0.6180	-0.2329 to 0.3919	-
Blinding: not reported	-0.2313	0.2890	-0.8003	0.4235	-0.7976 to 0.3351	-
Blinding: simple blind	-0.7550	0.0944	-7.9992	<.0001	-0.9400 to -0.5700	***

Note:

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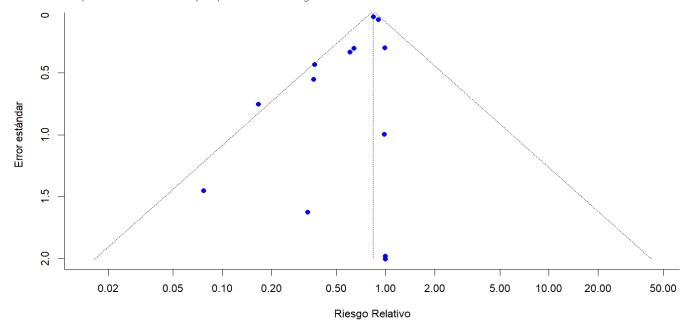
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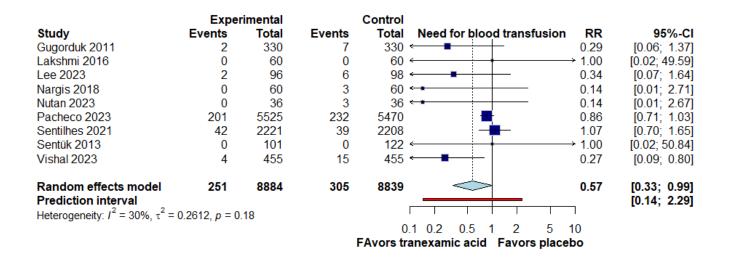
**SM13.** Funnel plot of the incidence of postpartum hemorrhage



# **Secondary outcomes**

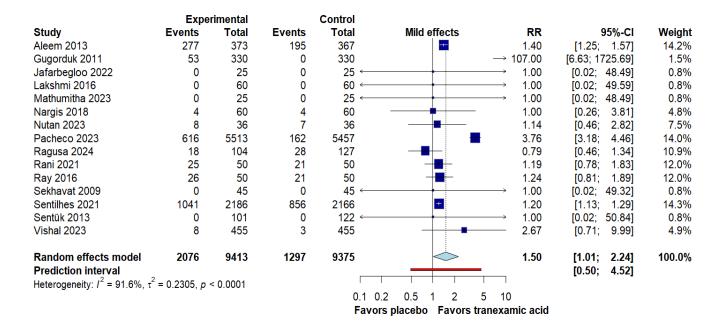
**SM14.** Additional uterotonics

	Exper	rimental		Control			
Study	Events	Total	Events	Total	Additional uterotonics	RR	95%-CI
Aleem 2013	1	373	1	367 ←	<u> </u>	$\rightarrow 0.98$	[0.06; 15.67]
Gugorduk 2011	28	330	48	330	<del></del>	0.58	[0.38; 0.91]
Lakshmi 2016	0	60	9	60 ←	<del></del>	0.05	[0.00; 0.88]
Lee 2023	48	96	52	98	<del>-                                      </del>	0.94	[0.72; 1.24]
Maged 2015	5	100	23	100 ←	<del></del>	0.22	[0.09; 0.55]
Nargis 2018	10	60	24	60	<del></del>	0.42	[0.22; 0.79]
Pacheco 2023	649	5525	732	5470	<b>=</b>	0.88	[0.80; 0.97]
Ray 2016	2	50	6	50 ←	<del>-    </del>	0.33	[0.07; 1.57]
Sentilhes 2021	130	2217	159	2206	<del>       </del>	0.81	[0.65; 1.02]
Sentük 2013	0	101	0	122 ←	<u> </u>	<b>→</b> 1.00	[0.02; 50.84]
Vishal 2023	45	455	65	455	-	0.69	[0.48; 0.99]
Random effects model Prediction interval Heterogeneity: $I^2 = 56\%$ , $\tau^2 =$	<b>918</b>	<b>9367</b>	1119	9318	<u></u>	0.67	[0.49; 0.91] [0.34; 1.33]
	, p			0.1	0.2 0.5 1 2 5	10	
			1	Favors tran	examic acid Favors plac	cebo	



SM16. Hospital stay

	E	(perim	ental		Co	ntrol				
Study	Total	Mean	SD	Total	Mean	SD	Hospital stay	SMD	95%-CI	Weight
Aleem 2013 Gugorduk 2011 Lee 2023 Pacheco 2023 Vishal 2023	373 330 96 5525 455	2.00 2.75 2.75	0.14 0.14	330 98 5470	2.75 2.75	0.10 0.14 0.14		0.00	[-0.14; 0.14] [-0.28; 0.28] [-0.04; 0.04] [-0.69; -0.42]	25.5% 0.0% 21.3% 27.3% 25.8%
Random effects model Prediction interval Heterogeneity: $I^2 = 95\%$ , $\tau^2$		′20, p <	0.01	6720	Fá	-2 avors tra	-1 0 1 nexamic acid Favors place	2	[-0.59; 0.30] [-1.45; 1.16]	100.0%



SM18. Serious event

	Expe	rimental		Control				
Study	Events	Total	<b>Events</b>	Total	Serious event	RR	95%-CI	Weight
Aleem 2013	0	373	0	367 ←	+	→ 1.00	[0.02; 50.27]	2.2%
Gugorduk 2011	0	330	0	330 ←	+	→ 1.00	[0.02; 50.25]	2.2%
Jafarbegloo 2022	0	25	0	25 ←	+	→ 1.00	[0.02; 48.49]	2.3%
Maged 2015	0	100	0	100 ←	+	→ 1.00	[0.02; 49.91]	2.3%
Mathumitha 2023	0	25	0	25 ←	+	→ 1.00	[0.02; 48.49]	2.3%
Nargis 2018	0	60	0	60 ←	+	→ 1.00	[0.02; 49.59]	2.3%
Nutan 2023	0	36	0	36 ←	+	→ 1.00	[0.02; 49.06]	2.3%
Pacheco 2023	12	5069	13	4996	<del>- 1</del>	0.91	[0.42; 1.99]	56.2%
Ragusa 2024	0	104	0	127 ←	+	→ 1.00	[0.02; 50.96]	2.2%
Rani 2021	0	50	0	50 ←	+	→ 1.00	[0.02; 49.43]	2.3%
Ray 2016	0	50	0	50 ←	+	→ 1.00	[0.02; 49.43]	2.3%
Sekhavat 2009	0	45	0	45 ←	+	→ 1.00	[0.02; 49.32]	2.3%
Sentilhes 2021	8	2049	2	2046	-	→ 3.99	[0.85; 18.79]	14.4%
Sentük 2013	0	101	0	122 ←	+	→ 1.00	[0.02; 50.84]	2.2%
Vishal 2023	0	455	0	455 ←	<b>+</b>	→ 1.00	[0.02; 50.29]	2.2%
Random effects model	20	8872	15	8834	<b>\langle</b>	1.16	[0.86; 1.55]	100.0%
Prediction interval							[0.61; 2.20]	
Heterogeneity: $I^2 = 0.0\%$ , $\tau^2$	= 0, p = 0.999	93					· · ·	
,	•			0.1	0.2 0.5 1 2 5	10		
				Favo	rs placebo Favors tra	nexamic aci	d	