Systematic review

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

Supplementary material

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SM1. Search strategy

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" OR "Postpartum Hemorrhage, Delayed" OR "Immediate Postpartum Hemorrhage" OR "Hemorrhage, Immediate Postpartum" OR "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'/exp OR 'amca' OR 'amcha'/exp OR 'amcha' OR 'cyklokapron'/exp OR 'cyklokapron' OR 'transamin'/exp 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
	FULL TEXT	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) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				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 total blood loss (Weigh) was 0	MD 195.71 lower (339.06 lower to 52.37 lower)

***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).
CI: confidence interval; MD: mean difference; SMD: standardised mean difference.

GRADE Working Group grades of evidence

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 in the effect estimate is limited: the true effect may be substantially different from the estimate of the 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.

Explanations

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 crosses the clinical decision threshold.
d. Downgraded one level due to randomisation process, desviations from the intended interventions.

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	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				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)

***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).
CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence

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 in the effect estimate is limited: the true effect may be substantially different from the estimate of the 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.

Explanations

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

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) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				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)

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

GRADE Working Group grades of evidence

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 in the effect estimate is limited: the true effect may be substantially different from the estimate of the 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.

Explanations

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

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

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	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)

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

GRADE Working Group grades of evidence

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 in the effect estimate is limited: the true effect may be substantially different from the estimate of the 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.

Explanations

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 crosses the clinical decision threshold.
c. Downgraded one level due to some concerns in selection of the reported result.
d. Downgraded one level due to high heterogeneity.

SM6. Meta-regression results

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

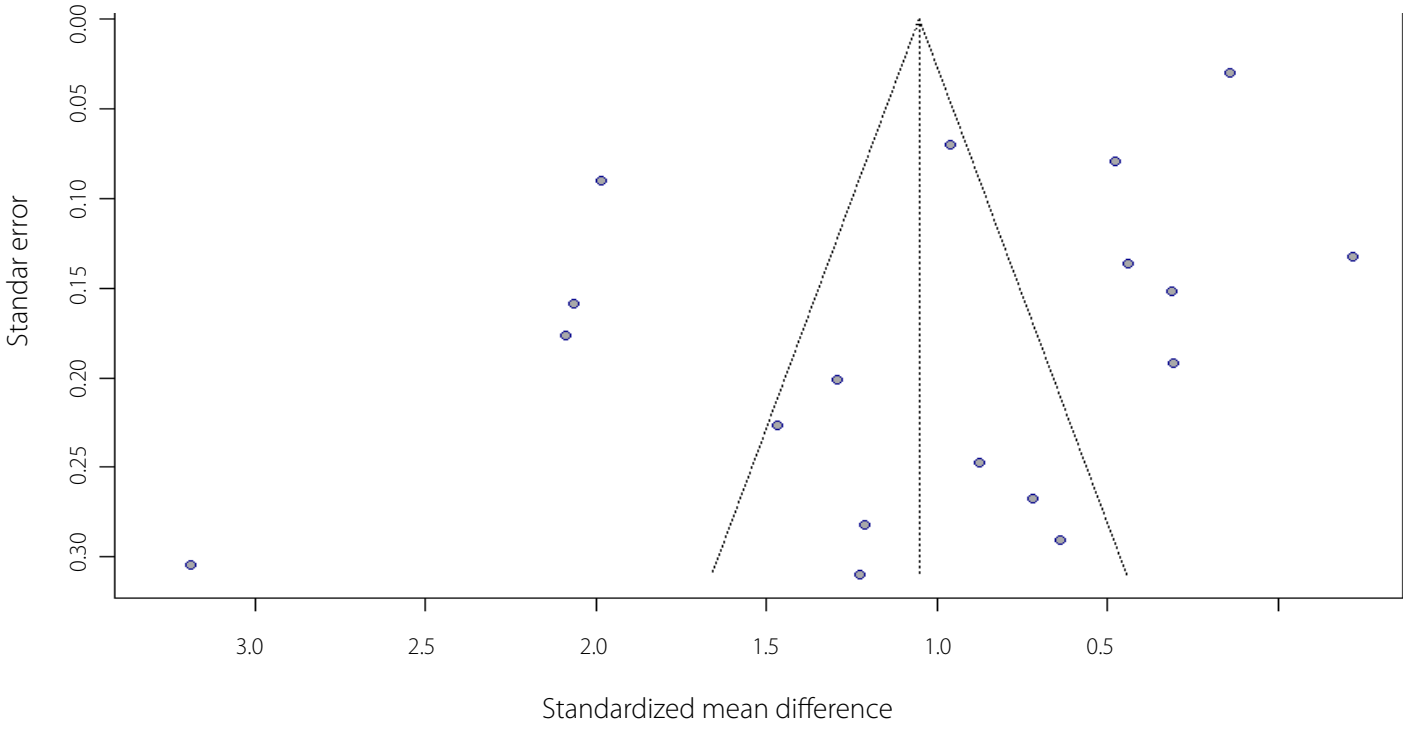
logLik	deviance	AIC.	BIC	AICc
-0.3298	0.6596	22.6596	0.6596	286.6596

tau^2 (estimated amount of residual heterogeneity): 0.0996 (SE = 0.1601)
tau (square root of estimated tau^2 value): 0.3155
I^2 (residual heterogeneity / unaccounted variability): 87.93 %
H^2 (unaccounted variability / sampling variability): 8.28
R^2 (amount of heterogeneity accounted for): 89.62 %

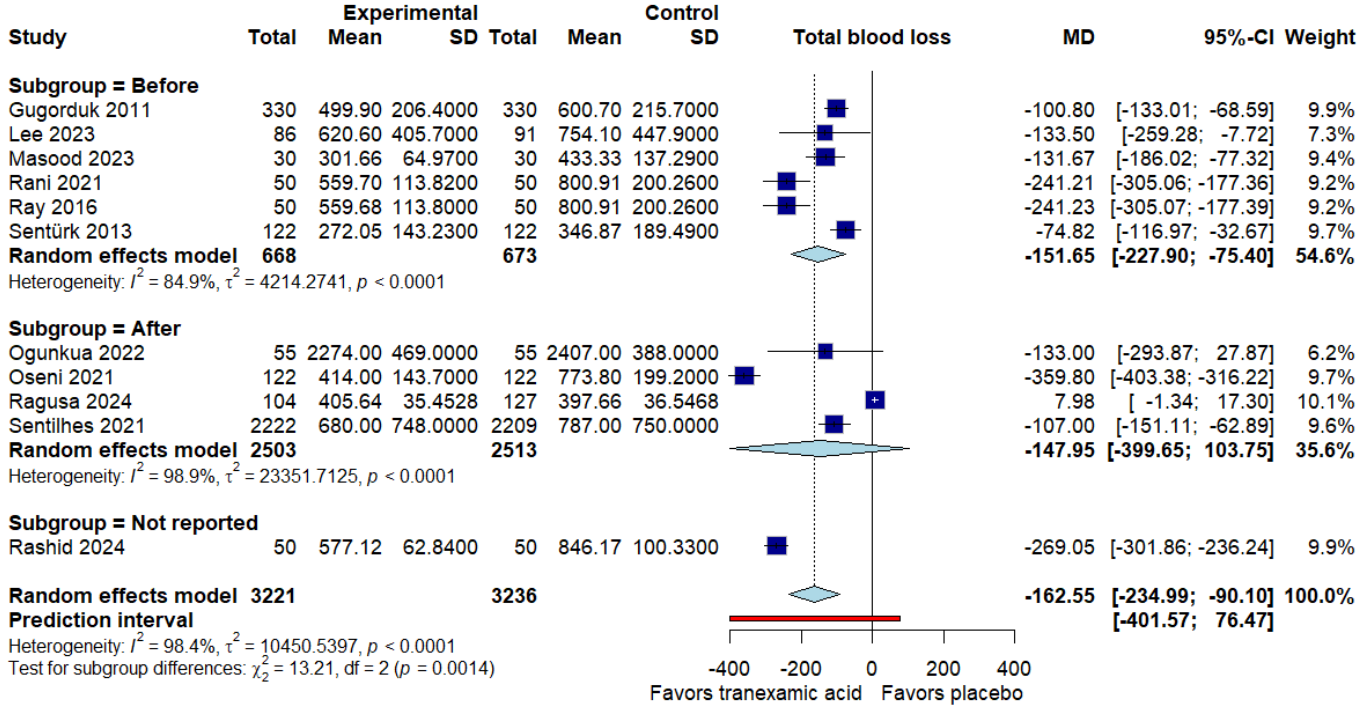
Variable	Estimate	Standard error	Z	p-value	95% CI	Significance
(Intercept)	-8.5767	2.8264	-3.0345	0.0024	-14.1163 to -3.0370	**
Administration15min before	-1.2242	0.7875	-1.5545	0.1201	-2.7678 to 0.3193	-
Administration no reported	-3.3408	1.0246	-3.2606	0.0011	-5.3489 to -1.3326	**
Blood loss calculation 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:

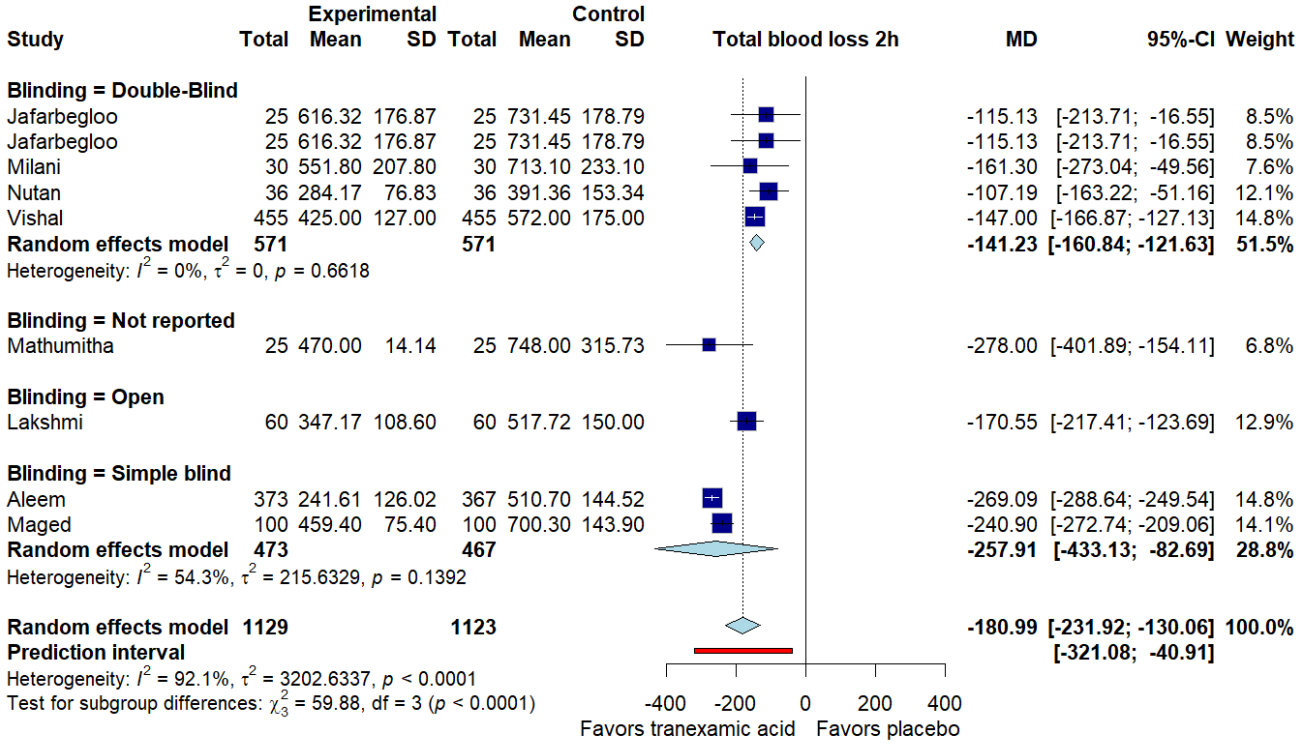
SM7. Evaluation of publication bias in total blood loss by funnel plot



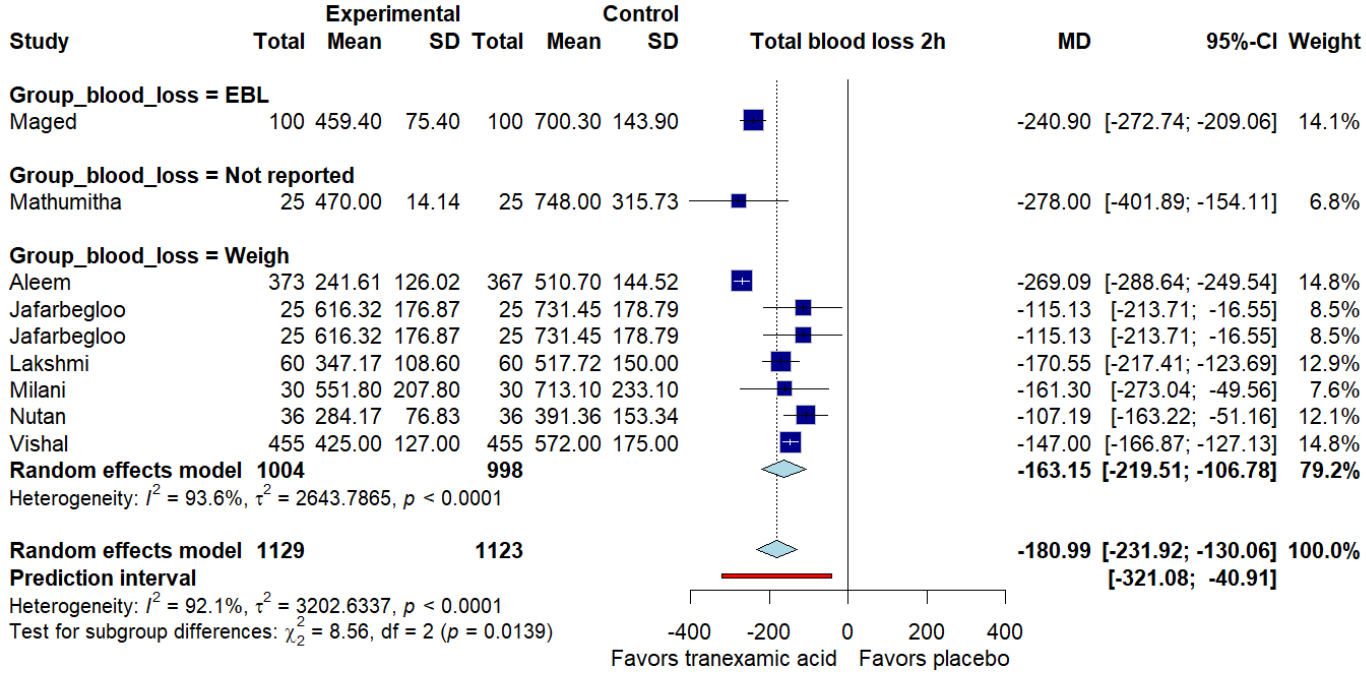
SM8. Total blood loss after and before of the cesarean section



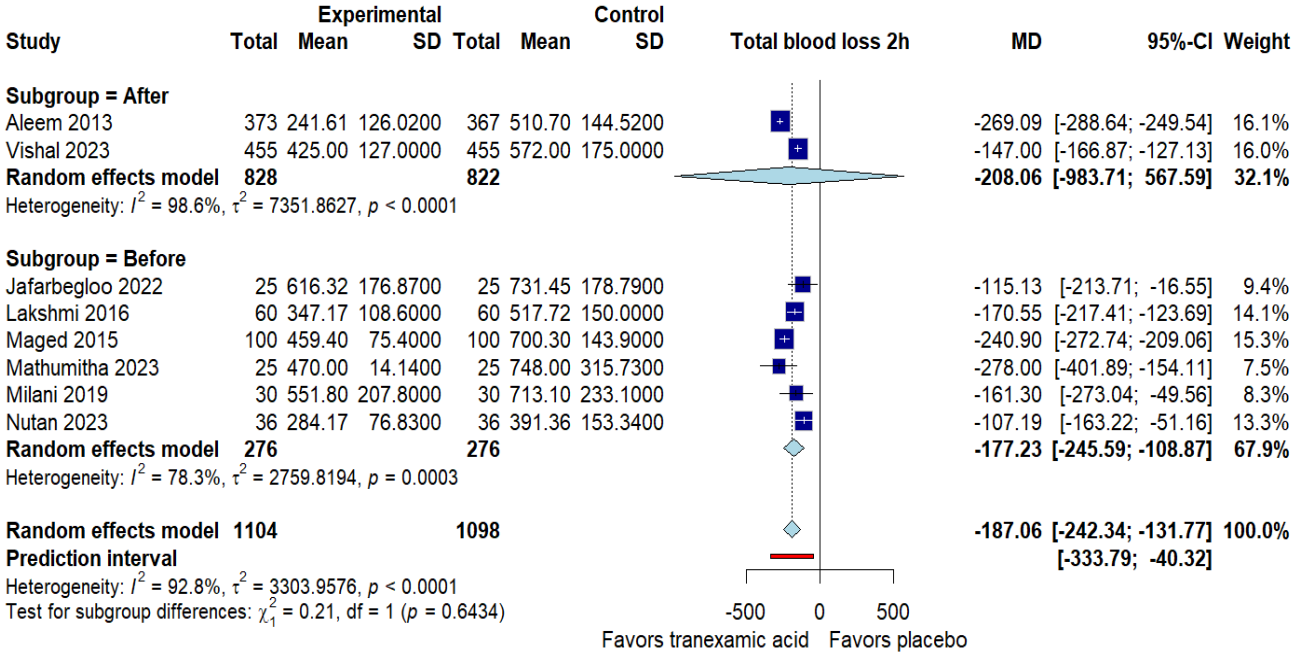
SM9. Subgroup analysis of total blood loss at two hours according to blinding



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



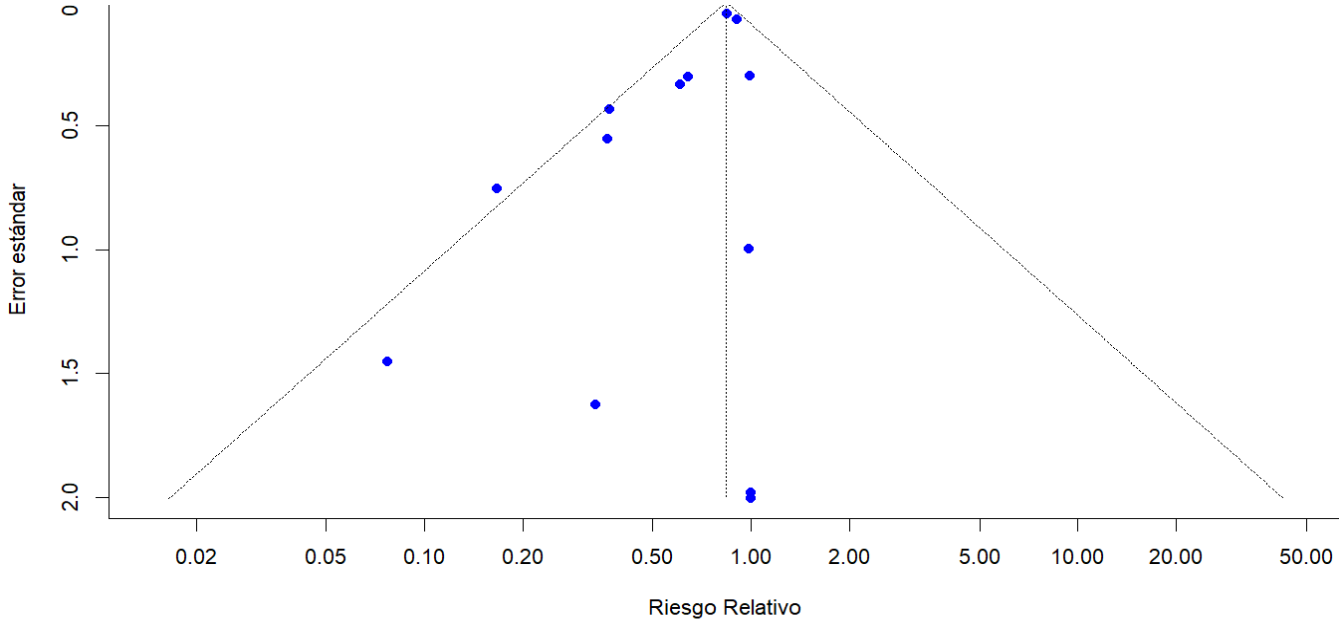
SM12. Metaregression of blood loss after two hours

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	***

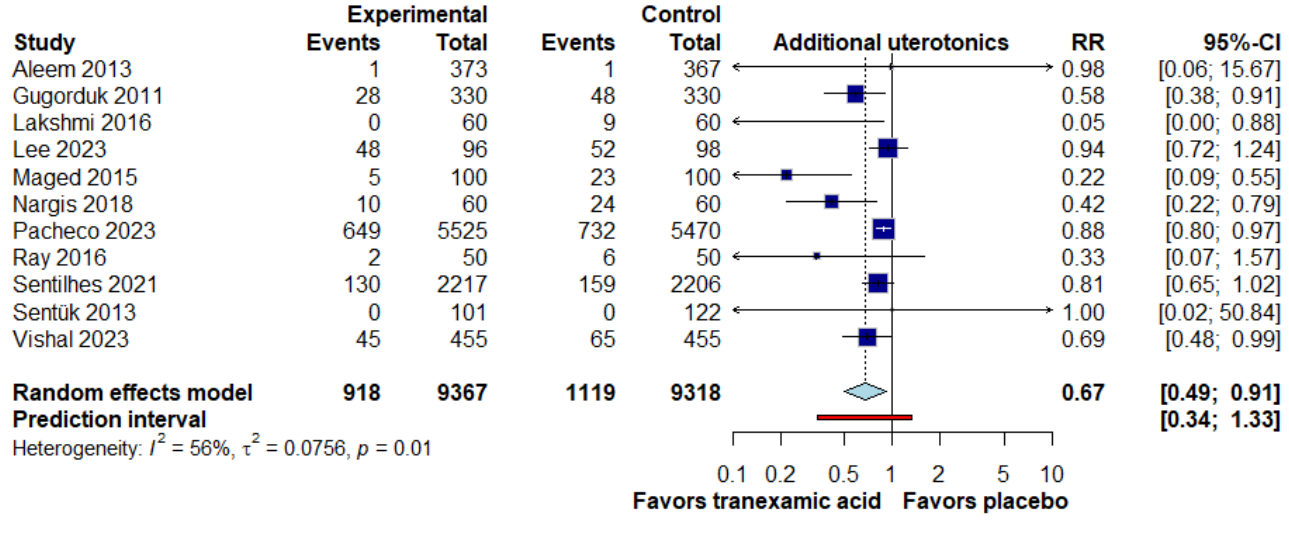
Note:
0 '***'
0.001 '**'
0.01 '*'
0.05 '.'
0.1 ' ' 1

SM13. Funnel plot of the incidence of postpartum hemorrhage

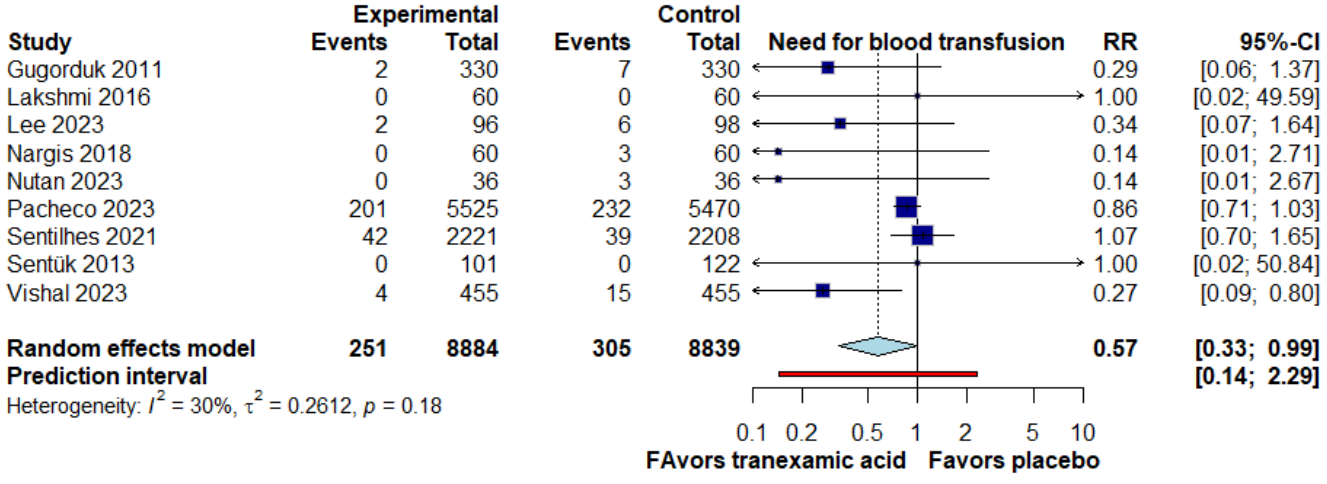


Secondary outcomes

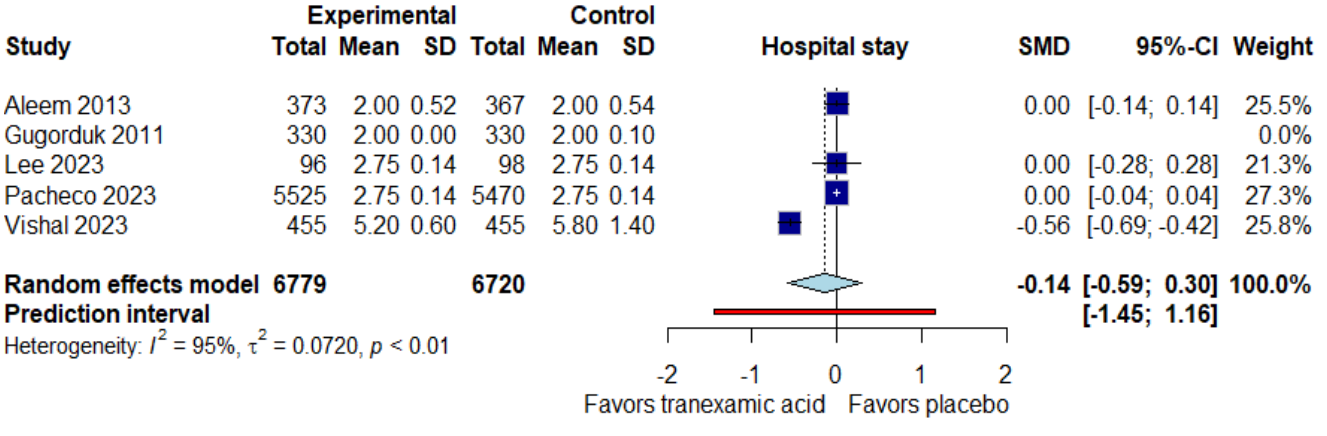
SM14. Additional uterotonics



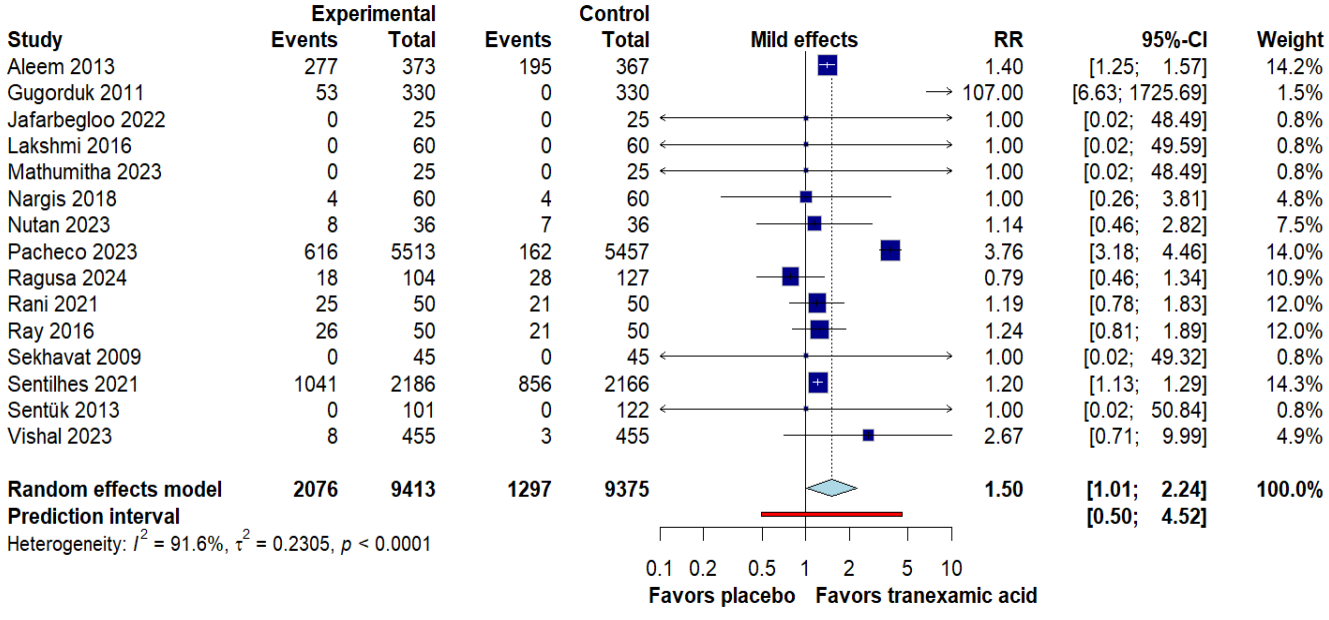
SM15. Need for blood transfusion



SM16. Hospital stay



SM17. Mild effects



SM18. Serious event