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REVIEW ARTICLE

Prophylactic use of tranexamic acid after vaginal delivery reduces the risk of primary postpartum hemorrhage

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ABSTRACT

Background: Postpartum hemorrhage (PPH) is responsible for about 25% of maternal deaths worldwide. Antifibrinolytic agents, mainly tranexamic acid, have been demonstrated to reduce maternal blood loss and need for transfusion requirements at delivery in some settings.

Objective: The aim of this meta-analysis of randomized controlled trials (RCTs) was to evaluate the effectiveness of tranexamic acid for the prevention of PPH after vaginal delivery.

Data sources: The search was conducted using electronic databases from the inception of each database through February 2018. Review of articles also included the abstracts of all references retrieved from the search. No restrictions for language or geographic location were applied.

Study design: Selection criteria included RCTs comparing the prophylactic use of tranexamic acid after vaginal delivery with control (either placebo or no treatment). Trials in women undergoing cesarean delivery and trials in women with established PPH were excluded. The primary outcome was the incidence of primary PPH. The summary measures were reported as summary relative risk (RR) with 95% confidence interval (CI) using the random-effects model of DerSimonian and Laird.

Tabulation, integration, and results: Four RCTs, including 4671 participants, evaluating tranexamic acid usually 1 g intravenous (IV) within 10 min after vaginal delivery in addition to oxytocin, cord traction, and uterine massage, at or near term for prevention of primary PPH, defined mostly as blood loss $\geq$500 mL in the first 24 h following delivery, were analyzed. Women who received prophylactic tranexamic acid after vaginal delivery had a significantly lower incidence of primary PPH (8.7 versus 11.4%; RR 0.61, 95% CI 0.41–0.91) and lower mean blood loss mean difference (MD) −84.74 mL, 95% CI −109.76 to −59.72). The risk of thrombotic events was not increased in the tranexamic acid group.

Conclusions: Prophylactic tranexamic acid 1 g IV within 10 min after vaginal delivery reduces the risk of primary PPH.

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KEYWORDS
Bleeding; cesarean delivery; mortality; operative delivery; postpartum hemorrhage

Introduction

Postpartum hemorrhage (PPH), defined by the World Health Organization as "blood loss from the birth canal in excess of 500 mL during the first 24 hours after delivery," [1] is responsible for 25% of maternal deaths worldwide [2,3]. PPH is the leading cause of maternal mortality in low-income countries and the primary cause of nearly one-quarter of all maternal deaths globally [1].

Different strategies have been described for preventing PPH, including active management of the third stage of labor [4–6]. Antifibrinolytic agents, mainly tranexamic acid have been demonstrated to prevent PPH [7–11]. There are several published clinical trials for the use of tranexamic acid at the time of vaginal delivery, but no consensus on its use or guidelines for management.

Objective

The aim of this meta-analysis of randomized controlled trials (RCTs) was to evaluate the effectiveness of prophylactic tranexamic acid administration for prevention of primary PPH after vaginal delivery.

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Materials and methods

Search strategy

This review was performed according to a protocol recommended for systematic review [12]. The search was conducted using Medline, Embase, Scopus, ClinicalTrials.gov, and Ovid and Cochrane Library as electronic databases. The citations were identified with the use of a combination of the following text words: "postpartum hemorrhage," "PPH," "tranexamic," "delivery," "bleeding," and "randomized" from the inception of each database through February 2018. Review of articles also included the abstracts of all references retrieved from the search. No restrictions for language or geographic location were applied.

Study selection

Selection criteria included RCTs comparing the use of prophylactic tranexamic acid after vaginal delivery with control (either placebo or no treatment) in the prevention of primary PPH. Trials in women undergoing cesarean delivery and trials in women with established PPH were excluded.

Quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudorandom sequence, e.g. odd/even hospital number or date of birth and alternation) were also excluded.

Risk of bias assessment

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [12]. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias [12].

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials.

Primary and secondary outcomes

The primary outcome was the incidence of primary PPH. Secondary outcomes included mean postpartum blood loss within 24 h of delivery, severe PPH (i.e. blood loss more than 1000 mL within 24 h of delivery), use of additional medical interventions to control PPH, thromboembolic events, hemoglobin and hematocrit drop 24 h after delivery, blood transfusions at, or immediately after delivery, severe maternal morbidity (e.g. intensive care unit admission,

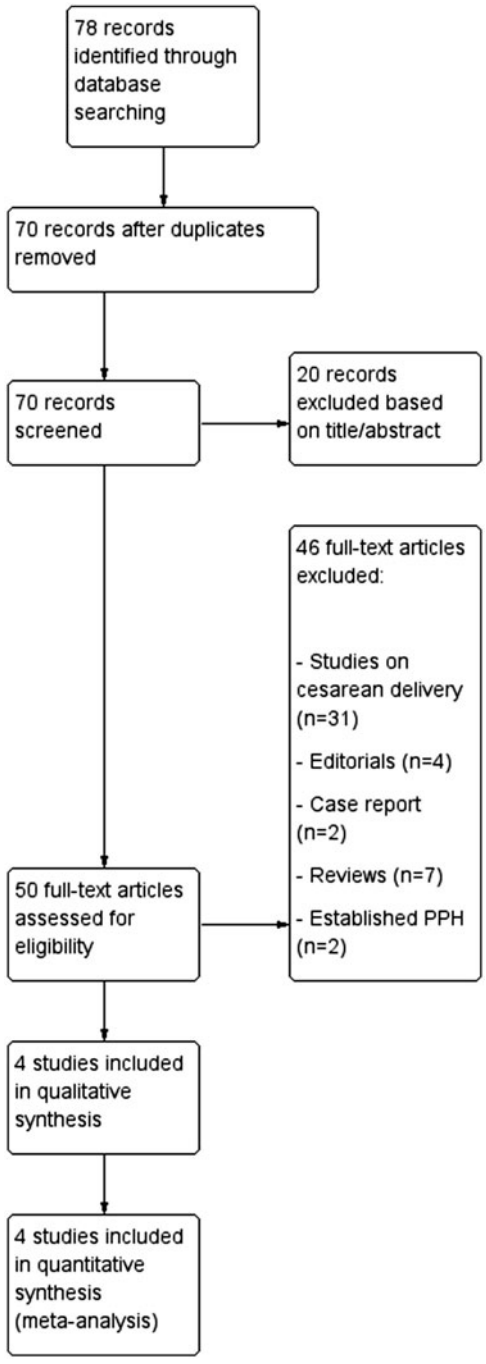

Figure 1. Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

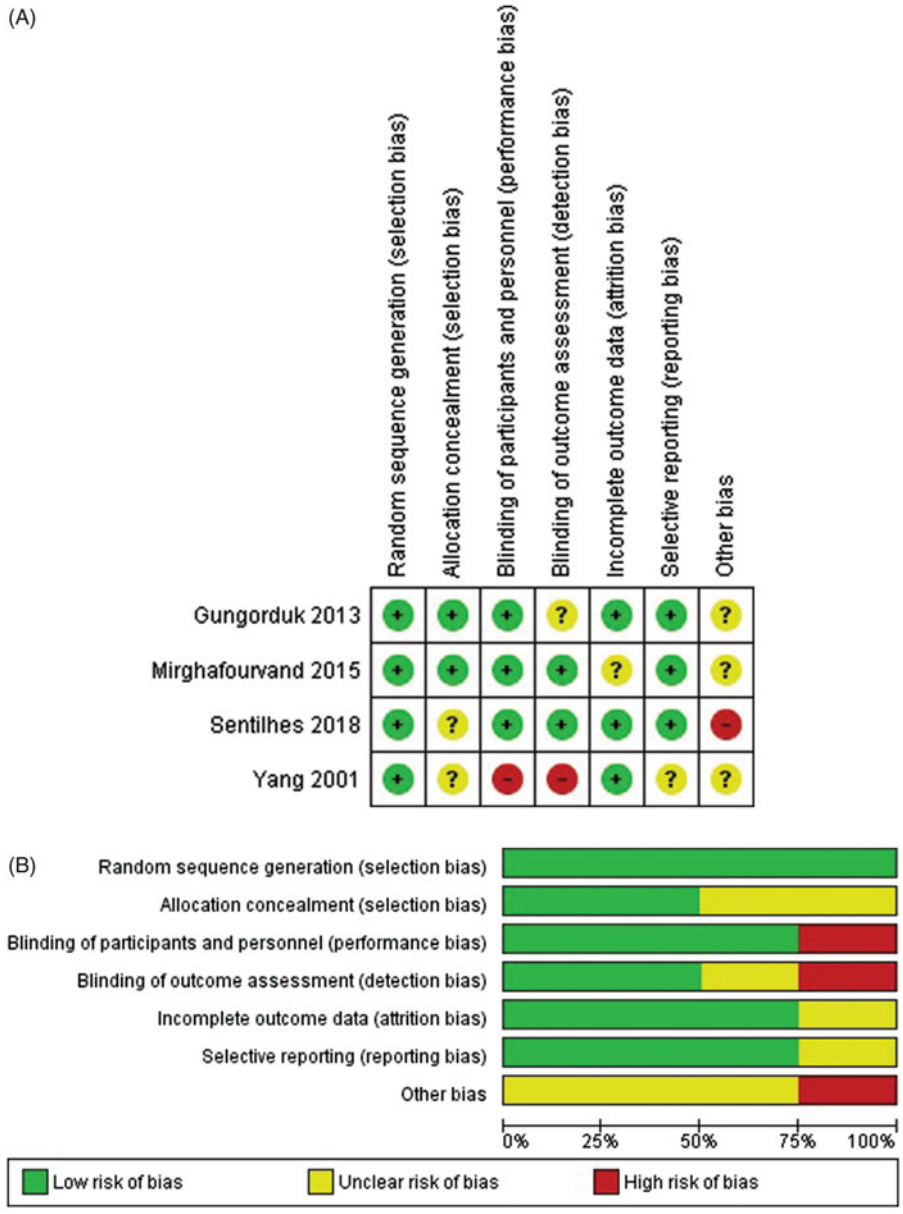

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

hysterectomy, and organ failure), and maternal adverse drug reactions.

Statistical analysis

The data analysis was completed independently by two authors (GS, LC) using Review Manager version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved by discussion. The summary measures were reported as summary relative risk (RR) or mean difference (MD) with 95% confidence interval (CI) using the random-effects model of DerSimonian and Laird. I-squared (Higgins I^2) greater than 0% was used to identify heterogeneity.

Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. A 2-by-2 table was assessed for RR; for continuous outcomes means ± standard deviation (SD) were extracted and imported into Review Manager version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). Sensitivity analysis for the primary outcome was

Table 1. Characteristics of the included trials.

	Yang [15]	Gungorduk [16]	Mirghafourv [17]	Sentilhes [18]
Study location	China	Turkey	Iran	France
Sample size[a]	273 (186 versus 87)	439 (220 versus 219)	120 (60 versus 60)	3839 (1921 versus 1918)
Number of fetuses	Singleton gestations	Singleton and twin gestations	Singleton gestations	Singleton gestations
Presentation	Vertex	Vertex	Vertex	Vertex
Parity	Nulliparous only	Nulliparous only	Nulliparous and multiparous	Nulliparous and multiparous
Gestational age at delivery	At term	>34 weeks	At term	At term
Mode of delivery	Spontaneous vaginal delivery	Vaginal delivery	Spontaneous vaginal delivery	Spontaneous vaginal delivery
Primary outcome	PPH	Mean blood loss	PPH	PPH
Definition of PPH	≥400 mL within 24 h after delivery	>500 mL within 24 h after delivery	≥500 mL within 24 h after delivery	≥500 mL within 24 h after delivery
Definition of severe PPH	Not reported	>1000 mL within 24 h after delivery	>1000 mL within 24 h after delivery	>1000 mL within 24 h after delivery
Method for estimation blood loss	Weight and volume of blood loss, immediately after the expulsion of placenta and from placenta expulsion till 2 h after delivery	Weight of a sheet soaked from the end of the delivery to 2 h after birth	Weight of a sterile graduated container with a plastic cover from the end of the delivery to 2 h after birth	A graduated bag (with 100 mL graduations) to collect and measure postpartum vaginal blood loss objectively was placed just after delivery and remained in place for at least 15 min and until the birth attendant considered that the bleeding had stopped

[a]Data are presented as total number (number in the intervention versus number in the control group).

Table 2. Management of the third stage of labor.

	Yang [15]	Gungorduk [16]	Mirghafourv [17]	Sentilhes [18]
Uterotonic standard prophylaxis	Oxytocin	Oxytocin	Oxytocin	Oxytocin
Oxytocin: dose	10 IU	10 IU	10 IU	10 IU
Oxytocin: when given	Immediately after delivery of the anterior shoulder	Within 2 min after birth	After delivery of placenta	At delivery of the anterior shoulder or within 2 min after birth
Controlled cord traction	Not reported	Performed routinely	Performed routinely	Left to discretion of the provider
Uterine massage	Not reported	Performed routinely	Performed routinely	Not performed routinely
Early versus delayed cord clamping	Not reported	Early cord clamping	Early cord clamping	Not reported
Intervention TXA i.v.: Dose	1 or 0.5 g	1 g	1 g	1 g
Intervention TXA i.v. Timing	Two–three minutes after delivery of the baby	Within 5 min after delivery of the anterior shoulder	Within 10 min after delivery of the anterior shoulder	After delivery of the baby
Control	No treatment	Placebo	Placebo	Placebo

PPH: postpartum hemorrhage; TXA: tranexamic acid.

planned in placebo-only trials. p Value $<.05$ was considered statistically significant.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [13].

Results

Study selection and study characteristics

The flow of study identification is shown in Figure 1. Six trials [11,14–18] were identified as relevant. Two of them were excluded because they studied the use of tranexamic acid in women with established PPH for prevention of hysterectomy [11,14]. Therefore, four trials, including 4671 participants, were included in the meta-analysis and were analyzed.

The quality of the RCTs included in our meta-analysis was assessed by using the seven criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Most of the included studies were judged as "low risk" of bias in most of the seven Cochrane domains related to the risk of bias. All the included studies had "low risk" of bias in "random sequence generation." In three double-blind placebo-controlled studies, neither the participants nor the investigators were aware of the treatment assignments (Figure 2). Statistically, heterogeneity within the trials was low with no inconsistency ($I^2 = 0\%$) for most of the outcomes.

All trials evaluated prophylactic use of tranexamic acid after vaginal delivery at or near term in mostly singleton nulliparous gestations in the prevention of primary PPH, defined mostly as blood loss $\geq$500 mL within 24 h of delivery (Table 1). In all the four trials, PPH prophylaxis with oxytocin 10 IU after delivery was used. When reported, the third stage was managed also with uterine massage and controlled cord traction in addition to oxytocin. In the study arm, tranexamic acid was given usually as 1 g IV soon (within 10 min) after delivery of the baby and compared in three of the four trials to placebo (Table 2) [5,19–21]. Risk factors for PPH are reported in Table 3. Three trials excluded women with preeclampsia, and two of them those with the history of PPH in a prior pregnancy, among other exclusions (Table 3).

Synthesis of results

Table 4 shows primary and secondary outcomes. Women who received prophylactic tranexamic acid after vaginal delivery had a significantly lower incidence of primary PPH (8.7 versus 11.4%; RR 0.61, 95%

Table 3. Risk factors for postpartum hemorrhage (PPH).

	Yang [15]	Gungorduk [16]	Mirghafourv [17]	Sentilhes [18]	Total
BMI	Not reported	30.4 ± 3.9 versus 29.7 ± 4.4	27.2 ± 3.1 versus 27.9 ± 4.2	Not reported	28.8 versus 28.8
Multiple gestation	Excluded	3/220 (1.4%) versus 1/219 (0.5%)	Excluded	Excluded	3/220 (1.4%) versus 1/219 (0.5%)
Polyhydramnios	Excluded	8/220 (3.6%) versus 6/219 (2.7%)	Excluded	Not reported	8/220 (3.6%) versus 6/219 (2.7%)
Fetal macrosomia	Excluded	7/220 (3.2%) versus 4/219 (1.8%)	Excluded	Not reported	7/220 (3.2%) versus 4/219 (1.8%)
Grand multiparity	Excluded	13/220 (5.9%) versus 14/219 (6.4%)	Excluded	Not reported	13/220 (5.9%) versus 14/219 (6.4%)
Preeclampsia	Excluded	4/220 (1.8%) versus 7/219 (3.2%)	Excluded	Excluded	4/220 (1.8%) versus 7/219 (3.2%)
Previous PPH	Excluded	2/220 (0.9%) versus 0/219	Excluded	Not reported	2/220 (0.9%) versus 0/219
Episiotomy or vaginal tears	Not reported	114/220 (51.8%) versus 100/219 (45.7%)	52/60 (87%) versus 52/60 (87%)	Not reported	166/280 (59.3%) versus 152/279 (54.5%)

Data are presented as r as mean ± standard deviation (intervention versus control group).

Table 4. Primary and secondary outcomes for the prevention of postpartum hemorrhage (PPH).

	Yang [15]	Gungorduk [16]	Mirghafourv [17]	Sentilhes [18]	Total	I^2	RR or MD (95% CI)
PPH	18/186 (9.7%) versus 22/87 (25.2%)	4/220 (1.8%) versus 15/219 (6.8%)	27/60 (45.0%) versus 34/60 (56.7%)	156/1902 (8.1%) versus 188/1902 (9.9%)	205/2368 (8.7%) versus 259/2268 (11.4%)	70%	**0.61 (0.41–0.91)**
Mean blood loss (mL)	243.1 ± 140.4 versus 314.8 ± 180.9	261.5 ± 146.8 versus 350 ± 188.8	518.9 ± 319.6 versus 659.3 ± 402.5	Not reported	–	0%	**−84.74 mL (−109.76 to −59.72)**
Severe PPH	Not reported	1/220 (0.5%) versus 5/219 (2.3%)	4/60 (6.7%) versus 11/60 (18.3%)	47/1902 (2.5%) versus 57/1902 (3%)	52/2182 (2.4%) versus 73/2181 (3.3%)	41%	0.57 (0.27–1.18)
Additional medications	Not reported	6/220 (2.7%) versus 19/219 (8.7%)	3/60 (5.0%) versus 7/60 (11.7%)	140/1902 (7.4%) versus 186/1902 (9.8%)	149/2182 (6.8%) versus 212/2181 (9.7%)	51%	0.55 (0.30–1.00)
Hemoglobin drop after 24 h (g/dL)	Not reported	Not reported	1.4 ± 0.8 versus 1.7 ± 1.0	0.76 ± 1.23 versus 0.78 ± 1.26	–	63%	−0.11 (−0.37–0.15)
Hematocrit drop after 24 h (%)	Not reported	Not reported	3.7 ± 2.3 versus 4.8 ± 3.0	1.97 ± 3.72 versus 1.94 ± 3.84	–	80%	−0.44 (−1.53–0.65)
Blood transfusion	Not reported	1/220 (0.5%) versus 3/219 (1.4%)	Not reported	17/1902 (0.9%) versus 18/1902 (0.9%)	18/2122 (0.8%) versus 21/2121 (1.0%)	0%	0.87 (0.46–1.64)
Admission to ICU	Not reported	0/220 versus 0/219	Not reported	Not reported	0/220 versus 0/219	Not applicable	Not estimable
Hysterectomy	Not reported	0/220 versus 0/219	Not reported	Not reported	0/220 versus 0/219	Not applicable	Not estimable
Organ failure	Not reported	0/220 versus 0/219	Not reported	Not reported	0/220 versus 0/219	Not applicable	Not estimable
Thromboembolic events	0/186 versus 0/87	0/220 versus 0/219	0/60 versus 0/60	1/1902 (0.1%) versus 4/1902 (0.2%)	1/2368 (0.1%) versus 4/2268 (0.2%)	Not applicable	0.25 (0.03–2.24)
Nausea	Not reported	33/220 (15%) versus 12/219 (5.5%)	2/60 (3.3%) versus 0/60 (0%)	133/1902 (7%) versus 61/1902 (3.2%)	168/2182 (7.7%) versus 73/2,181 (3.3%)	0%	**2.29 (1.75–2.99)**
Vomiting	Not reported	30/220 (13.6%) versus 14/219 (6.4%)	Not reported	133/1902 (7%) versus 61/1902 (3.2%)	163/2122 (7.7%) versus 75/2121 (3.5%)	0%	**2.17 (1.66–2.83)**

RR: relative risk; MD: mean difference; CI: confidence interval; ICU: intensive care unit.
Data are presented as number in the intervention versus number in the control group or as mean ± standard deviation. Boldface data, statistically significant.

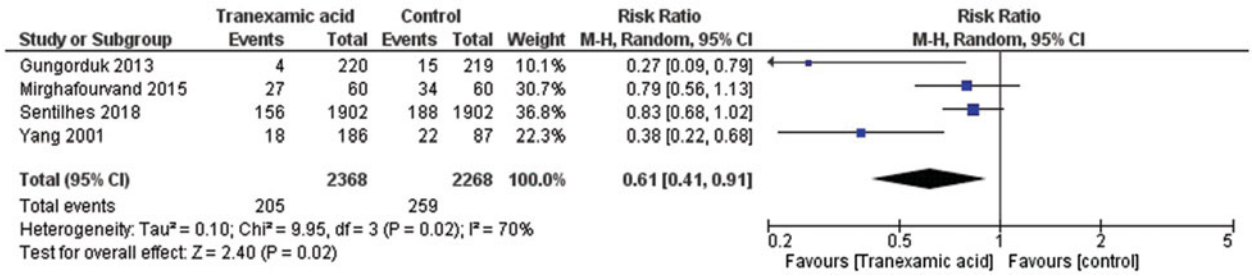

Figure 3. Forest plot for the risk of primary PPH.

CI = 0.41–0.91; Figure 3) and lower mean blood loss (MD = −84.74 mL, 95% CI = −109.76 to −59.72). Sensitivity analysis in placebo-only trials [16–18] concurred with the overall analysis for the primary outcome (187/2182 (8.6%) versus 237/2181 (10.9%); RR = 0.79, 95% CI = 0.66–0.94). There was no significant between-group difference in the other secondary outcomes, including thromboembolic events (0.1 versus 0.2%; RR = 0.25, 95% CI = 0.03–2.24). Women who received tranexamic acid had a significantly higher incidence of nausea (7.7 versus 3.3%; RR = 2.29, 95% CI = 1.75–2.99), and vomiting (7.7 versus 3.5%; RR = 2.17, 95% CI = 1.66–2.83). Other side effects, including diarrhea, pyrexia, tachycardia, headache, giddiness, shivering, and dizziness, were reported only by Gungorduk et al. [16] with no between-group difference.

Comment

This meta-analysis from four RCTs evaluated the use of tranexamic acid after vaginal delivery for prevention of primary PPH. When used as prophylaxis within 10 min after vaginal delivery usually at the dose of 1 g IV, in addition to standard prophylaxis with oxytocin, cord traction, and uterine massage, tranexamic acid reduced the risk of primary PPH and the mean postpartum blood loss. Tranexamic acid did not increase the risk of thrombotic events.

The four trials included had a low risk of allocation bias by Cochrane Collaboration tool assessment. Intent-to-treat analysis was used. To our knowledge, no prior meta-analysis on this issue is as large, up-to-date or comprehensive. Limitations of our study are mostly inherent to the limitations of the included studies. Only three trials, out of the four, used placebo as control and were double-blind. The major shortcoming was the lack of data regarding long-term outcomes. Incidence of thromboembolic events was so small that there was little power to generalize the non-significant findings. Women with thrombophilia and those with underlying renal disease were not included in the review.

Several prior meta-analyses evaluated harms and benefits of tranexamic acid in pregnant women. Simonazzi et al. found that prophylactic tranexamic acid given before cesarean skin incision in women undergoing cesarean delivery, under spinal or epidural anesthesia, significantly decreased blood loss, including PPH and severe PPH, in addition to the standard prophylactic oxytocin given after the delivery of the neonate [8]. Shakur et al. evaluated the effectiveness and safety of antifibrinolytic drugs for treating primary PPH. They found that tranexamic acid when administered intravenously reduced mortality due to bleeding in women with primary PPH without increasing the risk of thromboembolic events [22]. Unfortunately, this review did not include all currently available RCTs on vaginal delivery had, therefore, smaller numbers, and included cesarean delivery, too. Recently, Pilbrant et al. [23] evaluated the efficacy of tranexamic acid for the treatment of established primary PPH after delivery. This review, including two trials [11,14] with 14,363 participants, concluded that in women with established PPH after spontaneous vaginal delivery at term, use of tranexamic acid 1 g IV reduced the risk of hysterectomy [23]. This is the first meta-analysis specifically evaluating the prophylactic use of tranexamic acid after vaginal delivery.

Tranexamic acid is a lysine analog, which acts as an antifibrinolytic *via* competitive inhibition of the binding of plasmin and plasminogen to fibrin. Peak plasma concentration is obtained immediately after intravenous administration, then concentration decreases until the sixth hour. Its half-life is about 2 h [24]. Tranexamic acid is safe in pregnancy, being FDA category B. One concern regarding the use of tranexamic acid is the potential for thromboembolic events in a population at already high risk of thrombosis.

However, our pooled results showed no increased risk of thromboembolic events in the tranexamic group compared with the control group. These data on thromboembolic events were also supported by findings of prior meta-analyses on tranexamic acid use in pregnant women [8,22,23]. However, further studies should also include women with higher baseline risk of thromboembolic events [24,25], including women with antiphospholipid syndrome [24].

In summary, when used as prophylaxis within 10 min after vaginal delivery in addition to oxytocin, cord traction, and uterine massage, tranexamic acid 1 g IV reduces the risk of primary PPH.

Disclosure statement

No potential conflict of interest was reported by the authors.

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