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REVIEW ARTICLE

Tranexamic acid for treatment of primary postpartum hemorrhage after vaginal delivery: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Postpartum hemorrhage (PPH) is responsible for about 25% of maternal deaths worldwide. Antifibrinolytic agents, mainly tranexamic acid (TXA), have been demonstrated to reduce blood loss in patients with established PPH.

Objective: The aim of this meta-analysis of randomized controlled trials (RCTs) was to evaluate the effectiveness of TXA administration in women with established primary PPH after vaginal delivery.

Data sources: The search was conducted using electronic databases from 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 use of TXA in women with established primary PPH after vaginal delivery with control (either placebo or no treatment). Trials in women undergoing cesarean delivery and trials in prevention of PPH were excluded. The primary outcome was the incidence of hysterectomy. The summary measures were reported as summary relative risk (RR) with 95% of confidence interval (CI) using the random effects model of DerSimonian and Laird.

Tabulation, integration, and results: Two trials including 14,363 women with established primary PPH after vaginal delivery were analyzed. Women who received TXA soon after the diagnosis of PPH had a significantly lower incidence of hysterectomy (0.5% vs 0.8%; RR 0.63, 95% CI 0.42–0.94), compared to those who did not. The risk of thrombotic events was not increased in the TXA group.

Conclusion: In women with established PPH after vaginal delivery, the use of TXA reduces the risk of hysterectomy and does not increase the risk of thrombotic events. We recommend 1 g plus a second dose of 1 g if bleeding continues after 30 min.

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KEYWORDS
Postpartum hemorrhage; bleeding; mortality; operative delivery; cesarean delivery

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 h after delivery," [1] is responsible for 25% of maternal deaths worldwide [2,3].

Different strategies have been described for preventing PPH, including active management of the third stage of labor [4–6]. Once the diagnosis of PPH is established, the use of uterotonics has been shown to be beneficial. Antifibrinolytic agents, mainly tranexamic acid (TXA), have been demonstrated to reduce blood loss and need for transfusion requirements [7–11]. There are several published clinical trials for the use of TXA 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 TXA administration in women with established primary PPH after vaginal delivery.

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Methods

Search strategy

This review was performed according to a protocol recommended for systematic review [12]. The search was conducted using Medline, Embase, Web of Science, Scopus, ClinicalTrial.gov, Ovid, and Cochrane Library as electronic databases. The citations were identified with the use of a combination of the following text words: "PPH," "tranexamic," "delivery," "bleeding," and "randomized" from 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 TXA in women with established primary PPH after vaginal delivery with control (either placebo or no treatment). Trials in women undergoing cesarean delivery and trials in prevention of 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, 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 hysterectomy. The secondary outcomes were maternal death, thromboembolic events (e.g. deep-vein thrombosis, pulmonary embolism, myocardial infarction, and stroke), surgical interventions (e.g. intrauterine tamponade, embolization, brace sutures, arterial ligation) done after randomization to control bleeding and achieve hemostasis, blood transfusions, admission to intensive care unit (ICU), and organ failure.

Statistical analysis

The data analysis was completed independently by two authors (L.C. and G.S.) using Review Manager v. 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) with 95% of 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 two-by-two table was assessed for RR; for continuous outcomes means ± standard deviation were extracted and imported into Review Manager v. 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark).

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

Results

The flow of study identification is shown in Figure 1. Six trials [11,14–18] were identified as relevant. Four trials [15–18] were excluded because they evaluated prophylactic use of TXA after in prevention of PPH. Therefore, two trials were included in the meta-analysis [11,14].

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*. All the included studies had "low risk" of bias in "random sequence generation." Adequate methods for allocation of women were used. In one double-blind placebo-controlled trial, 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 the primary outcome.

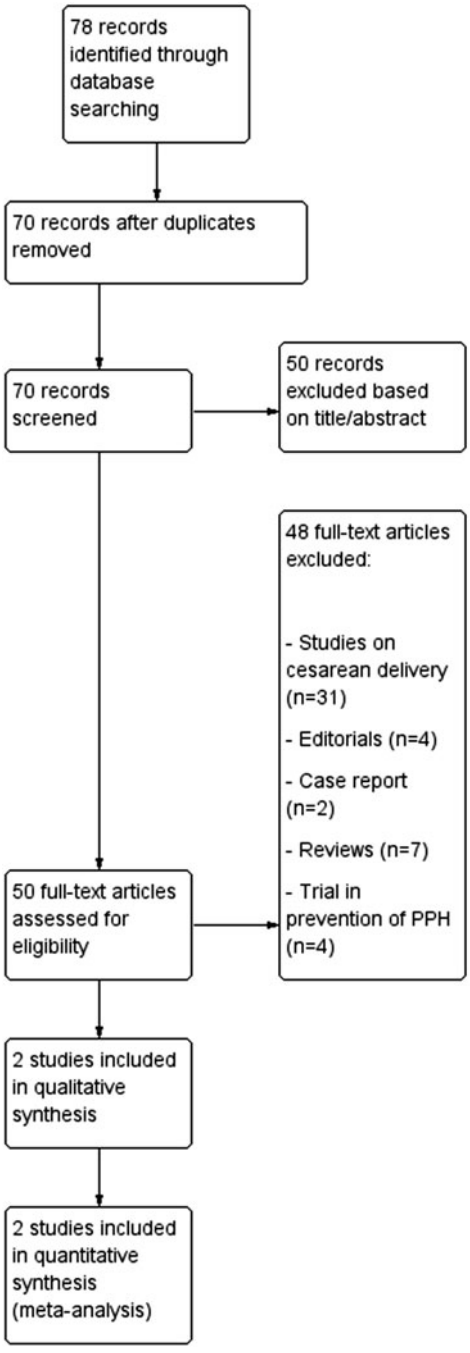

Figure 1. Flow diagram of studies identified in the systematic review. (PRISMA template.)

Table 1 shows the characteristics of the included trials. One study was conducted in France, while the WOMAN trial was a multicenter study done in 193 hospitals in 21 countries. Ducloy-Bouthors et al. included women with singleton gestations undergoing spontaneous vaginal delivery (SVD) at term with a diagnosis of primary PPH, defined as postpartum blood loss >800 ml within 24 h of delivery. In the WOMAN trial, although the diagnosis of PPH was clinical, the authors specified that diagnosis of primary PPH could be based on clinically estimated blood loss of more than 500 ml within 24 h of delivery or any blood loss sufficient to compromise hemodynamic stability. In both trials patients received all usual care (Table 2) but were also randomly allocated to receive either TXA, or no treatment in the French trial, or placebo in the WOMAN trial.

In Ducloy-Bouthors et al., all patients with PPH >500 ml were managed according to the same timing according to French practice guidelines: bladder catheter, manual removal of retained placenta if necessary, genital tract examination, uterine exploration, oxytocin (30 U/30 min) followed, if these procedures were ineffi-cacious, by sulprostone 500 μg in 1 h.

In the WOMAN trial, woman with PPH was managed according to local protocols. In most of the included hospitals protocol included bladder catheter, uterine massage, repairing of any vaginal or cervical lacerations, explorations of the uterus and use of uterotonics, with oxytocin as first-line therapy. In both trials, hysterectomies were performed at provider discretion.

Synthesis of results

Table 3 shows primary and secondary outcomes. Women who received TXA soon after the diagnosis of PPH had a significantly lower incidence of hysterectomy (0.5% vs 0.8%; RR 0.63, 95% CI 0.42–0.94; Figure 3), compared to those who did not. No significant differences were found in the incidence of other surgical interventions done after randomization to control bleeding and achieve hemostasis, in the incidence of blood transfusions, in the incidence of maternal death, and in the incidence of admission to ICU.

Comment

This meta-analysis from two RCTs evaluated the use of TXA in established PPH after SVD at term. We found that the use of TXA reduced the risk of hysterectomy. Our meta-analysis also showed that TXA did not increase the risk of thrombotic events.

Our study has several strengths. The two 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 one trial used placebo as control and was double-blind. Data regarding optimal dose was limited. More than half of the women included in the analysis came from one large

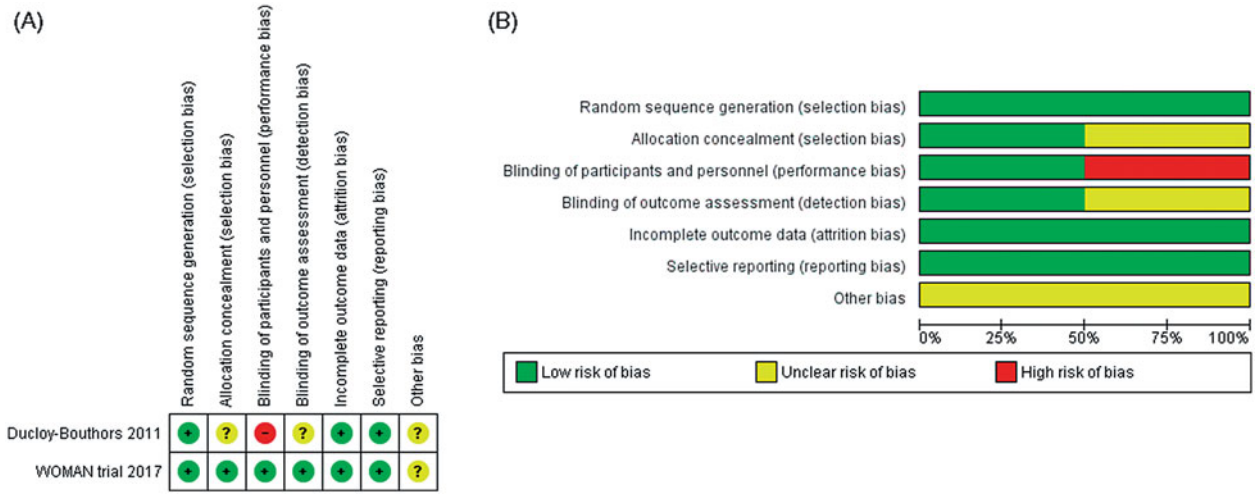

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Table 1. Characteristics of the included trials in women with established PPH.

	Ducloy-Bouthors et al. [14]	WOMAN trial [11]
Study location	France	International
Inclusion criteria	Established PPH after SVD at term, vertex presentation, singleton gestations	Established PPH after SVD at term, vertex presentation
Definition of PPH	>800 mL	>500 mL
Intervention TXA i.v. loading dose	4 g in 1 h	1 g
Intervention TXA i.v. continuing dosing	then 1 g/h over 6 h	Plus a second dose of 1 g if bleeding continued after 30 min or stopped and restarted within 24 h of the first dose
Control	No treatment	Placebo
Primary outcome	Mean blood loss	Composite of death from all causes or hysterectomy within 42 days of randomization
Sample size[a]	144 (72 vs 72)	14,219 (7093 vs 7126)
Method for estimation blood loss	Under-buttocks drape with a graduated collection pouch placed immediately after vaginal delivery	Not reported
Management of PPH >500 mL	Bladder catheter, manual removal of retained placenta if necessary, genital tract examination, uterine exploration, oxytocin (30 U/30 min) followed, if these procedures were inefficacious, by sulprostone 500 μg in 1 h.	Bladder catheter, uterine massage, repairing of any vaginal or cervical lacerations, explorations of the uterus and use of uterotonics

PPH: Postpartum hemorrhage; TXA: tranexamic acid; SVD: spontaneous vaginal delivery.
[a]Data are presented as total number (number in the intervention vs number in the control group).

Table 2. Management of PPH.

	Ducloy-Bouthors et al. [14]	WOMAN trial [11]
Oxytocin	Yes (30 IU/30 min)	Yes
Other uterotonics	Sulprostone (500 μg in 1 h)	Ergometrine, misoprostol, prostaglandin
Uterine massage	No	Yes routinely to all women
Bladder catheter	Yes routinely to all women	Yes routinely to all women
Manual removal of retained placenta	Yes if necessary	Yes if necessary 745/7080 (10.5%) vs 779/7108 (11%)
Intrauterine tamponade	Not reported	Yes 519 (7.3%) vs 547 (7.7%)
Other (embolization, brace sutures, arterial ligation, laparotomy for bleeding)	Yes if necessary	Yes if necessary

study [11], which therefore drives the statistics. The causes of PPH were not stated in the original studies, and therefore we cannot assess whether or not the causes of PPH effect on the intervention.

Several prior meta-analysis evaluated harms and benefits of TXA for PPH. Simonazzi et al. found that prophylactic TXA 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

Table 3. Primary and secondary outcomes in women with established PPH.

	Ducloy-Bouthors et al. [14]	WOMAN trial [11]	Total	I^2	RR (95% CI)
Hysterectomy	0/72 vs 2/72 (2.8%)	37/7080 (0.5%) vs 58/7108 (0.8%)	37/7152 (0.5%) vs 60/7180 (0.8%)	0%	**0.63 (0.42–0.94)**
Maternal death due to bleeding	0/72 vs 0/72	110/7083 vs 135/7108	110/7155 (1.5%) vs 135/7180 (1.9%)	Not applicable	0.82 (0.64–1.05)
Maternal death (all causes)	0/72 vs 0/72	148/7083 vs 172/7108	148/7155 (2.1%) vs 172/7180 (2.4%)	Not applicable	0.86 (0.69–1.07)
Deep-vein thrombosis	0/72 vs 0/72	Not reported	0/72 vs 0/72	Not applicable	Not estimable
PE	0/72 vs 0/72	Not reported	0/72 vs 0/72	Not applicable	Not estimable
Myocardial infarction	0/72 vs 0/72	Not reported	0/72 vs 0/72	Not applicable	Not estimable
Stroke	0/72 vs 0/72	Not reported	0/72 vs 0/72	Not applicable	Not estimable
Surgical intervention[a]	4/72 (5.6%) vs 5/72 (6.9%)	1375/7080 (19.4%) vs 1448/7108 (20.4%)	1379/7152 (19.3%) vs 1453/7180 (20.2%)	0%	0.95 (0.89–1.02)
Blood transfusions	10/72 (13.9%) vs 13/72 (18.1%)	Not reported	10/72 (13.9%) vs 13/72 (18.1%)	Not applicable	0.77 (0.63–1.64)
Admission to ICU	3/72 (4.2%) vs 5/72 (6.94%)	Not reported	3/72 (4.2%) vs 5/72 (6.94%)	Not applicable	0.60 (0.15–2.42)
Organ failure	0/72 vs 0/72	Not reported	0/72 vs 0/72	Not applicable	Not estimable

RR: relative risk; CI: confidence interval; PE: pulmonary embolism; ICU: intensive care unit.
Data are presented as number in the intervention vs number in the control group. Boldface data statistically significant.
[a]Surgical interventions done after randomization to control bleeding and achieve hemostasis excluding hysterectomy.

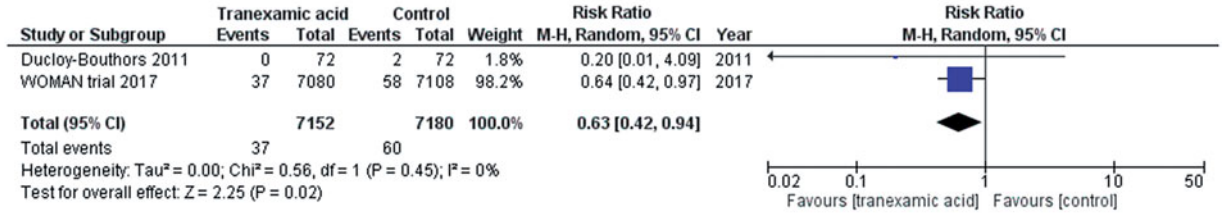

Figure 3. Forest plot for the risk of hysterectomy in women with established PPH.

safety of antifibrinolytic drugs for treating primary PPH. They found that TXA when administered intravenously reduced mortality due to bleeding in women with primary PPH without increasing the risk of thromboembolic events [19]. Unfortunately, this review did not include all currently available RCTs on vaginal delivery, had therefore smaller numbers, and included cesarean delivery too. This is the first meta-analysis specifically evaluating the efficacy of TXA in established PPH after vaginal delivery.

TXA 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 [20]. TXA is safe in pregnancy, being Food and Drug Administration (FDA) category B.

In the 2012, the World Health Organization (WHO) guidelines recommended that TXA should be used for the treatment of primary PPH when uterotonics fail to control the bleeding or when the bleeding is thought to be due to trauma [1]. The evidence for this recommendation was extrapolated from trials in surgery and trauma [21–23]. Our meta-analysis showed that the effect of TXA in PPH is consistent with the effects recorded in nonobstetrical trials. One concern regarding the use of TXA is the potential for thromboembolic events in a population at already high baseline risk of thrombosis. Actually, our pooled results showed no increased risk of thromboembolic events in the tranexamic group compared with the control group. However, further studies should also include women with higher baseline risk of thromboembolic events [15,24,25], including women with antiphospholipid syndrome [24].

In summary, in women with established primary PPH after vaginal delivery, the use of TXA reduces the risk of hysterectomy and does not increase the risk of thromboembolic events. We recommend 1 g i.v. soon after the diagnosis of PPH, plus a second dose of 1 g if bleeding continues after 30 min.

Disclosure statement

No potential conflict of interest was reported by the authors.

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