Systematic Review and Meta-Analysis

Medicine®

OPEN

Tranexamic acid for postpartum hemorrhage prevention in vaginal delivery

A meta-analysis

Yimeng Xia, MD, PhD[a], Brian B. Griffiths, PhD[b], QingSheng Xue, MD, PhD[a,*]

Abstract

Background: Tranexamic acid (TA) has been demonstrated to reduce blood loss and the incidences of postpartum hemorrhage (PPH) during caesarean sections. We compared the clinical efficacy of TA administration on vaginal deliveries with recently published papers.

Methods: Electronic databases of PubMed, Cochrane Library, Embase and Chinese CNKI (Chinese database) and Wanfang were searched through November 2019.The randomized controlled trials were selected between TA and control groups. The relevant studies included four trials with a total of 4579 patients.

Results: Patients treated with TA had a reduction in total blood loss ($P = .009$), lower postoperative blood loss ($P < .00001$), a reduced number of PPH ($P = .02$). However, the occurrence of nausea or/and vomiting is higher in the TA group (the incidence of nausea or vomiting [$P < .00001$], nausea [$P < .00001$] and vomiting [$P < .00001$]).

Conclusion: TA resulted in fewer occurrence rates of PPH, and no significant increase in occurrences of dizziness or photopsia, but higher incidence of vomiting and nausea.

Abbreviations: CIs = confidence intervals, DVT = deep venous thrombosis, PPH = postpartum hemorrhage, RCT = randomized clinical trials, RRs = relative risks, SD = standard deviation, TA = tranexamic acid, WMD = weighted mean difference.

Keywords: meta-analysis, postpartum haemorrhage, randomized controlled trials, tranexamic acid, vaginal delivery

1. Introduction

Postpartum hemorrhage (PPH), 1 of the most common complications after delivery both in caesarean sections and vaginal deliveries is a leading cause of maternal mortality worldwide.[1–5] Since the direct cause of PPH is poor contracting of the uterus, obstetric intervention, and uterotonic medications are recommended interventions.[6–8]

Recent findings have demonstrated that antifibrinolytic drugs like tranexamic acid (TA) can reduce excessive blood loss during cardiac surgery, major trauma, liver transplantation, and so on by decreasing fibrinolysis.[9–15] Moreover, TA has been shown to be safe for clinical use during pregnancy and breastfeeding.[16]

Previous randomized clinical trials (RCT) and meta-analyses suggest that TA reduces blood loss during and after caesarean delivery.[16–23] However, the only meta-analysis on the topic is limited to three trials totaling 740 patients, resulting in weak evidence on the effectiveness on vaginal delivery due to small samples and low methodology quality.[16]

After a thorough search of essential databases for studies on comparing TA treatment to a randomized control group, we found 1 emerging RCT[21] with 3891 patients. In order to assess the effects of prohylactic administration of tranexamic acid on global blood loss or on PPH incidence in vaginal delivery,we performed the present meta-analysis to compare the clinical efficacy of TA treatment for vaginal delivery.

2. Methods

2.1. Search strategy

The present study was conducted by searching the electronic databases of PubMed, Cochrane Library, Embase and Chinese CNKI (Chinese database) and Wanfang through November 2019 to collect relevant trials of TA treatment in vaginal deliveries. We applied the initial search involving the terms (TA OR TA OR TXA OR AMCA OR Cyclokapron) and (pregnancy OR gestation) and (randomized OR RCT OR RCT) and (vaginal delivery). Since the analyses were based on previously published papers, neither ethical

Editor: Bernhard Schaller.

Reprints will not be available from the authors.

The authors have no funding and conflicts of interest to disclose.

[a] Department of Anaesthesiology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China, [b] Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California.

[*] Correspondence: Qingsheng Xue, Department of Anaesthesiology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, No.197, RuijinEr Road, Shanghai, 200025, People's Republic of China (e-mail: 1076194501@qq.com).

How to cite this article: Xia Y, Griffiths BB, Xue Q. Tranexamic acid for postpartum hemorrhage prevention in vaginal delivery: A meta-analysis. Medicine 2020;99:3(e18792).

Received: 28 July 2019 / Received in final form: 9 December 2019 / Accepted: 13 December 2019

http://dx.doi.org/10.1097/MD.0000000000018792

approval nor patient consent is needed. The articles searched were limited to English or Chinese language.

2.2. Study selection

The first step of the procedure was to screen candidate abstracts and titles. In the second round, we performed full-text reviews. The trials were defined as eligible if they followed inclusion criteria:

(1) Clinical comparisons between tranexamic and control groups;
(2) RCTs;
(3) The outcomes of interest were total blood loss, intraoperative blood loss, postoperative blood loss, number of PPH, severe PPH, transfusion needs, and adverse effects, such as nausea and vomiting, dizziness and photopsia.

2.3. Data collection and risk of bias

Y.M. Xia and B.B. Griffiths performed the electronic search and data extraction independently. Any disagreements were resolved by a third author (Q.S. Xue). The data were extracted according to the following standard form: last name of the first author, publication year, country, the number of patients, age of patients, the dosage and time of intervention, and the definition of PPH.

According to Cochrane handbook criteria, we established a table to label 'risk of bias' of the selected studies as the following 6 parameters: adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Each parameter as "low," "high" or "unclear" was listed to clarify the risk of bias.

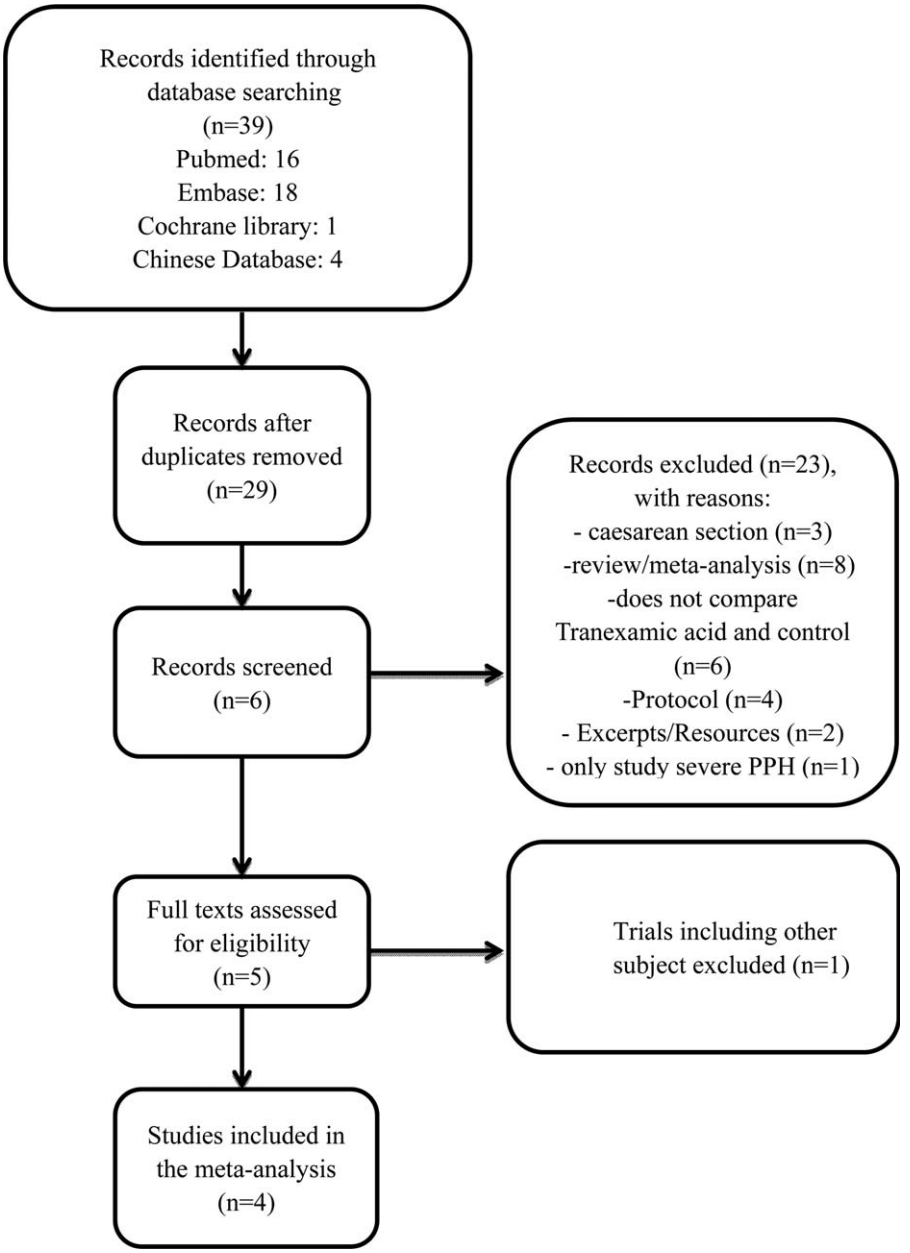

Figure 1. The process applied and studies identified in the present meta-analysis.

2.4. Statistical analysis

All statistical analyses were performed with Review Manager 5.3 software (Cochrane Collaboration, Copenhagen). When the outcome measure was dichotomous we reported the relative risks (RRs). When outcomes were represented as continuous data we reported the weighted mean difference (WMD). For both types of outcomes we reported the 95% confidence intervals (CIs). In cases of statistical heterogeneity, we calculated pooled estimates using a random effects model chi-square test. In cases of homogeneity we used a fixed effects model and calculated the *Z*-score to evaluate outcomes between studies sample variation is represented as the mean± standard deviation for continuous data and the I^2 statistic for heterogeneity data. $P < .05$ was regarded as statistically significant.

3. Results

Figure 1 displays the flowchart of the literature search and selection process. A total of 39 studies were found with electronic searches. After deleting duplicates, 29 papers were identified. Following the primary reviews of article titles and abstracts, 5 studies were included. However, 1 trial only comparing biological factors[24] was also excluded. Finally, 4 studies with a total of 4579 patients were included in the analysis.[17,19–21] The evaluated trials were obtained up until Nov. 2019. The baseline characteristics of the pooled studies were presented in Table 1, such as last name of the first author, publication year, country, the number and age of patients in different groups, the dosage and time of intervention, and the definition of PPH. The bias of risk assessment for each study was listed in Table 2.

3.1. Primary outcome

3.1.1. Blood loss (total, intraoperative, and postoperative).

All 4 trials[17,19–21] reported total blood loss. These studies indicated that TA resulted in a reduction in total blood loss compared to the control group. The pooled mean difference was significantly different (WMD: −65.61, 95% CI: −115.01 – −16.21, $P = .009$; Fig. 2A) between the TA and control group, suggesting the positive effect of TA administration.

For postoperative blood loss blood volume after TA treatment was evaluated in 2 trials.[17,20] The results suggested that TA significantly lowered the volume of postoperative blood loss with (TA vs control; WMD: –41.24, 95% CI: –55.50 – –26.98, $P < .0001$; Fig. 2C). However, 3 papers[17,20,21] that reported intraoperative blood loss observed no significant difference between the TA and control groups (WMD: –14.30, 95% CI: –28.39 – – 0.22, $P = .05$; Fig. 2B).

3.1.2. PPH and transfusion needs.

The incidence of PPH was investigated in all included studies,[17,19–21] and all concluded that TA treatment could significantly reduce the number of PPH (TA vs control; RR:0.48, 95% CI: 0.25 – 0.91, $P = .02$; Fig. 3A). However, the incidence of severe PPH seemed no difference in the 2 groups of 3 studies[19–21] (TA vs control; RR: 0.78, 95% CI: 0.54 – 1.13, $P = .19$;Fig. 3B).The number of required transfusions showed no significant difference (TA vs control; RR:0.87, 95% CI: 0.46 – 1.64, $P = .66$; Fig. 3C) in 2 trials.[19,21]

3.2. Secondary outcomes

3.2.1. Adverse effects (nausea or vomiting, nausea and vomiting).

Two studies[17,21] that included a total of 4164 patients reported the occurrence of nausea or vomiting, which

Table 1

Basic characteristics of included studies.

Study	Year	Country	Patient (No.)		Age, yr		Intervention	Definition of PPH	Outcomes used in this meta-analysis
			TA	Con	TA	Con			
Yang et al[17]	2001	China	94	94	27.6 ± 2.9	28.0 ± 2.6	TA:1g over 2–3 min after delivery of the fetus; Con: 5% glucose	>400mL	TBL,IBL,PBL,PPH,N or V,D,P
Gungorduk et al[19]	2013	Turkey	220	220	27.9 ± 4.9	27.6 ± 4.8	TA:1g over 5 min at delivery of the anterior shoulder; Con: 5% glucose	>500mL	TBL,PPH,SPPH,TN,N,V,D
Mirghafourvand et al[20]	2015	Iran	60	60	26.2 ± 4.8	26.1 ± 4.9	TA:1g over 10 min at delivery of the anterior shoulder; Con: placebo	>500mL	TBL,IBL,PBL,PPH, SPPH,N,D
Sentilhes et al[21]	2018	France	1921	1921	30.3 ± 4.7	30.2 ± 5.0	TA:1g at delivery of the anterior shoulder; Con: normal saline	>500mL	TBL,IBL,PPH,SPPH,TN,N or V,N,V,D,P

D = dizziness, IBL = intraoperative blood loss, N = nausea, P = photopsia, PBL = postoperative blood loss, PPH = postpartum hemorrhage, SPPH = severe postpartum haemorrhage, TA = tranexamic acid, TN = transfusion needs.

Table 2

Risk of bias in included studies.

Study	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomeassessment	Incomplete outcome data	Selective reporting
Yang et al[17]	2001	Unclear	Unclear	High	High	Low	Low
Gungorduk et al[19]	2013	Low	Low	Low	Low	Low	Low
Mirghafourvand et al[20]	2015	Low	Low	Low	Low	Low	Low
Sentilhes et al[21]	2018	Low	Low	Low	Low	Low	Low

was higher in the TA treatment group than control group (RR: 2.17, 95% CI: 1.62 – 2.90, $P < .00001$; Fig. 4A). In addition, 3 trials[19,21,25] compared nausea alone and the results also showed that TA resulted in increased incidence (RR: 2.24, 95% CI: 1.67 – 3.01, $P < .00001$; Fig. 4B). The incidence of vomiting alone was analysed by 2 studies,[19,21] and similar to the previous measures was higher in the TA treatment group than the control group (RR: 2.19, 95% CI: 1.56 – 3.07, $P < .00001$; Fig. 4C).

3.2.2. Adverse effects (dizziness and photopsia). We analyzed 4 studies[17,19–21] involving dizziness and 2[17,21] including photopsia reports between patients treated with TA or control groups. There was no significant difference in the incidence of dizziness (RR: 1.28, 95% CI: 0.83 – 1.95, $P = .26$; Fig. 4D), or photopsia (RR: 1.00, 95% CI: 0.25 – 3.99, $P = 1.00$; Fig. 4E).

4. Discussion

After careful screening, 4 studies[17,19–21] were included in the present meta-analysis. Similar to a previous meta-analysis,[16] we found that TA treatment resulted in a lower total and postoperative blood loss. Interestingly, our meta-analysis with one more paper and much more patients also demonstrated that TA administration lead to higher occurrence of minor adverse effects including vomiting and nausea, but dizziness or photopsia, compared to control groups.

Li et al[16] pointed out that their meta-analysis could not reach a definitive conclusion about the effect of TA usage on PPH number in vaginal delivery because the definition and criteria of obstetrical hemorrhage varies in different regions, which might cause a higher heterogeneity. In general, PPH is defined as loss of

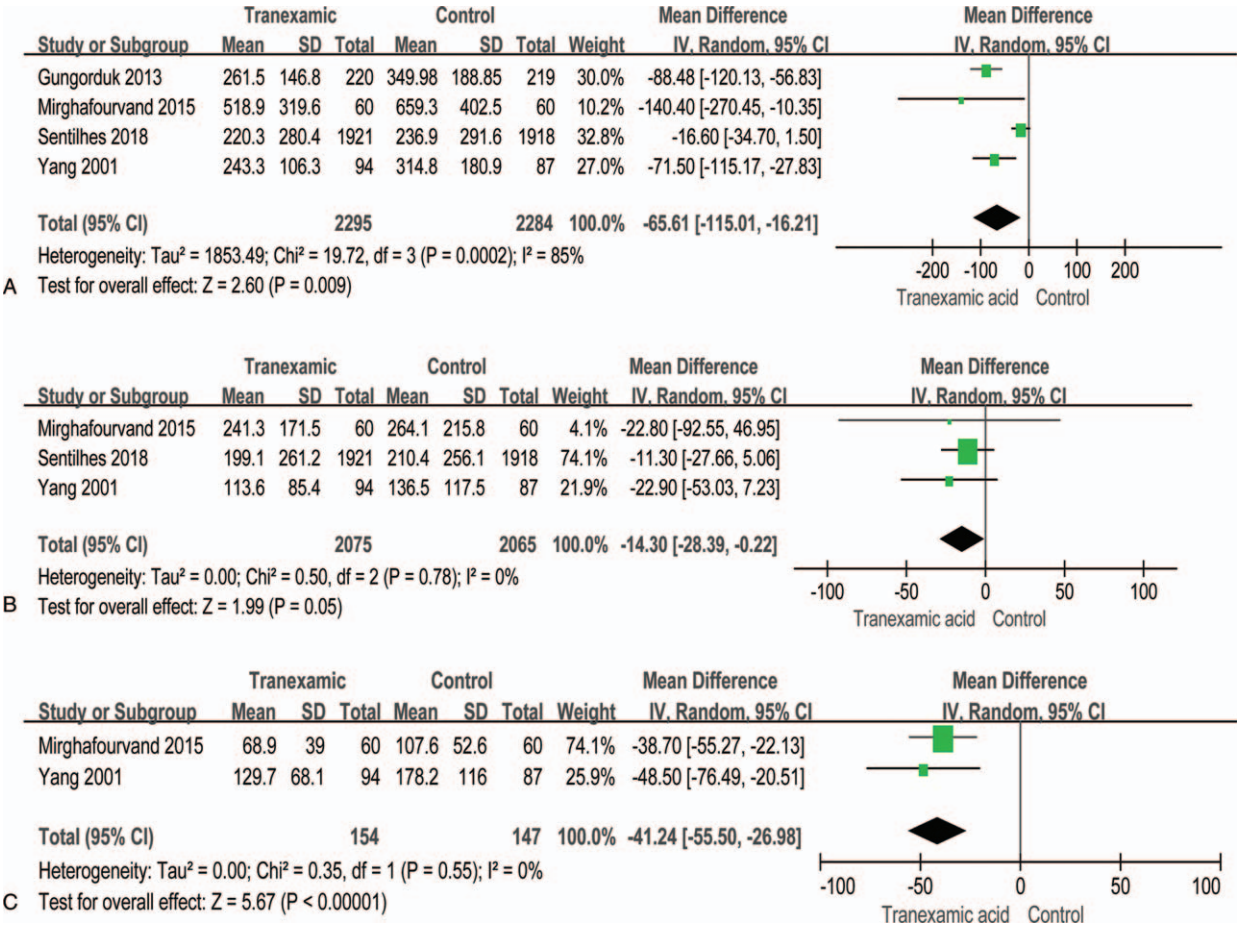

Figure 2. Comparison of primary outcomes between tranexamic acid (TA) and control groups for vaginal delivery. (A) total blood loss, (B) intraoperative blood loss, and (C) postoperative blood loss. 95% CI = 95% confidence interval, IV= inverse variance, random = random effect.

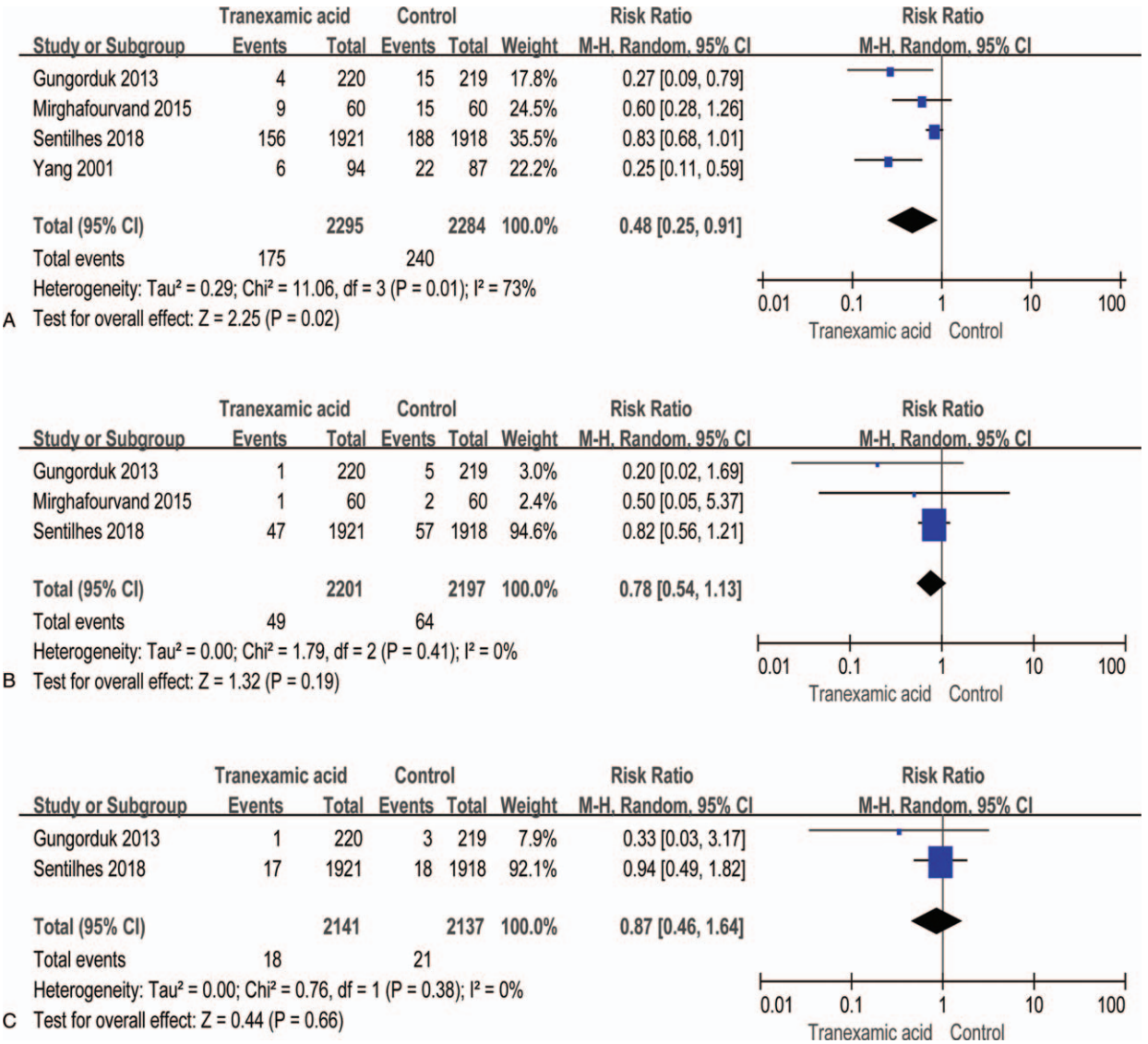

Figure 3. Forest plot diagram demonstrating the effect of tranexamic acid (TA) administration in vaginal delivery. (A) number patients with postpartum hemorrhages (PPH), (B) severe PPH and (C) those requiring transfusions.

500 mL of blood after vaginal birth.[26–28] In our study, three included trials[19–21] regarded PPH as over 500 mL while one used a 400 mL threshold.[17] The addition of 1 more high-quality paper,[21] including 3891 more patients, allowed us to reach the conclusion that TA is effective in reducing the occurrence of PPH.

Between 50% to 75% of mortality during childbirth worldwide is attributed to severe PPH,[29–33] which for the purposes of this study we defined as blood loss that exceeds 1000 mL in 24 hours, based on previous studies.[34] A published analysis that included only 2 trials[19,20] with 559 patients failed to find statistical significance of TA treatment for severe PPH ($P = .14$), and our metaanalysis with 1 additional study had the same result.

Pregnancy carries an increased risk of deep venous thrombosis (DVT),[1] which must be taken into account for any treatment that affects clotting. Several studies have found TA administration to be safe during surgery including for pregnant women.[7,16,35–37] However, only 1 paper[21] mirror those found by earlier studies that reported no increase in DVT after TA treatment in pregnant women. Moreover, physicians should be aware that TA can induce nausea and vomiting and take this into account when making decisions whether or not administer the treatment. It is our opinion that these adverse effects do not outweigh the potential benefits of decreased blood loss.

Though our results suggest TA is a safe treatment option to combat PPH, future studies need to determine whether lower dosages can achieve similar effects. In addition, more studies are needed on the effect TA administration has on neonates, though preliminary studies indicate it is potentially safe.[38,39]

We acknowledge that there exist several limitations to the present metaanalysis. First, only English or Chinese articles were obtained, and some of our analyses were conducted from the results of three or fewer studies. Thus, some of our conclusions may be based on relatively small numbers of patients when

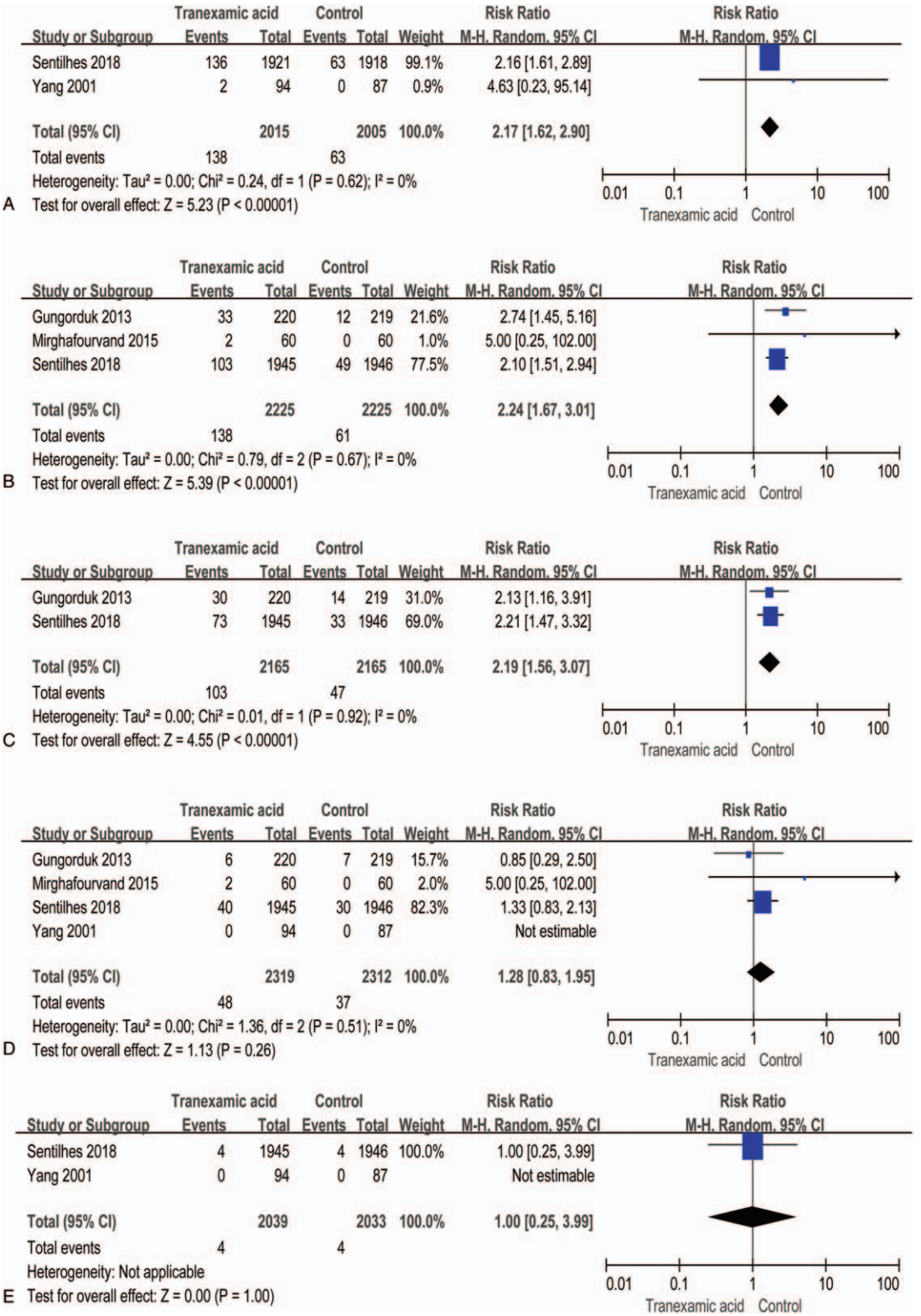

Figure 4. Adverse effects, tranexamic acid (TA) vs control groups. (A) nausea or vomiting, (B) nausea only, (C) vomiting only, (D) dizziness or (E) photopsia.

compared with others. Second, there was heterogeneity in some study characteristics, such as the dosage and duration of TA administration, different measures of blood loss, and so on. Finally, the influence of publication bias should be recognized.

In conclusion, TA treatment for vaginal delivery has been demonstrated to have substantial clinical efficacy resulting in reduced total/postoperative blood loss and fewer incidences of PPH. However, TA could lead to higher occurrences of minor

adverse effects including vomiting and nausea other than dizziness and photopsia.

Author contributions

Conceptualization: Yimeng Xia, Qingsheng Xue.
Data curation: Brian B. Griffiths.
Formal analysis: Yimeng Xia, Brian B. Griffiths.
Investigation: Yimeng Xia.
Project administration: Qingsheng Xue.
Software: Yimeng Xia, Brian B. Griffiths.
Supervision: Qingsheng Xue.
Validation: Qingsheng Xue.
Writing – original draft: Yimeng Xia.
Writing – review and editing: Qingsheng Xue.

References

[1] AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003;67:1–11.
[2] Driessen M, Bouvier-Colle MH, Dupont C, et al. Postpartum hemorrhage resulting from uterine atony after vaginal delivery: factors associated with severity. Obstet Gynecol 2011;117:21–31.
[3] Zargar M, Nikbakht R, Ahmadi M. The effect of tranexamic acid on preventing post-partum hemorrhage due to uterine atony: a triple-blind randomized clinical trial. Curr Clin Pharmacol 2018;13:136–9.
[4] Shady NW, Sallam HF, Elsayed AH, et al. The effect of prophylactic oral tranexamic acid plus buccal misoprostol on blood loss after vaginal delivery: a randomized controlled trial. J Matern Fetal Neonatal Med 2017; doi: 10.1080/14767058.2017.1418316.
[5] Alam A, Bopardikar A, Au S, et al. Protocol for a pilot, randomised, double-blinded, placebo-controlled trial of prophylactic use of tranexamic acid for preventing postpartum haemorrhage (TAPPH-1). BMJ open 2017;7:e018586.
[6] Al Wattar BH, Tamblyn JA, Parry-Smith W, et al. Management of obstetric postpartum hemorrhage: a national service evaluation of current practice in the UK. Risk Manag Healthc Policy 2017;10:1–6.
[7] Abdel-Aleem H, Alhusaini TK, Abdel-Aleem MA, et al. Effectiveness of tranexamic acid on blood loss in patients undergoing elective cesarean section: randomized clinical trial. J Matern Fetal Neonatal Med 2013;26:1705–9.
[8] Fawcus S, Moodley J. Postpartum haemorhage associated with caesarean section and caesarean hysterectomy. Best Pract Res Cl Ob 2013;27:233–49.
[9] Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57:1005–32.
[10] Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. Expert Opin Pharmacother 2011;12:503–16.
[11] Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011;(1):CD001886.
[12] Hunt BJ. The current place of tranexamic acid in the management of bleeding. Anaesthesia 2015;70(Suppl 1):50–3.e18.
[13] Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2015;6: CD007872.
[14] Sentilhes L, Daniel V, Darsonval A, et al. TRAAP - TRAnexamic Acid for Preventing postpartum hemorrhage after vaginal delivery: a multicenter randomized, double-blind, placebo-controlled trial, BMC pregnancy and childbirth. Study Protocol 2015;15:135.
[15] Pacheco LD, Saade GR, Hankins GDV. Medical management of postpartum hemorrhage: an update. Semin Perinatol 2018;43:22–6.
[16] Li C, Gong Y, Dong L, et al. Is prophylactic tranexamic acid administration effective and safe for postpartum hemorrhage prevention? A systematic review and meta-analysis. Medicine 2017;96:e5653.
[17] Yang H, Zheng S, Shi C. Clinical study on the efficacy of tranexamic acid in reducing postpartum blood lose: a randomized, comparative, multicenter trial. Zhonghua fu chan ke za zhi 2001;36:590–2.
[18] Ducloy-Bouthors AS, Jude B, Duhamel A, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit care 2011;15: R117.
[19] Gungorduk K, Asicioglu O, Yildirim G, et al. Can intravenous injection of tranexamic acid be used in routine practice with active management of the third stage of labor in vaginal delivery? A randomized controlled study. Am J Perinatol 2013;30:407–13.
[20] Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, et al. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. Aust N Z J Obstet Gynaecol 2015;55:53–8.
[21] Sentilhes L, Winer N, Azria E, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. N Engl J Med 2018; 379:731–42.
[22] Della Corte L, Saccone G, Locci M, et al. Tranexamic acid for treatment of primary postpartum hemorrhage after vaginal delivery: a systematic review and meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med 2018; doi: 10.1080/14767058.2018.1500544.
[23] Ferrer P, Roberts I, Sydenham E, et al. Anti-fibrinolytic agents in post partum haemorrhage: a systematic review. BMC Pregnancy Childbirth 2009;9:29.
[24] Ducloy-Bouthors AS, Duhamel A, Kipnis E, et al. Postpartum haemorrhage related early increase in D-dimers is inhibited by tranexamic acid: haemostasis parameters of a randomized controlled open labelled trial. Br J Anaesth 2016;116:641–8.
[25] Montufar-Rueda C, Rodriguez L, Jarquin JD, et al. Severe postpartum hemorrhage from uterine atony: a multicentric study. J Pregnancy 2013; http://dx.doi.org/10.1155/2013/525914.
[26] Karoshi M, Keith L. Challenges in managing postpartum hemorrhage in resource-poor countries. Clin Obstet Gynecol 2009;52:285–98.
[27] Shakur H, Elbourne D, Gulmezoglu M, et al. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. Trials 2010;11:40.
[28] Sentilhes L, Lasocki S, Ducloy-Bouthors AS, et al. Tranexamic acid for the prevention and treatment of postpartum haemorrhage. Br J Anaesth 2015;114:576–87.
[29] Mantel GD, Buchmann E, Rees H, et al. Severe acute maternal morbidity: a pilot study of a definition for a near-miss. Brit J Obstet Gynaec 1998;105:985–90.
[30] Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ 2001;322:1089–93.
[31] Brace V, Penney G, Hall M. Quantifying severe maternal morbidity: a Scottish population study. BJOG 2004;111:481–4.
[32] Zhang WH, Alexander S, Bouvier-Colle MH, et al. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. Bjog Int J Obstet Gy 2005;112:89–96.
[33] Nyflot LT, Sandven I, Stray-Pedersen B, et al. Risk factors for severe postpartum hemorrhage: a case-control study. BMC Pregnancy and Childbirth 2017;17:17.
[34] Carroli G, Cuesta C, Abalos E, et al. Epidemiology of postpartum haemorrhage: a systematic review, Best practice & research. Clin obst gyn 2008;22:999–1012.
[35] Cheriyan T, Maier SP2nd, Bianco K, et al. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. Spine J 2015;15:752–61.
[36] Sahhaf F, Abbasalizadeh S, Ghojazadeh M, et al. Comparison effect of intravenous tranexamic acid and misoprostol for postpartum haemorrhage. Niger Med J 2014;55:348–53.
[37] Shaaban MM, Ahmed MR, Farhan RE, et al. Efficacy of tranexamic acid on myomectomy-associated blood loss in patients with multiple myomas: a randomized controlled clinical trial. Reprod Sci 2016;23:908–12.
[38] Wesley MC, Pereira LM, Scharp LA, et al. Pharmacokinetics of tranexamic acid in neonates, infants, and children undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 2015;122:746–58.
[39] Gertler R, Gruber M, Grassin-Delyle S, et al. Pharmacokinetics of tranexamic acid in neonates and infants undergoing cardiac surgery. Br J Clin Pharmacol 2017;83:1745–57.