Systematic Review and Meta-Analysis

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Is prophylactic tranexamic acid administration effective and safe for postpartum hemorrhage prevention?

A systematic review and meta-analysis

Chunbo Li, MD[a], Yuping Gong[b], Lingling Dong, MD[a], Bingying Xie, MD[c], Zhiyuan Dai, MD[a,*]

Abstract

Background: To assess the efficacy and safety of tranexamic acid (TA) in reducing blood loss and lowering transfusion needs for patients undergoing caesarean section (CS) or vaginal delivery (VD).

Methods: An electronic literature search of PubMed, EMBASE, OVID, Cochrane library, Scopus, Central, and Clinical trials.gov was performed to identify studies that evaluating the usage of TA in CS or VD. The methodological quality of included trials was assessed and data extraction was performed.

Results: Finally, 25 articles with 4747 participants were included. Our findings indicated TA resulted in a reduced intra-, postoperative, and total blood loss by a mean volume of 141.25 mL (95% confidence interval [CI] −186.72 to −95.79, $P<0.00001$), 36.42 mL (95% CI −46.50 to −26.34, $P<0.00001$), and 154.25 mL (95% CI −182.04 to −126.47, $P<0.00001$) in CS. TA administration in VD was associated with a reduced intra-, postoperative, and total blood loss by a mean volume of 22.88 mL (95% CI −50.54 to 4.77, $P=0.10$), 41.24 mL (95% CI −55.50 to −26.98, $P<0.00001$), and 84.79 mL (95% CI −109.93 to −59.65, $P<0.00001$). In addition, TA could lower the occurrence rate of postpartum hemorrhage (PPH) and severe PPH, and reduce the risk of blood transfusions. No increased risk of deep vein thrombosis (DVT) after CS or VD was associated with TA usage, while the minor side effects were more common.

Conclusions: Our findings indicated that intravenous TA for patients undergoing CS was effective and safe. Although prophylactic TA administration is associated with reduced PPH, current existing data are insufficient to draw definitive recommendations about its clinical significance due to the poor to moderate quality of the included literatures. Thus, high-quality randomized controlled trials with larger samples are needed to validate our findings.

Abbreviations: CI = confidence interval, CS = caesarean section, DVT = deep vein thrombosis, PPH = postpartum hemorrhage, RCT = randomized controlled trial, TA = tranexamic acid, VD = vaginal delivery.

Keywords: caesarean section, meta-analysis, postpartum hemorrhage, tranexamic acid, vaginal delivery

1. Introduction

Postpartum hemorrhage (PPH) is a potential life-threatening complication of both vaginal (VD) or cesarean delivery.[1] It is reported that PPH accounts for nearly 25% of maternal deaths and approximately 12% survivors after PPH suffer from severe postpartum anemia.[1] Recently, the occurrence rate of caesarean section (CS) has increased in both developed and developing countries, which would result in an increased risk of PPH.[2] Although there has been a remarkable improvement in the prevention and treatment of PPH in recent years, deaths due to PPH remain relatively common in some parts of the world. To lower the occurrence rate of major morbidity and mortality due to PPH, it is very vital to reduce blood loss in CS and VD.

Tranexamic acid (TA), an antifibrinolytic agent, could exert its hemostasis effect via inhibiting the activation of plasminogen to plasmin.[3] Its efficacy and safety in reducing hemorrhage and lowering transfusion requirements have been well established in various elective surgeries.[4–6] Recently, TA has been reported to reduce blood loss in gynecology diseases such as menorrhagia, hysterectomy, and myomectomy.[7–9] Naoulou et al[7] reviewed all available evidence about the use of TA in menorrhagia and concluded that TA was effective and safe and could potentially improve quality of life of patients with heavy menstrual bleeding. Topsoee et al[8] performed a randomized controlled trail (RCT) and revealed that TA could reduce the total blood loss, the incidence of substantial blood loss, and the need for reoperations for patients who underwent benign hysterectomy. Shaaban et al[9] reported that TA reduced blood loss by a mean volume of 407 mL during and after myomectomy for patients with multiple uterine fibroids. Moreover, several studies evaluated the usage of

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[a] Department of Obstetrics and Gynaecology, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, [b] Department of Nursing, Zhongshan Hospital of Fudan University, [c] Department of Gynaecology and Obstetrics, Gynaecology and Obstetrics Hospital of Fudan University, Shanghai, China.

[*] Correspondence: Zhiyuan Dai, Department of Gynaecology and Obstetrics, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, 536 Changle Road, Shanghai 200040, China (e-mail: daizhiyuan@51mch.com).

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TA administration in CS[10–31] or VD[32–34] and showed satisfactory outcomes. Although published meta-analyses demonstrated that TA administration in CS or VD could result in a significant reduction in estimated blood loss, most of these studies limited the smaller samples and the poor quality of the included trials.[35–38] Moreover, data about clinical relevance of the reduced blood loss with TA intervention remained inadequate because these outcomes did not distinguish the efficacy of TA administration based on the mode of delivery.

Traditional, PPH is commonly defined as blood loss of more than 500 mL following a VD, or more than 1000 mL following a CS.[39] For a normal woman undergoing CS, a blood loss of 1000 mL seems to be common and had a minimal effect on women's health status. However, for a woman with severe anemia or cardiovascular disease undergoing VD, a blood loss of as little as 200 mL may be life-threatening and need additional intervention.[39,40] Thus, it is important to evaluate the efficacy and safety of TA on blood loss based on the mode of delivery. As we are aware of at least 8 additional trials[23–25,27–31] for CS and 1 trial[34] for VD published in recent 3 years, which are not included in any published meta-analyses. Thus, we aimed to identify all available data to evaluate whether the mode of delivery had a potential effect on the efficacy of TA in reducing estimated blood loss.

2. Materials and methods

2.1. Search strategy

The relevant literatures involving in intravenous TA for CS or VD were searched using the electronic databases such as Medline, PubMed, EMBASE, OVID, Cochrane library, Scopus, Central, Clinical trials.gov, and other databases such as Google scholar, Biomed central, CINHAL, and Chinese databases such as Wanfang, CNKI, and VIP databases. No restrictions for language or geographic location were applied. The combination of terms as medical subject headings (Mesh) for the database searchers were: (Tranexamic acid OR TA OR TXA OR AMCA OR Cyclokapron) AND (pregnancy OR gestation). The last search was updated in June 1, 2016. Reference lists of the included studies and other relevant publications, including case reports, reviews, and meta-analyses, were checked for any unidentified trials from the electronic searchers. Abstracts from relevant conferences or scientific meetings were hand-searched for additional studies. Due to the characteristic of meta-analysis, no ethics approval and patient consent was necessary for the study.

2.2. Inclusion criteria

The included studies must meet the following criteria: randomized trials in any language; participants with singleton pregnancy who underwent elective CS or intended to delivery vaginally; all published studies comparing intravenous usage of TA in treatment group and normal saline or 5% glucose in control group; and the evaluation of outcomes by estimated blood loss, transfusion requirements, and complications such as the occurrence rate of deep vein thrombosis (DVT), nausea, vomiting, headache, and dizziness. We excluded the articles according to the following criteria: review articles, case reports, conference proceedings, or repeated publications; no available data reported.

2.3. Study selection and data extraction

The potential studies meeting the included criteria were identified based on the title and abstract information. If there was a doubt existing, the full text would be reviewed for clarification. Then, data were extracted from each study using a standardized form. Demographic data including publication date, sample size, age, gestational age, interventions, and surgery time for each study were recorded. The outcomes of interest including estimated blood loss, the occurrence rate of PPH/severe PPH, transfusion requirements, and drug-induced complications were analyzed. The study selection and data extraction were performed by 2 authors independently (CBL and YPG). Any disagreement for study section between 2 authors was discussed with a senior and if all authors considered that a study did not meet the inclusion criteria, the study was excluded. In case of insufficient data, we would contact the authors of the trials for more information.

2.4. Quality assessment

The methodological quality of each trial was evaluated according to the recommended criteria of CochraneHandbook for systematic Reviews of interventions by 2 independent authors (CBL and YPG). Any differences of opinion regarding methodological quality of included trials were resolved by discussion with a senior author (ZYD).

2.5. Statistical analysis

All statistical analyses were performed according to the guidelines of the Cochrane Collaboration using Review Manager software (RevMan, version 5.2). For dichotomous data including rate of PPH and severe PPH, transfusion needs, and adverse events, the summary ratio risk (RR) with 95% confidence interval (CI) was calculated. For continuous data including total, intra-, and postoperative blood loss, the mean difference with 95% CI was applied. $P < 0.05$ was thought to be significant difference. Because of expected substantial heterogeneity, the synthesis of the outcomes for all studies was calculated as the weighted average rate by using a random effect model. Sensitivity analysis was performed to assess the strength and robustness of the pooled results by excluding low quality studies and repeating the analysis for outcomes of interest. When the number of studies allowed, publication bias was evaluated using Funnel plots.

3. Results

3.1. Study inclusion and characteristics

A total of 5647 studies were originally identified using the electronic search system. Subsequently, 5213 studies were readily excluded due to duplication, irrelevancy, or nonrandomized trials after screening the title or abstract and 434 studies remained for further evaluation. After the full-text was obtained and reviewed thoroughly, an additional 405 studies failing to meet the included criteria were excluded. Because no adequate data were obtained, 1 trial by Sharma et al[41] was excluded. One study by Sahhaf et al[42] comparing the antihemorrhagic effect of TA and Misoporostol for PPH and 2 studies by Shakur et al[43] and Ducloy-Bouthors et al[44] evaluating the therapeutic efficacy of TA in postpartum patients were excluded. Finally, a total of 25 randomized trials (22 trials[10–31] for CS and 3 trials[32–34] for VD) were included. The detailed study selection process was presented in Fig. 1.

A total of 25 articles[10–34] included a total of 4747 participants undergoing CS or VD, and no significant differences in preoperative baseline parameters were observed between TA

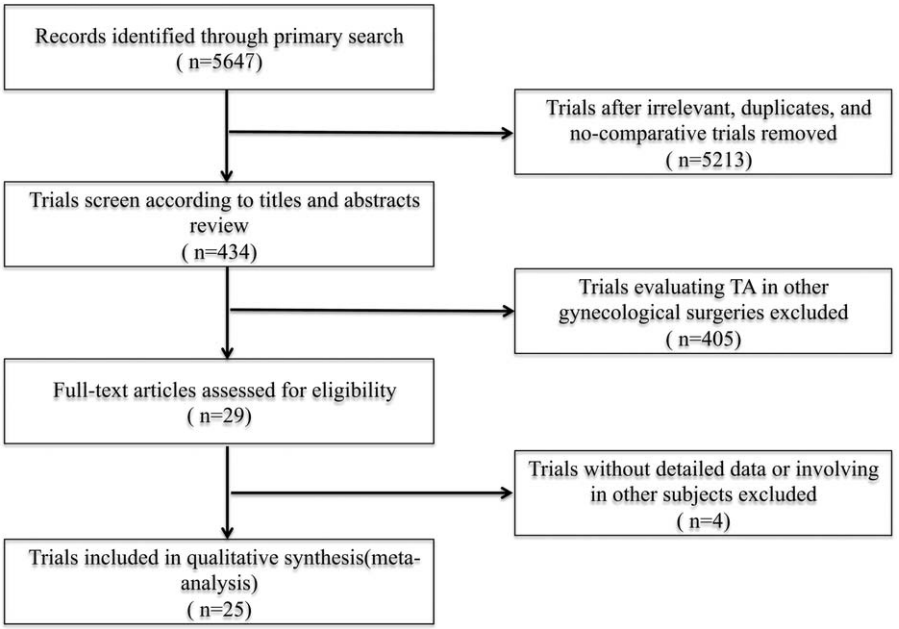

Figure 1. Flowchart of the study selection.

and control group within each study. All studies reported that TA was administrated intravenously using either a weighted or standard dose. For control group, a placebo (normal saline or 5% glucose) was given in all studies. The outcomes of interest including reduced blood loss, transfusion needs, the occurrence rate of PPH and severe PPH, and complications were recorded. The detailed characteristics of the included studies for CS and VD were presented in Table 1, respectively.

The majority of the included trials were small with sample sizes ranging from 60 to 740 patients. However, they were well designed and well implemented. Eighteen trials[10–12,14,15,17–19,21–24,28–31,33,34] provided detailed randomization techniques using a computer-generated randomization list, consecutively numbered sealed opaque envelopes or rand list software, while 7 trials[16,20,25–27,31,32] referred to randomization only without describing the detailed method. Eleven trials[10,11,13,16,21,23,25,31,32] had unclear bias in the allocation concealment while only 1 study[12] presented a higher bias. For the blinding of participants and personnel, there was a higher bias in 7 studies[10–12,17,20,23,32] due to a lack of information and 6 studies[13,21,25–27,31] had an unclear bias in the blinding measurement. Two studies[19,20] had an unclear bias due to incomplete outcome data reported, and no studies had selective outcome reporting. In addition, no other sources of bias were detected in any studies. The methodological quality for each study was summarized in Fig. 2.

3.2. Blood loss

There were 15 trials[10,11,13,14,16,17,20–23,26–29,31] for CS and 3 trials[32–34] for VD identified to evaluate the effect of TA on total reduced blood loss (from fetus delivery to 2 hours postpartum). Our results indicated TA administration in CS resulted in a reduced blood loss by a mean volume of 154.25 mL (95% CI −182.04 to −126.47; $I^2=98\%$) and a reduced blood loss by a mean volume of 84.79 mL (95% CI −109.93 to −59.65; $I^2=0\%$) in VD as compared to control group. The test for subgroup differences showed a significant difference ($P=0.0003$), indicating the efficacy of TA administration in reducing total blood loss was affected by the mode of delivery (Fig. 3A).

A total of 614 trials[10,11,13,15,17–19,22–25,27,28,31] and 2 trials[32,34] provided detailed data on the effect of TA on the intraoperative blood loss (from fetus delivery to placental delivery) in CS and VD, respectively. Our results indicated that TA administration in CS resulted in a reduced blood loss by a mean volume of 141.25 mL (95% CI −186.72 to −95.79; $I^2=99\%$) and a reduced blood loss by a mean volume of 22.88 mL (95% CI −50.54 to 4.77; $I^2=0\%$) in VD as compared to control group. However, the latter did not reach a statistical difference. The test for subgroup differences showed significantly difference ($P<0.0001$), indicating the efficacy of TA administration in reducing intraoperative blood loss was affected by the mode of delivery (Fig. 3B).

Data on the postoperative blood loss (from placental delivery to 2 hours postpartum) was available in 14 trials[10–13,15,17,18,22–25,27,28,31] for CS and 2 trials[32,34] for VD. Our results showed TA administration in CS resulted in a reduced blood loss by a mean volume of 36.42 mL (95% CI −46.50 to −26.34; $I^2=98\%$) and a reduced blood loss by a mean volume of 41.24 mL (95% CI −55.50 to −26.98; $I^2=0\%$) in VD as compared to control. However, the test for subgroup differences showed no significantly difference ($P=0.59$), indicating the mode of delivery had no significant effect on the efficacy of TA administration in reducing postoperative blood loss (Fig. 3C).

3.3. Rate of PPH or severe PPH

The outcome measure of PPH was available in 8 trials[10,11,17,18,22,25,28,29] in CS and 3 trials[32–34] in VD (Fig. 4A). Our results showed that TA administration lowered

Table 1

Characteristics of included trials.

Study, year	Country	TA/control (n)	Age, year	Gestational age, year	Intervention	Transfusion standardized	Adverse effects
Cesarean section							
Gai (2004)	China	91/89	TA: 29.71±4.18 CON: 29.75±4.01	TA: 38.80±1.11 CON: 38.67±1.03	TA: 1 g TA IV over 10 minutes before CS. CON: 5% glucose	NR	DVT
Mayur (2007)	India	50/50	TA: 24.3±3.65; CON: 24.89±3.99	TA: 38.85±1.29 CON: 38.64±1.24	TA: 1 g TA IV over 20 minutes before CS CON: normal saline	NR	DVT
Sekhavat (2009)	Iran	45/45	TA: 26.2±4.7 CON: 27.1±4.1	TA: 38.8±0.6 CON: 38.7±0.6	TA: 1 g TA IV over 10 minutes before CS. CON: 5% glucose	NR	DVT
Rashmi (2010)	India	50/50	TA: 25.70±3.70 CON: 25.10±4.73	TA: 37.85±1.09 CON: 37.80±0.95	TA: 1 g TA IV 30 minutes before CS. CON: normal saline	NR	DVT
Gungorduk (2011)	Turkey	330/330	TA: 26.3±3.5 CON: 26.6±3.6	TA: 38.8±0.6; CON: 38.7±0.6	TA: 1 g TA IV 10 minutes before CS. CON: 5% glucose	An estimated blood loss >1000 mL	DVT
Movafegh (2011)	Iran	50/50	20–40	Between 38^{+5} weeks and 40 weeks gestation	TA: 10 mg/kg TA IV over 20 minutes before CS CON: normal saline	Hb level was less than 8 g/dL	DVT
Poonia (2012)	India	50/50	NR	NR	TA: 1 g TA IV over 10 minutes before CS. CON: 5% glucose	NR	DVT, nausea, vomiting
Senturk (2013)	Turkey	101/122	TA: 30.2±6.83 CON: 29.22±6.93	NR	TA: 1 g TA IV 10 minutes before CS. CON: 5% glucose	NR	DVT
Xu (2013)	China	88/86	TA: 26.7±3.7 CON: 27.1±4.1	TA: 38.7±1.0 CON: 38.8±1.1	TA: 10 mg/kg TA IV 10–20 minutes before CS CON: normal saline	NR	DVT, nausea, vomiting, phosphene, dizziness
Shahid (2013)	Pakistan	38/36	TA: 24.18±3.93 CON: 24.89±4.16	TA: 38.32±0.80 CON: 38.47±0.910	TA: 1 g TA IV over 10 minutes before CS. CON: normal saline	NR	DVT
Goswami (2013)	India	60/30	TA: 23.6±2.5 CON: 24.3±2.6	NR	TA: 10 mg/kg or 15 mg/kg TA IV CON: 5% glucose	NR	DVT, Nausea
Abdel-Aleem (2013)	Switzerland	373/367	TA: 26.34±5.16 CON: 26.62±5.05	TA: 39.32±1.15 CON: 39.31±1.17	TA: 1 g TA IV 10 minutes before CS. CON: none	NR	DVT, headache, nausea, vomiting
Halder (2013)	India	50/50	TA: 26.06±2.51 CON: 26.04±2.50	NR	TA: 1 g TA IV 10 minutes before CS. CON: none	NR	DVT
Taj (2014)	Pakistan	60/60	TA: 23.56±3.82 CON: 24.18±3.47	TA: 39+2 CON: 39+2	TA: 1 g TA IV over 10 minutes before CS. CON: normal saline	NR	DVT, nausea, visual disturbances
Singh (2014)	India	100/100	TA: 25±1.46 CON: 26±1.24	TA: 39.1±1.24; CON: 39.3±1.28	TA: 1 g TA IV 20 minutes before CS. CON: none	NR	DVT, nausea, vomiting, diarrhea
Ahmed (2014)	Egypt	62/62	TA: 28.6±5.9 CON: 26.9±5.2	TA: 38.5±0.7 CON: 38.5±0/6	TA: 10 mg/kg TA IV before CS CON: normal saline	NR	DVT
Yehia (2014)	Egypt	106/106	TA: 28.4±4.9 CON: 28.6±4.7	TA: 39.1±1.1 CON: 39.0±1.2	TA: 1 g TA IV over 20 minutes before CS CON: normal saline	NR	DVT
Gobbur (2014)	India	50/50	TA: 23.62±3.429 CON: 24.5±3.982	NR	TA: 1 g TA IV before CS CON: normal saline	NR	DVT, nausea, vomiting
Ramani (2014)	India	60/60	TA: 24.9±3.9 CON: 24.4±3.7	NR	TA: 1 g TA IV 10 minutes before CS CON: normal saline	NR	DVT, sickle cell trait
Ghosh (2014)	India	70/70	TA:25.94±3.78 CON:26.04±3.39	TA: 38.62±0.779; CON: 38.72±0.671	TA: 1 g TA IV 10 minutes before CS CON: normal saline	Hb level was less than 7 g/dL	DVT, nausea, vomiting
Maged (2015)	Egypt	100/100	TA: 24.9±4.6 CON: 25.3±4.7	NR	TA: 1 g TA IV 20 minutes before CS CON: normal saline	NR	DVT
Sujata (2016)	India	31/29	TA: 29.4±4.16 CON: 30.27±4.31	NR	TA: 1 g TA IV 15 minutes before CS CON: normal saline	Hb level was less than 8 g/dL	DVT

Study, year	Country	TA/control (n)	Age, year	Gestational age, year	Intervention	Transfusion standardized	Adverse effects
Vaginal delivery							
Yang (2001)	China	94/87	TA: 27.6 ± 2.9 CON: 28.0 ± 2.6	NR	TA: 1 g TA IV over 2–3 minutes after delivery of the fetus; CON: 5% glucose	NR	DVT, nausea, dizziness
Gungorduk (2013)	Turkey	220/219	TA: 27.9 ± 4.9 CON: 27.6 ± 4.8	TA: 38.6 ± 1.4 CON: 39.0 ± 2.7	TA: 1 g TA IV over 5 minutes at delivery of the anterior shoulder; CON: 5% glucose	An estimated blood loss > 1000 mL	DVT, nausea, vomiting, diarrhea, pyrexia
Mirghafourvand (2015)	Iran	60/60	TA: 26.2 ± 4.8 CON: 26.1 ± 4.9	NR	TA: 1 g TA IV over 10 minutes at delivery of the anterior shoulder; CON: placebo	NR	DVT, nausea, dizziness

CON = control group, CS = caesarean section, DVT = deep vein thrombosis, NR = no report, TA = tranexamic acid.

the occurrence rate of PPH as compared to control group in CS (RR 0.32, 95% CI 0.16–0.61, $I^2 = 91\%$) and VD (RR 0.37, 95% CI 0.20–0.67, $I^2 = 28\%$). However, the test for subgroup differences showed no significant difference ($P = 0.75$), indicating the mode of delivery had no significant effect on the efficacy of TA administration in occurrence rate of PPH.

The outcome measure of severe PPH was available in 4 trials[14,17,29,30] in CS and 2 trials[33,34] for VD (Fig. 4B). Our results showed that TA administration in CS lowered significantly the occurrence rate of severe PPH as compared to control group (RR 0.32, 95% CI 0.12–0.84, $I^2 = 19\%$). For VD, no significant difference on the occurrence rate of severe PPH was found between TA and control group (RR 0.30, 95% CI 0.06–1.47, $I^2 = 0\%$). However, the test for subgroup differences showed no significant difference ($P = 0.95$), indicating the mode of delivery had no significant effect on the efficacy of TA administration in occurrence rate of severe PPH.

3.4. Transfusion needs

The outcome measure of transfusion needs was available in 8 trials[14,18,19,22,24,28,30,31] in CS and 1 trial[33] in VD (Fig. 4C). Our results showed that TA administration lowered the transfusion needs as compared to control in CS (RR 0.31, 95% CI 0.18–0.51, $I^2 = 0\%$) but not in VD (RR 0.33, 95% CI 0.03–3.17, $I^2 = 0\%$). The test for subgroup differences showed no significantly difference ($P = 0.95$), indicating the mode of delivery had no significant effect on the efficacy of TA administration in transfusion needs.

3.5. Adverse events

All component studies provided data on thromboembolic complication in CS and VD (Fig. 5A). However, only 4 trials[18,19,21,22] involving in women undergoing CS reported 4 DVT in TA group and 6 DVT in control group. The pooled results showed that TA administration had no significant difference (RR 0.60, 95% CI 0.20–1.85, $I^2 = 0\%$) between TA group and control group. Besides thromboembolic episodes, some other minor adverse events including nausea, vomiting, headache, and dizziness were compared between TA group and control group (Fig. 5B). Our results showed that TA administration resulted in increased risk of minor transient adverse events as compared to control group in CS (RR 1.74, 95% CI 1.13–2.68, $I^2 = 0\%$) or VD (RR 2.11, 95% CI 1.55–2.88, $I^2 = 0\%$).

3.6. Publication bias and sensitivity analysis

Thromboembolic complication was used to generate funnel plot analysis of publication bias (Fig. 6). The plot presented no clear asymmetrical, and all studies fell within the 95% CI axis, which indicated no existence of significant publication bias existing. Sensitivity analysis was conducted by repeating the analysis after excluding 4 studies[12,25,31,32] with high risk of bias, the results remained unchanged.

4. Discussion

Our meta-analysis demonstrated that intravenous TA administration for patients undergoing CS could effectively reduce blood loss and transfusion needs, as well as lower the occurrence rate of PPH and severe PPH with only minor side effects, yet do not result in an increased risk of postoperative DVT. However, the

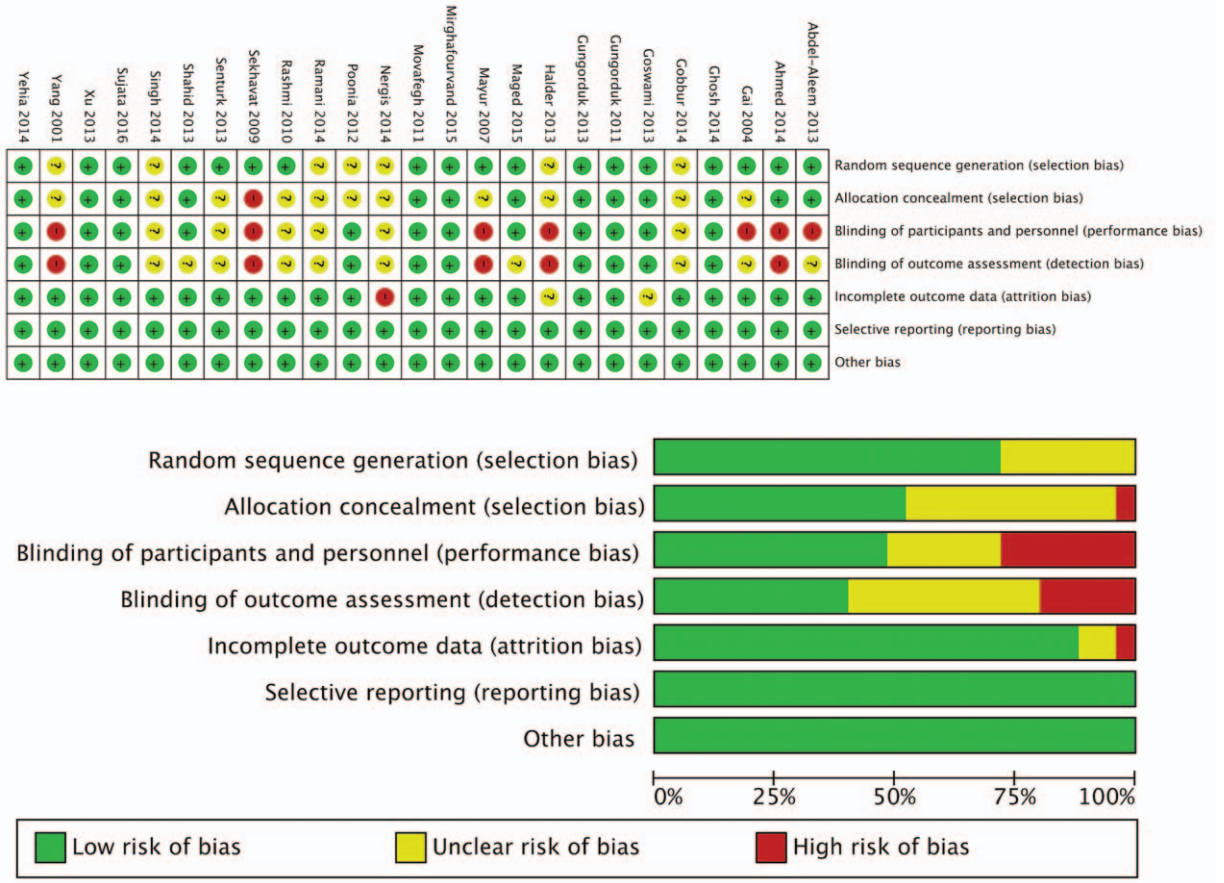

Figure 2. The methodological quality of included trials.

conclusion should be interpreted cautiously to assess the efficacy of TA for patients undergoing VD because of the smaller samples and the inadequate evidence from the included trials. In addition, the test of subgroup differences indicated the model of delivery had a potential effect on the efficacy of TA administration in reducing total and intraoperative blood loss.

TA, as an antifibrinolytic drugs, has been routinely used in cardiac, orthopedics, and oral surgeries.[5,6,8,9] Relevant studies have demonstrated TA administration could reduce perioperative blood loss.[45,46] Recent evidences from high-quality RCTs indicated that TA usage resulted in a significant reduction of blood loss in CS or VD.[10–34] A Cochrane systematic review published in 2010 identified 2 trials evaluating the TA administration in CS and VD.[38] Their study indicated that TA usage resulted in a significant reduction in total blood loss of 80.1 mL in CS and 71.5 mL in VD. Heesen et al[37] identified 7 trials in which 6 reported the usage of TA in CS and one reported the usage of TA in VD. Their results showed TA usage rendered a reduced blood loss by a mean volume of 140.29 mL blood loss as compared to control group. However, their study did not take into account the influence of model of delivery, which might introduce bias.[37] Faraoni et al[47] conducted a meta-analysis with 10 trials that evaluated the efficacy of TA administration in reducing blood loss for women undergoing CS or VD. They concluded that TA administration significantly reduced blood loss and lowered the occurrence rate of PPH regardless of the mode of delivery. To guard against the effect of bias from the mode of delivery, we identified all available data and assessed whether the mode of delivery had a potential effect on the efficacy of TA in reducing blood loss. In addition, this was the 1st study that hade valuated systematically the usage of TA in CS or VD according to 3 different time periods.

Our findings indicated TA administration reduced in total blood loss at a mean volume of 154.25 and 84.79 mL in CS and VD, respectively, and no increased risk of thromboembolic complications occurred. In addition, there was a higher heterogeneity existing, which may have caused several potential limitations. First, of the 25 studies, 23 trials measured the blood loss by visual estimation method and only 2 trials[14,33] evaluated the blood loss using a mathematical calculation estimation method. Although the current standard practice of PPH assessment is visual estimation, it has been reported to be inaccurate by many authors because the method depends strongly on the operators' subjective judgments.[48,49] Second, all authors in the included trials have clearly mentioned that their methods did not take amniotic fluid quantity into account. However, it was difficult for avoiding blood loss mixed by amniotic fluid, which might overestimate the amount of blood loss. Finally, the limitation was the usage of oxytocin regimens and other uterotonic drugs. In a trial by Movafegh et al,[15] patients received 30 units oxytocin during the first 8 hours postoperatively followed by 10 units of oxytocin in the case of uterine atony. Gohel Mayur et al[11] described that patients received 10 units oxytocin followed by 0.4 mg methylergometrine, whereas

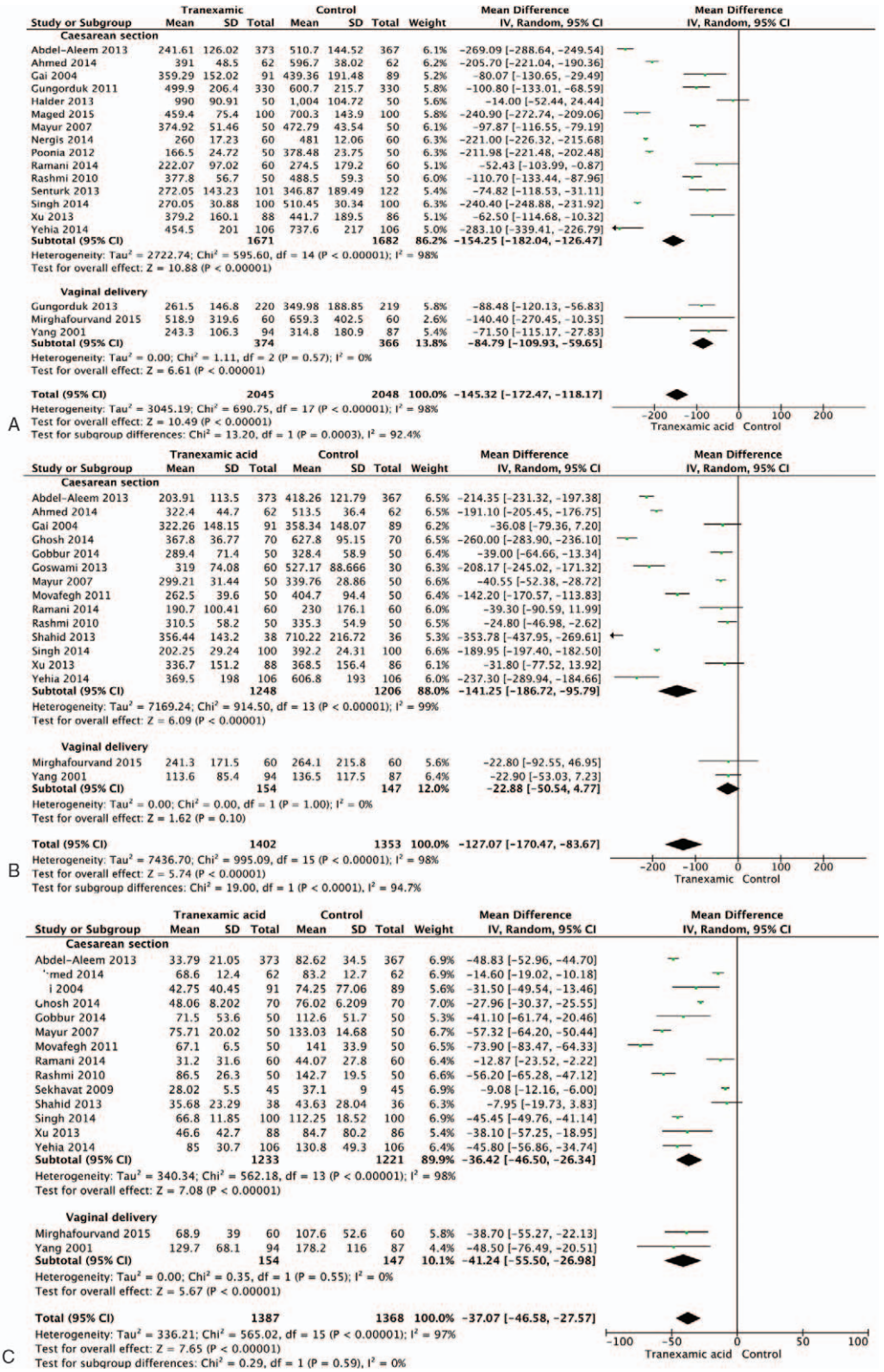

Figure 3. Forest plot diagram showing the effect of tranexamic acid (TA) administration in cesarean section and vaginal delivery on total blood loss (A), intraoperative blood loss (B), and postoperative blood loss (C).

Ramani and Nayak[31] applied the same dose of oxytocin infusion followed by 10 units as intramuscular along with 400 μg of table misoprostol sublingually after delivery of placenta. It is known that the oxytocin usage could reduce blood loss, which may overestimate the efficacy of TA. Although the use of TA resulted in a reduction of blood loss, statistically significant differences in blood loss might not always convey a parallel clinical significance because a mean blood loss of 150 mL was

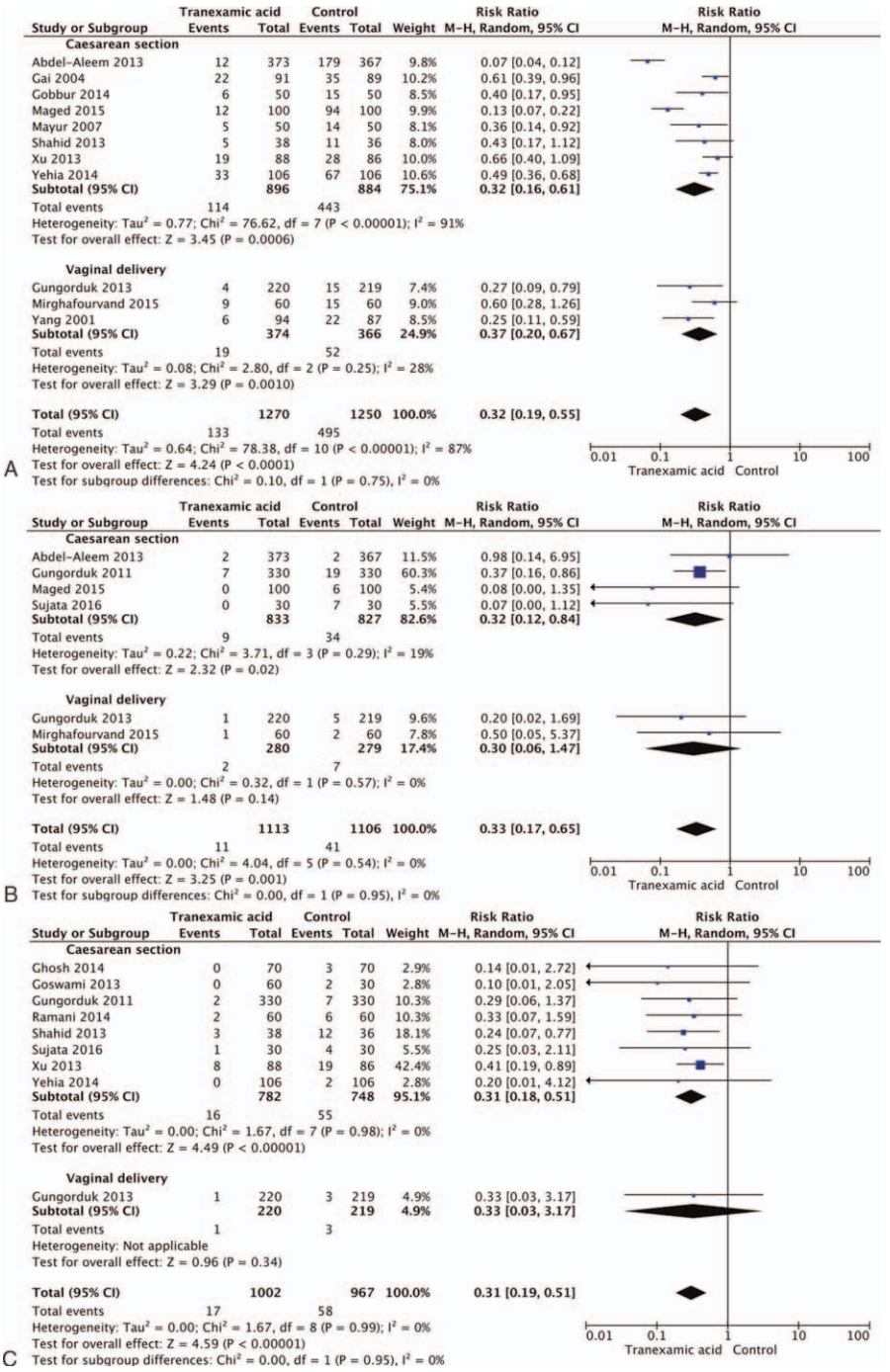

Figure 4. Forest plot diagram showing the effect of TA administration in cesarean section and vaginal delivery on the number of PPH (A), severe PPH (B), and transfusion needs (C). PPH = postpartum hemorrhage, TA = tranexamic acid.

common in pregnancy women and most of women undergoing CS or VD were young and healthy. However, for patients with severe anemia or cardiovascular diseases, blood loss of as little as 200 mL might be a life-threatening. In addition, it was unclear whether the reduction of the volume of blood loss was associated with other potential benefits of TA. Levy discussed the relation between the reduction of blood loss and the major favorable TA effect on mortality and morbidity in trauma patients and emphasized that the potential and unexplored side benefits of TA needed further research.[50]

Traditional, PPH has been defined as blood loss in excess of 500 mL following a VD, or a loss of more than 1000 mL following CS.[39] Because the occurrence rate of PPH will be influenced by the total volume of blood loss and also the response to treatment, the Royal College of Obstetricians and Gynaecologists (RCOG) recommended that 500 mL of blood loss is used as

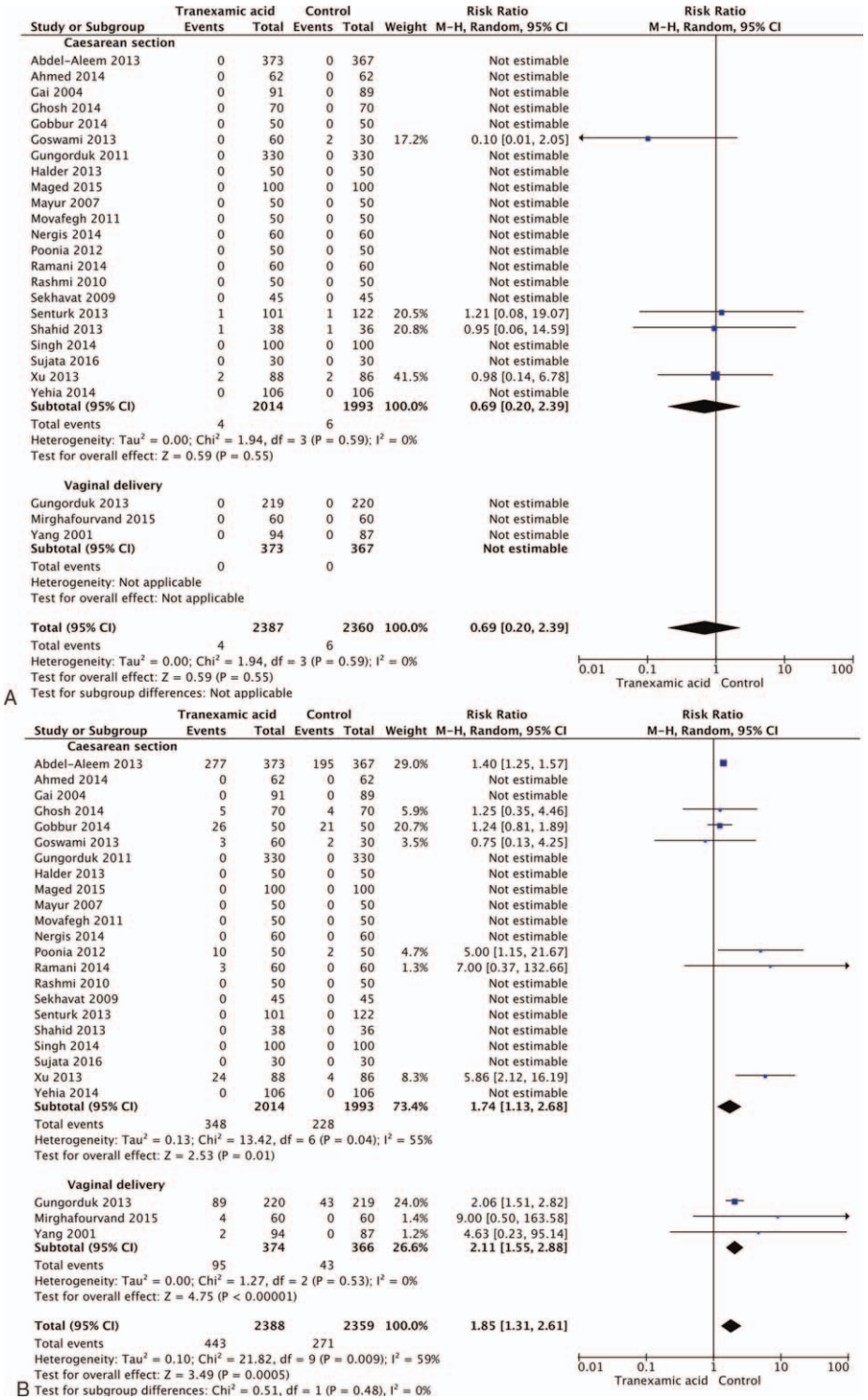

Figure 5. Forest plot diagram showing the effect of TA administration in cesarean section and vaginal delivery on occurrence rate of DVT (A), and other minor adverse events (B). DVT = deep venous thrombosis, TA = tranexamic acid.

a point of "alert," while treatment is only performed once the patient loses over 1000 mL of blood.[51] The effect of TA on PPH is important, especially for CS, as maternal deaths usually occur when blood loss is over 1000 mL.[51] Our findings indicated that TA usage rendered a significant reduction of PPH and severe PPH in both CS and VD. However, the current level of evidence was insufficient to reach a definitive conclusion. The rate of PPH varied greatly depending on the criteria that were used to define it, and it was not the same among different regions around the world, which might be associated with a higher heterogeneity.

The rate of thromboembolic events during pregnancy and puerperium is higher than that in the general population.[1] Thus,

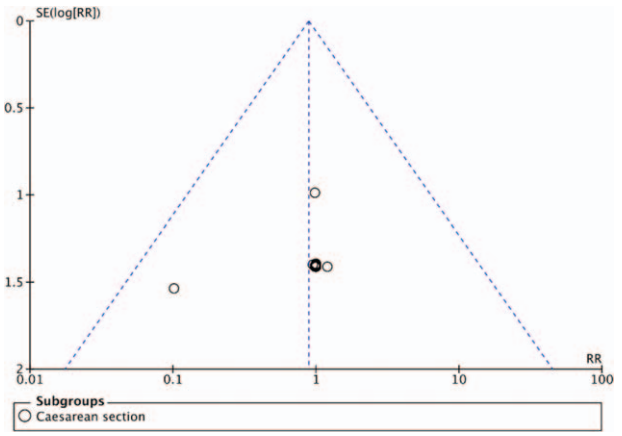

Figure 6. A funnel plot of the logarithm of effect size (RR) versus the SE for each study. RR = risk ratio, SE = standard error.

the safety of TA administration for pregnancy women must be evaluated carefully. Previous studies evaluating the usage of TA in oral, cardiac, and orthopedic surgeries, and recent studies evaluating the usage of TA in obstetrics have confirmed its safety.[1,5,8,9,42] A study by Heesen et al[37] evaluated the usage of TA in 1578 participants who undergoing CS or VD and showed no associated between TA usage and the incidence of thromboembolic events. Our findings showed 4 thromboembolic events in CS following TA administration, which had no significant difference with control group. However, caution was required in the interpretation of these results due to the lower rate of complication and the different methods of DVT screening. Thus, a prolonged treatment with TA should be monitored closely to avoid the risk for underlying thrombosis. Our study was not powered to address safety issues, because the minor side effects including gastrointestinal and neurological manifestations, which were mild and reversible, were higher in TA administration than control group. Although the minor side effects were not the same importance with thromboembolic events, it was essential to balance the clinical effect of TA in reducing blood loss with disabling symptoms. Whether a lower dosage of TA rendered a lower risk of complications needed further studies. In addition, studies evaluating the effective of TA on neonate reported no difference regarding neonatal Apagar score in both groups and no other adverse neonatal outcomes occurred after prophylactic TA administration. Thus, the usage of TA is safety for neonate.

4.1. Strength

The reliability and robustness of the pooled results were supported by the most rigorous assessment of methodology quality of included studies in our meta-analysis: the comprehensive literature search without language restrictions and including the gray literature and conference proceedings; a relative large number of studies in the systematic review, most of which were published in recent years; the quantitative summary of the evidence; the performance of subgroup analyses according to the mode of delivery; the analysis of blood loss according to the different time period; and the sensitivity analysis restricted to trials with low risk of bias.

5. Limitation

Some limitations of this study should be acknowledged. There was substantial statistical heterogeneity existing for several outcomes, especially for bleeding volume. Therefore, our findings should be interpreted in this context. To reduce the clinical heterogeneity among the included studies, we used random effects models to pool data across studies to attempt to incorporate any heterogeneity and explore possible sources of heterogeneity. In addition, the mean difference for evaluating the amount of reduced blood loss was adopted between TA and control group. Despite this, we could not explain most of the heterogeneity, which might be due to the differences in study population, doses of TA or usage of addition uterine drugs, cesarean delivery technique, surgical experience, method of assessment of blood loss, or study implementation. Only 3 studies with small samples were included to evaluate the usage of TA in VD, which might result in a certain bias of the conclusion. In addition, because unpublished data could not be required, we could not fully exclude the publication bias. The majority of studies included relatively small sample size, which perhaps affected the accuracy of the conclusion. Although some studies stated that TA was a cheap drug and did not increase the cost of patients, no study presented the detailed data in their results. Thus, the data were inadequate to pool and the conclusion of cost was unconvincing. Finally, similar with any meta-analyses, ours was limited by the quality of original data.

6. Conclusion

Based on the current evidence, the present meta-analysis demonstrates that TA administration in CS significantly could reduce blood loss, lower the incidence rate of PPH, and severe PPH, and render a significant reduction in blood needs without no apparent increase in harm. Thus, TA seems to be an efficacious and safe drug in patients undergoing CS. However, data are insufficient to evaluate the clinical effect of TA in patients undergoing VD because of the smaller samples and the lower methodology quality of included studies. Therefore, further well-designed RCTs with larger samples are needed to validate our findings.

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