Systematic Review and Meta-Analysis

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Tranexamic acid reduces postoperative blood loss in Chinese pediatric patients undergoing cardiac surgery

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Tranexamic acid has been increasingly used for blood conservation in cardiac surgery. However, the evidence supporting the routine use of tranexamic acid in Chinese pediatric patients undergoing cardiac surgery remains weak. This meta-analysis aimed to systematically review the efficacy of tranexamic acid when applying to Chinese pediatric patients undergoing cardiac surgery.

Participants: Chinese pediatric patients undergoing cardiac surgery.

Interventions: Tranexamic acid or control drugs (saline/blank).

Methods: PUBMED, Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP Data till May 4, 2021, database search was updated on August 1. Primary outcomes of interest included postoperative bleeding, allogeneic transfusion, and reoperation for bleeding. Secondary outcomes of interest included postoperative recovery. For continuous/dichotomous variables, treatment effects were calculated as weighted mean difference (WMD)/odds ratio and 95% confidence interval.

Results: A database search yielded 15 randomized controlled trials including 1641 patients, where 8 studies were allocated into non-cyanotic congenital group, 5 were allocated into cyanotic congenital group, and the other 2 were allocated into combined cyanotic/non-cyanotic group. This meta-analysis demonstrate that tranexamic acid administration can reduce the postoperative 24 hours blood loss in non-cyanotic, cyanotic, and combined cyanotic/non-cyanotic patients, the red blood cell transfusion in non-cyanotic and cyanotic patients, and the fresh frozen plasma transfusion in non-cyanotic and combined cyanotic/non-cyanotic patients.

Conclusion: This meta-analysis demonstrates that tranexamic acid is highly effective in reducing the blood loss in Chinese pediatric cardiac surgery, but it behaves poorly when it comes to the transfusion requirement. To further confirm this, more well-designed and adequately-powered randomized trials are needed.

Abbreviations: CHD = congenital heart disease, CI = confidence interval, CPB = cardiopulmonary bypass, FFP = fresh frozen plasma, RBC = red blood cells, RCT = randomized controlled trial, TXA = tranexamic acid, WMD = weighted mean difference.

Keywords: cardiac surgery, meta-analysis, pediatric, tranexamic acid

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Availability of data and materials: All data generated or analyzed during this study are included in this published article and its additional file.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

The pediatric patients undergoing cardiac surgery suffer from the high risk of bleeding and transfusion. Perioperative bleeding may lead to end-organ damage and increased complications such as hypotension, metabolic acidosis, infection, and acute respiratory distress.[1–3] Congenital heart disease (CHD) has been associated with abnormal coagulation, including low levels of fibrinogen and platelet dysfunction.[4–7] As there are differences between children and adults, pediatric patients should be separate from the adults during surgery for 2 reasons: the absolute blood volume of the pediatric patients is much smaller than the adults, which means that the minor blood loss in adults may cause significant blood loss in the pediatrics[8]; the pediatrics have effective compensatory mechanisms, which allows the pediatrics to remain normotensive till a large volume of blood is lost.[8]

Tranexamic acid (TXA), which has been increasingly used for blood conservation in cardiac surgery, is a synthetic antifibrinolytic agent acting by inhibiting tissue plasminogen and plasmin. Results from previous trials have shown that TXA can reduce blood loss and transfusion in patients undergoing cardiac surgery.[9–12] Therefore, current clinical practice guidelines usually recommend to use TXA in various kinds of surgical procedures including cardiac surgery.[13] However, as the guideline points out, clinical studies on the use of TXA in pediatric cardiac surgery have been limited by small sample sizes and marked heterogeneity in the data.

Furthermore, some biases may exist in the results mentioned above as most of the enrolled patients were White in the current studies. Especially, it has been reported that there are differences in blood coagulation function and fibrinolysis system between the Caucasian and the Asian population,[14,15] and many studies have proved that differences exist in the response of patients from different human races to some special anticoagulation drugs, such as warfarin.[16–18] Results from previous trials have reinforced that there are differences in coagulation function and rates of cardiovascular disease among different human races.[19–21] Individuals of East Asian origin (Chinese and Japanese) have been reported to have a significantly lower risk of venous thromboembolism.[19] Likewise, rates of cardiovascular disease are significantly higher in the South Asian population, but not in the East Asian population when compared with Caucasian population.[20] Ho et al[21] study indicated that: East Asian persons, defined as ethnic Chinese in they cohort, were found to have less prothrombotic parameters including a lower endogenous thrombin potential (ETP) than both Caucasians and "Other Asians," the "Other Asians" in this cohort were also had significantly higher ETP compared with Caucasians.

As the evidence supporting the routine use of TXA in Chinese pediatric patients undergoing cardiac surgery remains weak, we will perform a systemic review and meta-analysis in this paper to systematically evaluate the efficacy of TXA in Chinese pediatric patients undergoing cardiac surgery.

2. Methods and analysis

2.1. Search strategy

We conducted a systemic review according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis Quality of Reporting of Meta-analysis (PRIMSA) Guidelines.[22] The protocol of current meta-analysis was published in PROSPERO with the registration number of CRD42019127917. Relevant trials were identified by computerized searches of PUBMED, Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP Data till May 4, 2021, database search was updated on August 1, using different combination of search words as follows: (Cardiac Surgical OR cardiopulmonary bypass) AND Tranexamic Acid AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial) AND (China OR Chinese) AND pediatric (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A928). No language restriction was used. Additionally, we used the bibliography of retrieved articles to further identify relevant studies.

2.2. Inclusion and exclusion criteria

We included all randomized controlled trials (RCTs) comparing the efficacy of TXA with controls (saline/blank) on Chinese children undergoing cardiac surgery. Primary outcomes of interest included postoperative bleeding, allogeneic transfusion, and reoperation for bleeding. Secondary outcomes of interest included postoperative recovery: mechanical ventilation duration (MVD), lengths of stay (LOS) in the intensive care unit (ICU), LOS in the hospital. Exclusion criteria include studies published as review article, case report or abstract; studies based on animal models; duplicate publications; studies lacking information about outcomes of interest. Two authors (ZYZ and YTY) independently review the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion was further determined by examining the full text.

2.3. Study quality assessment

Two authors (ZYZ and YTY) independently assessed the risk of bias by using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions.[23] Additionally, modified Jadad score[24] was used independently by 2 authors (ZYZ and YTY) to evaluate the methodologic quality of each included trial.

2.4. Data abstraction

Two authors (YTY and LXH) independently performed data extraction: author, year of publication, and journal of included studies; total number of patients, number of patients in TXA, and Control groups, gender, age; surgical procedure; data regarding outcomes of interest. Disagreements were resolved by discussion among all authors during the process of data abstraction.

2.5. Statistical analysis

All data were analyzed by utilizing RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Pooled odds ratio (OR) and 95% confidence interval (CI) were estimated for dichotomous data, and weighted mean difference (WMD) and 95% CI for continuous data, respectively. Each outcome was tested for heterogeneity, and randomized-effects or fixed-effects model was used in the presence or absence of significant heterogeneity (Q-statistical test $P < .05$). Sensitivity analyses were done by examining the influence of statistical model on estimated treatment effects, and analyses which adopt the fixed-effects model were repeated again by using randomized-effects model and vice versa. In addition, sensitivity

analysis also was performed to evaluate the influence of individual study on the overall effects. Subgroup analyses were performed to evaluate possible effects of patient characteristics and control agents on the outcomes, if necessary. Publication bias was explored through visual inspection of funnel plots of the outcomes. All P values were 2-sided, and statistical significance was defined as $P < .05$.

2.6. Subgroup analysis and investigation of heterogeneity

The trials were divided into 3 subgroups according to the cyanotic CHD, non-cyanotic CHD, and combined cyanotic/non-cyanotic CHD.

2.7. Ethics and dissemination

This study was a meta-analysis of previously published literatures, ethical approval was not necessary under the ethical committee of Fuwai Hospital.

3. Results

3.1. Search results

As depicted in the flowchart (Fig. 1), database search identified 22 articles for complete evaluation. Finally, 15[25–39] eligible trials with a total of 1641 participants were included in the meta-analysis. Descriptive analyses of these articles were presented in

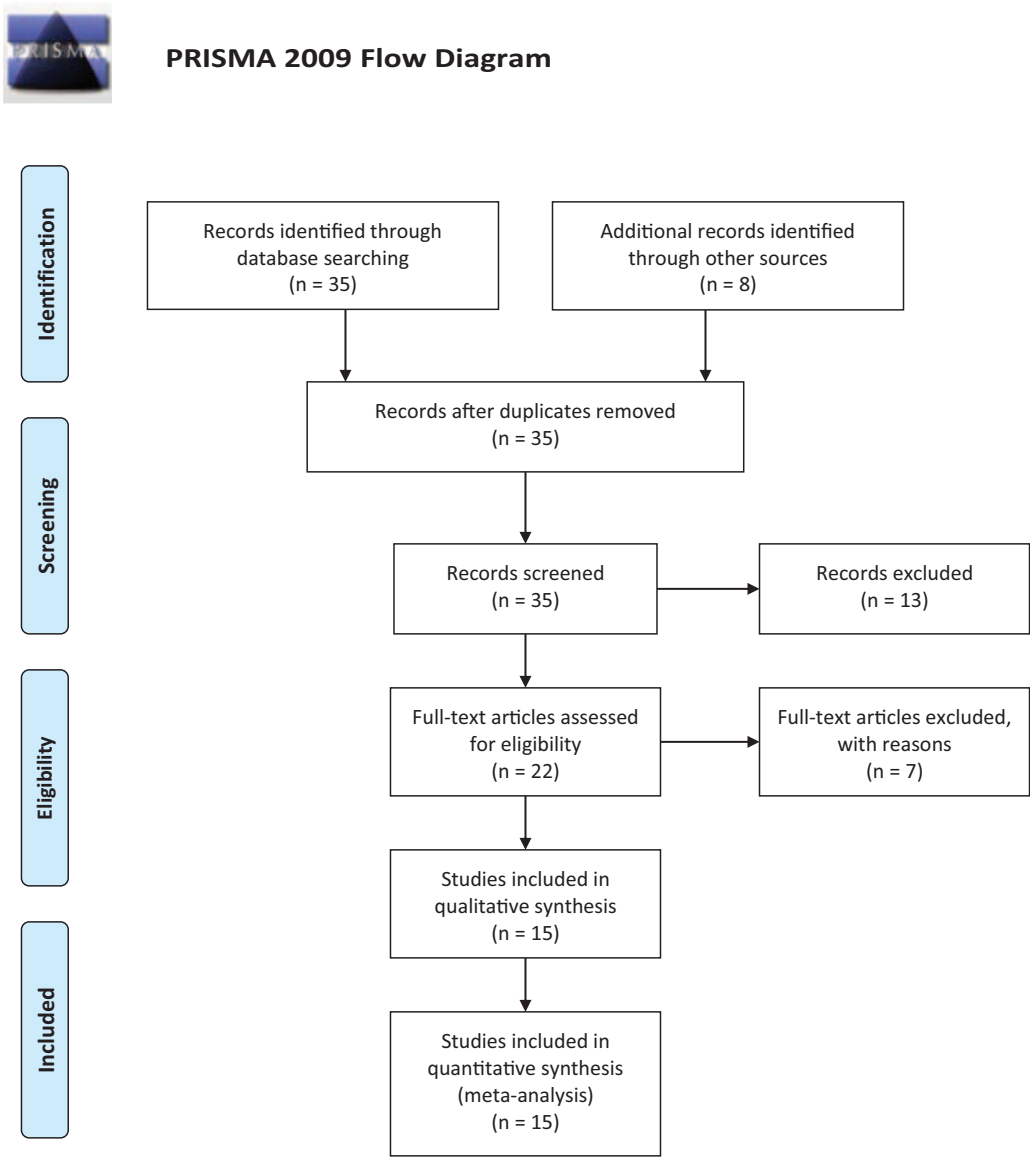

Figure 1. Flowchart of the included and excluded studies.

Table 1

Characteristic of tranexamic acid studies.

Studies	Design	Patients	Surgery	Sample size	Groups	Group TXA	Group control	Outcomes
Non-cyanotic CHD-C								
Di 2015[28]	RCT	Pediatrics	VSD-R	50	3	TXA (n = 25): 10 mg/kg iv. from patient into OR, 10 mg/kg in CBP prime	① Saline (n = 25) ② Hemo (n = 25) 0.3 U iv. in ultrafiltration end	①②③
Han 2015[27]	RCT	Pediatric	ASD-R, VSD-R	60	3	TXA (n = 20): 0.1 g iv. (<10 kg) or 0.2 g iv. (>10 kg) when EOP 30 minutes	① Saline (n = 20) ② Hemo (n = 20) 0.3 KU iv. (<10 kg) or 0.5 KU iv. (>10 kg) after surgery completing 30 minutes	①
Liu 2015(1)[26]	RCT	Pediatrics	VSD-R	100	2	TXA (n = 50): 20 mg/kg iv. during OP	Saline (n = 50)	③
Qin 2015[25]	RCT	Pediatrics	Non-Cyanotic CHD-C	100	2	TXA (n = 50) 25 mg/kg iv. before CBP, 40 mg/kg iv. during OP, 30 mg/kg iv. in CBP end	Saline (n = 50)	①⑤⑥
Wang 2012[29]	RCT	Pediatrics	Non-Cyanotic CHD-C	90	3	TXA (n = 30): 20 mg/kg iv. before SI, 20 mg/kg in CBP prime, 20 mg/kg iv. in CBP end	① Saline (n = 30) ② Aprotinin (n = 30) 2.5×10^4 KIU/kg iv. before SI, 2.5×10^4 KIU/kg iv. in CBP prime	①③⑤⑥⑦⑨⑩
Wang 2012[30]	RCT	Pediatrics	ASD-R, VSD-R	80	2	TXA (n = 40): 30 mg/kg iv. before SI, 30 mg/kg in CBP prime, 30 mg/kg iv. CBP end	Saline (n = 40)	①⑥⑩
Yue 2005[31]	RCT	Pediatrics	ASD-R, VSD-R	45	3	TXA (n = 15): 10 mg/kg *iv.* before SI, 5 mg/kg in CBP prime	① Saline (n = 15) ② Aprotinin (n = 15)	①
Ma 1998[32]	RCT	Pediatric	Non-Cyanotic CHD-C	24	2	TXA (n = 12): 10 mg/kg iv. before SI, 5 mg/kg in CBP prime	Saline (n = 12)	①②
Cyanotic CHD-C								
Xu 2020[37]	RCT	Pediatrics	Pediatrics	30	2	TXA (n = 15): 10 mg/kg iv. before SI, 0 mg/kg iv. till EOP	Saline (n = 15)	①
Xia 2015[33]	RCT	Pediatrics	TOF-C	56	2	TXA (n = 30): 10 mg/kg iv. before SI, 10 mg/kg/h till EOP	Saline (n = 26)	①②③④
Liu 2015(2)[34]	RCT	Pediatrics	TOF-C	100	4	TXA (n = 25): 20 mg/kg iv. till EOP	① Saline (n = 25): ② Uli (n = 25):10,000 U/kg iv. ③ TXA + Uli (n = 25): TXA 20 mg/kg iv. till EOP, 10,000 U/kg iv.	①②
Tu 2011[35]	RCT	Pediatrics	Cyanotic CHD-C	60	2	TXA (n = 30): 10 mg/kg iv. after induction, 10 mg/kg/h in CBP prime, 10 mg/kg/h iv. after protamine.	Saline (n = 30):	①②③⑥
Zhang 2010[36]	RCT	Pediatrics	Cyanotic CHD-C	45	3	① TXA (n = 15): 10 mg/kg iv. after induction, 10 mg/kg in CBP prime, 1 mg/kg/30 min iv. during CBP ② TXA (n = 15): 50 mg/kg iv. after induction, 50 mg/kg in CBP prime, 5 mg/kg/30 min iv. during CBP	Saline (n = 15)	①②③
Cyanotic and non-Cyanotic CHD-C								
Huang 2013[38]	RCT	Pediatrics	-	682	2	TXA (n = 353): 20 mg/kg iv. after induction	BLK (n = 329): No antifibrinolytics	①②
Wang 2011[39]	RCT	Pediatrics	-	119	3	① TXA (n = 40): 30 mg/kg iv. after induction, 2 mg/kg in CBP prime, 16 mg/kg/h iv. till EOP ② TXA (n = 40): 30 mg/kg iv. after induction, 30 mg/kg iv. begin and end CBP	Saline (n = 39):	①②③④

AI = anesthesia induction, ASD/VSD-R = atrial septal defect/ventricular septal defect-repair, BLK = blank, CHD-C = congenital heart disease-correction, CPB = cardiopulmonary bypass, DB = double-blinded, EOP = end of operation, g = gram, Hemo = hemocoagulase, iv. = intravenously, ivgtt. = intravenously guttae, kg = kilogram, KIU = Kallikrein inhibitor unit, KU = Kallikrein unit, mg = milligram, OR = operation, RCT = randomized controlled trial, SI = skin incision, TXA = tranexamic acid.

Reported outcomes:

① = bleeding.
② = postoperative transfusion rate of red blood cell and volume.
③ = postoperative transfusion rate of fresh frozen plasma and volume.
④ = postoperative transfusion rate of blood platelet and volume.
⑤ = mechanical ventilation duration.
⑥ = lengths of stay in the intensive care unit.
⑦ = lengths of stay in the hospital.
⑧ = reoperation.
⑨ = hospitalized mortality and morbidity.
⑩ = renal complications.

Table 1. Of the 15 trials, 2 were performed in the Hebei province,[26,34] 2 in Henan province,[29,35] 1 in Guangdong province,[38] 1 in Guangxi province,[35] 1 in Jiangxi province,[37] 1 in Qinghai province,[27] 1 in Shandong province,[28] 3 in Shanghai city,[30,36,39] 2 in Xinjiang province,[25,32] 1 in Zhejiang province.[31] All 15 studies were written in Chinese.

3.2. Included trials characteristics

As shown in Table 1, 15[25–39] trials included only children undergoing correction for CHD. Eight[25–32] included only children undergoing correction for non-cyanotic congenital heart diseases; 5[33–37] included only children undergoing correction for cyanotic congenital heart diseases; and 2[38,39] included only children undergoing correction for combined cyanotic/non-cyanotic heart diseases. TXA administration protocols (dosage, timing, and route) varied among included trials. The study by Zhang et al,[36] Wang et al[39] investigated 2 dosing protocols of TXA, it was therefore considered as 2 independent groups.

3.3. Risk of bias in included studies

Details regarding the performance of the studies against each domain were presented in the risk of bias graph (Fig. 2). Additionally, a visual summary of judgements about each methodological quality item for each included trial was shown in Fig. 3. Of the 15 included trials, 6 trials[26,27,31,32,34,39] had Jadad scores ≥3 and were considered as high-quality RCTs, shown in Table 2.

3.4. Effects on postoperative 24 hours bleeding volume

As shown in Table 1, 7 trials[26–32] (7 comparisons, 384 patients), 5 trials[33–37] (6 comparisons, 236 patients), and 2 trials[38,39] (3 comparisons, 801 patients) reported postoperative 24 hours bleeding volume in non-cyanotic, cyanotic, and combined cyanotic/non-cyanotic patients, respectively. Meta-analysis demonstrated that, TXA significantly reduced postoperative 24 hours bleeding volume in non-cyanotic patients ([WMD = −55.04; 95% CI: −103.92 to −6.17; $P = .03$] with heterogeneity [$I^2 = 99\%$, $P < .00001$]); in cyanotic patients ([WMD = −55.25; 95% CI: −92.58 to −17.92; $P = .004$] with heterogeneity [$I^2 = 91\%$, $P < .00001$]) and in combined cyanotic/non-cyanotic patients ([WMD = −27.03; 95% CI: −35.64 to −18.41; $P < .00001$] with heterogeneity [$I^2 = 0\%$, $P = .78$]) (Fig. 4).

3.5. Red blood cell transfusion volume

As depicted in Table 1, 2 trials[28,32] (2 comparisons, 74 patients), 4 trials[33–36] (5 comparisons, 206 patients), and 2 trials[38,39] (3 comparisons, 801 patients) reported postoperative red blood cell (RBC) transfusion volume in non-cyanotic, cyanotic, and combined cyanotic/non-cyanotic patients, respectively. Meta-analysis demonstrated that, TXA significantly reduced postoperative RBC transfusion in non-cyanotic patients ([WMD = −103.12; 95% CI: −182.90 to −23.34; $P = .01$] with heterogeneity [$I^2 = 91\%$, $P = .001$]); in cyanotic patients ([WMD = −142.70; 95% CI: −266.18 to −19.23; $P = .02$] with heterogeneity [$I^2 = 96\%$, $P < .00001$]). TXA did not reduce postoperative RBC transfusion volume in combined cyanotic/non-cyanotic patients ([WMD = 18.57; 95% CI: −137.20 to 174.34; $P = .82$] with heterogeneity [$I^2 = 99\%$, $P < .00001$]) (Fig. 5).

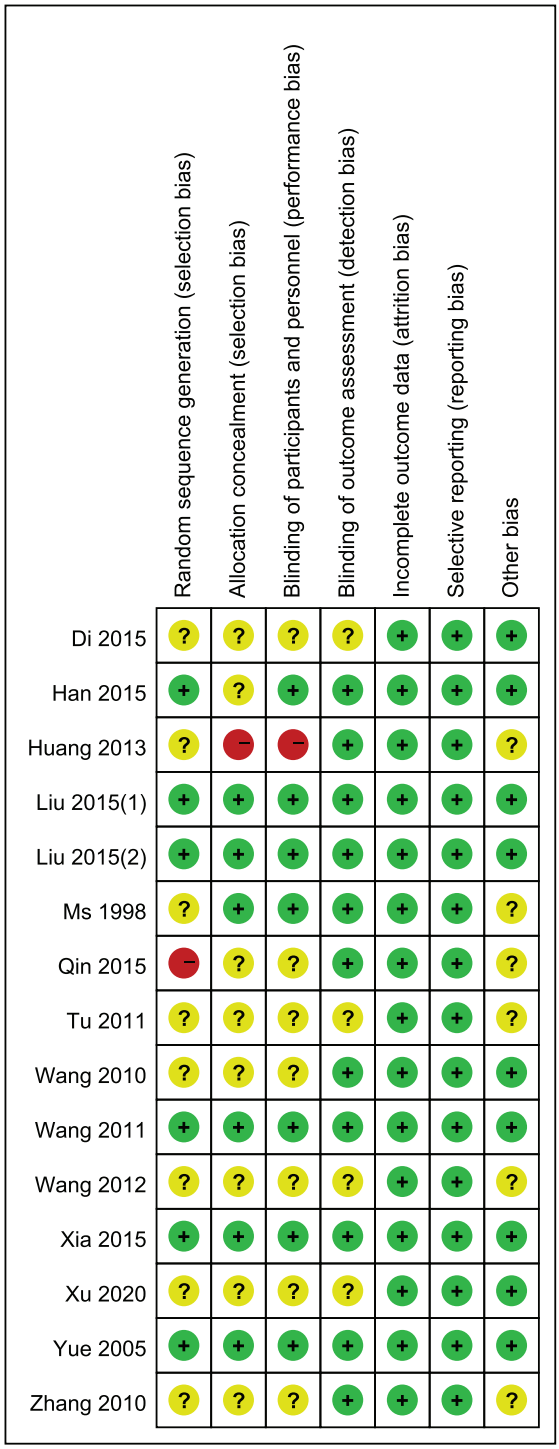

Figure 2. Risk-of- bias graph for each included study. Green (+), red (–), and yellow(?) circles indicate low, high, and unclear risk of bias, respectively.

3.6. Fresh frozen plasma transfusion volume

As depicted in Table 1, 3 trials[26,28,29] (3 comparisons, 210 patients), 3 trials[33,35,36] (4 comparisons, 156 patients), and 1trial[39] (2 comparisons, 119 patients) reported postoperative fresh frozen plasma (FFP) transfusion volume in non-cyanotic, cyanotic, and combined cyanotic/non-cyanotic patients, respectively.

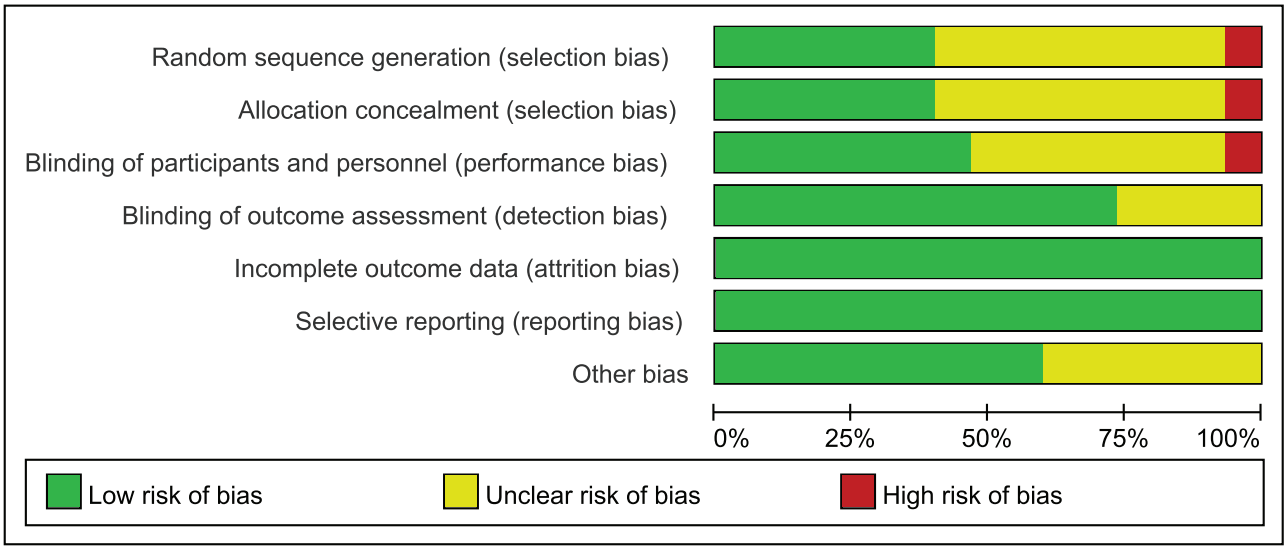

Figure 3. Risk-of-bias summary for each included study. Green (+), red (–), and yellow(?) circles indicate low, high, and unclear risk of bias, respectively.

Meta-analysis demonstrated that postoperative FFP transfusion volume were similar between the TXA group and control group in non-cyanotic patients ([WMD = –102.23; 95% CI: –230.58–26.12; $P = .12$] with heterogeneity [$I^2 = 99\%$, $P < .00001$]); in cyanotic patients ([WMD = –45.98; 95% CI: –149.72 to 57.76; $P = .39$] with heterogeneity [$I^2 = 95\%$, $P < .00001$]). TXA significantly reduced postoperative FFP transfusion volume in combined cyanotic/non-cyanotic patients ([WMD = –44.48; 95% CI: –62.99 to –25.97; $P < .00001$] with heterogeneity [$I^2 = 0\%$, $P = .60$]) (Fig. 6).

3.7. Postoperative recovery

As shown in Table 1, in non-cyanotic patients 2 trials[25,29] (2 comparisons, 160 patients), 3 trials[25,29,30] (3 comparisons, 240 patients) reported postoperative MVD and LOS in the ICU, respectively. Meta-analysis demonstrated that TXA group had comparable MVD ([WMD = 21.54; 95% CI: –21.24–64.31; $P = .32$] with heterogeneity [$I^2 = 100\%$, $P = .32$]; postoperative LOS in the ICU [WMD = –0.51; 95% CI: –1.55–0.52; $P = .33$] with heterogeneity [$I^2 = 100\%$, $P = .32$]) to control group (Fig. 7).

3.8. Sensitivity analyses and publication bias

Sensitivity analysis showed that treatment effects on all the outcomes were not affected by the choice of statistical model (Table 3). Sensitivity tests were also performed by exclusion of some studies to analyze the influence of the overall treatment effect on high heterogeneity outcomes (Table 4) but no contradictory results were found. No significant publication bias was detected by funnels plot examination for postoperative 24 hours bleeding volume (Fig. 8).

4. Discussion

To our best knowledge, this is the first meta-analysis dedicated to evaluate the efficacy of TXA for Chinese pediatric patients undergoing cardiac surgery. TXA administration can reduce the

Table 2

Quality assessment of included studies.

Study	Sample size	Jadad score			
		Randomization	Blindness	Withdrawals	Total
Di 2015[28]	50	1	0	0	1
Han 2015[27]	40	2	1	1	4
Huang 2013[38]	682	1	0	0	1
Liu 2015(1)[26]	100	2	1	0	3
Liu 2015(2)[34]	100	2	1	0	3
Ma 1998[32]	24	1	2	0	3
Qin 2015[25]	100	0	0	0	0
Tu 2011[35]	60	1	0	0	1
Wang 2012[30]	80	1	0	0	1
Wang 2011[39]	119	2	1	1	4
Wang 2012[29]	60	1	0	0	1
Xia 2015[33]	56	2	0	0	2
Xu 2020[37]	30	1	0	0	1
Yue 2005[31]	30	2	2	0	4
Zhang 2010[36]	45	1	0	0	1

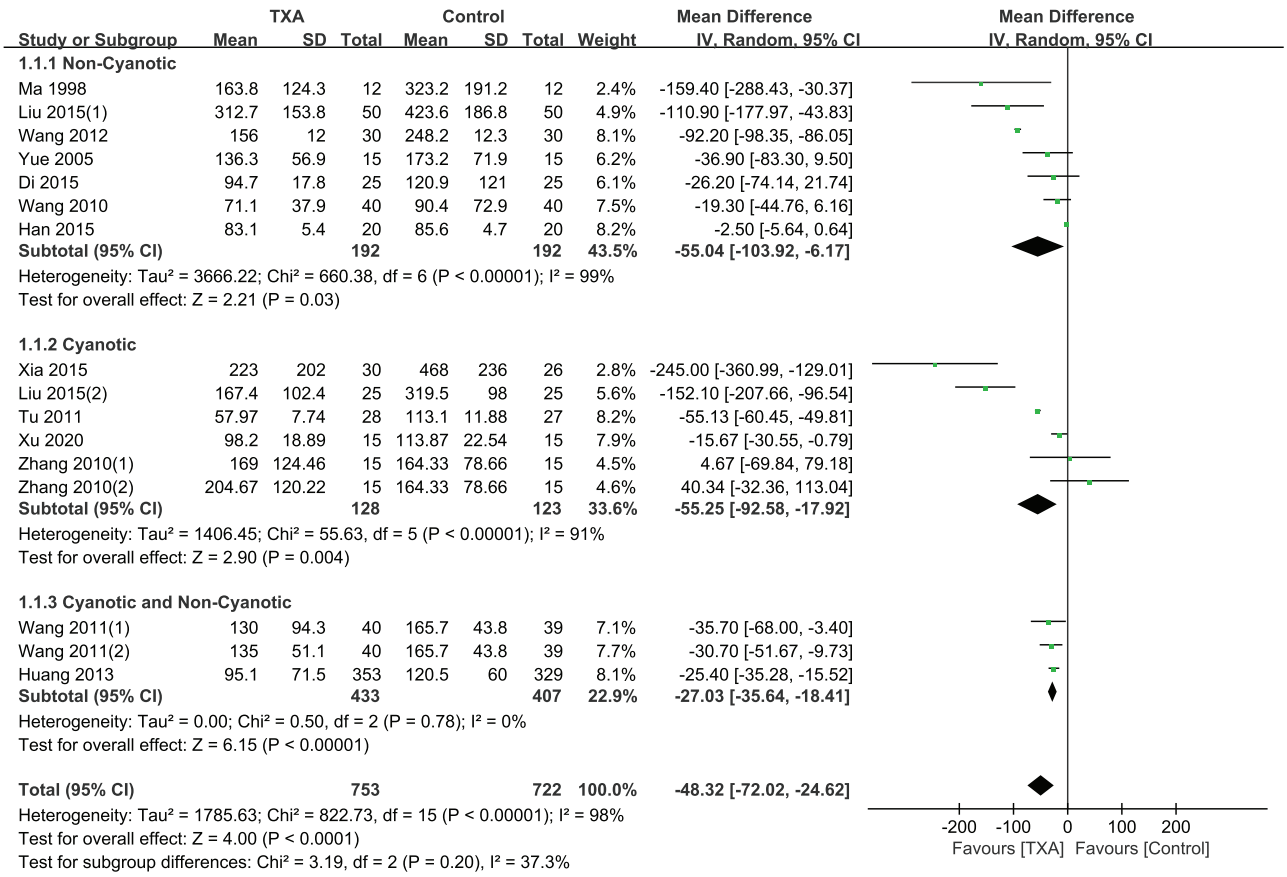

Figure 4. Forest plot of postoperative 24 hours bleeding volume.

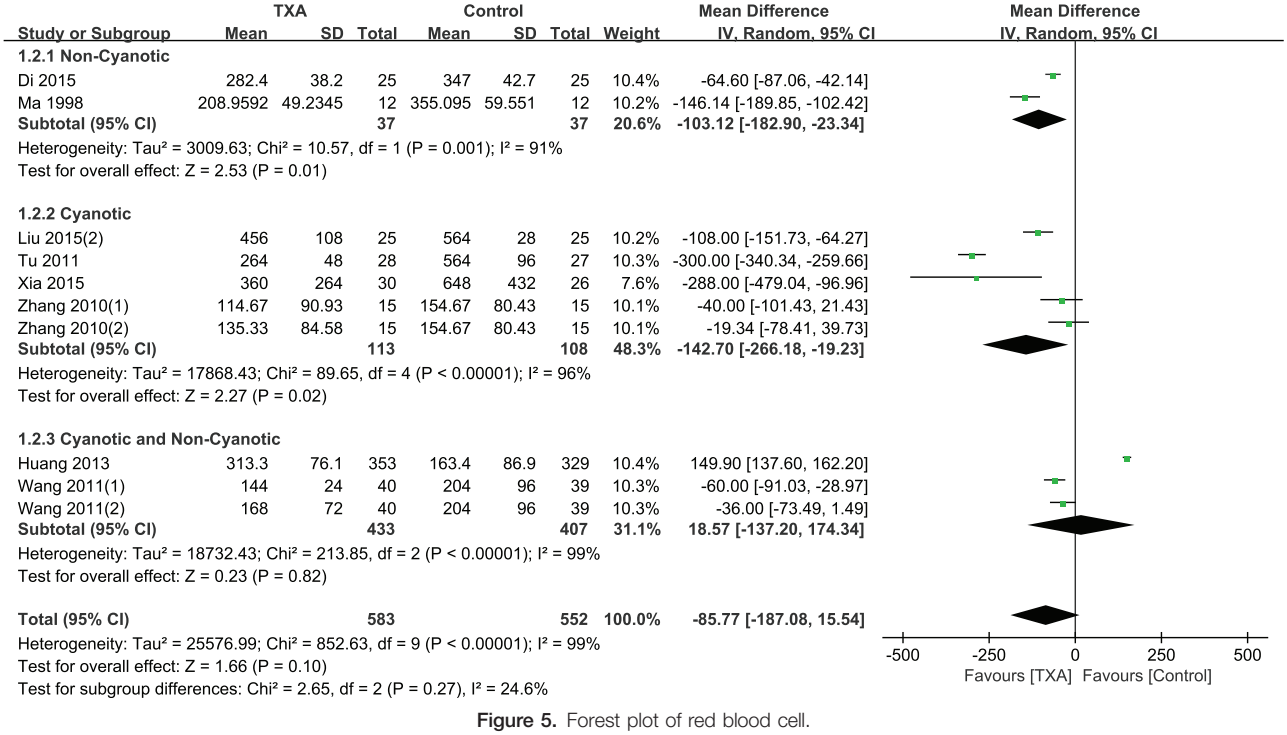

Figure 5. Forest plot of red blood cell.

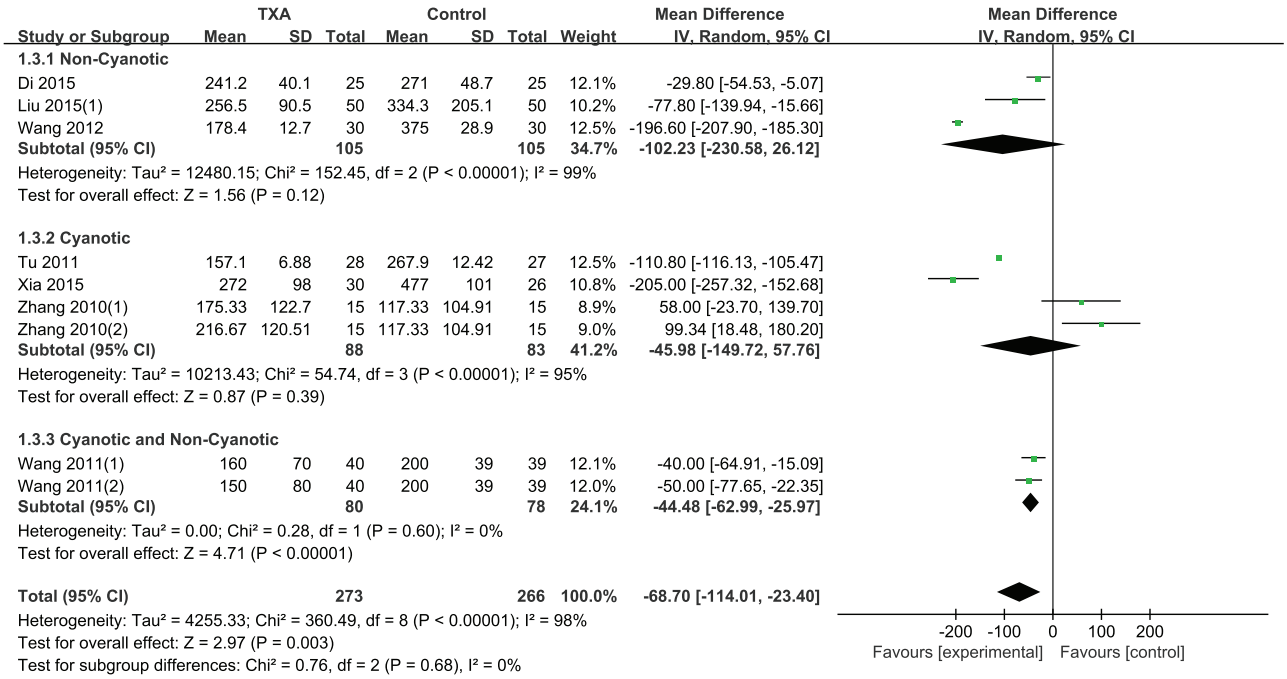

Figure 6. Forest plot of fresh frozen plasma transfusion volume.

postoperative 24 hours blood loss in non-cyanotic, cyanotic, and combined cyanotic/non-cyanotic patients, the RBC transfusion in non-cyanotic and cyanotic patients, and the FFP transfusion in non-cyanotic and combined cyanotic/non-cyanotic patients. Our meta-analysis results are consistent with those studies including Asians[40–42] showing that TXA is effective in reducing the blood loss in pediatric cardiac surgery but works poorly when it comes to the transfusion requirement. The retrospective cohort study published by Zhang et al[40] in Fuwai Hospital, where 2026 consecutive pediatric patients undergoing surgical repair of atrial or ventricular septal defect or complete repair of Tetralogy of Fallot were included, suggests that TXA is effective in reducing postoperative blood loss but works poorly for the allogeneic transfusion requirement, particularly in infants weighing <10 kg and children with cyanotic. Another retrospective cohort study published by Zhang et al[41] in Fuwai Hospital, to evaluate the efficacy of TXA in perioperative blood conservation in pediatric patients undergoing complete repair of Tetralogy of Fallot, the results of this study suggested that TXA can decrease postoperative blood loss, but has little impact on the allogeneic blood transfusion. The RCTs published by Shimizu et al[42] where a total number of 160 pediatric patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) were included, shows that TXA is effective in reducing blood loss but not the transfusion requirement.

Evidence has suggested that there might be significant differences among different human races with respect to blood coagulation

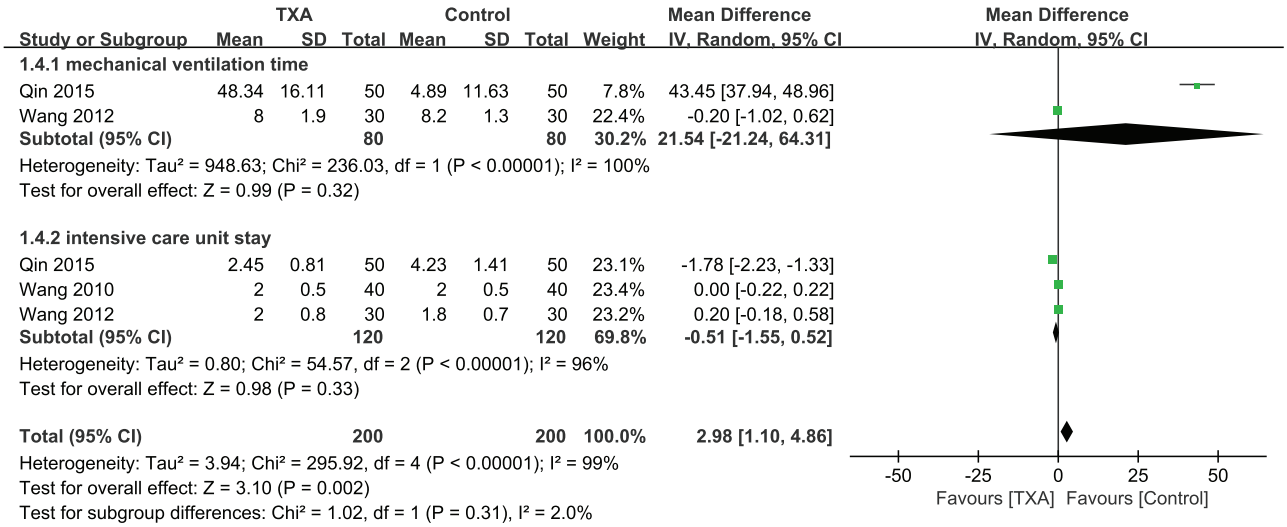

Figure 7. Forest plot of post-operative recovery.

Table 3

Influence of statistical model on TXA efficacy of primary outcomes.

Subgroup	Statistical model	Post-op bleeding, mL WMD (95% CI)	Post-op RBC(u) WMD (95% CI)	Post-op FFP, mL WMD (95% CI)	MVD, h WMD (95% CI)	LOS in the ICU, d WMD (95% CI)
Cyanotic	Fixed effects	−21.30 (−24.06, −18.53)	−81.62 (−101.60, −61.65)	−165.41 (−175.55, −155.27)	–	–
	Random effects	−55.04 (−103.92, −6.17)	−103.12 (−182.90, −23.34)	−102.23 (−230.58, 26.12)	–	–
Non-cyanotic	Fixed effects	−51.16 (−56.12, −46.19)	−154.31 (−178.45, −130.17)	−110.16 (−115.44, −104.87)	0.76 (−0.06, 1.57)	0.76 (−0.06, 1.57)
	Random effects	−55.25 (−92.58, −17.92)	−142.70 (−266.18, −19.23)	−45.98 (−149.72, 57.76)	21.54 (−21.24, 64.31)	−0.51 (−1.55, 0.52)
Cyanotic and non- cyanotic	Fixed effects	−27.03 (−35.64, −18.41)	108.03 (97.09, 118.96)	−44.48 (−62.99, −25.97)	–	–
	Random effects	−27.03 (−35.64, −18.41)	18.57 (−137.20, 174.34)	−44.48 (−62.99, −25.97)	–	–

95% CI = 95%confidence interval, d = day, FFP = fresh frozen plasma, h = hour, LOS in the ICU = lengths of stay in the intensive care unit, mL = milliliter, MVD = mechanical ventilation duration, OR = odds ratio, Post-op = postoperative, RBC = red blood cell, u = unit, WMD = weighted mean difference.

Table 4

Sensitivity analyses of high heterogeneity outcome.

Subgroup	Heterogeneity outcome	Excluded trials	Group TXA (n)	Group C (n)	Heterogeneity I^2 (%)	Heterogeneity *P*	Analysis model	WMD/OR	95% CI	Overall effect *P*
Non-cyanotic	Post-op bleeding, mL	[28,32]	165	165	99	<.00001	IV, Fixed	−21.18	(−23.95, −18.41)	<.00001
	Post-op RBC (u)	[28]	24	24	81	.02	IV, Fixed	−184.99	(−264.34, −105.65)	<.00001
	Post-op FFP, mL	[28]	80	80	93	.0002	IV, Fixed	−141.29	(−257.44, −25.15)	.02
Cyanotic	Post-op bleeding, mL	[36]	98	93	94	<.00001	IV, Fixed	−81.31	(−123.56, −39.07)	.0002
	Post-op RBC (u)	[36]	83	78	95	<.00001	IV, Fixed	−224.85	(−382.02, −67.68)	.005
	Post-op FFP, mL	[36]	58	53	92	.0004	IV, Fixed	−154.16	(−246.18, −62.14)	.001
Cyanotic and non-cyanotic	Post-op bleeding, mL	[38]	80	78	0	.8	IV, Fixed	−32.18	(−49.77, −14.60)	.0003
	Post-op RBC (u)	[38]	80	78	0	.33	IV, Fixed	−50.24	(−74.15, −26.34)	<.0001

95% CI = 95% confidence interval, d = day, FFP = fresh frozen plasma, h = hours, mL = milliliter, OR = odds ratio, Post-op = postoperative, RBC = red blood cell, TXA = tranexamic acid, u = unit, WMD = weighted mean difference.

and fibrinolysis functions.[14,15,19–21] Previous meta-analysis by Faraoni et al[43] and Siemens et al,[44] demonstrated that TXA administration reduced both postoperative bleeding and blood transfusion requirement in Caucasian pediatrics undergoing cardiac surgery. Our meta-analysis including only Chinese (Asian) pediatric cardiac surgical patients showed similar results.

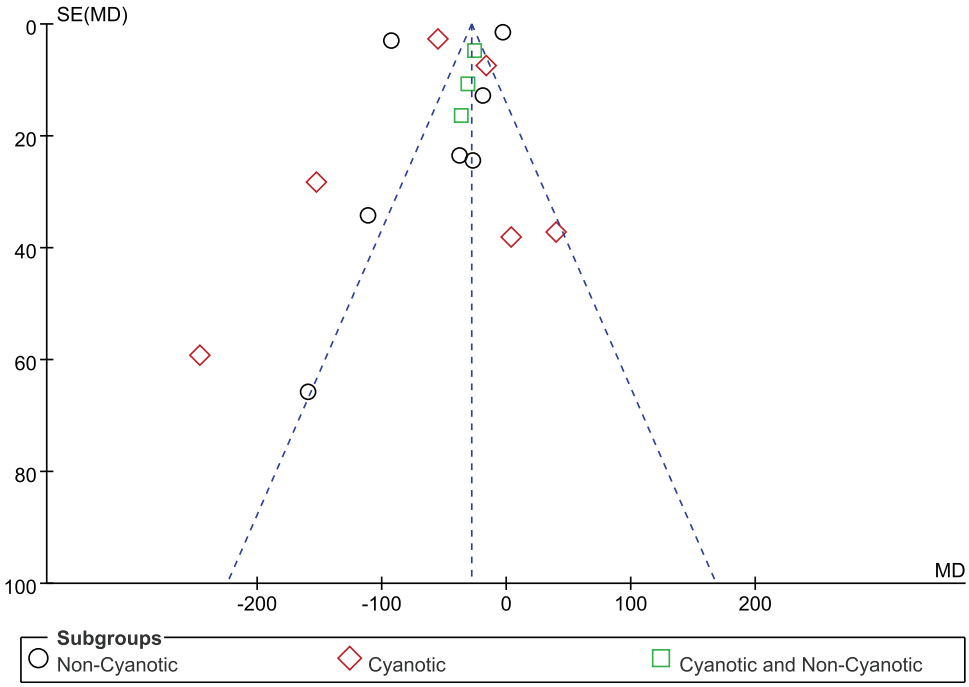

Figure 8. Funnels plot examination for postoperative 24 hours bleeding volume.

The inconsistencies in the findings between our meta-analysis and meta-analysis mentioned above are likely caused by the difference in human races of patients. For this reason, in order to complete the objective of this review, we made a comparison with the Caucasian pediatric population to show its relevance or really if this discrepancy exists.

4.1. Comparison with the Caucasian pediatric population:

Database search identified 5 articles[45–49] for complete evaluation. Of the 5 trials, 3[45,47,49] included only Caucasian children undergoing correction for non-cyanotic congenital heart diseases; 3[46,47,49] included only Caucasian children undergoing correction for cyanotic congenital heart diseases; and 2[48,49] included only Caucasian children undergoing correction for combined cyanotic/non-cyanotic heart diseases.

Meta-analysis demonstrated that, TXA administration can reduce the postoperative 24 hours blood loss in cyanotic and combined cyanotic/non-cyanotic Caucasian pediatric patients (Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A925), the RBC transfusion in non-cyanotic Caucasian pediatric patients (Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A926), and the FFP transfusion in cyanotic Caucasian pediatric patients (Figure S3, Supplemental Digital Content, http://links.lww.com/MD2/A927).

The results of meta-analysis between the Caucasian and Chinese pediatric populations showing that TXA is effective in reducing the blood loss in both Caucasian and Chinese pediatric cardiac surgery but works inconsistently when it comes to the transfusion requirement.

The efficacy of TXA on postoperative RBC and FFP transfusion requirement are inconsistent between the cyanotic and combined cyanotic/non-cyanotic patients groups, which is mainly caused by the fact that: cyanotic heart disease is often characterized by a complex coagulation disorder that increases both the thrombotic and the hemorrhagic risk in children and adults who undergo cardiac surgery.[37–40] Cyanotic children undergoing cardiac surgery reportedly have significantly preoperative coagulation anomalies and require more fibrinogen supplementation postoperatively.[50] Standard coagulation tests have numerous limitations in predicting thrombotic or bleeding events after complex cardiac surgical corrections.[51,52] Firstly, prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests are conducted on plasma, while the events related to the hemostasis and thrombosis occur in vivo in the blood stream where cells and clotting factors synergistically interact. Secondly, the platelet count does not provide information on the platelet function. The efficacy of TXA in antifibrinolytic, anti-platelet activation, and anti-inflammatory might be more beneficial in infants weighing <10 kg and pediatric patients with cyanotic,[40] while trails included in our meta-analysis did not have a subgroup analysis through weight.

Several factors may explain the high degree of heterogeneity observed between the included studies.

(1) The guideline of applying TXA as well as the pharmacological data of TXA in pediatric cardiac surgery are not yet available.

Since the suspension of aprotinin in 2007, TXA has become the main antifibrinolytic agent for preventing blood loss in cardiac surgery.[53] However, as the guideline points out, clinical studies on the use of TXA in pediatric cardiac surgery have been limited by small sample sizes and marked heterogeneity in the data.[54] In fact, no pharmacological data on TXA are available in the pediatric cardiac surgery population. Therefore, the choice of the TXA dosage was not based on pharmacodynamics data about the fibrinolytic inhibiting activity of the drug. Instead, the anesthesiologist decides whether to apply TXA for blood protection in pediatric cardiac surgery according to their personal experience. At present, there is wide variation in the dosage of TXA recommended for use during pediatric cardiac surgery (loading doses of TXA ranged from 10 to 100 mg/kg and maintenance doses ranged from 1 to 15 mg/kg/h).[55] In the included studies, the variability in the dosage schemes used is striking (Table 1). After anesthetic induction, some studies used a single bolus that ranged from 10 to 100 mg/kg.[26,27,38] Others used several boluses: at anesthetic induction, in the CPB priming, after protamine administration and end of operation.[25,28–33,35–38] Still other studies used continuous infusion during and after CPB.[34]

(2) Allogeneic transfusion protocols inconsistent.

Most of the included studies did not describe the transfusion protocols that have been used. In the absence of this information, the efficacy of TXA is difficult to evaluate.

(3) Several of the published studies are drawn from the same team.

For this reason, we performed a sensitivity analysis to evaluate the impact on the results. The exclusion of these studies reduces the number of patients included in our analysis but did not change the overall results.

4.2. Limitations

This study has some limitations. Meta-analysis can increase the power of analysis by pooling many small low-quality studies, but different administration modalities of TXA (e.g., dose, timing), varied surgical operation types and different clinical practices, quality and heterogeneity issues of included studies may limit the certainty of the findings of meta-analysis. There were significant differences among the 15 clinical trials included in the meta-analysis with respect to sample size, study design, outcome definition, allogeneic transfusion protocols, etc; so the statistical analysis results of the current study should be explained with caution. To confirm this, more well designed and adequately-powered randomized trials are needed.

5. Conclusion

To conclude, TXA is highly effective in reducing the blood loss in Chinese pediatric cardiac surgery, but it works poorly when it comes to the transfusion requirement. To further confirm this, more well-designed and adequately-powered randomized trials are needed.

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