Is tranexamic acid effective and safe for patients undergoing revision total hip and knee arthroplasty: a meta-analysisIs

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Abstract

Background: The use of tranexamic acid (TXA) during primary total joint arthroplasty （pTJA） is well documented. However, whether TXA is safe for patients undergoing revision total joint arthroplasty (rTJA) remains to be resolved. Methods: This meta-analysis included 12 studies that involved 2195 cases. The primary outcomes were indicators of TXA effectiveness during perioperative perid, including blood loss, haemoglobin (Hb) level changes, allogeneic blood transfusion (ABT) rate, and number of red blood cell (RBC) units transfused per patient. The secondary outcomes included thromboembolic complications, non-thromboembolic complications, and length of hospital stay. Results: TXA administration was associated with statistically significant decreases in the primary outcomes, including ABT rate (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.14–0.41; P < 0.00001), change in Hb level (mean difference [MD], −0.84; 95% CI, −1.28 to −0.41; P=0.002), and number of RBC units transfused per patient (MD, −0.49; 95% CI, −0.61 to −0.38; P < 0.00001) in the patients undergoing rTJA. Secondary outcome assessments showed no statistically significant differences in venous thromboembolism (OR, 0.99; 95% CI, 0.31–3.14; P=0.98) and non-thromboembolic complications (OR, 0.54; 95% CI, 0.18–1.68; P=0.29) between the patients who received and those who did not receive TXA in the revision total knee arthroplasty subgroup, while a significant decrease in length of hospital stay was found in those who received TXA (MD, −2.89; 95% CI, −4.85 to −0.93; P=0.004). Conclusion: In this meta-analysis, we found that the use of TXA acid can effectively reduce the number of blood transfusions in patients undergoing TJA without increasing the complication rate.

Background

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are major orthopaedic treatment procedures for end-stage knee or hip diseases [1, 2]. Over time, the use of revision joint arthroplasty has been increasingly considered as the prevalence of primary total joint arthroplasty (pTJA) has significantly increased, especially among young people [3-5]. Compared with pTJA, revision TJA (rTJA) has greater blood loss due to the more complicated osteotomy and muscle release, which results in higher blood transfusion requirements. In this case, the patient may need a blood transfusion during the perioperative period [6,7]. Although allogeneic blood transfusion (ABT) is widely used in the clinic, considering its potential side effects, it is still a risk factor of potential complications such as allergic reactions, haemolysis, and even infections around the prosthesis [8,9]. Conversely, from the patient's point of view, it may extend the length of hospital stay, delay the initiation of the rehabilitation program, and increase the cost of hospitalisation, thus increasing patient burden [10]. Therefore, in view of the above-mentioned reasons, we have explored how to improve the perioperative blood management strategy to reduce perioperative blood loss and blood transfusion rate to reduce the economic burden of patients.

Tranexamic acid (TXA) blocks the lysine binding site on plasminogen molecules and inhibits the formation of plasminogen. In the past decade, TXA has been widely used in patients undergoing primary joint replacement, and the proportion of patients requiring transfusion during the perioperative period has also been significantly reduced [11,12]. Although sufficient studies have confirmed that TXA can effectively reduce the perioperative blood loss and transfusion rate in pTJA, large trials to study the role of TXA in rTJA are still lacking [13-15]. To clarify this issue, we conducted a meta-analysis to assess whether TXA could play an active role in rTJA.

Methods

Search strategy

We followed not only the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [16] but also the recommendations of the Cochrane Collaboration [17] in our present meta-analysis. Computer-retrieved databases such as PubMed, Cochrane Library, Embase, Web of Science, and Ovid were searched. The search time limit was March 2019. We restricted the search article language type to English. The English search keywords used were 'tranexamic', 'knee', 'hip', 'joint', 'replacement', 'arthroplasty', and 'revision'. We combined free words and keywords to develop retrieval strategies. We also used a manual search to filter the list of references for all the relevant studies to complement our search. If several publications reported the same group of patients, we selected the latest study. The study titles and abstracts identified in the search were independently reviewed by the two authors to exclude studies that were clearly unrelated. Disagreements were resolved by consulting the third reviewer to reach a final consensus.

Inclusion and exclusion criteria

The included studies met the following conditions: 1) randomised controlled trials (RCTs) or non-randomised controlled trials (non-RCTs) reporting comparisons between groups with and without TXA during rTJA intervention, and 2) articles that reported at least one of the outcome indicators, namely blood loss, change in haemoglobin levels, blood transfusion rates, number of red blood cell units per patient infusion, thromboembolic complications (deep vein thrombosis or pulmonary embolism), other non-thromboembolic complications, and length of hospital stay (LOHS). Articles that did not evaluate the above-mentioned parameters were excluded. Case reports, letters, and summary of meetings were also excluded. Any disputes were cross-checked and resolved by the senior authors.

Data extraction

A literature data extraction form was developed, and the two researchers independently read the relevant literature and extracted the following information: 1) research characteristics, including the name of the first author, the year of publication, the nationality of the author, the category of the article, and the specific location of the joint; 2) patient demographic details such as study sample size, participant sex, mean age, mean body mass index, mean American Society of Anesthesiologists (ASA) score, and mean preoperative haemoglobin levels; and 3) specific interventions such as TXA administration, venous thromboembolism (VTE) prevention method, and transfusion protocols.

Statistical analysis

Data were processed using the Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) and Stata 11.0 software (Stata Corp, College Station, Texas, USA). The odds ratio (OR) or mean difference (MD) with the 95% confidence intervals (CIs) of the dichotomous or continuous outcome were assessed separately. I^2 was used to judge the heterogeneity between studies. When I^2 was ≤50%, no statistical heterogeneity was considered, and a fixed effect model was used. Otherwise, when I^2 was >50%, statistical heterogeneity was considered present. At this time, a random-effects model was used, and a sensitivity analysis was performed if necessary. A P value of <0.05 was considered significant. Begg's funnel plot and Egger's linear regression test were used to detect publication bias in the included studies.

Sensitivity analysis and publication bias

A sensitivity analysis was performed to find the source of heterogeneity when I^2 was >50% to evaluate whether any single study had the weight to skew on the overall estimate and data. Subgroup analyses were planned according to the type of arthroplasty (THA vs TKA). We quantified publication bias using the Egger method. A P value of >0.05 obtained with the Egger method indicated no significant publication bias. If publication bias existed, we tested its influence on the results using the rim-and-fill method.

Quality assessment

The Jadad scale was used on the basis of the randomisation, blinding, numbers of withdrawals and dropouts, inclusion and exclusion criteria, adverse reactions, and statistical analysis scores ranging from 0 to 5, with studies with scores > 3 points considered as "high-quality" [18]. Two authors evaluated the included non-RCTs according to the Newcastle-Ottawa Scale (NOS) using the following items: the selection of study groups, the comparability of groups, and the ascertainment of either exposure or outcome of interest for case-control and cohort studies. The total score was 9 points, and studies with scores > 7 points were considered high-quality studies [19]. They eventually reached a consensus on each study; otherwise, they consulted the third author to resolve the dispute.

Results

Study selection

On the basis of the above-mentioned search strategy, 190 possible related references were initially identified from the following electronic databases: 54 from EMBASE, 73 from Web of Science, 40 from PubMed, 8 from Ovid, and 15 from the Cochrane Library. After excluding 94 replicates, 72 unrelated articles were excluded on the basis of the title and abstract comments. When the full text of the remaining 24 studies were examined, 12 articles without useful data were excluded. Finally, 12 trials that involved 2159 patients between 2009 and 2018 met the selection criteria and were included in the present meta-analysis (Figure 1).

Study characteristics

The baseline characteristics of the studies are shown in Table 1. No significant differences in preoperative haemoglobin levels were found in 9 studies. Nine studies reported no significant difference in ASA score between the two groups. Eight studies included the use of chemoprevention for thromboembolic complications, such as warfarin, low-molecular-weight heparin, or rivaroxaban. The route of TXA administration was different, and most regimens were administered intravenously (IV). The blood transfusion protocol was repeated in 9 studies, of which only one RCT had a wider blood transfusion indication[1] than the other 8 observational studies (haemoglobin level, <10 g/dL; haematocrit level, <30%). In summary, the pre-recorded demographic data and blood variables showed no statistically significant differences between the TXA and control groups.

Quality assessment

Table 2 summarises the methodological quality assessments of the 12 selected studies. Only one study was a RCT with a Jadad score of 5, which showed high quality. In the other 12 non-RCTs (2 prospective cohorts and 9 retrospective cohorts), the NOS scores ranged from 6 to 8, indicating that the quality of these studies was also acceptable.

Primary outcomes

1. Allogenic blood transfusion rate

Eleven trials [13-15, 20-27] were used in the meta-analysis of the transfusion requirements (Figure 2.1). Significant heterogeneity was observed, and a random-effects model was used (I^2 = 73%, P < 0.0001). The transfusion rate was lower in the TXA group than in the control group (OR = 0.24; 95% CI, 0.14–0.41; P < 0.00001). Both the revision THA subgroup with five studies and the TKA subgroup with 7 studies had a significantly lower allogenic blood transfusion rate than the control group (OR = 0.24; 95% CI, 0.10–0.61; P = 0.003; OR = 0.24; 95% CI, 0.11–0.50; P = 0.0001).

2. Reduction in haemoglobin level

Of the 12 studies [13-15, 20-28], 5 trials with 1022 patients [14, 21, 22, 24, 26] compared preoperative and postoperative Hb levels in patients undergoing revision TJA with or without TXA (Figure 2. 2). High heterogeneity was observed, and a random-effects model was used (I^2 = 76%, P = 0.002). The pooled MD in the Hb levels in the experimental group was less decreased than that in the control group (MD = −0.84; 95% CI, −1.28 to −0.41, P = 0.002). Compared with TKA (MD = −0.63; 95% CI, −0.97 to −0.30, P = 0.0002), TXA was more effective in the THA group regarding the reduction in haemoglobin level (MD = −1.28; 95% CI, −2.00 to −0.57; P = 0.0004).

3. Number of RBC units transfused per patient

Nine studies that involved 1,467 subjects [14, 15, 20-26] provided data for this result (Figure 2.3). As no significant heterogeneity was observed, a fixed-effect model was used (I^2 = 24%, P = 0.22). The number of RBC infusions per patient in the TXA group was significantly lower than that in the control group (MD = −0.49; 95% CI, −0.61 to −0.38; P < 0.00001). The number of RBC units infused per patient in the revision THA subgroup was significantly lower as compared with that in the control group (MD = −0.81; 95% CI, −1.20 to −0.43; P < 0.0001). Similarly, the number of RBC units infused per patient in the revision TKA subgroup was also lower (MD = −0.46; 95% CI, −0.58 to −0.35; P < 0.00001).

4. Blood loss

Data from 8 studies [13-15, 20-22, 24, 25] that involved 1,116 patients were used to examine blood loss (Figure 2.4). Owing to the high statistical heterogeneity, a random-effects model was used (I^2 = 91%, P < 0.00001). The use of TXA in revision TJA resulted in significantly less blood loss than that in the control group (MD = −260.87; 95% CI, −394.88 to −126.86; P = 0.0001). Compared with the control group, the blood loss in the TKA subgroup was significantly reduced (MD = −428.61; 95% CI, −754.37 to −102.84; P = 0.010). However, such statistical significance was not observed in the THA subgroup (MD = −225.59; 95% CI, −475.99 to 24.82; P = 0.08).

Secondary outcomes

5. Venous thromboembolic complications

Seven studies [15, 21, 23, 25-28] reported the postoperative incidence rates of deep vein thrombosis and PE (Figure 2.5). No significant heterogeneity was observed, and a fixed-effects model was used (I^2 = 0%, P = 0.78). No statistically significant differences were found between the patients in the TKA subgroup (OR = 0.99; 95% CI, 0.31–3.14; P = 0.98). However, the patients with modified THA using TXA had higher venous thromboembolic complication rates, although no statistically significant difference was observed (OR = 1.56; 95% CI, 0.43–5.59; P = 0.50).

6. Non-thromboembolic complications

Four studies [21, 24, 25, 27] that included 802 subjects described other non-thromboembolic complications (Figure 2.6). Overall, 9 patients developed postoperative infections, 6 had recurrent dislocation, and 4 had periprosthetic fractures. Owing to the high statistical heterogeneity found, a random-effects model was used (I^2 = 78%, P = 0.001). In rTJA, the incidence of other complications was reduced in the TXA group as compared with the control group, but the difference did not reach statistical significance (OR = 0.54; 95% CI, 0.18 –1.68; P = 0.29). The OR in the THA and TKA groups were 0.44 (95% CI, 0.03–5.44; P = 0.52) and 0.71 (95% CI, 0.32–1.54; P = 0.38), respectively.

7. Leng<href="#/javascript:;">th<href="#/javascript:;">of hospital <href="#/javascript:;">stay

Two studies [14, 26] that reported LOHS were included in the meta-analysis (Figure 2.7). High statistical heterogeneity was found, and a random-effects model was used (I^2 = 75%, P = 0.05). A trend toward a reduction in hospital stay was observed in the TXA group as compared with the control group in the TKA subgroup (MD = −2.89; 95% CI, −4.85 to −0.93; P = 0.004).

Sensitivity analysis

We found a significant heterogeneity in several outcome indicators. To find the source of heterogeneity, we performed a sensitivity analysis to examine whether the presence of a single study had a decisive effect on the results by removing each study in turn (Figure 3). In the sensitivity analysis for the transfusion rate group, we found that when the studies by Reichel et al. [25] and Huerfano et al. [21] were removed, the results changed significantly, indicating that they were the main sources of heterogeneity. In addition, the studies by Mariani et al. [23] and Ortega et al. [14] may be potential sources of heterogeneity. In the sensitivity analysis for the altered haemoglobin group, we found that when the studies by Smi et al. [26] and Park et al. [24] were removed, the results changed significantly, indicating that they were the main sources of heterogeneity. In the sensitivity analysis for the blood loss group, we found that when the study by Peck et al. [28] was removed, the results changed significantly, indicating the study by Peck et al. [28] was the main source of heterogeneity. Heterogeneity was also observed in terms of complications and LOHS. However, owing to the inadequate number of articles included, the definition of complications and LOHS in different regions were different; thus, heterogeneity could not be avoided. We expect more randomised controlled studies with precise conclusions in the future.

Publication bias

We quantitatively analysed publication bias using the Egger method (Figure 4). Except for the outcome group of blood transfusion rate, the other P values were all >0.05, indicating no significant publication bias. In the transfusion rate outcome group, the P values were <0.01, indicating a significant publication bias. However, after removing the missing studies and adding them in the analysis, and then recalculating the effect size, the OR did not change significantly, indicating that our results were relatively robust.

Discussion

Compared with pTJA, rTJA is a time-consuming procedure with higher blood loss and increased postoperative transfusion rates. These are important factors of increased morbidity, resource utilisation, and healthcare costs [29], which remains major challenges for orthopaedic surgeons [6]. Although allogeneic blood

transfusions are now safer because of improved detection methods, allergic reactions, cross-matching or transfusion errors, and potential risk factors of infections around the prosthesis, and even death still occur [30-32]. Some scholars believe that autologous blood transfusion can reduce the risk of allogeneic blood transfusion but still cannot control non-immune adverse events [10]. Effective blood management strategies are needed to control perioperative bleeding.

TXA is a commonly used antifibrinolytic agent and has become increasingly popular in recent years. Administration of TXA is one of the most cost-effective strategies for oral, IV, or topical administration [33]. Numerous studies have shown that the use of this drug can be effective in pTJA. Li et al. [34] conducted a meta-analysis that involved 5 RCTs that demonstrated the efficacy of oral TXA in reducing blood loss in primary THA and TKA. Gianakos et al. [35] found that the use of IA TXA alone or in combination with IV TXA reduced the amount of total blood loss and excretion in patients with TJA. Fillingham et al. [36] reported that topical, IV, and oral TXA were not associated with an increased risk of VTE after TJA, with an ASA score of ≥3, and confirmed that the benefits of using TXA appeared to exceed the potential risk of VET events, even in patients with higher comorbidities.

Although significant effects on perioperative blood protection in primary TJA, without increased risk of VTE events, had been reported, relatively few studies have examined the role of TXA in rTJA. However, in addition, the American Society of Plastic Surgeons also reported that studies on the safety and efficacy of TXA in revision surgery are lacking; thus, it is impossible to make a definitive conclusion [37]. As no strong evidence exists that proves the safety of TXA in rTJA, we conducted this meta-analysis.

The primary finding of this meta-analysis was that the use of TXA may reduce transfusion rates, haemoglobin levels, and the number of RBC infusion units, confirming the role of TXA in rTJA. As for the amount of blood loss, the results between the subgroups were different. The amount of bleeding was significantly reduced as compared with that in the control group in the modified TKA subgroup (MD = −428.61; 95% CI, −754.37 to −102.84; P = 0.010), whereas that in the THA subgroup was not statistically different (MD = −225.59; 95% CI, −475.99 to 24.82; P = 0.08). Previous studies produced different results for the estimated differences in blood loss during different revisions in the hip subgroup. Garvin et al. [38] found the highest rate of blood loss in implantation of femoral prostheses, followed by repair of femoral and acetabular prostheses and correction of acetabular prostheses. Peck et al. [39] emphasised that the primary revision group produced the largest total blood loss, followed by the isolated femoral repair group, isolated acetabular repair group, and head and liner exchange group. Zarin et al. [40] reported that the highest blood loss occurred after repair of the two components but found no significant difference between the isolated femur and acetabular prosthesis repairs.

Various blood loss measurement methods from pooled studies may lead to this result, and the most consistent method is to determine the estimated amount of blood loss (EBL). Intraoperative blood loss (IBL) and induced blood loss (DBL) were not completely reliable for assessing perioperative blood loss in TJA, as the amount of recessive blood loss accounts for almost 50% of total blood loss (TBL). The heterogeneity of indications within each revision group may affect blood loss. Most previous authors ruled out reimplantation or repair of septic loosening. Kazi et al. [22] included Phase II revision procedures in their research plans, while Waddell et al. [27] used topical TXA for patients with post-TKA infections in the first- and second-phase revisions. Only Reichel et al. [25] included sterility revisions and reimplantation in a two-stage exchange procedure for rTHA and rTKA. Lin et al [41] showed no correlation between TXA and any major complications of pTJA. Wu et al. [42] reported that combined intravenous and topical TXA in revision THA did not increase the risk of deep vein thrombosis and pulmonary embolism as compared with intravenous injection alone. Therefore, the drug treatment pathway may not have a significant correlation with the complications during TJA repair.

In our analysis of secondary outcomes, the application of TXA in rTJA also did not increase the VTE complication rates as compared with the control (OR = 1.21; 95% CI, 0.51–2.86; P = 0.66), which indicated the safety of TXA in rTJA. However, the VTE complication rate was higher in the revision THA subgroup using TXA than in the control group, although the difference did not reach statistical significance (OR = 1.56; 95% CI, 0.43–5.59; P = 0.50). In short, strict control of the indications is important, and concerns still exist regarding the safety of TXA administration, especially regarding the risk of VTE events in high-risk patients undergoing revision THA. Huerfano et al. [21] found that the use of topical TXA in revision TKA appears to be attractive for patients at greater risk of thromboembolic and cardiovascular complications. Serrano et al. [43] described that topical administration was preferred by the senior author owing to the lack of contraindications. As for non-thromboembolic events, the TXA group had reduced incidence rates as compared with the control group, although a statistically significant difference was not reached for both revision TKA and THA (OR = 0.54; 95% CI, 0.18–1.68; P = 0.29). Moreover, TXA could decrease the LOHS and reduce the economic burden of patients indicated for revision TKA in a way (MD = −2.89; 95% CI, −4.85 to −0.93; P = 0.05).

Limitations And Strengths

The main advantages of our research include the following: (1) We searched for all available clinical trials that directly compared the safety and efficacy of TXA in rTJA (TKA and THA). (2) All the studies included in our meta-analysis were of high quality. (3) On the basis of the large sample size, we extracted and analysed the maximum number of clinical outcome variables. (4) Our study was the first meta-analysis to systematically confirm the safety of TXA in rTJA. The current meta-analysis also included a number of limitations as follows: (1) A RCT, 2 prospective studies, and 9 retrospective studies were included in the meta-analysis, so the qualities of the studies were uneven owing to the uncontrolled bias that led to some inherent heterogeneity. The heterogeneity of the included studies can explain the minor differences in the factors that affected blood loss and postoperative complication parameters such as the type of anaesthesia and surgical technique used. (2) TXA was administered in different ways, with different doses and amounts, so we did not recommend giving specific doses in rTJA. (3) As the recognised language was limited to English, publication bias was inevitable.

Conclusions

Administration of TXA in patients undergoing revision TJA resulted in a significant reduction in transfusion rates, haemoglobin level, and number of RBC units infused per patient, without increasing complications.

Abbreviations

tranexamic acid: TXA; primary total joint arthroplasty: pTJA; revision total joint arthroplasty: rTJA; haemoglobin: Hb; allogeneic blood transfusion: ABT; red blood cell: RBC; total knee arthroplasty: TKA; total hip arthroplasty: THA; randomised controlled trials: RCTs; non-randomised controlled trials: non-RCTs; length of hospital stay: LOHS; American Society of Anesthesiologists: ASA; venous thromboembolism: VTE; odds ratio: OR; mean difference: MD; confidence intervals: CIs; intravenously: IV; estimated amount of blood loss: EBL; intraoperative blood loss: IBL; induced blood loss: DBL; total blood loss: TBL.

Declarations

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Not applicable.

Authors' contributions

Conceived and designed the analysis: WQ,WSH and LLS. Performed the analysis: XJN, WSH and ZLJ. Revised the paper: HLX and LLS. Wrote the paper: WQ, LLS. All authors read and approved the final manuscript.

Ethics approval and consent to participate

No ethics approval or patients consent was required because all analyses were based on previous published studies.

Consent for publication

Not applicable.

Competing interests

The authors report no conflicts of interest in this study.

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Tables

Table1-characteristics of the included studies

Study/year	Country	Design	Location	Size With/without	Age	Male	BMI	ASA score	Pro-HB	Intervention	VTE prophylaxis	Blood transfu protocol
Gill2009	USA	RCT	Hip	5/5	66.6/61.4	1/2	NM	NM	123/138	IV	Warfarin	HB<10+Hct<
Kazi2012	UK	PC	Hip	30/30	72/73	20/19?	28/27	2.8/2.6	122/117	IV	LMWH	HB<7/HB<8
Aguilera2012	Spain	RC	Knee	19/28	75/74	2/9	29/31	NM	132/134	IV	LMWH	HB<8/HB<8.5
Smit2013	Canada	RC	Knee	246/178	68.9/69.8	121/87	34.4/34.8	NM	132/130	IV	LMWH	HB<7/HB=8-9
Samujh2014	USA	RC	Knee	43/68	65.4/64.7	14/29	NM	NM	132/135	IV	Rivaroxaban	HB<8+D9
Ortega2016	Spain	RC	Knee	44/43	68.8/74.2	12/11	31/30	2.3/2.5	141/138	IV	NM	HB<8/HB<10
Park2016	USA	RC	Hip	114/56	63/69	48/22	29/28	2.3/2.9	129/130	IV	NM	HB<7/HB<8
Waddell2016	USA	RC	Knee	20/29	67.8/61.6	6/13	34/33	NM	NM	Topical	Warfarin	HB<7/HB<8
Huerfano2018	USA	RC	Knee	76/205	62/66	39/93	30/31	2.2/2.4	127/127	Topical	Aspirin/Rivaroxaban/ Apixaban/LMWH	NM
Mariani2018	Argentina	RC	Hip	61/64	67.5/69.7	34/23	28.2/29	NM	131/129	IV	NM	HB<7/HB<10
Peck2018	Canada	RC	Hip	109/91	68/67	31/38	28.2/27.3	2.7/2.7	NM	IV	NM	NM
			Hip	60/28	70.5/74	32/17	30.4/26.9	2.6/2.5				
			Hip	148/78	65/70	44/22	28.3/27	2.5/2.6				
			Hip	85/35	64/66	26/16	28.2/29.7	2.6/2.4				
Reichel2018	Germany	PC	Hip	96/103	66.1/68.6	39/47	NM	2.5/2.5	NM	IV	LMWH	NM
			Knee	51/52	65.5/66.1	25/24	NM	2.5/2.4		IV	LMWH	

Abbreviations:

TXA,tranexamicacid;

RCT,randomized controlled trial;

PC, prospective cohort study;

RC,Retrospective cohort study;

BMI,body mass index ;

ASA,American Societyof Anesthesiologists ;

Hb, hemoglobin;

VTE,venous thromboembolism;

LMWH,low-molecular-weight heparin;

IV,intravenous;

NM,not mentioned.

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Table2-The quality of the included studies was assessed using the New Castle-Ottawa Scale(NOS) or Jadad scale.

NOS	Selection				Comparability		Exposure/Outcome			Total score
	1	2	3	4	5A	5B	6	7	8	
Kazi2012	▯	▯	▯		▯		▯	▯		6
Aguilera2012	▯	▯	▯		▯		▯	▯		6
Smit2013	▯	▯	▯	▯	▯		▯	▯	▯	8
Samujh2014	▯	▯	▯	▯	▯		▯	▯		7
Ortega2016	▯	▯	▯		▯		▯	▯		6
Park2016	▯	▯	▯	▯	▯		▯	▯		7
waddell2016	▯	▯	▯		▯		▯	▯	▯	7
Huerfano2018	▯	▯	▯	▯	▯		▯	▯		7
Mariani2018	▯	▯	▯	▯	▯		▯	▯		7
Peck2018	▯	▯	▯	▯	▯		▯	▯	▯	8
Reichel2018	▯	▯	▯	▯	▯		▯	▯		7
Jadad scale	Randomization				Blinding			Cohort		Score
Gill2009	2				2			1		5

Figures

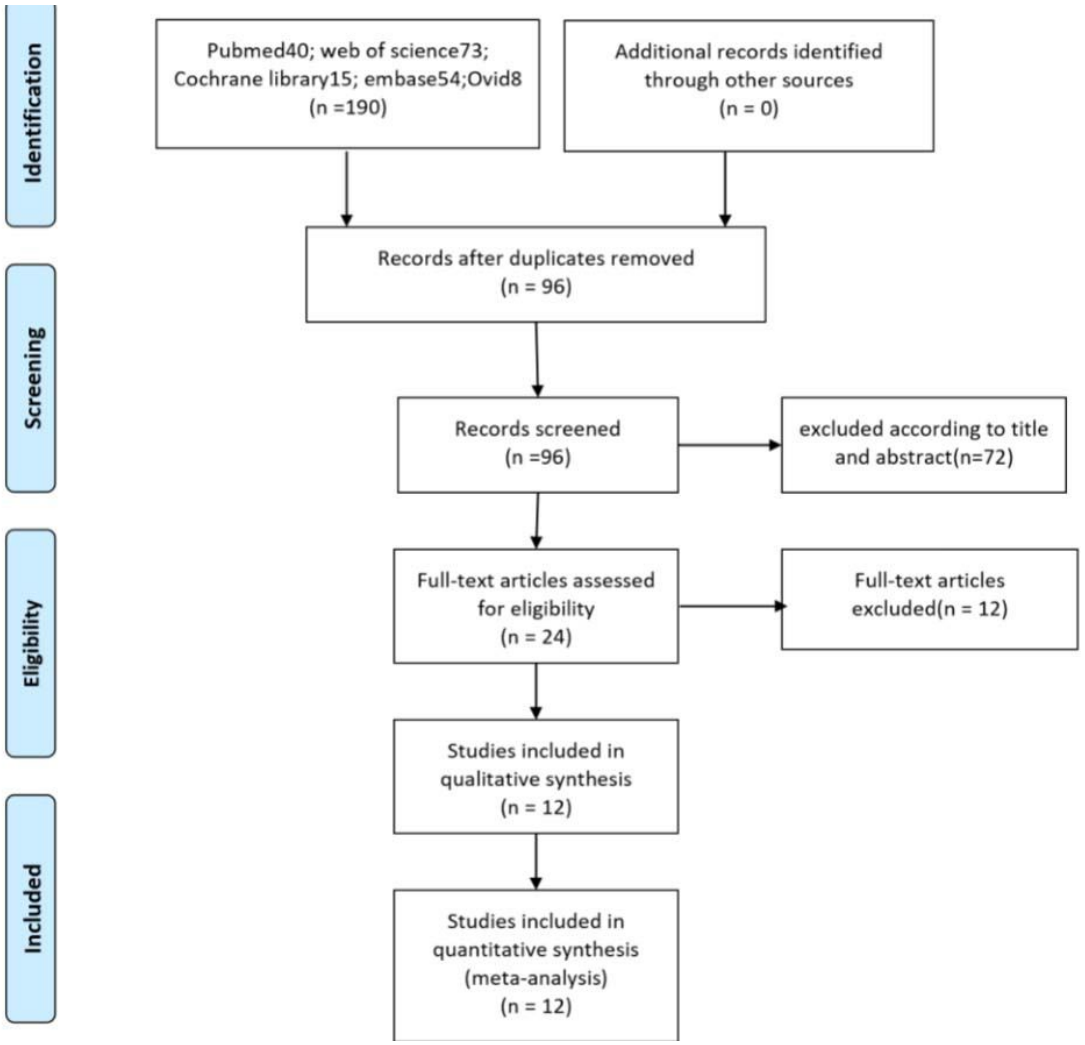

Figure 1

PRISMA flow diagram describing the selection process for relevant clinical trials used in this meta-analysis.

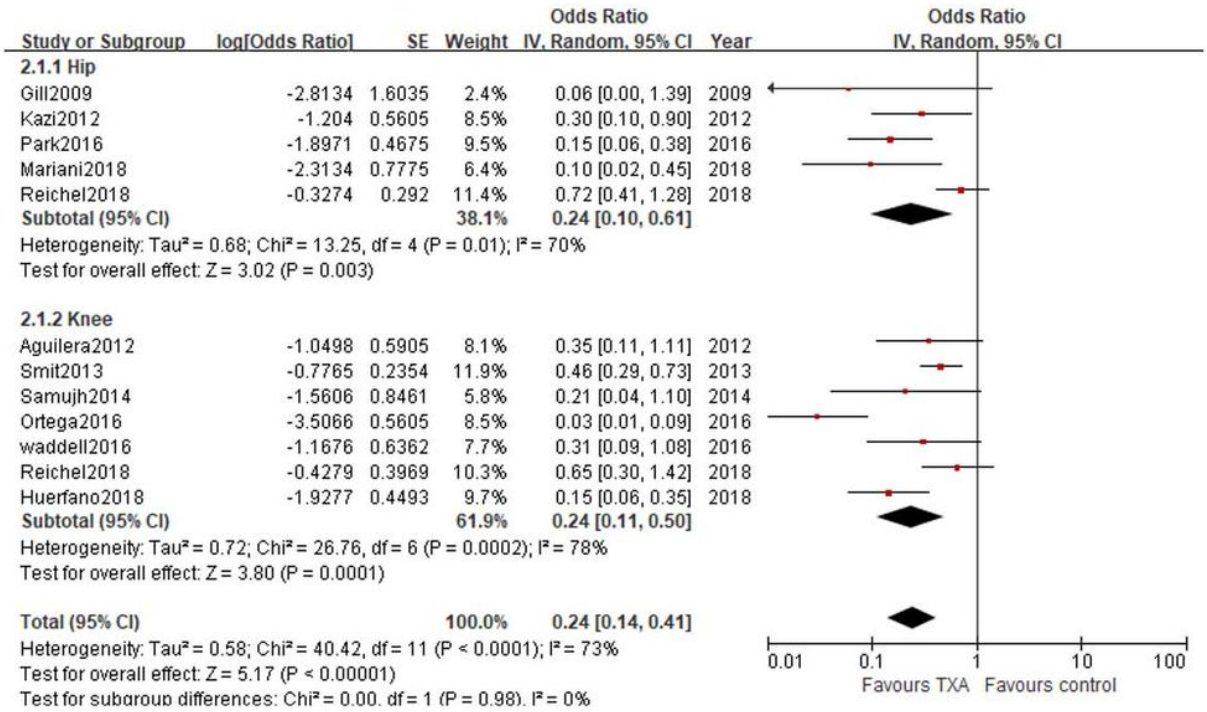

Figure 2

Figure2.1-Forest plot of allogenic blood transfusion rate

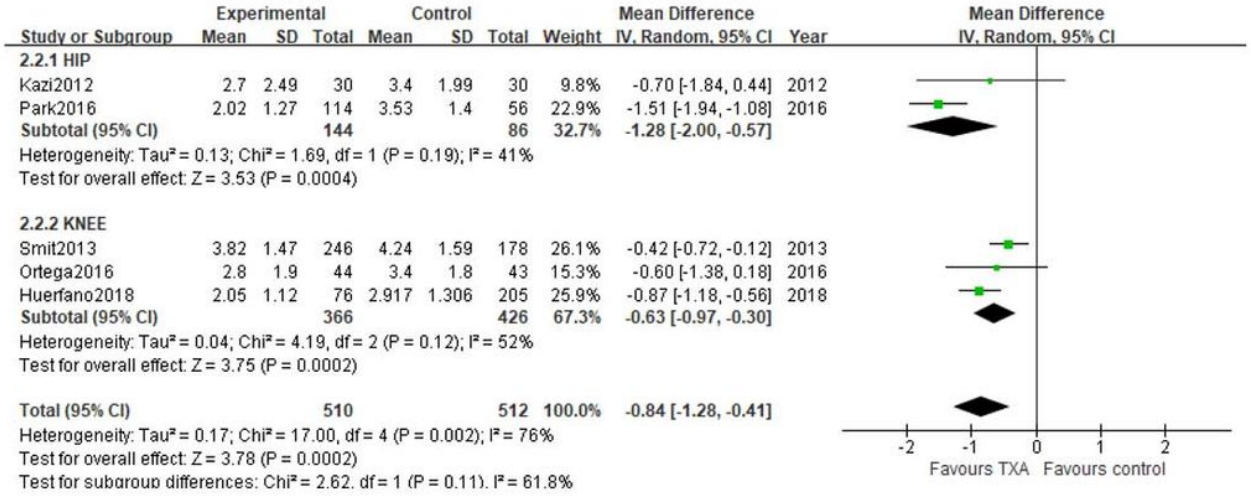

Figure 3

Figure2.2-Forest plot of hemoglobin reduction

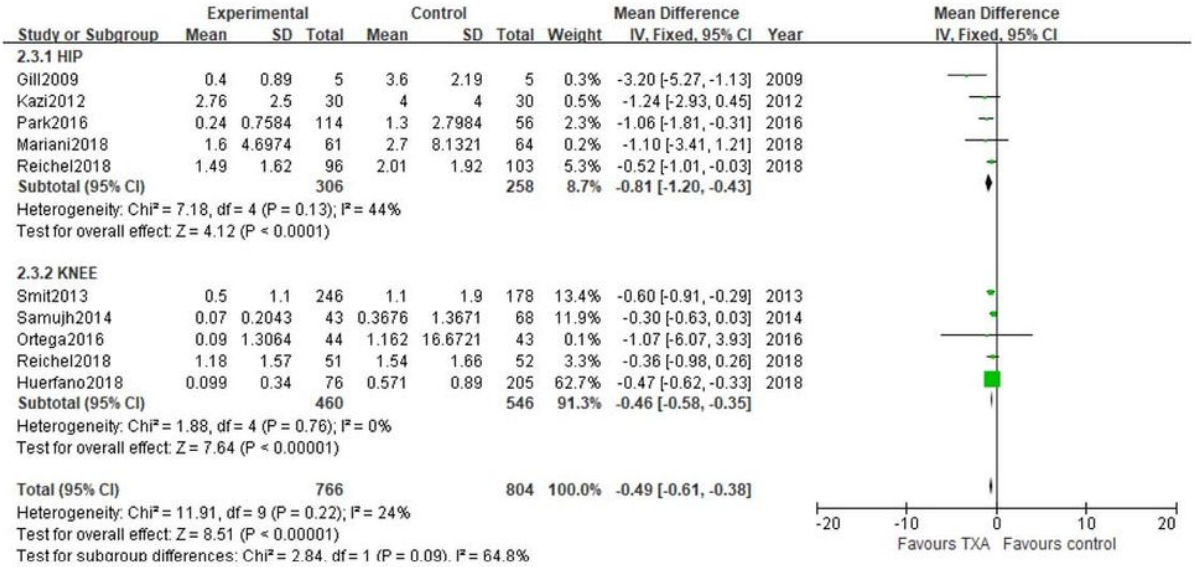

Figure 4

Figure2.3-Forest plot of number of RBC units transfused

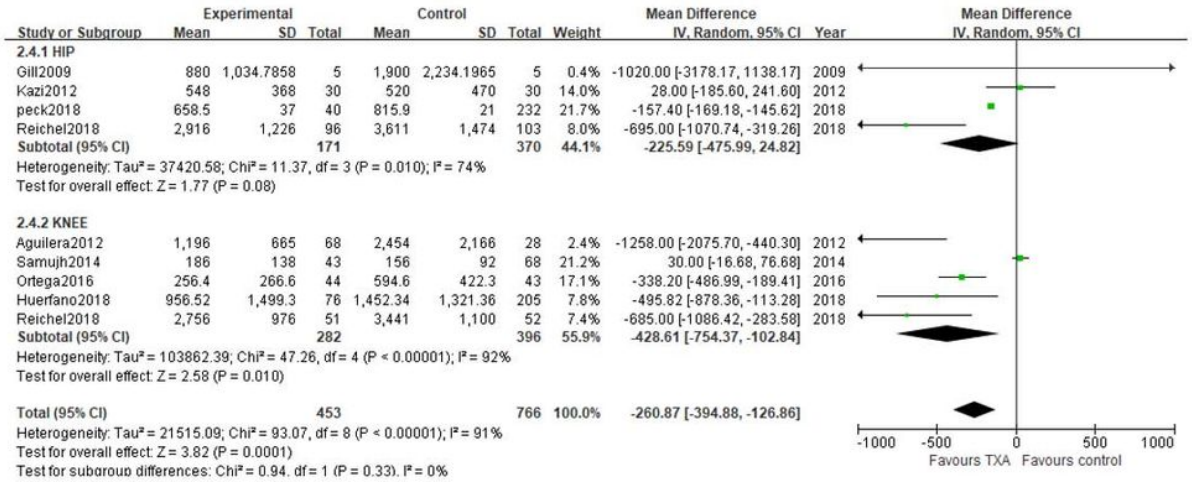

Figure 5

Figure2.4-Forest plot of blood loss

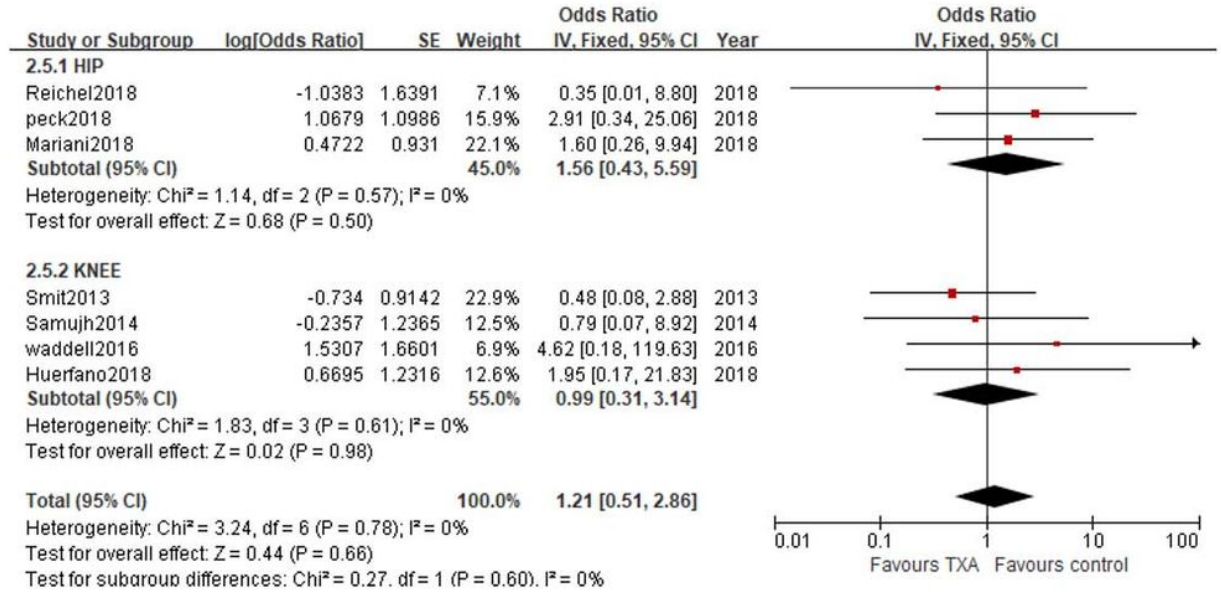

Figure 6

Figure2.5-Forest plot of VETcomplications

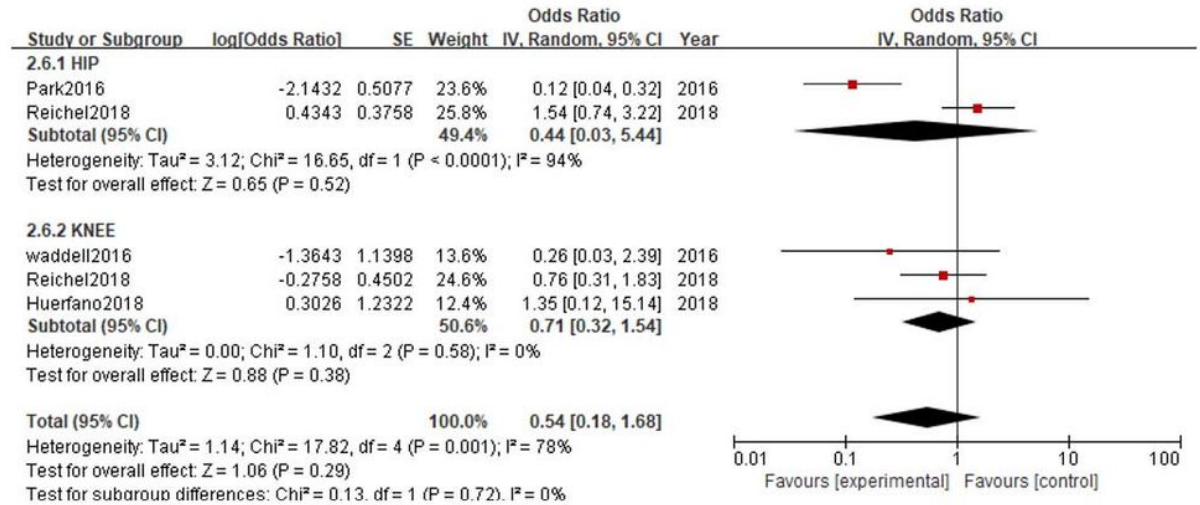

Figure 7

Figure2.6-Forest plot of nonthromboembolic complications

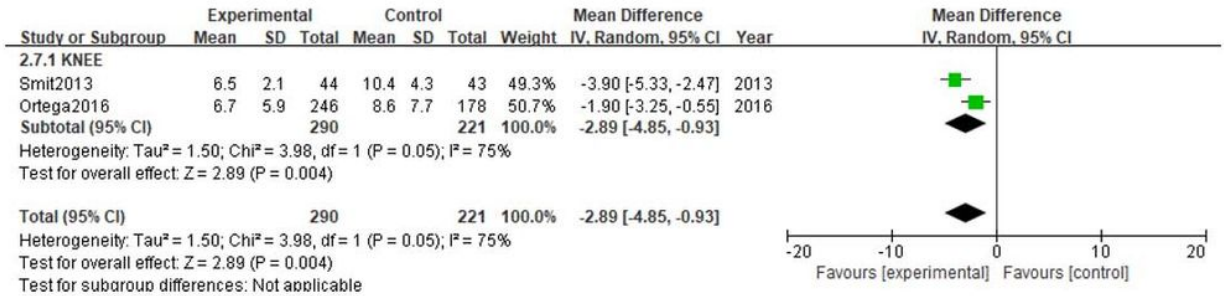

Figure 8

Figure2.7-Forest plot of length of hospital stay

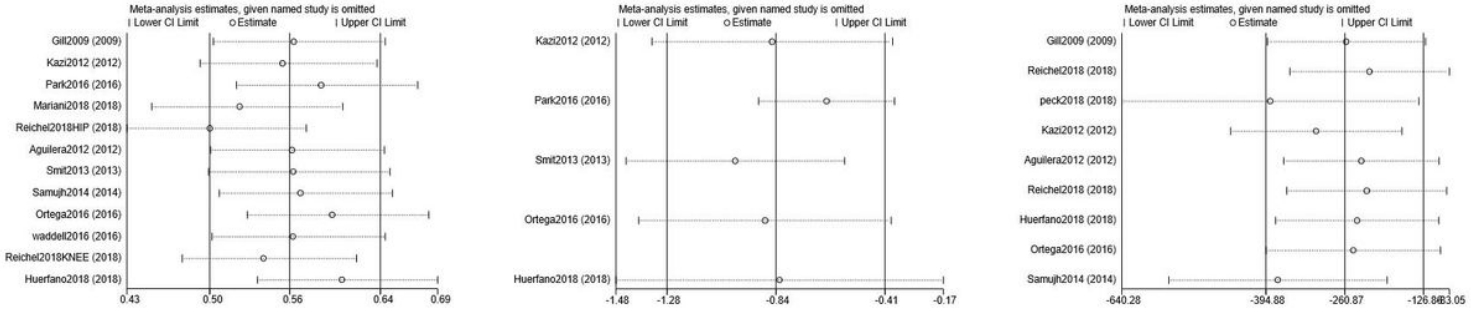

Figure 9

Figure3-Sensitivity analysis

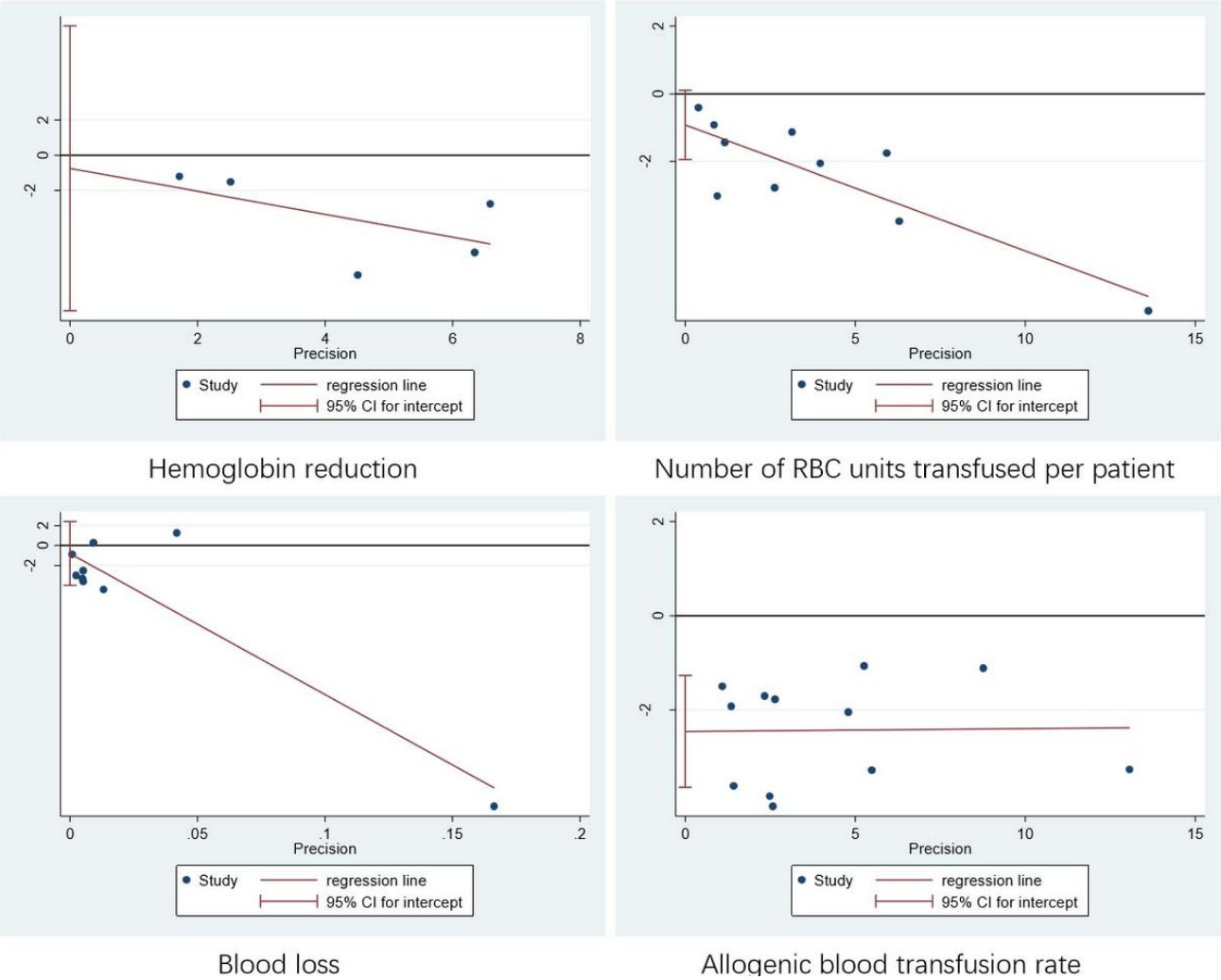

Figure 10

Figure4-Publication bias