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Perioperative use of tranexamic acid in elderly patients undergoing hemiarthroplasty for neck of femur fractures: Is it worth using in every patient? An updated systematic review and Meta-analysis

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Abstract

Hemiarthroplasty becomes the procedure of choice for hip fracture in elderly population with blood loss as its complication. Tranexamic acid (TXA) has been used with no systematic review conducted to evaluate its efficacy and safety. The PRISMA guidelines were followed to conduct literature screening and selection. Main outcomes were extracted for qualitative analysis and quantitative analysis. Blood loss level and haemoglobin drop was significantly reduced in TXA group as compared to the control group. TXA is also deemed as protective factor for transfusion requirement. TXA use may be considered in every patient undergoing hemiarthroplasty procedure unless absolute contraindication exists.

Keywords: Tranexamic acid, Fracture neck of femur, Hemiarthroplasty, Hip fracture, Perioperative tranexamic acid.

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INTRODUCTION

The burden of hip fractures, estimated to reach global incidence of 6.3 million in 2050, remain a pressing health concern for all age groups (elderly due to low-energy trauma, and younger populations due to high-energy trauma) [1]. Hip fractures, especially displaced ones, may lead to the disruption of the vascularity of femoral neck, which results into osteonecrosis, non-union and delayed union [1,2]. Fractures of femoral neck in elderly patients with multiple comorbidities (including dementia), and low baseline preinjury mobility are often treated with hemiarthroplasty as compared to open reduction and internal fixation. The unpredictability of salvaging femoral head post neck of femur fracture, and necessity to mobilise at earliest makes hemiarthroplasty the procedure of choice in elderly patients with significant comorbidities, however, the procedure has multiple potential complications including blood loss [1,3].

The disruptive nature of trauma in hip fractures, and post injury adverse events lead to further deterioration with a high one-year mortality rate [3]. Hidden fracture haemorrhages with superimposed intra-operative procedural blood loss can amount to a total of up to 1500 ml [3-5]. The higher collective peri-operative blood loss leads to increased risk of perioperative hypotension, shock, and mortality. Increased perioperative blood loss results in higher blood transfusion rates (20-60% of patients), and ultimately leads to higher transfusion related reactions, and infections, longer lengths of stay, and financial burden [3-5]. Intraoperative antifibrinolytics have been used in general practice worldwide to control bleeding, and hence the need for transfusion. Tranexamic acid (TXA) is a synthetic derivative of lysine, which competitively inhibit plasmin activation and prevent degradation of fibrin. Previous studies have demonstrated the efficacy and safety of intraoperative TXA including reduced blood loss, rates of transfusion, and mortality; Conflicting results have been presented about the increased risk of TXA in various studies [3-6].

Despite the increasing evidence of TXA's safety and efficacy in hemiarthroplasty procedures, its use has not been evidently proven to fit all population, especially for patients with metabolic, cardiovascular, and pulmonary comorbidities [3]. Hemiarthroplasty is indicated in intracapsular neck of femur fractures in elderly patients with multiple comorbidities wherein one quick, and less complex operation can help mobilise the patient next post-operative day. Prevention of intraoperative blood loos in these patients up to any extent is a welcome approach. Therefore, further evidence-based study is needed to evaluate the efficacy and safety of perioperative administration of TXA for every patient profile. To mitigate this problem, we conducted a systematic review and meta-analysis assessing the efficacy and safety of TXA administration in hip hemiarthroplasty for the elderly patients with neck of femur fractures.

MATERIALS AND METHOD

The systematic review and meta-analysis were conducted by adhering to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement to ensure proper search and selection of relevant studies [7].

Eligibility Criteria

Pre-determined inclusion and exclusion criteria were set to filter primary studies investigating the use of tranexamic acid on hip hemiarthroplasty. The eligibility criteria also included PICO (Patients, Interventions, Control, and Outcomes) as summarized in Table 1. Elderly patients with femoral neck fractures undergoing hip hemiarthroplasty and receiving tranexamic acid during peri-operative period were included in the study. Randomized controlled trial, observational studies (prospective & retrospective cohort; case control; cross-sectional) were included in this review. Meanwhile, studies were excluded if any of the following exclusion criteria were met: (1) Review articles (including systematic review), case series, and letters to editor; (2) abstract only articles; (3) articles without efficacy, and safety results; (4) articles with more than one intervention; (5) Inadequate data in articles; and (6) non-English articles.

Search Strategy

Literature search was performed by two independent investigators (LW; BCE) in a blinded fashion. Discrepancies were resolved through discussion and thorough review by chief investigator (VS). The search was conducted through four scientific databases – MEDLINE (PubMed), Scopus, Google Scholar, and Cochrane Library – to discover published studies or articles up to January 12th, 2021. The search strategy was developed using pre-determined keywords and medical subject headings (MeSH) related to: (1) Tranexamic acid; (2) Hemiarthroplasty; (3) Femoral neck fracture – with different combinations. The retrieved results of each database were then subsequently deduplicated and screened against the pre-determined eligibility criteria.

Selection Process

Retrieved literature search result in the proposed database were then stored in web-based systematic review software, DistillerSR (Evidence Partners, Ottawa, Canada). The screening process was done by two independent reviewers (LW, BCE) and was validated through discussion with chief investigator (VS). Initial screening of studies was performed based on PICO criteria.

Data Extraction

Data extracted from each final study by two investigators (LW, BCE) were recorded on pre-set form created on DistillerSR (Evidence Partners, Ottawa, Canada). The following variables were recorded: Name of authors, year of publication, geological location of the study, study design, sample or population size (case/control), preoperative parameters (haemoglobin and haematocrits levels), and tranexamic acid delivery details (dosage, frequency, route of administration, time). The following outcomes columns were created -operation time, drop in haemoglobin level, total blood loss, transfusion requirements, ICU admission, in-hospital mortality, 30-day mortality, 1-year mortality, 30-day readmission, 1-year readmission, and complications found in each study. Finally the data were imported in tables to summarize all relevant findings of each included studies by another independent investigator (A).

Risk of Bias Assessment

Every study underwent quality assessment to appraise each article on methodological qualities, ensure low risk of bias and inferential errors of the extracted data. Two investigators (LW, BCE) independently assessed the quality of all included studies using Cochrane Risk of Bias Assessment Tool over DistillerSR software [8]. Each article was assessed on several categories of bias, including: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; blinding for harms; incomplete outcome data; selective outcome reporting; The summary of quality assessment and graph were then generated.

Quantitative Analysis (Data Synthesis)

The eligible studies were selected based on the similar data component noted on the data extraction. Randomized controlled trial are included in the quantitative analysis to avoid bias in the cumulative outcomes. Blood loss level and reduction in haemoglobin level were then used in the further analysis. Quantitative analysis was conducted using DistillerSR and OpenMeta-Analylist [9]. Cumulative outcomes were set at 95% confidence interval (CI). The odds ratio (OR) was utilized for dichotomous outcomes, while mean difference was used for the continuous outcomes. The analysis uses independent T-test to compare the data from both groups. The meta-analytic models were based on random effects with the use of the Higgins-I2 method as a heterogeneity variance estimator.

RESULTS

On the initial literature screening, 544 studies were identified across the databases. Sixty studies were extracted as 470 studies were excluded during title and abstract assessment. Finally, 12 studies were included as 48 studies out of 60 didn't satisfy our inclusion criteria (Figure 1). There were 5 retrospective cohort [4,5,11,12,17], one case control [15] and 6 randomized controlled trials [10,13,14,16,18,19]. Collectively, there were 3331 patients: 1189 in the TXA group and 2142 in the control group, respectively. Six studies were then included for quantitative analysis.

There was no significant age difference between the two groups (76.21 for TXA group vs. 77.32 for Control group; t=0,25; p=0.80), body mass index (23.35 for TXA group vs. 22.58 for Control group; t=1.78; p=0.17) in the comparative analysis of the available extracted data. Female sex predominance was seen in almost all studies except for Emara et al (18;12)[14], Kwak et al (36:24)[15], and Borkar et al (46;24)[18]. Base hemoglobin level of samples was extracted, and no significant difference were found (12.37 for TXA group and 12.49 for Control group; t=2.36; p=0.30). The included studies' characteristics can be found in Table 2.

Main outcome from the included studies were described in Table 3. Blood loss level from various included studies were compared and shown significant difference between TXA and control group (377.9 mL for TXA group and 481.5 mL for Control group; t=-3.48; p=0.01). The drop or reduction of Haemoglobin level were also found to be significantly minimal in the TXA group as compared to the control group (Hb drop of -15.6 in TXA group and -2.26 in control group; t=1.97; p=0.03) during the post-operative day 1 (POD1). Similar trend is also found in the post-

operative day 3 (POD3) for haemoglobin level, however the differences are not significant (-1.91 for TXA group and -2.43 for control group; t=1.08; p=0.16). The haemoglobin level comparison between TXA group and control group showed lower level of haemoglobin in the intervention group both in POD1 and POD3 (Figure 3).

Eight studies presented the need for more postoperative transfusion[4,5,10-12,15-17]. Apart from the study of Watts et al where the need for transfusion was similar in the two groups, it was found greater in the control group as compared to the TXA group. The quantitative analysis (Figure 2) also shown similar trend with the use of TXA as a protective factor for transfusion after the intervention (OR = 0.33 [0.23-0.47], I2 = 55.37%, p = 0.03).

The secondary outcomes were described in Table 4. 30-day day mortality was reported in 5 studies; two studies reported equal deaths in treatment and control groups, while three studies reported higher mortality in the control groups. Overall, 33 patients died within 30 days in the TXA group and 102 patients in the control group. Four studies reported mortality after 1 year follow-up. Study by Kwak et al,[15] found no difference between the two subgroups (5.4% vs 5.4%), whereas Liu et al[11] observed 3 deaths after a year of follow up (2 in the TXA group and 1 in the control group). Two other studies observing 1-year mortality reported higher mortality in the control group compared to the TXA group (8 vs. 19 for Lee et al5; and 100 vs. 276 for Ashkenazi et al[4]). Pooled analysis of four studies mentioned,[4-5,11,15] showed 114 deaths in the TXA group and 300 in the control group with statistically insignificant difference (t = 3.18; p = 0.36). Only two studies observed admission rates after 30 days. Both studies reported higher readmission rate in the TXA group compared to the control group (10.60% vs 6.10% in Watts et al,[10]; 11.90% vs 11.10% in Askhenazi et al[4]. Only Askhenazi, et al[4] reported 1-year readmission rate, which was higher in TXA group (3.30% vs 2.60%).

Surprisingly, length of stay reported in various studies had erratic results, four studies (Lee et al, 2015; Liu et al, 2018; Xie et al, 2019; Kwak et al, 2019)[5,11-12,15]reported. Patients of the TXA groups spent slightly less time compared to control groups (14.85 days vs 15.72 days) whereas 7 studies (Watts et al, 2017; Lee et al, 2015; Xie et al, 2019; Askhenazi et al, 2020; Emara et al, 2014; Kwak et al, 2019; Kang et al, 2016)[4-5,10,12.14-16] reported higher operative time in the TXA group (95.66 mins vs 93.55 mins). None of this was statistically significant (Table 5).

Four studies reported the risk of DVT in TXA administration, two studies administered TXA intravenously while the other two used topical TXA. Watts, et al[10] reported four cases of DVT in the control group and one case in the TXA group, Liu, et al[11] reported three cases of DVT in the control group and one case in the TXA group. Emara, et al[14] reported five cases in the group under intravenous TXA and one case in the control group, while Kwak et al[15] found three cases in IV TXA group and one case in the control group.

Risk of bias assessment (Figure 4) yielded low risk of bias in blinding, missing outcome data, and selective outcome reporting were the main bias subtypes included in the study. High risk of bias was found in six studies due to their retrospective data collection method or inclusion-based method, while three studies did not clearly state their method of randomization. One study showed high risk of bias in allocation concealment, while five did not provide sufficient information. However, these high risk of biases in random sequence generation and allocation concealment were deemed to be unattributable to the results by the reviewers, as proper blinding was conducted, and sample characteristics turned out to represent every subgroup equally.

DISCUSSION

The present study analyses the effects of perioperative use of tranexamic acid in acute neck of femur fractures in elderly undergoing for hemiarthroplasty. The following are the primary outcomes studied, intraoperative blood loss, blood transfusion requirement, and postoperative hemoglobin level reduction. Furthermore, mortality, readmission, and deep venous thrombosis (complications) were the secondary outcomes looked in the included studies.

All the included studies have shown differences in the primary outcome reported. Most studies reported the blood loss level, hemoglobin level reduction after the surgery, on the first and third post-operative day. The primary outcomes reported by all included studies has shown improvement in patients undergoing TXA administration compared to the control or placebo group. Post-operative blood loss and haemoglobin reduction values were significantly lower in the TXA group. Similar trend was observed in the postoperative blood transfusion requirement with TXA being protective factor for transfusion.

Out of 544 articles in the initial hit of article search, there were twelve articles [4-5,10-19] included in the systematic review with six articles were included for the meta-analysis. There was no significant difference of age and BMI in the included studies. Six studies used intravenous whereas five studies used topical TXA, and one study used both.

On the quantitative analysis, seven studies[4,5,10-12,14-15] reported statistically significant reduction in blood loss with use of TXA group as compared to controls (RD=0.18). Furthermore, post-operative day 1 and 3 reduction in hemoglobin was significantly lower in TXA group. Although, operative time was higher in TXA group, the length of stay was comparatively shorter in TXA as compared to placebo, and both parameters were statistically insignificant. Often elderly patients have multiple comorbidities which makes them prone to complications, and eventually succumb to trauma related deaths. Additional blood loss during hip surgery in these elderly patients with neck of femur fractures further compromise the physiological balance and leads to perioperative complications. Hence, TXA administration has led to direct, and indirect beneficial effects in peri-operative periods in such patients [20-21].

Adding further, post-operative Hb drop in TXA group was significantly lowered as compared to controls. This steady maintenance of Hb in such patients lead to indirect evidence of beneficial effect of TXA in perioperative period. This has been supported by many studies including by Wenming et al and Gupta et al, of which showed similar result in other orthopaedic surgeries [20-21]. Other indirect measure of reduced blood was post-operative reduction in transfusion rate. Several of the included studies reported the difference between the transfusion rate of TXA group and the placebo. Seven articles mentioned the transfusion rate of both groups[4,5,11,14-17], and reported significantly lower transfusion rate post-operatively. The transfusion rate of the TXA group is ranged from 5% to 36.1%, while the control or placebo group showed transfusion rate, which ranging from 35% to 66%.

The prognosis of each respective group can also be shown with the ICU admission, re-admission, and mortality rate. ICU admission is only reported by one study which showed lower admission rate as compared with the placebo. These studies reported, three sub divisions of mortality assessment, -hospital mortality, 30-days, and 1-year mortality. Out of the five studies[4-5,10-12] which mentioned 30-days mortality, two studies[11-12] reported no difference, while three claimed the superiority of TXA group[4-5,10]. If one year mortality is analysed, the reporting is quite erratic, no difference was seen in one study[15] whereas higher mortality in TXA group in one study[12] and placebo or controls in two studies[4,11]. Surpisingly, 30-days and 1-year re-admission was found higher in the TXA group in two studies[4,10].

As TXA is a synthetic derivative of lysine, which competitively inhibit plasmin activation and prevent degradation of fibrin3, there is theoretical risk of DVT. The risk of DVT was quite diverse as compared to placebo. While one study[15] found more DVT event as compared with placebo, two other studies[10,15] showed more DVT in the TXA group. This has been supported by the use TXA in other arthroplasties and non-orthopaedic studies[23-24]. It is also observed that the length of stay was shorter in the TXA group as compared to the placebo. This refers to general notion that less blood loss and faster recovery in post op period could lead to significant reduction in hospital stay and eventually, sooner discharge from the hospital.

Tranexamic acid has been advocated to be used either in intravenous or topical forms. It is postulated that topical TXA should omit the systemic effects of intravenous TXA. In this review, six studies used intravenous TXA[4,5,12,13,17,19], and five studies used topical[8,11,15,16,18] while one studies used both[14]. No comparison is made on the analysis, one study by Emara et al,[14] shown considerable difference between IV and topical use of TXA. Emara et al[14] reported that haemoglobin and haematocrit reduction was better in the IV group as compared to topical group. Similar trend was found in the platelet count. Blood loss was more prominent in the IV group; however, it was deemed insignificant. Combined administration IV and topical TXA has been used in total hip arthroplasty, while it did show better outcome, no significant difference is found[24].

Kwak et al. (2014)[15] reported perioperative ITU admissions in TXA group [28(38.90%) patients] were lower as compared to control groups [35 (48.6%)]. This highlights the role of perioperative blood loss reduction in TXA group which prevents the risk of physiological compromise, and hence ITU admissions. 30 days mortality in TXA group was three times less than control groups. This information adds up to rational use of TXA in such patients. As mentioned earlier, out of five studies, two reported no difference (Liu et al[11]; Xie et al.[12]) whereas three studies reported higher mortality in non TXA group (for example Ashkenazi et al[4] and Lee et al[5]). Again, this information adds up to rational use of TXA in such patients. The risk of DVT is not significantly increased with TXA use but there is significant reduction in DVT incidences with topical TXA as compared to IV. Hence, in high-risk patient for DVT, topical TXA is a good substitute to reduce intraoperative bleeding[10,11,14].

CONCLUSION

TXA is proven to significantly reduce the perioperative blood loss level and Haemoglobin reduction hence, transfusion requirement. for patients undergoing hemiarthroplasty in fracture neck of femur. The indirect effects can be observed in less ITU admissions, and decreased mortality in few studies. There is potential risk of DVT in high-risk patients where local TXA use can be more logical, but future RCT will be needed to support this. Furthermore, meta-analysis suggested a cumulative outcome in favour of TXA group.

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Conflict of Interest

The author declares no conflict of interest in the making of this manuscript.

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Table 1: PICO criteria used, consists of four parameters: patient, intervention, control, and objective criteria

Parameter of PICO	Inclusion criteria
Patient	Elderly patients with femoral neck fracture
Intervention (Index test)	Perioperative tranexamic acid (TXA)
Control (Reference test)	Patients who did not get TXA in perioperative period
Outcomes	Blood loss level, postoperative haemoglobin level, complications

Table 2: Characteristics of the study populations

Author, Published Year	Rental	Design	Number of Participants	Number of TXA Group	Number of Control Group	Mean Age of Patients			Gender (Male:Female)			Mean BMI		Hemoglobin Level		
						TXA		*Control*	*TXA*		*Control*	*TXA*	*Control*	*TXA*		*Control*
						IV	Topical		IV	Topical				IV	Topical	
Watts *et al*, 2017[10]	Rochester	Randomized controlled trial	138	69	69		81	82.2		21:48	22:47	25.1	25.1		12.2	12.5
Lee *et al*, 2015[5]	United Kingdom	Retrospective cohort study	271	84	187	85.95		84.66	32:52		53:134			12.51		12.33
Liu *et al*, 2018[11]	China	Retrospective cohort study	103	54	49		84.98	85.38		15:39	10:39				11.95	12.26
Xie *et al*, 2019[12]	China	Retrospective cohort study	609	289	320	84.41		85.21	91:198		106:214	24.12	22.11	12.3		12.07
Askhenazi *et al*, 2020[4]	Israel	Retrospective cohort study	1722	504	1218	84.2		83.2	167:337		434:784					
Selvakumar *et al*, 2019[13]	South India	Randomized controlled trial	40	20	20	67.1			18:22							
Emara *et al*, 2014[14]	Egypt	Randomized controlled trial	60	20 (IV); 20 (topical)	20	56.5	55	56	12:8	10:10	14:6			13.3	12.8	13.2
Kwak *et al*, 2019[15]	South Korea	Case controlled study	144	72	72		80.1	80.9		18:54	18:54	22.3	21.8		11.5	12.1
Kang *et al*, 2016[16]	South Korea	Randomized controlled trial	80	40	40		78.75	78.62		10:30	12:28	21.9	21.33		11.83	11.81
Pillai *et al*, 2020[17]	India	Retrospective cohort study	70	40	30	72.12		71.53	26:14		20:10					
Borkar *et al*, 2017[18]	India	Randomized controlled trial	60	30	30		63.2	65.5		12:18	14:16				13.9	13.7
Ansari *et al*, 2016[19]	India	Randomized controlled trial	34	17	17											

Table 3: Main outcomes of the included studies (Blood loss, hemoglobin level reduction, blood transfusion requirement)

Author, Published Year	# Participants	# TXA Group	# Control Group	Blood loss (mL)*		Hemoglobin level (reduction)						# Blood transfusion requirement	
						Pre-OP		POD 1*		POD 3			
				TXA	*Control*	*TXA*	*Control*	*TXA*	*Control*	*TXA*	*Control*	*TXA*	*Control*
Watts et al, 2017	138	69	69	731	973	12.2	12.5					18	18
Lee et al, 2015	271	84	187			12.51	12.33	11.08 (-1.43)	10.67 (-1.66)	10.57 (-1.94)	9.90 (-2.43)	5	35
Liu et al, 2018	103	54	49	119.44	122.24	11.95	12.26			9.32 (-2.63)	8.71 (-3.55)	5	12
Xie et al, 2019	609	289	320	488.54	589.13	12.3	12.07	11.17 (-1.13)	10.73 (-1.34)	10.82 (-1.48)	10.42 (-1.65)	25	77
Askhenazi et al, 2020	1722	504	1218					(-1.38)	(-1.76)			88	541
Selvakumar et al, 2019	40	20	20	234.5	296.7			10.6	10.4				
Emara et al, 2014	60	20 (IV) 20 (Topical)	20	640 (IV) 625 (Topical)	1100	13.3 (IV) 12.8 (Topical)	13.2	10.5 (-2.8) [IV] 10.7 (-2.1) [Topical]	9 (-4.2)			1 (IV) 1 (Topical)	7
Kwak et al, 2019	144	72	72	440	531.3	11.5	12.1	10.2 (-1.3)	9.5 (-2.6)	9.9 (-1.6)	10.0 (-2.1)	26	47
Kang et al, 2016	80	40	40	701	884	11.83	11.81	10.25 (-1.58)	9.66 (-2.15)			18	24
Pillai et al, 2020	70	40	30	102.5	274.6			(-0.99)	(-2.46)			7	20
Borkar et al, 2017	60	30	30	206	208	13.9	13.7	12.6 (-1.3)	11.8 (-1.9)				
Ansari et al, 2016	34	17	17										

Table 4: Description of secondary outcomes for the different included studies

Author, Published Year	# Participants	# TXA Group	# Control Group	Blood loss (mL)		30-day mortality		1-year mortality		30-day readmission		1-year readmission	
				TXA	*Control*	*TXA*	*Control*	*TXA*	*Control*	*TXA*	*Control*	*TXA*	*Control*
Watts et al, 2017	138	69	69	731	973	7.20 %	4.30%			10.60 %	6.10%		
Lee et al, 2015	271	84	187			4	9	8	19				
Liu et al, 2018	103	54	49	119.44	122.24	1	1	2	1				
Xie et al, 2019	609	289	320	488.54	589.13	0	0						
Askhenazi et al, 2020	1722	504	1218			4.60 %	7.30%	19.80 %	22.70 %	11.90 %	11.10 %	3.20 %	2.60%
Selvakumar et al, 2019	40	20	20	234.5	296.7								
Emara et al, 2014	60	20 (IV) 20 (Topical)	20	640 (IV) 625 (Topical)	1100								
Kwak et al, 2019	144	72	72	440	531.3			4(5.4 %)	4(5.4 %)				
Kang et al, 2016	80	40	40	701	884								
Pillai et al, 2020	70	40	30	102.5	274.6								
Borkar et al, 2017	60	30	30	206	208								
Ansari et al, 2016	34	17	17										

Table 5: Descriptive analysis of length of stay and operating time

	Hospital Stay (days)		***Operation Time (min.)***	
	TXA	Control	TXA	Control
Mean	14.85	15.7275	95.66286	93.55143
Standard Error	3.840647	3.737948	13.42189	13.05958
Median	16.41	16.98	88.19	92.35
Standard Deviation	7.681293	7.475896	35.51099	34.5524
Minimum	5.38	5.55	45	42
Maximum	21.2	23.4	143.4	92.35

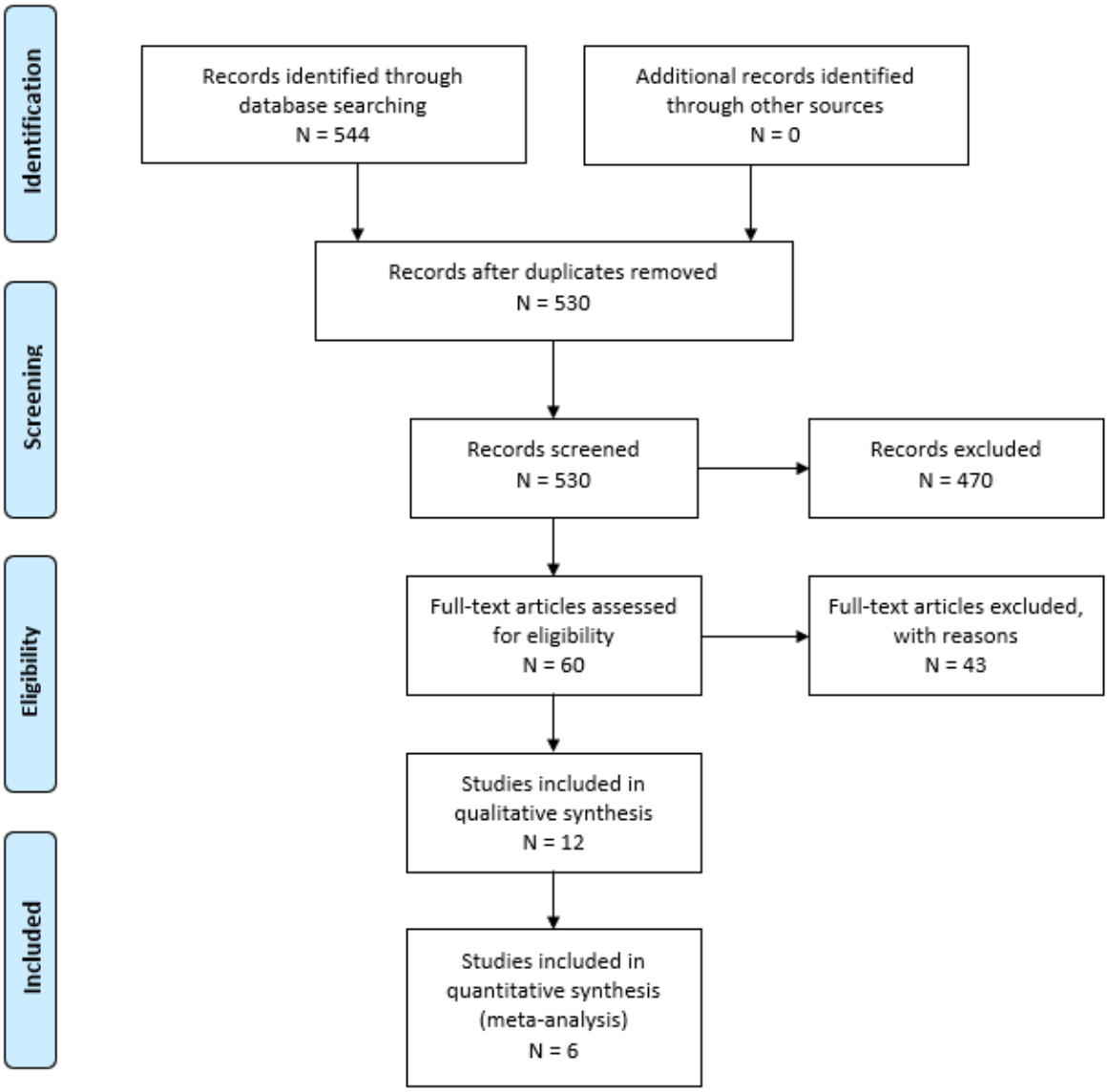

Figure 1: PRISMA flowchart of search results

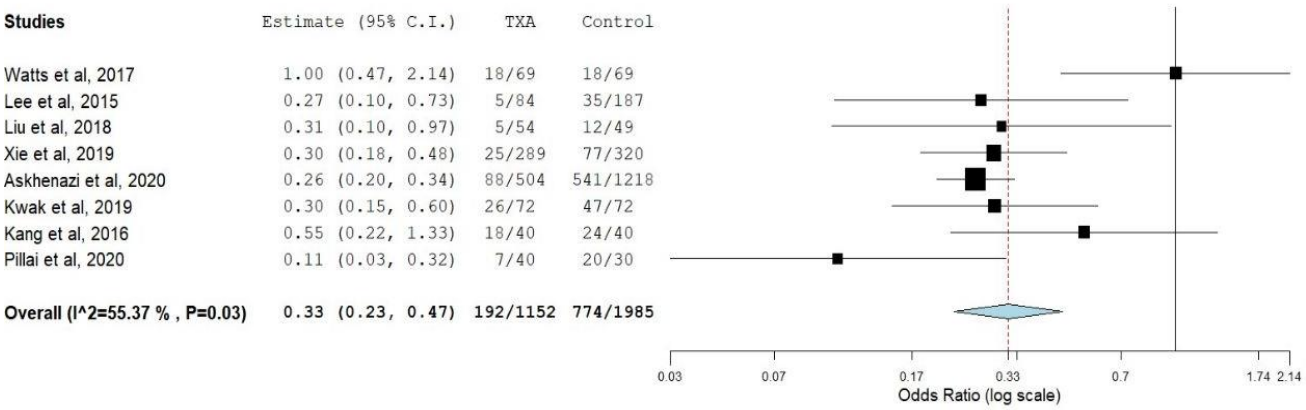

Figure 2: Forest plot of transfusion requirement comparison between the TXA and control group

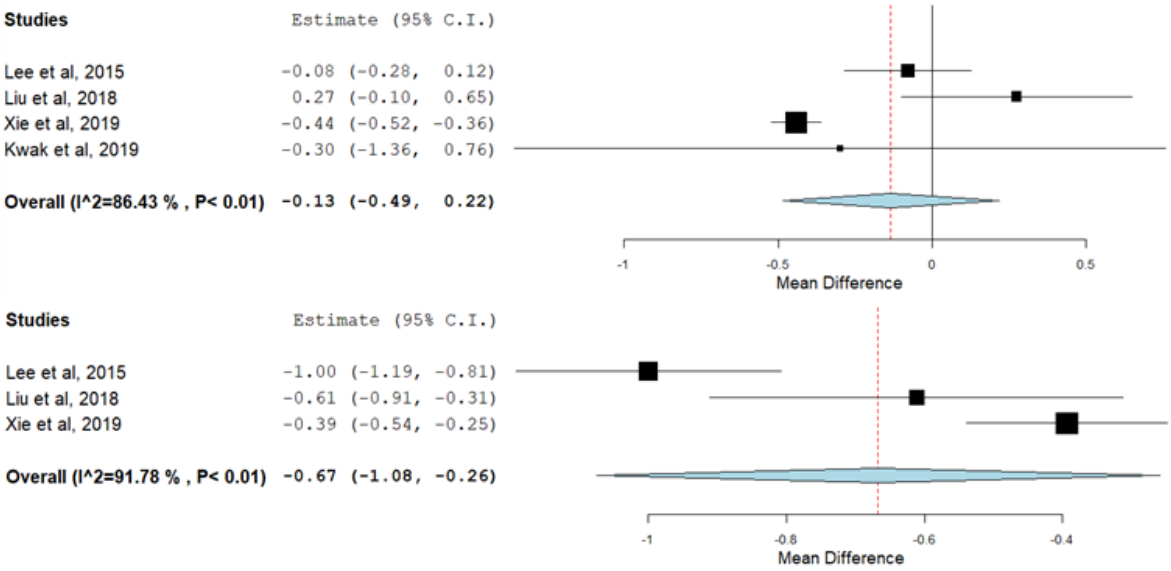

Figure 3: Difference in haemoglobin level between TXA group and control group on day 1 (up) and 3 (down) post-operation

Figure 4: Risk of bias assessment result in Cochrane Risk of Bias Tool (RoB Tool)