The Efficacy and Safety of Tranexamic Acid Combined with Rivaroxaban in Prevention of Clinical Events in Patients after Total Knee/ Hip Arthroplasty: A Meta-analysis

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Abstract

Purpose

To evaluate the efficacy and safety of tranexamic acid combined with rivaroxaban in prevention of clinical events in patients after TKA/THA through meta-analysis of randomized controlled trials.

Materials and Methods

RCTs were retrieved from medical literature databases. RR, SMD and 95% confidence intervals (CI) were calculated to compare the primary and safety endpoints.

Results

In total, 16 articles (23 trial comparisons) were retrieved which contained 2179 patients. In general, 1257 patients (57.7%) were randomized to experimental group whereas 922 patients (42.3%) were randomized to control group. The result showed that TXA combined with rivaroxaban significantly reduce TBL, BTV, BTR and the incidence of MB compared to the control group; there were no significant differences in NMB between experimental group and control group.

Conclusions

This meta-analysis reveals that TXA combined with rivaroxaban can significantly reduce TBL, BTV, the incidence of blood transfusion and the incidence of MB compared to the control group, which proved that its efficacy and safety are trustworthy.

Background

In recent years, total knee arthroplasty (TKA) has become an important method for the clinical treatment of severe knee joint diseases, while total hip arthroplasty (THA) is also widely used in the treatment of end-stage femoral head necrosis, hip ankylosis and other hip related diseases [1]. As the techniques of TKA and THA become more and more mature, one of the biggest problems that afflict these two types of surgery are the large amount of blood loss during the perioperative period and the need for blood transfusion after operation [2]. Therefore, the prevention and treatment of perioperative complications and postoperative rehabilitation on the success or failure of the operation and to ensure the postoperative recovery of patients cannot be ignored [3].

TXA is a commonly used hemostatic drug in clinic, which can competitively prevent and inhibit the binding of fibrin with fibrinogen and fibrinolytic enzyme, and then play a hemostatic effect, several studies have confirmed that the use of TXA before and during THA/TKA can effectively reduce blood loss [4]. However, there may be a risk of keeping venous blood in a hypercoagulable state at the same time [5, 6]. Patients undergoing major orthopedic surgery, especially lower limb joint replacement, are inherently at high risk of venous thromboembolism (VTE). Both the American Academy of Orthopedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) have developed new evidence-based guidelines for venous thromboembolic prophylaxis after total joint arthroplasty [7, 8].

Low molecular weight heparin (LMWH) is still commonly used in anticoagulant, but LMWH needs to be adjusted when it is used, and subcutaneous injection leads to poor compliance of patients after discharge. Rivaroxaban is a direct oral anticoagulant, which is used to prevent VTE in THA/TKA [9]. At the same time, rivaroxaban is given orally without adjusting the dose. Despite its clinical efficacy in VTE prophylaxis, orthopedic surgeons are still skeptical regarding the routine use of rivaroxaban in knee and hip surgery and, in particular, the increased risk of bleeding complications [10].

Therefore, how to balance antifibrinolysis and anticoagulation is a challenge. Some studies have pointed out that we should guard against the risk of postoperative VTE associated with antifibrinolytic drugs and the risk of bleeding caused by anticoagulant drugs [5, 6]. There are also studies suggest that TXA has a short half-life in plasma and its antifibrinolytic effect only lasts for 3–4 hours [11], or according to others, up to 6–8 hours [12]. This time interval is well shorter than, or may just coincide with, the initiation of anticoagulant administration to patients after joint replacement surgery. In theory, therefore, no “contradiction” in the combined use of such agents exists, the added use of TXA does not increase rates of thromboembolic events after total joint replacement surgery [13–15]. The application of TXA combined with rivaroxaban is relatively few and lacks clinical significance. The purpose of this study was to explore the efficacy and safety of TXA combined with rivaroxaban in patients with THA or TKA to provide more options for the clinical application of anticoagulants.

Methods

Search strategy

Two researchers searched for published articles comparing the efficacy and safety of TXA combined with rivaroxaban in patients with THA or TKA following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The RCTs were systematically searched in the databases such as the Cochrane Library, Embase, PubMed, Google Scholar, Baidu Scholar, CNKI and VIP with no restrictions on language or publication date from inception to 16 May 2019. The following keywords and MeSH terms were used: (“total knee arthroplasty” OR “total hip arthroplasty”) AND “tranexamic acid” AND “rivaroxaban”. Additional relevant studies were retrieved from reviews, meta-analyses, and other literature. Two authors screened and double-reviewed the retrieved studies. Where disputes were encountered, they were resolved by consulting a third author. In this meta-analysis, all data were extracted from previously published studies, thus no patient consent and ethical approval were required.

Inclusion And Exclusion Criteria

The following inclusion criteria were used: (1) Studies that assessed the efficacy and safety of TXA combined with rivaroxaban in patients with THA or TKA; (2) The study was a randomized controlled trial (RCT); (3) The study subjects were patients undergoing THA or TKA (both primary and revision cases); (4) General information (e.g. gender, age, disease type) of the experimental group and the control group was not statistically different at baseline; (5) At least one of the evaluated groups was based on TXA combined with rivaroxaban; (6) TXA and rivaroxaban had no limitation in usage and dose; (7) Included articles provide sufficient data for analysis; (8) Language was limited to English or Chinese.

The following exclusion criteria were used: (1) Nonclinical trials, case reports or series; (2) Animal experiments; (3) Semi-randomized controlled trials or non-randomized trials; (4) Articles with incorrect or incomplete data, or articles whose data could not be extracted; (5) Studies that compared the efficacy and safety of TXA versus rivaroxaban in patients after THA or TKA.

Endpoints

The primary endpoints for this study were total blood loss (TBL), blood transfusion volume (BTV) and blood transfusion rate (BTR). The secondary endpoints for this study were hidden blood loss (HBL), intraoperative blood loss (IBL), postoperative drainage, (activated partial thromboplastin time) APTT, (fibrinogen) FG, (hemoglobin) Hb and (prothrombin time) PT. The safety endpoints included major bleeding (MB), non-major bleeding (NMB) (including clinically relevant non-major bleeding, minor bleeding, any overt bleeding, etc) and venous thromboembolism (VTE).

Data Extraction

Two authors independently reviewed the contents of the retrieved studies. The primary endpoints were extracted by two authors and verified by a third author. The data extracted included the following primary information: first author's name, year of publication, test type/region, sample size, sex ratio, average age, body mass index (BMI), intervention, operative type, follow-up time and endpoints measured in each study. If the contents of the studies needed clarification, the first author of the study was contacted. Disagreements were resolved through consensus or by consulting a third author.

Risk-of-bias Assessments

The methodological quality of the included studies was estimated independently by two authors based on The Cochrane Risk of Bias criteria. Each quality item was graded as low risk, high risk, or no clear risk. The seven items used to assess bias in each trial included the randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

Statistical analysis

Stata (version 12.0, Stata Corp, College Station, Texas) was used to analyze and pool the individual research results. Pooled results were recorded as risk ratios (RR) Standard mean difference (SMD) and 95% confidence intervals (CI) with two-sided P-values. P-values < 0.05 were considered to be statistically significant. Heterogeneity was evaluated using the I^2 test. The heterogeneity was considered to be small when $I^2 < 50\%$ and substantial when $I^2 > 50\%$. The fixed effect model was used when $I^2 < 50\%$, while the random effect model was used when $I^2 > 50\%$. A funnel plot was generated to examine the publication bias and to explore the sources of heterogeneity if more than ten studies were included to assess this endpoint. Subgroup analysis was performed according to the administration, operative type, follow-up period and dosage of TXA.

Results

Studies Retrieved and Characteristics

A total of 3298 relevant studies were enrolled according to PRISMA guidelines. The titles and abstracts of the studies were screened to exclude irrelevant studies. Then, we further eliminated the unfit studies by reading the full text of the articles. Finally, 16 studies [12, 16–30] (23 trial comparisons) were included according to the inclusion and exclusion criteria and they had a total of 2179 patients as shown in Fig. 1. In general, 1257 patients (57.7%) were randomized to experimental group whereas 922 patients (42.3%) were randomized to control group. All studies included in this meta-analysis were RCTs. The basic characteristics of the individuals from the trials are described in Table 1.

Table 1
Characteristics of studies included in meta-analysis.

Author	Year	Country	Sample size		Women, No. (%)		Average age (years)		BMI		Intervention		Op typ
			E	C	E	C	E	C	E	C	E	C	
Jianbao Li[16]	2014	China	45	45	25(55.5)	21(46.6)	55.47 ± 13.32	52.58 ± 14.21	N/A	N/A	TXA: 15 mg/kg, tid, intravenous drip. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TH
Guokuan Xing[17]	2015	China	60	60	42(70.0)	46(76.6)	70.34 ± 7.41	69.32 ± 7.21	27.3	26.7	TXA: 1.5 g, intraarticular injection; 1.0 g local perfusion. Rivoraxaban: 15 mg/day, orally.	LMWH: 2 500 AXa IU /d, hypodermic injection.	TK
Junwen Wang[18]	2016	China	100	98	74(74.0)	72(77.6)	68.19	69.60	28.2	28.1	TXA: 1.0 g, intraoperative injection. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TK
Fulin Li a[19]	2017	China	30	30	7(23.3)	10(33.3)	62.20 ± 6.60	62.20 ± 7.30	21.8	21.3	TXA: 10 mg/kg before skin incision, intravenous drip. Rivoraxaban: 10 mg/day, orally.	100 ml 0.9% NS, intravenous drip	TH
Fulin Li b[19]	2017	China	30	30	8(26.7)	10(33.3)	62.70 ± 6.50	62.20 ± 7.30	21.4	21.3	TXA: 15 mg/kg, before skin incision, intravenous drip. Rivoraxaban: 10 mg/day, orally.	100 ml 0.9% NS: intravenous drip.	TH
Fulin Li c[19]	2017	China	30	30	9(30.0)	10(33.3)	61.80 ± 13.00	62.20 ± 7.30	21.1	21.3	TXA: 15 mg/kg, before skin incision and after 3 h, intravenous drip. Rivoraxaban: 10 mg/day, orally.	100 ml 0.9% NS: intravenous drip.	TH
Fulin Li d[19]	2017	China	30	30	8(26.7)	10(33.3)	62.40 ± 7.40	62.20 ± 7.30	21.4	21.3	TXA: 15 mg/kg, before skin incision, intravenous drip; 1.0 g, local wet compress. Rivoraxaban: 10 mg/day, orally.	100 ml 0.9% NS: intravenous drip.	TH
Guokuan Xing[20]	2017	China	50	50	36(72.0)	38(76.0)	61.40 ± 6.60	63.10 ± 3.80	26.3	27.4	TXA: 1.0 g, intravenous drip; 1.0 g, local perfusion. Rivoraxaban: 15 mg/day, orally.	LMWH: 2 500 AXa IU /d, hypodermic injection.	TK
Hongjian Xu[21]	2017	China	75	75	35(46.6)	34(45.3)	65.18 ± 3.32	65.22 ± 3.28	N/A	N/A	TXA: 1.0 g, local wet compress. Rivoraxaban: 10 mg/day, orally.	LMWH: 0.01 ml/kg, q12h, hypodermic injection.	TH
Jinwei Xie[22]	2017	China	96	98	74(96.0)	86(98.0)	65.20 ± 5.50	66.80 ± 7.40	25.4	25.6	TXA: 15 mg/kg, intravenous before tourniquet deflation; 1.0 g, injected into the articular cavity through the drainage tube. Rivoraxaban: 10 mg/day, orally.	TXA: 15 mg/kg, intravenous before tourniquet deflation; 1.0 g, injected into the articular cavity through the drainage tube. LMWH: 0.4 ml 4000 IU, hypodermic injection.	TK
Keming Xia a[23]	2017	China	49	49	N/A	N/A	66.00 ± 10.40	62.40 ± 11.30	25.4 ± 3.9	25.4 ± 3.3	TXA: 10 mg/kg,0.5 h before operation, intravenous. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TK

Author	Year	Country	Sample size		Women, No. (%)		Average age (years)		BMI		Intervention		Op typ
			E	C	E	C	E	C	E	C	E	C	
Keming Xia b[23]	2017	China	49	49	N/A	N/A	64.10 ± 9.20	62.40 ± 11.30	25.9 ± 4.1	25.4 ± 3.3	TXA: 10 mg/kg,0.5 h before operation, intravenous; 50 ml, local injection after operation. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TK
Shih-Hsiang Yen a[24]	2017	China	31	30	27(87.1)	24(80.0)	69.13	70.87	28.4	28.3	TXA: 1.0 g, intraoperative bolus injection. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TK
Shih-Hsiang Yen b[24]	2017	China	32	30	19(59.4)	24(80.0)	69.66	70.87	28.1	28.3	TXA:3.0 g, intraarticular injection. Rivoraxaban:10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TK
Weina Zhou[25]	2017	China	33	33	N/A	N/A	66.30 ± 7.40	66.30 ± 7.40	23.9	23.9	TXA:1.0 g, intraarticular injection. Rivoraxaban:15 mg/day, orally.	TXA:1.0 g intraarticular injection. LMWH: 2500 IU /d, hypodermic injection.	TH
Yanmei Fan[26]	2017	China	65	65	N/A	N/A	60 ~ 87	60 ~ 87	N/A	N/A	TXA: 0.5 g, local wet compress. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TK
Yanan Fan[27]	2017	China	30	30	13(43.3)	10(33.3)	57.03 ± 10.23	55.55 ± 7.11	22.8 ± 2.7	23.4 ± 3.5	TXA: 1.0 g, preoperative intravenous drip;100 ml, after sewing. Rivoraxaban: 10 mg/day, orally.	TXA: 1.0 g, preoperative intravenous drip;100 ml, after sewing. LMWH: drug administration as appropriate	TH
Fang Lan a[28]	2018	China	70	78	37(52.9)	46(58.9)	62.50 ± 15.40	63.70 ± 11.90	N/A	N/A	TXA: 10 mg/kg (preoperative intravenous drip) 10 mg/kg (postoperative intravenous drip) Rivoraxaban: 10 mg/day, orally.	250 ml 0.9% NS: intravenous drip.	TK
Fang Lan b[28]	2018	China	92	78	54(58.7)	46(58.9)	64.40 ± 12.60	63.70 ± 11.90	N/A	N/A	TXA: 2.0 g, intraarticular injection. Rivoraxaban: 10 mg/day, orally.	250 ml 0.9% NS: intravenous drip.	TK
Wen Li[29]	2018	China	33	33	13(44.2)	16(48.5)	67.80 ± 7.20	68.50 ± 7.80	N/A	N/A	TXA: 1.0 g, intraarticular injection. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TK
Xingjing Wu[30]	2018	China	73	73	N/A	N/A	≥60	≥60	N/A	N/A	TXA: 2.0 g, intraarticular injection. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TH
A. Clavé a[12]	2019	France	76	75	45(59.2)	42(56.0)	65.00	64.40	27.5	26.6	TXA: 1.0 g, intravenous injection, at 0 hour and postoperative hour 3. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TH
A. Clavé b[12]	2019	France	78	75	44(56.4)	42(56.0)	67.10	64.40	25.3	26.6	TXA: 1.0 g, intravenous injection, at 0 hour and postoperative hours 3, 7, and 11. Rivoraxaban: 10 mg/day, orally.	Rivoraxaban: 10 mg/day, orally.	TH

Literature quality evaluation

The Cochrane Risk of Bias criteria was used to evaluate the quality of the retrieved studies by two authors. The included studies were all randomized controlled trials. 16 studies [12, 16–30] described random sequence generation and allocation concealment. 4 studies [12, 16, 18, 24] described blinding of participants and personnel. 4 studies [12, 16, 18, 24] described blinding of outcome assessment. None of the studies described other biases. The literature quality score is shown in Table 2.

Table 2
Assessment of Methodological Quality of Included Studies.

Study	Random allocation	Hidden distribution	Blind method	Incomplete Outcome Data	Selective reporting of results	Other bias	Quality grade
Jianbao Li[16]	Randomized	No clear	Single-blind	Low	Low	Low	C
Guokuan Xing[17]	Randomized	No clear	No clear	Low	Low	Low	C
Junwen Wang[18]	Randomized	No clear	Double-blind	Low	Low	Low	B
Fulin Li[19]	Randomized	No clear	No clear	Low	Low	Low	C
Guokuan Xing[20]	Randomized	No clear	No clear	Low	Low	Low	C
Hongjian Xu[21]	Randomized	No clear	No clear	Low	Low	Low	C
Jinwei Xie[22]	Randomized	No clear	No clear	Low	Low	Low	B
Keming Xia[23]	Randomized	No clear	No clear	Low	Low	Low	C
ShihHsiang Yen[24]	Randomized	No clear	Double-blind	Low	Low	Low	B
Weina Zhou[25]	Randomized	No clear	No clear	Low	Low	Low	C
Yanmei Fan[26]	Randomized	No clear	No clear	Low	Low	Low	C
Yanan Fan[27]	Randomized	No clear	No clear	Low	Low	Low	C
Fang Lan[28]	Randomized	No clear	No clear	Low	Low	Low	C
Wen Li[29]	Randomized	No clear	No clear	Low	Low	Low	C
Xingjing Wu[30]	Randomized	No clear	No clear	Low	Low	Low	C
A. Clavé[12]	Randomized	No clear	Double-blind	Low	Low	Low	B

Primary Endpoints

TBL

Thirteen studies [12, 16–18, 20–24, 26, 27, 29, 30] (16 trial comparisons) reported TBL. In total, 1712 patients were involved to evaluate TBL, wherein 936 were assigned to experimental group and 776 were assigned to control group. The result showed that patients' TBL in experimental group was significantly less than that in control group (SMD: -1.34, 95% CI -2.03 to -0.64, I^2 = 97.7%) as shown in Fig. 2. The random effect model was applied. Subgroup analysis was performed according to the administration, operative type, follow-up period and dosage of TXA.

The result of the administration subgroup showed that patients' TBL in experimental group was significantly less than that in control group when TXA were local wet compressed or intravenous injected (SMD: -2.22, 95% CI -3.21 to-1.23; SMD: -0.76, 95% CI -0.99 to -0.52); there was no significant difference when TXA were intravenous dripped, intraarticular injected or intravenous dripped and intraarticular injected at the same time (SMD: -0.63, 95% CI -1.42 to 0.16; SMD: -1.87, 95% CI -3.82 to 0.07; SMD: -1.05, 95% CI -2.60 to 0.51).

The result of operative type subgroup showed that patients' TBL in experimental group was significantly less than that in control group when undergoing THA (SMD: -2.43, 95% CI -3.84 to-1.01); there was no significant difference between the TXA group and control group when undergoing TKA (SMD: -0.73, 95% CI -1.53 to 0.06).

The result of the follow-up period subgroup showed that patients' TBL in experimental group was significantly less than that in control group when the follow-up period was half a month or 6 months (SMD: -1.63, 95% CI -2.37 to-0.89; SMD: -4,85, 95% CI -7.82 to -1.87); there was no significant difference between experimental group and control group when the follow-up period was 3 months (SMD: -0.15, 95% CI -0.80 to 0.49).

The result of dosage subgroup showed that patients' TBL in experimental group was significantly less than that in control group at 1 g or 2 g dosage (SMD: -1.11, 95% CI -2.10 to -0.13; SMD: -2.99, 95% CI -4.86 to -1.12); there was no significant difference between experimental group and control group at other dosage (SMD: -0.64, 95% CI -1.81 to 0.53).

BTV

Four studies [16, 17, 20, 21] (4 trial comparisons) reported BTV. In total, 460 patients were involved to evaluate BTV, wherein 230 were assigned to the experimental group and 230 were assigned to control group. The result showed that patients' BTV in experimental group was significantly less than that in control group (SMD: -1.42, 95% CI -2.04 to -0.80, I^2 = 88.8%) as shown in Fig. 3. The random effect model was applied. Subgroup analysis was performed according to the operative type. The result of operative type subgroup showed that patients' BTV in experimental group was significantly less than that in control group when undergoing THA or TKA (SMD: -1.60, 95% CI -2.25 to -0.95; SMD: -1.25, 95% CI -2.49 to-0.01)

BTR

Thirteen studies [16–18, 20–24, 26–30] (16 trial comparisons) reported blood transfusion. In total, 77 out of 950 patients in experimental group experienced blood transfusion while 158 out of 784 patients in the control group experienced blood transfusion. The result showed that TXA combined with rivaroxaban significantly reduce the incidence of blood transfusion compared to the control group (8.1% vs 20.2%) (RR: 0.39, 95% CI 0.31 to 0.49 I^2 = 0.0%) as shown in Fig. 4. The fixed effect model was applied. Subgroup analysis was performed according to the administration, operative type, follow-up period and dosage of TXA.

The result of administration subgroup showed that TXA combined with rivaroxaban significantly reduce the incidence of blood transfusion compared to the control group when TXA was intravenous driped, intraarticular injected, intravenous driped and intraarticular injected or local wet compressed at the same time (RR: 0.47, 95% CI 0.32 to 0.68; RR: 0.35, 95% CI 0.23 to 0.53; RR: 0.37, 95% CI 0.22 to 0.63; RR: 0.33, 95% CI 0.16 to 0.72).

The result of operative type subgroup showed that TXA combined with rivaroxaban significantly reduce the incidence of blood transfusion compared to the control group when undergoing THA or TKA (RR:0.36, 95% CI 0.24 to 0.55; RR:0.40, 95% CI 0.30 to 0.54).

The result of follow-up period subgroup showed that TXA combined with rivaroxaban significantly reduce the incidence of blood transfusion compared to the control group when the follow-up period was half a month, 1 month, 3 months, 6 months (RR:0.39, 95% CI 0.28 to 0.55; RR:0.33, 95% CI 0.18 to 0.61; RR:0.37, 95% CI 0.23 to 0.59; RR:0.52, 95% CI 0.28 to 0.99).

The result of dosage subgroup showed that TXA combined with rivaroxaban significantly reduce the incidence of blood transfusion compared to the control group at 1 g, 2 g or other dosage (RR:0.36, 95% CI 0.19 to 0.69; RR:0.41, 95% CI 0.26 to 0.64; RR:0.39, 95% CI 0.29 to 0.53).

Secondary Endpoints

The result showed that compared to the control group, TXA combined Rivaroxaban could significantly reduce the HBL (SMD: -0.89, 95% CI -1.62 to -0.17, I^2 = 97.5%); IBL(SMD:-0.64, 95% CI -1.15 to -0.12, I^2 = 93.7%); postoperative drainage (SMD: -1.37, 95% CI -2.02 to -0.72, I^2 = 96.8%); PT (SMD: -1.01, 95% CI -1.93 to -0.09, I^2 = 97.0%).

The result showed that compared to the control group, TXA combined Rivaroxaban could significantly increase the APTT (SMD: 0.26, 95% CI 0.13 to 0.38, I^2 = 5.6%); Hb (SMD: 1.49, 95% CI 0.24 to 2.74, I^2 = 97.9%).

There was no significant difference between the TXA combined Rivaroxaban and the control group on FG (SMD: -0.12, 95% CI -0.32 to 0.07, I^2 = 0.0%).

Safety Endpoints

The result showed that compared to the control group, TXA combined Rivaroxaban could significantly reduce the incidence of MB (1.5% vs 3.4%) (RR: 0.27, 95% CI 0.10 to 0.71, I^2 = 27.5%).

There was no significant difference between the TXA combined Rivaroxaban and the control group on NMB (21.0% vs 28.1%) (RR: 0.85, 95% CI 0.69 to 1.04, I^2 = 48.2%) and VTE (3.34% vs 4.35%) (RR: 0.80, 95% CI 0.51 to 1.26, I^2 = 0.0%).

Publication Bias And Sensitivity Analysis

The funnel plot showed that there was bias among retrieved articles as shown in Supply Fig. 1–7. The results of the sensitivity analysis were shown in Supply Fig. 8–10.

Discussion

THA/TKA is one of the operations with large blood loss in orthopedic surgery [31]. TXA, a hemostatic, is often used to prevent perioperative bleeding in TKA/THA [32]. However, the antifibrinolytic effect of TXA may increase the risk of DVT [33]. Anticoagulant drugs should be given within 6–12 hours after the application of TXA [34]. As a direct oral anticoagulant, rivaroxaban has been used clinically for more than a decade, and its antithrombotic effect has been widely recognized [35]. Applying TXA and rivaroxaban at the same time in clinic is contradictory, so the efficacy and safety of TXA combined with rivaroxaban in the prevention of clinical events in patients undergoing TKA/THA are still controversial [36].

Nowadays, there are many meta-analyses to study TXA in patients after THA/TKA. They all concluded that TXA was effective after THA/TKA. Grandhi et al [37], Wei et al [14], Dong et al [38], and Kuo et al [39] conducted meta-analyses to evaluate the effectiveness and safety of aminocaproic acid for reducing blood loss in total knee and hip arthroplasty; Li et al [40], Chen et al [41] and Yang et al [42] conducted meta-analyses to comprise the efficacy and safety of topical, system and intravenous tranexamic acid usage in total knee and hip arthroplasty; Zhang et al [43] and Han et al [44] conducted meta-analyses to compared the efficacy and safety of oral compared with intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty. However, they only focused on the administration of TXA itself, but did not analysed other influencing factors. Yu et al [45] and Wu et al [46] compared tranexamic acid plus diluted-epinephrine versus tranexamic acid alone for blood loss in total joint arthroplasty, but they only retrieved several studies and only focused on blood loss and transfusion rate. As a result, whether TXA combined with anticoagulant are effective and safe enough to apply in clinical is still inconsistent.

This is the first meta-analysis to evaluate the efficacy and safety of TXA combined with rivaroxaban in the prevention of clinical events in patients undergoing TKA/THA. The result showed that TXA combined with rivaroxaban significantly reduce TBL, BTV, BTR and the incidence of MB compared to the control group (SMD: -1.34, 95% CI -2.03 to -0.64; SMD: -1.42, 95% CI -2.04 to -0.80; RR: 0.39, 95% CI 0.31 to 0.49; RR: 0.27, 95% CI 0.10 to 0.71); there were no significant differences in NMB between experimental group and control group (RR: 0.85, 95% CI 0.69 to 1.04).

When evaluating the primary endpoints, we found that the results were highly heterogeneous, so we did sensitivity analyses to decompose it. The results showed that after excluding Wu et al 's article [30], the overall effect of TBL has been greatly affected; after excluding Wang et al 's article [18], the overall effect of NMB has been greatly affected; the heterogeneity of BTV cannot be explore by sensitivity analysis, which may be caused by the lack of studies. In the study of Wu et al [46], the TBL was calculated according to the formula provided by Good et al [47], which was somewhat different from the calculation methods in other studies. (In this formula, the TBL was calculated without blood transfusion.) It would easily lead to heterogeneity; in the study of Wang et al,[14] rivaroxaban was used in control group. As a direct oral anticoagulant, it is not surprising that the use of rivaroxaban increases the risk of NMB.

Subgroup analyses were performed according to the administration, operative type, follow-up period and dosage of TXA when evaluating primary endpoints. And subgroup analyses were performed only if there were more than two trial comparisons per subgroup. In the administration that TXA combined with rivaroxaban was more effective in reducing TBL during local wet compression or intravenous injection Thus, the administration should be paid attention to in the clinical use. In the operative type subgroup analysis, the effects of TXA combined with rivaroxaban on patients undergoing THA or TKA were different, which may be due to the different wound size, operation time and the severity of primary disease. In the follow-up time subgroup analysis, the results showed that except that the 3-month group had no effect on TBL, each group could reduce TBL and BTR. This may be due to the imbalance in the number of people in each subgroup. In the dosage of TXA subgroup analysis, the results showed that except that other group had no effect on TBL, each group could reduce TBL and BTR. Because the dosage of TXA included in the article is different, we only distinguish it from the clinical commonly used 1 g and 2 g, and combine the other doses into one group, so different doses may be the main reason for the invalidity of other group.

The potential clinical implications of this meta-analysis are as follows: (1) This is the first study focusing on the efficacy and safety of TXA combined with rivaroxaban in patients after THA/TKA. Previous articles evaluated the efficacy of TXA after THA/TKA, but there was no specific meta-analysis to assess the applying of TXA combined with rivaroxaban. Our article just filled the gap. (2) 16 RCTs were retrieved which included a large sample size of 2179 participants compared to previous studies. (3) Subgroup analyses were performed according to the administration, operative type, follow-up period and dosage of TXA to explain the influence of different factors on the overall effect. (4) Sensitivity analyses were conducted to decompose heterogeneity and explore the influence of sample size on the overall effect. (5) We evaluated 12 indicators, including TBL, BTV, BTR, HBL, IBL, postoperative drainage, APTT, FG, Hb, PT, MB and NMB, which were more comprehensive than previous articles.

The limitations of this study are as follows: (1) Several baseline characteristics (diabetes, hypertension, older age or other drug use) were not considered and this may lead to mixed bias. (2) We used the outcome events reported in the retrieved studies to integrate the results of this meta-analysis. Therefore, it is difficult to assess the effect of these baseline characteristics on the results. (3) This study could not explore the interactions among the subgroup analysis because of the limitations inherent in the included studies. (4) The intervention measures in the control group were different. Some groups were given saline intravenously, some groups were treated with rivaroxaban or TXA alone and the dosage was different, so subgroup analysis could not be carried out, which may lead to significant heterogeneity. However, in view of ethical factors, it is immoral to require the original author not to use any hemostatic or anticoagulant interventions, so we have included all of these articles. (5) Only two retrieved articles have been published in what are considered high-impact orthopaedic surgical journals of the English literature. Seven of the retrieved papers have been published in Chinese journals, and the remaining in journals of general medicine. As a result, we have correctly tried to address this issue by evaluating the quality of the retrieved studies, assigning a grade C to most.

Conclusion

This meta-analysis reveals that TXA combined with rivaroxaban can significantly reduce TBL, BTV, the incidence of blood transfusion and the incidence of MB compared to the control group, which proved that its efficacy and safety are trustworthy.

Abbreviations

RCT = Randomized Controlled Trials, RR = Risk ratios, SMD = Standard mean difference, CI = confidence intervals, TXA = Tranexamic acid, TBL = total blood loss, BTV = blood transfusion volume, BTR = blood transfusion rate, HBL = hidden blood loss, IBL = intraoperative blood loss, APTT = activated partial thromboplastin time, FG = fibrinogen, Hb = hemoglobin, PT = prothrombin time. MB = major bleeding, NMB = non-major bleeding, VTE = venous thromboembolism.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Authors' contributions

M.J. design the study; M.J. and H.D. pooled the data; M.J. analysed the data; M.J., S.L. and X.X wrote the article; B.Z. reviewed the article. All Authors read and approved the manuscript

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Supplementary Figure Legends

Supply Figure 1. Comparison of TBL between the experimental group and the control group. (funnel plot)

SMD= standardized mean difference

Supply Figure 2. Comparison of BTR between the experimental group and the control group. (funnel plot)

RR= Risk Ratio

Supply Figure 3. Comparison of HBL between the experimental group and the control group. (funnel plot)

SMD= standardized mean difference

Supply Figure 4. Comparison of IBL between the experimental group and the control group. (funnel plot)

SMD= standardized mean difference

Supply Figure 5. Comparison of Postoperative drainage between the experimental group and the control group. (funnel plot)

SMD= standardized mean difference

Supply Figure 6. Comparison of non-major bleeding between the experimental group and the control group. (funnel plot)

RR= Risk Ratio

Supply Figure 7. Comparison of APTT between the experimental group and the control group. (funnel plot)

SMD= standardized mean difference

Supply Figure 8. Comparison of TBL between the experimental group and the control group. (sensitivity analysis)

SMD= standardized mean difference

Supply Figure 9. Comparison of BTV between the experimental group and the control group. (sensitivity analysis)

SMD= standardized mean difference

Supply Figure 10. Comparison of NMB between the experimental group and the control group. (sensitivity analysis)

RR= Risk Ratio

Figures

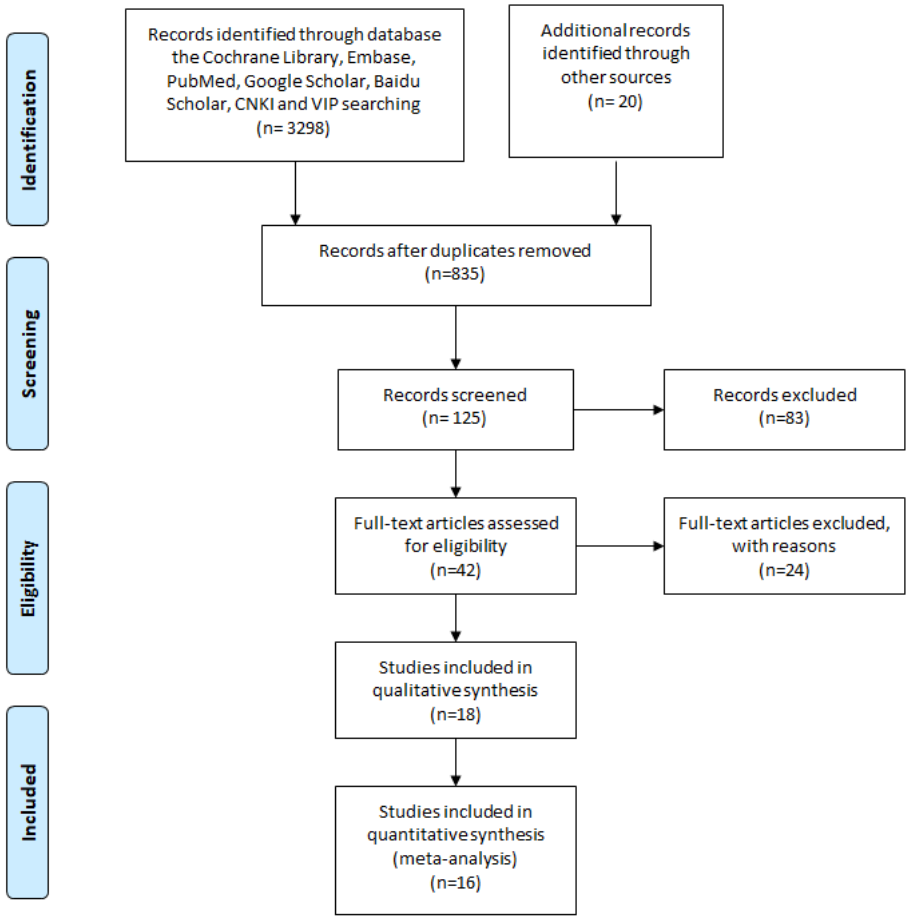


Figure 1

Flow diagram of the study selection process. CNKI=China national knowledge infrastructure, VIP=China Science and Technology Journal Database

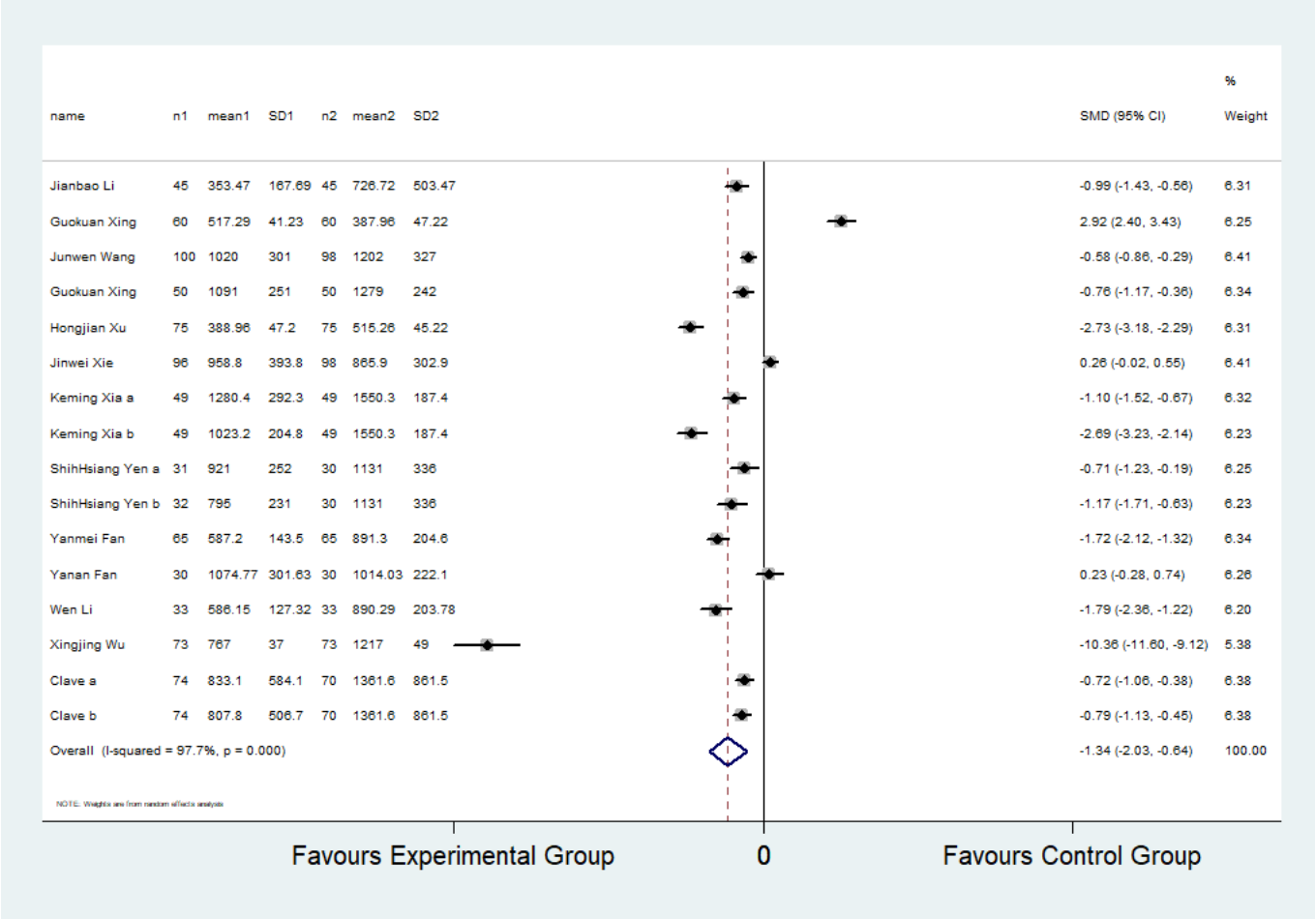


Figure 2

Comparison of TBL between the experimental group and the control group. SMD= standardized mean difference

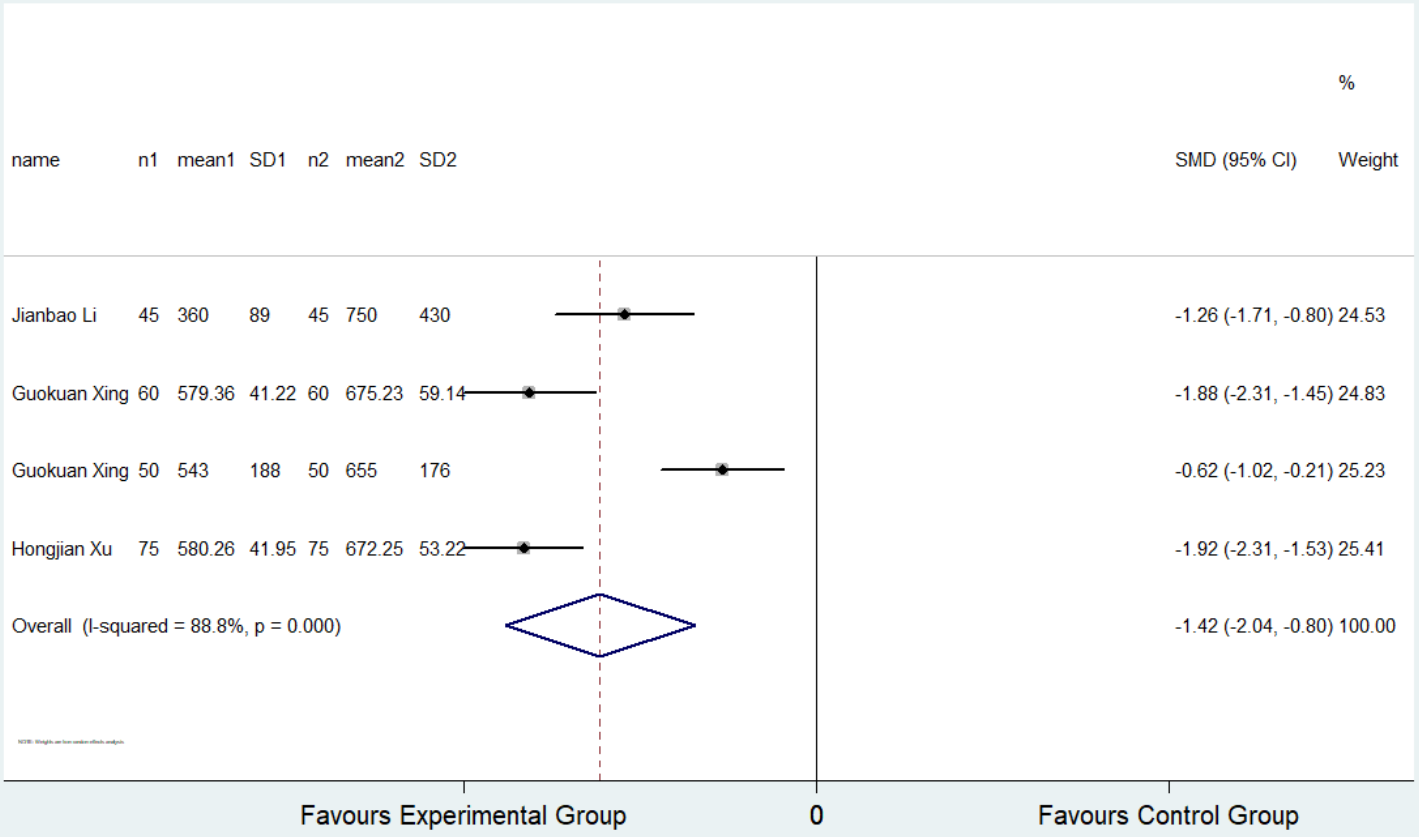


Figure 3

Comparison of BTV between the experimental group and the control group. SMD= standardized mean difference

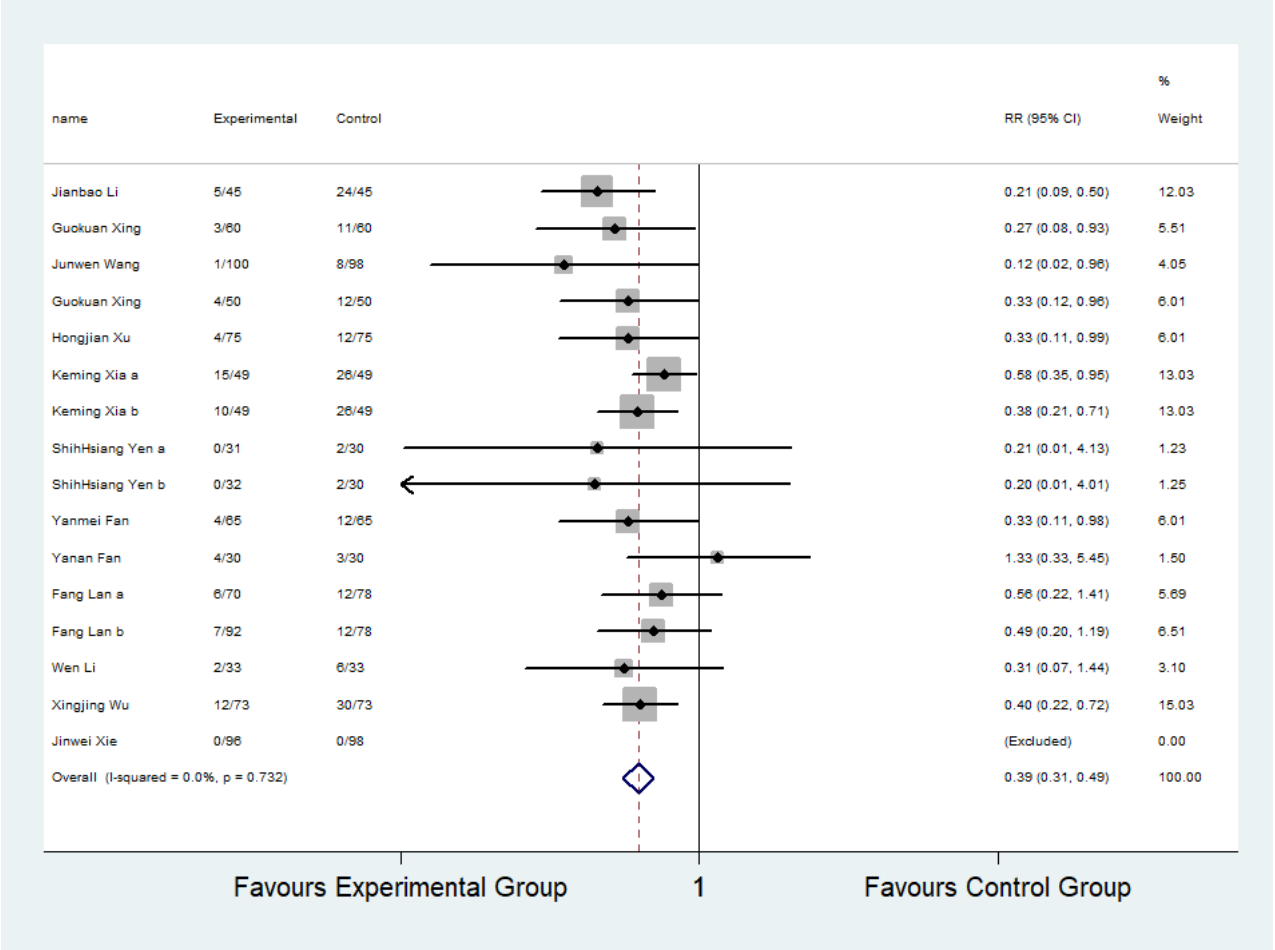
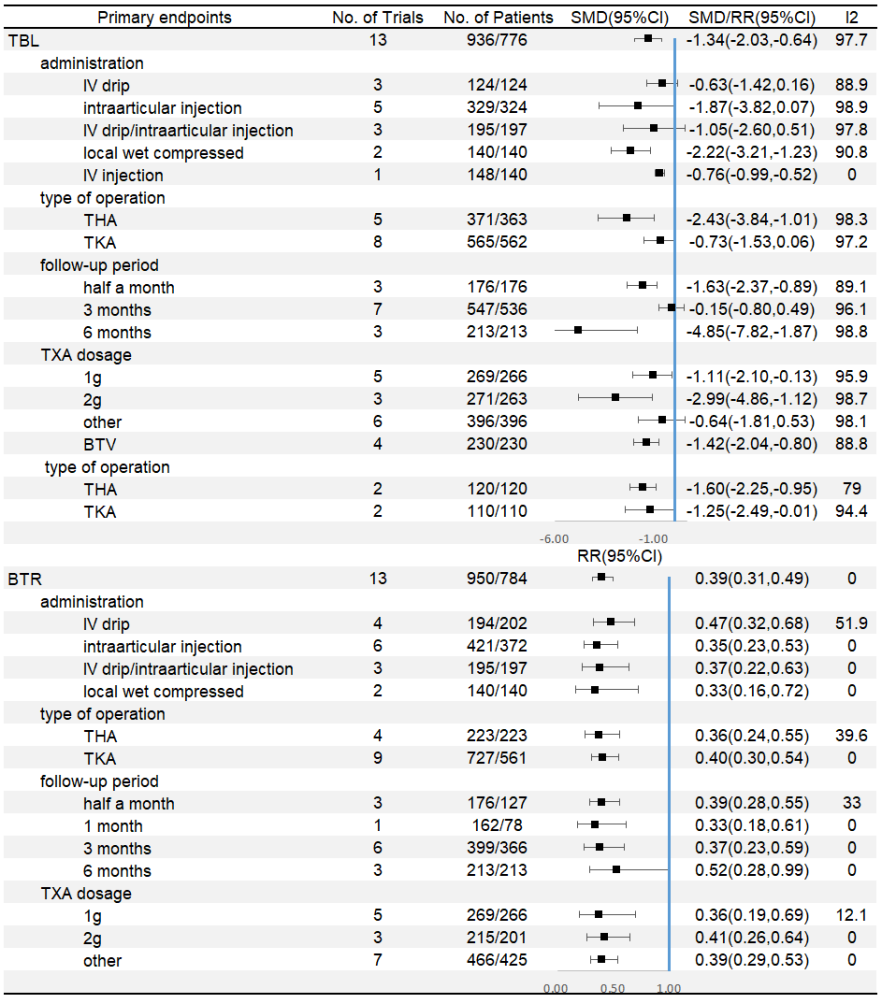


Figure 4

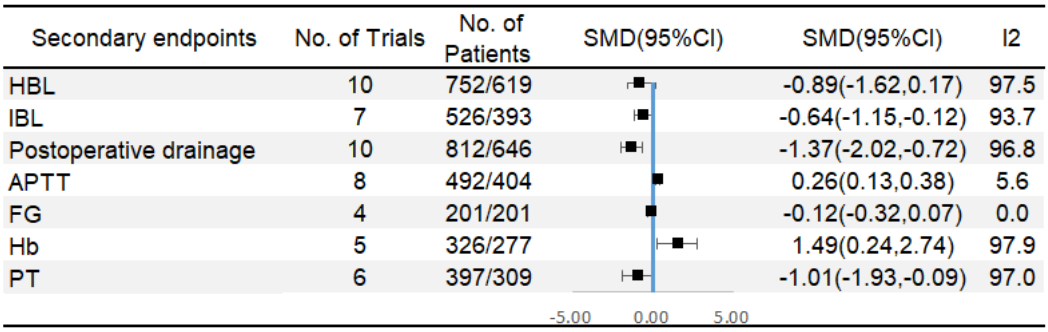
Comparison of BTR between the experimental group and the control group. RR= Risk Ratio



Primary endpoints	No. of Trials	No. of Patients	SMD/RR(95%CI)	I2
TBL	13	936/776	-1.34(-2.03,-0.64)	97.7
administration				
IV drip	3	124/124	-0.63(-1.42,0.16)	88.9
intraarticular injection	5	329/324	-1.87(-3.82,0.07)	98.9
IV drip/intraarticular injection	3	195/197	-1.05(-2.60,0.51)	97.8
local wet compressed	2	140/140	-2.22(-3.21,-1.23)	90.8
IV injection	1	148/140	-0.76(-0.99,-0.52)	0
type of operation				
THA	5	371/363	-2.43(-3.84,-1.01)	98.3
TKA	8	565/562	-0.73(-1.53,0.06)	97.2
follow-up period				
half a month	3	176/176	-1.63(-2.37,-0.89)	89.1
3 months	7	547/536	-0.15(-0.80,0.49)	96.1
6 months	3	213/213	-4.85(-7.82,-1.87)	98.8
TXA dosage				
1g	5	269/266	-1.11(-2.10,-0.13)	95.9
2g	3	271/263	-2.99(-4.86,-1.12)	98.7
other	6	396/396	-0.64(-1.81,0.53)	98.1
BTV	4	230/230	-1.42(-2.04,-0.80)	88.8
type of operation				
THA	2	120/120	-1.60(-2.25,-0.95)	79
TKA	2	110/110	-1.25(-2.49,-0.01)	94.4
BTR	13	950/784	0.39(0.31,0.49)	0
administration				
IV drip	4	194/202	0.47(0.32,0.68)	51.9
intraarticular injection	6	421/372	0.35(0.23,0.53)	0
IV drip/intraarticular injection	3	195/197	0.37(0.22,0.63)	0
local wet compressed	2	140/140	0.33(0.16,0.72)	0
type of operation				
THA	4	223/223	0.36(0.24,0.55)	39.6
TKA	9	727/561	0.40(0.30,0.54)	0
follow-up period				
half a month	3	176/127	0.39(0.28,0.55)	33
1 month	1	162/78	0.33(0.18,0.61)	0
3 months	6	399/366	0.37(0.23,0.59)	0
6 months	3	213/213	0.52(0.28,0.99)	0
TXA dosage				
1g	5	269/266	0.36(0.19,0.69)	12.1
2g	3	215/201	0.41(0.26,0.64)	0
other	7	466/425	0.39(0.29,0.53)	0

Figure 5

Comparison of TBL and BTR between the experimental group and the control group. (subgroup analysis) SMD= standardized mean difference RR= Risk Ratio



Secondary endpoints	No. of Trials	No. of Patients	SMD(95%CI)	I2
HBL	10	752/619	-0.89(-1.62,0.17)	97.5
IBL	7	526/393	-0.64(-1.15,-0.12)	93.7
Postoperative drainage	10	812/646	-1.37(-2.02,-0.72)	96.8
APTT	8	492/404	0.26(0.13,0.38)	5.6
FG	4	201/201	-0.12(-0.32,0.07)	0.0
Hb	5	326/277	1.49(0.24,2.74)	97.9
PT	6	397/309	-1.01(-1.93,-0.09)	97.0

Figure 6

Comparison of HBL, IBL, postoperative drainage, APTT, FG, Hb and PT between the experimental group and the control group. SMD= standardized mean difference

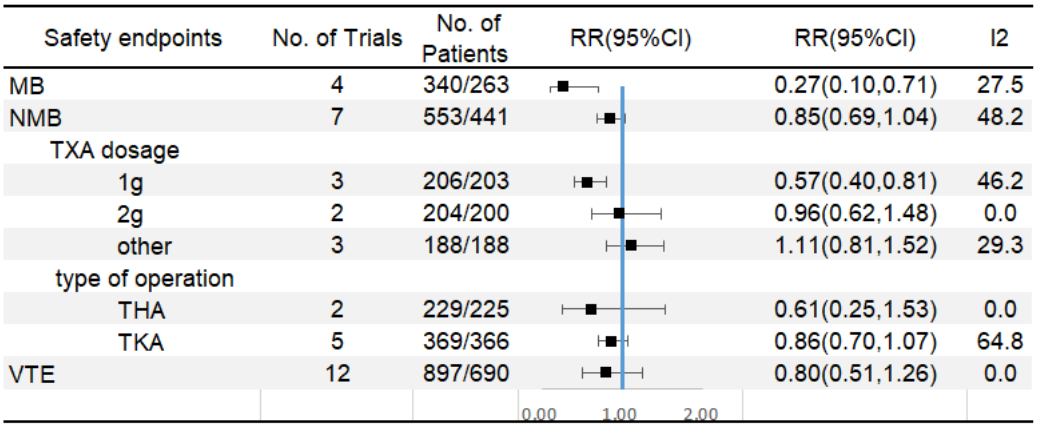


Figure 7

Incidence of adverse reaction between the experimental group and the control group. RR= Risk Ratio

Supplementary Files

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- 9PRISMADTAChecklist.doc
- SupplyFig.17.tif
- SupplyFig.810.tif