REVIEW ARTICLE

Efficiency and Safety of Intravenous Tranexamic Acid in Simultaneous Bilateral Total Knee Arthroplasty: A Systematic Review and Meta-analysis

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The objective of this systematic review and meta-analysis was to evaluate the efficacy and safety of i.v. tranexamic acid (TXA) in simultaneous bilateral total knee arthroplasty (TKA). Potentially relevant published reports were identified from the following electronic databases: Medline, PubMed, Embase, ScienceDirect and Cochrane Library. RevMan v5.3was used to pool data. Two randomized controlled trials and four case-control studies met the inclusion criteria. The current meta-analysis identified significant differences between TXA group and control groups in terms of postoperative hemoglobin concentration ($P < 0.01$), drainage volume ($P < 0.01$), transfusion rate ($P < 0.01$) and units transfused ($P = 0.006$). There were no significant differences in length of stay ($P = 0.66$), operation time ($P = 0.81$) or and incidence of adverse effects such as infection ($P = 0.42$), deep venous thrombosis (DVT) ($P = 0.88$) and pulmonary embolism (PE) ($P = 0.11$). Our results show that i.v. administration of TXA in simultaneous bilateral TKA reduces postoperative drops in hemoglobin concentration, drainage volume, and transfusion requirements and does not prolong length of stay or operation time. Moreover, no adverse effects, such as infection, DVT or PE, were associated with TXA.

Key words: Blood loss; Meta analysis; Total knee arthroplasty; Tranexamic acid

Introduction

Total knee arthroplasty (TKA) is an effective means of relieving pain and maintaining motor function in patients with end-stage osteoarthritis of the knee joint. However, because primary TKA requires extensive soft tissue dissection, long operative time and considerable cutting of bone, patients undergoing this procedure are particularly prone to considerable intra- and post-operative blood loss. Substantial blood loss is potentially associated with numerous problems, which can result in unsatisfactory outcomes and systemic decline, especially in older individuals[1,2]. Many techniques for addressing management of blood loss, including tourniquets, blood transfusion, administration of hemostatic agents and autologous donation have been tried[3]. Allogenic blood transfusion is associated with a risk of adverse effects such as viral infection, immunologically mediated disease and cardiovascular dysfunction and may thus cause increased financial burdens and potential ill-health[4].

Recently, tranexamic acid (TXA), administered via various routes, has been increasingly investigated as an adjunct to joint replacement. TXA, which is a synthetic analog of the amino acid lysine, inhibits dissolving of blood clots by plasminogen[5]. Several studies have reported that i.v. administration or topical application of TXA achieves the expected results of reducing perioperative blood loss and units transfused. Wong *et al.* assess the efficiency and safety of topical application of TXA in primary TKA in a randomized controlled trial (RCT) in 124 patients[6]. At the conclusion of TKA with cement, tranexamic acid was applied topically directly to the surgical wound; postoperative bleeding was reduced by 20%–25%, or 300–400 mL, resulting in 16%–17% higher postoperative hemoglobin concentrations compared with placebo, with no clinically important increase

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in complications being identified in the treatment group. Furthermore, a meta-analysis of high quality RCTs indicated that TXA is effective and safe for management of blood loss in primary unilateral TKA[7]. Fu *et al.* performed a meta-analysis to investigate the efficacy and safety of i.v. TXA in TKA by pooling 22 RCTs[8]. Thy found that i.v. TXA benefits patients undergoing TKA, significantly reducing total blood loss, postoperative blood loss, transfusion rate and volume transfused.

Patients who have bilateral knee arthritis may undergo simultaneous or staged bilateral TKAs; the outcomes of these two options have been widely debated. Simultaneous bilateral TKA has the advantage that there is only one operation, anesthetic, hospitalization, recovery period and analgesia regimen. Thus, the medical cost is lower. However, studies have shown a high incidence of cardiac and thrombotic complications, even death, in patients undergoing simultaneous bilateral TKAs[9]. On the contrary, some studies have reported opposite conclusions[10]. However, the 90-day mortality of unilateral, simultaneous and staged bilateral TKAs is reportedly similar[11]. Generally, it is difficult to compare simultaneous with staged bilateral TKAs because a majority of patients who are disappointed with their first unilateral TKA, and those who die, do not undergo the planned contralateral TKA.

There is no doubt that simultaneous bilateral TKA is associated with greater declines in hemoglobin concentrations and higher transfusion requirements than unilateral TKA, together with a higher risk of complications such as deep vein thrombosis (DVT) and pulmonary embolism (PE). One study reported that an estimated 2.6 units of red blood cells are transfused per patient in bilateral TKA[12]. To our knowledge, i.v. administration of TXA in patients undergoing bilateral TKAs has rarely been reported. We therefore performed this systematic review and meta-analysis to evaluate the efficiency and safety of i.v. TXA for management of blood loss in patients undergoing bilateral TKA.

Methods

Search Strategy

Potential relevant published reports were identified from electronic databases including Medline (1966 to November 2015), PubMed (1966 to November 2015), Embase (1980 to November 2015), ScienceDirect (1985 to March 2015) and Cochrane Library (inception to July 2016). Gray academic studies were also identified from the reference of included reports. There was no language restriction. The key words "Bilateral knee replacement OR arthroplasty" and "tranexamic acid," 'blood loss," "blood transfusion" were used in combination with Boolean operators AND or OR. The search process was performed as presented in Fig. 1.

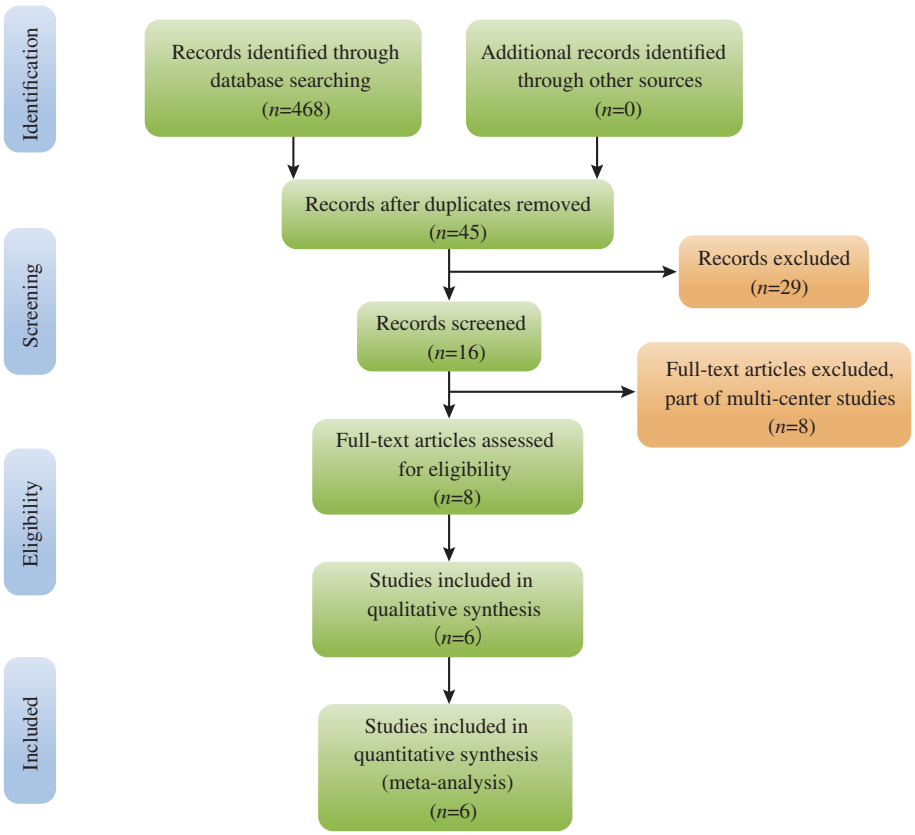


Fig. 1 Search results and selection procedure.

Inclusion and Exclusion Criteria

Published reports were selected if they met the following criteria: (i) clinical trial (RCT or non-RCT); (ii) patients with knee osteoarthritis undergoing simultaneous bilateral TKA, experiment group received intravenous TXA, control group received normal saline or nothing; (iii) reported surgical outcomes included hemoglobin decline or postoperative hemoglobin concentration, blood loss, drainage volume, transfusion requirements, length of stay, operation time and surgery-related adverse effects such as wound infection, DVT and PE. Exclusion criteria comprised incomplete data, participants with a known allergy to TXA, severe cardiovascular dysfunction, history of thromboembolic event, renal failure or other contraindication to TXA.

Selection Criteria

The abstracts of the potential published reports were independently scanned by two reviewers (MJX and JX), after which full texts of the studies that met the inclusion criteria were screened and final decisions made. Disagreements were resolved by consulting a senior reviewer.

Data Extraction

Data were independently extracted from the included studies by two of the authors (MJX and JX). The corresponding authors were contacted to obtain missing data. The following data were extracted: first author names, published year, baseline for comparisons, intervention procedures, samples size, indications for transfusion, and outcome variables. Other relevant data were also extracted from individual articles.

Quality Assessment

Quality assessment of RCTs was based on the Cochrane Handbook[13] and performed by one reviewer, who assessed the details of the randomization procedures, allocation concealment, blinding and follow-up, each item being recorded as "Yes," "No," or "Unclear." "Yes" indicated a low risk of bias and "No" a high risk of bias. "Unclear" indicated a lack of information or unknown risk of bias. For non-RCTs, quality assessment was performed according to the Methodological Index for Non-Randomized studies (MINORs)[14], in which scores range from 0 to 24. Disagreement was resolved by consulting a third reviewer.

Data Analysis and Statistical Methods

Pooling of data was carried out with RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom). Statistical heterogeneity was assessed based on the values of P and I^2 using a standard χ^2 test. When $I^2 > 50\%$, $P < 0.1$, indicating significant heterogeneity, meta-analysis was performed using the random effects model. Otherwise, the fixed effects model was used. If possible, sensitivity analysis was conducted to determine the origins of any heterogeneity. Dichotomous outcomes are expressed as risk difference (*RD*) with 95% confidence intervals (*CI*s). For continuous outcomes, mean differences (*MD*s) and 95% *CI*s were calculated.

Results

Search Result

The initial search identified 468 studies. Scanning of the abstracts resulted in exclusion of 463 of these reports from this meta-analysis. No gray references were included. Finally, six articles reporting two RCTs[15,16] and four case-control studies (CCTs)[17–20] that had been published between 2011 and 2015 were selected for the present meta-analysis. These studies contained a total of 274 participants in the experiment groups and 293 control patients.

Assessment of Risk of Bias

Relevant patient characteristics provided in the included articles are summarized in Table 1. The Cochrane Handbook for Systematic Review of Interventions was consulted to assess the quality of RCTs. Both RCTs provide clear inclusion and exclusion criteria and the methodology used for randomization; randomization was computer-generated in one study[15]. None of them had concealed allocation by closed envelope or other techniques. Double blinding was implemented in both RCTs and one of them had attempted to blind assessors[15]. Intent–to-treatment analysis was not performed in the included RCTs; thus, there was a potential risk of type II statistical error. There was no unclear bias attributable to incomplete outcome data or selective outcome

TABLE 1 Relevant study characteristics

Studies	Year	Cases (T/C)	Mean age (T/C)	Female patient (T/C)	Prophylactic antithrombotic	Type of study indication for	Transfusion
Bagsby *et al*.[17]	2015	46/57	60.4/61.7	23/29	LMWH, NS	CCT	Hb less than 8 g/L or anemia symptom
Kelley *et al*.[19]	2014	51/70	69.8/67.2	36/45	Aspirin 325 mg, Bid	CCT	Hb less than 9 g/L or Hct less than 27%
Karam *et al*.[18]	2014	37/50	63.5/65.5	14/22	Aspirin 325 mg, Bid	CCT	Hb less than 8 g/L or anemia symptom
Dhillon *et al*.[20]	2011	52/56	65.8/67.2	34/36	LMWH, NS	CCT	Hb less than 9 g/L or Hct less than 27%
Karaaslan *et al*.[15]	2015	41/40	65.9/65.6	32/35	LMWH, 40 mg	RCT	Hb less than 10 g/L
MacGillivray *et al*.[16]	2011	20/20	62/66	13/15	Warfarin 2.5–5 mg	RCT	Hb less than 8 g/L

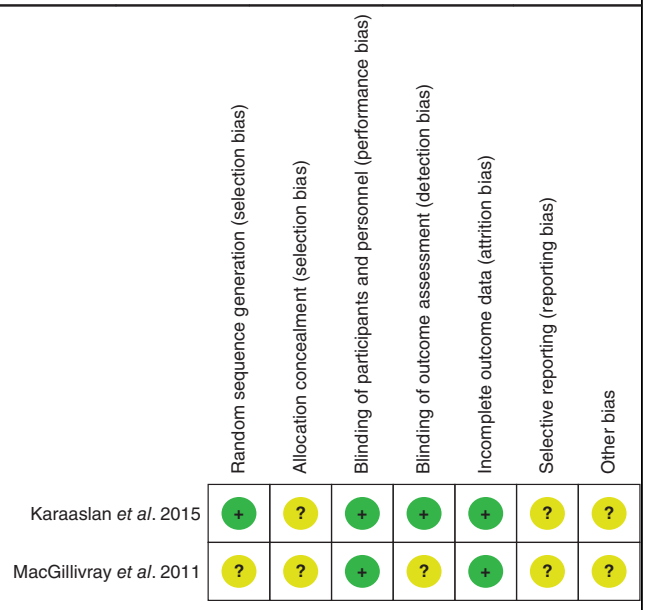
C, control; Hct, hematocrit; LMWH, low molecular weight heparin; NS, not state; T, tranexamic acid.

reporting in the RCTs. The MINORS scale was applied for non-RCTs. Quality assessment of methodologies is summarized in Tables 2 and 3.

Study Characteristics

The included studies had from 40 to 121 participants. Only studies of patients with sustained end-stage knee arthritis were included in this meta-analysis. Experimental groups had received i.v. TXA and control groups normal saline or nothing. Doses of TXA ranged from 10 g/L to 20 g/L. Only one study reported that bilateral TKA was performed by the same senior surgeon[16]. General anesthesia was used in three studies; the other studies did not provide this information. Tourniquets were routinely utilized in all studies[15–17]. In two studies a midline skin incision was followed by subvastus or medical parapatellar arthrotomy[15,17]. All the included studies indicated that cemented prostheses were used except for the study by Bagsby *et al.*[17]. A passive motion machine was used for early rehabilitation in two studies[15,17]. Postoperative drainage was used in all patients. Details of antithrombotic therapy are presented in Table 1. All studies reported indications for transfusion in detail, these being based on postoperative hemoglobin, hematocrit or anemia symptoms. All studies provided outcomes for at least 95% of the patients.

TABLE 2 Quality of methodology of the RCTs



+, low risk of bias; ?, unclear risk of bias.

Outcomes of Meta-analysis

Postoperative Hemoglobin Concentration

Postoperative hemoglobin concentrations were supplied for five studies[15–18,20]. No significant heterogeneity having been found, the fixed effects model was applied (χ^2 = 3.42, df = 4, I^2 = 0, P = 0.49). The difference between the two groups was significant (*MD* = 1.17; 95% *CI*, 0.90–1.44, $P < 0.01$; Fig. 2).

Transfusion Rate

Six studies reported the blood transfusion rate following bilateral TKA[15–20]. There being no significant heterogeneity (χ^2 = 9.23, df = 5, I^2 = 46%, P = 0.10), the fixed effects model was used. Pooling results demonstrated that the transfusion rate was significantly higher in the control than in the TXA groups (*RD* = −0.35, 95% *CI*, −0.42 to −0.27, $P < 0.01$; Fig. 3).

TABLE 3 Quality assessment of non-randomized trials

Variable	Bagsby *et al.*[17] 2015	Kelley *et al.*[19] 2014	Karam *et al.*[18] 2014	Dhillon *et al.*[20] 2011
A clearly stated aim	2	2	2	2
Inclusion of consecutive patients	2	2	2	2
Prospective data collection	2	2	2	2
Endpoints appropriate to the aim of the study	2	1	2	1
Unbiased assessment of the study endpoint	0	0	0	0
A follow-up period appropriate to the aims of study	2	2	1	2
Less than 5% loss to follow-up	2	2	2	2
Prospective calculation of the sample size	0	0	0	0
An adequate control group	2	2	2	2
Contemporary groups	1	1	1	1
Baseline equivalence of groups	2	2	2	2
Adequate statistical analyses	2	2	2	2
Total score	19	18	18	18

0, item not reported in the article evaluated; 1, reported but inadequately; 2, reported adequately.

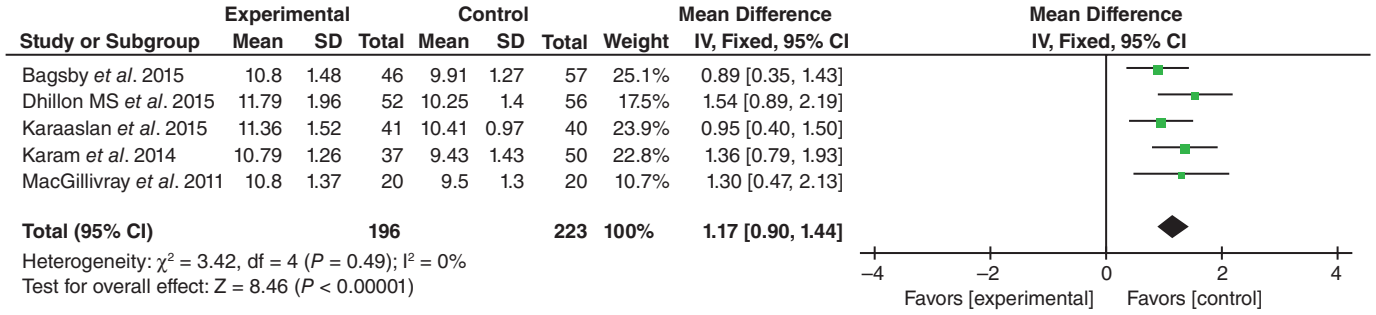


Fig. 2 Forest plot diagram showing effect of TXA on postoperative hemoglobin concentration.

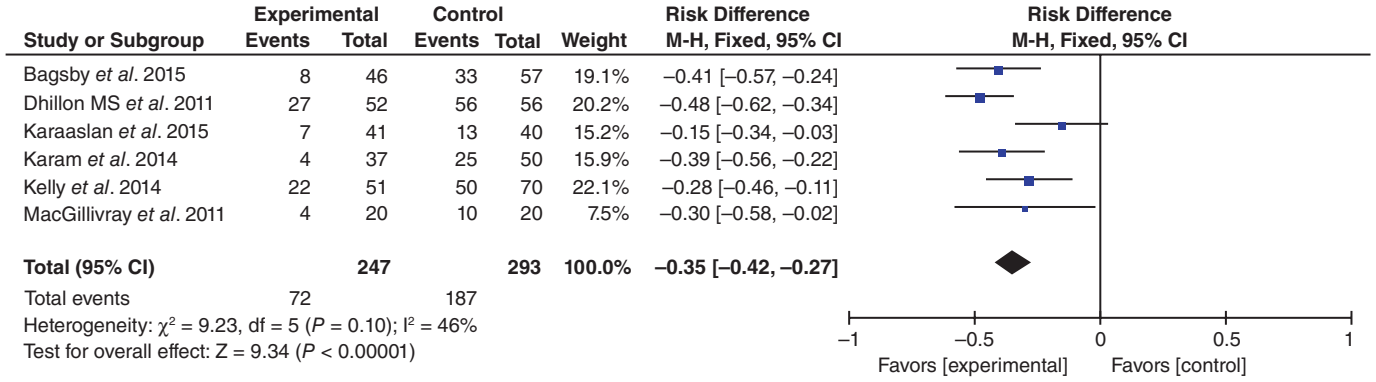


Fig. 3 Forest plot diagram showing effect of TXA on transfusion rate.

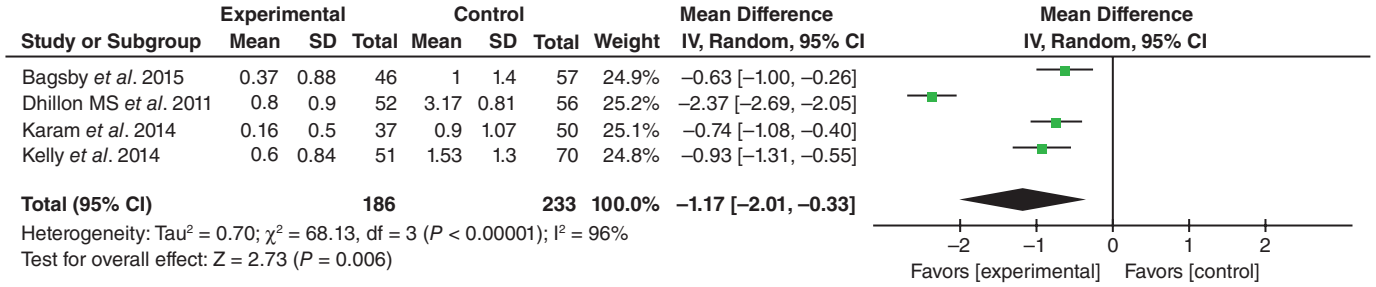


Fig. 4 Forest plot diagram showing effect of TXA on units transfused.

Units Transfused

Units transfused were shown in four studies[17–20]. Significant heterogeneity being found, the random effects model was applied (χ^2 = 68.13, df = 3, I^2 = 96%, P < 0.01). The difference between the two groups was statistically significance (MD = −1.17, 95% CI, −2.01 to −0.33, P = 0.006; Fig. 4).

Drainage Volume

Drainage volume was provided in two studies[19,20]. No significant heterogeneity being found, the fixed effects model was used (χ^2 = 0.74, df = 1, I^2 = 0%, P = 0.39). Drainage volume was significantly higher the in control than in the TXA groups (MD = −547.82, 95% CI, −608.71 to −486.92, P < 0.01; Fig. 5).

Operation Time

Operation time was reported in two studies[17,18]. No significant heterogeneity being found, the fixed effects model was used (χ^2 = 0.22, df = 1, I^2 = 0%, P = 0.64). There was no significant heterogeneity between the two groups (MD = − 0.75, 95% CI, −6.82 to 5.31, P = 0.81; Fig. 6).

Length of Hospital Stay

Two studies reported the length of hospital stay according to group[17,18]. Significant heterogeneity was shown for pooled results, thus the random effects model was used (χ^2 = 4.57, df = 1, I^2 = 78%, P = 0.03). The difference between the groups was not significant (MD = 0.11, 95% CI, −0.22 to 0.45, P = 0.66; Fig. 7).

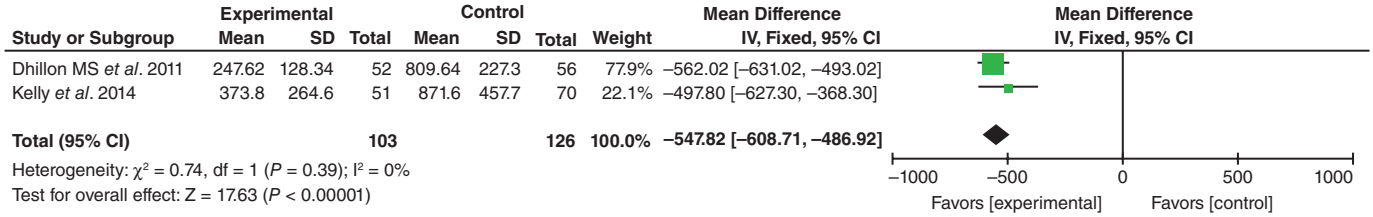


Fig. 5 Forest plot diagram showing effect of TXA on drainage volume.

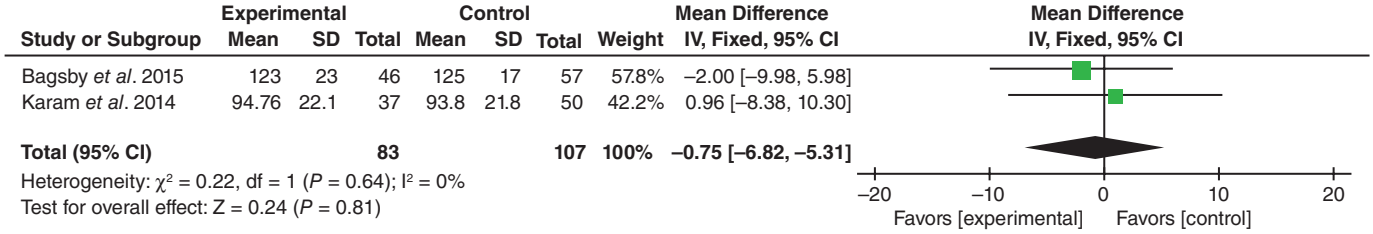


Fig. 6 Forest plot diagram showing effect of TXA on operation time.

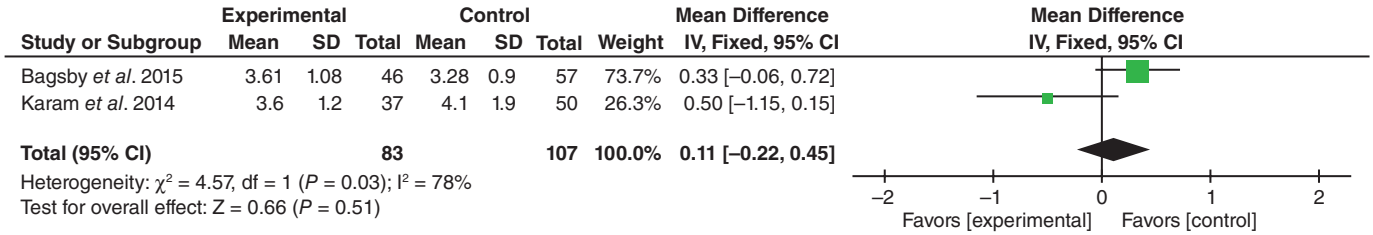


Fig. 7 Forest plot diagram showing effect of TXA on length of stay.

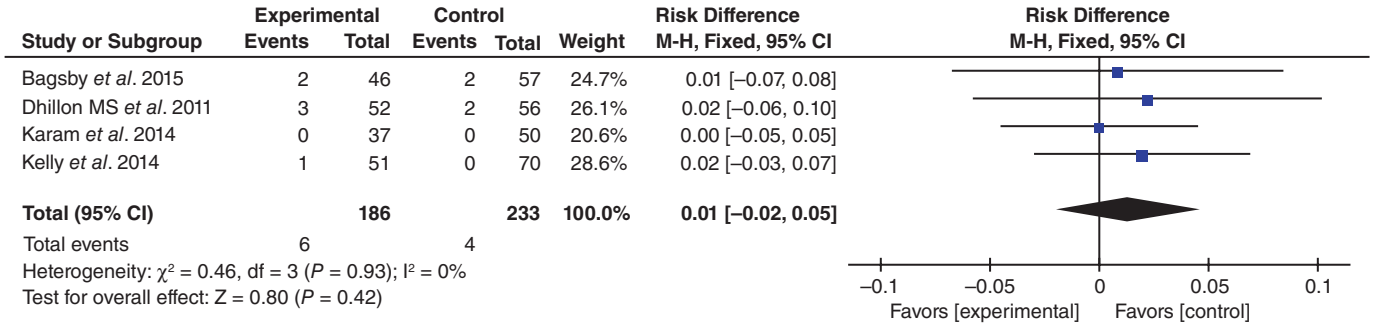


Fig. 8 Forest plot diagram showing effect of TXA on risk of wound infection.

Wound Infection

Wound infection was reported in four studies[17–20]. No significant heterogeneity being found, the fixed effects model was used (χ^2 = 0.46, df = 3, I^2 = 0%, P = 0.93). The difference between the two groups was not significant (RD = 0.01, 95% CI, −0.02 to 0.05, P = 0.42; Fig. 8).

Deep Vein Thrombosis

Six articles reported the incidence of DVT following bilateral TKA[15–20]. The fixed effects model was used because of the significantly low heterogeneity (χ^2 = 1.80, df = 5, I^2 = 0%, P = 0.88). No significant difference was found between groups (RD = 0.00, 95% CI, −0.02 to 0.03, P = 0.88; Fig. 9).

Pulmonary Embolism

PE was reported in six studies[15–20]. No significant heterogeneity being found, the fixed effects model was used (χ^2 = 0.77, df = 5, I^2 = 0%, P = 0.98). There was no significant difference between the two groups (RD = 0.00, 95% CI, −0.02 to 0.02, P = 0.11; Fig. 10).

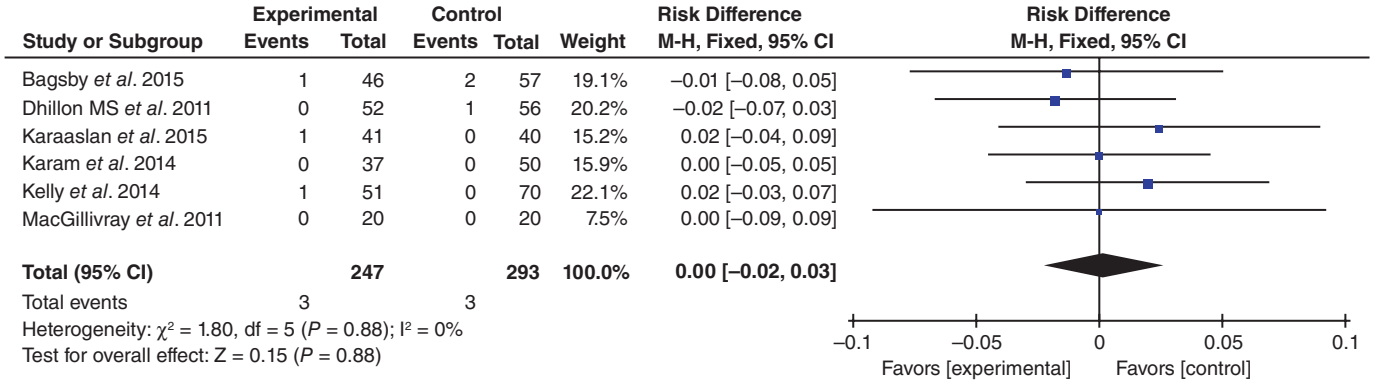


Fig. 9 Forest plot diagram showing effect of TXA on risk of DVT.

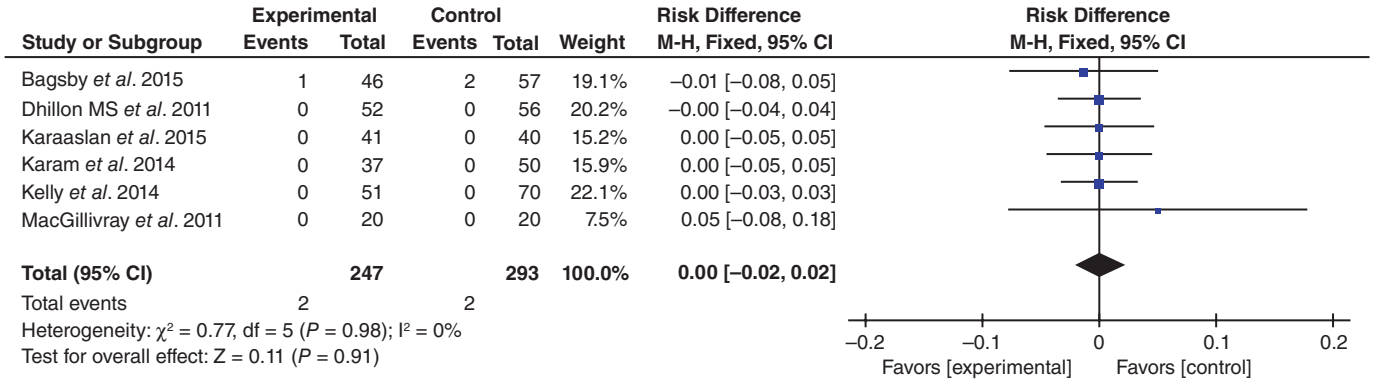


Fig. 10 Forest plot diagram showing effect of TXA on risk of PE.

Discussion

New Discoveries in the Current Meta-analysis

To our knowledge, this is the first systematic review and meta-analysis evaluating efficiency and safety of i.v. tranexamic acid in bilateral TKA. The most important finding of this-analysis is that i.v. tranexamic acid in bilateral TKA reduces postoperative hemoglobin decline, transfusion requirements and drainage volume with no identified increased risk of infection, DVT or PE. Furthermore, no TXA-related adverse effects were identified.

Six studies were included in the current meta-analysis, two of which were RCTs. However, both RCTs had methodological weaknesses that influenced the strength of point estimates. Both RCTs were of overall good methodologic quality. Randomization was reported in both RCTs; however, only one mentioned the randomization method[15]. Both provided a methodology for the blinding of participation and one of them attempted to blind the assessors. Intent-to-treat analysis was not performed in either RCT; thus, type II statistical error potentially influenced their results[8]. We also included non-RCTs because there were so few published RCTs. This inclusion would, to some extent, have decreased the level of evidence of this meta-analysis and should be taken into consideration when analyzing the pooling results. Though we searched the selected electronic databases systematically, language and publication bias may have resulted in omission of some report. In addition, all eligible studies were relatively small.

Controversy Concerning Simultaneous Bilateral TKA

The aging of the population has contributed to the increased incidence of knee osteoarthritis. Approximately 10% of patients undergo contralateral TKA in the years following a unilateral TKA[11]. Simultaneous bilateral TKA is considered superior to staged unilateral TKA in terms of lower surgical cost, shorter total length of stay, earlier rehabilitation, better knee function outcome and lower incidence of postoperative complications; it is thus frequently performed for bilateral knee osteoarthritis[21]. However, this procedure is characteristically associated with substantial blood loss, and consequently high transfusion requirements. Allogeneic blood transfusion carries infective and non-infective risks[22]. Autologous blood transfusion is an alternative strategy; however, this is a high-cost procedure with multiple difficulties for some medical centers. Blood loss management is still one of the foremost issues for surgeons, especially in major operations such as joint replacement.

Advances in Hemostatic Agents

Recently, hemostatic agents such as Floseal hemostatic matrix (Baxter International, Chicago, IL, USA), aprotinin and TXA have attracted our attention because of their high efficiency and cost-effectiveness, as reported in several studies[18,23,24]. TXA, a known antifibrinolytic agent, has commonly been used in surgical procedures because of its low cost and allergenicity. Several high quality RCTs have confirmed better outcomes using TXA in unilateral TKA. However, blood loss is expected to be higher following bilateral TKA[25,26]. Bleeding can flow into soft tissues around the knee joint, causing pain and stiffness and prolonging length of stay and duration of rehabilitation[27]. Furthermore, prolonged bed time increases the risk of thrombotic events. The current meta-analysis indicates that i.v. TXA significantly reduces blood loss following simultaneous bilateral TKAs. Additionally, postoperative hemoglobin and hematocrit are significantly higher in TXA than control groups.

Clinical Effect of TXA in Bilateral TKA

Substantial previous reports have shown that estimated total blood loss in patient undergoing unilateral TKA without antifibrinolytics ranges from 761 to 1784 mL and 7.7%–18.93% of these patients require transfusion[28–35]. Obviously, bilateral TKA is more commonly associated with perioperative blood loss and associated with higher blood transfusion rates and number of units transfused than is unilateral TKA. Transfusion is considered undesirable because of the associated risks of various adverse reactions. The current meta-analysis shows that i.v. administration of TXA significantly reduces the transfusion rate and units transfused following simultaneous bilateral TKAs.

Prolonged confinement to bed and operation times increase operation costs. More importantly, adverse events such as hypostatic pneumonia, DVT and PE increase morbidity and mortality. Early weight bearing and rehabilitation has proven to contribute to better functional outcomes after TKA. The present meta-analysis indicates that i.v. TXA does not prolong time confined to bed or operation time following simultaneous bilateral TKAs.

Wound infection occurs; however, it is disastrous for patients once it happens and may necessitate revision surgery. Moreover, sinus formation following inflammatory reactions leads to delayed union and poor joint function outcomes. The current meta-analysis did not identify a significant difference in incidence of infection, which was 6/186 in the TXA groups and 4/233 in the controls. The overall incidence was 2.39%, which is in accordance with previous reports of 1%–3%[36]. However, there was a tendency toward higher risk of infection in the intervention group. Large sample size and high quality trails are required to further explore the correlation between infection and use of TXA.

DVT is a common complication of TKA and may lead to PE and even death. All participants in the assessed studies received routine prophylactic antithrombotic therapy. Previous studies have reported that there is a higher risk of developing DVT and PE when TXA is used, possibly because antifibrinolytic agents theoretically increase the risk of clotting[37]. However, in the present analysis, we found no significant differences in incidence of DVT or PE between groups.

Current Limitations of this Meta-analysis

This meta-analysis had several potential limitations that should be noted. (i) Only six studies were included, four of which were non-RCTs and the sample sizes were relatively small. (ii) Some outcome variables such as total blood loss and range of motion were not fully described, preventing us from subjecting them to meta-analysis. (iii) The small numbers of participants in the included studies prevented us from performing subgroup analysis; we therefore could not identify the source of heterogeneity. (iv) The short-term follow- ups may have led to underestimation of complications. (v) Publication bias is an inherent weakness of all meta-analysis.

TXA has been used in surgical field for more than 50 years. Recently, substantial studies have shown the efficiency of TXA in primary unilateral TKA. TXA in bilateral TKA has seldom been reported. Despite the above limitations, this is the first meta-analysis to pool the results from controlled clinical trials to evaluate the efficiency and safety of i.v. TXA in simultaneous bilateral TKA. Well-designed, long-term follow up of RCTs is needed to explore the optimal dose and adverse effects.

Conclusions

Intravenous administration of TXA in simultaneous bilateral TKA could reduce postoperative hemoglobin decline, drainage volume and transfusion requirements and would not prolong the length of stay or operation time. Moreover, no adverse effects, such as infection, DVT or PE were associated with TXA. We believe that TXA demonstrates excellent clinical efficacy and safety in simultaneous bilateral TKAs.

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