Int J Clin Exp Med 2019;12(1):67-77
www.ijcem.com /ISSN:1940-5901/IJCEM0075515

Review Article

Best strategy of thromboembolic prophylaxis after knee arthroscopy: a systematic review and meta-analysis of 9 randomized trials

Zhen Lyu[1*], Bing Li[1*], Xiaofei Zhang[1], Bo Li[1], Xinglong Ma[2], Jinxing Ma[2], Jun Liu[1]

[1]*Department of Joint Surgery, Tianjin Hospital, Tianjin, China;* [2]*Orthopedic Institute of Tianjin, Tianjin, China.*
[*]*Equal contributors.*

Received March 6, 2018; Accepted October 9, 2018; Epub January 15, 2019; Published January 30, 2019

Abstract: Introduction: Currently, prevention of deep vein thrombosis after arthroscopic knee surgery is in dispute. The aim of this study was to conduct a meta-analysis of all randomized controlled trials published, determining whether anticoagulation should be performed after knee arthroscopies (KA). Materials and methods: A comprehensive literature search was conducted through October 24, 2017. PubMed, Embase, Web of Science, Cochrane Library, CISCOM, CINAHL, and Google Scholar databases were searched. The aim was to determine the relationship between the use of different chemical anticoagulation strategies and the risk of deep venous thrombosis after knee arthroscopies. A meta-analysis of pooled and stratified data was performed and assessed using Mantel-Haenszel fixed effects models. Results: A total of nine randomized clinical trials met the eligibility criteria and were included for quantitative analysis. Thromboprophylaxis was shown to significantly decrease the risk of symptomatic DVT (P = 0.914, 95% CI = 0.10-0.22) and asymptomatic distal DVT (P = 0.107 95% CI = 0.18–0.45) after KA. There was no significant association between anticoagulation drugs and risk of bleeding events (P = 0.092, 95% CI = 0.56-1.06). Use of LMWH after KA may significantly reduce the risk of distal asymptomatic DVT. Three kinds of chemical prevention measures can reduce incidence of symptomatic DVT, without increasing the risk of bleeding events. Conclusion: The present study confirms that thromboprophylaxis after arthroscopic surgery is significant, without increasing the risk of bleeding events. Oral antithrombotic drugs are a better prophylactic strategy than subcutaneous injections of LMWH.

Keywords: Thromboprophylaxis, LMWH, rivaroxaban, aspirin, knee arthroscopy, meta-analysis

Introduction

Knee arthroscopy (KA) is the most common orthopedic procedure performed on a day-care setting, with more than 5 million procedures per year in Western countries [1, 2]. Venous thromboembolism (VTE) is a common and clinically relevant complication to major orthopedic surgery. However, it has been considered rare in the setting of elective knee arthroscopy based on reported retrospective articles [3-5]. Some reports have reported that incidence of objectively proven deep-vein thrombosis (DVT) after KA ranges from 0.6% to 18% (symptomatic DVT 0% to 1%) [6-8], without thrombus prophylaxis [9-12]. Recently, a large population case-control study reported a 18-fold increased risk of DVT in the first three months following KA [13]. Common clinical symptoms of DVT include unilateral leg swelling, skin temperature rise, or positive Homan examination. The most serious clinical manifestation is the emergence of fatal pulmonary embolism (PE), which is difficult to diagnostic.

Whether drug therapy can reduce the risk of VTE has been the focus of much attention. Some randomized trials have demonstrated efficacy in this regard. Marlovits [7] found that the use of subcutaneous low molecular weight heparin (LMWH) can reduce incidence of DVT after arthroscopic surgery to 2.8%, while incidence of the control group was 41.2%. Michot [14] reported that incidence of DVT can be effectively reduced to 1.5% using LMWH, while incidence of the control group was 15.6%. Compared with subcutaneous low molecular weight heparin, aspirin can be given orally, with

Table 1. Characteristics of included studies in this meta-analysis

Author	Year	Experiment Group			Control Group			Intervention (dose first dose after surgery)		Type of study	Diagnoses of DVT	Follow up
		Age	M/F	BMI	Age	M/F	BMI	Experiment	Control			
Delis [12]	2001	45.0	60/42	27.6	44.4	60/42	26.8	Oral Aspirin 300 mg daily 7 days	No treatment	RCT	CFD	118 days
Kaye [31]	2015	46.0	38/28	27.2	43.4	66/38	26.8	Oral Aspirin 325 mg daily 14 days	No treatment	RCT	Ultrasound	7/28 days
Camporese [32]	2016	44.9	78/44	27.6	45.9	84/35	28.1	Oral Rivar-oxaban 10 mg daily 9hours	Placebo	RCT	CCDU	90 days
Munoa [33]	2012	52.4	149/88	27.8	55.7	53/27	29.3	Oral Rivar-oxaban 10 mg daily 6-8 hours	Placebo	RCT	__	30/90 days
Marlovits [14]	2007	29.9	45/27	23.7	30.2	37/31	24.4	Subcutaneous LMWH 40 mg daily 3-8 days	No treatment	RCT	MRV	28 days
Camporese 1 [34]	2008	41.9	406/251	25.3	42.3	412/248	25.5	Subcutaneous LMWH 3800 IU anti-Xa 7 days	Placebo	RCT	Ultrasound	90 days
Camporese 2 [34]	2008	42.5	273/171	25.5	42.3	412/248	25.5	Subcutaneous LMWH 3800 IU anti-Xa 14 days	Placebo	RCT	Ultrasound	90 days
Wirth [35]	2001	37.6	81/36	26.1	28.5	98/24	25.9	Subcutaneous LMWH 1750 IU anti-Xa 14 days	No treatment	RCT	Ultrasound	90 days
Michot [7]	2002	42.0	40/26	26.2	46.5	46/18	27.8	Subcutaneous LMWH 2500 IU anti-Xa 14 days	Placebo	RCT	Ultrasound	12/31 days

RC: Randomized controlled trial; CFD: Colour Flow duplex; CCDU: colour-coded Doppler Ultrasound; MRV: Magnetic Resonance Venography.

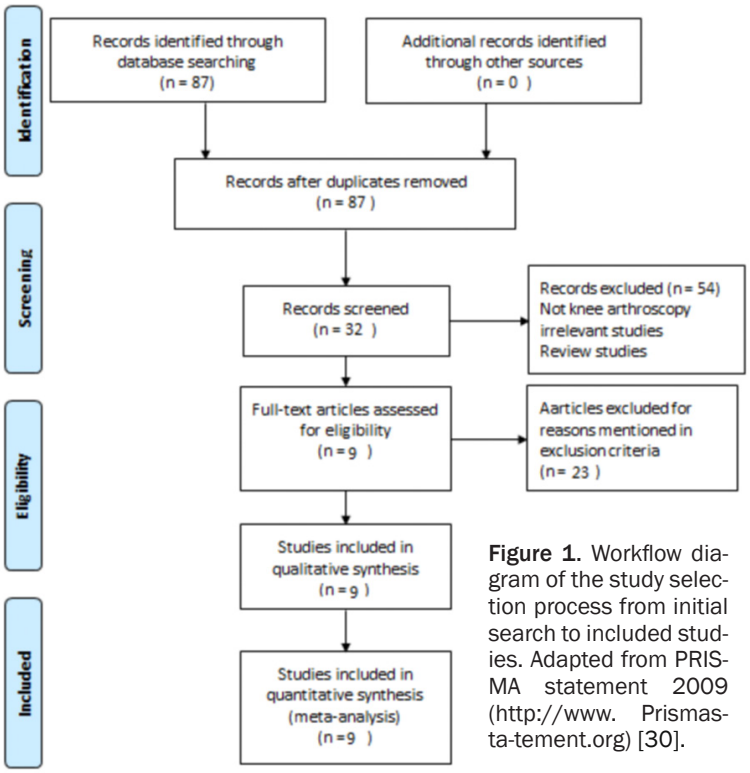

Figure 1. Workflow diagram of the study selection process from initial search to included studies. Adapted from PRISMA statement 2009 (http://www. Prismasta-tement.org) [30].

Table 2. Results of anticoagulation VS. control groups

	P value	RR	95% CI
Symptomatic DVT	0.914	0.14	(0.10–0.22)
Asymptomatic Distal DVT	0.107	0.28	(0.18–0.45)
Bleeding events	0.092	0.77	(0.56-1.06)

decreased costs, and decreased risk of bleeding. It has good preventive effects, having been successfully used in orthopedic surgery VTE prophylaxis [15, 16]. The American Academy of Orthopedic Surgeons and the American College of Chest Physicians have included aspirin as an acceptable form of chemoprophylaxis against VTE following hip and knee arthroplasty. An RCT by Kaye found that the use of aspirin in a low-risk population undergoing arthroscopic knee surgery was not warranted [17]. Rivaroxaban is a highly selective direct factor-Xa inhibitor. It has been approved for VTE prevention after orthopedic operations. It has been used in non valvular atrial fibrillation patients to treat and prevent strokes [18-20]. Recently, new oral drugs, such as rivaroxaban, have been shown to improve results from thromboprophylaxis in patients undergoing knee arthroscopy surgery [21-24].

Although the risk of deep venous thrombosis (DVT) after knee arthroscopy is a real problem, some studies have suggested that chemical prophylaxis could reduce the risk of VTE. Some articles have recommended the use of antithrombotic drugs [25] after arthroscopic knee surgery to prevent thrombosis, because of a lack of medicine-based evidence. Several countries and international organizations, including the American College of Chest Physicians, recommend that young low-risk patients after knee arthroscopic surgery do not use anticoagulant drugs. Similarly, the American Association of Orthopedic Surgeons has not objected to the use of preventative drugs after knee arthroscopies. The present meta-analysis analyzed the incidence of DVT, bleeding events, and other aspects, comparing a variety of anticoagulant drugs on the prevention of deep vein thrombosis. The aim was to provide evidence-based medical evidence for the development of clinical standard guidelines.

Methods

Data sources and searches

A comprehensive literature search was conducted up through October 24, 2017 using PubMed, Embase, Web of Science, Cochrane Library, CISCOM, CINAHL, and Google Scholar databases. Previous meta-analyses and abstracts/presentations from annual meetings about antithrombotic therapy and prevention of thrombosis (American College of Chest Physicians Evidence-Based Clinical Practice Guidelines) were also screened. All research articles published with a combination of the following search terms were matched: “Aspirin”, “Factor Xa inhibitors”, “Low molecular weight

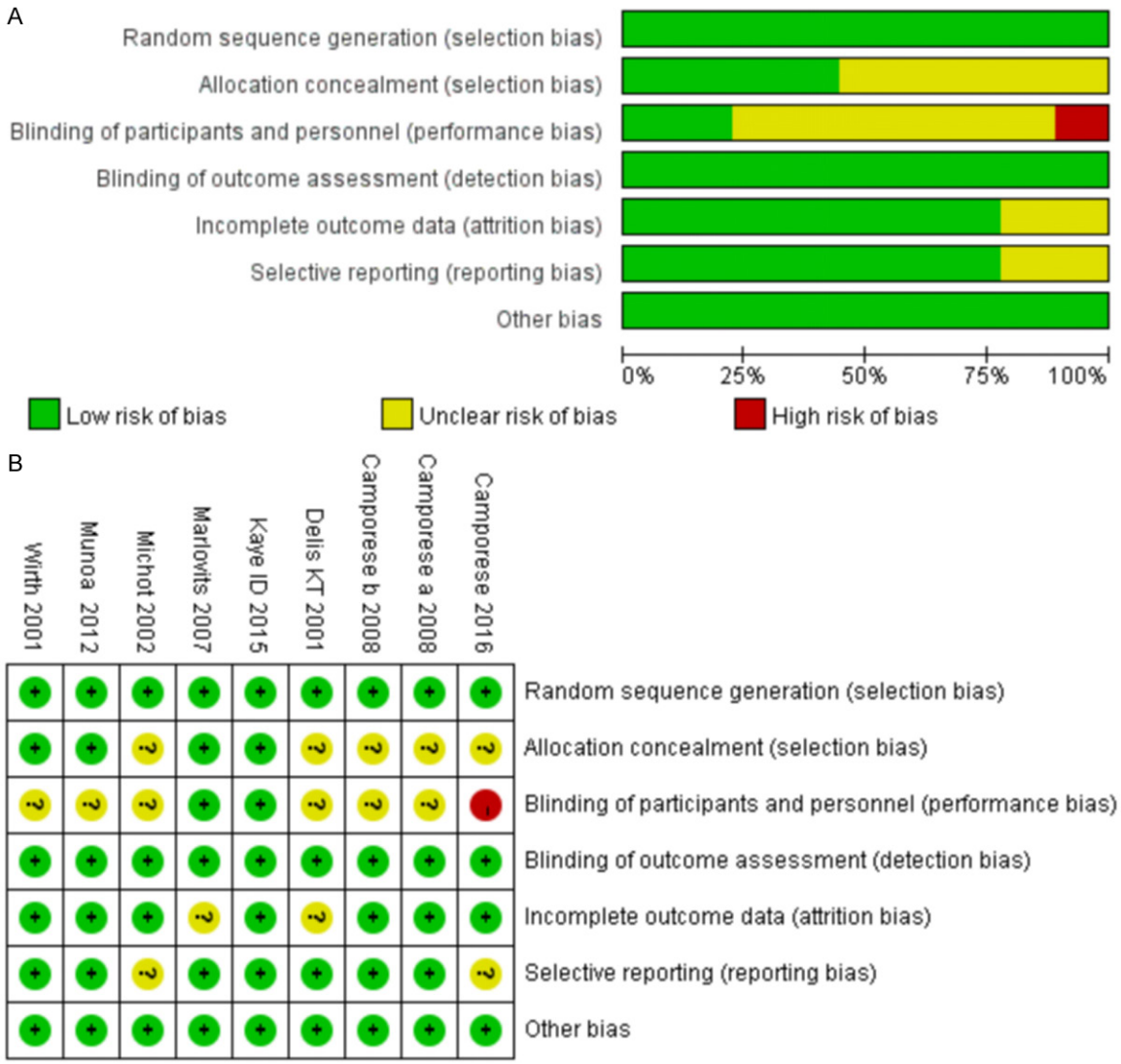

Figure 2. Quality assessment of included studies using QUADAS-2 tool criteria. A. Each risk of bias item is presented as percentages across all included studies; B. Each risk of bias item for each included study.

heparin", "thrombosis", "knee arthroscopy", and "Randomized trials". No language, date, or other publication restrictions were imposed. The most updated/inclusive data on each study was used for abstraction. Reference lists of relevant studies were also scanned.

Selection criteria and quality assessment

Inclusion criteria were: 1) Human studies; 2) RCTs comparing the effect and safety of a single anticoagulant drug to a control group with a placebo or no treatment; 3) Studies reporting re-specified outcomes of interest; and 4) RCTs concerning post-knee arthroscopic surgery. Exclusion criteria were: 1) Non-randomized registries; 2) Several anticoagulants were used in combination of the experimental group; 3) The control group used anticoagulants; 4) Upstream administration by study design of another anticoagulant prior to randomization; and 5) Follow-up was not relevant to the meta-analysis.

The present study used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to evaluate the quality of included studies. Details of evidence profiles for outcomes are presented in **Table 2**. GRADE level of evidence was high for symptomatic deep vein thrombosis and asymptomatic

Table 3. Subgroup analysis results of anticoagulation VS. control groups

	P value	RR	95% CI
Symptomatic DVT			
Oral	0.824	0.12	(0.04–0.32)
Aspirin	0.826	0.15	(0.03–0.62)
Rivaroxaban	0.435	0.09	(0.02–0.36)
LMWH	0.709	0.14	(0.09-0.22)
Asymptomatic Distal DVT			
Oral	0.262	0.51	(0.26-0.98)
Aspirin	0.721	0.90	(0.40-2.39)
Rivaroxaban	0.090	0.13	(0.03–0.49)
LMWH	0.939	0.19	(0.10-0.36)
Bleeding events			
Oral	0.409	0.78	(0.28-2.17)
Rivaroxaban	0.683	0.58	(0.19-1.71)
LMWH	0.092	0.77	(0.56-1.06)

distal symptomatic thrombosis. Scores were mid-level for clinically relevant non-major bleeding events.

Quality assessment of studies was conducted using QUADAS-2 tool criteria. One study was considered to be at high risk of bias. Eight studies had an unclear risk of bias. High risk of bias was based on the use of blinding of participants and personal reasons (performance bias). Details of the risk of bias for each study are presented in **Figure 2**.

Statistical analysis

To examine the strength of anticoagulant drugs preventing thrombosis after knee arthroscopy surgery, pooled odds ratios (ORs) and their corresponding 95% confidential intervals (CIs) were estimated for each study. Subgroup analysis was also performed by drug (defined as aspirin, rivaroxaban, and LMWH) and by the method (defined as oral and subcutaneous) for thrombosis with anticoagulant drugs.

Departure of frequencies of thrombosis with anticoagulant drugs after knee arthroscopy surgery was calculated by Chi-squared tests for the controls. Forest plots were created to visually assess major contributors to heterogeneity. Possible publication bias was tested using Begg's [26] funnel plot and Egger's [27] regression test ($P < 0.5$ indicates statistically significant publication bias). Sensitivity analysis was performed to examine the impact on individual studies. Odds ratios (ORs) and a 95% confidence intervals (95% CIs) were used to determine whether a fixed or random-effects model [28] would be applied. For *p* values of 0.05 and 50%, between-study heterogeneity was considered to be significant and a random-effects model was used to calculate the OR. If no significant heterogeneity was observed, a fixed-effects model was used (DerSimonian-Laird method). I^2 statistics was employed to quantify inter-study variability, with larger values suggesting an increased degree of heterogeneity [29].

All statistical analyses in this study were performed using the statistical software package Stata (Stata Statistical Software: release 11.0 College Station, TX, StataCorp. LP).

Results

Study search

Figure 1 presents a detailed summary of the study selection process. Of the 87 articles screened, 79 were excluded according to exclusion criteria. A total of 9 randomized clinical trials met the eligibility criteria and were included for quantitative analysis.

Study characteristics

Study characteristics of included studies are presented in **Table 1**. Of the randomized controlled trials, two used aspirin, two used rivaroxaban, and five used LMWH. Each randomized controlled trial was reviewed. Data was extracted for the following elements: author, year, age, gender, BMI, intervention (dose first dose after surgery), type of study, diagnoses as DVT, and follow up. Prophylactic agents were as follows: 1) Aspirin (oral aspirin 300 mg daily); 2) Rivaroxaban (oral rivaroxaban 10 mg daily); and 3) Low molecular-weight heparin (LMWH) (1. Subcutaneous LMWH 3000-3800 IU anti-Xa 7 days, 2. Subcutaneous LMWH 1750-2500 IU anti-Xa14 days).

Symptomatic DVT

Nine randomized controlled trials, including 2,931 participants, compared anticoagulation drugs with placebo or no treatment. Anticoagulation drugs were associated with a signifi-

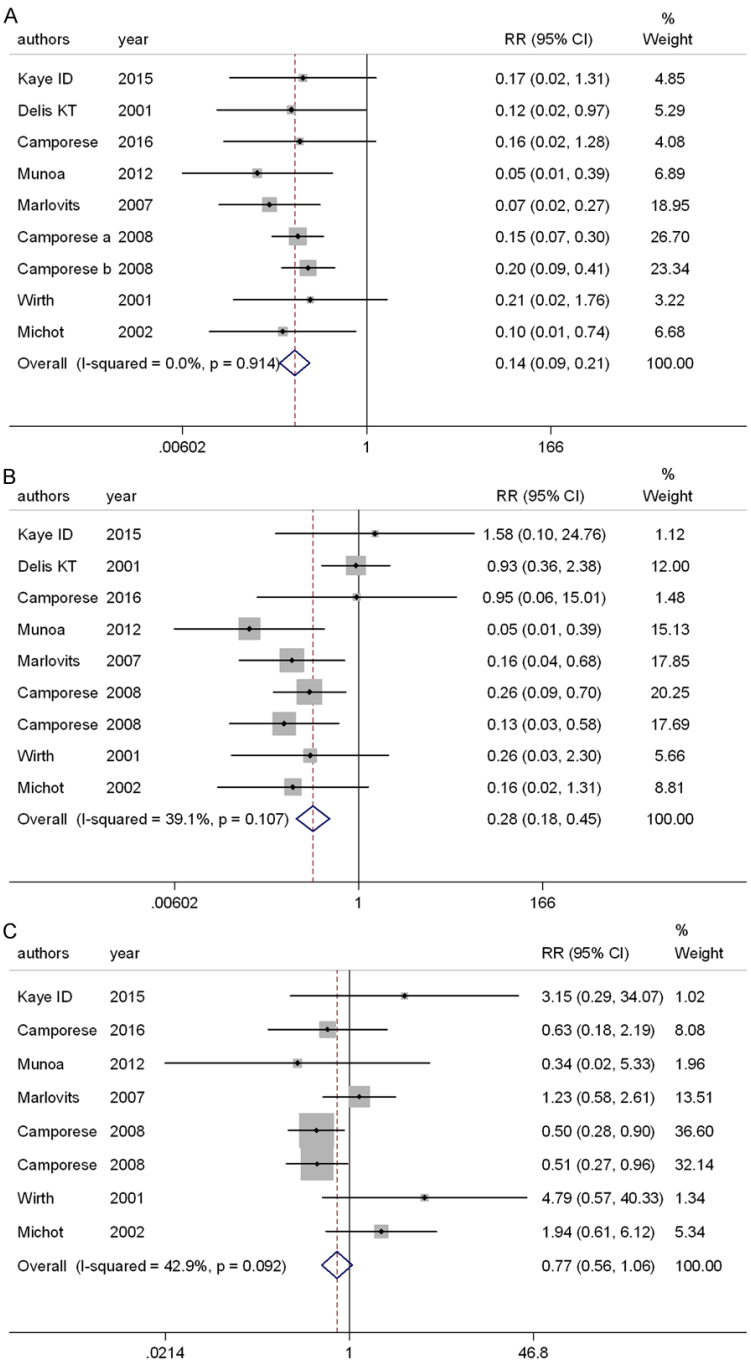

Figure 3. Odds ratio of primary analysis associated with anticoagulation vs. control therapy. (A) Symptomatic DVT, (B) Asymptomatic Distal DVT (C) Bleeding events.

cant decrease in risk of Symptomatic DVT (relative risk (RR) = 0.14, 95% CI 0.10 to 0.20, P = 0.914; I^2 = 0%; **Table 2**; **Figure 2**).

Asymptomatic distal DVT

In nine randomized controlled trials, including 3,023 participants, anticoagulation drugs were associated with a significant decrease in the risk of asymptomatic distal DVT (RR = 0.28, 95% CI 0.18 to 0.45 P = 0.107; I^2 = 39.1%; **Table 2**; **Figure 2**).

Bleeding events

Since an aspirin experiment did not report a bleeding event, a total of eight studies were included in this meta-analysis. There was no significant association with anticoagulation drugs and risk of bleeding events (RR = 0.77, 95% CI 0.56 to 1.06, P = 0.092; I^2 = 42.9% **Table 2**; **Figure 2**).

Subgroup analysis

Subgroup analysis, according to the type of anticoagulant drugs and routes of administration, was performed (**Table 3**). Three kinds of anticoagulation drugs were associated with a significant decrease in risk of symptomatic DVT. Aspirin and rivaroxaban showed no significant decrease in the risk of asymptomatic distal DVT. LMWH significantly decreased the risk of thrombosis. Oral anticoagulation drugs did not decrease thrombosis risk while subcutaneous anticoagulation drugs did decrease thrombosis risk (**Table 3**; **Figure 3**). There was no significant association for anticoagulation drugs and risk of bleeding events in oral and subcutaneous groups (**Table 3**).

Heterogeneity and publication bias

Heterogeneity in terms of ORs of rivaroxaban was found in asymptomatic distal DVT subgroup analysis. Since *P* values were < 0.5, a fixed effects model was used.

Publication bias causes a disproportionate number of studies with positive results, reducing accuracy and reliability of meta-analyses.

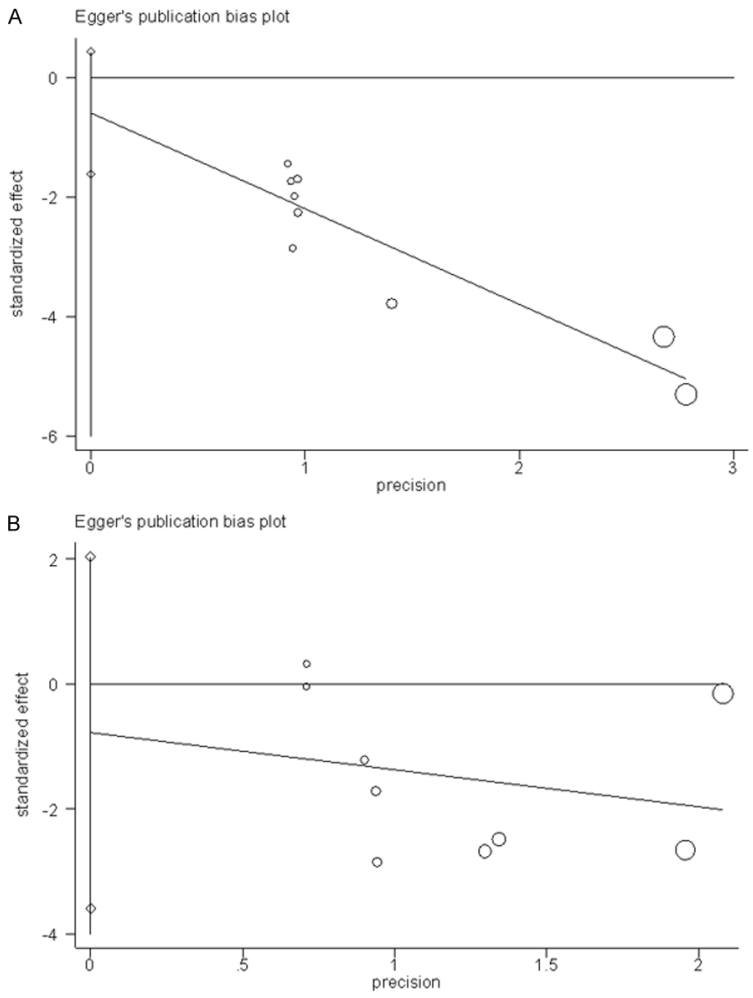

Figure 4. Egger's funnel plot of symptomatic DVT (A) and asymptomatic distal DVT (B) and anticoagulation drugs after KA in the dominant model. Each circle represents an individual study, while the circle size is proportional to the study weight. Logger natural logarithm of odds ratio.

There was no evidence of publication bias found in the present meta-analysis (**Figure 4**).

Sensitivity analyses for pooled studies

Sensitivity analysis concerning the association of anticoagulation drugs and thrombosis risk was performed to assess the impact of each study on pooled ORs. Results suggest that pooled ORs were not altered by the omission of any individual study (**Figure 5**).

Discussion

According to pooled statistical analysis, incidence of symptomatic deep venous thrombosis (DVT) in patients receiving a knee arthroscopy was highly dependent on the use of the anticoagulant prophylactic treatment. Specifically, incidence of DVT was 12.1% with no treatment and only 1.5% with anticoagulant prophylactic treatment. This equated to a reduction of 10.6% in patients developing DVT. These findings were in accord to those reported by Adele in 2011 [36]. Using aspirin, the incidence of symptomatic DVT after knee arthroscopy was reduced to 0.6%, while that of the control group was 4.3%. Regarding aspirin, both rivaroxaban and low molecular weight heparin (LMWH) significantly reduce incidence of symptomatic DVT after knee arthroscopies, 0.6-10% less than controls. It was concluded that anticoagulant therapy after knee arthroscopies can indeed reduce incidence of DVT. The present study revealed that incidence of symptomatic DVT in patients treated with aspirin and rivaroxaban was 0.6%. In contrast, it was 1.7% with LMWH. The effects of oral anticoagulants seemed to be better with thromboembolic prophylaxis, only in terms of incidence. However, there is a lack of randomized controlled trials to support this conclusion. In general, symptomatic DVT after knee arthroscopy is rare [7, 14, 32-35]. To the best of our knowledge, all current publications confirm that LMWH can prevent thrombosis. There are no reports on thromboprophylaxis of oral anticoagulants. Low-cost LMWH not only reduces thromboembolic events during knee arthroplasty but also during knee arthroscopy. However, LMWH requires subcutaneous injections and is, therefore, only cost-effective if the patient or caregiver can inject the drug at home [37, 38]. Oral anticoagulants could be used as an alternative.

Clinical manifestations of asymptomatic distal DVT include unilateral leg swelling, skin tem-

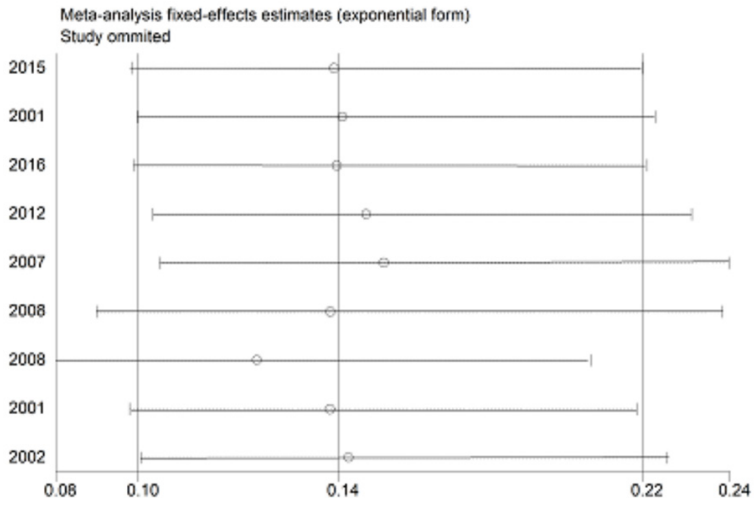

Figure 5. Sensitivity analysis of summary odds ratio coefficients on incidence of DVT after KA and anticoagulant prophylaxis with susceptibility to osteoarthritis under the dominant mode.

perature rise, redness, and a positive Homan examination, which can be checked and confirmed by color ultrasonography [32]. Incidence of asymptomatic DVT in the anticoagulant-treated group was 1.2%, 3.8% lower than the control group of patients that did not receive treatment (**Table 2**). Williams reported a higher detection rate of 3.5% for asymptomatic distal DVT within two weeks after knee arthroscopy without anticoagulant therapy [8]. The discrepancy between these studies is likely due to differences in follow-up times, as the average follow-up time in the literature is 30 days. Compared to the control group, LMWH had a significant eightfold lower incidence of asymptomatic distal DVT in patients that received anticoagulant therapy (0.9%) (P = 0.939, 95% CI 0.10 to 0.36). Results remained ambiguous on whether the two oral anticoagulants, aspirin and rivaroxaban, can reduce incidence of asymptomatic distal DVT since no significant differences were observed between control and treatment groups.

Minor complications caused by antithrombotic drugs, such as minor bleeding, wound hematoma, and even re-operation due to bleeding [39], are unpredictable [31]. Wirth [35] reported a higher incidence of bleeding events in the experimental group, compared to the control group. The present study, however, found no statistically significant correlation between the use of anticoagulant prophylactic treatment and bleeding incidence.

Limitation

Even though the present meta-analysis has demonstrated that anticoagulant therapy is beneficial after knee arthroscopies, this study only included nine randomized controlled trials. Also, there were only four studies regarding rivaroxaban or aspirin use and the strength of evidence for subgroup analyses was not high. Moreover, the use of anticoagulant drugs differed between studies but were within the scope of clinical recommendations. However, this may have led to heterogeneity between groups. Moreover, the duration of follow-ups in each study was different. For LMWH and rivaroxaban, the durations were the same but they were significantly different from the two studies using aspirin. Fortunately, the results of all included studies agreed.

Conclusion

In conclusion, this is the first meta-analysis examining the use of anticoagulants to prevent DVT after knee arthroscopies. The use of anticoagulants must balance the prevention of thrombosis with the potential for complications. The present study confirmed that anticoagulant treatment after arthroscopic surgery significantly contributes to the prevention of thrombosis without increasing the risk of bleeding events. Current adopted prevention strategies require daily subcutaneous injections of LMWH. However, Munoa [33] reported that, post-surgery, patients often did not receive their anticoagulant treatment before the prescribed LMWH date. Several studies have reported [40-43] a lower risk and better safety performance associated with the use of aspirin, compared to other traditional antithrombotic agents after knee and hip replacement surgery. The same conclusions were drawn using a randomized controlled trial with aspirin for the prevention of thrombus after knee arthroscopy. Furthermore, a rigorous double-blind and randomized controlled study showed that the use of rivaroxaban after knee arthroscopies significantly reduced the risk of DVT, without increas-

ing the risk of bleeding [44]. It was believed that oral administration is more appropriate than subcutaneous administration because it allows for self-management of the drug, ensuring the safety of the prescription. In general, symptomatic DVT after knee arthroscopies is rare and there is no requirement to use anticoagulant therapy for low-risk patients. However, it is recommended that oral anticoagulation is used for high-risk patients to prevent DVT.

Acknowledgements

This research supported by grants from the Health Bureau Science and Technology Fund of Tianjin (No. 2013KZ063) and Health and Family Planning Fund of Tianjin (No. 14KG123).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jun Liu, Department of Joint Surgery, Tianjin Hospital, 406 Jiefang Street, Hexi District, Tianjin, China. Tel: +86 15602176472; E-mail: doctorliutj@163.com

References

[1] Hoppener MR, Ettema HB, Henny CP, Verheyen CC, Büller HR. Low incidence of deep vein thrombosis after knee arthroscopy without thromboprophylaxis a prospective cohortstudy of 335 patients. Acta Orthop Scand 2006; 77: 767-771.

[2] Graham WC, Flanigan DC. Venous thromboembolism following arthroscopic knee surgery: a current concepts review of incidence, prophylaxis and preoperative risk assessment. Sports Med 2014; 44: 331-43.

[3] Bohensky MA, Dsteiger R, Kondogiannis C, Sundararajan V, Andrianopoulos N, Bucknill A, McColl G, Brand CA. Adverse outcomes associated with elective knee arthroscopy: a population-based cohort study. Arthroscopy 2013; 29: 716-25.

[4] Hetsroni I, Lyman S, Do H, Mann G, Marx RG. Symptomatic pulmonary embolism after outpatient arthroscopic procedures of the knee: the incidence and risk factors in 418,323 arthroscopies. J Bone Joint Surg Br 2011; 93: 253-7.

[5] Maletis GB, Inacio MD, Reynolds S, Funahashi TT. Incidence of symptomatic venous thromboembolism after elective knee arthroscopy. J Bone J Surg Am 2012; 94: 714-20.

[6] Williams JS Jr, Hulstyn MJ, Fadale PD, Lindy PB, Ehrlich MG, Cronan J, Dorfman G. Incidence of deep vein thrombosis after arthroscopic knee surgery. Thromb Haemost 1997; 79: 183.

[7] Michot M, Conen D, Holtz D, Erni D, Zumstein MD, Ruflin GB, Renner N. Prevention of deep vein thrombosis in ambulatory arthroscopic knee surgery: a randomized trial of prophylaxis with low-molecular weight heparin. Arthroscopy 2002; 18: 257-263.

[8] Williams JS, Hulstyn M, Fadale PD, Lindy PB, Ehrlich MG, Cronan J, Dorfman G. Incidence of deep vein thrombosis after arthroscopic knee surgery; a prospective study. Arthroscopy 1995; 11: 701-5.

[9] Demers C, Marcoux S, Ginsberg JS, Laroche F, Cloutier R, Poulin J. Incidence of venographically proved deep vein thrombosis after knee arthroscopy. Arch Intern Med 1998; 158: 47-50.

[10] Dahl OE, Gudmundsen TE, Haukeland L. Late occurring clinical deep vein thrombosis in joint operated patients. Acta Orthop Scand 2000; 71: 47-50.

[11] Jareguito JW, Greenwald AE, Wilcox JF, Paulos LE, Rosenberg TD. The incidence of deep venous thrombosis after arthroscopic knee surgery. Am J Sports Med 1999; 27: 707-10.

[12] Delis KT, Hunt N, Strachan RK, Nicolaides AN. Incidence, natural history and risk factors of deep vein thrombosis in elective knee arthroscopy. Thromb Haemost 2001; 86: 817-21.

[13] van Adrichem RA, Nelissen RG, Schipper IB, Rosendaal FR, Cannegieter SC. Risk of venous thrombosis after arthroscopy of the knee: results from a large population based case-control study. J Thromb Haemost 2015; 13: 1441-8.

[14] Marlovits, Striessnig G, Schuster R, Luxl M, Trattnig S, Vécsei V. Extended duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective,randomized, placebo-controlled study. Arthroscopy 2007; 23: 696-702.

[15] Collaboration AT. Collaborative overview of randomized trials of antiplatelet therapy-III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. BMJ 1994; 308: 235-46.

[16] Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention trial. Lancet 2000; 355: 1295-302.

[17] Kaye ID, Patel DN, Strauss EJ, Alaia MJ, Garofolo G, Martinez A, Jazrawi LM. Prevention of venous thromboembolism after arthroscopic knee surgery in a low-risk population with the use of aspirin. A randomized trial. Bull Hosp Jt Dis (2013) 2015; 73: 243-8.

[18] Turpie AG, Lassen MR, Eriksson BI, Gent M, Berkowitz SD, Misselwitz F, Bandel TJ, Homering M, Westermeier T, Kakkar AK. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. Thromb Haemost 2011; 105: 444-53.

[19] Prins MH, Lensing AW, Brighton TA, Lyons RM, Rehm J, Trajanovic M, Davidson BL, Beyer-Westendorf J, Pap ÁF, Berkowitz SD, Cohen AT, Kovacs MJ, Wells PS, Prandoni P. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomised studies. Lancet Haematol 2014; 1: e37-46.

[20] Prins MH, Lensing AW, Bauersachs R, et al. ROCKET AF Investigators. N Engl J Med 2011; 365: 883-91.

[21] Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008; 358: 2765-75.

[22] Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S; RECORD2 Investigators. Extended duration rivaroxaban versus short-therm enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double blind, randomised controlled trial. Lancet 2008; 372: 31-3.

[23] Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Eng J Med 2008; 358: 2776-86.

[24] Lassen MR, Borris LC, Christiansen HM, Boll KL, Eiskjaer SP, Nielsen BW, Schøtt P, Olsen AD, Rodenberg JC, Lucht U. Prevention of thromboembolism in 190 hip arthroplasties: comparison of LMW heparin and placebo. Acta Orthop Scand 1991; 62: 33-8.

[25] Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. Chest 2012; 141 Suppl: e278S-e325S.

[26] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-101.

[27] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

[28] DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015; 45: 139-45.

[29] Hildebrand KA, Frank CB, Hart DA. Gene intervention in ligament and tendon: current status, challenges, future directions. Gene Ther 2004; 11: 368-78.

[30] Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

[31] Kaye ID, Patel DN, Strauss EJ, Alaia MJ, Garofolo G, Martinez A, Jazrawi LM. Prevention of venous thromboembolism after arthroscopic knee surgery in a low-risk population with the use of aspirin. A Randomized Trial. Bull Hosp Jt Dis 2015; 73: 243-8.

[32] Camporese G, Bernardi E, Noventa F, Bosco M, Monteleone G, Santoro L, Bortoluzzi C, Freguja S, Nardin M, Marullo M, Zanon G, Mazzola C, Damiani G, Maniscalco P, Imberti D, Lodigiani C, Becattini C, Tonello C, Agnelli G; ERIKA Study Group. Efficacy of rivaroxaban for thromboprophylaxis after knee arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study. Thromb Haemost 2016; 116: 349-55.

[33] Muñoa L, González AB, Díaz de Rada P, Valentí A. Rivaroxaban is as efficient and safe as bemiparin as thromboprophylaxis in knee arthroscopy. Musculoskelet Surg 2014; 98: 21-5.

[34] Camporese G, Bernardi E, Prandoni P, Noventa F, Verlato F, Simioni P, Ntita K, Salmistraro G, Frangos C, Rossi F, Cordova R, Franz F, Zucchetta P, Kontothanassis D, Andreozzi GM; KANT (Knee Arthroscopy Nadroparin Thromboprophylaxis) Study Group. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. Ann Intern Med 2008; 149: 73-82.

[35] Wirth T, Schneider B, Misselwitz F, Lomb M, Tüylü H, Egbring R, Griss P. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): results of a randomized controlled trial. Arthroscopy 2001; 17: 393-9.

[36] Adala R, Anand A, Kodikal G. Deep vein thrombosis and thromboprophylaxis in arthroscopic anterior cruciate ligament reconstruction. Indian J Orthop 2011; 45: 450-3.

[37] Dahl OE, Pleil AM. Investment in prolonged thromboprophylaxis with dalteparin improves clinical outcomes after hip replacement. J Thromb Haemost 2003; 2: 896-906.

[38] Davies LM, Richardson GA, Cohen AT. Economic evaluation of enoxaparin as postdischarge prophylaxis for deep vein thrombosis in elec-

tive hip surgery. Value Health 2000; 3: 397-406.
[39] Marlovits S, Striessnig G. Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study. Arthroscopy 2007; 23: 696-702.
[40] Bozic KJ, Vail TP, Pekow PS, Maselli JH, Lindenauer PK, Auerbach AD. Does aspirin have a role in venous thromboembolism prophylaxis in total knee arthroplasty patients? J Arthroplasty 2010; 25: 1053-60.
[41] Brown GA. Venous thromboembolism prophylaxis after major orthopaedic surgery: a pooled analysis of randomized controlled trials. J Arthroplasty 2009; 24 Suppl: 77-83.
[42] Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, Hirsh J. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fracturedhip. Arch Intern Med 1989; 149: 771-4.
[43] Dorr LD, Gendelman V, Maheshwari AV, Boutary M, Wan Z, Long WT. Multimodal thromboprophylaxis for total hip and knee arthroplasty based on risk assessment. J Bone Joint Surg Am 2007; 89: 2648-57.
[44] Committee for Proprietary Medicinal Products. Points to consider on clinicalinvestigation of medicinal products for prophylaxis of intra- and post-operativevenous thromboembolic risk. London: European Agency for the Evaluation ofMedicinal Products; BMC medical genetics 2000: Available at http://www.emea.europa.eu/pdfs/human/ewp/070798en.pdf. Accessed on May 20, 2008.