Original Article

Aspirin for venous thromboembolism prophylaxis after hip or knee arthroplasty: An updated meta-analysis of randomized controlled trials

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ABSTRACT

Background: Patients who undergo knee or hip arthroplasty are at a significant risk of venous thromboembolism (VTE) development (pulmonary embolism and/or deep-vein thrombosis). Many different thromboprophylactic strategies have been used for the prevention of VTE in these patients with different outcomes. Therefore, our aim was to evaluate the efficacy and safety of aspirin prophylaxis when compared with placebo or anticoagulants in this population of patients.

Methods: A comprehensive electronic database search was conducted for all randomized controlled trials (RCTs) comparing the clinical outcomes of aspirin versus placebo or anticoagulants for the prevention of VTE after knee or hip arthroplasty. The primary outcome was VTE incidence. Secondary outcomes included any bleeding, major bleeding and mortality. We calculated risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model at the longest possible follow-up period.

Results: We included 13 RCTs with a total of 20,115 patients with a mean age of 67.15 ± 9.54 and 24.39% males. Aspirin was found to be associated with a non-significantly reduced VTE events compared with other thromboprophylactic methods (RR 0.87; 95% CI: 0.61–1.23; $P = 0.43$). Compared with placebo, aspirin was associated with significant reduction of VTE (RR 0.65; 95% CI: 0.47–0.89; $P = 0.008$). There were no significant differences in the clinical outcomes between all groups with regard to mortality (RR 0.98; 95% CI: 0.86–1.11; $P = 0.72$), major bleeding events (RR 0.96; 95% CI: 0.50–1.84; $P = 0.91$), and any bleeding events (RR: 1.09; 95% CI: 0.82–1.44; $P = 0.56$).

Conclusion: Among patients who underwent knee or hip arthroplasty, aspirin prophylaxis was found to be associated with similar efficacy and safety outcomes when compared with anticoagulants. When compared with placebo, aspirin prophylaxis was associated with significantly reduced VTE and a comparable safety profile.

1. Introduction

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism, which are considered major complications following hip and knee joint-replacement surgery. Such complications carry a poor outcome with increased morbidity and mortality, and prevention of VTE is considered a cornerstone in management of these patients.^{1–3}

Current guidelines suggest that DVT prophylaxis should be continued for at least 14 days following surgery, and may be extended to 35 days in patients at high risk for VTE.⁴ Pharmacologic anticoagulation is the most commonly used form of management for DVT prophylaxis in

orthopedic surgeries.⁴

While anticoagulants are considered effective in prevention of VTE, they carry several downfalls. An increased risk of bleeding is an inherent side effect of anticoagulation. Substantial cost of medication often limits options, especially with regard to the Novel Oral Anticoagulants (NOACs). Additionally, inconvenience of certain anticoagulants forms a significant barrier to compliance, especially regarding subcutaneous injections, thus the search for more convenient and safer strategies remains necessary.⁵

Aspirin is an inexpensive and widely available medication; many studies have proven its efficacy in VTE prophylaxis for patients undergoing joint replacement surgeries.⁶

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Table 1
Jadad scoring of included studies.

Author	Jadad score
Harris 1977	5
Alfaro 1986	3
Power 1989	5
Gent 1996	5
Kim 1998	3
Rodgers 2000	5
Gelfer 2006	3
Westrich 2006	2
Anderson 2013	5
Kulshrestha 2013	5
Jiang 2014	3
Zou 2014	3
Anderson 2018	5

There have been several randomized controlled trials (RCTs) comparing various types of anticoagulants, including low-molecular-weight heparin (LMWH) and NOACs.^{7–12}

In light of the various comparative trials, we aimed to conduct a meta-analysis evaluating the safety and efficacy of aspirin in primary prevention of VTE for patients who had undergone hip or knee-replacement surgeries while comparing it to placebo and various other types of anticoagulants.

2. Methods

2.1. Data source

We conducted our meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015.¹³ We performed a comprehensive literature search of PubMed, Embase, the Cochrane Collaboration Central Register of Controlled Trials. TH, MB and YZ performed the search independently from inception to August 2018 and MSM resolved any disagreements. We used the following search terms in combination: aspirin, antiplatelet, arthroplasty, joint replacement, knee arthroplasty, hip arthroplasty, knee replacement, hip replacement,VTE, DVT, deep vein.

2.2. Selection criteria and data extraction

The inclusion criteria were as follows: 1) All studies must be RCTs 2) All studies must compare aspirin as thromboprophylaxis with another prophylactic modality. 3) Study subjects must be post-operative after either knee or hip arthroplasty.MB and MSM extracted data independently. Any discrepancies were resolved via consultation with TH. From each RCT we extracted trial characteristic, patient demographics, and clinical outcomes.

2.3. Quality assessment

The quality of the included studies was assessed independently by two authors (TH and YZ) based on the study design, number of sites, blinding to outcomes, treatment assignment generation, and proportion of follow-up completion in addition to the Jadad scoring (Table 1).

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

2.4. Clinical outcomes

The primary outcome was VTE. Secondary outcomes included mortality, major bleeding events, and any bleeding events. All outcomes were analyzed at the longest follow-up period.

2.5. Statistical analysis

We calculated the pooled risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model and the Mantel-Haenszel method. In addition, we calculated heterogeneity using I² statistics. Furthermore, we constructed a funnel plot to assess for any publication bias. All data were analyzed using RevMan v5.3.

3. Results

Fig. 1 shows the study selection process. We included 13 RCTs with 20,115 total patients with a mean age of 67.15 ± 9.54 and 24.39% male patients.

Tables 2 and 3 illustrates the characteristics of the included trials and patients demographics respectively.

In these 13 studies, 20,115 patients undergoing joint arthroplasties were included. All studies were randomized controlled trials.

Of these 13 studies, 3 studies assessed VTE in both knee and hip arthroplasty, 6 studies assessed VTE in hip arthroplasty alone and 4 studies assessed VTE in knee arthroplasty alone only. Ten trials included only elective surgeries while the remaining 3 included both urgent and elective surgeries, or fracture-related urgent surgeries alone.

Aspirin dosing varied from 81 mg (mg) daily to 1200 mg per day, with reported thromboprophylactic regimens spanning from 14 to 35 days. Follow-up duration ranged from 4 weeks to 1 year. Other comparative thromboprophylactic measures included either new oral

Table 2
Details of the randomized clinical trials.

Author	Country	Total number of patients & those receiving ASA	Comparative treatment	Aspirin Dose	Follow-up period	Type of surgery
Harris 1977	USA	95 ASA:44	ASA vs Placebo	600 mg bd for 7–10 d post operatively	NR	Total hip replacement
Alfaro 1986	Spain	120 ASA:60	Placebo vs Low dose ASA vs High dose ASA vs combination of Heparin + dihydroergotamine heparin-DHE	125 mg bd or 500 mg bd, 7 d post operatively	NR	Total hip replacement
Power 1989	Canada	194 ASA:66	Warfarin VS ASA VS Placebo	650 mg bd for 21 d post operatively or until dc	3 m	Total hip replacement
Gent 1996	Canada	251 ASA:126	Orgaran vs ASA	100 mg bd 14 d post operatively or until dc	3 m	Total hip replacement
Kim 1998	Korea	150 ASA:50	Placebo vs ASA vs Dextran	1200 mg daily, 14 d post operatively	NR	Total hip replacement
Rodgers 2000	New Zealand	13,356 ASA:6679	ASA vs Placebo	160 mg/d, 35 d post operatively	5 weeks	Either total hip or knee replacement
Gelfer 2006	Israel	121 ASA:61	WizAir continuous enhanced circulation therapy + aspirin vs Enoxaparin	100 mg once daily	3 m	Total hip replacement
Westrich 2006	USA	275 ASA:136	Enoxaparin vs ASA	325 mg bd, 30 d post operatively	6 weeks	Total knee replacement
Anderson 2013	Canada	778 ASA:380	Dalteparin vs ASA	81 mg once daily between post operative day 11 and 28	90 d	Either total hip or knee replacement
Kulshrestha 2013	India	673 ASA:194	routine anticoagulation vs risk stratification	325 mg bd, 28 d post operatively	1 year	Total knee replacement
Jiang 2014	China	120 ASA:60	ASA + mechanical VS LMWH and rivaroxaban	100 mg/d, 14 d post operatively	6 weeks	Total knee replacement
Zou 2014	China	324 ASA:110	Rivaroxaban vs LMWH vs ASA	100 mg/d, 14 d post operatively	4 weeks	Total knee replacement
Anderson 2018	Canada	3424 ASA:1707	Rivaroxaban vs ASA	81 mg once daily starting at day 6 post operatively for an additional 9 days after total knee arthroplasty or for 30 days after total hip arthroplasty.	3 m	Either total hip or knee replacement

Abbreviations: d:days; bd:twice daily; m:months; ASA:aspirin; LMWH:low molecular weight heparin; dc:discharge; NR:not reported; vs:versus;USA:United States of America.

anticoagulant, heparin, low molecular weight heparin or placebo.

Aspirin was associated with non-significantly reduced VTE compared with other thromboprophylactic strategies (RR 0.87; 95% CI: 0.61–1.23; $P = 0.43$). Subgroup analysis showed that aspirin was associated with significant reduction of VTE compared with placebo (RR 0.65; 95% CI: 0.47–0.89; $P = 0.008$) (Fig. 2).

There were no significant differences in the clinical outcomes between all groups with regard to mortality (RR 0.98; 95% CI: 0.86–1.11; $P = 0.72$), major bleeding events (RR 0.96; 95% CI: 0.50–1.84; $P = 0.91$), and any bleeding events (RR: 1.09; 95% CI: 0.82–1.44; $P = 0.56$) (Figs. 3–5).

4. Discussion

In this meta-analysis of 13 RCTs, Aspirin was compared to placebo and other various anticoagulation methods including NOAC, warfarin, LMWH, and heparin. Aspirin showed a significant reduction of VTE in patients undergoing arthroplasty compared to placebo and a non-significant reduction of VTE events when compared to all other anticoagulation methods, in the exception of warfarin where Powers et al. were able to prove the superiority of warfarin (used as prophylaxis) compared to aspirin in VTE prophylaxis. However it was only one study with a small sample of only 196 patients. Therefore further larger studies are needed in the future in that regards.

Several retrospective studies have evaluated the role of aspirin in VTE prophylaxis and demonstrated the noninferiority of aspirin to anticoagulants, less bleeding events with aspirin, and less blood transfusions with aspirin.^{14–16} Of these retrospective studies, a large retrospective analysis of nearly 307,000 Korean patients undergoing joint replacement surgeries showed that the risk of VTE associated with aspirin was less than LMWH, similar to rivaroxaban, and slightly higher than fondaparinux, however, aspirin was associated with less blood transfusion rates and lower risk of bleeding.¹⁴

In a pooled analysis of phase III RCTs comparing the efficacy and safety of enoxaparin with rivaroxaban or dabigatran, enoxaparin held similar efficacy to dabigatran in prevention of VTE, mortality, and risk of bleeding, while rivaroxaban was associated with a 50% reduction of VTE and mortality with reduced risk of bleeding.¹⁷

Several meta-analyses have evaluated the role of primary prevention of VTE. Sahebally et al. has concluded that aspirin is effective in primary prevention of VTE in orthopedic surgeries when compared to other anticoagulants and is more effective than placebo in surgical patients. Their study involved mixed surgical populations such as orthopedic surgery fracture repairs, elective surgical procedures, and high risk non-cardiac surgeries. Additionally RCTs, meta-analyses, and prospective trials were included in their analysis.¹⁸ Another meta-analysis involving patients with a hip fracture, knee replacement, or hip replacement surgery showed the noninferiority of aspirin in comparison

Table 3
Patients demographics.

Author	Treatment (N)	Age (years) Mean $\pm$ SD	Male sex (N)	Previous VTE (N)	DM (N)	HTN (N)	Stroke or TIA (N)	Smoker (N)	Time in OR in Min, Mean $\pm$ SD	Length of stay, Day, mean	Malignancy (N)	Heart disease (N)	BMI, Mean $\pm$ SD
Harris 1977	ASA (44)	> 40	23										
	Placebo (51)	> 40	25										
Alfaro 1986	Placebo (30)	61.99 $\pm$ 7.17	19	0					< 3 h		0	5	
	ASA, Low dose (30)	66.06 $\pm$ 8.93	17	2					< 3 h		0	4	
	ASA, high dose (30)	62.04 $\pm$ 10.99	15	1					< 3 h		0	2	
	Heparin-DHE (30)	58.43 $\pm$ 10.39	14	1					< 3 h		0	4	
Power 1989	Warfarin (65)	74.5	23	4									
	ASA (66)	73.0	19	3									
	Placebo (63)	76.6	12	4									
Gent 1996	Oragan (125)	76.6	23	7							20		
	ASA (126)	76.6	24	4							12		
Kim 1998	Placebo (50)		41										
	ASA (50)		38										
	Dextran (50)		40										
Rodgers 2000	ASA (6679)	79	973										
	Placebo (6677)	79	960										
Gelfer 2006	Enoxaparin (60)	67 $\pm$ 8.7	23		10	26		6		9.9 $\pm$ 2.7	8	12	29 $\pm$ 4.8
	CECT + aspirin (61)	68 $\pm$ 10.4	21		3	26		10		8.8 $\pm$ 1.9	5	5	28 $\pm$ 4
Westrich 2006	Enoxaparin (139)	68.9 $\pm$ 9.6	99/275										
	VenaFlow, and aspirin (136)	69.0 $\pm$ 12.1											
Anderson 2013	LMWH (398)	57.9 $\pm$ 12.2	213	8	30	144	6	64	91.9 $\pm$ 49	4.8	13	25	27.9 $\pm$ 5.8
	ASA (380)	57.6 $\pm$ 11.9	231	5	33	137	4	53	92.1 $\pm$ 37	4.6	8	20	29.3 $\pm$ 5.9
Kulshrestha 2013	Routine anticoagulation (450)	64.9 $\pm$ 8	161										27.8 $\pm$ 5.2
	Risk stratification (450)	62.6 $\pm$ 8	167										27.1 $\pm$ 4.1
Jiang 2014	Aspirin + mechanical (60)	65.1 $\pm$ 7.5	5						82.5 $\pm$ 4.7				24.2 $\pm$ 3.3
	LMWH + rivaroxaban (60)	63.8 $\pm$ 6.7	4						83.0 $\pm$ 4.3				24.6 $\pm$ 3.6
Zou 2014	Rivaroxaban (102)	63.5 (50–82)	32						84.5 (70–87)				27.5 (18–39.5)
	LMWH (112)	65.7 (54–80)	20						84.4 (81–87)				27 (20.3–37)
	ASA (110)	62.7 (47–79)	28						90.6 (80–94)				27.8 (17.8–40)
Anderson 2018	Rivaroxaban (1717)	62.7 $\pm$ 10.1	833	44				157	1.4 $\pm$.6	3.4 $\pm$ 1.6	38		31.0 $\pm$ 6.6
	ASA (1707)	62.9 $\pm$ 10.1	804	37				162	1.4 $\pm$ 0.6	3.5 $\pm$ 1.8	42		31.1 $\pm$ 6.8

Abbreviations: ASA: aspirin; LMWH: low molecular weight heparin; CECT: continuous enhanced circulation therapy; DM: diabetes mellitus; HTN: hypertension; BMI: body mass index; SD: standard deviation; (N): patients number; TIA: transient ischemic attack; OR: operating room; DHE: dihydroergotamine heparin; VTE: venous thromboembolism; Min: minutes.

Fig. 2. Forest plot of primary outcome (venous thromboembolism).

to anticoagulants, and aspirin was associated with decreased risk of bleeding.¹⁹

An et al. performed a meta-analysis and was able to prove that aspirin, both alone and in multimodal approaches to thromboprophylaxis, confers a low rate of VTE, with a low risk of major bleeding complications. However this study included only 10 RCTs and other low quality retrospective and prospective cohort studies.²⁰

The strengths of our meta-analysis include an extensive search of the available literature. Furthermore, we included only RCTs, which helps eliminate the likelihood of confounding biases from non-randomized studies. However, there are several limitations in the included clinical trials. First, blinding was a major concern in the included RCTs as it was deemed not feasible in multiple studies, which

could have introduced performance bias in the result. Second, due to various trial designs and protocols, there were major differences in the aspirin dosing and the different thromboprophylaxis methods used. Third, only a few clinical trials enrolled high-risk patients defined by older age or higher BMI, and few trials included patients undergoing emergency arthroplasty or patients with fractures.

5. Conclusion

This meta-analysis showed that among patients who underwent hip or knee arthroplasty, aspirin prophylaxis was associated with similar efficacy and safety outcomes compared with anticoagulants. Compared with placebo, aspirin prophylaxis was associated with a significantly

Fig. 3. Forest plot of mortality.

Fig. 4. Forest plot of major bleeding events.

Fig. 5. Forest plot of any bleeding events.

reduced rate of VTE and a similar safety profile. Future studies are warranted to determine the exact aspirin dosing and its role in emergent arthroplasty VTE prophylaxis.

Conflicts of interest

No conflict of interest to declare.

Financial disclosure

No financial disclosure to declare.

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