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Aspirin

An Alternative for Pulmonary Embolism Prophylaxis After Arthroplasty?

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Abstract

Background The most effective agent for prophylaxis against venous thromboembolic disease after total joint arthroplasty (TJA) remains unknown. The paucity of literature comparing different methods of pulmonary embolism (PE) prophylaxis and fear of litigation make it difficult for surgeons to abandon the use of aggressive chemical prophylaxis.

Questions/purposes We compared the (1) overall frequency of symptomatic PE, (2) risk of symptomatic PE after propensity matching that adjusted for potentially confounding variables, and (3) other complications and length of stay before and after propensity matching in patients undergoing TJA at our institution who received either aspirin or warfarin prophylaxis.

Methods A total of 28,923 patients underwent TJA between January 2000 and June 2012 at our institution, had either aspirin (325 mg twice daily; 2800 patients) or warfarin prophylaxis (26,123 patients), and were registered in our institutional electronic database. The incidence of symptomatic PE, symptomatic deep vein thrombosis (DVT), hematoma formation, infection, wound complications, and mortality up to 90 days postoperatively was collected from the database. We performed multivariate analysis and 3:1 and 5:1 propensity score matching for comorbid and demographic variables.

Results The overall symptomatic PE rate was lower ($p < 0.001$) in patients receiving aspirin (0.14%) than in the patients receiving warfarin (1.07%). This difference did not change after matching. The aspirin group also had significantly fewer symptomatic DVTs and wound-related problems and shorter hospital stays, which did not change after matching.

Conclusions After publication of the American Academy of Orthopaedic Surgeons' guidelines, some surgeons have utilized aspirin as thromboprophylaxis after TJA. Based on our findings from a large institutional database, aspirin offers suitable prophylaxis against symptomatic PE in selected patients.

Level of Evidence Level III, therapeutic study. See Instructions for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Introduction

The ideal chemical thromboprophylaxis after total joint arthroplasty (TJA) remains unknown. An ideal agent would not only prevent venous thromboembolism (VTE) occurrence

but also minimize bleeding risks. Warfarin is commonly used for VTE prophylaxis. Although effective, it is still associated with clinically significant pulmonary embolism (PE) and deep vein thrombosis (DVT) rates, bleeding risks, and the need for regular monitoring.

Aspirin is a widely used antiplatelet drug. It prevents platelet aggregation by inhibiting the production of thromboxane A_2 by activated platelets [8]. Aspirin increases the bleeding time without affecting other coagulation parameters. Its use for secondary prevention of heart attacks and strokes has been well established [32]. However, some controversy still exists concerning its ability to prevent VTE incidents after arthroplasty procedures.

The American Academy of Orthopaedic Surgeons (AAOS) has endorsed aspirin for VTE prevention after TJA [23]. In 2012, the American College of Chest Physician (ACCP) evidence-based clinical practice guidelines (9^{th} edition), for the first time, acknowledged the use of aspirin as a means of PE chemoprophylaxis after TJA (Grade IB recommendation) [13, 18]. However, the paucity of literature comparing different methods of VTE prophylaxis and fear of litigation make it difficult for surgeons to abandon more aggressive chemical prophylaxis.

Because important questions remain on this subject, we compared the (1) overall frequency of symptomatic PE, (2) risk of symptomatic PE after propensity matching was performed to try to adjust for potentially confounding variables, and (3) other complications and length of stay before and after propensity matching in patients undergoing TJA at our institution who received either aspirin or warfarin prophylaxis.

Patients and Methods

At our institution, a prospective database has been in place over the last decade to track complications that occur after TJA. We performed retrospective data collection from our electronic database on 28,923 patients who have undergone TJA between January 2000 and June 2012. The standard of care at our institution was to give warfarin to all patients for postoperative VTE prevention, until 2010 when, after the publication of the AAOS guidelines, the standard of care was changed to aspirin for all patients except those at high risk for VTE as determined by the treating physician. As a result, a total of 2800 patients received aspirin (325 mg twice daily) as prophylaxis against VTE and 26,123 received warfarin aiming for an international normalized ratio (INR) of between 1.5 and 1.8. Both drugs were administered for 6 weeks after index surgery. Thus, warfarin and aspirin were administered to patients with TJA during the same time period. Twenty-four patients received heparin or heparin derivatives and were excluded from our cohort. All patients included in our cohort received spinal anesthesia at the time of surgery.

We reviewed retrospective patient data for 90 days after index surgery to identify any VTE that might have happened in or outside the hospital setting. The incidence of symptomatic PE, symptomatic DVT, wound complications (hematoma formation, acute infection [within 30 days postoperatively], prolonged wound drainage), and mortality were collected. Investigation for symptomatic PE followed our institutional protocol [42]. Patients exhibiting signs and symptoms of tachypnea, dyspnea, new onset arrhythmia, tachycardia, chest pain, or hemoptysis were assessed with pulse oximetry, vital signs, an ECG, a chest radiograph, and a set of cardiac enzymes. Patients with an oxygen saturation of less than 90% were placed on 2 L oxygen by nasal cannula for 10 minutes. If the hypoxia persisted, a multidetector CT of the chest or a ventilation-perfusion scan was performed. Based on clinical suspicion, a total of 1167 patients were investigated for PE by ventilation-perfusion or CT scan; 24.3% of clinically suspected cases had positive diagnostic studies. Patients exhibiting signs of swelling, erythema, pain or tenderness in one or both legs, or a positive Homan sign were investigated with an ultrasound duplex of the lower extremities.

A logistic regression model was used to estimate the probability of a patient receiving aspirin or warfarin based on demographic and clinical factors. Matching was then performed so that the probabilities of receiving aspirin were equal for both groups, in effect retroactively randomizing the study and controlling for potentially biased variables such as age, sex, BMI, Charlson Comorbidity Index (CCI), time of surgery, joint (hip or knee), procedure (primary or revision arthroplasty), and uni/bilaterality. We used the CCI as a mean of assessing patient health; it predicts the overall 10-year mortality risk of patients with comorbid conditions [9, 10, 12]. Patients receiving warfarin prophylaxis were matched in 3:1 and 5:1 ratios to patients receiving aspirin prophylaxis. Demographic and procedure data for unmatched patients (Table 1) and 3:1 and 5:1 matched patients (Table 2) are shown.

In addition, a multivariate analysis was performed for the following outcomes (if occurring within 90 days after index surgery): symptomatic PE, symptomatic DVT, acute infection, hematoma/bleeding, prolonged wound drainage, and 90-day mortality. Matching implicitly controls for potentially biased variables. A multivariate analysis, on the other hand, permits the explicit estimation of each variable's effect. We chose to analyze the data by these two different methods to show consistency in our findings.

Fisher's exact test was used to analyze categorical variables. Propensity score matching (MatchIt package for R) and other calculations were performed using R 2.14.2 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

In the entire unmatched cohort, symptomatic PE developed in 284 of 28,923 patients, accounting for an overall incidence of 0.98%. The percentage of patients developing symptomatic PE was lower in the aspirin group (0.14%, or four of 2800) than in the warfarin group (1.07%, or 280 of 26,123) ($p < 0.001$) (Table 3). Fisher's exact test showed an odds ratio (OR) of 7.57 (95% CI: 2.92–28.00) for symptomatic PE with warfarin compared to aspirin.

The risk of symptomatic PE remained lower in the aspirin group even after propensity score matching was performed. With 3:1 matching, the symptomatic PE rate was lower in the aspirin group (0.11%) than in the matched warfarin group (0.67%) ($p = 0.002$) (Table 4). Fisher's exact test showed an OR of 6.36 (95% CI: 1.64–54.50) for PE with warfarin compared to aspirin. With 5:1 matching, the symptomatic PE rate was also lower in the aspirin group (0.11%) than in the matched warfarin group (1.02%) ($p < 0.001$). Fisher's exact test showed an OR of 9.69 (95% CI: 2.61–81.21) for symptomatic PE with warfarin compared to aspirin.

In the unmatched patients, the incidence of symptomatic DVT was significantly lower in the aspirin group (0.29%) than in the warfarin group (0.99%) (OR = 3.50; 95% CI: 1.75–8.19) ($p < 0.001$) (Table 3). The risk of symptomatic DVT remained lower in the aspirin group than in the warfarin group even after propensity score matching was performed. With 3:1 matching, the symptomatic DVT rate

Table 1. Unmatched Demographics and Procedures

	Warfarin		Aspirin		p-value
	Incidence or Mean	Standard Deviation	Incidence or Mean	Standard Deviation	
Males	42.6 %	-	46.8 %	-	<0.001
Age (years)	64.3	12.2	61.1	11.2	<0.001
CCI	2.11	1.39	1.29	1.22	<0.001
LOS (days)	4.08	3.09	2.48	1.26	<0.001
BMI (kg/m^2)	30.01	6.69	29.36	5.51	<0.001
Prim. THA	45.0 %	-	58.5 %	-	-
Prim. TKA	41.9 %	-	36.8 %	-	-
Rev. THA	8.0 %	-	3.7 %	-	
Rev. TKA	5.1 %	-	0.9 %	-	

CCI = charlson comorbidity index, LOS = length of stay, BMI = body mass index, Rev. = revision, Prim. = primary, THA = total hip arthroplasty, TKA = total knee arthroplasty.

Table 2. Demographics and procedures of 3:1 and 5:1 propensity score-matched patients

Variable	Aspirin	Warfarin 3:1	p value	Warfarin 5:1	p value
Number of patients	1890	5670		9450	
Males (%)	44.7	44.1		44.2	
Age (years)*	61.6 (11.25)	62.7 (11.86)	< 0.001	63.0 (11.89)	< 0.001
Charlson Comorbidity Index*	1.09 (1.20)	1.58 (1.39)	< 0.001	1.80 (1.38)	< 0.001
Length of stay (days)*	2.31 (1.21)	3.26 (3.22)	< 0.001	3.26 (3.22)	< 0.001
BMI (kg/m^2)*	29.39 (5.51)	29.80 (5.83)	0.014	29.80 (5.83)	0.002
Type of surgery (%)			< 0.001		< 0.001
Primary THA	58.7	50.8		49.1	
Primary TKA	38.7	43.2		43.8	
Revision THA	2.3	4.3		5.8	
Revision TKA	0.4	1.8		1.4	

* Values are expressed as mean, with SD in parentheses.

Table 3. Ninety-day complication rates of the unmatched aspirin and warfarin groups

Complication	Number of patients		Odds ratio (95% CI)	p value
	Warfarin (n = 26,123)	Aspirin (n = 2800)		
Pulmonary embolism	280 (1.07%)	4 (0.14%)	7.57 (2.92–28.00)	< 0.001
Deep vein thrombosis	259 (0.99%)	8 (0.29%)	3.50 (1.75–8.19)	< 0.001
Acute infection	198 (0.76%)	11 (0.39%)	1.94 (1.06–3.95)	0.033
Hematoma/bleeding	33 (0.13%)	0 (0%)		0.070
Wound drainage	198 (0.57%)	1 (0.04%)	16.06 (2.84–636.99)	< 0.001
90-day mortality	85 (0.03%)	1 (0.04%)	9.14 (1.60–364.72)	0.003

Table 4. Ninety-day complication rates of the 3:1-matched aspirin and warfarin groups

Complication	Number of patients		Odds ratio (95% CI)	p value
	Warfarin (n = 5670)	Aspirin (n = 1890)		
Pulmonary embolism	38 (0.67%)	2 (0.11%)	6.37 (1.64–54.50)	< 0.001
Deep vein thrombosis	51 (0.90%)	2 (0.11%)	8.57 (2.25–72.58)	< 0.001
Acute infection	30 (0.53%)	4 (0.21%)	2.51 (0.88–9.81)	0.077
Hematoma/bleeding	5 (0.09%)	0 (0%)		0.341
Wound drainage	8 (0.14%)	0 (0%)		0.214
90-day mortality	0 (0%)	0 (0%)		1.000

Table 5. Ninety-day complication rates of the 5:1-matched aspirin and warfarin groups

Complication	Number of patients		Odds ratio (95% CI)	p value
	Warfarin (n = 9450)	Aspirin (n = 1980)		
Pulmonary embolism	96 (1.02%)	2 (0.11%)	9.69 (2.61–81.21)	< 0.001
Deep vein thrombosis	76 (0.80%)	2 (0.11%)	7.65 (2.04–64.46)	< 0.001
Acute infection	55 (0.58%)	4 (0.21%)	2.76 (1.02–10.50)	0.051
Hematoma/bleeding	14 (0.15%)	0 (0%)		0.147
Wound drainage	27 (0.29%)	0 (0%)		0.016
90-day mortality	2 (0.02%)	0 (0%)		1.000

was lower in the aspirin group (0.11%) than in the warfarin group (0.91%) (OR = 8.57; 95% CI: 2.25–72.58) ($p < 0.001$) (Table 4). With 5:1 matching, the symptomatic DVT rate was also lower in the aspirin group (0.11%) than in the warfarin group (0.81%) (OR = 7.65; 95% CI: 2.04–64.46) ($p < 0.001$) (Table 5). In the unmatched patients, the incidences of wound-related problems and 90-day mortality were significantly higher in the warfarin group than in the aspirin group (Table 3). However, after propensity score matching, the incidences were not significantly different between groups (Tables 4 and 5), except for wound drainage, which was lower in the aspirin group than in the warfarin group after 5:1 matching ($p = 0.016$). Unmatched (Table 1) and matched (Table 2) analyses both showed the mean length of hospital stay to be significantly shorter for patients receiving aspirin.

Multivariate analyses of the above-mentioned outcomes showed anticoagulation to be an important factor only for PE and DVT. Reduced models for PE (Table 6) and DVT (Table 7) are presented.

Table 6. Multivariate analysis for pulmonary embolism (reduced model)

Variable	Odds ratio	95% CI	p value
Warfarin	7.14	1.77–28.87	0.006
TKA	3.27	2.33–4.59	< 0.001
Revision procedure	1.58	0.86–2.90	0.137
Charlson Comorbidity Index	1.34	1.23–1.46	< 0.001
BMI	1.02	1.00–1.04	0.040

Table 7. Multivariate analysis for deep vein thrombosis (reduced model)

Variable	Odds ratio	95% CI	p value
Warfarin	2.48	1.22–5.05	0.012
TKA	1.70	1.29–2.24	< 0.001
Revision procedure	2.23	1.50–3.31	< 0.001
Charlson Comorbidity Index	1.36	1.26–1.46	< 0.001

Discussion

The rapidly expanding literature regarding prevention of VTE is at times confusing and contradictory. Although the morbidity and mortality associated with PE has been markedly reduced in recent years, the risk still remains clinically important [14, 39]. In the 9th edition of the ACCP guidelines, for the first time, aspirin was recognized as an effective method of thromboprophylaxis for low- to standard-risk patients undergoing TJA (Grade IB) [13]. In this study, we compared the incidence of PE and other complications after primary and revision arthroplasty in patients treated either with warfarin or aspirin.

There are some limitations to this study. First, after the switch in postoperative thromboprophylaxis standard of care, some treating physicians still administered warfarin for patients they deemed "high risk" for VTE. Even after propensity score matching, we still found some statistically significant disparities in the sex, age, BMI, and CCI of our two cohorts. A selection bias exists; however, the magnitude of these differences is relatively small (Table 1). We purposefully used propensity score matching and multivariate analysis to account for those variables. Second, our PE rate is comparable to those reported in the literature [3, 26, 35]. However, even with meticulous chart review, it is possible that we still missed patients who presented with PE to outside hospitals. We do not identify patients with a prior history of VTE since our hospital uses the same coding for pre- and postoperative VTE. We thus opted not to use codes to identify patients with VTE but went through individual imaging reports for better reliability. Third, as for the data pertaining to the INR levels, a dedicated clinic is in charge of following patients and maintaining INR at therapeutic levels. Some patients may have inadvertently had a few episodes of supra- or even subtherapeutic levels along the 6 weeks after surgery.

Several studies have already evaluated the efficacy of aspirin in preventing VTE. Vulcano et al. [40] reported that aspirin is a safe and effective way of preventing postoperative VTE events in low-risk patients with TJA. Hamilton et al. [19] found that inpatient enoxaparin followed by outpatient aspirin in patients with standard VTE risk was an effective means of thromboprophylaxis after TJA. Similarly, many other studies have also found aspirin to be as effective as or more effective than other agents at VTE prevention [1, 2, 4–6, 11, 28, 33, 34, 41]. Our analysis showed that the incidence of PE was significantly lower in the aspirin group than in the matched and unmatched warfarin group. For patients receiving warfarin postoperatively, the risk of developing a PE was more than six times as high as the risk of developing a PE while on aspirin. These findings are in agreement with findings of a study by Bozic et al. [5] who reported that the adjusted OR for developing DVT or PE was 1.36 times higher in patients receiving warfarin compared with patients receiving aspirin after TJA. This may be explained by the transient hypercoagulable state caused by the early depletion of protein C, a naturally occurring anticoagulant, compared to the other factors of the coagulation cascade. Accordingly, 81% of all PE in our warfarin prophylaxis cohort occurred within the first 3 days postoperatively.

Furthermore, from a clinical perspective, warfarin is difficult to dose properly, and if not dosed properly (particularly if supratherapeutic), warfarin can be associated with bleeding complications. It has several interactions with food and drugs and can be affected by an individual's genetic predisposition [21]. It also has a narrow therapeutic index and undergoes hepatic metabolism, making its onset, duration, and offset of action unpredictable. Excessive and therapeutic anticoagulation are associated with increased rates of minor and major bleeding, prolonged wound drainage, and periprosthetic joint infection [30, 31]. Sachs et al. [37] found twice as many wound problems (including superficial and deep infections and wound necrosis) in patients receiving warfarin postoperatively when compared to a control group not receiving any form of thromboprophylaxis after TKA. In contrast, several studies cite only a low risk of adverse bleeding events in patients receiving aspirin after TJA [27, 36], while many have reported on clinically important bleeding risks associated with warfarin administration [15–17, 20, 22, 24–26, 29]. Sharrock et al. [38] conducted a systematic review evaluating the association between anticoagulation regimens and all-cause mortality rates after TJA. Patients receiving aspirin were reported to have a significantly lower rate of all-cause mortality compared to patients on warfarin (0.19% versus 0.40%, respectively). Furthermore, Callaghan et al. [7] reported no deaths in a cohort of 427 patients with TKA who received aspirin as part of their VTE prevention protocol.

We believe this observational retrospective study provides the necessary data and justifies the need for future prospective trials aimed at defining safer and more effective postoperative thromboprophylactic modalities. After analyzing and presenting our data in three different methods, symptomatic PE and symptomatic DVT incidences remained consistently higher with warfarin when compared to aspirin. The clinical success of less aggressive protocols in conjunction with an increasing number of young, healthy patients who are undergoing hip and knee arthroplasties seem to indicate that aspirin can be an adequate method of chemical anticoagulation in selected patients after orthopaedic surgeries. In addition, it is well tolerated, inexpensive, and easy to administer.

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