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Clinical Outcome of Different Post-operative Prophylactic Strategies on Symptomatic Venous Thromboembolism after Total Knee Arthroplasty

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ABSTRACT

Introduction. The objective of this study was to evaluate the use of different post-operative prophylactic strategies on the rates of symptomatic venous thromboembolic events (VTE) incidence after primary total knee arthroplasty (TKA).

Methods. A retrospective study of patients who underwent primary TKA procedure was performed from January 2015 through July 2020. Outcomes examined prophylaxis medication used during inpatient and outpatient care, amount of medication, length of medication, complications occurring within 90 days post-operatively, including symptomatic VTE (deep venous thrombosis (DVT), and pulmonary embolism (PE)), gastrointestinal (GI) bleeding requiring medical attention, change in management protocols after post-operative complications, and mortality.

Results. In total, 5,663 cases were included (mean age 66 ± 10 years, mean BMI 34.1 ± 7.1kg/m^2). The overall post-operative complication rate was 0.9% (DVT: 0.5%, PE: 0.3%, VTE: 0.04%, and GI bleeding: 0.09%). Enoxaparin use as inpatient anticoagulation medication was reduced significantly (67% vs. 13%, $p < 0.001$), and apixaban was increased significantly (6% vs. 49%, $p < 0.001$). Average hospital stays were reduced significantly among the years (3 ± 2 days vs. 2 ± 1 days, $p < 0.001$), and complication rates were not significantly different between the five years (~1%, $p < 0.001$). Most post-operative complications occurred on either aspirin 325 mg (36%) or apixaban (26%). However, the relative risk ratio results indicating that utilization of warfarin, rivaroxaban, and aspirin 81 mg as outpatient anticoagulation medication were more likely to increase the risk of symptomatic VTE incidence compared to other anticoagulants. The average time of complication detected was 21 ± 21 days (range: 1 - 87 days). More than 54% of complication events occurred after the patient had completed their medication (enoxaparin, rivaroxaban, and apixaban).

Conclusions. The observed incidence of symptomatic VTE in this study was similar to previous studies regardless of the type of post-operative inpatient or outpatient prophylaxis prescribed. The ultimate choice of prophylaxis should remain with the treating physician and their knowledge of a particular patient's medical history.

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INTRODUCTION

Total knee arthroplasty (TKA) is one of the most common orthopedic surgical procedures whereby the diseased knee joint is replaced with artificial material. This procedure accounts for more than one million cases annually in the U.S., and a dramatic increase in the number of TKAs will likely be seen.[1] Patients undergoing this procedure are at high risk of venous thromboembolic events (VTEs), including deep venous thrombosis (DVT) and pulmonary embolism (PE), post-operatively.[2-7] VTE after TKA is of great concern because of the associated increases in morbidity and mortality reported in the literature.[2,3,5,6] To prevent VTE after TKA, administration of prophylaxis is recommended by both the American Academy of Orthopaedic Surgeons and the American College of Chest Physicians.[8-11]

Prophylactic strategies to prevent VTE after primary TKA vary widely and are influenced by surgeon experience, current research, and historical precedent. Aspirin, enoxaparin, apixaban, rivaroxaban, and coumadin are the most common methods of DVT chemoprophylaxis used by orthopedists.[3,5,10,12-16] However, anticoagulation after TKA can pose unique challenges because anticoagulation medications must balance the reduction in blood clot formation, with the risk of post-operative bleeding, hematoma formation, revision surgery, and infection.[17-19] Despite decades of clinical experience, new technology on implant design, better surgical procedure, improved physical therapy protocol, and hundreds of studies, the ideal method of VTE prophylaxis remains controversial. This has resulted in variability and inconsistency of prophylaxis for TKA patients and a concern that many patients may be left at risk with no prophylaxis or suboptimal prophylaxis. The specific aim of this study was to evaluate the use of different post-operative prophylactic strategies on the rates of symptomatic VTE incidence after primary TKA.

METHODS

Subjects. Institutional Review Board approval was obtained for this study. This retrospective study reviewed the clinical charts of patients (greater than 18 years of age) who had undergone primary TKA procedures from January 2015 through July 2020 from hospitals within a single institution in the Midwest region. Patients who underwent unicompartmental knee arthroplasty, revision knee arthroplasty, same day bilateral TKAs, or had less than 90 days follow-up without any complication were excluded from this study.

Variables. The retrospective chart review gathered patient demographic data including age, gender, body mass index (BMI), surgical date, site of procedure, prophylaxis medication used during inpatient care and outpatient care, amount of medication, length of medication, and length of hospital stay. Post-operative complications included those occurring within 90 days post-operatively including symptomatic VTEs and upper and lower gastrointestinal (GI) bleeding requiring medical attention. Change in management protocols after post-operative complications and mortality also were recorded.

Statistical Analysis. Descriptive statistics of the mean, standard

deviation, range, and percentages were determined for subject demographics, prophylaxis medication used during inpatient care and outpatient care, length of medication, and complications. One-way analysis of variance (ANOVA) with the Least Significant Difference (LSD) multiple comparisons post hoc test method was utilized to determine significant observed differences among different parameters (e.g., age, BMI, length of hospital stay, prophylaxis medication used during inpatient care, and post-operative complications) between the five years. All statistical testing methods were performed using IBM® SPSS Statistics software (version 24.0.0.0; IBM® Corporation, Armonk, NY), and the statistically significant relationships were defined as those with $p < 0.05$. Relative risk ratio with 95% confidence interval was utilized to compare complication rates among therapies. A risk ratio greater than 1.0 indicated an increased risk of complication compared among the other therapies.

RESULTS

There were 6,440 primary TKA cases identified, with only 5,663 of those cases (2,254 males and 3,409 females) included in this study due to exclusion criteria or incomplete inpatient medication. The mean age was 66 ± 10 years (range: 23 - 96 years) and the mean BMI was 34.1 ± 7.1 kg/m^2 (range: 17.7 - 79.1 kg/m^2). The mean hospital stay was 2.1 ± 1.3 days (range: 0 - 34; Table 1). There were 155 patient deaths recorded in this study, and 10% (n = 15) were within 90 days post-operatively due to natural causes or other medical conditions.

There were 0.9% (n = 50) post-operative complications including symptomatic DVT (0.5%), PE (0.3%), unspecified VTE (0.04%), and upper and lower GI bleeding (0.09%). The mean age for these complication groups was 65 ± 11 years (range: 41 - 83 years) and the mean BMI was 33.6 ± 6.0 kg/m^2 (range: 22.4 - 50.0 kg/m^2). The mean hospital stay for all complication groups was 3.1 ± 2.6 days (range: 1 - 12; Table 1).

There were seven different anticoagulants prescribed as inpatient medication in this study: enoxaparin, rivaroxaban, warfarin, apixaban, aspirin 325 mg, aspirin 81 mg, and heparin (Table 2). Enoxaparin (34% of the patients) was the most frequently used medication for inpatient anticoagulation for DVT chemoprophylaxis. Utilization of rivaroxaban, aspirin 325 mg, aspirin 81 mg, and heparin as inpatient anticoagulation medication were more likely to increase the risk of symptomatic VTE incidence compared to other anticoagulants.

When comparing the yearly breakdown, utilization of enoxaparin as inpatient anticoagulation medication was reduced significantly over the five years (67% vs. 13%, $p < 0.001$), except the years 2018 and 2019 ($p = 0.61$). The other inpatient anticoagulation medications were increased significantly over the years, especially apixaban (6% vs. 49%, $p < 0.001$; Figure 1). Average hospital stays were reduced significantly among the years (2.8 ± 1.7 days vs. 1.5 ± 1.0 days, $p < 0.001$), except the years 2018 and 2019 ($p = 0.61$). The complication rates were not significantly different across the five years (~1%), except the years 2016 and 2019 (0.4% vs 1.2%, $p = 0.04$; Table 3).

The three most common outpatient anticoagulation medications prescribed were apixaban (31%), aspirin 325 mg (38%), and enoxaparin (14%). Of the post-op complications, the most common outpatient medications used were apixaban (26%) and aspirin 325 mg (36%). However, the relative risk ratio results indicating that utilization of warfarin, rivaroxaban, and aspirin 81 mg as outpatient anticoagulation medication were more likely to increase the risk of symptomatic VTE incidence compared to other anticoagulants. The average time of complication detection was 20.8 ± 21.1 days (range: 1 - 87 days), and 40% of the complications found occurred after the patient had completed their anticoagulation medication (Table 4).

When comparing the time of complication and length of time on outpatient anticoagulation medication, the results of this study demonstrated that when enoxaparin, rivaroxaban, and apixaban were used as outpatient anticoagulation medications, more than 54% of complication events occurred after the patient had completed their medication (Table 5).

Table 1. Patient demographics.

Variable	Overall (N = 5,663)	Complication (N = 50)	DVT (N = 28)	PE (N = 15)	VTE (N = 2)	GI Bleed (N = 5)
Gender, n (%)						
Female	3,409 (60%)	30 (60%)	14 (50%)	12 (80%)	2 (100%)	2 (40%)
Male	2,254 (40%)	20 (40%)	14 (50%)	3 (20%)	-	3 (60%)
Age, mean years ± SD (range)	66 ± 10 (23 - 96)	65 ± 11 (41 - 83)	65 ± 12 (41 - 82)	63 ± 10 (47 - 77)	70 ± 4 (67 - 72)	73 ± 11 (56 - 83)
BMI, mean kg/m^2 ± SD (range)	34.1 ± 7.1 (17.7 - 79.1)	33.6 ± 6.0 (22.4 - 50.0)	32.2 ± 5.1 (22.4 - 49.0)	35.5 ± 6.1 (23.8 - 43.9)	41.0 ± 12.6 (32.1 - 50.0)	32.9 ± 5.7 (26.8 - 40.3)
Site of Procedure, n (%)						
Left	2,743 (48%)	25 (50%)	15 (54%)	8 (53%)	-	2 (40%)
Right	2,920 (52%)	25 (50%)	13 (46%)	7 (47%)	2 (100%)	3 (60%)
Hospital stay, mean days ± SD (range)	2.1 ± 1.3 (0 - 34)	3.1 ± 2.6 (1 - 12)	2.3 ± 1.7 (1 - 9)	4.7 ± 3.7 (1 - 12)	2.5 ± 0.7 (2 - 3)	2.8 ± 1.1 (1 - 4)

Table 2. Inpatient medication effects on complications.

Inpatient Medication	Overall (N = 5,663)	Complication (n = 50)	Relative Risk Ratio (RR)	95% RR Confidence Interval	DVT (n = 28)	PE (n = 15)	VTE (n = 2)	GI Bleed (n = 5)
Enoxaparin	1,941 (34%)	16 (32%)	0.9	(0.6 - 1.6)	9 (32%)	4 (27%)	1 (50%)	2 (40%)
Rivaroxaban	484 (9%)	6 (12%)	1.5	(0.4 - 3.4)	6 (21%)	-	-	-
Warfarin	182 (3%)	1 (2%)	0.6	(0.1 - 4.4)	-	1 (7%)	-	-
Apixaban	1,785 (32%)	10 (20%)	0.5	(0.5 - 1.1)	2 (7%)	4 (27%)	1 (50%)	3 (60%)
Aspirin (325 mg)	1,140 (20%)	13 (26%)	1.4	(0.5 - 2.6)	9 (32%)	4 (27%)	-	-
Aspirin (81 mg)	122 (2%)	2 (4%)	1.9	(0.3 - 7.7)	1 (4%)	1 (7%)	-	-
Heparin	9 (0.2%)	2 (4%)	26.2	(0.3 - 91.8)	1 (4%)	1 (7%)	-	-

Table 3. Yearly comparison of complication to hospital stay time and complication rate.

	Year 2015 (n = 1,020)	Year 2016 (n = 1,089)	Year 2017 (n = 1,094)	Year 2018 (n = 1,203)	Year 2019 (n = 1,032)
Hospital stay (days)	2.8 ± 1.7 (1 - 34)	2.6 ± 1.2 (1 - 20)	2.2 ± 1.0 (0 - 10)	1.5 ± 1.1 (0 - 14)	1.5 ± 1.0 (0 - 9)
Complication	10 (1.0%)	4 (0.4%)	8 (0.7%)	11 (0.9%)	12 (1.2%)

Note: Year 2020 was excluded due to only have four months of data.

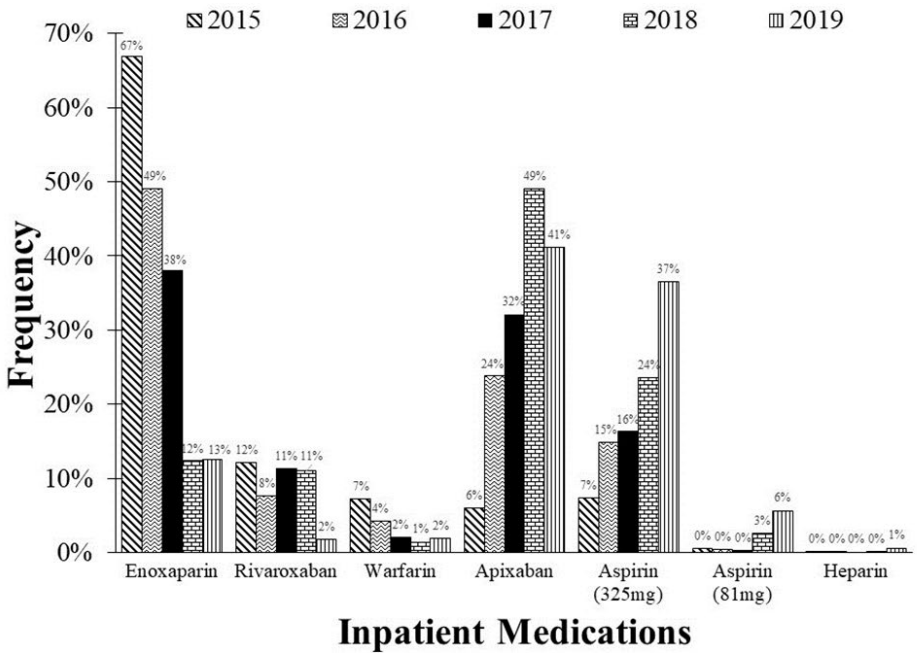

Figure 1. Yearly comparison of inpatient medications.

Table 4. Outpatient medication effects on complications.

	Overall (N = 5,663)	Complication (n = 50)	Relative Risk Ratio	95% RR Confidence Interval	DVT (n = 28)	PE (n = 14)	VTE (n = 2)	GI Bleed (n = 5)
Outpatient Medication								
Enoxaparin	800 (14%)	7 (14%)	1.0	(0.5 - 2.2)	3 (11%)	1 (7%)	1 (50%)	2 (40%)
Rivaroxaban	266 (5%)	3 (6%)	1.3	(0.3 - 4.1)	3 (11%)	-	-	-
Warfarin	284 (5%)	5 (10%)	2.1	(0.4 - 5.3)	1 (4%)	4 (27%)	-	-
Apixaban	1,766 (31%)	13 (26%)	0.8	(0.5 - 1.5)	5 (18%)	5 (33%)	1 (50%)	2 (40%)
Aspirin (325 mg)	2,167 (38%)	18 (36%)	0.9	(0.6 - 1.6)	14 (50%)	3 (20%)	-	1 (20%)
Aspirin (81 mg)	295 (5%)	4 (8%)	1.6	(0.4 - 4.4)	2 (7%)	2 (13%)	-	-
Time to Complication	-	21 ± 21 (1 - 87)	-	-	23 ± 23 (2 - 87)	14 ± 14 (2 - 54)	51 ± 16 (40 - 62)	19 ± 19 (1 - 50)
Complication vs. on/off regimen								
On	-	30 (60%)	-	-	17 (61%)	11 (73%)	-	2 (40%)
Off	-	20 (40%)	-	-	11 (39%)	4 (27%)	2 (100%)	3 (60%)

Table 5. Outpatient medication regimen on complications.

	Time on Outpatient Medication (Days)	Time of Complication (Days)	On Regimen	Off Regimen
Overall complication (N = 50)	22.2 ± 18.0 (0 - 90)	20.8 ± 21.1 (1 - 87)	30 (60%)	20 (40%)
Outpatient Medication				
Enoxaparin (n = 7)	8.4 ± 1.7 (7 - 12)	16.0 ± 15.8 (1 - 40)	3 (43%)	4 (57%)
Rivaroxaban (n = 3)	11.0 ± 2.7 (9 - 14)	39.3 ± 19.7 (26 - 62)	-	3 (100%)
Warfarin (n = 5)	50.0 ± 45.8 (0 - 90)	8.6 ± 7.8 (2 - 22)	4 (80%)	1 (20%)
Apixaban (n = 13)	19.1 ± 17.7 (9 - 60)	25.9 ± 23.2 (2 - 75)	6 (46%)	7 (54%)
Aspirin (325 mg) (n = 18)	26.2 ± 7.8 (6 - 32)	22.1 ± 24.2 (2 - 87)	13 (72%)	5 (28%)
Aspirin (81 mg) (n = 4)	30.0 ± 0.0 (30 - 30)	8.3 ± 4.2 (4 - 14)	4 (100%)	-

DISCUSSION

The specific aim of this study was to evaluate the use of different post-operative prophylactic strategies on the rates of symptomatic VTE incidence after primary TKA. Complication rates were not significantly different across the five years despite which inpatient or outpatient anticoagulation prophylaxis was used. Forty percent of the complications took place after patient had completed their anticoagulation medication, and when looking specifically at enoxaparin, rivaroxaban, and apixaban as outpatient prophylaxis, more than 54% of complications occurred after the patient had completed their medication.

Patients undergoing TKA are at high risk of VTE if they do not receive anticoagulation as it is considered as the third most frequent cause for hospital readmission after TKA.[20] There is considerable debate regarding the appropriate post-operative prophylactic agent for patients undergoing primary TKA,[21-23] with many surgeons making decisions based on anecdotal evidence and historical precedent. As VTE is an uncommon event with reported rates of symptomatic VTEs within 90 days of TKA at less than 2%,[24,25] and the mortality rates from VTE following lower limb arthroplasty low (less than 1%),[25-28] it is difficult to acquire sufficient statistical power to discern differences between agents.

Over the five-year study period, there was a transition from using enoxaparin to oral anticoagulation therapy such as apixaban, rivaroxaban, and aspirin. At the end of the study period, some surgeons' preference was to prescribe all their patients one of the direct oral inhibiters (e.g., apixaban, rivaroxaban), whereas others were risk stratifying based on patients' history. Due to this study being a retrospective review, there was no standardization of medication or length of time. Patients that were on anticoagulation before the procedure also were restarted on their previous regimen after surgery.

Two previous meta-analyses found that low-dose aspirin has a similar efficacy in the prevention of VTE when compared to enoxaparin.[29-31] Recently, there has been more literature comparing low dose aspirin to high-dose aspirin. In a study by Faour et al.[32], low-dose aspirin was found to be as efficacious to high-dose aspirin in the prevention of VTE following TKA. In another study by Parvizi et al.[33], the efficacy and adverse event profiles of low-dose (81 mg twice daily) versus high-dose aspirin (325 mg twice daily) regimens were examined

high-dose aspirin (325 mg twice daily) regimens were examined for patients undergoing total hip and knee arthroplasty and they also found that low dose aspirin was as efficacious to high-dose aspirin in the prevention of VTE. A meta-analysis of randomized controlled trials comparing dabigatran, rivaroxaban, apixaban, and enoxaparin reported incidence of symptomatic VTE as 0.7%, 0.5%, 0.5%, and 0.8%, respectively.[34] None of these studies mentioned compared prophylaxis regimens in patients with known hypercoagulable risk factors such as those with inherited blood clotting disorders, history of previous VTE, obesity, malignancy, estrogen therapy, and varicose veins and increased age.[35]

One result of this study captured VTEs occurred at an average of 20 days after discharge, and 40% of those patients had completed their anticoagulation medication at the time of VTE complication. Specifically, the average length of apixaban, rivaroxaban, and enoxaparin dosing were 17, 10, and 8 days, respectively, while 54% of the apixaban, 100% of the rivaroxaban, and 57% of the enoxaparin post-op symptomatic VTEs occurred after medication completion. These findings were similar to a study by Warwick et al.[36] in 2007, where they found that mean times to VTE after TKA was 9.7 days (SD 14.1 days), but 27% of patients who received the recommended forms of prophylaxis were no longer receiving it after 7 days. Current treatment guidelines for patients following TKA recommended the routine administration of a prophylactic anticoagulant for at least 10 days after the operation.[37] The American Academy of Orthopaedic Surgeons (AAOS) and the American College of Clinical Pharmacy (ACCP) guidelines for VTE prophylaxis for patients undergoing elective TKA also stated the duration must be at least 10 to 14 days, and up to 35 days regardless of the medication being used.[19] This indicated it was likely some complications could have been avoided by extending the duration of the medications.

One possibility for the average time to VTE to occur after average medication completion could be due to a rebound hypercoagulable effect. In 2018, Li et al.[38] reported that although a rebound effect is controversial, physicians should be aware of the possibility. The mechanism behind this rebound hypercoagulable phenomenon after discontinuation is uncertain. It has been suggested for rivaroxaban that decreased plasma concentration after its discontinuation results in loss of prothrombinase/factor Xa inhibition at the thrombotic sites, thus leading to prothrombotic activity.[39] Another possibility is the anticoagulation medications were masking the symptoms of the VTE or preventing it from enlarging. Often DVTs are created intraoperative, confirmed by venographic and leg-scanning studies, but are asymptomatic or silent until they can enlarge due to prolonged impairment of venous function, sustained hypercoagulability, or impairment of the endogenous anticoagulant systems.[40]

Limitations. This study had certain limitations. First, a small sample size of post-operative complications found made applying tests of significance to certain variables difficult. A total of 3,400 patients would afford an adequate trial at 95% power and 5% significance, assuming a baseline symptomatic VTE event rate of 1%. Second, this study was a retrospective chart review study that introduced the possibility of selection and/or observation bias, as it was neither randomized nor blinded. Third, patient compliance (or lack thereof) to the post-operative prophylactic regime was not available. Fourth, the information in this study was limited to the specified time within a single institution and there is a possibility of under-reporting that may have played a role, as many DVTs are diagnosed in the outpatient clinic or in the community. Fifth, minor bleeding complications, such as surgical site hematoma and post-operative transfusions, were not recorded in a consistent manner, therefore not included in this study. Sixth, medications purchased over the counter (e.g., aspirin) or provided as samples by physicians were not available in the recorded data. Lastly, a power analysis was not performed since the data were reviewed retrospectively. Further evaluation in a larger randomized controlled study is required to support the findings of this study. The plan is to use these data and perform a quality improvement project to standardize prophylactic anticoagulation strategies after primary TKA in the future.

CONCLUSIONS

Choice of post-operative prophylaxis agents after primary TKA remains an important issue. The observed incidence of symptomatic VTE events in this study is similar to previous literature, regardless of the type of post-operative prophylaxis regimen prescribed after TKA procedure. A higher rate of VTE incidence was observed after completion of apixaban, rivaroxaban, and enoxaparin therapies, suggesting that a longer treatment course may reduce VTE incidence further. In conclusion, the ultimate choice of prophylaxis remains with the treating physician and his or her unique knowledge of a patient's medical history, especially for patients with known risk factors for VTEs.

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