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Effective VTE prophylaxis with enoxaparin after elective THR or TKR: a retrospective observational study

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Abstract

Background: Orthopedic patients are at the highest risk for venous thromboembolism (VTE). Nowadays, with VTE prophylaxis as a routine in patients undergoing total hip replacement (THR) and total knee replacement (TKR), fatal pulmonary embolism (PE) is rare and the rates of symptomatic VTE within 3 months dropped to 1.3%–10%, compared with the rates of 50%–70% before VTE prophylaxis implementation. In this study, we aim to evaluate the VTE prophylaxis and incidence in patients who underwent THR and TKR in Centro Hospitalar Universitário de Santo António (CHUdSA).

Methods: We included 483 patients who underwent elective THR or TKR in CHUdSA from March 2019 to February 2020 and who were under enoxaparin as a VTE prophylaxis drug. All data related to prescribed enoxaparin were collected from the nationwide common electronic drug prescription system (PEM).

Results: Of the 483 eligible patients, 192 (39.75%) underwent elective THR and 291 (60.25%) underwent TKR. Enoxaparin was prescribed for 31.86 ± 5.98 and 30.28 ± 5.97 days, on average, for the THR and TKR groups, respectively ($P = .005$). Patients completed, on average, 29.38 ± 8.12 days and 28.20 ± 7.32 days of VTE prophylaxis with enoxaparin in the THR and TKR groups, respectively ($P = .098$). The incidence of VTE was approximately 3.13% and 0.69% in the THR and TKR groups, respectively ($P = .064$).

Conclusion: In CHUdSA, we usually prescribe enoxaparin 40 mg once daily for up to 35 days for VTE prophylaxis after THR or TKR. High therapeutic compliance rates resulted in very few events.

Keywords: total hip replacement, total knee replacement, venous thromboembolism, prophylaxis

Introduction

All medical and surgical patients are at risk for venous thromboembolism (VTE) during and after hospitalization.[1-3] Approximately two-thirds of patients with symptomatic VTE experience deep venous thrombosis (DVT) alone, while one-third will suffer associated pulmonary embolism (PE).[4,5] Orthopedic patients are at the highest risk among all patients for DVT and PE.[1] In fact, VTE is an important complication after joint replacement surgery of the lower extremity,[6-8] and without prophylaxis, DVT occurs in 50%–60% of the patients undergoing total hip replacement (THR)[7,9,10] and in 50%–70% of those undergoing total knee replacement (TKR).[7,11,12] VTE can occur up to three months after THR or TKR[1,13] and is the most common cause of readmission after THR.[1]

Orthopedic patients undergoing a major surgery encompass all pathophysiologic processes included in Virchow triad involved in VTE: the use of a tourniquet, immobilization, and bed rest cause venous blood stasis; surgical manipulations of the limb cause endothelial vascular injuries; trauma is associated with tissue factor release leading to increased coagulation; and the use of polymethylmethacrylate (PMMA) bone cement increases hypercoagulability.[1]

Nowadays, with VTE prophylaxis as a routine among patients undergoing THR and TKR, fatal PE is rare and the rates of symptomatic VTE within 3 months dropped to 1.3%–10%.[1,8] Thus, VTE is a serious but decreasing complication after major orthopedic surgery.[14]

Several international guidelines have been published for VTE prophylaxis in major orthopedic surgery. The American College of Chest Physicians (ACCP) ninth edition guidelines are probably the most complete and used worldwide.[8] These guidelines recommend the use of the following for a minimum of 10–14 days and up to 35 days: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose vitamin K antagonist (VKA), aspirin (grade 1B), or an intermittent pneumatic compression device (IPCD) (grade 1C).[14] ACCP recommends the use of LMWH in preference to the other pharmacologic agents listed as alternatives,[14] and it should be started either 12 hours or more preoperatively or 12 hours or more postoperatively.[14]

Despite these recommendations, aspirin has been the most commonly used agent for VTE prophylaxis in the United States of

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America for a while now.[15] In fact, there seems to be no difference in the risk of developing a VTE event after prophylaxis with aspirin when compared with other prophylactic agents, while aspirin patients experience lower rates of bleeding, wound infection, and periprosthetic joint infection.[15] Therefore, the International Consensus Meeting for VTE: Hip & Knee (ICM-VTE: Hip & Knee), in a recently published article (2022), recommends low-dose aspirin as the most effective and safest method of thromboprophylaxis in these patients.[15]

In this study, we aim to describe the number of days of VTE prophylaxis with enoxaparin prescribed by orthopedic surgeons and the respective compliance of patients undergoing THR or TKR surgeries from March 2019 to February 2020 in Centro Hospitalar Universitário de Santo António (CHUdSA), Porto, Portugal. Our secondary aim is to evaluate the incidence of symptomatic VTE in these patients.

Methods

Data source

All data related to prescribed enoxaparin were collected from the nationwide common electronic drug prescription system (PEM). In this platform, one can verify the prescribed quantity of a certain drug and the number of tablets from that drug that the patient actually bought at the pharmacy. Considering that patients pay a percentage of the price of the enoxaparin they buy at the pharmacy, we assumed they administered all the enoxaparin they bought. Hence, the number of days enoxaparin was prescribed resulted from the sum of the number of days the patient stayed in the hospital after surgery and the quantity of enoxaparin prescribed for home; the number of days enoxaparin was administered to each patient resulted from the sum of the number of days the patient stayed in the hospital after surgery and the quantity of enoxaparin the patient bought at the pharmacy.

Patient population

All patients who underwent elective THR or TKR in CHUdSA from March 2019 to February 2020 were analyzed.

Of the 523 patients in this situation, 483 were eligible. 40 patients were excluded for one of the following reasons: 25 patients were already under an antithrombotic regimen before this surgery for other causes; 14 patients were already dead by the time we collected the information and PEM is blocked for deceased people, so we did not have access to their information; and one patient was prescribed with a novel oral anticoagulant (NOAC) instead of enoxaparin.

Ethics

All data were collected following CHUdSA board approval.

TABLE 1

Baseline characteristics of patients

	Total Hip Replacement Cohort (n = 192)	Total Knee Replacement Cohort (n = 291)	Entire Cohort (n = 483)
Age, y			
Mean ± SD	65.70 ± 11.15	69.95 ± 8.416	68.26 ± 9.81
Range	31–87	22–88	22–88
Sex, No. (%) female	94 (48.96)	226 (77.66)	320 (66.25)

Statistical analysis

Data analysis was performed using Microsoft Office Excel 2016 and SPSS Statistics V25. Comparisons between groups were performed using unpaired two-tailed *t* test, Mann-Whitney *U* test, and Fisher exact test. A P value $<.05$ was considered significant.

Results

In CHUdSA, a University Hospital and one of the largest hospitals in Portugal, the most common VTE prophylaxis regimen prescribed for patients undergoing elective THR or TKR is 40 mg of enoxaparin once daily (qd) begun 12 hours postoperatively. As mentioned in this study, we excluded patients under antithrombotic treatments for other reasons or the ones prescribed with other prophylactic regimens rather than enoxaparin.

Between March 1, 2019, and February 29, 2020, we identified 483 eligible patients. Of these patients, 192 (39.75%) underwent elective THR and 291 (60.25%) underwent TKR. The cohort consisted of 320 (66.25%) female and 163 (33.75%) male patients, with a mean age of 68.26 years (69.20 ± 9.77 for women and 66.42 ± 9.71 for men). The baseline characteristics of the patients are presented in Table 1.

On average, patients in the TKR group were significantly older than the ones in the THR group (69.95 ± 8.41 vs 65.70 ± 11.15; $P < .001$). The THR group stayed, on average, 6.20 ± 5.00 days at the hospital after surgery, whereas the TKR group stayed, on average, 5.21 ± 2.91 days ($P < .001$).

On the one hand, enoxaparin was prescribed for 31.86 ± 5.98 and 30.28 ± 5.97 days, on average, for the THR and TKR groups, respectively (Figs. 1 and 2). This difference is statistically significant ($P = .005$). On the other hand, patients in the THR group completed, on average, 29.38 ± 8.12 days and patients in the TKR group completed, on average, 28.20 ± 7.32 days of VTE prophylaxis with enoxaparin (Figs. 3 and 4). These results are not statistically different ($P = .098$). We had a rate of compliance (patients who completed all days of prescribed enoxaparin) of approximately 83.23%, whereas 11 patients (2.28%) completed less than 10 days of enoxaparin.

Finally, concerning the incidence of thromboembolism, we had no cases of PE, five cases of DVT, and three cases of superficial venous thrombosis (SVT). Of the DVT cases, four occurred in the THR group, while one occurred in the TKR group. Regarding SVT, we found two cases in the THR group of patients and one in the TKR group. Thus, the incidence of VTE was approximately 3.13% and 0.69% in the THR and TKR groups, respectively ($P = .064$). As mentioned in the Methods section, 14 patients were dead by the time we collected the information; of those, we could retrieve information for nine patients, and none had died due to thrombotic disease or pulmonary embolism.

Discussion

As mentioned above, patients undergoing major orthopedic surgery (where THR and TKR are included) are at the highest risk for VTE during and after hospitalization. However, the incidence of VTE after these surgeries dropped significantly with the implementation of mechanical and, mainly, pharmacologic VTE prophylaxis. In CHUdSA, enoxaparin is the drug of choice for pharmacologic VTE prophylaxis after THR and TKR, which is in accordance with the ACCP guidelines.[14] Despite these recommendations, recent studies show the superiority of rivaroxaban and other NOACs in preventing VTE, without increasing major bleeding or all-cause mortality,

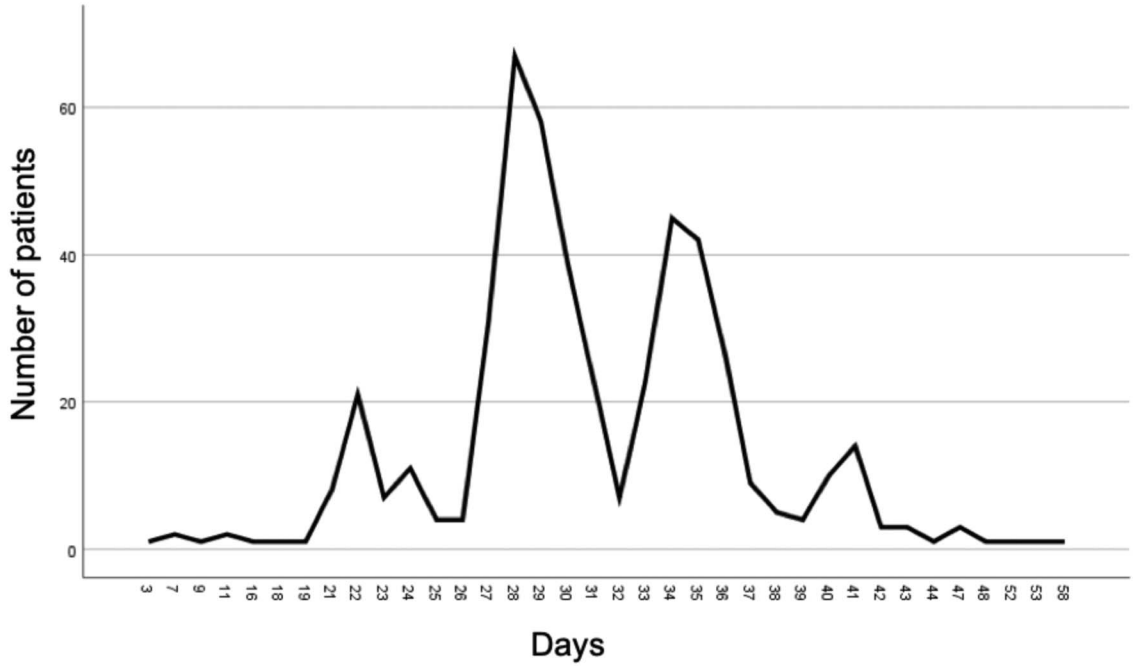

Figure 1. Total number of days of prescribed thromboprophylaxis (THR and TKR).

compared with enoxaparin.[16-19] Furthermore, even more recently, the ICM-VTE: Hip & Knee recommendations state aspirin as the most effective and safest choice.[15]

In our analysis, we found out that women compose the vast majority of the patients undergoing TKR (77.66%) in this hospital (Table 1), so one might point out that the incidence of knee osteoarthritis might be bigger in women. The numbers between sexes are similar in the THR group (Table 1). On average, women treated in this hospital with these elective procedures were older than men (Table 1).

In addition, TKR patients were older than THR patients. These results were statistically significant, so we may suppose that the pathologies treated with an elective THR (mainly, hip osteoarthritis) develop earlier.

Our study points out to a statistically significant difference in the number of days of enoxaparin prescribed in our hospital for these

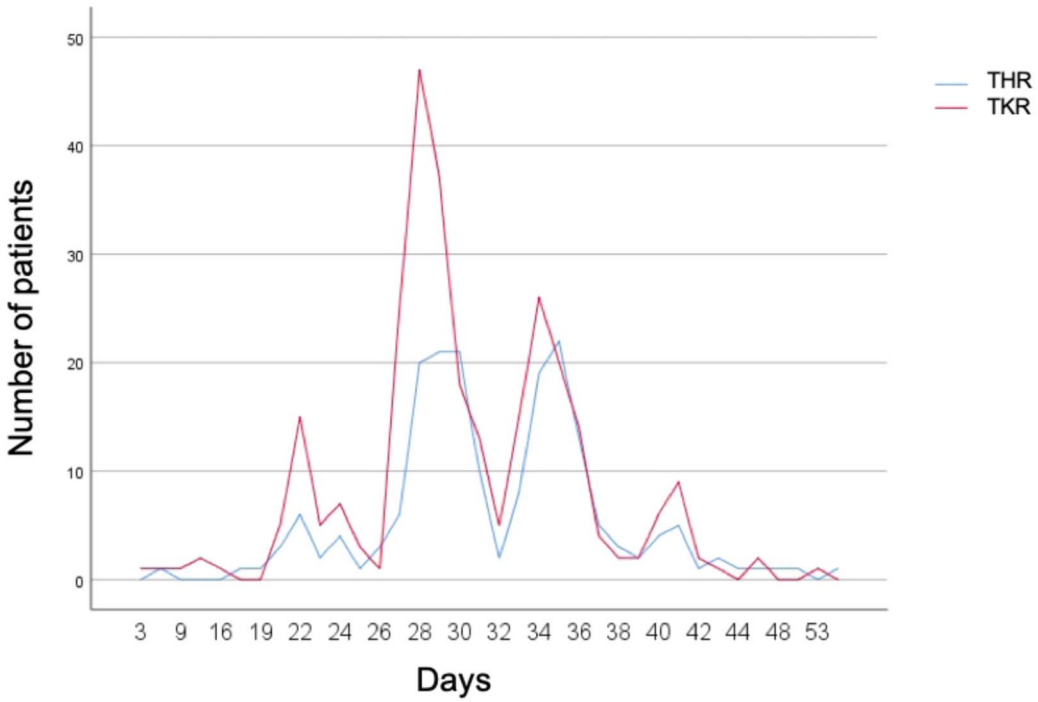

Figure 2. Number of days of prescribed thromboprophylaxis by procedure.

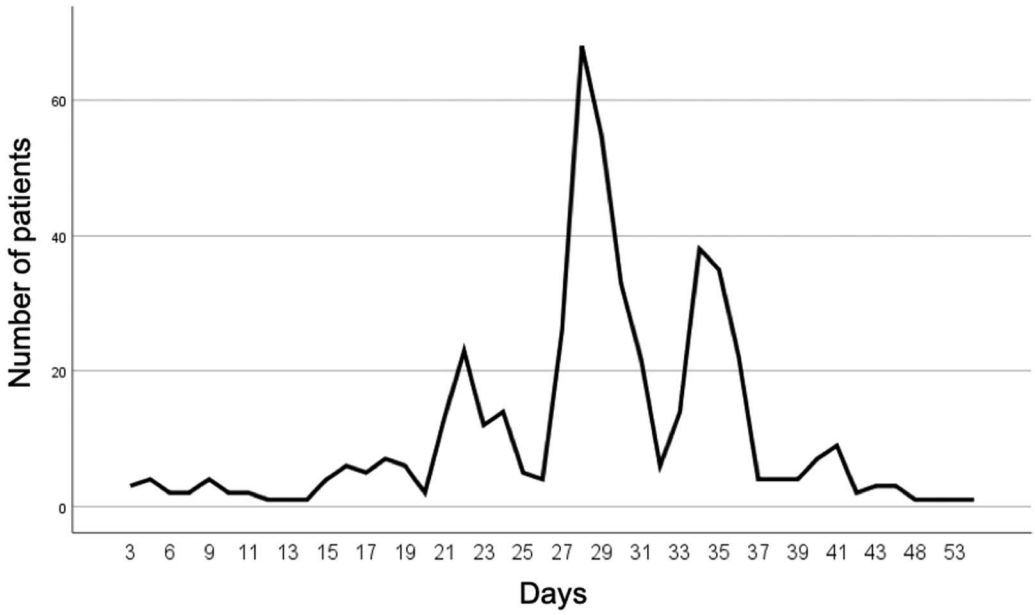

Figure 3. Total number of days of thromboprophylaxis completed (THR and TKR).

two groups of patients. Apparently, there is no reason for this situation, but it is important to note out that, in both groups, our prescriptions are in accordance with the ACCP guidelines (31.86 ± 5.98 days and 30.28 ± 5.97 days in the THR and TKR groups, respectively).

The incidence of VTE was higher in the THR group in our patients (3.13% vs 0.69%), and although the difference did not reach the statistical difference ($P = .064$), it came really close to doing so, which might lead us to think that patients undergoing THR are more predisposed to thromboembolic events when compared with the TKR procedure. These, nonetheless, somehow contradict what was stated in the works produced before VTE prophylaxis was the norm, where the incidence of VTE seemed higher after a TKR surgery than a THR surgery (50%–70% vs 50%–60%, respectively).[7,9-12] In addition, according to ICM-VTE: Hip & Knee, patients undergoing TKR have indeed a higher VTE risk than THR patients,[15] which did not seem to be true in our institution.

In addition, we had a very low rate of VTE events in our study, and curiously, the cases we found were among patients who had

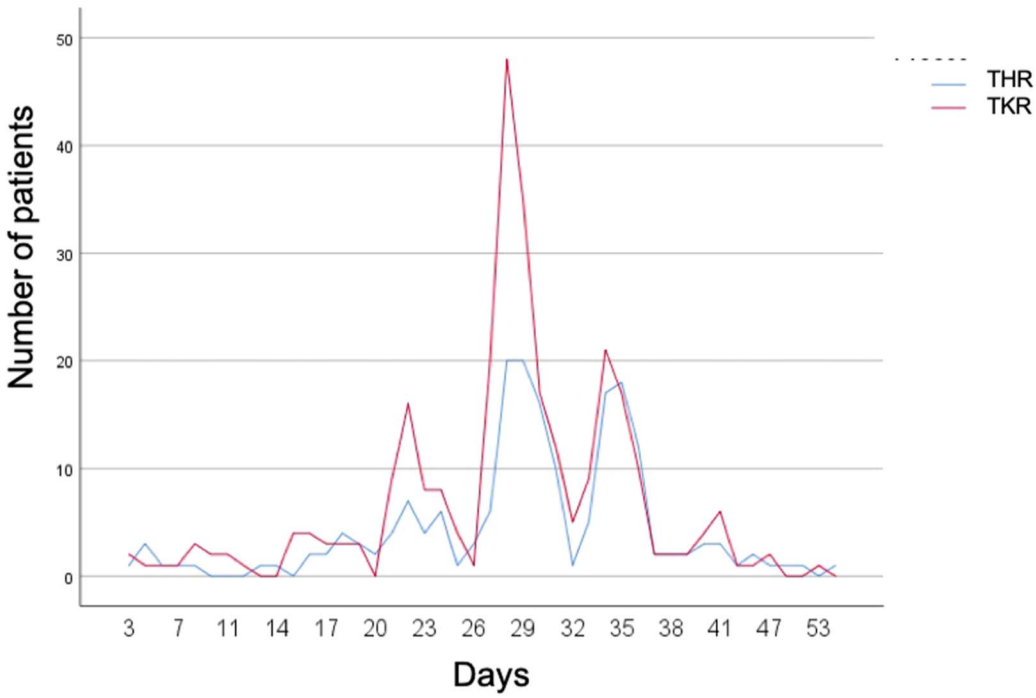

Figure 4. Number of days of thromboprophylaxis completed by procedure.

fulfilled (according to our criteria) the prescribed prophylaxis. Because we had a very high rate of compliance (83.23% of the patients completed the total number of days of prescribed enoxaparin) and only 2.28% did not fulfill the minimum number of days of thromboprophylaxis as recommended by the ACCP (10 days), these results may show that our current strategy (in accordance with the ACCP guidelines) is very efficient in preventing VTE events, explaining these low rates of events.

As far as the limitations of our study are concerned, it is important to refer that we excluded all patients who were dead by the time we collected the data. Considering the short amount of time between this elective surgery and their death, one might think their death could have been related to acute events after surgery (such as fatal PE), and if so, we would have underestimated our rate of VTE events. In fact, the national system is blocked for deceased people, so we can only know the reason of death for the ones who died at our institution. Despite this fact, the number of deaths was small (14 in 523), and the ones we could find information of died of unrelated causes.

Another limitation is that we considered that all the enoxaparin bought by the patient was actually administered, which might not be true. Despite such limitation, the fact that patients have to pay a percentage of the price of enoxaparin at the pharmacy might have helped improve their compliance. Moreover, our low rate of events might also point out a very high compliance rate.

It is also important to state that we did not consider safety issues related to the use of anticoagulants, as bleeding rates.

Conclusion

Patients undergoing major orthopedic surgery, such as THR or TKR, are at the highest risk for VTE events. For this reason, they should be under a VTE prophylaxis regimen. In our hospital, we usually prescribe enoxaparin 40 mg qd for up to 35 days, according to ACCP guidelines, and the high rates of compliance resulted in very few events.

As for the future, we believe it could be important to compare the results of VTE prophylaxis with enoxaparin vs aspirin (or even NOACs) in our patients because these agents seem to be at least as effective and are of oral administration.

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Conflicts of interest

The authors declare no conflicts of interest.

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