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ORIGINAL ARTICLE

Protocol implementation for venous thromboembolism prophylaxis: a before-and-after study in medical and surgical patients*

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ABSTRACT

Objective: This study aimed to assess the adequacy of venous thromboembolism (VTE) prophylaxis prescription after a protocol implementation. **Methods:** This was a before-and-after study conducted in a tertiary care hospital in Rio Grande do Sul, Southern Brazil. Medical and surgical inpatients aged 18 years or older were assessed for VTE risk and subsequently for thromboprophylaxis adequacy, according to their risk. The evaluations occurred before and after the protocol strategy implementation; it consisted of an online platform to access the protocol, a public posting of the protocol diagram, clinical alerts on the medical staff TV, e-mail alerts, and pop-up alerts on the computerized physician order entry system. The main outcome measure was the adequacy of VTE prophylaxis prescription according to the protocol. **Results:** A total of 429 patients were evaluated for thromboprophylaxis adequacy (213 before and 216 after). The prevalence of adequacy increased from 54% to 63% (pre and post-intervention, respectively), and after adjustment for patient type and phase of the study, the prevalence ratio reached (PR)=1.20, 95% confidence interval (CI) 1.02-1.42. **Conclusion:** The results showed that the overall appropriateness of thromboprophylaxis prescription was weakly improved. Despite these results, this study provides evidence to date a bunch of strategies for protocol implementations in private institutions in middle-income countries with an open medical staff, as there are few studies investigating these simple and pragmatic interventions.

Keywords: Venous thromboembolism; Guideline adherence; Prevention; Thromboprophylaxis.

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition in populations with chronic diseases, especially in hospitalized patients.[1] Epidemiologic studies report that about 900,000 people are affected each year in the United States.[2] The mortality in the United Kingdom is estimated in 25,000 deaths from preventable hospital-acquired VTE every year,[3] while in Brazil the estimates are probably underreported: less than 2,000 deaths due to DVT and PE in 2015.[4]

In hospitals, VTE is a major cause of morbidity and mortality[5] and, despite efforts to guide evidence-based practice,[3,6] thromboprophylaxis rates remain low worldwide.[7,8] Factors related to healthcare resources, medical staff and reimbursement patterns have been associated with low protocol adherence and, consequently, VTE prophylaxis inadequacy.[9]

In this regard, quality improvement (QI) strategies to engage hospital staff and increase prescription of prophylaxis[6,8,10] have been tested, though methods such as multifaceted interventions still require further study.[11] Kahn et al.[5,7] have suggested that multifaceted interventions with an alert component may be the most effective initiative to improve thromboprophylaxis in hospitalized patients, highlighting the importance of context with respect to the adoption of specific QI interventions.[12] Thus, this study aimed to describe a pragmatic intervention for a protocol implementation, which included a computerized alert for prescribers and assess the adequacy of the prescriptions to thromboprophylaxis before and after this implementation.

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METHODS

Design

This was a before and after study performed at Hospital Moinhos de Vento (HMV), a 380-bed private non-profit tertiary hospital in Rio Grande do Sul, Brazil.

Participants

In both phases, patients were prospectively interviewed according to their availability to answer the questionnaire. Eligible participants included those admitted for one day or longer for medical or surgical conditions. Patients were not eligible if they met any of the following exclusion criteria: (1) age younger than 18 years old; (2) VTE diagnosis at admission; (3) anticoagulant treatment at admission; (4) direct admission to an intensive care unit; (5) length of stay above 120 days; or (6) pregnancy. Patients were classified as medical or surgical based on the reason for admission.

Procedures

Data regarding VTE risk factors such as, bleeding risk, admitting specialty and surgical procedure were obtained through interviews and chart reviews, and recorded on a data collection form. Pharmacological prophylaxis data were abstracted from the electronic medical record (EMR) system.

Physicians with management VTE expertise and clinical research participated in planning all phases of the study, including testing the form before its application. The interviews were conducted by pharmacists and nurses previously trained. The same form was used for both phases of the study. The baseline collection occurred in 2014, before the protocol implementation.

The local VTE prophylaxis protocol was developed based on the 9th Edition of the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines.[13] For VTE risk evaluation, the protocol applies the Padua Prediction Score risk assessment model[14] for medical patients, while for surgical patients risk is assessed according to patient-specific characteristics, incorporating surgery-specific risk in addition to medical factors.[15] According to the local protocol, pharmacologic prophylaxis must be considered for patients at risk for VTE who are not at high risk for major bleeding complications. For medical patients, the thromboprophylaxis was considered adequate when patients were at high risk for VTE, without risk of bleeding, and received the first prescription of anticoagulant up to 24 hours of their admission. For surgical patients, the appropriate prescription was defined when they were at intermediate or at high risk of VTE, without risk of bleeding, and received the first prescription of anticoagulation up to 24 hours after surgery.

Risk of bleeding was considered present if a patient had multiple risk factors such as (1) active gastroduodenal ulcer; (2) bleeding (episodes that required transfusion, hospitalization or surgical intervention for control, excluding dental, nasal and skin-related, and hemorrhoids) over the 3 months before admission; or (3) had a platelet count <50,000 per mm^3.[13] An International Normalized Ratio (INR) >1.5 was considered as an additional risk factor for bleeding. If no platelet count or INR test were available (or requested) and no risk factors identified during the interview, the risk of bleeding was assumed as low or absent. Recommended thromboprophylaxis is presented in Table 1. The protocol does not recommend an adjusted-dose vitamin K antagonist or aspirin for thromboprophylaxis. Mechanical prophylaxis was recommended only if pharmacological prophylaxis was contra-indicated.

The protocol development was the first component of the intervention. All recommendations previously described were implemented through a web-based platform called IPROTOCOLOS that allows easy access to clinical pathways. The strategies described in Table 2 were developed and implemented along with IPROTOCOLOS tool.

The second phase of the data collection was performed in 2015, after the implementation of all components of the intervention.

In both phases, the enrollment stopped when the exact number of patients defined in the sample size calculation was achieved.

Table 1. Pharmacological thromboprophylaxis recommended.

Type of patient		Recommendation
Medical and surgical	**LMWH**	Enoxaparin 40mg, subcutaneously, every 24h; 40mg, subcutaneously, every 12h if patient >140kg
		OR
	UFH	Sodium heparin 5,000IU subcutaneously every 12h; 5,000IU subcutaneously every 8h if patient >140kg
		OR
	Fondaparinux	2.5mg every 24h (just for patients under risk for thrombocytopenia induced by heparin)
Orthopedic surgery only	**Direct thrombin inhibitors**	Rivaroxaban 10mg, every 24h
		OR
		Dabigatran 220mg, every 24h

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

Sample size calculation and statistics

The sample size was calculated considering a *p*-value of 0.05, 90% power, a 50% rate of VTE thromboprophylaxis adequacy prior to protocol implementation, and an expected absolute increase of 16% in adequacy following protocol implementation.[16] These parameters required 396 patients. In order to ensure the required sample, we planned a 10% enrollment increase, considering possible inadequate information provided by participants that would leave to withdraws. Therefore, the final sample size was 436 patients (218 in each of the study's phases).

Patient characteristics are expressed as mean and standard deviation or median and interquartile range for continuous variables, and frequency and percentage for categorical variables. Group comparisons between the two study phases were made using the *t*-test or a non-parametric test for continuous variables, and the chi-square test for categorical variables. Chi-square testing was used to detect differences in adequacy between 2014 and 2015 (before and after implementation).

Poisson regression with robust variance was used to calculate prevalence ratio (PR) of adequacy (95% confidence interval) when controlled by phase and type of patient (medical or surgical).

All reported *p*-values are two-tailed. p<0.05 was considered statistically significant. The data were analyzed using Stata/IC 15 (StataCorp LLC, TX).

Ethics approval

The study was approved by the HMV Ethics Research Board under number 700.551. All procedures were in accordance with national ethics guidelines[17] and with the 1964 Helsinki declaration.[18] All patients provided written informed consent prior to involvement in this study.

RESULTS

We interviewed a total of 454 patients, 227 patients in each phase (before and after implementation). Of these, we excluded 25 patients (14 in the first phase and 11 in the second phase): 4 patients who had been previously included during the ongoing hospitalization (duplicated), 3 with a length of stay above 120 days and 18 admitted for the treatment of VTE or receiving anticoagulant treatment on admission. At the end of the study, we assessed a total of 429 patients for thromboprophylaxis adequacy (213 before protocol implementation and 216 after).

Table 3 summarizes the characteristics of patients included in the two phases. The main differences between patients included in both phases were the length of stay (two days more in the second phase than in the first phase, $p < 0.05$), the type of patient according to admission service (greater proportion of surgical patients in the first phase, $p < 0.01$), and proportion of acute infection or rheumatologic disorder (which was almost doubled in the second phase, $p < 0.01$). Considering the VTE risk factors, reduced mobility and age over 70 years old were the more prevalent in both phases.

Patients at intermediate or high risk of VTE represented more than three quarters of the patients evaluated in both phases. Considering the contraindication to pharmacological prophylaxis, active ulcer and bleeding at hospital admission were the only variables evaluated, since the platelet count and INR were unavailable for 43.5% and 87.5% of the patients, respectively.

The thromboprophylaxis more frequently prescribed was unfractionated heparin before and after the protocol implementation (Table 4), followed by low molecular weight heparin. In our sample, we did not find either oral anticoagulants prescribed for VTE prophylaxis or mechanical prophylaxis.

Overall thromboprophylaxis adequacy was 54% before the intervention and 63% after the intervention, a 9% increase in the appropriateness of thromboprophylaxis prescription which did not achieve statistical significance (p=0.06). Table 5 demonstrates the prevalence by type of patient, showing that the increase in thromboprophylaxis was due to surgical patients (PR=1.33; 95% CI 1.09-1.62). The prevalence ratio of after vs before intervention overall adequacy of

Table 2. Pragmatic strategy.

Component	Description
Clinical Practice Guideline flowchart	Three simplified flowcharts for orthopedic and non-orthopedic surgical and medical patients were developed. Protocols were posted in the physician common area. Another flowchart with the complete protocol information for surgical patients was posted at the surgical facility.
Clinical alerts on medical staff television	Televisions used for physician updates were used to convey information about the VTE protocol. The information consisted of a visual model of a flowchart with the following text: *Venous thromboembolism: your engagement is key to reduce this risk - Access the platform*
E-mail alerts	E-mail alerts were sent to medical staff informing about the protocol and the link for its access.
Computerized alerts for prescribers	This strategy consisted of a pop-up alert upon the first prescription and at 24h, 48h, and 7 days after admission (for any prescriber accessing the computerized physician order entry system). The alert was shown only for patients aged 18 or more with the following information: "Dear Doctor (name of the attending physician): it is essential that you assess venous thromboembolism risk for your patient and prescribe appropriate prophylaxis."

VTE: Venous Thromboembolism.

Table 3. Characteristics of patients included in the two phases of the study.

Variable	Before (n=213)	After (n=216)	p-value*
Age, median years (Q1; Q3)	64 (46;77)	67.5 (50.5;79.5)	0.135
Female sex, n (%)	131 (61.5)	131 (60.6)	0.856
Body-mass index (kg/m^2), mean (SD)	26.5 (4.9)	26.1 (4.8)	0.387
Length of stay,[a] median days (Q1, Q3)	9 (3;19)	11 (6;22)	<0.05
Admission service			
Medical, n (%)	82 (38.5)	120 (55.1)	<0.01
Surgical, n (%)	132 (61.5)	98 (44.9)	
Risk factors for VTE			
Active cancer,[b] n (%)	47 (22.1)	43 (19.9)	0.583
Previous VTE, n (%)	22 (10.3)	16 (7.4)	0.287
Reduced mobility,[c] n (%)	130 (61.0)	145 (67.1)	0.188
Thrombophilia, n (%)	2 (0.94)	4 (1.8)	0.421
Age ≥70 years, n (%)	88 (41.3)	99 (45.8)	0.345
Heart and/or respiratory failure, n (%)	41 (19.2)	44 (20.4)	0.771
Acute myocardial infarction or ischemic stroke, n (%)	5 (2.3)	6 (2.8)	0.778
Acute infection or rheumatologic disorder, n (%)	50 (23.5)	91 (42.1)	<0.01
Obesity (BMI ≥ 30 Kg/m^2), n (%)	43 (20.2)	46 (21.3)	0.777
Hormonal treatment, n (%)	23 (10.8)	17 (7.9)	0.297
Patients at intermediate or high risk of VTE[d]	181 (85.0)	171 (79.2)	0.117
Contraindication to pharmacological prophylaxis[e]			
Active gastroduodenal ulcer, n (%)	8 (3.8)	6 (2.8)	0.569
Bleeding at hospital admission, n (%)	29 (13.5)	17 (7.9)	0.060

Q1: first quartile; Q3: third quartile; SD: standard deviation; VTE: Venous Thromboembolism; BMI: Body Mass Index. *p value of Pearson χ2 test for categorical variables and of Wilcoxon rank-sum test for numerical variables; [a]Calculated based as the day of the discharge minus the day of admission; [b]Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months, including hormonal blockade; [c]Bedrest with bathroom privileges, more than half of the day; [d]Assesment according to protocol definition, Padua prediction score >=4 for medical patients and type of surgery + individual risc factors for surgical patients; [e]Contraindications defined in accordance with local protocol based on the 9th ACCP.[19]

Table 4. Type of prophylaxis prescribed at the day of the evaluation.

Prophylaxis	Before the intervention (n=213)	After the intervention (n=216)
Unfractionated heparin	84 (57.5)	105 (59.7)
Low molecular weight heparin	62 (42.5)	70 (39.8)
Fondaparinux	-	1 (0.6)
Total	146 (100.0)	176 (100.0)

Table 5. Prevalence and prevalence ratio of thromboprophylaxis adequacy before and after intervention.

	Before (n=213) n (%)	After (n=216) n (%)	p-value*	Prevalence Ratio (CI 95%)	Prevalence Ratio adjusted** (CI 95%)
All patients	115 (54.0)	136 (63.0)	0,06	1.17 (0.99-1.37)	1.20 (1.02-1.42)
Medical	43 (52.4)	65 (54.6)	0,76	1.04 (0.80-1.35)	
Surgical	72 (55.0)	71 (73.2)	<0.05	1.33 (1.09-1.62)	

CI 95%: 95% confidence interval. *p value of Pearson χ^2 test; **Adjusted through Poisson regression (robust variance) for type of patient (medical or surgical) and phase of the study.

thromboprophylaxis increase significantly (PR=1.20; 95% CI 1.02-1.42), just when adjusted for patient type and phase of the study.

DISCUSSION

We describe the results of a pragmatic intervention for a protocol implementation in a tertiary hospital in Southern Brazil. The intervention started through a web-based platform allowing easy access to clinical pathways, followed by other simple initiatives, together with an electronic alert for prescribers physicians. Although there are limitations to assume that the changes in adequacy are exclusively due to the strategies applied,[20] the results found suggest some future considerations for the decision making using such simple interventions. The findings of our implementation are discussed as follows.

First, the main result regarding the overall appropriateness of thromboprophylaxis prescription, after protocol

implementation, showed significant improvement just for adjusted analyses, supported by a significant increase in adequacy for surgical patients after the intervention. This result is sustained by previous evidence in which thromboprophylaxis adequacy is greater in surgical patients and remains inadequate in medical hospitalized patients.[21-23] Nevertheless, this was a stratified analysis which was conducted in order to improve the efficiency of the estimation.[24]

Second, this humble improvement in overall adequacy must be analyzed in depth in further studies conducted using this type of intervention. The current literature shows that just a protocol implementation should be responsible for increasing around 15% in adequacy.[16] In fact, for years cross-sectional studies around the world have documented underprescription of thromboprophylaxis, with adequacy ranging from 10% to 70%,[9,19,21,25] and our overall appropriateness for VTE prophylaxis was similar to previous data.[9,26-28] A recent systematic review of randomized trials showed that electronic alerts were associated with an improvement in prophylaxis prescription (risk difference=16%; 95% CI 12% to 20%).[7] However, it is still unclear how multifaceted interventions (education, reminders, audit and feedback), including electronic alerts, are associated with an increase in the proportion of patients receiving prophylaxis and even for the reduction in symptomatic VTE.[7] On the other hand, studies have demonstrated that the percentage of patients with adequate prophylaxis may reach 90% or more when the protocol is enhanced by other QI and high-reliability strategies, for example the integration of the VTE protocol into order sets.[6,8,19] Additional strategies, such as engagement of multidisciplinary teams and well-structured QI institutional initiatives are described as responsible for changes in culture and reduction of VTE events.[6,8] Facing these controversies, we agree that the success of different approaches depends on the adaptation of the strategies to differences in the context in which the QI initiative takes place.[12]

Third, our implementation strategies did not engage multidisciplinary teams, being directed only to the medical staff. If, on the one hand, we expected only a slight improvement in adequacy, on the other, we felt it is important to attempt a simple set of strategies to evaluate protocol adherence before implementing other initiatives. Many studies have demonstrated the impact of electronic tools and other QI strategies,[8,29-32] but none in a setting characterized by an "open" medical staff, a reality that may negatively impact protocol adherence.

Fourth, the inadequacy of thromboprophylaxis prescription highlights a great concern in which the frequency of underutilization of prophylaxis was large in medical patients. Besides, anticoagulant prescription in both low-risk patients and in those with high-risk of bleeding confirmed overprescription in our scenario. Other studies have already described this problem, in which high-risk patients are undertreated and low-risk patients are overtreated.[23,29] Further, as platelet counts and INR results were unavailable for almost half of the interviewed patients (43.5% without platelet counts and 87.5% without INR results), it is possible to assume that the inadequacy is even greater than documented.

Finally, according to our results, several additional actions should be planned to achieve protocol adherence and consequently better appropriateness of thromboprophylaxis. When we compare our results with those from other low- and middle-income countries, it is possible to observe that, despite our better hospital infrastructure, our results are not better.[21,23,26,27]

The current study has a number of limitations. First, we used an uncontrolled before and after study design to investigate while pragmatic interventions were able to achieve adequacy of thromboprophylaxis in hospitalized patients. These studies are a relatively weak method of distinguishing cause and effect, since any observed change might plausibly be attributed to other causes, such as secular trends. However, these were the first results of a culture change and here we are generating hypothesis about a set of strategies used for this implementation. In general, there are no measures for this type of intervention since a more rigorous design was not practical in our situation.[33] Second, this study was carried out in a single private hospital, which may reduce the generalizability of our results, with additional studies being necessary to better understand if the same strategy would be effective in other settings. There are several characteristics, including physician's behavior that were not accounted for in our study. Third, the prescribing physicians were not interviewed, so we cannot exclude the possibility that in some cases additional clinical information obtained prior to admission had been taken into account in making decisions which in this study appeared inadequate on the basis of hospital data alone. In fact, we assumed that a lack of platelet count would be included as known just by physicians, mainly for surgical patients whose tests are performed outside hospital previous to the procedure. Nevertheless, we assumed no misclassification of the risk of bleeding, even if platelet count or INR values were missing, considering both medical records review and interviews were conducted. Moreover, requesting coagulation tests routinely if a patient presents a negative bleeding history is still questionable and it is not a consensus among physicians.[34,35]

In summary, after a protocol implementation, the results showed that the overall appropriateness of thromboprophylaxis prescription was weakly improved, despite the efforts. Although the study was performed at a single institution, it may provide the best evidence to date a bunch of strategies for the protocol implementation in private institutions in middle-income countries with an open medical staff, as there are few studies investigating these simple and pragmatic interventions. The lessons learned and the data obtained will support other institutional initiatives such as engaging multidisciplinary teams and elaborating a plan to adopt a computerized clinical decision support tool in future efforts to improve VTE prophylaxis.

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