Journal of Critical Care 36 (2016) 49–53

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Prevalence and factors associated with the absence of pharmacologic venous thromboembolism prophylaxis: A cross-sectional study of Georgia intensive care units

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ARTICLE INFO

Available online xxxx
Keywords:
Venous thromboembolism
Anticoagulants
Prophylaxis
Thrombosis
Hemorrhage
Observational study

ABSTRACT

Purpose: The need for venous thromboembolism prophylaxis is well accepted in the intensive care unit (ICU) and supported by a variety of guideline recommendations. Several studies have highlighted poor adherence to these recommendations, but it is unknown why this discrepancy exists. The aim of this study is assess the prevalence of pharmacoprophylaxis and characterize the practice of withholding prophylaxis.
Materials and methods: Multicenter, cross-sectional study conducted in adults admitted to a Georgia ICU at participating institutions on March 12, 2014. Data were collected on eligible patients regarding need for and omission of pharmacoprophylaxis.
Results: Three hundred sixty-four patients across 9 institutions were included in the study. Patients had a mean age of 58 years and a median Sequential Organ Failure Assessment score of 5. Physical activity was completely bedridden or restricted in 87% of the cohort. Forty-five percent of patients were not receiving pharmacoprophylaxis. The most common reasons for withholding prophylaxis were receipt of mechanical prophylaxis, recent surgery or central nervous system bleed, and thrombocytopenia. Over 16% of the cohort was inappropriately not receiving thromboprophylaxis. Patients with an elevated international normalized ratio had lower odds of receiving prophylaxis (0.2).
Conclusions: Venous thromboembolism prophylaxis is commonly omitted in ICU patients, and reasons for omission vary. An elevated international normalized ratio is associated with withholding of pharmacologic prophylaxis.

1. Introduction

The development of venous thromboembolism (VTE) is a complication that is well described throughout the literature and recognized by practitioners. Venous thromboembolisms can present as deep vein thrombosis or pulmonary embolism and have been reported in as many as 23% of critically ill adult patients [1], and up to one third of all VTE-related deaths are postsurgical patients [2]. Because of risk factors such as physical immobility, vascular endothelial injury, and venous stasis in hospitalized patients, it is standard practice to administer pharmacologic prophylaxis, such as subcutaneous injection of unfractionated heparin, low molecular weight heparins, or fondaparinux. Sequelae associated with the development of a VTE include prolonged duration of mechanical ventilation, intensive care unit (ICU) and hospital length of stay, postthrombotic syndrome, and a trend toward higher hospital mortality [3], further emphasizing the need for pharmacologic prophylaxis.

When superimposed with critical illness, however, the prescription of prophylactic measures deviates from standard practice. Critically ill patients have a seemingly higher risk of VTEs [4], but they are frequently scheduled for surgical procedures, postoperative, or have some degree of thrombocytopenia, anemia, or coagulopathy. For these reasons, the risk of hemorrhage is thought to exceed the benefit of preventing VTEs, thus necessitating omission of pharmacologic thromboprophylaxis. With a lack of robust literature to establish quantitative cutoffs, a variety of guideline recommendations [5-9] are

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http://dx.doi.org/10.1016/j.jcrc.2016.06.013
0883-9441/

vague, making prescription of pharmacologic prophylaxis open for interpretation.

Because of the subjectivity in weighing risk-benefit of prescribing pharmacoprophylaxis in critically ill patients and the lack of a validated risk stratification tool, we performed a prospective, multicenter, point prevalence study to evaluate thromboprophylaxis administration and factors influencing this practice among several institutions across the state of Georgia in the United States.

2. Materials and methods

The protocol was approved by the institutional review boards at each hospital and affiliated university, and the need for informed consent was waived. All patients at least18 years of age and admitted to an adult ICU at participating institutions on the study date were eligible for inclusion. Patients were only excluded from analysis if they were currently receiving therapeutic systemic anticoagulation. On the study date, clinical pharmacists at participating institutions prospectively collected demographic, laboratory, and clinical data on all eligible patients. Sequential Organ Failure Assessment (SOFA) scores were calculated for all patients. For patients that did not have a recent arterial blood gas, Spo_2:Fio_2 ratio was substituted for Pao_2:Fio_2 ratio [10]. For patients who were not receiving pharmacologic VTE prophylaxis, the pharmacists were instructed to ask the attending physician and/or the medical team the reason for omission. A list of potential reasons for omission was provided to the clinical pharmacists, who could select all relevant reasons for omission. For patients who were receiving pharmacologic VTE prophylaxis, the medication, dose, and frequency were collected. To reduce bias, data on the prescription of pharmacoprophylaxis were to be collected before patient rounds. In the instance that prophylaxis was recommended on rounds, this was captured as an omission of therapy.

To identify reasons to withhold pharmacologic prophylaxis, a MEDLINE literature review was conducted using PubMed for English language articles using search terms *venous thromboembolism*, *bleeding risk*, *critical illness*, *pharmacologic prophylaxis*, *contraindications*, and *risk factors*. References of relevant articles were also reviewed for inclusions. Articles were reviewed for statistically significant risk factors for bleeding in critically ill patients. Additional potential conditions that may lead to withholding pharmacologic prophylaxis were included in the survey based on general consensus among the authors. Although not all of these are proven risk factors for bleeding, the intent was to provide study sites with a comprehensive list of possible reasons for withholding treatment for ease of data entry and to limit free text responses. Appropriate reasons were defined as platelet count less than 100×10^3/mL [6,9,11,12], planned surgical intervention or invasive procedure in the next 24 hours [6], current acute or chronic hemorrhage, hepatic failure with a Model for End-Stage Liver Disease score greater than or equal to 10 [13], cardiac surgery within previous 48 hours [6], other surgery within previous 24 hours [6], central nervous system (CNS) hemorrhage including subdural, subarachnoid, intraventricular, or intraparenchymal within previous 48 hours [14], thrombolytics administered within previous 24 hours for ischemic stroke [15], lumbar puncture or epidural within previous 24 hours [6], patient or caregiver wishes, and an international normalized ratio (INR) >2 or activated partial thromboplastin time (aPTT) >80 seconds in the absence of liver failure [9,12]. *Current acute major bleeding* was defined as the patient requiring at least 2 U of blood/products transfused in previous 24 hours [16], and *current chronic bleed* was defined as clinically significant and measureable bleeding in previous 48 hours. A drop in hemoglobin of 2 g/dL was not used in the definition. Authors speculated this definition was not specific to bleeding because of a dilutional drop in hemoglobin with large volume resuscitation. Two investigators independently reviewed patients not receiving pharmacoprophylaxis to categorize appropriateness.

Study data were collected and managed using Research Electronic Data Capture electronic data capture tools hosted at Emory Healthcare. Research Electronic Data Capture is a secure, Web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources [17].

3. Statistical methods

All statistical methods were carried out using SPSS 21.0 (SPSS, Chicago, IL). Continuous patient variables were examined using histograms, and distributions were examined for normality. Continuous variables that were normally distributed were summarized using mean ± SD, and continuous variables that were non-normally distributed were summarized using median (Q1, Q3). Categorical variables were summarized using number and frequency (%).

Binary logistic regression was performed to determine what factors were associated with prescription of pharmacologic VTE prophylaxis. Forward likelihood ratio selection was used with a cutoff value of $P = .1$ for entry into the final model. Variables that were considered for selection included: hospital type, pharmacist's role in the ICU, patient age, body weight, lowest platelet count in 24 hours, renal function, lowest hemoglobin in 24 hours, most recent aPTT and INR, SOFA score, recent surgery, the amount of current physical activity, and the patient's highest bilirubin in 24 hours. Physical activity was determined by speaking with either nurse or physician. For all variables that were selected into the final model point estimates, 95% confidence intervals (CIs) and *P* values were reported for odds ratios (ORs). After the model was fitted in this fashion, SOFA score was forced back into the model because the investigators suspected residual confounding. Residual confounding was suspected because higher hemoglobin values were associated with less odds of receiving VTE prophylaxis in the model. The Nagelkerke R^2 and Hosmer-Lemeshow statistic were reported for the final model as measures of model discrimination and calibration.

Separately, we performed bivariate logistic regression to determine the crude association between the pharmacists' role in the ICU and appropriate withholding of VTE pharmacoprophylaxis because this was a question of particular interest to the investigators. The OR, 95% CI, and *P* value were reported.

4. Results

Data were collected from 364 patients admitted to ICUs across the 9 medical centers from all patients in the ICU on March 12, 2014. Thirty-eight patients were receiving therapeutic systemic anticoagulation negating the potential need for pharmacologic thromboprophylaxis; these patients were included in the baseline demographics but withheld from further analysis, leaving 326 patients to be included.

Fifty percent of the patients represented an academic public institution. Other hospital data were summarized in Table 2. The role of the pharmacist varied among these institutions but correlated with hospital type, where a majority of pharmacists participated in daily rounds. The cohort represented all types of ICUs. (See Table 1.)

Baseline patient demographics are summarized in Table 3. The mean age was 58 ± 17 years, and 56% were men. Median SOFA score was 5 [3,7]. On average, patients were on their sixth and seventh days of ICU and hospital stay, respectively. Primary reason for ICU admission varied with a majority being due to respiratory and neurologic insults. A majority of patients were considered to be bedridden or of limited mobility.

Forty-five percent of patients did not receive pharmacologic prophylaxis. Each patient averaged 1.3 reasons for no prophylaxis prescribed. Nine of these patients did not receive pharmacoprophylaxis because of clinical oversight; the remaining 139 were deemed to have contraindications by the primary medical team or supervising physician.