Thrombosis Research 134 (2014) 1220–1223

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Risk-assessment and pharmacological prophylaxis of venous thromboembolism in hospitalized patients with chronic liver disease

Hanin Bogari [1,2], Asad E. Patanwala [*,2], Richard Cosgrove [2], Michael Katz [2]

Department of Pharmacy Practice & Science, College of Pharmacy, The University of Arizona, 1295N Martin Ave, PO Box 210202, Tucson, AZ, 85721, USA

ARTICLE INFO

Article history:
Received 24 July 2014
Received in revised form 2 September 2014
Accepted 16 September 2014
Available online 2 October 2014

Keywords:
Liver diseases
Liver cirrhosis
Thromboembolism
Venous thromboembolism
Anticoagulants
Heparin

ABSTRACT

Introduction: There is a lack of evidence regarding the need for thromboprophylaxis in hospitalized patients with liver disease. The purpose of this study was to evaluate the Padua Predictor Score (PPS) as a risk-stratification tool for the development of venous thromboembolism (VTE) in patients with chronic liver disease.
Methods: This was a retrospective cohort study conducted in an academic medical center in the United States. Consecutive adult patients admitted with chronic liver disease were included. Patients were categorized into two groups based on whether they developed a VTE or not. The risk for VTE in each patient was evaluated using the Padua Predictor Score (PPS). Patients were risk stratified using the PPS score as high-risk (score ≥ 4) and low-risk (score <4). The risk of VTE based on PPS categorization was evaluated using logistic regression.
Results: A total of 163 patients with liver disease were included in the study cohort. Of these, 18 (11%) developed VTE. Mean PPS was significantly greater in the VTE group than the non-VTE group (5.8 ± 2.0 versus 3.0 ± 2.1, respectively; $p < 0.001$). In high-risk patients 22% ($n = 16/72$) developed VTE and in low-risk patients 2% (2/91) developed VTE ($p < 0.001$). High-risk patients were more likely to have VTE (OR 12.7, 95% CI 2.8 to 57.4, $p = 0.001$).
Conclusion: The PPS is an effective risk assessment tool for VTE in patients hospitalized with chronic liver disease.

Introduction

Anticoagulant prophylaxis is recommended for most acutely ill patients who are at increased risk of venous thromboembolism (VTE) [1]. However, in patients with chronic liver disease (CLD), the utility of thromboprophylaxis continues to be debated [2]. Previously, it was accepted that elevated international normalization ratio in patients with CLD conferred protection from VTE because of an acquired coagulopathy, resulting from a decreased production of coagulation factors. However, it is now believed that these patients are conversely at an increased risk of VTE because of a decreased production of endogenous anticoagulants such as protein C [2] as well as elevated levels of von Willebrand factor, which can promote platelet adhesion [3]. Thus there is a delicate balance between prothrombotic and antithrombotic factors, which contribute to the risk for VTE. This balance may be affected by various factors including acute illness, inflammation, or comorbidities. At this time, it is common that VTE prophylaxis is avoided in these patients, even though they may be at high-risk based on traditional scoring systems. Thus there is a need to determine if traditional risk-assessment methods apply to patients with CLD and to determine if pharmacological prophylaxis for VTE is indicated in these patients.

Current guidelines do not specifically address the use of thromboprophylaxis or risk-assessment in patients with CLD [1]. This is because of the perceived risk of bleeding complications, laboratory evidence of potential coagulopathy, and lack of large clinical trials to assess the safety and efficacy of thromboprophylaxis in these patients. The Padua Predictor Score (PPS) is considered to be the best method for risk-assessment of hospitalized patients and guideline recommendations are based on risk-stratification using this system. A few studies have evaluated potential risk factors for VTE in patients with CLD, however none have assessed the utility of the PPS in this population [3–8].

The primary objective of this study was to evaluate the PPS as a risk-stratification tool for the development of VTE in hospitalized patients with CLD. The secondary objective was to compare the occurrence of VTE in CLD patients with and without pharmacological prophylaxis stratified by PPS. We hypothesized that patients with a high-risk assessment on PPS would have a greater risk for VTE and would benefit from pharmacological prophylaxis.

* Corresponding author at: 1295 N. Martin, PO Box 210202, Tucson, AZ 85721. Tel.: +1 520 626 5404; fax: +1 520 626 7355.
E-mail addresses: bogari_h@hotmail.com (H. Bogari), patanwala@pharmacy.arizona.edu (A.E. Patanwala), Richard.Cosgrove@uahealth.com (R. Cosgrove), katz@pharmacy.arizona.edu (M. Katz).
[1] Present address: Clinical Pharmacy Faculty of Pharmacy, King Abdulaziz University, Aljamaah District, PO Box 80200, Jeddah, 21589, Saudi Arabia.
[2] (Institution where work was performed).

http://dx.doi.org/10.1016/j.thromres.2014.09.031
0049-3848/

Methods

Study Design, Setting and Patient Selection

This was a retrospective cohort study conducted in an academic medical center in the United States. The Institutional Review Board of the university approved the study prior to data collection. All consecutive patients with a discharge diagnosis of CLD were identified from the electronic medical record between May 1, 2010 and May 1, 2013 based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. These included alcoholic fatty liver (571.0), alcoholic cirrhosis liver (571.2), chronic hepatitis (571.4), biliary cirrhosis (571.6), and chronic liver disease (571.9). All patients were included if they were 18 years of age or older. Patients who had active bleeding present upon admission or those who received therapeutic anticoagulation upon admission were excluded.

Data Collection

All data were collected on standard data collection forms by one of the investigators for those patients who met inclusion criteria. Data collected included patient demographics (age, gender, race), reason for admission, etiology of liver cirrhosis, Model for End-stage Liver Disease (MELD) score, and laboratory parameters on admission (serum creatinine, blood urea nitrogen, international normalization ratio, activated partial thromboplastin time, total bilirubin, aspartate aminotransferase, alanine aminotransferase, albumin, hemoglobin and platelet counts). In addition, the use of prophylaxis for VTE (pharmacological or non-pharmacological), vitamin K, or blood product administration was recorded. The PPS was also generated for each patient as an indicator of risk for VTE [9]. The prediction score includes 11 variables that incorporate pertinent demographics and past medical history. Variables included in the score are listed below and followed by the assigned value in parenthesis: active cancer (3), previous VTE (3), reduced mobility (3), known thrombophilic condition (3), recent trauma or surgery (2), elderly >70 years old (1), heart or respiratory failure (1), acute myocardial infarction or ischemic stroke (1), acute infection or rheumatologic disorder (1), obesity with body mass index >30 (1), and ongoing hormonal treatment (1). The PPS is the final totaled value of all variables. A score of ≥4 is considered to be high-risk for VTE.

Outcomes

The primary outcome measure was the occurrence of symptomatic VTE was based on physician diagnosis and confirmed by venous Doppler ultrasound, or spiral CT of the chest during hospital stay or within 30-days of discharge. The occurrence of VTE after discharge was obtained from follow-up clinic notes from primary care providers and readmission data. The primary predictor of interest was a PPS of ≥4. The secondary measure of interest was a comparison of the occurrence of VTE in patients with and without pharmacological prophylaxis. The comparison was stratified by PPS of ≥4 (high-risk) and <4 (low-risk). Other outcomes recorded included bleeding, length of hospital stay, and mortality (up to 30 days of discharge).

Statistical Analysis

The cohort was divided into two groups based on occurrence of VTE. Patients who developed VTE were compared to patients who did not develop VTE with respect to PPS, demographic and laboratory variables. Continuous data were compared using a Student's t-test and expressed using the means and standard deviations. Categorical data were compared using the Fisher's exact test and were expressed as percentages. The PPS was dichotomized as <4 (low-risk) and ≥4 (high-risk) because these are accepted definitions used [1,9]. Odds ratios with 95% confidence intervals using logistic regression were reported to determine the association between PPS category and VTE. None of the variables in the study has missing data, thus there was no need for imputation. No formal *a priori* power analysis was conducted for this study. Based on previous reports of CLD patients at our institution, we estimated that consecutive inclusion of CLD patients during a 3-year period would be sufficient to test our primary hypothesis. Statistical significance was defined as alpha less than 0.05. All statistical analyses were performed using STATA 13 (STATA, College Station, TX, USA).

Results

Study Cohort

A total of 163 patients were included in the study cohort. Of these, 18 (11%) developed VTE. VTE included deep venous thrombosis (n = 12), portal vein thrombosis (n = 4) and pulmonary embolism (n = 2). The mean age was 54 ± 11 years, 106 (65%) were male, and 83 (51%) were of White race. Patients were admitted to the medicine service (n = 125, 77%), surgery service (n = 20, 12%), or other (n = 18, 11%). The most common cause of CLD was hepatitis C (n = 85, 52%), followed by alcoholic liver disease (n = 37, 23%), and other (n = 41, 25%). The most common cause of hospital admission was infection (n = 54, 33%), followed by hepatic encephalopathy (n = 34, 21%), and other (n = 75, 46%). The baseline comparison of patient's in the VTE and non-VTE groups is in Table 1.

Main Results

Mean PPS was significantly greater in the VTE group than the non-VTE group (5.8 ± 2.0 versus 3.0 ± 2.1, respectively; p < 0.001). In high-risk patients (score ≥4) 22% (95% CI 13 to 34%) (n = 16/72) developed VTE and in low-risk patients (score < 4) 2% (95% CI 0 to 8%) (n = 2/91) developed VTE (p < 0.001). High-risk patients were

Table 1
Patient Characteristics.

Variable	VTE (n = 18)	No VTE (n = 145)	P value
Demographics			
Age (years), mean ± SD	54 ± 17	54 ± 10	0.861
Sex (male), n (%)	12 (67)	94 (65)	1.000
Race (white), n (%)	11 (61)	72 (50)	0.456
Laboratory Values			
INR, mean ± SD	1.4 (0.3)	1.5 (0.6)	0.207
aPTT (seconds), mean ± SD	37.8 (6.1)	36.0 (15.8)	0.361
Platelets (/ml), mean ± SD	184.3 (114.5)	123.7 (74.9)	0.041
Hemoglobin (g/dl), mean ± SD	11.0 (2.7)	12.1 (2.2)	0.116
AST (U/L), mean ± SD	74.2 (82.3)	94.6 (136.1)	0.372
ALT (U/L), mean ± SD	35.3 (22.6)	53.7 (77.6)	0.031
Albumin (g/dl), mean ± SD	2.6 (0.7)	2.6 (0.7)	0.653
Total Bilirubin (mg/dl), mean ± SD	6.1 (10.3)	4.1 (5.9)	0.425
Serum creatinine (mg/dl), mean ± SD	1.6 (1.4)	1.5 (1.4)	0.715
BUN (mg/dl), mean ± SD	28.2 (22.8)	22.8 (18.6)	0.345
MELD score, mean ± SD	17.8 (9.6)	16.8 (8.0)	0.677
Comorbidities			
Heart failure, n (%)	4 (22.2)	10 (6.9)	0.052
Renal disease, n (%)	3 (16.7)	24 (16.6)	1.000
Malignancy, n (%)	4 (22.2)	28 (19.3)	0.757
Lung disease, n (%)	10 (55.6%)	34 (23.5%)	0.009
Trauma, n (%)	1 (5.6%)	6 (4.1%)	0.566
Infection, n (%)	12 (66.7%)	83 (57.2%)	0.613
History of VTE, n (%)	0 (0)	1 (0.7%)	1.000
Post-operative, n (%)	7 (38.9)	22 (15.2)	0.021
Bedridden, n (%)	5 (27.8)	5 (3.5)	0.002
Diabetes, n (%)	7 (38.9%)	53 (36.6%)	1.000

VTE = venous thromboembolism; INR = international normalization ratio; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen, MELD = Model for End-stage Liver Disease.