Predictors and safety of venous thromboembolism prophylaxis among hospitalized inflammatory bowel disease patients

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Abstract

Introduction: Inflammatory bowel disease (IBD) patients are at increased risk of venous thromboembolism (VTE) especially during hospitalization. We assessed the safety and predictors of VTE prophylaxis in this population.

Methods: We conducted a retrospective study of 974 IBD admissions between February 2010 and May 2012. We abstracted data on clinical characteristics, VTE prophylaxis and bleeding events, and conducted multivariate analysis to determine predictors of prophylaxis.

Results: Pharmacological VTE prophylaxis was administered to 80% of admissions; 63% were within 24 h of admission. Patients on the surgical service (adjusted OR [aOR], 3.82; 95% CI: 2.00–7.29) and general medicine (aOR, 2.40; 95% CI: 1.39–4.12) were more likely to receive VTE prophylaxis compared to those on the gastroenterology service. Rectal bleeding on admission was associated with lower prophylaxis (aOR, 0.58; 95% CI: 0.35–0.97). The VTE prophylaxis rate increased from 47% to 73% (P < 0.001) on non-surgical services with the introduction of a pharmacist advocate. The rates of major and minor bleeding were similar between patients who did and did not receive VTE prophylaxis (0.26 vs. 0 per 1000 person-days, P = 0.7; 4.18 vs. 2.53 per 1000 person-days, P = 0.4 respectively), and the major bleeding events (n = 2) were post-operative. VTE prophylaxis was not associated with major postoperative bleeding (0.4% vs. 0%, P = 0.96).

Conclusions: VTE prophylaxis was more frequent on the surgical service, where standardized protocols exist. The introduction of a pharmacist advocate greatly increased VTE prophylaxis on the non-surgical services. Prophylactic anticoagulation is safe in IBD despite the presence of rectal bleeding on admission.

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1. Introduction

Patients with inflammatory bowel disease (IBD), comprising of ulcerative colitis (UC), Crohn’s disease (CD), or indeterminate colitis (IC), have a well-established, increased risk of sustaining venous thromboembolic events (VTE), compared to the general population.1–6 Individuals with IBD have a more than threefold risk for developing VTE compared to the general population. Among occurrences of VTE, deep venous thrombosis (DVT) and pulmonary embolism (PE) represent significant morbidity and mortality. The incidence of DVT and PE was 30 per 10,000 person-years and 10–20 per 10,000 person-years, respectively, in a population-based study.5

There is a higher risk of VTE in hospitalized IBD patients, which may in part reflect periods of increased inflammation.7 This increased risk is nearly 6 times higher than the absolute risk in an ambulatory IBD flare (37.5/1000 p-y vs. 6.4/1000 p-y).8 The mortality associated with IBD-related VTE ranges from 8% to 25%.1,2,9–11 Furthermore, a VTE event during hospitalization has been associated with a greater than 2-fold increased in mortality, compared to VTE-related mortality in the general population.7 A population-based study showed that the rates of VTE are rising with time in both UC and CD—possibly reflecting a greater recognition of VTE in the IBD patients.

Despite the increasing evidence regarding the risks of VTE rates in the IBD population, there may be some reservations regarding initiating VTE prophylaxis. This uncertainty can occur when disease is quiescent, or in the presence of rectal bleeding, which is a common presentation during a flare.12 Anticoagulation has been frequently used in the treatment of UC—with heparin playing a role in the reversal of endothelial dysfunction.13–17 A meta-analysis which included clinical trials comparing heparin formulations to conventional therapy for the treatment of ulcerative colitis showed few serious adverse events in treatment arms with or without heparin administration.18 While this relatively small meta-analysis of 268 patients indirectly suggest that heparin is safe during an IBD flare, the carefully selected study populations and conditions of clinical trials do not necessarily reflect the safety of anticoagulation in real-world settings.

The primary aim of this study was to characterize the safety profile of prophylactic anticoagulation among IBD patients outside the context of clinical trials. Moreover, we sought to determine predictors and barriers to VTE prophylaxis in the IBD population. We also assessed whether the introduction of a pharmacist advocate for VTE prophylaxis resulted in improved VTE prophylaxis rates.

2. Methods

2.1. Data source

A retrospective chart review was conducted, looking at all admissions for IBD at the Mount Sinai Hospital Centre for Inflammatory Bowel Disease, Toronto, Ontario between February 1, 2010 and May 31, 2012. Data was extracted from electronic charts, with access to clinical information, laboratory investigations, endoscopic evaluations, pharmacological records, and discharge summaries.

2.2. Eligibility criteria

We identified admissions with a most responsible diagnosis for IBD using ICD-9 and ICD-10 codes for UC (556.x and K51, respectively) and CD (555.x and K50 respectively). The charts were electronically reviewed to confirm diagnosis. Patients with a non-IBD diagnosis were excluded—such as self-limited infectious colitis, or ischemic colitis—without underlying IBD.

2.3. Data collection

Data were collected from the hospital electronic medical record. Patient characteristics were collected and included: age at admission, sex, type of IBD, and concomitant comorbidities, using the Charlson Index.19 Risk factors for VTE were collected including any previous history of VTE and IBD-related surgery during admission. Phenotype data was also abstracted and included disease extent for UC and disease location and behavior for CD. We additionally captured data on potential predictors of VTE prophylaxis including: primary service under which the patient was admitted (Gastroenterology, Other Medicine, or Surgery); and presence of rectal bleeding, anemia, thrombocytosis, and coagulopathy on admission. We queried the electronic medical administration record to determine whether VTE prophylaxis was ordered and when it was administered. Among those who did receive pharmacological prophylaxis, we collected data on type of VTE prophylaxis used and duration of therapy. Complications such as major or minor bleeding and whether they occurred in the context of the post-operative setting were recorded from the medical chart. We defined major bleeding as: intracranial, intraspinal, or retroperitoneal bleeding; bleeding into any major organ; or bleeding that led to re-operation. We also documented heparin-induced thrombocytopenia and in-hospital death.

2.4. Implementation of pharmacist advocate

Mount Sinai Hospital introduced the role of a pharmacist advocate for VTE prophylaxis as a part of a quality improvement initiative on November 1, 2011. As part of routine protocol, pharmacists review the medication orders of all newly admitted patients and reconcile them with pre-admission medications. The new protocol involved a real-time audit of medication orders to determine whether VTE prophylaxis was ordered among eligible patients, including those with an IBD diagnosis. The service caring for the patient was notified by the pharmacist if an eligible patient was not written for VTE prophylaxis within 24 h (on non-weekend days) and requested an order for prophylaxis or a reason for not ordering it.

2.5. Statistical analysis

We performed statistical analysis using Stata 10MP (StataCorp LP, College Station, Texas). Descriptive analysis was conducted to compare demographic and clinical characteristics between those who did and did not receive VTE prophylaxis. The chi-square and Fisher exact test were used to compare categorical variables while the Student’s t-test was used to compare continuous variables. Multivariate logistic regression
was used to identify predictors of VTE prophylaxis while simultaneously adjusting for each of the predictors. The unadjusted proportion of patients who received VTE prophylaxis and those who received it within 24 h were calculated and stratified by primary service. Separate values were also calculated before and after introduction of the pharmacist advocate. The crude rates of minor and major bleeding were calculated by dividing the total number of events by the number of total person-days on prophylactic anticoagulation. For those who did not receive VTE prophylaxis, the rate was calculated using the total person-days in hospital as the denominator.

2.6. Ethical considerations

The Research Ethics Board at Mount Sinai Hospital, Toronto, Ontario, approved the study protocol.

3. Results

There were 974 hospitalizations for IBD during the study period, of which 581 were for CD (60%), 388 for UC (40%), and 5 (0.5%) for IBD-unclassified. Among these, 59% underwent major abdominal surgery for IBD, and 62% were admitted under the surgical service, while 28% and 9% were admitted under the gastroenterology and another medicine specialty service (i.e., general internal medicine), respectively. A fourth (26%) of IBD admissions occurred following the pharmacist intervention to improve VTE prophylaxis.

3.1. Pharmacological VTE prophylaxis

Pharmacological VTE prophylaxis was administered to 80% of hospitalized IBD patients, and 63% received anticoagulation within 24 h of admission. At our institution, low-molecular weight heparin (93.2%) was used more frequently than unfractionated heparin (6.3%), while warfarin or fondaparinux were used in the remaining 0.5%. Pharmacological VTE prophylaxis was widely implemented on the surgical service (96%) and significantly less so on the gastroenterology (50%) and general medicine service (68%). Prior to the implementation of a pharmacist advocate, the rates of pharmacological VTE prophylaxis and prophylaxis within 24 h were 78% and 62%, respectively (Fig. 1). In the post-implementation period, the VTE prophylaxis rate increased to 87%, while the prophylaxis rate within 24 h did not change (63%). The presence of a pharmacist advocate was most pronounced for the non-surgical services in which the VTE prophylaxis rate increased from 47% to 73% (P < 0.001), and the rate of prophylaxis within 24 h increased from 32% to 56% (P < 0.001) (Fig. 1).

The demographic and clinical characteristics of patients who did and did not receive VTE prophylaxis are shown in Table 1. Patients who received pharmacological VTE prophylaxis were more likely to be on the surgical service (75% vs. 13%, P < 0.001) and have undergone major abdominal surgery (71% vs. 7%, P < 0.001). Moreover, UC patients with extensive disease were also more likely than those with more proximal disease to receive VTE prophylaxis (92% vs. 82%, P = 0.03). Those who received VTE prophylaxis were less likely to present

with active rectal bleeding on admission (14% vs. 47%, P < 0.001).

3.2. Predictors of pharmacological VTE prophylaxis

Using multivariate logistic regression, we identified predictors of VTE prophylaxis while simultaneously adjusting for each of the predictors (Fig. 2). IBD patients were more likely to receive pharmacological VTE prophylaxis if they were on the surgical service (adjusted odds ratio [aOR], 3.82; 95% CI: 2.00–7.29) and general medicine service (aOR, 2.40; 95% CI: 1.39–4.12), which was independent of whether they actually underwent surgery. These associations were independent of whether the patient underwent major abdominal surgery during admission, which was associated with a greater than 10-folder higher likelihood of receiving VTE prophylaxis (aOR, 11.5; 95% CI: 5.32–24.77). IBD patients who presented on admission with rectal bleeding were less likely to receive VTE prophylaxis (aOR 0.58; 95% CI: 0.35–0.97). Being admitted following the implementation of a pharmacist advocate was associated with higher rates of VTE prophylaxis (aOR, 2.46; 95% CI: 1.52–3.98).

3.3. Safety of pharmacological VTE prophylaxis

The rate of major bleeding was not significantly higher in the group who received VTE prophylaxis compared to those who did not (0.26 vs. 0 per 1000 person-days, P = 0.7). All episodes (n = 2) of major bleeding occurred in the postoperative setting. Similarly, the rate of minor bleeding was not significantly higher among those who received pharmacological VTE prophylaxis compared to those who did not (4.18 vs. 2.53 per 1000 person-days, P = 0.4). Among those who experienced minor bleeding while on VTE prophylaxis, 91% occurred in the postoperative setting. Among those who initially presented with rectal bleeding, only 6.6% continued to have minor bleeding while on prophylactic anticoagulation, and none developed major bleeding.

The proportion of patients who experienced minor postoperative bleeding following major abdominal surgery was not...
significantly higher among those who received VTE prophylaxis compared to those who did not (5.4% vs. 0%, \( P = 0.5 \)). The proportion of individuals with major post-operative bleeding was also similar between those who received pharmacological VTE prophylaxis and those who did not (0.4% vs. 0%, \( P = 0.96 \)). There were 2 deaths in the VTE prophylaxis group (0.3%) and 1 death in the non-prophylaxis group (0.5%), and all were unrelated to VTE or bleeding. There were no cases of heparin-induced thrombocytopenia during the study period.

### 4. Discussion

Our current study is among the first and largest to report on the safety of prophylactic doses of anticoagulation in the hospitalized IBD population. These findings highly support the widespread implementation of pharmacological VTE prophylaxis in this population given their high susceptibility to VTE and the favorable safety profile of a prophylactic dose anticoagulation. Furthermore, it has identified significant variations in the implementation of VTE prophylaxis amongst the various clinical services. The introduction of a pharmacist advocate for VTE prophylaxis has reduced that variation.

The decision to administer VTE prophylaxis is influenced by the inherent risk of VTE as well as the risk of hemorrhage. There is ample evidence that inflammatory bowel disease patients have elevated risk of VTE compared to the general population, in both the outpatient and inpatient settings. Consequently, gastrointestinal societies from North America and Europe have advocated the use of pharmacological prophylaxis among hospitalized IBD patients. The implementation of VTE prophylaxis is listed as an inpatient IBD quality indicator in the Adult Inflammatory Bowel Disease Physician Performance Measures Set released by the American Gastroenterology Association. However, there has been sparse attention to the relative dearth of data on the safety of pharmacological prophylaxis in these IBD patients. The American College of Chest Physician's 2012 guidelines for VTE prophylaxis lists the presence of bleeding within 3 months of admission, a common presentation in IBD, as an important risk factor for major or significant bleeding while on pharmacological prophylaxis. Yet, most gastroenterologists who care for a high number of IBD patients feel comfortable providing...
anticoagulation for IBD patients even in the presence of rectal bleeding — perhaps through anecdotal experience. However, nearly 15% of gastroenterologists who had less experience in caring for IBD patients believed rectal bleeding to be a contraindication to pharmacological prophylaxis. In our own study, the presence of rectal bleeding on admission was associated with nearly 50% lower likelihood of receiving VTE prophylaxis. The only evidence for the safety of anticoagulation in IBD patients during an active flare comes indirectly from clinical trials in which heparin was used as a treatment for UC. A meta-analysis of these studies showed that 3 subjects from one study comprising moderate–severe UC patients had to withdraw because of worsening rectal hemorrhage. The remaining 7 clinical trials showed no bleeding-related adverse events in the heparin group. However, most of these studies include patients with mild–moderate disease. Only two of remaining studies enrolled patients with severe UC, and only one included CD patients. Thus, these clinical trial populations may not reflect real-life IBD patients, particularly those with CD, who are admitted to hospital. Our current study, comprising both CD and UC patients reflects real-world experience with VTE prophylaxis and supports its safety in hospitalized IBD patients. Furthermore, our study suggests that pharmacological VTE prophylaxis is also safe in the postoperative setting given the low rate of major bleeding. Thus, pharmacological prophylaxis is also indicated in postoperative IBD patients who have at least moderate risk of VTE.

Our study showed significant variation in VTE prophylaxis by admitting service. The high implementation on surgical service is likely explained by standardized surgical protocols at our institution which include routine administration of VTE prophylaxis unless contraindicated. The proportion of inpatients receiving VTE prophylaxis on non-surgical services reflects those reported among general medical patients in international multi-center studies. The introduction of a pharmacist advocate at our institution contributed to a substantial increase in overall VTE prophylaxis and prophylaxis within 24 h of admission among those on non-surgical services. However, an inherent limitation of pre- and post-intervention analysis is that there may have been other temporal factors, such as increasing knowledge of the association between IBD and VTE, that may have contributed to the improved VTE prophylaxis rates.

A significant limitation of our study is that it arises from a single IBD tertiary center. As a consequence, our results may not be generalizable to other hospitals, as they reflect the practices of a limited number of IBD specialists. Thus, we must cautiously interpret the rates of VTE prophylaxis and the clinical and physician factors that may influence them. However, we believe that our safety data on anticoagulation among IBD patients is more robust and widely applicable, as we expect bleeding-related outcomes to be consistent across academic and community hospitals. Another limitation of our study is that we were not able to capture the use of mechanical VTE prophylaxis and may have underestimated the use of VTE prophylaxis of any type. However, we focused on predictors of pharmacological prophylaxis because it is preferred over mechanical prophylaxis, and recommended in guidelines.

While electronic records are accurate in recording demographics and medication administration, it does not allow us to delineate the multiple steps in the decision
process leading VTE prophylaxis. Among these steps are: physician recognition of need for VTE prophylaxis; physician ordering of medication; patient acceptance of prophylaxis; and nurse administration. A compromise of any of these steps may become a barrier to VTE prophylaxis. We can conclude that physician services with standardized protocols for VTE prophylaxis have very high implementation. It also appears that collaboration with pharmacy to ensure timely order, seem to have a positive impact on ensuring that more patients with IBD receive VTE prophylaxis.

The implication of this study for clinicians is better characterization of the risk-benefit profile for prophylactic anticoagulation in hospitalized IBD patients. Our data facilitate the interpretation of ACCP VTE prevention guidelines in the context of IBD patients since there is a strong emphasis on stratification of bleeding risk. In both non-surgical and postoperative IBD patients, we can conclude that the bleeding risk with VTE prophylaxis is no greater than in its absence. While the benefits of VTE prophylaxis are clear, rectal bleeding on admission was a strong negative predictor of pharmacological VTE prophylaxis. The favorable safety profile of prophylactic anticoagulation from our study should reassure a minority of gastroenterologists, and perhaps non-gastroenterologists, who are less comfortable with providing pharmacological prophylaxis in a bleeding patient as long as it is not hemodynamically significant. Even in the presence of standardized admission protocols, the presence of rectal bleeding is, anecdotally, one of the most frequently cited reasons for not administering pharmacological VTE prophylaxis. Consequently, there must be educational directives to distinguish the presence of any rectal bleeding from hemodynamically significant bleeding when considering the risk of anticoagulation. Our safety data on anticoagulation in hospitalized IBD patients serves as further groundwork for educational and quality improvement initiatives to promote widespread implementation of VTE prophylaxis in this susceptible population.

Author contributions

G.C.N. conceived and designed the study, performed all analyses, and contributed to drafting of the manuscript. G.R. contributed to the design of the study, performed chart review, and drafted the manuscript. R.T. and S.R. contributed to the design and interpretation of the study and both reviewed and approved the manuscript.

Conflict of interest statement

The authors have no conflicts of interest.

References

