Increased Risk of Postoperative Deep Vein Thrombosis and Pulmonary Embolism in Patients With Inflammatory Bowel Disease

A Study of National Surgical Quality Improvement Program Patients

Andrea Merrill, MD; Frederick Millham, MD

Hypothesis: Patients with inflammatory bowel disease (IBD) undergoing surgery are at increased risk for postoperative thromboembolism, including deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke.

Design: Retrospective cohort study.

Setting: Two hundred eleven hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program.

Patients: All 271,368 patients from the National Surgical Quality Improvement Program 2008 Participant Use Data File were examined, and 2,249 patients with IBD were compared with 269,119 patients without IBD.

Main Outcome Measures: Occurrence of DVT, PE, myocardial infarction, or stroke within 30 days of surgery.

Results: Of 268,703 National Surgical Quality Improvement Program patients, 2,249 (0.8%) had IBD. There were 2,655 cases of DVT or PE (1.0%). Occurrence of DVT or PE was more common in patients with IBD (2.5%) overall (P < .001). Nonintestinal surgical cases had a higher rate of DVT or PE (5.0%; P = .002). Regression analysis, controlling for confounders, confirmed that IBD was associated with increased risk for DVT or PE (odds ratio = 2.03; 95% CI, 1.52-2.70). For nonintestinal surgery, risk of DVT or PE for patients with IBD was increased (odds ratio = 4.45; 95% CI, 1.72-11.49). Inflammatory bowel disease had no effect on risk of postoperative myocardial infarction or stroke.

Conclusions: Patients with IBD are at increased risk for developing postoperative DVT or PE. This risk persists when potential confounding variables are controlled for. Risk of DVT or PE appears to be even higher for patients with IBD who are having nonintestinal surgery. Cardiac and stroke risks do not appear to be increased by IBD. Perhaps standards for DVT and PE prophylaxis in these cases should be reconsidered.


Patients with inflammatory bowel disease (IBD) are at increased risk for thromboembolic events, especially deep vein thrombosis (DVT) and pulmonary embolism (PE). This association was first described in 1936 by Bargen and Barker, who described 18 patients with thromboembolic disease (predominantly venous) in more than 1,000 patients treated for IBD at Mayo Clinic. Recent publications suggest that patients with IBD have increased risk of venous thromboembolism varying from as low as 1.5 times that of nonaffected patients to as high as 4.7-fold for patients with Crohn disease in a population-based cohort study. Moreover, patients with IBD who have PE appear to have increased risk of death compared with others. Despite these findings, standard DVT and PE prophylaxis guidelines do not recommend enhanced prophylaxis for patients with IBD. Recent data suggest that patients with IBD who require surgery are at very high risk for DVT. Scarpa et al. have reported that, compared with patients with cancer undergoing colon resections, patients with ulcerative colitis have an odds ratio (OR) of 7.4 for having postoperative DVT.

We wondered whether patients with IBD undergoing surgery in the American College of Surgeons National Surgical Quality Improvement Program were at increased risk for DVT and PE. In this study, we examined the risk of DVT and PE in patients with IBD undergoing surgery.
Table 1. Definition of Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>ICD-9-CM Code</th>
<th>Podiag Field Definition</th>
<th>Patients, No. % (n = 2249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>555</td>
<td>Regional enteritis</td>
<td>36 (1.6)</td>
</tr>
<tr>
<td>555.0</td>
<td>Regional enteritis of small intestine</td>
<td>284 (12.6)</td>
</tr>
<tr>
<td>555.1</td>
<td>Regional enteritis of large intestine</td>
<td>238 (10.6)</td>
</tr>
<tr>
<td>555.2</td>
<td>Regional enteritis of small intestine with large site</td>
<td>225 (10.0)</td>
</tr>
<tr>
<td>555.9</td>
<td>Regional enteritis, unspecified site</td>
<td>363 (16.1)</td>
</tr>
<tr>
<td>555-555.9</td>
<td>Regional enteritis</td>
<td>363 (16.1)</td>
</tr>
<tr>
<td>556</td>
<td>Ulcerative colitis</td>
<td>40 (1.8)</td>
</tr>
<tr>
<td>556.0</td>
<td>Ulcerative colitis, (chronic) enterocolitis</td>
<td>30 (1.3)</td>
</tr>
<tr>
<td>556.1</td>
<td>Ulcerative colitis, (chronic) ileocolitis</td>
<td>24 (1.1)</td>
</tr>
<tr>
<td>556.2</td>
<td>Ulcerative colitis, (chronic) proctitis</td>
<td>55 (2.4)</td>
</tr>
<tr>
<td>556.4</td>
<td>Ulcerative colitis, pseudopolyposis of colon</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>556.5</td>
<td>Ulcerative colitis, left-sided ulcerative colitis</td>
<td>47 (2.1)</td>
</tr>
<tr>
<td>556.6</td>
<td>Ulcerative colitis, universal colitis</td>
<td>244 (10.8)</td>
</tr>
<tr>
<td>556.8</td>
<td>Ulcerative colitis, other ulcerative colitis</td>
<td>101 (4.5)</td>
</tr>
<tr>
<td>556.9</td>
<td>Ulcerative colitis, unspecified</td>
<td>520 (23.1)</td>
</tr>
</tbody>
</table>


Table 2. Definition of Intestinal Surgery

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Definition</th>
<th>Patients, No. a (n = 84539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40005-44160</td>
<td>Incision or excision of small or large bowel</td>
<td>40 900</td>
</tr>
<tr>
<td>44180-44238</td>
<td>Laparoscopic procedure, small or large bowel</td>
<td>20 128</td>
</tr>
<tr>
<td>44300-44346</td>
<td>Formation of stoma</td>
<td>50</td>
</tr>
<tr>
<td>44602-44680</td>
<td>Closure, plication, or stricturoplasty</td>
<td>507</td>
</tr>
<tr>
<td>44900-44979</td>
<td>Surgery on appendix</td>
<td>22 465</td>
</tr>
<tr>
<td>45000-45999</td>
<td>Surgery on rectum</td>
<td>489</td>
</tr>
</tbody>
</table>


a A total of 2149 patients with inflammatory bowel disease had intestinal surgery.

We dichotomized patient demographic characteristics, history, and preoperative laboratory data, taking care to indicate missing variables where appropriate. Crohn disease was defined as present in any case where the postoperative diagnosis field, “podiag,” contained International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 555-555.9 (regional enteritis). Ulcerative colitis was defined as present in any case where the podiag field contained ICD-9-CM codes 555-555.9 (ulcerative colitis). Table 1 lists the ICD-9-CM codes defining the inclusion criteria for these diseases and the frequencies of each code in the database. Inflammatory bowel disease was defined as any case meeting criteria for either Crohn disease or ulcerative colitis. Intestinal surgery was defined as being present in any record with a principle procedure Current Procedural Terminology code indicating surgery on the small or large bowel. Table 2 lists Current Procedural Terminology codes defining intestinal surgery.

OUTCOMES

The NSQIP variables are rigorously defined using a standardized dictionary. Data are abstracted by specifically trained nurses whose performance is subject to yearly validation. The NSQIP dictionary definitions of these occurrences are listed in the appendix (http://www.archsurg.com). We defined DVT as any record with a value greater than 0 recorded in the “nchdvt” field. Similarly, PE was defined as value greater than 0 in the “ncpembol” field, myocardial infarction (MI) as a value greater than 0 in the “ncdmci” field, and stroke as a value greater than 0 in the “ncncsca” field. Because DVT and PE are thought to represent different manifestations of the same process, the spontaneous formation of thrombus in the central veins and the migration of such thrombi centrally, we created a composite variable to identify any patient who had either DVT or PE. Similarly, because MI and cerebrovascular accident may represent spontaneous arterial thrombosis and migration of thrombi, we created a composite variable to identify patients who had either an MI or a stroke. Death was defined as having occurred in any

DATA ACQUISITION AND PATIENT SELECTION

We used the NSQIP PUF for 2008 to evaluate rates of DVT and PE in surgical patients with and without IBD. The NSQIP 2008 PUF contains complete records on 271 368 procedures or ad-

Improvement Program (NSQIP) member hospitals had a similar risk of DVT or PE. The NSQIP collected data from more than 170 hospitals in 2008. These data were gathered by specifically trained nurses working from a rigorously defined and validated data definition dictionary. The purpose of the NSQIP is to provide risk-adjusted clinical outcomes data to participating hospitals. The NSQIP Participant Use Data File (PUF) is a deidentified research database available to NSQIP participants. As such, the NSQIP PUF data set presents an opportunity to examine the relationship of DVT and PE with IBD in a large group of patients and the frequencies of each code in the database. Inflammatory bowel disease was defined as any case meeting criteria for either Crohn disease or ulcerative colitis. Intestinal surgery was defined as present in any record with a principle procedure Current Procedural Terminology code indicating surgery on the small or large bowel. Table 2 lists Current Procedural Terminology codes defining intestinal surgery.

PREOPERATIVE VARIABLES

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The NSQIP 2008 PUF database included 271,368 patients who underwent surgery. Characteristics of patients with and without IBD are shown in Table 3. Patients with and without IBD differed in many ways. There were 2249 patients (0.8%) identified as having a diagnosis of IBD, 57 of whom (2.5%) had DVT or PE, compared with 1.0% of patients without IBD (P < .001). A total of 1164 patients (0.4%) without IBD and 9 patients (0.4%) with IBD had a cerebrovascular accident or MI (P = .68). Patients with IBD were more commonly male and white or Hispanic than patients without IBD (P < .001). Patients with IBD were younger, had on average more relative value units per procedure, and had a longer average length of stay. Patients with IBD were less commonly admitted from home, were smokers, or were obese (P < .001). More than 36% of patients with IBD had used steroids compared with fewer than 3% of patients without a diagnosis of IBD (P < .001). Patients with IBD were less likely to undergo surgery as outpatients or emergencies (P < .001) and more likely to have American Society of Anesthesiologists scores of 1 or 2 (P < .001), but they were more likely to have an elevated white blood cell count, have an organ space infection, sepsis, or septic shock, or to dehisce their fascial closure (P < .001). However, they had lower postoperative mortality rates (P = .04).

Of the multivariate logistic regression models constructed to try to account for these various confounding factors, the most efficient is shown in Table 4. This model includes all variables available in the NSQIP that add to the power to predict DVT or PE. When these numerous confounders are controlled for, IBD remains a significant predictor of DVT or PE (OR = 2.03; 95% CI, 1.52-2.70). In fact, only a history of brain tumor or postoperative neurologic deficit have a higher OR in this model. Mortality occurred in 224 of 2608 patients without IBD who had DVT or PE (8.6%) and 5 of 57 patients without IBD who had DVT or PE (8.8%) (P > .99).

When patients with procedures on the small and large bowel were excluded, 100 patients with IBD remained. Of these, 5 (5.0%) had DVT or PE compared with 1778 cases of DVT or PE among 213,402 patients without IBD (0.8%) (P = .002). When a regression model is constructed for this subset of patients undergoing nonintestinal procedures, the patients with IBD are found to have a 4.45-fold increased risk of DVT or PE (P = .002) compared with patients without IBD.

We repeated the modeling exercise for the composite outcome of perioperative MI and stroke. This analysis revealed no association between IBD and this outcome or its individual components.
surgery. Patients with IBD frequently require surgical intervention, and an understanding of their risk of venous thromboembolism is therefore an important issue. This study aimed to examine rates of DVT and PE in patients with IBD undergoing surgery using data from the NSQIP.

Our findings are consistent with others in this area. We found that IBD increases the risk of perioperative DVT or PE 2-fold (OR = 2.03; 95% CI, 1.52-2.70). Bernstein and Nabalahma found that in patients hospitalized in Canada, IBD resulted in a DVT relative risk of 1.32 to 1.53, depending on age group. Using a survey method, Miehsler et al found that 6.2% of patients with IBD reported an episode of thromboembolism, resulting in an OR of 3.6 (95% CI, 1.7-7.8). Most recently, using data from the National Inpatient Sample, Nguyen and Sam found that hospitalized patients with IBD had an OR for DVT or PE of 2.5 (95% CI, 1.83-3.43).

The only previous study to examine perioperative DVT, a report of the 7-year experience of a single institution where patients with ulcerative colitis and colorectal cancer both received low-molecular-weight heparin at a dosage of 4000 IU/d, found that patients with ulcerative colitis had an OR of 7.4 (95% CI, 1.14-44.4) for experiencing DVT. The broad CIs in this relatively small study suggest that the statistical model may be unstable. Yet, the result comports well with our findings.

We find no support for the claim that DVT or PE in the setting of IBD is more lethal than DVT or PE occurring in the absence of IBD as has been described by Nguyen and Sam and Murthy and Nguyen.

Arterial thromboembolic events are also reported to be increased in patients with IBD. We found no support for this conclusion in our data. In this case, we may have been limited by the lack of data on arterial thrombotic events not involving the coronary or cerebral vessels. It may be that if arterial thromboembolism were a reported NSQIP complication, such a relationship would appear.

This increased risk of DVT or PE in patients with IBD has been shown to be an extraintestinal manifestation specific to IBD and not solely due to the inflammatory state of the disease. Miehsler et al compared the risk of thromboembolism in patients with IBD, celiac disease, and rheumatoid arthritis and control subjects. While they found an association between increased frequency of thromboembolic events and IBD, there was no such association in patients with the inflammatory conditions of celiac disease or rheumatoid arthritis.

Many theories have been proposed to explain this extraintestinal manifestation of IBD. Factors implicated in the pathogenesis of thromboembolism in patients with IBD include platelet hyperactivation mediated by the CD40-CD40 ligand pathway, hyperhomocysteinemia (secondary to malabsorption and medications), increased coagulation factors, and impaired fibrinolysis. Furthermore, studies have even shown a paradoxical improvement in symptoms of inpatients with ulcerative colitis treated with heparin.

There are important strengths and weaknesses associated with using the NSQIP PUF data set for outcomes research. Among the weaknesses, perhaps the most important is that the NSQIP was designed to compare overall outcomes across many hospitals. It was not designed to answer specific research questions regarding specific diseases or procedures. The NSQIP is a database of operations where postoperative diagnosis is cataloged, but most other diagnoses are not specifically recorded. In this study, it is possible that some patients with IBD for whom this was not the principle postoperative diagnosis may have been missed, therefore introducing a classification bias.

Second, because this is a database of operations and not of individual patients, it is possible that particular patients who had multiple admissions during 2008 may be captured more than once in the data set. Presumably the size of the data set would minimize the effect of multiple admissions, but where IBD was a relatively rare diagnosis and the fact that it often requires multiple hos-
hospitalizations may create an opportunity for sample bias toward sicker patients with IBD.

There are a number of strengths in the NSQIP that we believe outweigh these potential sources of bias. First, these data are gathered by specifically trained nurses, accountable to a rigid quality assurance program and working from a well-defined data dictionary. To our knowledge, no other data set offers such reliable and well-validated information. For an investigation like this one, aiming to test an association between 2 relatively uncommon problems, only a prospective multicenter trial enrolling thousands of patients could approach this question. The NSQIP provides an economical alternative.

The second advantage to using the NSQIP is that it not only aggregates data from a large number of centers but also biases toward centers committed to quality improvement. One may assume that, if not all, of the contributing centers are aware of best practices (Surgical Care Improvement Program, for example) and engage in state-of-the-art DVT and PE prophylaxis and detection. No other administrative data set has a bias toward quality that the NSQIP has.

In conclusion, this study of patients enrolled in the NSQIP database demonstrates that patients with IBD who undergo surgery have a 2-fold increased risk of DVT or PE. In patients with IBD who are having nonintestinal surgery, this risk may be even higher. These findings suggest that standard DVT and PE prophylaxis should be reconsidered for this patient group.

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Correspondence: Frederick Millham, MD, Department of Surgery, Newton Wellesley Hospital, 2000 Washington St, Ste 670, Green MOB, Newton, MA 02462 (fmillham@partners.org).

Author Contributions: Study concept and design: Merrill and Millham. Analysis and interpretation of data: Millham. Drafting of the manuscript: Merrill and Millham. Critical revision of the manuscript for important intellectual content: Merrill and Millham. Statistical analysis: Millham.

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REFERENCES


INVITED CRITIQUE

Use of National Surgical Quality Improvement Program Outcomes Data to Change Guidelines

A Sound Idea?

Merrill and Millham1 provide compelling data to associate patients with inflammatory bowel disease (IBD) with an increased postoperative risk for deep venous thrombosis (DVT) and pulmonary embolism. Using National Surgical Quality Improvement Program (NSQIP) data, the results likely confirm what many physicians who treat patients with IBD already believe. Current guidelines from the American College of Chest Physicians 2008 Conference on Antithrombotic and Thrombolytic Therapy...