The impact of preoperative steroid use on short-term outcomes following surgery for inflammatory bowel disease

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Abstract

Background: Inflammatory bowel disease (IBD) patients are frequently treated with steroids prior to surgery. We characterized the association between preoperative steroid use and postoperative complications in a large prospective cohort.

Methods: We identified patients who underwent major IBD-related abdominal surgery in the American College of Surgeon's National Surgical Quality Improvement Program (ACS-NSQIP) between 2005 and 2012. We compared the risk of postoperative complications and 30-day mortality between preoperative steroid users and non-users.

Results: We identified 8260 Crohn's disease (CD) and 7235 ulcerative colitis (UC) patients who underwent major abdominal surgery. Preoperative steroid use was associated with higher risk of postoperative complications, excluding death, in both CD (22.6% vs. 18.5%, P < 0.0001) and UC (30.1% vs. 22.5%, P < 0.0001). The adjusted odds ratio for any postoperative complication associated with steroids was 1.26 (95% CI: 1.12–1.41) for CD and 1.44 (95% CI: 1.28–1.61) for UC. Infectious complications were more frequent with steroid use in both CD (15.2% vs. 12.9%, P = 0.004) and UC (19.4% vs. 15.6%, P < 0.0001), specifically intra-abdominal infections and sepsis. Steroid use was associated with increased risk of venous thromboembolism (VTE) in both CD (OR, 1.66; 95% CI: 1.17–2.35) and UC (OR, 2.66; 95% CI: 2.01–3.53). 30-day mortality did not differ among steroid users and non-users (6.8/1000 vs. 5.8/1000, P = 0.58 for CD; 13.5/1000 vs. 15.2/1000, P = 0.55 for UC).

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1. Introduction

The inflammatory bowel diseases (IBDs), comprising Crohn’s disease (CD) and ulcerative colitis (UC) are chronically relapsing conditions that frequently lead to complications requiring intestinal surgery. Nearly 40% of CD patients undergo intestinal resection within 20 years of disease onset. A third of these individuals will require a second surgery within 10 years of the initial surgery. For UC, the 20-year cumulative risk of colectomy is 15%. However, unlike CD, surgery for UC is curative.

Surgery is usually only recommended after IBD patients have failed conventional medical therapy. Corticosteroids remain a mainstay of conventional medical therapy and up to half of IBD patients are treated with at least one course of steroids during their first 5 years of diagnosis. While the use of steroids in CD remains stable, it seems to be increasing in UC. Because steroids are frequently used prior to surgery, their association with poor wound healing and infectious complications has raised concerns regarding their potential impact on postoperative outcomes. A number of small studies have shown conflicting results as to whether steroids are associated with infectious or overall complications. The vast majority of these studies were underpowered to detect differences in steroid-associated postoperative complications. A meta-analysis of the aforementioned studies has demonstrated an increase in aggregate risk of infectious and overall postoperative complications associated with steroids, but was not able to assess individual complications.

The American College of Surgeons’ National Surgical Quality Improvement Program (ACS-NSQIP) is a geographically diverse database of surgeries throughout the United States that contains over 100 quality-controlled clinical variables. Its large study population of IBD patients who have undergone major abdominal surgery is nearly 10-fold greater than the total number of individuals in the above meta-analysis and provides a unique opportunity to definitively characterize the impact of corticosteroid use on a myriad of individual postoperative short-term complications.

2. Methods

2.1. Study population

The ACS-NSQIP was designed to assess short-term surgical outcomes and their predictors. These clinical data are prospectively collected from individuals who are 15 years old and older at participating hospitals. The NSQIP database and methodology have been previously described. We used ICD-9 codes to identify all individuals between 2005 and 2012 with a diagnosis of Crohn’s disease (555.x) and ulcerative colitis (556.x) who underwent open or laparoscopic large or small bowel resection (CPT codes: 44005–44160; 44180–44238); stoma formation (CPT codes: 44300–44346); stricturoplasty (CPT codes: 44615); fistula repair (CPT codes: 44602–44680); and resection of the rectum (CPT codes: 45110–45397).

2.2. Predictor variables

The primary predictor variable was the preoperative use of steroids for >10 days for chronic inflammatory conditions (including IBD) within 30 days prior to surgery. The specific indication for and dosage and route of administration of corticosteroids were not recorded. Other predictor variables included age, sex, smoking status, functional status, body mass index, weight loss, anemia, selected preoperative comorbidities (diabetes, anemia, cardiovascular disease, renal disease), predicted mortality and morbidity scores (based on logistic regression models incorporating preoperative variables that were developed in general surgery and vascular patients), and emergency status.

2.3. Outcome variables

Primary outcomes included 30-day mortality, return to operating room, infectious complications (superficial and deep wound infections, intra-abdominal infection, pneumonia, urinary tract infection); wound dehiscence; cardiac complications (cardiac arrest and myocardial infarction); neurological sequelae (stroke and coma); renal complications (acute renal failure and progressive renal insufficiency); and venous thromboembolism. In the subset of patients admitted for surgery in 2011 and 2012, data on 30-day readmissions and unplanned reoperations were also available and analyzed in this subgroup.

Measures of resource utilization, including total length of stay and postoperative length of stay were also measured. We used the work relative value unit (RVU) to estimate the quantity of physician services associated with each surgery.

2.4. Statistical analysis

Analyses were performed using the Stata 10.0 SE software package (Stata Corp LP, College Station, Texas). Categorical variables were compared between steroid users and non-users using the chi-square or Fishers exact test, while continuous variables were compared using the unpaired Student’s t-test. Multiple logistic regression models were used to assess for predictors of select postoperative outcomes while simultaneously adjusting for other predictors and accounting for clustering using the robust variance estimator.
3. Results

There were 15,945 IBD patients (8260 CD and 7235 UC) who underwent bowel surgery between 2005 and 2012. The prevalence of preoperative steroid use was 41% and was slightly more frequent with UC compared with CD (42% vs. 39%, P = 0.001). The demographic and clinical characteristics of steroid users and non-users among CD and UC subgroups are shown in Table 1. CD and UC patients who used steroids in the preoperative setting were younger than non-users. They were also more likely to have anemia, experienced a >10% weight loss at the time of surgery and undergone surgery under emergent circumstances. The predicted morbidity scores based on preoperative characteristics were higher among steroid users than non-steroid users for both CD (19.7% vs. 15.8%, P < 0.0001) and UC (25.9% vs. 19.4%, P < 0.0001). Preoperative steroids were also associated with higher predicted mortality among those with CD (0.9% vs. 0.7%, P = 0.001) but not UC (1.7% vs. 2.0%, P = 0.10).

3.1. Overall postoperative complications

The overall rate of postoperative complications, not including death, was 20% and 26% for CD and UC, respectively. Preoperative steroid use was associated with higher risk of postoperative complications for both CD (22.6% vs. 18.5%, P < 0.0001) and UC (30.1% vs. 22.5%, P < 0.0001). After adjustment for age, sex, smoking status, body mass index (BMI), functional status, preoperative weight loss and anemia, coexisting diabetes, and emergent status, preoperative steroid use was associated with higher risk of postoperative complications for CD (OR, 1.26; 95% CI: 1.12–1.41). This association was slightly more pronounced for UC (OR, 1.44; 95% CI: 1.28–1.61). For CD patients, functional status had a significant impact on postoperative complications; partially dependent individuals had more than 2-fold higher risk of complications (OR, 2.41; 95% CI: 1.72–3.37) while being completely dependent had a nearly 5-fold effect (OR, 4.71; 95% CI: 2.26–9.80). Similarly, in UC, being partially dependent (OR, 2.18; 95% CI: 1.59–2.99) and completely dependent (OR, 3.80; 95% CI: 2.41–6.00) were also associated with greater likelihood of postoperative complications. Undergoing emergent surgery was associated with higher risks of postoperative complications in CD (OR, 1.16; 95% CI: 1.01–1.34) and UC (OR, 1.35; 95% CI: 1.17–1.56). Current smokers with CD and UC exhibited higher postoperative complication rates than those who did not smoke at the time of surgery (Table 3). Female CD patients experienced more frequent postoperative complications than their male counterparts. The presence of anemia and preoperative weight loss increased the risk of postoperative complications in both CD and UC, while coexisting diabetes was a predictor of outcomes only in CD (Table 3).

3.2. Infectious postoperative complications

Table 2 shows the incidence of specific postoperative complications. Overall infectious complications were more common in the presence of steroid use for both CD (15.2% vs. 12.9%, P = 0.004) and UC (19.4% vs. 15.6%, P < 0.0001) patients. Both CD and UC patients who used steroids prior to surgery were at high risk of intra-abdominal infection, sepsis, and sepsis leading to shock. UC patients with preoperative steroid use were at additional risk for pneumonia in the postoperative setting (Table 2). After adjustment for the aforementioned confounders, the odds ratios for any postoperative infection associated with preoperative steroid use were 1.22 (95% CI: 1.06–1.39) for CD and 1.30 (95% CI: 1.14–1.49) for UC.

3.3. Other postoperative complications

Steroid use was associated with increased wound dehiscence in both CD (1.8% vs. 1.0%, P = 0.002) and UC (2.4% vs. 1.1%,
Steroid users compared to non-users were also more likely to have bleeding that required transfusion following surgery for CD (7.0% vs. 5.7%, \( P = 0.01 \)) and UC (9.8% vs. 6.0%, \( P = 0.01 \)). Moreover, in the presence of preoperative steroid use, the need to return to the operating room following bowel surgery was more frequent for both CD (7.9% vs. 5.4%, \( P = 0.01 \)) and UC (9.1% vs. 6.9%, \( P < 0.0001 \)).

Interestingly, the rate of postoperative venous thromboembolism (VTE) was higher among preoperative steroid users with CD (2.2% vs. 1.3%, \( P = 0.003 \)) and UC (5.4% vs. 2.0%, \( P < 0.0001 \)). While the risk of both deep venous thrombosis (DVT) and pulmonary embolism was increased with steroid use in UC, it was associated with only DVT risk in CD (Table 2). After adjustment for age, sex, emergent status, BMI, smoking status, functional status, calendar year, anemia, and presence of weight loss, the adjusted odds ratio for developing VTE in CD was 1.66 (95% CI: 1.17–2.35). For UC, the association was even stronger (OR, 2.66; 95% CI: 2.01–3.53).

### 3.4. 30-day postoperative outcomes

The overall 30-day mortality for all IBD patients undergoing bowel surgery was 10.1 per 1000, was 6.2 per 1000 for CD and was 14.5 per 1000 for UC. Mortality at 30 days did not differ between preoperative steroid users and non-users among those with CD (6.8 vs. 5.8 per 1000, \( P = 0.58 \)) or UC (13.5 vs. 15.2 per 1000, \( P = 0.55 \)).

The rate of return to the operating room for major surgery within 30 days was higher among these with preoperative steroid use for both CD (7.9% vs. 5.4%, \( P < 0.0001 \)) and UC (9.1% vs. 6.9%, \( P = 0.001 \)). Data on whether this subsequent major surgery was related to the index bowel surgery was only available after 2011. The 30-day re-operation rate, defined as a return to the operating room for unplanned surgery that was related to the index bowel surgery, was 7.6% for UC and was higher among steroid users compared with non-users (9.8% vs. 6.0%, \( P = 0.01 \)). For CD patients, the rate of re-operation at 30 days was similar between those who used preoperative steroids and those who did not (6.6% vs. 6.7%, \( P = 1.0 \)).

Readmission rates at 30 days also did not differ between steroid users and non-users with CD (9.8% vs. 6.0%, \( P = 0.01 \)) and UC (23.7% vs. 19.7%, \( P = 0.09 \)). The proportion of individuals who remained in hospital 30 days after surgery was 1.9% and 2.5% for CD and UC, respectively, and did not differ with respect to preoperative steroid use.

### 3.5. Resource utilization

Among those who underwent surgery for CD, those with preoperative steroid use experienced longer total hospital length of stay (9.5 vs. 8.4 days, \( P < 0.0001 \)) and postoperative length of stay (7.5 vs. 7.2 days, \( P = 0.03 \)). Similarly, UC patients who used steroids prior to surgery exhibited greater total (10.7 vs. 8.7 days, \( P < 0.0001 \)) and postoperative (8.4 vs. 7.7 days, \( P = .0001 \)) length of stay. The physician work relative value unit (RVU) was higher among

### Table 2 Short-term outcomes following abdominal surgery for inflammatory bowel disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All IBD patients (N = 15,495)</th>
<th>Preoperative steroid use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Crohn’s disease (Yes N = 3248) No (N = 5012)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1.0%</td>
<td>0.7% 0.6%</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>15.5%</td>
<td>15.2% 12.9% *</td>
</tr>
<tr>
<td>Deep wound</td>
<td>1.9%</td>
<td>1.8% 2.1%</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>6.9%</td>
<td>7.9% 5.6% *</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6.4%</td>
<td>6.5% 5.3% *</td>
</tr>
<tr>
<td>Septic shock</td>
<td>1.6%</td>
<td>2.0% 1.1% *</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.0%</td>
<td>1.9% 1.7%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.5%</td>
<td>2.8% 2.7%</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1.5%</td>
<td>1.8% 1.0%</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>6.8%</td>
<td>7.0% 5.7% *</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>0.5%</td>
<td>0.4% 0.4%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.2%</td>
<td>0.1% 0.3%</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0.3%</td>
<td>0.3% 0.1%</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>0.3%</td>
<td>0.3% 0.1%</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0.1%</td>
<td>0.09% 0.02%</td>
</tr>
<tr>
<td>Coma</td>
<td>0.1%</td>
<td>0.03% 0.02%</td>
</tr>
<tr>
<td>Peripheral nerve injury</td>
<td>0.1%</td>
<td>0.12% 0.08%</td>
</tr>
<tr>
<td>Renal complications</td>
<td>1.1%</td>
<td>0.7% 0.9%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0.4%</td>
<td>0.3% 0.3%</td>
</tr>
<tr>
<td>Progressive renal insufficiency</td>
<td>0.7%</td>
<td>0.4% 0.6%</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.5%</td>
<td>2.2% 1.3% *</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>2.0%</td>
<td>1.8% 1.0%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.7%</td>
<td>0.7% 0.5%</td>
</tr>
<tr>
<td>Return to operating room</td>
<td>7.1%</td>
<td>7.9% 5.4% *</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \).
preoperative steroid use for CD (24.0 vs. 23.5, P < 0.0001) and UC (31.6 vs. 29.3, P < 0.0001). Preoperative steroid use was associated with slightly longer operating times for UC (234 vs. 210 min, P < 0.0001) but not for CD (165 vs. 166 min, P = 0.67).

4. Discussion

We present prospectively collected data from a large surgical cohort of IBD patients to assess the impact of preoperative steroid use on short-term outcomes following IBD surgery. Though 30-day mortality did not differ among users and non-users of preoperative steroid use, there was an increase in overall postoperative complications other than mortality, especially infectious complications. Interestingly, steroid use was associated with increased incidence of both postoperative DVT and PE.

The association of preoperative steroid use with wound dehiscence and postoperative infectious is consistent with findings from the TREAT registry in which steroid use was linked to serious infections in Crohn’s disease.20,21 Numerous studies, mostly retrospective, have assessed whether preoperative steroid use led to poor perioperative outcomes.4,14,22 These studies were markedly heterogenous with respect to their study population and study outcomes. Seven of these studies included only CD patients; 2 comprised of both CD and UC patients; and 3 studies incorporated only UC patients. While half of the studies assessed in-hospital outcomes, the other half evaluated 30-day adverse events; 7 studies documented overall complications but did not distinguish by type, and 6 recorded only infectious complications. While results from the individual studies were conflicting, a meta-analysis demonstrated a 1.7-fold increased risk of postoperative infectious complications and 1.4-fold increased risk of overall complications.14 However, among the limitations inherent to this meta-analysis was that it could not assess specific infectious or non-infectious complications, nor could it characterize predictors of complications or adjust for the same consistent set of confounders. The sample size of our current study was more than 10-fold higher than the combined sample size from all the studies in the meta-analysis, and provided sufficient power to definitively evaluate a more diverse range of specific complications and conduct multivariable analyses to account for a consistent array of confounders. We were able to assess infrequent outcomes such as 30-day mortality and demonstrated that it was similar between steroid users and non-users.

Our large study population enabled us to discern specific infectious complications among steroid users. The most concerning of these complications are sepsis and septic shock, which may arise from both an increased risk of intra-abdominal infection and wound dehiscence. These findings should prompt increased vigilance and appropriate use of indwelling catheters in the postoperative setting. We also found that steroid users were more likely to have postoperative bleeding requiring blood transfusion. This association is likely multifactorial and driven by a higher burden of active disease among those requiring steroids. IBD steroid utilizers had greater prevalence of preoperative anemia and may have had more complicated surgeries due to their disease as reflected by modestly longer operating times (for UC).

Interestingly, the use of preoperative steroids was associated with VTE in both CD and UC. It is possible that corticosteroids are a crude surrogate indicator for disease severity, which is a risk factor for VTE and not captured by the NSQIP study.23 The fact that these patients were hospitalized and undergoing IBD-related surgery reflects their inherent aggressive disease course. Our analysis also accounted for the emergent status of the surgery and other measures of functional status. However, disease activity likely remained a residual confounder. Steroids, however, may also have an independent thrombogenic effect. A recent population-based case–control study from Denmark showed that steroid use within the last 90 days was associated with more than a 2-fold increase in risk of VTE.24 Regardless of whether it directly causes VTE or is a surrogate indicator for other VTE risk factors, individuals who use steroids preoperatively are at high risk for VTE. Though steroid use may not be avoidable, VTE is preventable in the hospital setting with anticoagulant prophylaxis and should be strongly considered in the postoperative setting. Standardized provision of VTE prophylaxis would be consistent with the American College of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Multivariable logistic regression analysis to assess predictors of postoperative complications following bowel surgery for Crohn's disease and ulcerative colitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crohn's disease adjusted odds ratio (95% CI)</td>
</tr>
<tr>
<td>Preoperative steroid use</td>
<td>1.26 (1.12–1.41)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.01 (1.00–1.01)</td>
</tr>
<tr>
<td>Female vs. male</td>
<td>1.21 (1.09–1.37)</td>
</tr>
<tr>
<td>Body mass index (per unit)</td>
<td>1.01 (1.00–1.02)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.24 (1.09–1.41)</td>
</tr>
<tr>
<td>Functional status (%)</td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>Ref (1.00–1.00)</td>
</tr>
<tr>
<td>Partially dependent</td>
<td>2.41 (1.72–3.37)</td>
</tr>
<tr>
<td>Dependent</td>
<td>4.71 (2.26–9.80)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.72 (1.52–1.95)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1.40 (1.17–1.67)</td>
</tr>
<tr>
<td>Emergent surgery</td>
<td>1.16 (1.01–1.34)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.55 (1.18–2.05)</td>
</tr>
<tr>
<td>Year of operation</td>
<td>1.09 (1.05–1.13)</td>
</tr>
</tbody>
</table>

Ref = reference category.
Chest Physicians’ guidelines for the prevention of VTE in non-orthopedic surgical patients in patients with moderate to high risk.25

Our study had several limitations. Firstly, though the NSQIP is a prospective multicenter study, it did not capture key clinical variables related to IBD. Important confounders such as disease phenotype and severity were neither measured nor accounted for. Thus, our analysis may have been vulnerable to confounding by indication in which individuals with the worse prognosis may have been more likely to receive immunosuppressive therapy, including steroids. We should, however, note that because all individuals in this study required surgery for IBD, their disease activity would likely be at least moderate to severe. Moreover, we did not have data on other IBD medications, particularly immunomodulators and biologics. Data from other retrospective studies, including population-based analyses, provide strong evidence that the preoperative use of biologics is not associated with adverse postoperative outcomes following surgery for UC.26–30 In CD, the literature is more conflicting but suggests that the impact of preoperative biologics on postoperative outcomes, if any, would be modest.28,31–35 Similarly, the preoperative use of immunomodulators, including thiopurines and cyclosporine, has not been shown to increase the risk of postoperative complications.36,37 Consequently, we do not believe that the use of concomitant immunosuppressants would contribute significantly to the adverse outcomes that we observed with steroid use. An additional limitation was the lack of data on the specific dosing of preoperative steroids which precluded a dose–response analysis or whether escalation of steroid dose during hospitalization was associated with adverse outcomes. Our study also did not collect data on the context of steroid use (e.g., steroid-dependence or fulminant disease) or whether intravenous steroids were administered during hospitalization. Thus, we could not explore whether there was a differential effect between intravenous administration and oral steroid administration.

Despite the above limitations, this study has definitively established the association between preoperative steroid use in the largest IBD surgical cohort to date. The large sample size has enabled us to identify specific infectious complications and other extra-intestinal sequelae, particularly VTE. The use of preoperative use of steroids is unavoidable in the majority of IBD patients undergoing surgery because it is considered first-line therapy for induction of remission in moderate–severe disease. Consequentially, a cardinal focus of postoperative management should be increased vigilance and prevention especially for life-threatening complications such as sepsis and VTE. Process measures such as the optimal management of indwelling catheters, standardized infection control procedures, and prompt initiation of pharmacological VTE prophylaxis may reduce some of the impact of preoperative steroid use on postoperative complications. For IBD patients on chronic steroids for whom elective bowel surgery is anticipated, consideration should be given to stopping steroids at least 30 days prior to the procedure when possible. Per clinical guidelines, those with acute severe UC should be promptly assessed for non-response to steroids within 3 days in order to promptly proceed to second-line medical therapy or surgery since those who wait too long for colectomy may have a higher risk of postoperative complications.38,39 Moreover, consideration should be given to preoperative use of biologics in lieu of steroids for patients with a high probability of requiring surgery.

Disclaimer

The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Conflict of interest

G.C.N. has served as a consultant for Janssen and Abbvie, which were in no way involved with the design or interpretation of this study.

References

Steroids and IBD surgery


