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Opioid Use and Outcomes in Patients Hospitalized With Acute Severe Ulcerative Colitis

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Background: Opioid use has not been shown to improve hospitalized inflammatory bowel disease patient pain scores and may prolong the length of stay (LOS). Additional clinical implications of opioid use, particularly high amounts, in the hospital setting have not yet been explored. We sought to determine how high opioid use impacts clinical outcomes in acute severe ulcerative colitis (ASUC).

Methods: In this single-center study, we identified all patients hospitalized with ASUC who received intravenous corticosteroids from July 1, 2014 to December 31, 2021. Clinical outcomes including opioid exposure, cumulative intravenous corticosteroid dose, biologic rescue therapy initiation date, colectomy rate, opioid prescription at discharge, LOS, and hospitalization cost were collected. High opioid use was defined as ≥40 oral morphine equivalents (OMEs) per day. A univariable logistic regression was performed to evaluate the association of high opioid use with ASUC outcomes.

Results: 185 eligible hospitalizations for ASUC were evaluated. 75 patients (41%) received opioids during hospitalization, and 20 patients (11%) received ≥40 OMEs/day. High opioid use was associated with a median 3-day delay in biologic rescue therapy initiation when compared with low/no opioid use ($P = .02$). 70% of patients with high opioid use received an opioid prescription at discharge compared with 10% of those with low/no use ($P < .001$). Opioid use was not associated with LOS, duration of corticosteroid therapy, colectomy rate, or hospitalization cost.

Conclusions: Among ASUC hospitalizations, high opioid use was associated with delayed biologic rescue therapy initiation and higher rates of opioid prescriptions at discharge.

Lay Summary

In this single-center study of patients hospitalized with acute severe ulcerative colitis, opioid use was associated with delayed initiation of biologic rescue therapy and higher rates of discharge prescriptions for opioids.

Key Words: ulcerative colitis, opioid analgesics, biologic therapy

Introduction

Approximately 70% of patients with inflammatory bowel disease (IBD) experience pain, which is often exacerbated during active disease flares.[1] Pain during hospitalizations for disease flares is frequently treated symptomatically with opioids[2] while awaiting the benefits of disease-modifying treatments, such as intravenous steroids and rescue biologic therapy. However, prior studies suggest that opioid use does not improve hospitalized IBD patient-reported pain scores and may prolong the length of stay (LOS).[3-5] Thus, recent single-institution efforts have focused on provider education promoting non-opioid analgesia for IBD flares, resulting in reduced opioid exposure while maintaining similar patient-reported pain scores.[4,6]

Beyond pain scores, the clinical- and systems-level implications of opioid use in the inpatient setting have been minimally explored. Research from the outpatient setting indicates that opioids are associated with increased risk of infection and mortality in IBD,[2,7-9] as well as more frequent emergency room visits and higher healthcare costs.[10] For these reasons, opioid use is discouraged for IBD patients.[11] For the hospitalized IBD patient, a recent meta-analysis by Sheehan et al concluded that inpatient opioid use was associated with longer LOS but did not increase the risk of IBD-related surgery during admission.[12] The high variability among the included studies in this meta-analysis supports the need for additional research on the clinical implications of inpatient opioid use. The relationship between opioid use and outcomes specific to the hospitalized IBD patient, such as length of intravenous corticosteroid treatment, time to rescue therapy initiation, and hospitalization cost, requires further elucidation.

Accordingly, we sought to evaluate the impact of opioid use and dosage on outcomes for patients hospitalized with acute severe ulcerative colitis (ASUC). In particular, we focused on patients receiving the highest amounts of opioids, who we

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Key Messages

What is already known?

Opioid use for patients with inflammatory bowel disease is associated with increased mortality and infections in the outpatient setting, but clinical implications of inpatient opioid use for patients hospitalized with acute severe ulcerative colitis (ASUC) remain unclear.

What is new here?

High opioid use in hospitalized ASUC patients is associated with delay in administering biologic rescue therapy and higher rates of new opioid prescriptions at discharge.

How can this study help patient care?

Early identification of ASUC patients receiving opioids and discussion of rescue therapy early and often may serve as key interventions to decrease the time to rescue therapy initiation and reduce both inpatient and outpatient opioid use.

hypothesized would be at greatest risk for complications from opioid therapy and thus could benefit most from interventions and resources to address pain and their severe disease early in the hospital course.

Methods

All adult patients hospitalized at the University of California San Francisco from July 1, 2014 to December 31, 2021 with ASUC as defined by Truelove and Witts criteria and who received intravenous corticosteroids were included in this study. Patients were identified retrospectively using hospitalization International Classification of Diseases (ICD)-9 and ICD-10 codes associated with ulcerative colitis ($n = 352$), and then verified by manual chart review ($n = 185$). Demographics, clinical characteristics, endoscopic Mayo severity score, analgesic medication use, and clinical outcomes were collected from the electronic health record. Opioid analgesic use and dosage were manually extracted from the medication administration record, excluding opioids administered for endoscopic sedation. Specific opioid agents included oxycodone, hydromorphone, morphine, fentanyl, hydrocodone, and codeine. Tramadol was not included as an opioid medication given its mixed mechanism of action. Patients were stratified by opioid dosage, calculated as oral morphine equivalents (OMEs) per day. Opioid dosage of ≥40 OMEs/day was defined as the a priori threshold for high opioid use based on 3 publications of opioid use among hospitalized IBD patients.[3,4,13] 40 OMEs/day was the top quartile[3,13] or top half[4] of inpatient opioid use in these studies. Patients who underwent colectomy during the hospitalization were included in the analysis, but only preoperative opioid use was included in the OME calculation.

Pearson chi-square and Kruskal–Wallis testing were performed for categorical and continuous variables, respectively. Univariable logistic regression was performed to identify significant and clinically relevant variables associated with high opioid use. A P-value <.05 was considered statistically significant. Data were analyzed using STATA v17.0.

Results

185 ASUC hospitalizations met the inclusion criteria for this study. 75 patients (41%) received opioids during hospitalization, with a median daily dose of 8.7 OMEs. 20 patients (11%) received high opioid doses (≥40 OMEs per day), with a median daily dose of 83.5 OMEs. The low/no opioid use group included all patients who had received <40 OME/day, including the 110 patients who received no opioids during their hospitalization. There was no difference in age, disease duration, disease extent, or ulcerative colitis medication use between low/no and high opioid recipients (Table 1). There was female gender predominance in the high opioid use group (85% female compared with 60% female in the low/no opioid group, $P = .03$). The majority of patients in both groups had been exposed to biologics previously—63% in the low/no opioid use group and 70% in the high opioid use group ($P = .54$). 65% of patients in the high opioid use group had an outpatient opioid prescription at the time of admission compared with 7.3% of those in the low/no opioid group. Notably, patients with high opioid use had significantly more prior hospitalizations than those with low/no opioid use ($P = .003$), including 50% of high opioid recipients being hospitalized ≥2 times previously for ASUC.

ASUC-related disease severity at presentation was similar between the high and low/no opioid use groups, including maximum temperature and heart rate in the first 24 hours, C-reactive protein, hemoglobin values (Table 2), and Mayo endoscopic score. Rates of *Clostridioides difficile* toxin positivity on admission and of colonic dilation on initial imaging were also similar between groups. ASUC management, including the hospital day of flexible sigmoidoscopy, duration and total cumulative dose of intravenous corticosteroid therapy, frequency of rescue therapy administration, and rate of surgical consultation during admission, was also similar between groups. For pain management, patients in the high opioid use group were as likely as the low/no opioid use group to receive non-opioid analgesia, such as acetaminophen and nonsteroidal anti-inflammatory drugs, and the partial opioid agonist tramadol (Table 2).

Table 3 outlines the clinical- and systems-related outcomes associated with opioid exposure. Univariable logistic regression identified gender, prior hospitalization, opioid use at the time of admission, and hospital day of rescue therapy initiation as variables associated with high opioid use. Rescue biologic therapy was initiated later in the hospital course for patients with high opioid use ($P = .02$). For low/no opioid use, the median day of biologic administration was hospital day 4 (interquartile range [IQR] 3-5). For high opioid use, the median day of biologic initiation was hospital day 7 (IQR 4-7). We reviewed the charts of the patients in the high opioid use group who received biologic rescue therapy ($n = 9$) to identify possible factors associated with delay. Through a root cause analysis of the patients with biologic therapy administered after day 4 ($n = 5$), we identified the following factors in biologic initiation delay: patient concern about biologic safety or cost, a clinical complication of disease during hospital course, opioid-related complication (eg, misleading symptom improvement from the use of patient-controlled analgesia pump, opioid-induced ileus), and logistical (eg, holiday weekend). In 1 case, the reason for the delay in rescue therapy initiation was not clearly documented in the primary team, consult, and nursing notes.

Table 1. Patient and disease characteristics associated with opioid use among patients with acute severe ulcerative colitis.

Characteristic	Low/no opioid use (<40 OMEs/day) *n* = 165	High opioid use (≥40 OMEs/day) *n* = 20	*P*-value
Age, median (IQR)	34 (18-73)	33 (23-39)	.34
Female gender, *n* (%)	99 (60%)	17 (85%)	.03
Disease duration, median years (IQR)	4 (1-9.3)	5.8 (4-10.5)	.13
Extensive or pan-colitis, *n* (%)	163 (99%)	20 (100%)	.14
Number of prior colitis-associated hospitalizations			.003
0	81 (49%)	2 (10%)	
1	43 (26%)	8 (40%)	
2+	41 (25%)	10 (50%)	
Medications at time of admission, *n* (%)			
Mesalamine	56 (34%)	10 (50%)	.15
Systemic steroids	89 (54%)	13 (65%)	.34
Immunomodulator	22 (13%)	4 (20%)	.41
Anti-TNF	63 (38%)	9 (45%)	.55
Opioids	12 (7.3%)	13 (65%)	<.01
Prior medication exposure, *n* (%)			
Mesalamine	143 (87%)	18 (90%)	.67
Systemic steroids	137 (83%)	18 (90%)	.42
Immunomodulator	26 (16%)	4 (20%)	.62
Any biologic	104 (63%)	14 (70%)	.54
Anti-TNF	96 (58%)	14 (70%)	.31
Prior number of biologic or small molecule therapies, median (IQR)	1 (0-2)	1.5 (0-2)	.32

Abbreviations: IQR, interquartile range; OMEs, oral morphine equivalents; TNF, tumor necrosis factor.

Colectomy rates during admission and within 90 days of discharge were similar between groups. At hospital discharge, 14 patients (70%) with high opioid use received an opioid prescription compared with 11% of those with low/no use ($P < .001$). Within the high opioid use group, 50% of the patients who received a discharge prescription for opioids did not have a prior outpatient opioid prescription.

Discussion

Expert opinion recommends against opioid use for patients hospitalized with ASUC largely based on extrapolation of data from the outpatient setting showing harm.[2,7-9] Accordingly, we sought to further elucidate the potential harms of opioid use in the inpatient setting. Our study of more than 180 patients hospitalized with ASUC at a tertiary care center determined that nearly half of patients (41%) received opioids while admitted, including 11% who received ≥40 OMEs/day. Pre-hospitalization opioid use, prior ASUC-related hospitalization, and female gender were associated with high opioid use. Ulcerative colitis disease severity did not correlate with opioid use. High opioid use was associated with negative clinical outcomes, including delay in rescue therapy initiation by a median of 3 days and frequent opioid prescriptions at discharge.

Prior research indicates that inpatient opioid use for patients with ASUC is common yet without clear analgesic benefits. According to a recent meta-analysis,[2] 62% of patients hospitalized for IBD receive opioids. Included studies ranged from 20% to 89% of patients receiving opioids inpatient.[3,13-15] Patients with psychiatric illness, comorbid disorders of gut–brain interaction, high healthcare utilization, and exposure to biologic therapy are at increased risk for inpatient opioid use.[9,12,13] Concerningly, opioid use may not improve pain scores for hospitalized patients with IBD,[3] and thus this subset of patients may be only at risk for deleterious side effects of opioids, such as somnolence, respiratory depression, and bowel dysmotility.[16,17]

Our study found similarly high rates of inpatient opioid use for patients with ASUC despite being a tertiary center with IBD expertise and general increased awareness of the risks of opioid use during the study period. Patients with prior hospitalizations for ASUC are more likely to receive high amounts of opioids. However, other factors commonly associated with disease severity, such as a number of prior biologic treatments and disease duration, did not predict opioid use. Instead, prior hospitalization may indicate higher healthcare utilization. For instance, patients with prior hospitalizations may have prior inpatient opioid exposure, with the practice of opioids for pain control being carried forward into subsequent hospitalizations even as opioid prescribing practices changed over the past 2 decades.

Another novel finding of our study is that opioids were associated with a median 3-day delay in biologic rescue therapy initiation. On average, patients with high opioid use received biologic rescue therapy on hospital day 7, which is well beyond the hospital day 3-5 rescue therapy timing recommended in society guidelines.[18] This delay did not correlate with longer LOS as seen in some[4,5,12] but not all[3] prior research on inpatient opioid use. On chart review of the patients within the

Table 2. Clinical presentation and management characteristics associated with opioid use for patients with acute severe ulcerative colitis.

Characteristic	Low/no opioid use (<40 OMEs/day) *n* = 165	High opioid use (≥40 OMEs/day) *n* = 20	*P*-value
Initial data			
Febrile in first 24 h (TMax ≥37.8 °C)	30 (18%)	4 (20%)	.83
Maximum heart rate in first 24 h (bpm), median (IQR)	100 (89-115)	110 (94.5-117.5)	.15
Initial C-reactive protein (mg/L), median (IQR)	48.2 (16.3-97.2)	57.1 (10.5-164.5)	.46
Initial ESR (mm/h), median (IQR)	40 (23-61)	39 (27-52.5)	.93
Admission hemoglobin (g/dL), median (IQR)	11.8 (9.9-14.1)	11.3 (9.6-12.4)	.37
Hospital day of flexible sigmoidoscopy, median (IQR)	2 (1-3)	1 (1-2)	.42
Surgery consultation during admission, *n* (%)	74 (45%)	12 (60%)	.20
Non-opioid analgesics administered during hospitalization, *n* (%)[a]			
Acetaminophen	127 (77%)	17 (85%)	.41
Tramadol	55 (33%)	8 (40%)	.57
Maximal 24-h OMEs received, median (IQR)	0 (0-10)	125.8 (72.3-216.8)	.001
Mean daily opioid dose (OMEs), median (IQR)	0 (0-1.8)	83.5 (59.5-144.3)	.001
Duration of IV corticosteroid therapy (d), median (IQR)	5 (3-7)	5 (3-10)	.86
Cumulative corticosteroid dose (mg in prednisone equivalents), median (IQR)	250 (190-360)	340 (210-695)	.06
Rescue therapy administered during hospitalization, *n* (%)	93 (56%)	9 (45%)	.34

Abbreviation: ESR, erythrocyte sedimentation rate; IQR, interquartile range; OMEs, oral morphine equivalents.
[a]Nonsteroidal anti-inflammatory drugs were administered to <1% of patients in both groups.

Table 3. Clinical- and systems-related outcomes associated with opioid use among patients with acute severe ulcerative colitis.

Outcome	Low/no opioid use (<40 OMEs/day) *n* = 165	High opioid use (≥40 OMEs/day) *n* = 20	*P*-value
Hospital day of biologic initiation, median (IQR)	4 (3-5)	7 (4-7)	.02
Length of stay (days), median (IQR)	8 (6-12)	9 (6-12.5)	.73
Hospitalization cost (USD), median (IQR)	$29 949 ($17 785-44 967)	$31 804 ($19 920-47 675)	.57
Opioid prescription at discharge, *n* (%)	18 (11%)	14 (70%)	.001

Abbreviation: IQR, interquartile range; OMEs, oral morphine equivalents.

high opioid use group who received rescue therapy (*n* = 9), multiple factors led to delay in biologic initiation. Although no unifying theme appeared among patients who received biologic therapy after day 4 of hospitalization (*n* = 5), opioid use definitively contributed in some cases. For example, high opioid use confounded bowel movement frequency, leading to difficulty assessing response to intravenous corticosteroid therapy. The small size of this cohort limits the ability to capture certain other factors that may contribute to delay (eg, provider bias, comorbid psychiatric illness) and prevents definitive conclusions about the reasons for the biologic delay. However, these early data suggest that opioids play a direct role in biologic delay to some degree.

Delayed rescue therapy initiation also correlates with negative long-term colitis outcomes. Sjöberg et al found that rescue therapy initiation after hospital day 5 was associated with an increased risk of colectomy.[19] Case studies have also suggested that timely biologic use may improve outcomes for patients with ASUC and concomitant *C. difficile* infection.[20] Our study indicates that patients receiving high opioid doses may require early and more frequent discussion of rescue biologic therapy to minimize treatment delays.

Of concern, 11% of patients in the low/no opioid use group were discharged with an opioid prescription. Within the high opioid use group, 70% of patients were prescribed an opioid at discharge, half of whom were opioid naive at the time of hospitalization. Opioid prescriptions at discharge from hospital medicine services have been consistently associated with increased odds of chronic opioid use.[21,22] This finding suggests that inpatient opioid prescribing may create a cycle of escalating opioid use. Future education and quality improvement efforts should focus on minimizing opioid prescriptions at discharge, particularly for ulcerative colitis patients who are at increased risk of the deleterious side effects of opioids as described in the outpatient-based literature.[7-9]

The largest limitation of this research was the use of data from a single-center academic referral center population and the consequent small sample size. The sample size limits the ability to detect small intergroup differences in clinical outcomes with less frequent occurrence such as colectomy rate and colonic dilation on imaging. There is a high risk of type II statistical error with this small sample size and thus definitive conclusions about these key clinical outcomes could not be made. The sample size also did not allow for subgroup

analyses, such as examining results for opioid-naive patients who were within the high OME group, due to insufficient power. Overall, multicenter or national database studies are needed to validate this study's findings, including the risk of biologic delay with opioid use and opioid prescribing patterns.

Additional limitations include the fact that long-term opioid use patterns after discharge were not available for analysis in this study and are an area of future interest. Data on comorbid psychiatric and substance use disorders were also not available but should be explored in the future given the possible interplay with delay in rescue therapy initiation. Lastly, the academic referral center population may not be reflective of the general hospitalized ASUC population; opioid use and rescue therapy delays may be even more pronounced in the nonacademic hospital setting. Collectively, these limitations highlight the need for large, multicenter studies to provide nuance to the relationship between opioid use and outcomes for hospitalized ASUC patients.

Providers should continue to minimize opioid prescribing for patients hospitalized with ASUC, as opioids are associated with delay in rescue therapy initiation and increased risk for continuing opioid use at discharge, including for opioid-naive patients. A key next step is to further investigate the factors leading to delay in rescue therapy initiation, which we preliminarily explored in this study. Large, multicenter studies are needed to explore this topic, as well as other important clinical outcomes and their relationship with opioid use for ASUC.

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Conflicts of Interest

U.M.: consultant for Janssen, AbbVie, Pfizer, and Takeda. R.M.: consultant for Pfizer; promotional speaker for AbbVie, Bristol Myers Squibb, Eli Lilly, and Pfizer. All other authors have no disclosures to declare.

Ethical Considerations

This study was approved by the University of California San Francisco Institutional Review Board (IRB #16-20503).

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