Does Colonoscopy Cause Increased Ulcerative Colitis Symptoms?

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Background: Ulcerative colitis (UC) patients often report symptom flares after colonoscopy. However, this has not been documented in the literature.

Objectives: 1. Determine whether colonoscopy is associated with increased UC symptoms. 2. Determine whether there is a need for escalation of UC medications after colonoscopy. 3. Identify baseline variables associated with increased symptoms after colonoscopy.

Methods: Firty-five outpatients with a history of UC, intact colon, and quiescent disease were enrolled in a prospective case-crossover study. Subjects were evaluated with the Simple Clinical Colitis Activity Index (SCCAI) before colonoscopy, 1 week and 4 weeks after colonoscopy. A mixed model analysis was used to accommodate nonindependence of repeated measurements on the same patients.

Results: Fifty-one (91%) subjects completed the study. Six subjects had clinical relapse defined by a score of 5 or greater on the SCCAI during the week after colonoscopy. Five subjects increased their 5-aminosalicylic acid (5-ASA) medications immediately postcolonoscopy, two of whom had a SCCAI 5 or greater. Multivariate modeling demonstrated a clear association between the week immediately after colonoscopy preparation and increased disease activity, with the time period being predictive of increased SCCAI (week 1 vs. week 4, $P = 0.0127$). The baseline SCCAI (P value < 0.0001) and prednisone use ($P = 0.0120$) were predictive of increased SCCAI postcolonoscopy. Thiopurines ($P < 0.001$) were protective against increased symptoms.

Conclusions: In our study, 1 in 8 subjects had UC relapse by SCCAI immediately postcolonoscopy, and 1 in 10 subjects required an increase in their 5-ASA medications. Clinicians should be cognizant of this effect of colonoscopy in patients with UC.

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Colonoscopy is a commonly used tool in the diagnosis and management of ulcerative colitis (UC). The early literature suggests an association between colonoscopy preparation and toxic megacolon in severe UC.[1–4] Previous reports have also demonstrated left-sided colonic mucosal ulcerations secondary to sodium phosphate and polyethylene glycol.[5–12] Additional studies have found an association between residual glutaraldehyde on endoscopes and colitis symptoms in patients without UC.[13–23]

However, no trials have directly assessed the impact of colonoscopy on UC symptoms. Anecdotally, we have noted an increase in symptoms in UC patients after colonoscopy. The etiology of this phenomenon is unknown. Animal models have shown that agents that induce ulceration in the colon (i.e., piroxicam) can promote colitis, and hypertonic colonoscopy preparations may produce the same effect in patients.[24] The aims of our study were to assess the following: 1) the relationship of colonoscopy to disease activity in UC; 2) the necessity of steroids or escalation of UC medications within 4 weeks after colonoscopy; and 3) the identification of demographic factors, disease characteristics, or medications associated with increased symptoms after colonoscopy.

MATERIALS AND METHODS

Selection of Patients

This study was conducted at a large academic hospital endoscopy unit between October 2004 and October 2005. With investigational review board approval, a prospective cohort of patients was approached in the waiting room before their colonoscopy appointment. Participants aged 18 and older with established UC by biopsy were eligible for participation. The indication for colonoscopy in each patient was colon cancer surveillance. Patients without an intact colon and patients with active symptoms identified by an affirmative answer to the question "Are you having this colonoscopy for an increase in your symptoms?" were excluded from our study. For our initial sample size calculation, we estimated that the average Simple Clinical Colitis Activity Index (SCCAI) increase in subjects after colonoscopy preparation would be 2 points, with a standard deviation of 2. With a

power of 80% and a two-sided alpha of 0.05, this produced a sample size of 29 subjects. We added two subjects to allow for dropouts, producing a sample size of 31. Because these were only crude estimates of the event rate and effect size, an interval data analysis was planned at a cost of 0.01 in *P* value at 31 subjects. This preliminary analysis revealed a smaller effect size than estimated, and the sample size was adjusted to 51 subjects, with a threshold of *P* less than 0.04 for statistical significance in the final analysis.

Study Design

A crossover study design was used to determine subject outcomes after colonoscopy.[25] This is a well-established study design that uses statistical techniques that are an extension of the paired *t* test. This design is appropriate when an intermittent exposure (colonoscopy) may increase the risk of an outcome (UC flare) over a short period of time, and this effect "washes out" quickly. This design compares each subject's outcome during a period of exposure with the putative risk factor to the subject's outcome during a period of nonexposure. A mixed-model analysis allows matching of each subject to themselves across time periods, much like a paired *t* test. Because each subject serves as their own control, variability is reduced, producing increased statistical power for this pilot study. This is commonly performed retrospectively; however, this approach can be applied to prospective studies with short exposures to a putative risk factor, and the mixed model analysis allows the assessment of the affect of other covariates on disease activity.[26,27]

Our subjects had baseline disease activity measurements from the week before colonoscopy, which allowed us to control for the baseline disease activity when evaluating the effect of the colonoscopy preparation. One week after colonoscopy, we measured the effects of exposure to colonoscopy preparation. By the fourth week, we assumed that the preparation effect would wash out. We then measured disease activity during the fourth week when there was again no exposure to the colonoscopy preparation.

Data on potentially relevant covariates was collected in a precolonoscopy survey. This survey of 21 questions collected demographic data including the subjects' age, sex, and racial group. Information relevant to the subjects' UC history such as duration of diagnosis, current UC medications, average number of flares per year, corticosteroid use, or hospitalizations in the past 5 years was also collected. Risk factors for UC relapse were also obtained including smoking history/recent smoking cessation, medication compliance history, nonsteroidal anti-inflammatory drug use, and antibiotic use.

To measure disease activity, subjects were asked to complete the SCCAI at the time of colonoscopy (week 0) and 1 week and 4 weeks after colonoscopy. This instrument was developed by Walmsley et al[28] and further validated by Jowett et al[29] in 2003, when a threshold of 5 or more points was defined as a relapse. The SCCAI is a survey of six questions with a point system that measures UC symptoms. The SCCAI specifically assesses the urgency and number of bowel movements, the presence and the amount of blood in the stool, the occurrence and number of nocturnal bowel movements, the presence of extracolonic manifestations, and the patient's general well-being. In 2005, Higgins et al[30] found that endoscopy contributed little additional information in the assessment of UC disease activity and that non-invasive indices such as the SCCAI could accurately assess disease activity.

The initial SCCAI assessment was performed in person before colonoscopy, and phone surveys were performed 1 week and 4 weeks after colonoscopy consisting of the SCCAI and additional questions that assessed the need for an increase in UC medications, corticosteroids, or hospitalizations. Subjects who were unable to be contacted for their preassigned phone interviews (at week 1 or 4) were excluded from further study involvement.

The primary endpoint of our study was to evaluate the effect of exposure to colonoscopy on the change in the continuous outcome of the SCCAI. As a secondary outcome, we planned to evaluate the dichotomous outcome of UC relapse, as defined by (2a) the need for either 5-aminosalicylic acids (5-ASA), prednisone, or hospitalization for increased symptoms, or (2b) a SCCAI score of 5 or greater indicating UC disease relapse. We report the incidence of these dichotomous outcomes, but flare events were too infrequent (<10 by both definitions) to allow an analysis of the effects of covariates on the likelihood of flare. Because the exposure to the colonoscopy preparation and the colonoscopy itself were nearly coincident, this design does not allow us to determine whether the preparation or the colonoscopy itself is associated with increased symptoms of colitis.

Data Analysis

The primary endpoint was disease activity as measured by the SCCAI, which was evaluated initially with paired *t* tests to compare the SCCAI values at each evaluation time point in an initial analysis. The SCCAI was then treated as the dependent variable in a mixed-model analysis. The baseline SCCAI at week 0 was included as an independent covariate in all models. The exposure to colonoscopy was treated as an independent variable and was coded as 1 for week 1 (exposure to preparation) and 0 for week 4 (no exposure). Additional potential covariates were tested one by one in a bivariate analysis (with the baseline SCCAI) to determine the estimated coefficient and significance of each covariate. A multivariate mixed model was then constructed using the baseline SCCAI and all of the potential covariates that had a *P* value of less than 0.3 in the bivariate analysis. The least significant variables were then removed from the model one by one until the model was constructed only of factors with

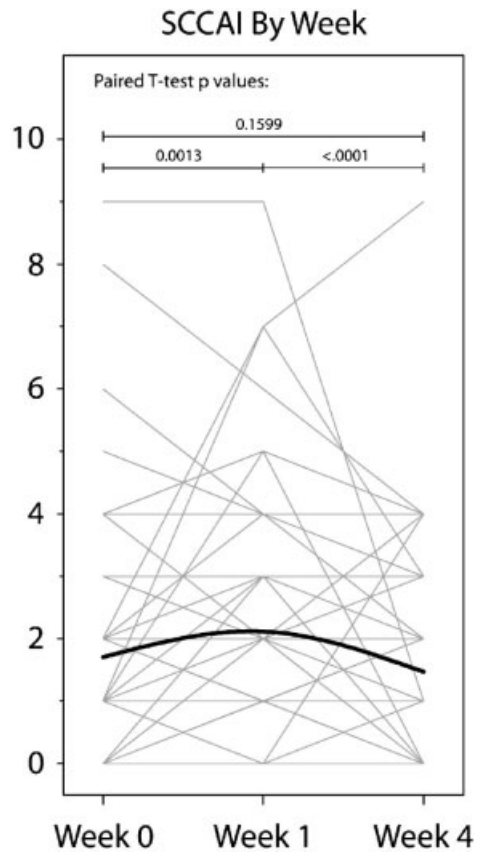

FIGURE 1. Plot of individual and loess smoothed Simple Clinical Colitis Activity Index (SCCAI) at baseline, week 1 and week 4. Subject's SCCAI score at week 0, 1, and 4 (gray lines). One gray line may represent multiple subjects. Loess smoothed average SCCAI for all patients (black line). Statistically significant differences between SCCAI measured at week 0 versus week 1, $P = 0.0013$, and week 1 and week 4, $P < 0.0001$, were found with paired t tests. No statistically significant difference between week 4 SCCAI and week 0 baseline SCCAI, $P = 0.1599$. Average SCCAI measured at baseline, week 1, and week 4.

P values of 0.05 or less. Potential factors were then added back one by one and tested for significance. The final model was a multivariate mixed model using type 3 tests of fixed effects and an autoregressive variance model.

The secondary endpoint of UC symptom flare is reported for both definitions of flare. Because fewer than 10 flare events occurred for each definition of flare, no analysis of the effect of covariates on the likelihood of flare was performed. All analyses were conducted using two-sided tests. The threshold for statistical significance for the final analysis was set at 0.04 because of the interim analysis performed after 31 subjects were enrolled. Analyses were performed with SAS version 9.1 (Cary, NC).

RESULTS

A total of 55 subjects were enrolled before colonoscopy. Fifty-one subjects completed the study (91% completion rate) (Fig. 1). The median age of the participants was 49 (range, 22–78) years, 55% of the subjects were men, and 96% were white. Participants had a history of UC for a average of 12 (range, 1–54) years. For colonoscopy preparation, 79% of subjects used fleets phosphosoda. The rest of the subjects (21%) used polyethylene glycol solution as their colonoscopy preparation. Table 1 lists additional data detailing the demographics, disease history, and medications of our subject sample.

Data was also collected regarding possible confounders such as medication noncompliance, antibiotic use, nonsteroidal anti-inflammatory drug (NSAID) use, and smoking cessation, which may contribute to an increase in UC symptoms. Fifty-three percent of subjects reported never forgetting to take their UC medication, whereas 14% forgot their medication once per month, 17% forgot once per week, and 4% forgot once per day. Interestingly, only 18% of subjects reported forgetting a dose of their medication within 1 week of their colonoscopy. All subjects denied recent smoking cessation, whereas 18% of subjects reported NSAID use within the week before colonoscopy, and 14% had reported recent antibiotic use. Only 10% of subjects believed at the

TABLE 1. Demographics and Ulcerative Colitis (UC) Disease Characteristics

Variable	Number	Percentage
Demographic characteristics		
Sex		
Female	23	45
Male	28	55
Age		
20–40	15	29
41–60	22	43
≥60	14	27
Race		
White	49	96
Other	2	4
UC medications		
5-aminosalicylic acid	36	71
Thiopurines	15	29
Prednisone	10	20
No UC medication	7	16
	Median	Range
Baseline UC disease activity		
Length of disease (yr)	12	1–54
Hospitalizations in last 5 yr	0	0–5
Flares per year	2.0	2–12
Flares requiring steroids in last 5 yr	0	0–12
Baseline SCCAI	1.0	0–9

SCCAI, Simple Clinical Colitis Activity Index.

TABLE 2. Bivariate Analysis of Simple Clinical Colitis Activity Index (SCCAI) Outcome with Baseline SCCAI as Second Covariate

Variable	Estimate	*P* Value
Colonoscopy variables		
Week before colonoscopy	−0.6471	<0.001
Golytely preparation	−0.0577	0.9192
Subject believed colon prep worsens symptoms	−0.5478	0.4987
Demographic variables		
Age (decade)	0.0349	0.8430
Female	−0.7388	0.1239
White	1.1979	0.2395
Disease characteristics		
Years of UC (decade)	−0.3932	0.0688
Hospitalizations in last 5 yr	0.1744	0.4382
Flares/yr	0.2073	0.0072
No. of steroids/5 yrs	0.1895	0.0311
Baseline SCCAI	0.5369	<0.0001
Medication regimen		
5-aminosalicylic acid use	0.3222	0.5422
Prednisone use	1.6244	0.0054
Proctofoam	−0.8100	0.6413
Other possible confounders		
NSAIDS	0.0476	0.9400
Antibiotics	0.1403	0.4581
Never smoked	0.0582	0.9044
Thiopurine use	−0.8611	0.8708
Forget UC medications rarely	−0.4237	0.5450
Forget UC medications frequently (5 levels)	0.1534	0.4528

Positive estimates are associated with increased SCCAI scores, whereas negative estimates are associated with decreased SCCAI scores.
UC, ulcerative colitis; NSAIDS, nonsteroidal anti-inflammatory drugs.

TABLE 3. Multivariate Analysis of Simple Clinical Colitis Activity Index (SCCAI) Outcome

Variable	Estimate	*P* Value
Intercept	1.0747	0.0029
Week 1 (post colon prep) vs. week 4	0.6471	0.0127
Baseline SCCAI	0.4636	<0.0001
Thiopurine use	−1.3542	0.0045
Prednisone use	1.4359	0.0120
Female sex	−0.5677	0.1188

Positive estimates are associated with increased SCCAI scores, whereas negative estimates are associated with decreased SCCAI scores.

start of the study that colonoscopy preparation caused a flare in their UC symptoms, and 6% of subjects were unsure if colonoscopy preparation had any effect on their UC symptoms.

The baseline median SCCAI score for the week before colonoscopy was 1.0 (range, 0–9.0). During the week postcolonoscopy, the median SCCAI was 2.0 (range, 0–9), and during the fourth week postcolonoscopy, the median SCCAI was 1.0 (range, 0–9) (Fig. 1). Using multivariate mixed modeling, we identified statistically significant predictors of increased SCCAI postcolonoscopy (Tables 2 and 3). Predictors associated with worsening SCCAI postcolonoscopy included the exposure to colonoscopy, week 1 versus week 4 ($P = 0.0127$), higher baseline SCCAI ($P < 0.0001$), and the use of prednisone at the time of colonoscopy ($P = 0.0120$). Protective factors against an increased SCCAI postcolonoscopy included maintenance thiopurines ($P = 0.0045$), and there was a trend toward a protective effect of female sex ($P = 0.1188$). Using the coefficients obtained from the multivariate mixed model, one can predict the average SCCAI score during the week after colonoscopy, as illustrated in Table 4.

The sample size of our study was calculated for the continuous primary endpoint of SCCAI score; consequently, our study was underpowered for the secondary dichotomous endpoints of UC flare (need for UC medications or SCCAI > 5). However, these dichotomous endpoints generally have greater clinical relevance than changes in continuous scales; therefore, we evaluated the significant covariates from the multivariate model for SCCAI to determine whether they had effects on clinically relevant outcomes.

For the secondary endpoint of UC flare as defined by the need for additional UC medications, a total of eight (16%) subjects had a flare of their UC symptoms. Five subjects required an increase in their 5-ASA medications the week immediately postcolonoscopy, and two of these subjects also fulfilled our primary endpoint with a SCCAI score of 5 or greater. The other three subjects increased their 5-ASA medications for worsening symptoms for a 1 to 3 point increase in their SCCAI. Between week 1 and week 4, three additional subjects increased their UC medications because of perceived worsening of symptoms. Interestingly, two of these subjects had an unchanged SCCAI score, whereas the last subject's SCCAI improved by 1 point. No subjects required the use of prednisone or were hospitalized for an increase in symptoms postcolonoscopy.

We also evaluated the secondary dichotomous endpoint of UC relapse as defined by Jowett et al[29] as an SCCAI of 5 or greater. With use of this definition, six subjects had a clinical relapse in the week after colonoscopy. Four weeks postcolonoscopy, only one of the six subjects continued to have disease relapse, with a SCCAI of 7. This suggests that this effect does largely wash out between week 1 and week 4.

TABLE 4. Estimates of Effects of Each Variable in Multivariate Model Used to Predict Average SCCAI at 1 Week after Colonoscopy in Patients with Different Baseline Characteristics

Patient	Intercept	Colonoscopy	Baseline SCCAI Effect	Prednisone use Effect	Thiopurine use Effect	Sex Effect	Total Predicted SCCAI at Week 1 after Colonoscopy
Male on prednisone, baseline SCCAI = 4	1.0747	0.6471	4*.4636 = 1.85	1.4359	0	0	5.01
Female on thiopurine, baseline SCCAI = 4	1.0747	0.6471	4*.4636 = 1.85	0	−1.3542	−0.5677	1.65

As shown, a male patient on chronic steroids with a baseline SCCAI of 4 would be expected to have a mild relapse, defined by Jowett et al as SCCAI ≥ 5. In contrast, a female patient with the same baseline SCCAI, but on thiopurines, would on average have minimal symptoms 1 week after colonoscopy.

DISCUSSION

Colonoscopy is a widely used procedure for diagnosis, disease assessment, and cancer surveillance in UC. Our results suggest that recent colonoscopy can cause a mild relapse in UC symptoms; this is not affected by concomitant NSAID, antibiotic use, smoking cessation, or the type of colonoscopy preparation. This finding is most prominent in the week immediately after colonoscopy and largely resolves by the fourth week after colonoscopy. The etiology of this association is unknown. Previous studies have described colonic mucosal abnormalities associated with sodium phosphate preparation and polyethylene glycol.[5–12] These mucosal abnormalities are primarily visualized in the left colon in 2.6% to 24.5% of colonoscopies. In all of these studies, the subjects were clinically asymptomatic. Driman and Preiksaitis[8] demonstrated an increase in crypt cell apoptosis and crypt epithelial proliferation in the mucosa affected by colonoscopy preparation. These changes are thought to be metabolically induced rather than secondary to direct topical injury. Animal model studies have shown that agents that induce ulceration in the colon can also promote colitis[24] and that standard preparations may cause oxidative stress that leads to colonic mucosal damage.[31]

Beyond the described mucosal changes, colonoscopy preparation has been identified as a trigger in precipitating toxic megacolon. General clinical consensus since the early 1980s has been to avoid colonoscopy preparation in the severely ill UC patient and if necessary to proceed only with an unprepped flexible sigmoidoscopy for evaluation.[1–4] The etiology for this association between preparation and toxic megacolon is unknown, although electrolyte disturbances and the release of inflammatory mediators have been suggested as predisposing factors leading to inhibitory effects on colonic muscular tone.[32–35] An alternative explanation of this phenomenon is that the induction of increased disease activity is caused by the colonoscopy itself. This could be caused by direct trauma to the mucosa by biopsies or looping, increasing mucosal permeability to colonic bacteria. Alternatively, UC patients with increased mucosal permeability may be especially sensitive to small amounts of residual glutaraldehyde on colonoscopes.

In our study, 10% of our subjects required an increase in 5-ASA medications within a week of colonoscopy; however, none required corticosteroids or hospitalization. Surprisingly, the SCCAI did not always predict the perceived need for increased UC medication. Four subjects with SCCAI 5 or greater did not require an increase in medications, whereas three subjects with a score less than 5 increased their medications. The reason for this discordance is unknown; however, presumably there are some unmeasured variables that contribute to the subject's perception of a flare. Anecdotally, we have also observed that some subjects require hospitalization for postcolonoscopy UC flares. However, our study size was underpowered to assess this uncommon event.

The subject's baseline SCCAI and the use of chronic prednisone were both directly related to their likelihood of experiencing a flare. A higher baseline SCCAI and chronic prednisone dependence likely both identify subjects with more tenuous control of their UC symptoms. This is supported by Faubion's[36] study of the natural history of corticosteroid initiation for IBD in Olmsted County. Only 49% of UC patients maintained remission without surgery or prolonged corticosteroid therapy over the following year, indicating that the need for corticosteroid therapy was a marker of relatively poor prognosis.

In our cohort, the use of thiopurines was protective against UC symptom recurrence. Thiopurines are immunomodulators used as second-line treatment when 5-ASA medications prove ineffective. Thiopurines used for maintenance therapy in UC have been shown by some studies to be effective steroid-sparing agents.[37–41] Hawthorne et al[39] conducted a 1 year randomized controlled trial of azathioprine withdrawal in UC patients and found a relapse rate of 59% for patients on placebo compared with 36% for patients who continued on azathioprine. Our study is significant in that it shows both a strong association between colonoscopy exposure and increased UC symptoms and also shows that thio-

purine use is associated with decreased UC symptoms after colonoscopy preparation.

Interestingly, in our study population, there was also a trend toward significance relative to the participant's sex, with women being less likely to experience a flare from colonoscopy preparation. The lack of statistical significance may be secondary to inadequate power. However, no data in the IBD literature has ever shown sex as a predictor of the patient's subsequent course of this chronic disease.

There are several potential limitations to this study. First, our study involved ambulatory patients referred to a single tertiary care center, and thus, our patient population may not be representative of the community setting. Although subjects were not randomized, they served as their own controls, and the crossover design reduces the variability from unmeasured confounders that are constant across time such as age or sex. However, this design does not control for variables that change over time, including the subjects' self-adjustment of their medication dosing. We did not expect to see frequent self-adjustment of 5-ASA medication dosing by subjects without consulting their gastroenterologists, but this clearly occurs and may confound the results of this and other clinical studies. Third, 4 of our 55 subjects were unable to be contacted for follow-up surveys, and their data could affect the significance of our results. Fourth, our analysis assumes that the risk of increased disease activity during the period of colonoscopy is caused by the preparation. This is not necessarily true. Any factor that is associated with the colonoscopy, including the procedure itself, or any residue of the cleaning solution, glutaraldehyde, left on the colonoscopes could potentially cause the effects we found.[21,42,43] It is possible that UC patients are particularly sensitive to small amounts of glutaraldehyde because of their increased mucosal permeability. Also, we may have introduced bias in our study by asking the subjects to assess their bowel symptoms after colonoscopy, possibly causing these patients to exaggerate their symptoms.

In designing this pilot study, we were unsure of the impact that colonoscopy would have on the disease course of UC. Therefore, we thought it judicious to use a continuous variable (change in SCCAI) as our primary endpoint. However, by using the change in SCCAI as our primary endpoint, it made our study size significantly smaller and limited our power to look at dichotomous endpoints such as the need for increased UC medication postcolonoscopy. We can now use these data in future studies to power for more clinically useful endpoints. Finally, our study relied on self-reporting for the week before surveys, and the imprecision of recalled symptoms could affect or possibly bias our results.

Previously, the association between UC relapse and colonoscopy in quiescent patients has been anecdotal. In this pilot study, we show a significant association between colonoscopy and an increase in UC symptoms, most prominent in the week immediately after colonoscopy. Sixteen percent of our subjects had UC flare as defined by SCCAI 5 or greater, whereas 10% required an increase in their 5-ASA medications immediately postcolonoscopy. The relapse is mild, at most requiring an increase in 5-ASA medications in this sample, and typically resolving within a few weeks. Both the baseline SCCAI and the use of prednisone were predictive of disease flare, whereas chronic thiopurine use was protective. Clinicians should be aware of this effect of preparation for colonoscopy or the colonoscopy itself in patients with UC.

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