

Adjunctive Pharmacotherapy Use in Patients With Ileal Pouch–Anal Anastomosis (IPAA)

Custon T. Nyabanga, MD,^{*,*} Jordan E. Axelrad, MD, MPH,[†] Xian Zhang, PhD,[‡] Edward L. Barnes, MD, MPH,[‡] and Shannon Chang, MD[†]

Background: This study evaluated the prevalence of adjunctive pharmacotherapies use among ileal pouch-anal anastomosis (IPAA) patients.

Methods: The IBD Partners database was queried to compare IPAA patients with and without pouch-related symptoms (PRS). Within the cohort of patients with PRS, patient reported outcomes were compared among opioid, nonsteroidal anti-inflammatory drug (NSAID), and probiotic users.

Results: There were no differences in patient reported outcomes based on NSAID or probiotic usage. Opioid users reported increased bowel frequency, urgency, poor general well-being, abdominal pain, and depression ($P < 0.05$ for all variables).

Conclusions: In IPAA patients with PRS, opioid use, but not NSAIDs or probiotics, was associated with a higher burden of PRS.

Lay Summary

This study explored the frequency of use of medications such as probiotics, nonsteroidal anti-inflammatory drugs, and opioids in patients with an ileal pouch-anal anastomosis (“pouch”). Pouch patients who use opioids tended to have more pouch symptoms.

Key Words: ulcerative colitis, ileal pouch-anal anastomosis, pouch-related symptoms, patient reported outcomes, quality of life

INTRODUCTION

Patients with medically refractory ulcerative colitis (UC) require surgical intervention with restorative proctocolectomy and ileal pouch-anal anastomosis (IPAA).¹ Often preferred over total proctocolectomy with end ileostomy, IPAA restores bowel continuity and eliminates the need for a permanent ileostomy.² For the majority of patients, the IPAA

is well-tolerated with patients reporting improved quality of life (QOL).^{1,3,4} However, nearly 50% of these patients report long-term complications. The most common complication being pouchitis, an idiopathic and nonspecific inflammation of the pouch associated with diarrhea, increased bowel frequency, abdominal pain, fecal incontinence, hematochezia, and fecal urgency.^{1,5} In a large sample of inflammatory bowel disease (IBD) patients with IPAA, more than 80% reported a history of pouch-related symptoms (PRS) within 6 months of survey and scored unfavorably on patient reported outcomes (PROs) in multiple domains of physical and psychosocial functioning.⁶

Patients frequently incorporate adjunctive therapies including over-the-counter therapies, such as probiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Data on the prevalence of use and association of these medications with QOL in IBD patients with IPAA are sparse.^{7–10} Reporting of use of these adjunctive medications during healthcare encounters may not be reliable.

The IBD Partners is an internet-based cohort of IBD patients.¹¹ The goal of this study was to utilize the IBD Partners database to evaluate the prevalence of use of these adjunctive therapies in patients with IPAA with or without PRS utilizing PROs based on validated disease activity and QOL questionnaires. By evaluating the use of these adjunctive pharmacotherapies in patients with IPAA, both patients and clinicians may gain some insight into the prevalence and potential clinical implications of these medications.^{1,3,6,12}

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*Department of Internal Medicine, NYU Grossman School of Medicine, New York, New York, USA; †Division of Gastroenterology and Hepatology, NYU Langone Health, New York, New York, USA; ‡Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Address correspondence to: Shannon Chang, MD, Division of Gastroenterology, NYU Langone Medical Center, 240 East 38th Street, 23rd Floor, New York, NY 10016 (shannon.chang@nyulangone.org).

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MATERIALS AND METHODS

Study Population

Patients with history of IPAA were identified from the IBD Partners research registry. IBD Partners is an online, patient-powered research network that studies patients with UC and Crohn disease. IBD Partners includes patients with heterogeneous treatment backgrounds and has been described in detail before, validated, and utilized in prior studies.^{6,11,13,14} Participants in IBD Partners are recruited via various methods including e-mail rosters, social media, chapter events, and other Crohn's & Colitis Foundation promotional activities. Once recruited, participants complete a baseline survey, and follow-up surveys at 6-month intervals to collect longitudinal data, on disease characteristics and activity, medication use, and PROs. The participants were stratified based on subjective reporting of PRS in the 6 months prior to completion of the survey. PRS were defined as presence of abdominal pain, cramping, urgency, or frequent bowel movements.

We included patients age 18 years and older with a diagnosis of either UC or indeterminate colitis who had undergone IPAA, and had completed at least 1 survey that included answers regarding adjunctive medication usage. Patients under the age of 18 and those not meeting the above criteria, including those with Crohn's disease or with ostomies, were excluded from the study.

Study Variables

Using existing data from the IBD Partners surveys, we performed a secondary analysis to evaluate adjunctive pharmacotherapy use and symptomatology among IBD patients with IPAA with and without PRS. In this cross-sectional study, baseline demographics and relevant clinical variables were compared between patients with and without PRS within the 6 months prior to the survey. Baseline clinical information included: age, sex, body mass index, race, smoking status, diagnosis at time of colectomy, diagnosis of primary sclerosing cholangitis, family history of IBD, and current IBD treatment medications. Patient-reported use of adjunctive medications including NSAIDs, opioids, and probiotics at the time of the survey was also collected ([Supplementary Data Table 1](#)).

As noted above, patients were dichotomized based on whether they had PRS (abdominal pain, cramping, urgency, or frequent bowel movements) in the preceding 6 months. For patients with multiple completed surveys, the first survey where the patient endorsed PRS in the preceding 6 months was used for the analysis. If multiple surveys from the same patient were negative for PRS, the last survey entered was used for the purposes of this analysis.

Patients answered questionnaires including the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and the Simple Clinical Colitis Activity Index (SCCAI). The SIBDQ is a concise, reliable, and validated disease-specific health-related QOL questionnaire that has demonstrated the ability to indicate meaningful changes in IBD.¹⁵ SIBDQ includes questions about abdominal pain, feelings of depression, anger, or ability to relax. The SIBDQ was used under a license from McMaster University. The SCCAI, developed as a noninvasive measure of UC disease activity, is a validated clinical assessment tool in UC.¹⁶ Both the SIBDQ and SCCAI have been utilized in prior studies evaluating patients from the IBD Partners cohort.^{6,14,17,18} Specific questions from the SIBDQ (abdominal pain, feelings of depression) and SCCAI (day/night bowel frequency, urgency of defecation, and general well-being) were used to evaluate relevant symptoms in patients with IPAA ([Supplementary Data Table 2](#)).

Pouch-Related Symptoms

Patient responses were dichotomized based on their subjective reporting ([Supplementary Data Table 2](#)). High bowel frequency was considered to be a self-reported 24-hour average frequency of 7 or more bowel movements during the day or 4 or more bowel movements at night. Patients reporting immediate urgency of defecation or incontinence were considered to have significantly burdensome urgency of defecation. If patients described their well-being as poor, very poor, or terrible on average, they were considered to be having poor general well-being. Significant abdominal pain was determined to be in patients reporting their experience of abdominal pain as happening "A good bit of the time," "Most of the time," or "All the time." Those reporting their experience of feelings of depression as happening often, always, a good bit of time, or all of the time, were considered to have significant depression symptoms.

As per IBD Partners survey design, there was no requirement to answer all survey questions each time a participant completed a survey. Therefore, only those with answers for each variable of interest were available for analysis.

Statistical Analysis

Collected variables were reported as frequencies and percentages. Groups were compared using the Student *t* test and the Cochran–Mantel–Haenszel χ^2 tests where appropriate. Within the cohort of patients reporting PRS, PROs were compared to determine any association of adjunctive medication use with disease activity and QOL determinants in these symptomatic patients.

Ethical Considerations

This study was approved by the Institutional Review Board at our institution.

RESULTS

Patient Characteristics

A total of 363 patients with history of UC with IPAA were identified from the IBD Partners research database. Of these patients, 266 (73%) reported having PRS on at least 1 survey. When comparing patients with and without PRS, no significant differences were noted on baseline demographics including age, sex, body mass index, race, smoking status, diagnosis at the time of colectomy, presence of primary sclerosing cholangitis, and family history of IBD. In addition, use of oral steroids, mesalamine, immunomodulators, probiotics, and NSAIDs was not significantly different between the 2 groups (Table 1). Of those reporting PRS, daytime bowel frequency (43%), abdominal pain (21%), depression feelings (21%), and poor general well-being (19%) were the most common PRS reported (Table 2).

Though other forms of steroid drugs were not associated with differences in PRS, the use of rectal/topical steroids was significantly higher in those with PRS ($P < 0.01$). Tumor necrosis factor inhibitor use was not commonly reported among this cohort of IPAA patients, with only 21 patients (6%) reporting use of tumor necrosis factor inhibitors after IPAA. Within this sample, more patients with PRS reported using adalimumab ($P = 0.04$). There was a higher prevalence of opioid use among those reporting PRS, 12% compared to 4% in the non-PRS group ($P = 0.03$). Antibiotic use of ciprofloxacin, metronidazole, and other unspecified antibiotics was higher in the PRS group compared to non-PRS group ($P < 0.01$).

Adjunctive Therapies in Patients Reporting PRS

NSAIDs

Of the 266 patients who reported PRS, 222 patients responded to the question on NSAID use, and 90 patients (41%) reported NSAID use within the 6 months before the survey. Among those reporting PRS, there was no difference between users and nonusers of NSAIDs in the reporting symptoms of bowel frequency (day or night time), urgency, abdominal pain, and general well-being (Table 3).

Probiotics

Of the 266 patients who reported PRS, 259 patients responded to the survey question on probiotic use, and 102 patients (39%) reported probiotic use within the 6 months before the survey. There was no significant difference in reported bowel frequency (day or night), urgency, general well-being, or abdominal pain in patients with PRS based on reported use of probiotics (Table 4).

Opioid

Of the 266 patients who reported PRS, 259 patients responded to the question regarding opioid use, and 31 patients (12%) reported use of any opioid in the 6 months prior to the survey. Among those with PRS, opioid use was associated with worse QOL measures, including day and night bowel frequency ($P = 0.02$ and < 0.01 , respectively), urgency ($P = 0.03$), general well-being ($P < 0.01$), abdominal pain ($P < 0.01$), and feelings of depression ($P < 0.01$) (Table 5). Of the opioid users reporting PRS, 13 (42%) and 11 (35%) were concurrently using antibiotics and probiotics, respectively (Table 6).

DISCUSSION

Pouchitis is prevalent among patients who have undergone IPAA surgery, with most studies reporting an incidence between 23%–59% and more than 40% reporting PRS within the first year of pouch creation.^{1,5,19} In this analysis of participants in the IBD Partners cohort, 73% reported having PRS. Within the PRS group, the predominant symptoms were high daytime bowel frequency, abdominal pain, depression feelings, and poor general well-being. This high percentage of patients reporting PRS is notable and speaks to the need for improved understanding of and treatment of PRS. After creation of the IPAA in patients with UC, the need for maintenance medications to treat UC is obviated. However, PRS are often debilitating, affecting daily activities, and are a significant source of distress and a reason to seek medical care.^{20,21} Patients' perception of symptom severity has a significant effect on their QOL and contributes to perceived disease burden. Assessment of the effect of these symptoms through validated measures has gained traction in the last decade and can be used to understand disease burden, guide clinical management and research, and to improve QOL.^{14,15,22}

Adjunctive therapies are infrequently studied, but their use is commonly considered by patients. The prevalence of use of these medications is not well-defined, particularly in patients with IPAA. Clinicians may not ask about adjunctive therapies when reviewing medication reconciliations, thus underestimating the prevalence of use in healthcare settings. This study, utilizing the IBD Partners patient cohort provides insight into the prevalence of use of NSAIDs, probiotics, and opioids in IPAA patients.

There is an association between NSAID use and development of PRS, including pouchitis.^{10,23} Discontinuation of NSAIDs in symptomatic IPAA patients has been shown to improve disease activity scores in 1 small study.²⁴ With these results, clinicians generally advise against NSAID use in patients with IPAA. In this study, 39% of patients reported taking NSAIDs. It is unknown whether reported NSAID use was taken for PRS control or for unrelated ailments. There are conflicting data regarding the role of NSAIDs in pouchitis management. In 1

TABLE 1. Comparison of Baseline Characteristics of IPAA Patients, With vs Without PRS Within 6 Months of Survey

	All IPAA (n = 363)		Without PRS (n = 97)		With PRS (n = 266)		P
	n	%	n	%	n	%	
Age, years							0.24
18–39	171	47	42	41	130	49	
40–59	142	39	38	38	104	39	
≥60	50	14	19	19	32	12	
Sex, female	247	68	62	64	185	70	0.31
BMI, kg/m ² (median and IQR)	24	21–27	24	21–27	24	21–27	0.56
Race							0.61
Caucasian	328	90	87	90	241	91	
African American/Black	7	2	1	1	6	2	
Other/not indicated	28	8	9	9	19	7	
Smoking status							0.22
Never	250	69	62	64	188	71	
Former	110	30	35	36	75	28	
Current smoker	3	1	0	0	3	1	
Diagnosis at time of colectomy							0.06
UC	328	90	86	89	242	91	
Indeterminate colitis	22	6	4	4	18	7	
Unknown	13	4	7	7	6	2	
Primary sclerosing cholangitis	10	3	0	0	10	4	0.05
Family history of IBD	32	9	5	5	27	10	0.21
Current medications							
Corticosteroids							
Oral corticosteroids	10	3	1	1	9	3	0.30
Steroids, rectal	19	5	0	0	19	7	<0.01
Budesonide	14	4	1	1	13	5	0.12
Mesalamine							
Oral	4	1	1	1	3	1	1.00
Rectal	18	5	1	1	17	7	0.05
Immunomodulator therapy							
Azathioprine/6-MP	4	1	0	0	4	2	0.58
Oral methotrexate	3	1	0	0	3	1	0.57
Injectable methotrexate	4	2	0	0	4	2	0.58
Anti-TNF biologics							
Infliximab	7	2	2	2	5	2	1.00
Adalimumab	12	3	0	0	12	3	0.04
Golimumab	1	<1	0	0	1	<1	1.00
Certolizumab	1	<1	0	0	1	<1	1.00
Opioids	35	10	4	4	31	12	0.03
Probiotics	129	36	27	28	102	39	0.06
NSAIDs	119	39	29	35	90	41	0.43
Antibiotics							
Ciprofloxacin	46	13	1	1	45	17	<0.01
Metronidazole	27	8	1	1	26	10	<0.01
Other antibiotics	31	9	0	0	31	12	<0.01

*Patients were not required to answer all questions.

6-MP, 6-mercaptopurine; BMI, body mass index; IQR, interquartile range; TNF, tumor necrosis factor.

TABLE 2. Frequency of Specific Symptoms Among Patients With PRS

	Patients With PRS	
	n	%
High bowel frequency, daytime	96	43
High bowel frequency, nighttime	24	11
Urgency of defecation	24	11
Poor general well-being	49	19
Abdominal pain	38	21
Depression feelings	38	21

*The maximum possible number of responses was 266 for patients with PRS. Patients were not required to answer all questions.

TABLE 3. Patient-Reported Outcomes in Patients With PRS Based on NSAID Use

	No NSAID Use		NSAID Use		<i>P</i>
	n	%	n	%	
High bowel frequency, daytime	47	45	32	39	0.43
High bowel frequency, nighttime	9	9	6	7	0.75
Urgency of defecation	10	10	6	7	0.59
Poor general well-being	28	21	11	12	0.08
Abdominal pain	18	23	11	15	0.24

*The maximum possible number of responses were 132 and 90 for “No NSAID” use and “NSAID use” cohorts, respectively. Patients were not required to answer all questions.

TABLE 4. Patient-Reported Outcomes in Patients With PRS Based on Probiotic Use

	No Probiotic Use		Probiotic Use		<i>P</i>
	n	%	n	%	
High bowel frequency, daytime	60	45	34	38	0.26
High bowel frequency, nighttime	12	9	12	13	0.32
Urgency of defecation	12	9	11	12	0.45
Poor general well-being	28	18	21	21	0.63
Abdominal pain	23	21	15	21	0.91

*The maximum possible number of responses were 157 and 102 for “No Probiotic use” and “Probiotic use” cohorts, respectively. Patients were not required to answer all questions.

TABLE 5. Patient-Reported Outcomes in Patients With PRS Based on Opioid Use

	No Opioid Use		Opioid Use		<i>P</i>
	n	%	n	%	
High bowel frequency, daytime	77	40	17	63	0.02
High bowel frequency, nighttime	17	9	7	26	0.01
Urgency of defecation	17	9	6	22	0.03
Poor general well-being	30	13	19	63	<0.01
Abdominal pain	24	15	14	61	<0.01
Depression feelings	38	17	14	45	<0.01

*The maximum possible number of responses was 314 and 31 for “No Opioid use” and “Opioid use” cohorts, respectively. Patients were not required to answer all questions.

TABLE 6. Use of Medications for Pouchitis and Other Inflammatory Conditions of the Pouch Among Patients With PRS Using Opioid Medications

	n	%
Antibiotics	13	42
Probiotics	11	35
Mesalamine		
Oral mesalamine	1	3
Topical (rectal) mesalamine	4	13
Immunomodulator (thiopurine or methotrexate)	1	3
Biologic therapy	2	6
Corticosteroids		
Oral corticosteroids	3	10
Steroids, rectal	4	13
Budesonide	1	3

study, less frequent use and perhaps lower doses of NSAIDs in IBD was not associated with active disease.²⁵ In this study, focusing only on those IPAA patients with PRS, specific PROs were not significantly different between those taking NSAIDs and those who were not.

Probiotics have been shown to alter the microflora of the gut, and benefit IBD patients through suppression of pathogenic bacteria, improvement of barrier function, and modulation of immune system and pain perception.^{23,26} The pathophysiology of pouchitis is linked to dysbiosis, which is the basis for using antibiotics as the first line of therapy.^{27–29} In pouchitis, the use of probiotics in maintaining remission has been studied, however conflicting results and inadequately powered studies make it difficult to draw clinically relevant conclusions.^{7,8,30,31} There is low-level evidence supporting the use of probiotics for prophylaxis against pouchitis and maintenance therapy in refractory pouchitis.^{32–34} Probiotics are readily available, and seem to be quickly adopted by patients. In our study, 36% of patients

reported probiotic use overall. Among those reporting PRS, being on probiotics did not affect any PROs/QOL measures assessed. This is not a surprising finding given conflicting data on the efficacy of probiotics in treatment and maintenance of remission in pouchitis.^{8,30,35} The role of probiotics in the treatment of pouchitis still needs to be elucidated with more robust randomized clinical trials.

In the overall cohort, there was a significant association between opioid use and PRS. Those with PRS who used opioids also reported worse QOL and symptom measures. A high proportion of patients with PRS using opioids also reported concurrent use of antibiotics and probiotics. Opioids should be used as a last resort given limited short-term analgesia benefits and high risk for dependence and complications.³⁶ The literature reports use of opioids in the range of 10%–15% of IBD patients, similar to rates reported in this study.^{37,38} Of note, opioids used for control of bowel frequency such as diphenoxylate-atropine and tincture of opium may not have been considered by patients to be opioids when answering survey questions.

Higher rectal steroid use was also reported among those with PRS. Given the small numbers of those reporting use, no clinically significant conclusions could be drawn. It is generally expected that most patients on rectal steroids have failed treatment with antibiotics and 5-aminosalicylic acids, and therefore have more persistent PRS.³⁹ Similarly, a higher rate of biologic use in patients with PRS can be expected, since biologics are generally utilized as rescue therapy for recalcitrant chronic pouchitis.^{40–42} In this study, the significant difference in PRS among those taking adalimumab is likely a result of a very small sample size.

There are multiple strengths of this study. Contrary to most published studies on IPAA that focus on antibiotics and IBD therapies, this study informs clinicians regarding the prevalence of use of adjunctive medications including NSAIDs, probiotics, and opioids. The findings from this retrospective analysis are based on a relatively large cohort of IPAA patients from diverse backgrounds and international geography, making findings more generalizable. The data for this study were obtained voluntarily and anonymously by patients and therefore may facilitate disclosure of habits that patients might otherwise not disclose to their provider. Given most clinicians take care of a very small number of IPAA patients, this study provides insights into the use of these adjunctive therapies that could inform both patients and providers on management of patients with IPAA.

There are also several limitations to this study. Given that data were accumulated over a series of follow-up questionnaires, missing data does exist, potentially creating a reporting bias. Given that this is a cross-sectional comparison of patients with and without PRS after IPAA, it is impossible to make conclusions regarding effect or causation. Dosing and specific medication names in each group of adjunctive therapies are not specified. The SIBDQ and SCCAI are not validated for

assessing patients with IPAA but were collected for IPAA patients in IBD Partners. Individual questions from these tools were utilized for clinical assessment of applicable PRS. Finally, as all information from surveys is patient-reported, clinician assessments are not available.

CONCLUSIONS

This study highlights the prevalence of probiotic, NSAID, and opioid use in this unique, large cohort of IPAA patients worldwide. NSAID use remains prevalent among patients with IPAA, though guidelines discourage use in the IBD population. Probiotics, also widely used and recommended, do not seem to be associated with changes in PROs in IPAA patients. Opioids were associated with worse symptoms and QOL measures. Clinicians should use this information in advising patients regarding the use of these adjunctive medications.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

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DATA AVAILABILITY

A copy raw deidentified dataset for this study will be made available on request by contacting the designated corresponding author. Please refer to the title page for the contact information.

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