Original Article

Opioid Use is Associated with Decreased Quality of Life in Patients with Crohn's Disease

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ABSTRACT

Background/Aims: Quality of life is an important consideration in the management of patients with Crohn's disease. Previous studies suggest that Crohn's disease patients using opioids may have decreased quality of life and increased risk of mortality. Our aim was to determine the association between health-related quality of life (HRQoL) and opioid use in patients with Crohn's disease while controlling for disease severity. **Patients and Methods:** We conducted a cross-sectional study recruiting Crohn's disease patients at our center. Disease activity was measured using the Harvey-Bradshaw Index (HBI), and HRQoL was measured using the Inflammatory Bowel Disease Questionnaire (IBDQ). **Results:** We enrolled 38 Crohn's disease patients using opioids and 62 patients not using opioids. Patients using opioids had an increased duration of disease (median 18.5 vs. 9 years, $P = 0.005$), increased surgeries related to Crohn's disease (median 3 vs. 0, $P < 0.001$), and increased prednisone use (29% vs. 11.3%, $P = 0.03$). Patients using opioids had increased disease activity (median HBI score 9.0 vs. 3.0, $P < 0.001$). Quality of life was lower in patients using opioids (mean IBDQ score 109.3 vs. 162.9, $P < 0.001$). This finding was significant when controlling for HBI scores, number of previous surgeries, and prednisone use ($P = 0.003$). **Conclusions:** Opioid use in Crohn's disease patients appears to be associated with disease activity and severity. HRQoL is markedly decreased in patients using opioids and this association is significant even when controlling for variables reflecting disease severity. Our findings suggest that Crohn's disease patients using opioids are likely to be significantly impacted by their disease.

Key Words: Chronic pain, Crohn's disease, disease activity, opioids, quality of life

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Crohn's disease (CD) is a chronic immune-mediated inflammatory condition of the intestinal tract that is frequently associated with abdominal pain. The disease may also induce inflammation in extraintestinal areas, and is associated with arthritis in the axial skeleton and peripheral joints. Although advances have been made in recent years in pharmacologic treatment to ameliorate this inflammation, for some patients, pain relief remains inadequate, and analgesics, particularly opioids, are required to control symptoms. Recent studies have shown that opioid use is a strong predictor of premature death in patients with CD.[1] It is not clear if this association represents a causal relationship or if opioid use is simply a marker for disease severity or another potential cause of mortality in this group.

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It has also been demonstrated in several studies that clinical disease severity in CD patients correlates strongly with decreased general and disease-specific health-related quality of life (HRQoL).[2-5] It has been previously reported that in general, patients with CD have significantly lower HRQoL than healthy age- and sex-matched controls.[6] Improvement in HRQoL is an important goal in the management of CD, and it is an outcome measure in most major clinical trials involving the treatment of CD. At our center, our clinical experience suggests that many patients with CD using opioids for pain control subjectively appear to have markedly reduced quality of life.

The objectives of this cross-sectional study were to quantify opioid analgesic use in a group of patients with CD seen in a specialized clinic dedicated to the treatment of patients with inflammatory bowel disease (IBD), determine their disease

severity, assess their HRQoL, and determine the relationship between opioid use and HRQoL.

PATIENTS AND METHODS

Overview and patient selection

We performed a cross-sectional study and recruited patients between June 2010 and August 2012 at a specialized Inflammatory Bowel Disease Clinic at London Health Sciences Centre, London, Ontario, Canada. Three authors (DS, PT, AT) recruited and enrolled patients in the study. Patients were informed of the study at follow-up appointments and recruitment took place intermittently over the 26 months of the study period. Sequential patients to the clinic were not approached to participate if the recruiter was engaged in enrolling another patient. If patients presented to clinic at the same time, those using opioid narcotics were preferentially enrolled in the study, as they were more difficult to recruit. Patients were approached to enrol in the study if they had a definite diagnosis of CD for at least 6 months as determined by the treating gastroenterologist. Exclusion criteria included age less than 18 years and the presence of an ostomy.

Measurement tools and data collection

The Harvey-Bradshaw Index (HBI) was used to assess disease activity and was administered by the authors of the study. The HBI is a 5-item questionnaire that is based on five clinical parameters and has been validated using the Crohn's disease activity index as a measure of disease severity in CD.[7] The Inflammatory Bowel Disease Questionnaire (IBDQ) was used to determine HRQoL and was completed independently by the study participants during the clinic visit. The IBDQ is a 32-item survey (total scores ranging from 32 to 224) that was developed as a measure of HRQoL specifically for patients with IBD. It was validated using other measures of disease activity and HRQoL, including the Short form (36) Health Survey (SF-36).[8,9] Throughout the survey, a research assistant was available to answer participants' questions regarding the survey.

Data on use of medications, including opioids, was collected by self-report from the study participants and verified by reviewing the patients' health records. For the purpose of our investigation, the participants who were classified as using opioids had to A) confirm that this was to control CD-associated pain (verified with patients' health records) and B) be using at least one opioid drug weekly. From this information, opioid dosages were converted to daily oral morphine equivalent based on guidelines from two previously published sources, so as to compare and standardize opioid use among the participants.[10,11] Demographic data including age, sex, disease location (colon, small bowel, upper), disease duration, number of surgeries, and number of hospital admissions related to CD were also collected. Disease location was determined based on results from the most recent endoscopic or radiographic studies. Upper disease was defined as documented involvement proximal to the duodenum. Disease site was not mutually exclusive; for example, a patient could have disease affecting both the colon and upper gastrointestinal (GI) tract.

Ethical considerations

All patients gave informed consent for study participation and received a $10 restaurant gift certificate for participating in the study to compensate patients for their time. The treating physicians did not have access to patient responses. This study was approved by the Office of Research Ethics at Western University, London, Canada (REB#: 6976).

Sample size and statistical analysis

We calculated that a sample size of 70 would be sufficient to detect a 20-point difference between IBDQ scores, based on a previously published standard deviation of approximately 30 using a two-tailed *t*-test of difference between means, a significance level of 5%, and a power of 80%.[12-14] Descriptive statistics and unpaired *t*-tests were used to compare the differences in continuous variables between opioid and non-opioid users. For categorical variables, Chi-squared analysis, Fisher's exact test, and Wilcoxon two-sample analysis were used. Fisher's exact test was used when the sample size of the two groups was small. Wilcoxon two-sample analysis was used to compare variables between the two groups when we were uncertain of the probability distribution of the data. Analysis of covariance (ANCOVA) was used to compare the HRQoL scores between the two groups, controlling for disease severity using HBI scores and the number of surgeries. Spearman's *r*-coefficient was calculated to determine statistical dependence between HRQoL scores and daily opioid dose. Spearman's rank correlation test was used to determine the significance of these coefficients. ANCOVA was used to compare the HRQoL scores according to opioid dose.

Statistical analysis was performed using SAS software (version 9.3). Statistical power for the study was calculated using the open source calculator published on www.openepi.com, which is based on the normal approximation method (http://www.openepi.com/OE2.3/Menu/OpenEpiMenu.htm).[13]

RESULTS

We recruited 100 patients with CD between June 2010 and August 2012. Six patients who were approached declined to participate in the study and one study participant was later excluded after realization that the patient had an ileostomy. Sixty-two of the patients enrolled did not use opioid medications and 38 of the patients used opioids.

Table 1 shows the demographic information, medications, and HBI scores for each group. There was no association between sex or age of participants and opioid use. The median duration of disease was significantly longer in patients using opioids compared to non-opioid users (18.5 vs. 9 years, $P = 0.005$). Patients using opioids also had a greater number of hospital admissions (median 5 vs. 1, $P < 0.001$) and surgeries related to their CD (median 3 vs. 0, $P < 0.001$). The participants' medications used to treat CD are listed in Table 1. There was more frequent prednisone use among opioid users (29% vs. 11.3%, $P = 0.03$). There was a trend toward increased use of biologics [i.e., tumor necrosis factor (TNF)-alpha antagonists and monoclonal antibodies] in patients using opioids [36.8% (opioid users) vs. 21.0% (non-opioid users), $P = 0.08$]. Disease activity, as measured by median HBI scores, was higher in patients using opioids (9.0 vs. 3.0, $P < 0.001$), indicating more active disease.

Quality of life (IBDQ) scores were significantly lower in participants using opioids (109.3 vs. 162.9, $P < 0.001$). After adjustment for disease severity, the number of previous surgeries related to CD, and prednisone use by ANCOVA, the difference between IBDQ scores remained significant ($P = 0.003$). The latter two variables were selected as they were found to strongly correlate with disease activity (HBI scores). Mean scores were also lower on each of the four different IBDQ domains for participants using opioids, as shown in Figure 1 ($P < 0.001$). This finding was significant when adjusted for disease severity, number of previous surgeries, and prednisone use for domains involving bowel function, emotional health, and social function ($P < 0.05$), although not for systemic systems ($P = 0.086$).

Total daily opioid dose was inversely associated with HRQoL and this is shown in Table 2 (Spearman coefficient −0.58, $P < 0.001$). We calculated equianalgesic doses for each patient, converting the daily opioid dose to an equivalent oral morphine dose. We chose to compare the HRQoL of patients using an equianalgesic dose less than or equal to 50 mg of oral morphine ($n = 22$) with those using more than 50 mg ($n = 16$) [Table 3]. A cut-off point of 50 mg was chosen, as this was close to the daily mean equianalgesic dose of 41.8 mg ($n = 100$). Patients using more than 50 mg of oral morphine per day had significantly lower mean IBDQ scores when adjusted for disease severity and number of previous surgeries than those persons using less than 50 mg, respectively (99.3 vs. 116.6, $P = 0.001$). This difference was significant when we controlled for number of surgeries and prednisone use. Patients using more than 50 mg of oral morphine per day also had significantly lower scores than patients using less than 50 mg of morphine on each subsection of the IBDQ ($P < 0.05$).

Prednisone use was also associated with HRQoL. In our study group, 18 patients were using prednisone and 82 were not. Patients using prednisone did have lower median IBDQ scores than those not using prednisone (113.4 vs. 148.8, $P = 0.02$). This difference was significant when adjusting for HBI scores and number of previous surgeries ($P = 0.03$), but not significant when also adjusting for opioid use ($P = 0.07$).

Table 1: Demographic information of participants and association with opioid use

	Opioid use		*P* value
	No (*n*=62)	Yes (*n*=38)	
Age			
Mean (SD)	40.0 (15.5)	43.3 (10.3)	0.245[T]
Sex-f (%)			
Male	27 (43.6)	14 (36.8)	0.508[X]
Location of active disease-f (%)			
Colitis	37 (60.0)	20 (52.6)	0.490[X]
Small bowel	44 (71.0)	25 (65.8)	0.587[X]
Upper	1 (1.6)	5 (13.2)	0.028[F]
History of Crohn's disease -median (Q1, Q3)			
Disease duration	9.0 (3,17)	18.5 (7, 24)	0.005[W]
#Surgeries	0.0 (0,1)	3.0 (1,4)	<0.001[W]
#Admissions	1.0 (0,3)	5.0 (3, 12)	<0.001[W]
Current Crohn's medications-f (%)			
Prednisone	7 (11.3)	11 (29.0)	0.026[X]
Budesonide	5 (8.1)	1 (2.6)	0.403[F]
Anti-TNF	13 (21.0)	14 (36.8)	0.083[X]
Azathioprine	14 (22.6)	13 (34.2)	0.204[X]
6-MP	0 (0.0)	1 (2.6)	0.380[F]
Methotrexate	6 (9.7)	6 (15.8)	0.365[F]
5-ASA or derivative	8 (12.9)	2 (5.3)	0.311[F]
Clinical trial drug	4 (6.5)	3 (7.9)	>0.999[F]
HBI score			
Median (Q1, Q3)	3.0 (1,6)	9.0 (5,14)	<0.001[TL]
IBDQ score			
Mean (SD)	162.8 (38.9)	109.3 (33.1)	<0.001[TL]

[X]Chi-squared; [F]Fischer's exact test; [W]Wilcoxon two-sample; [TL]Unpaired *t* based on log-transformed data; [#]Number of participants. Number of surgeries and admission include those directly related to Crohn's disease. There was a strong correlation of disease duration, number of admissions, and number of surgeries and opioid use. Adjustment was made in multivariable (adjusted) comparisons for the number of surgeries in addition to HBI score

Table 2: Quality of life scores and relationship with daily morphine equianalgesic dose (*N*=100)

IBDQ	Spearman *r*	*P* value
Total score	−0.58	<0.001
Bowel systems	−0.55	<0.001
Emotional health	−0.56	<0.001
Systemic systems	−0.49	<0.001
Social function	−0.55	<0.001

IBDQ: Inflammatory bowel disease questionnaire

Table 3: Quality of life among opioid users separated by opioid dose (*n*=38)

	Opioid use			*P* value	
	No. (*n*=62)	Dose≤50 mg (*n*=22)	Dose>50 mg (*n*=16)	Unadjusted (ANOVA)	Adjusted for HBI score and number of surgeries (ANCOVA)
IBDQ-mean (SD)					
Total	162.8 (38.9)	116.6 (31.8)	99.3 (33.4)	<0.001	0.001
Bowel systems	5.2 (1.1)	4.0 (1.1)	3.4 (1.3)	<0.001	0.011
Emotional health	5.0 (1.3)	3.6 (1.1)	3.1 (1.2)	<0.001	0.003
Systemic systems	4.3 (1.5)	3.2 (1.0)	2.4 (0.9)	<0.001	0.025
Social function	5.7 (1.6)	3.6 (1.6)	3.3 (1.6)	<0.001	0.002

IBDQ: Inflammatory bowel disease questionnaire, SD: Standard deviation, ANOVA: Analysis of variance, ANCOVA: Analysis of covariance, HBI: Harvey-bradshaw index

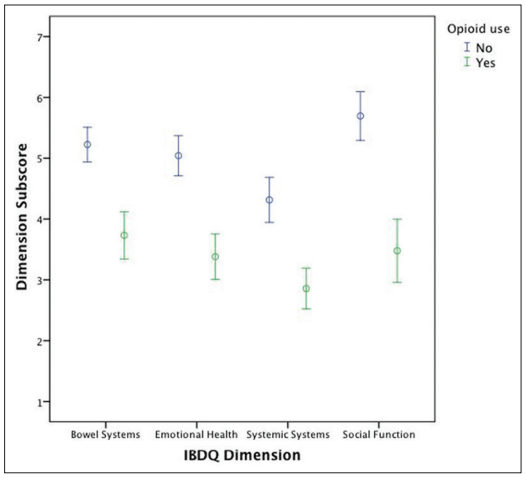

Figure 1: Mean scores for the four different domains of the IBDQ, bowel systems, emotional health, systemic systems, and social function, in CD patients using opioids and not using opioids. Domain scores are given values from 1 to 7. Error bars show 95% confidence intervals

DISCUSSION

Our results suggest that opioid analgesic use may be associated with disease activity and severity in CD. A median HBI score of 9 suggests that many patients in the opioid users group have moderate disease activity.[14] In contrast, a median score of 3 in the non-opioid using group probably suggests that many of the patients in this group could be considered to be in "clinical remission." The HBI was originally described in 1980 and was found to correlate with the longer Crohn's Disease Activity Index, also used to measure disease activity.[15] There are limitations in using either of these disease activity indices, and some studies have reported relatively low correlation with endoscopic findings or serum markers of inflammation.[16]

Several other associations, in addition to increased HBI score, suggest more severe disease among opioid users. Opioid users had an increased number of surgeries and hospital admissions related to CD, and both likely reflect disease severity and perhaps failure of medical therapy in some patients. The longer duration of disease observed in the opioid group may also reflect disease severity; many patients with long-standing, well-controlled CD would be discharged or seen less frequently in the IBD clinic at our center. A recent study by Long *et al.* also demonstrated increased prevalence of IBD-related surgeries (52.4 vs. 28.6%, $P = 0.02$) and a longer duration of disease (9 vs. 5.5 years, $P = 0.02$) in opioid users who had either CD or ulcerative colitis.[17] In addition, in a retrospective case-control study by Hanson *et al.*, it was found that opioid use in IBD was associated with increased surgeries.[18] In our group, patients using opioids were also more likely to have upper GI involvement (duodenum or above), and this may be associated with more severe disease or an earlier age of disease onset.[19]

The increase in prednisone use in the opioid group is of concern, and suggests that this group is at increased risk for disease and treatment-related morbidity and mortality. The 5-year follow-up data from the TREAT™ registry of Crohn's patients taking infliximab has been recently published. This study identified baseline opioid narcotic use and prednisone use as the only variables associated with both a higher risk for severe bacterial infections and death.[1] The hazard ratios for mortality were 1.79 [95% confidence interval (CI) 1.29-2.48] and 2.14 (95% CI 1.55-2.95), respectively. The authors of the TREAT registry also reported that increased disease activity and infliximab use were associated with increased risk of serious bacterial infections, although the risk was less than opioid or prednisone use. Also, increased disease activity and infliximab use were not significantly associated with mortality. We found a trend toward increased use of biologics, azathioprine and methotrexate, in patients using opioid narcotics, although this difference was not statistically significant. We suspect that this difference may be real and increased use of these drugs may reflect increased disease severity and need for medical treatment in these patients.

Improvement in quality of life is an important goal in the treatment of CD. CD manifests as a chronic disease in a majority of patients and it affects multiple aspects of a person's life, including relationships, employment, self-image, and disability.[20] Our results suggest that HRQoL was markedly lower in patients using opioid medications than

in those not using opioid medications. In our population, the mean total IBDQ values for both groups were relatively low. The clinical interpretation of a specific IBDQ score or range is challenging, but it has been previously reported that an IBDQ score of 168 or above correlates with patients being in remission.[21] This suggests that a significant proportion of patients in our study were not in remission. This finding may reflect a bias in our study as patients were enrolled at a tertiary referral center and were perhaps more likely to have relatively severe or active disease. The scores in each of the four subsections of the IBDQ (bowel systems, systemic systems, social function, and emotional health) were significantly lower in patients using opioids. These subsections have been shown to correlate with disease activity scores.[3]

The finding that opioid use is associated with lower HRQoL when controlling for disease severity and prednisone use suggests that other factors also influence HRQoL in this group. The clinical implication of this finding is unclear, and we cannot infer from this study that use of opioids actually contributes to decreased HRQoL. Our findings are consistent with a previous retrospective study in which lower HRQoL, as measured by the short IBDQ (SIBDQ), was reported in Crohn's patients using opioids compared with patients not using opioids.[22] There may have been some bias related to this finding, as SIBDQ scores were only available for 99 out of 291 patients in this previous study.

Factors such as disability and employment status affect quality of life in CD patients, and it is possible that patients using opioids have greater difficulty in these areas.[23] We did not specifically collect information on employment. A previous publication by Cross *et al.* reported higher rates of disability in Crohn's patients using opioids (15.4 vs. 3.6%, $P = 0.001$).[22] They defined disability as unemployment status combined with receipt of disability income. There have been previous reports suggesting that psychiatric and mood disorders may be more prevalent in IBD patients using opioids. A small retrospective study by Edwards *et al.* reported a higher prevalence of psychiatric diagnoses in patients using opioid analgesics compared with controls [6/9 (67%) vs. 2/24 (8%), $P = 0.002$)].[24] This relationship has also been reported by Hanson *et al.* who found the prevalence of anxiety and depression to be approximately two times higher in IBD patients using chronic opioid narcotics in a retrospective case-control study.[17] The authors of this study also found increased prevalence of substance abuse and history of sexual, physical, and emotional abuse in this group.

We anticipate that our finding that opioid use in CD is associated markedly with decreased HRQoL may reflect many clinicians' experience in treating patients with CD. Managing pain in patients with CD is challenging for a variety of reasons, and there are few alternatives to opioid analgesics to treat severe chronic pain. Our findings, in conjunction with the recent results from the TREAT registry, suggest that opioid use in CD may predict severe and often poorly controlled disease and low HRQoL. Our clinical experience suggests that Crohn's patients using opioids experiencing pain require careful monitoring of their disease and aggressive management of active disease. Also, we attempted to identify the factors that may modulate pain and HRQoL in patients who appear to have adequate disease control, such as comorbid medical and psychiatric illnesses.

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