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ORIGINAL ARTICLE

Increased Sedation Requirements During Endoscopy in Patients with Celiac Disease

Benjamin Lebwohl · Benjamin Hassid · Steven Ludwin · Suzanne K. Lewis · Christina A. Tennyson · Alfred I. Neugut · Peter H. R. Green

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Abstract
Background Celiac disease (CD) is associated with increased rates of neuropsychiatric disease and irritable bowel syndrome, and patients may exhibit visceral hypersensitivity.
Aim The purpose of this study was to determine whether patients with CD have increased sedation requirements during endoscopic procedures.
Methods In this retrospective cohort study, we identified CD patients undergoing either a colonoscopy or esophagogastroduodenoscopy (EGD), but not a dual procedure. CD patients were matched with control patients according to age, gender and endoscopist. For sedation requirements we defined "high" as falling outside of the 75th percentile of the entire cohort.
Results In the colonoscopy analysis we identified 113 CD patients and 278 controls. In the CD group, 29 individuals (26%) required high amounts of both opioids and midazolam, as compared to 46 (17%) controls ($P = 0.05$). Differences were similar when considering only opioids ($P = 0.06$) and midazolam ($P = 0.06$). In the EGD analysis we identified 314 CD patients and 314 controls who met the inclusion criteria. Among the CD patients, 70 (22%) required high amounts of both opioids and midazolam compared to 51 (16%) controls ($P = 0.05$). Differences were similar when considering only opioids ($P = 0.06$) and midazolam ($P = 0.04$).
Conclusions Patients with CD require higher doses of sedation during upper and lower endoscopy compared to age and gender-matched controls. Putative explanations, such as visceral hypersensitivity, chronic opioid/anxiolytic use, or underlying neuropsychiatric illness, should be evaluated prospectively.

Keywords Celiac disease · Gastrointestinal endoscopy · Colonoscopy · Conscious sedation

B. Lebwohl (✉) · B. Hassid · S. Ludwin · S. K. Lewis · C. A. Tennyson · P. H. R. Green
The Celiac Disease Center at Columbia University, 180 Fort Washington Avenue, Suite 936, New York, NY, USA
e-mail: BL114@columbia.edu

B. Hassid
e-mail: BH2185@columbia.edu

S. Ludwin
e-mail: SL3154@columbia.edu

S. K. Lewis
e-mail: SKL3@columbia.edu

C. A. Tennyson
e-mail: CT2398@columbia.edu

P. H. R. Green
e-mail: PG11@columbia.edu

A. I. Neugut
Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, Room R7-725, 722 West 168th St., New York, NY 10032, USA
e-mail: AIN1@columbia.edu

Introduction

Celiac disease (CD) is an autoimmune disorder affecting the gastrointestinal tract and multiple extra-intestinal organs, triggered by the ingestion of gluten in genetically predisposed individuals [1]. While a rapid clinical response and an eventual histological response to the diet is observed in the majority of patients, a significant proportion of individuals with CD experience ongoing abdominal pain despite adherence to the gluten-free diet [2]. These

abdominal symptoms often mimic the symptoms observed in irritable bowel syndrome (IBS), and it is thought that this pain may be caused by gastrointestinal motor abnormalities similar to those found in patients with IBS [3]. For example, in a cohort of CD patients (most of whom were not following a gluten-free diet), 84% experienced the feeling of incomplete evacuation, a hallmark symptom of IBS [3]. The reverse has also been shown, as a high prevalence of CD has been found in cohorts of IBS patients [4].

IBS has classically been associated with an increased sensation in response to visceral stimuli, a concept known as visceral hypersensitivity. Visceral hypersensitivity is thought to result from hypersensitization of visceral afferent nerves in the bowel, triggered by bowel distension. This phenomenon can be measured using balloon rectal distension, and it has been found that IBS cohorts tolerate a lower volume of distension [5]. It is currently unknown whether visceral hypersensitivity affects CD patients as well, but there is some evidence that it may. A recent study found that 36% of a CD cohort and none of a control cohort had evidence of visceral hypersensitivity based on rectal balloon distension testing [3]. CD has also been linked with anxiety disorders [6, 7]. As a common co-morbid condition in CD patients, anxiety disorders may also affect processing of painful stimuli in these patients.

One possible consequence of both visceral hypersensitivity and concomitant anxiety disorders is increased sedation requirements during endoscopic procedures. Previous evidence has found that patients with IBS are more sensitive to pain during colonoscopy [8]. We aimed to determine whether patients with CD require increased amounts of sedation medication during endoscopic procedures as compared to a control group matched for age, gender, and endoscopist.

Materials and Methods

This study was a retrospective cohort study of patients undergoing esophagogastroduodenoscopy (EGD) and colonoscopy at Columbia University Medical Center. This study originated as a posthoc analysis of colorectal neoplasia rates in patients with CD [9]. In that study, patients with CD undergoing colonoscopy from March 2006 through December 2009 were identified and matched to controls undergoing colonoscopy during that same period. Matching was done by three parameters: gender, age decile, and endoscopist ($n = 11$). Up to two control patients were matched to each CD patient.

For the present analysis, patients in that cohort were excluded if they underwent EGD during the same session, if the procedure included the assistance of an anesthesiologist, or if the sedation type and dosage was not recorded in the procedure note. After this colonoscopy cohort was analyzed, we then identified an additional, separate cohort of patients with CD who underwent EGD during this time period. These patients were matched to controls using the same exclusion criteria as those used for the colonoscopy analysis. Given the higher number of patients with CD who underwent EGD as compared to colonoscopy at this institution, an adequate sample size could be achieved by matching controls to CD patients in a 1:1 ratio. If more than one EGD or colonoscopy was performed on a given individual, the earliest chronological colonoscopy in the database was included.

Patients in these cohorts received fentanyl, demerol, and midazolam in various combinations. The quantity, type, and frequency of sedative administration was left to the discretion of the endoscopists. Opioid requirement was measured in units of fentanyl-equivalents [10].

We compared the amount of fentanyl-equivalents and midazolam during colonoscopy and EGD of the CD cohorts compared to the control cohorts. Using sedation administration as a continuous variable, we employed the Mann–Whitney test to compare CD patients and controls with regard to sedation requirement. We also defined a priori high opioid or benzodiazepine requirements as those falling within the 75th percentile of the overall cohort for EGD and again in the overall cohort for colonoscopy. We then compared CD patients to controls with regard to the proportion of each group who required high amounts of opioids, benzodiazepines, or both. We used the chi-square test to compare these proportions. Two-sided P values are reported for all calculations.

All statistical calculations were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA). The Institutional Review Board at Columbia University Medical Center approved this study.

Results

Colonoscopy Analysis

There were 526 patients originally included in the colonoscopy cohort: 181 with CD and 345 controls [9]. After excluding patients who had an EGD on the same date ($n = 117$), had an anesthesiologist assist in the procedure ($n = 11$), or did not have the type or amount of sedation documented ($n = 7$), 391 patients remained in the analysis of sedation requirements, including 113 patients with CD and 278 controls (Table 1). The overall cohort was 69% female, with a mean (±SD) age of 59.9 ± 11.4 years. The distribution of indication differed significantly between CD patients and controls ($P = 0.0003$), and this was driven by

Table 1 Characteristics of celiac disease (CD) patients and controls undergoing colonoscopy

Characteristics	CD patients ($n = 113$)	Controls ($n = 278$)	P value
Age (mean ± SD)	60.2 ± 11.5	59.7 ± 11.3	0.68
Female	76 (67)	193 (69)	0.67
Indication			
Screening	29 (26)	81 (29)	0.0003
Surveillance	16 (14)	59 (21)	
Diarrhea	30 (27)	25 (9)	
Anemia/heme positive stool	29 (26)	80 (29)	
Other	9 (8)	33 (12)	
Fentanyl equivalents (mean mcg)	140	132	0.03
Midazolam (mean mg)	4.5	4.0	0.01
≥75th percentile of opioids	36 (32)	62 (22)	0.06
≥75th percentile of midazolam	53 (47)	102 (37)	0.06
≥75th percentile of opioids and midazolam	29 (26)	46 (17)	0.05

Values given as n (%) unless otherwise noted

Table 2 Characteristics of celiac disease (CD) patients and controls undergoing esophagogastroduodenoscopy (EGD)

Characteristics	CD patients ($n = 314$)	Controls ($n = 314$)	P value
Age (mean ± SD)	50.4 ± 17.4	50.3 ± 17.4	0.9446
Female	227 (72)	227 (72)	1.0
Indication			
Dyspepsia	58 (18)	110 (35)	<0.0001
Reflux	27 (9)	82 (26)	
Diarrhea/suspected CD	45 (14)	66 (21)	
Anemia/heme positive stool	14 (4)	10 (3)	
Follow-up of CD	149 (47)	–	
Other	21 (7)	46 (15)	
Fentanyl equivalents (mean mcg)	124	117	0.02
Midazolam (mean mg)	4.0	3.7	0.002
≥75th percentile of opioids	94 (30)	73 (23)	0.06
≥75th percentile of midazolam	105 (33)	81 (26)	0.04
≥75th percentile of opioids and midazolam	70 (22)	51 (16)	0.05

Values given as n (%) unless otherwise noted

a greater proportion of CD patients undergoing colonoscopy for evaluation of diarrhea (27% vs. 9%, $P < 0.0001$).

Of the 113 patients with CD, a date of diagnosis was known in 80 (71%); seven of these 80 patients (9%) had been diagnosed with CD within 1 year prior to this colonoscopy. The mean (±SD) number of months following diagnosis was 99 (±74). There was no correlation between time since diagnosis and sedation requirements (opioids $r = 0.14$; midazolam $r = 0.23$).

The mean midazolam requirement was 4.5 mg among CD patients compared to 4.0 mg in the control group ($P = 0.01$). Similarly, the mean opioid requirement was significantly higher in the CD patients (140 mcg) than in the control group (132 mcg; $P = 0.03$).

The 75th percentile of fentanyl-equivalents and midazolam requirements was 175 mcg and 5 mg, respectively. High requirements of midazolam were present in 47 and 37% of CD patients and controls ($P = 0.06$), and high requirements of opioids were present in 32 and 22% of CD patients and controls ($P = 0.06$). The percentage of patients who had high requirements of both midazolam and opioids was higher in CD patients compared to the control group (26% compared to 17%; $P = 0.05$).

EGD Analysis

We identified 314 CD patients and matched them to 314 controls who met the inclusion criteria (Table 2). Females comprised 72% of the patients, with a mean (±SD) age of 50.3 ± 17.4 years. The distribution of indication differed significantly between CD patients and controls ($P < 0.0001$), and this was driven by a greater proportion of control patients undergoing EGD for evaluation of dyspepsia (35% vs. 18%, $P < 0.0001$) and reflux (26% vs. 9%, $P < 0.0001$).

Of the 314 patients with CD, a date of diagnosis was known in 158 (50%); 16 of these 158 patients (10%) had been diagnosed with CD within 1 year prior to this EGD. The mean (±SD) number of months following diagnosis was 100 (±108). As was the case in the colonoscopy analysis, there was no correlation between time since diagnosis and sedation requirements (opioids $r = -0.07$; midazolam $r = 0.13$).

In the CD patients, the mean midazolam requirement was 4.0 mg compared to 3.7 mg in the controls ($P = 0.002$). The mean opioid requirement was 124 mcg fentanyl-equivalents in the CD group compared to 117 mcg in the controls ($P = 0.02$). The 75th percentile of fentanyl-equivalents and midazolam requirements were 150 mcg and 5 mg, respectively. High amounts of midazolam were required in 33% of CD patients compared to 26% of controls ($P = 0.04$), while high requirements for opioids were present in 30% of CD patients compared to 23% of controls ($P = 0.06$). High requirements of both opioids and benzodiazepines were present in 22% of CD patients and 16% of controls ($P = 0.05$).

Discussion

In this retrospective cohort study, patients with CD required higher doses of opioids or benzodiazepines during colonoscopy and EGD as compared to a control group matched by age, gender, and endoscopist. These differences were present when comparing average total dose of each agent, or when comparing the proportion of CD patients to controls with regard to proportions requiring high doses (as defined a dose within the 75th percentile of the entire cohort in each analysis). These differences do not appear to be driven by outliers, as the proportion of patients with very high requirements of either agent was similar in CD patients and controls (Fig. 1). The increased requirement for medications did not change with time after the diagnosis of CD.

There are multiple potential explanations for these findings. One possibility is that visceral hypersensitivity may be more common in patients with CD. Recent studies have suggested that colonic abnormalities associated with IBS may also be found in patients with CD. For example, IBS may be associated with increased lymphocytes in the small and large colon, and similar pathological findings have also been found in CD [11, 12]. Moreover, a gluten-free diet has been found to potentially induce regression of rectal mucosal inflammation in patients with CD [12]. Information regarding adherence to the gluten-free diet was not available in the present study.

The results of these analyses suggest that visceral pain sensation may be altered in celiac disease. These findings support previous studies showing that rectal distension is felt more sensitively in CD patients [3]. Despite the fact that this phenomenon of visceral hypersensitivity has classically been associated with IBS, it appears that there is more overlap between IBS and CD than previously realized. It is now estimated that over 50% of patients with CD have IBS-like symptoms, and presence of these symptoms correlates with significantly lower health-related quality of life [13]. These symptoms are somewhat, but not completely, relieved by adherence to a gluten-free diet. The mechanism of visceral hypersensitivity is largely unknown but thought to result from disturbances at every level of the brain-gut axis, including the enteric, autonomic, and central nervous system input [14]. The consequence of this disturbance is over-sensitization of visceral afferents, spinal hyperalgesia, and alterations in reflex activity and central nervous system input [3].

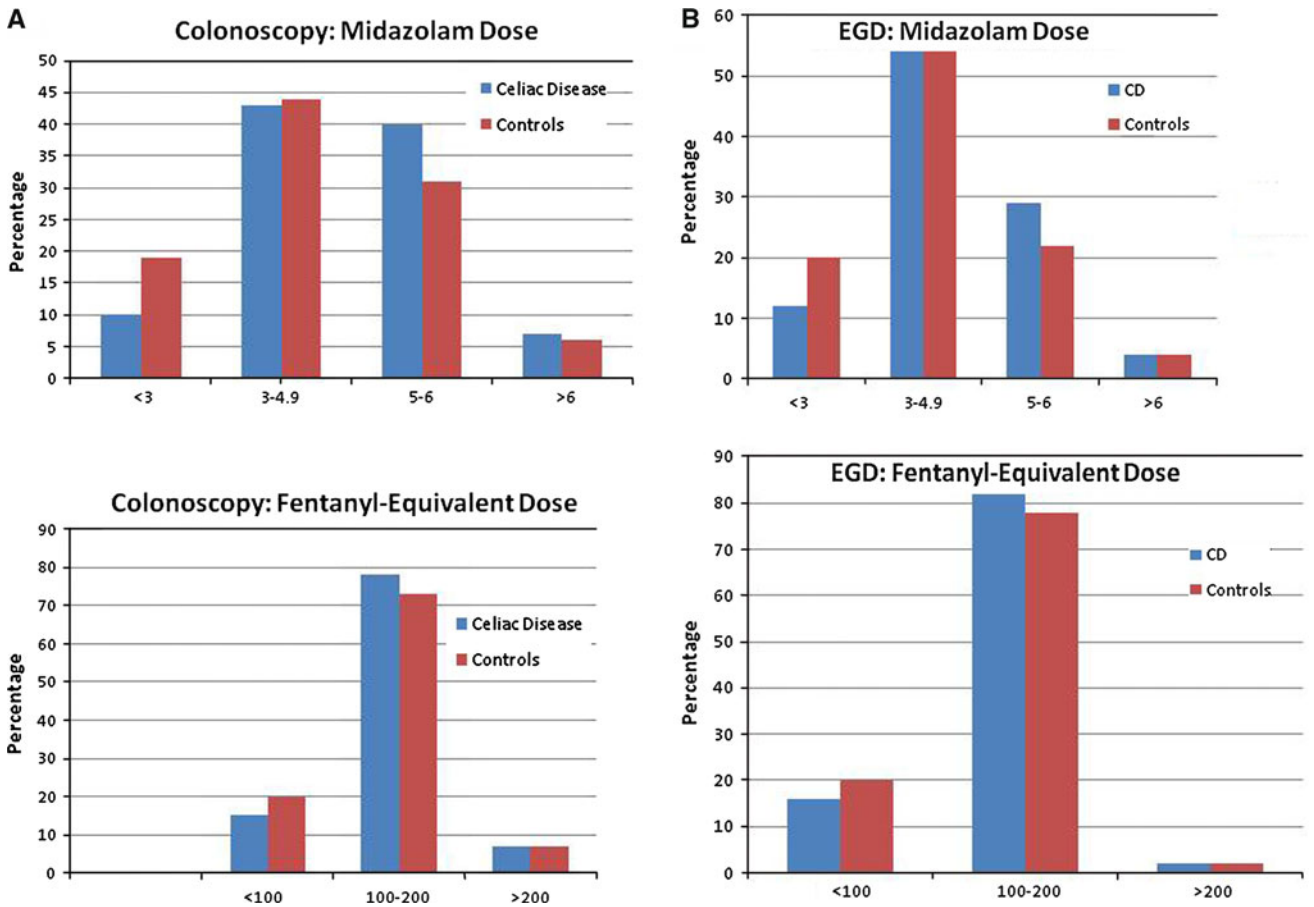

Fig. 1 Histograms of sedation requirements among patients undergoing colonoscopy (**a**) and esophagogastroduodenoscopy (EGD) (**b**)

An increased prevalence of anxiety disorders and depression in patients with CD is another potential explanation for these findings. Several studies have observed an association between CD and anxiety/mood disorders. One case control study found that CD patients on a gluten-free diet had higher levels of self-reported anxiety compared to matched controls [6], and another study with similar design found that a CD cohort scored higher on a self-reported depression scale [15]. A previous study of patients attending the Celiac Disease Center at Columbia University found that psychosocial factors such as psychological distress and coping strategies were more strongly predictive of self-perceived health-related quality of life than disease-related symptoms such as diarrhea [16]. It is therefore plausible that an effect from the primary psychiatric disorder is explaining the observed difference in sedative requirements rather than intrinsic celiac disease-related activity or visceral hypersensitivity.

The relative contributions of visceral hypersensitivity and anxiety to the increased sedation requirements observed in this study cannot be known for certain, but both factors are likely responsible for these results. An isolated greater opioid requirement in the absence of a greater benzodiazepine requirement might suggest that pain perception is the driving force for these results, and an isolated increased benzodiazepine requirement would indicate that anxiety is the primary cause of increased sedation administration in CD patients. The fact that both agents were administered in greater doses in CD patients, and that the differences in high requirements as compared to controls was of similar magnitude for each agent, suggest that the two hypotheses of visceral hypersensitivity and anxiety may both be correct.

Celiac disease has been associated with several neurologic abnormalities, including peripheral neuropathy, gait ataxia, MRI signal abnormalities in the brain, and cerebral perivascular IgA deposition [17–21]. Therefore, altered effects from sedation may result from a mechanism apart from visceral hypersensitivity or anxiety. Moreover, these differences in sedation requirements may reflect other underlying gastrointestinal pathology leading to acute or intermittent abdominal pain, such as intussusception [22, 23].

We found no correlation between time since diagnosis of CD and requirements of opioids and anxiolytics. In the years subsequent to diagnosis of CD, the salubrious effect of the gluten-free diet might theoretically result in decreased anxiety and visceral hypersensitivity, yielding decreased sedation administration. Alternatively, the increase in body-mass index observed among underweight patients after CD diagnosis might result in increased medication dosage requirements. The relative contribution of these potential contributors to sedation dosage could not be ascertained given the limited clinical details available in this analysis. However, the fact that CD patients require more medication during endoscopy than controls regardless of time on the gluten-free diet implies that this difference is likely due to long-standing distinctive clinical characteristics in this group.

This study has a number of limitations. Comorbid illnesses such as previous diagnoses of IBS, anxiety disorders, depression, and smoking status, were not available for inclusion in this analysis. Medication history, such as chronic opioid or benzodiazepine use, was not available for this analysis. The generalizability of these results is not known, as the Celiac Disease Center at Columbia University is a major referral center for the management of CD, and patients undergoing endoscopic procedures at this institution may have more severe or complicated disease than other patients with CD, or than those with undiagnosed CD. It is not known whether increased sedation requirements are unique to CD among digestive disorders, or whether this is shared among other diseases that feature chronic inflammation. Lastly, though the increased sedation requirement is intriguing and is consistent in both analyses (EGD and colonoscopy), the clinical significance of this modest difference is unknown.

We conclude that patients with CD required greater amounts of medication for sedation during endoscopic procedures as compared to non-CD patients matched by age group, gender, and endoscopist. This difference was present in analyses of both colonoscopy and EGD. Putative explanations, such as visceral hypersensitivity, chronic opioid/anxiolytic use, or underlying neuropsychiatric illness, should be evaluated prospectively.

Conflict of interest Dr. Green is a consultant for Shire and Alba Therapeutics, and is on the Scientific Advisory Board of Alvine Pharmaceuticals.

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