Anxiety is associated with impaired tolerance of colonoscopy preparation in inflammatory bowel disease and controls☆☆,☆☆,★,★★

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KEYWORDS
Abdominal pain; Bowel cleansing; Inflammatory bowel disease; Gastrointestinal-specific anxiety

Abstract

Background and aim: Pain and nausea are often reported during bowel cleansing (BC) for ileocolonoscopy (IC). We aimed to explore putative mechanisms associated with impaired tolerance to BC.

Methods: A 1:1 (100 IBD and 100 controls) sex and age matched case–control study was performed. Patients completed the hospital anxiety and depression scale (HADS-A/HADS-D), visceral sensitivity index (VSI) and state-trait anxiety inventory, state scale (STAI-S), in addition to self-assessment of BC and abdominal pain and nausea ratings during BC. Endoscopists reported the Mayo score, Harvey Bradshaw index (HBI), simple endoscopic score for Crohn’s disease, and Boston bowel preparation scale (BBPS).

Results: Higher VSI and depression scores were observed in IBD patients. VSI (P < 0.0001) and age (P = 0.008) showed a positive and negative association with abdominal pain during BC,

Abbreviations: IBD, inflammatory bowel diseases; IC, ileocolonoscopy; BC, bowel cleansing; HADS, hospital anxiety and depression scale; VSI, visceral sensitivity index; STAI-S, state-trait anxiety inventory, state scale; HBI, Harvey Bradshaw index; BBPS, Boston bowel preparation scale; GI, gastrointestinal; VAS, visual assessment scale; SES-CD, simple endoscopic score for Crohn’s disease; OR, odds ratio; CI, confidence interval; IQR, interquartile range.

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1. Introduction

Inflammatory bowel diseases (IBD) are chronic relapsing and remitting conditions characterized by inflammation in the entire gastrointestinal (GI) tract with predilection for the small bowel and colon. Complete ileocolonoscopy (IC) is a key diagnostic tool in the diagnosis and management of IBD. IC is considered the gold standard for the diagnosis of Crohn’s disease and ulcerative colitis through the endoscopic features and the histologic assessment of biopsy samples collected during endoscopy. Moreover, it is the standard investigation and the histologic assessment of biopsy samples collected for the disease and ulcerative colitis through the endoscopic features.

Most patients undergoing colonoscopy will testify that BC is more demanding than the procedure itself because bowel preparation is usually unpleasant and several complications may occur such as dehydration, renal insufficiency, and electrolyte imbalance with their potential consequences. Therefore, it is not surprising that up to 20% of patients will present to their colonoscopy with a poor BC given its complexity and demanding nature. Furthermore, patient perception of quality of BC is often unreliable. Patients often overestimate the quality of their bowel preparation. There is scant data assessing the correlation between the endoscopist’s observation and the patient’s assessment. In a study by Harewood et al., the overall correlation with endoscopists’ rating was very low, r = 0.08, with a sensitivity of 75%, a specificity of 34%, and an accuracy of 50%.

Patients in general but IBD patients in particular often complain of nausea, vomiting, bloating, and abdominal cramping during large volume BC, but it remains unclear which factors influence these symptoms. Further, whether these symptoms are more pronounced in IBD patients have not been studied. Several hypotheses have been emitted on the role of active inflammatory disease or luminal obstruction to explain these symptoms. In addition, with data about the putative role of psychological factors being especially sparse, one can only extrapolate from studies on irritable bowel syndrome that psychological comorbidities might be contributory.

The aim of our study was therefore threefold. First, we aimed to compare the quality (both endoscopist- and patient-rated) and tolerance (i.e. associated symptoms) of BC between IBD patients and matched non-IBD controls. We hypothesized a poorer quality and tolerance of BC in the IBD group. Second, we aimed to study the putative association between psychological factors and the tolerance of BC, controlling for potentially relevant sociodemographic and clinical factors. We hypothesized that higher levels of psychological symptoms would be associated with higher symptom reports (i.e. poorer tolerance) during BC. We also investigated the putative association between disease activity and the quality and tolerance of BC in the IBD group, with the hypothesis that a higher disease activity would be associated with poorer quality and tolerance of BC. Third, we aimed to study whether quality and tolerance of BC are associated with anxiety levels immediately prior to IC. We hypothesized that poor tolerance of BC would be associated with higher anxiety levels. Fourth, we evaluated the correlation between IBD disease activity parameters and psychological factors, postulating a positive correlation between them.

2. Materials and methods

2.1. Study design and patients

We performed a 1:1 matched case-control study comparing cases with IBD undergoing full IC with complete BC to controls without IBD. Patients in this study were prospectively recruited from the University of Leuven IBD database, a comprehensive database of all IBD patients followed at our tertiary care center. We identified adult IBD patients scheduled for IC and requiring complete BC between October 2011 and March 2012, as well as control patients without IBD who are also undergoing total colonoscopy with full BC. Controls were chosen randomly from our electronic record database to match to the identified cases based on gender and age (within 5 years). Patients and controls received similar BC protocols with reduced volume solutions (EndoFalk, Picoprep, Moviprep, KleanPrep). Standard ICs with or without intubation of the terminal ileum were performed on the entire cohort.
During the procedure, conscious sedation using a combination of meperidine and midazolam without the assistance of an anesthesiologist, general anesthesia or no sedation was required. All patients were aware of possible therapeutic interventions but were told that this will be determined only during the endoscopy if required. Procedures were done by either expert gastroenterologists or gastroenterology residents supervised by a staff physician. The choice of endoscopist was random (IC performed by the first available endoscopist) at our center and patients were not aware of who will be the endoscopist prior to the procedure. Subjects whose medical charts were incomplete were excluded.

2.2. Data collection

Prior to their endoscopic procedure, all patients were asked to fill out the hospital anxiety and depression scale (HADS-A/HADS-D), visceral sensitivity index (VSI), state-trait anxiety inventory, state scale (STAI-S), clinical Mayo score, self-assessment of quality of BC, and a 10-cm visual analog scale (VAS) for abdominal pain and nausea during BC.

Endoscopists blinded to the clinical history of the patient reported the endoscopic Mayo score, Harvey Bradshaw index (HBI), simple endoscopic score for Crohn's disease (SES-CD), presence and location of strictures, and the Boston bowel preparation scale (BBPS).

The electronic medical records were reviewed and the following data from each patient were obtained: age, sex, diagnosis, phenotype of disease at diagnosis (Montreal classification), number of previous total colonoscopies, history of abdominal surgery, presence of obstructive symptoms, and history of strictures and their location.

2.3. Assessment questionnaires

The HADS (see Box S1) is a self-assessment scale that yields a validated score for assessing symptom severity and diagnosis of anxiety disorders and depression in the general population as well as in psychiatric and primary care patients.\(^{13,14}\) It consists of two 7-item subscales for anxiety and depression, respectively.

The VSI (see Box S2) is a validated and reliable clinical tool for measuring GI symptom-specific anxiety that has been widely used for the evaluation of patients with functional bowel disorders, mainly irritable bowel syndrome.\(^{15,16}\) It measures five dimensions of GI-related cognitions and behaviors namely worry, fear, vigilance, sensitivity, and avoidance. It has 15 items rated on a 6-point scale ranging from strongly agree to strongly disagree with total scores ranging from 0 (no GI-specific anxiety) to 75 (severe GI-specific anxiety).

The STAI-S (see Box S3) is a well-validated and widely used instrument for measuring anxiety in adults.\(^{17–19}\) It helps determine anxiety level at a specific moment, in this case just prior to endoscopy. It has 20 items rated on a 4-point scale ranging from not at all to very much so.

Patients’ self-assessment of quality of bowel preparation was based on 3 categories: not good (formed stool present), good (liquid stool with some residues), and very good (clear liquid stools with no residues).

The BBPS is the most validated tool for the assessment of quality of bowel preparation.\(^{20}\) It is based on 4 categories ranging from 0 to 3: score 0, unprepared colon segment with mucosa not seen because of solid stool that cannot be cleared; score 1, portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen because of staining, residual stool, and/or opaque liquid; score 2, minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well; and score 3, entire mucosa of colon segment seen well with no residual staining, small fragments of stool and/or opaque liquid.\(^{21}\)

2.4. Statistical analysis

All analyses were performed using SAS Enterprise Guide 4.2 software (SAS Institute, Cary, NC, USA). Statistical significance was set at a two-tailed P-value of 0.05 or less. Distribution of continuous variables was checked using the Shapiro–Wilk test and non-parametric statistics was used when appropriate. Because of the skewed distribution of some (ordinal) variables, dichotomization was used for number of previous ICs, BBPS, and VAS scores for nausea and pain during BC, as will be reported in the respective paragraphs of the results section. The BBPS was documented for the right colon (0–3), transverse colon (0–3), and left colon (0–3) and the scores were added to a maximum of 9 points (ranging from 0 to 9).\(^{21}\)

To address our first aim, cases and controls were compared using one-way non-parametric ANOVA (Kruskal–Wallis test) and Fisher exact tests for continuous and categorical parameters, respectively.

To address our second aim, two separate multiple logistic regression models were used to test the association between psychological factors (VSI, HADS-A, HADS-D) (independent variables) and presence of nausea and abdominal pain during BC (dependent variables). The analyses were controlled for potentially relevant sociodemographic (gender, age) and clinical parameters (number of previous ICs, quality of BC as rated by the endoscopist), which were added as additional independent variables to the model. Further, in the IBD group only, simple logistic regression models were used to test the association between disease activity parameters (independent variables) and presence of nausea, pain and quality of BC (rated by the endoscopist) during BC (dependent variables).

To address our third aim, a multiple linear regression model was used to test the association between BC tolerance (nausea, pain) (independent variables) and state anxiety levels obtained immediately preceding IC (dependent variable). The analyses were controlled for potentially relevant sociodemographic (gender, age) and clinical parameters (number of previous ICs, quality of BC), which were added as additional independent variables to the model.

To address our fourth aim, Pearson correlations were used to test the association between disease activity parameters and psychological factors.

2.5. Ethical considerations

The study was approved by the University Hospital of Leuven ethics committee (S53520) and the Belgian Health Authority...
Patients were required to sign an informed consent form. All authors had access to the study data and had reviewed and approved the final manuscript.

3. Results

3.1. Patients: Descriptive characteristics

We identified 100 cases, of which 63 had Crohn’s disease and 37 ulcerative colitis (Table 1). One hundred controls presenting for screening colonoscopy, follow-up of cancer, or investigation of non-specific abdominal symptoms were age and gender-matched to the cases (52% female). The median age of cases at the time of endoscopy was 40 years (range, 19–66 years) and the median age of the controls was 41 years (range, 19–69 years). The vast majority of ICs were done under conscious sedation using a combination of meperidine and midazolam (91% of controls and 87% of IBD patients) without the help of an anesthesiologist. In the IBD group, 7% had colonoscopy with general anesthesia versus 1% in the controls. Patients were advised about this method of sedation. The remainder of patients (8% of controls and 6% of IBD patients) had no sedation at their own request. Only 5 patients in the IBD group and none in controls had advanced therapeutic intervention using balloon dilatation.

Cases had higher VSI (P = 0.0003) and HADS-depression (P = 0.01) scores as well as, not surprisingly, a history of previous surgery (P = 0.01) or strictures (P = 0.0001), and a higher number of previous IC as compared to controls (P = 0.0001) (Table 1).

3.2. Aim 1: Quality and tolerance of bowel cleansing in IBD patients and controls

Given the highly skewed distribution of the BBPS (Shapiro–Wilk test P < 0.0001), with 65% of patients receiving the maximum score of 9, and the lack of significant difference between IBD patients and controls (Kruskal–Wallis test P = 0.13), we used the 1st quartile (7) as the cut-off of 7 for “adequate BC” in all patients. Similarly, the distribution of the VAS ratings of nausea and pain during BC was highly skewed, with >50% of the patients reporting a score of 0 or 1, and the lack of significant difference between IBD patients and controls (Kruskal–Wallis test P = 0.21 and 0.26 for nausea and pain, respectively), we used the 3rd quartile (5) as the cutoff for presence of significant nausea or pain in all patients, which also corresponds with 50% of the maximum.

Cases and controls were similar in terms of presence of nausea or abdominal pain during BC, and presence of “adequate BC” as rated by the endoscopist (% BBPS ≥7). However, although all patients judged their BC to be good or very good, 84% of the controls judged their BC to be very good, compared to 71% of the IBD patients (P = 0.04) (Table 1). Thus, contrary to our hypothesis, BC tolerance did not differ between IBD patients and controls. Further, the endoscopist-rated quality of BC did not differ between both groups, but less IBD patients rated their BC as “very good” compared to controls.

In the IBD group (n = 100), contrary to our hypothesis, there was no significant association between any of the disease activity parameters (HBI, SES-CD and Mayo score) on the one hand and bowel preparation as assessed by the BBPS on the other, with all P values >0.17 (Table 2). When

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 100)</th>
<th>Controls (n = 100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>40, 31–49</td>
<td>41, 31–51</td>
<td>0.69</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52%</td>
<td>52%</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>48%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>History of surgery</td>
<td>34%</td>
<td>18%</td>
<td>0.01</td>
</tr>
<tr>
<td>History of stricture</td>
<td>17%</td>
<td>0%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Obstructive symptoms</td>
<td>14%</td>
<td>6%</td>
<td>0.06</td>
</tr>
<tr>
<td>VAS nausea</td>
<td>33%</td>
<td>22%</td>
<td>0.08</td>
</tr>
<tr>
<td>VAS abdominal pain</td>
<td>27%</td>
<td>19%</td>
<td>0.18</td>
</tr>
<tr>
<td>BBPS ≥7</td>
<td>81%</td>
<td>76%</td>
<td>0.39</td>
</tr>
<tr>
<td>Self-assessment of quality of BC</td>
<td>71%</td>
<td>84%</td>
<td>0.04</td>
</tr>
<tr>
<td>No. of previous IC</td>
<td>3</td>
<td>0</td>
<td>0.0001</td>
</tr>
<tr>
<td>STAI-S</td>
<td>41.5, 34.0–49.5</td>
<td>39.0, 30.5–49.5</td>
<td>0.18</td>
</tr>
<tr>
<td>VSI</td>
<td>29.0, 16.5–43.5</td>
<td>18.5, 5.0–35.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>HADS-anxiety</td>
<td>6.0, 3.0–9.0</td>
<td>5.0, 2.0–8.0</td>
<td>0.09</td>
</tr>
<tr>
<td>HADS-depression</td>
<td>5.0, 4.0–7.0</td>
<td>4.0, 3.0–5.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Significant differences are shown in bold.


a P-value calculated by non-parametric one-way ANOVA (Kruskal–Wallis test).
b P-value calculated by Chi-square and Fisher’s exact tests.
c Remains significant after Bonferroni correction for multiple testing.
d Dichotomized, cutoff = 5.
assessing the association of these IBD disease activity parameters and presence of nausea or pain during BC, the only significant association found was between HBI and presence of abdominal pain (P = 0.0006) (Table 2).

3.3. Aim 2: Factors associated with impaired tolerance to BC

Given that we did not observe a significant difference in the rate of nausea and abdominal pain during BC between cases and controls (Table 1), we evaluated the association between psychological factors (VSI, HADS-A, HADS-D) and impaired tolerance to BC (presence of pain, nausea) in the entire cohort, controlling for sociodemographic (gender, age) and clinical parameters (number of previous ICs, quality of BC) as rated by the endoscopist). In multiple logistic regression, VSI (P < 0.0001) showed a positive association while age (P = 0.0077) showed a negative association with abdominal pain during BC, controlling for gender and clinical factors which were not found to be significantly associated with pain (Table 3). HADS-anxiety (P = 0.0087) and female sex (P = 0.018) were positively associated with nausea, while age (P = 0.024) showed a negative association (Table 4). These results are generally in line with our a priori hypothesis on the association between anxiety scores and the quality of BC.

3.4. Aim 3: Factors associated with anxiety levels before IC

In a multiple linear regression model controlling for age, gender and (endoscopist-rated) quality of BC, features independently associated with anxiety in the moments prior to endoscopy as assessed by the STAI-S were nausea during BC (P = 0.0071), abdominal pain during BC (P = 0.0029), as predicted in our hypothesis, and a lower number of previous ICs (P = 0.032) (Table 5).

3.5. Aim 4: Correlations between anxiety and disease activity

Several significant correlations between disease activity parameters and the level of anxiety and GI-specific anxiety were found (Table 6). More specifically, the VSI demonstrated a strong correlation with the HBI (r = 0.51, P = 0.0001) and SES-CD (r = 0.55, P = 0.001), whereas the STAI-S correlated strongly with the SES-CD (r = 0.53, P = 0.001).

4. Discussion

There is scant data assessing the role of disease activity on the development of symptoms during bowel preparation as well as the quality of bowel preparation. IBD patients often complain of nausea, vomiting, bloating, and abdominal cramping during large volume BC. The reasons behind this potential reduced tolerance have not been studied so far. As an attempt to explain these observations, several hypotheses have been proposed such as greater disease activity, presence of strictures, repeated endoscopy, or increased visceral sensitivity.22 In addition, it is thought that psychological factors such as anxiety and depression could play a significant role however, this aspect has not been fully studied. This has lead to the introduction of different types and regimens of bowel preparation agents but the results are still unsatisfactory. Researchers have been struggling for a long time to provide us with the ideal laxative: one that can

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### Table 2  Associations between disease activity and degree of symptoms during bowel preparation in IBD patients.

<table>
<thead>
<tr>
<th></th>
<th>Nausea a OR (95% CI)</th>
<th>P value c</th>
<th>Abdominal pain b OR (95% CI)</th>
<th>P value c</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBI</td>
<td>0.98 (0.89–1.07)</td>
<td>0.59</td>
<td>1.26(1.10–1.43)</td>
<td>0.0006 e</td>
<td>0.07 (0.97–1.17)</td>
</tr>
<tr>
<td>SES-CD</td>
<td>1.01 (0.94–1.10)</td>
<td>0.74</td>
<td>1.06 (0.98–1.15)</td>
<td>0.15</td>
<td>1.04 (0.96–1.14)</td>
</tr>
<tr>
<td>Mayo score</td>
<td>1.06 (0.89–1.27)</td>
<td>0.50</td>
<td>1.13 (0.94–1.36)</td>
<td>0.19</td>
<td>1.02 (0.81–1.28)</td>
</tr>
</tbody>
</table>

a Dichotomized, cutoff = 5, probability modeled = presence of nausea during bowel preparation.
b Dichotomized, cutoff = 5, probability modeled = presence of abdominal pain during bowel preparation.
c A priori hypothesis on the association between anxiety scores and the quality of BC.
d Dichotomized, cutoff = 7, probability modeled = inadequate bowel preparation.
e Remains significant after Bonferroni correction for multiple testing, significances in bold.

### Table 3  Factors associated with presence of abdominal pain during bowel cleansing in cases and controls: multiple logistic regression.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P value c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.96 (0.92–0.99)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Gender a</td>
<td>0.58 (0.26–1.28)</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of previous ICs b</td>
<td>0.77 (0.36–1.65)</td>
<td>0.50</td>
</tr>
<tr>
<td>BBPS c</td>
<td>1.32 (0.54–3.23)</td>
<td>0.54</td>
</tr>
<tr>
<td>VSI</td>
<td>1.05 (1.03–1.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HADS-anxiety</td>
<td>1.003 (0.90–1.12)</td>
<td>0.96</td>
</tr>
<tr>
<td>HADS-depression</td>
<td>1.05 (0.89–1.24)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

a Reference category = female.
b Dichotomized, reference category ≥ 1 ileocolonoscopy.
c Dichotomized, cutoff = 7, reference category = adequate bowel cleansing.
provide excellent visualization of the colonic mucosa while being pleasant and convenient for the patient with the least adverse events possible.

A complete IC is the gold standard for the diagnosis and a key tool for the management of IBD but requires large volume laxatives to achieve a high quality BC. Not surprisingly, we observed a higher number of previous ICs in the IBD patients (3 vs. 0, P = 0.0001), once again stressing the essential role this tool plays. Giving the complexity of the preparation, it is not surprising that up to 20% of patients will have a poor quality bowel preparation, preventing adequate examination of the mucosa. Similar rates of inadequate preparation were found between cases and controls (19% vs. 24%), which is consistent with previously published data. We also observed that all patients judged their BC to be at least 'good', but a higher proportion of controls rated their cleansing as ‘very good’ which was not reflected in the scores given by the endoscopists.

In addition, IBD patients had a higher HADS-depression and VSI. The mean VSI score for IBD patients was 31.5. This interestingly compares with mean scores of IBS patients published by Labus et al. in this study, individuals with symptoms meeting the diagnostic criteria for IBS according to the Rome II but where not to know to be IBS patients had a VSI score of 28. Furthermore, the BBPS was poorly associated with the endoscopic disease activity as well as the clinical disease activity scores. For the first time, these findings demonstrate that despite having active symptomtic disease, the vast majority of IBD patients were able to achieve adequate BC.

One of the objectives of this study was to identify factors associated with poor tolerance of bowel preparation (nausea, abdominal pain) in IBD patients and in non-IBD controls. Our results demonstrate that a higher HBI was associated with abdominal pain during bowel preparation, indicating that presence of symptomatic disease could be responsible for symptoms during BC in Crohn’s disease. However, an increased IBD disease activity was not associated with worse bowel preparation.

The ability to achieve adequate BC does not preclude the fact that patients still developed intolerance to the preparation. We used the 10-cm VAS for nausea and abdominal pain to evaluate the degree of intolerance and symptoms associated with the large volume bowel preparation. First, we did not notice a significant difference between the cases and controls in terms of intolerance to BC (33% vs. 22%, P = 0.082 for presence of nausea and 27% vs. 19%, P = 0.18 for presence of abdominal pain). This could indicate that the significant factor causing the symptoms during BC is the large volume of laxatives, independent of the type of pathology. However, in the patients with Crohn’s disease, a higher HBI was the only disease activity score associated with abdominal pain (and not nausea) during BC. This was not the case for SES-CD (P > 0.15) or the Mayo score for ulcerative colitis patients (P > 0.19).

Given that the HBI is based mainly on subjective symptoms reported by patients, it is not unexpected that those patients with a high score will develop abdominal pain during BC. In addition, the Mayo score and SES-CD include a more objective endoscopic assessment whereas the clinical component of the Mayo score does not account for abdominal pain in the questionnaire. Unfortunately, we were unable to evaluate the role of intestinal strictures on disease activity since the number of strictures was very limited.

We further evaluated the relationship between the anxiety and depression as assessed by the various psychological scores and the disease activity. The HBI correlated strongly with the VSI (r = 0.51) whereas the SES-CD correlated strongly with the VSI (r = 0.55) and the STAI-S (r = 0.53). It is not unexpected that the HBI relates to the VSI given the fact that they are both based on patient’s self-report of symptoms. We have also mentioned previously that the HBI was significantly associated with abdominal pain during bowel preparation, hence all pointing in the same direction. It is intriguing to notice that the SES-CD, which is a more objective measure of disease activity in Crohn’s disease, was linked to anxiety prior to endoscopy and to a higher GI-specific anxiety. Given the fact that this is a

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**Table 4** Factors associated with presence of nausea during bowel cleansing in cases and controls: multiple logistic regression.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97 (0.94–0.99)</td>
<td>0.024</td>
</tr>
<tr>
<td>Gender *</td>
<td>0.42 (0.21–0.87)</td>
<td>0.018</td>
</tr>
<tr>
<td>Number of previous ICs</td>
<td>0.86 (0.44–1.70)</td>
<td>0.67</td>
</tr>
<tr>
<td>BBPS †</td>
<td>0.99 (0.44–2.27)</td>
<td>0.99</td>
</tr>
<tr>
<td>VSI</td>
<td>1.01 (0.99–1.03)</td>
<td>0.30</td>
</tr>
<tr>
<td>HADS-anxiety</td>
<td>1.15 (1.04–1.27)</td>
<td>0.0087</td>
</tr>
<tr>
<td>HADS-depression</td>
<td>0.99 (0.84–1.16)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Probability modeled = presence of nausea during bowel cleansing. Significant associations shown in bold. The c-statistic of the model (area under the receiver operating characteristic curve) = 0.75. BBPS: Boston bowel preparation score, IC: ileocolonoscopy, STAI-S: state-trait anxiety inventory, state scale, VSI: visceral sensivity index, HADS: hospital anxiety and depression scale.

* Reference category = female.
† Dichotomized, reference category ≥ 1 ileocolonoscopy.
‡ Dichotomized, cutoff = 7, reference category = adequate bowel cleansing.

**Table 5** Factors associated with state anxiety level immediately preceding ileocolonoscopy in cases and controls: multiple linear regression.

<table>
<thead>
<tr>
<th></th>
<th>β ± SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.008 ± 0.07</td>
<td>0.91</td>
</tr>
<tr>
<td>Gender *</td>
<td>−2.64 ± 1.59</td>
<td>0.10</td>
</tr>
<tr>
<td>Number of previous ICs</td>
<td>3.34 ± 1.57</td>
<td>0.032</td>
</tr>
<tr>
<td>BBPS †</td>
<td>−1.79 ± 1.91</td>
<td>0.35</td>
</tr>
<tr>
<td>Nausea ‡</td>
<td>−5.36 ± 1.97</td>
<td>0.0071</td>
</tr>
<tr>
<td>Abdominal pain §</td>
<td>−6.33 ± 2.10</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

BBPS: Boston bowel preparation score, IC: ileocolonoscopy.

* Reference category = female.
† Dichotomized, reference category ≥ 1 ileocolonoscopy.
‡ Dichotomized, cutoff = 7, reference category = adequate bowel cleansing.
§ Dichotomized, cutoff = 5, reference category = presence of nausea during bowel preparation.
§§ Dichotomized, cutoff = 5, reference category = presence of abdominal pain during bowel preparation, significant associations shown in bold, R² of the model = 0.17.
cross-sectional study, this association can be interpreted in two ways, not mutually excluding each other. First, more active disease could lead to increased anxiety prior to endoscopy, as patients with more active disease may be reminded more of "bad" experiences with previous ICs. However, we did not find an association between any of the disease activity parameters and symptoms during BC, which may be an indirect argument about a putative association between disease activity and higher symptom levels during or after (previous) ICs. Second, higher (chronic) GI-specific anxiety may lead to higher disease activity, as anxiety is associated with impaired vagal function, which may in turn increase inflammation due to the cholinergic anti-inflammatory effect of the vagus nerve. It should, however, be noted that these interpretations remain speculative.

In light of the finding that bowel preparation was adequate in most cases and controls, we elected to identify factors associated with poor tolerance to bowel preparation in the entire cohort. We also made use of validated psychological questionnaires to evaluate the role of psychological factors on BC and their association to disease activity. During BC, a higher VSI was associated with abdominal pain whereas a higher HADS-anxiety was associated with nausea. These results nicely demonstrate that anxiety, and more specifically GI-specific anxiety, plays a role in symptom development during bowel preparation. This is also consistent with studies in irritable bowel syndrome where higher HADS-Anxiety and VSI scores were associated with higher levels of functional GI symptoms. Interestingly, when evaluating factors associated with anxiety in the moments prior to endoscopy (STAI-S), we observed that presence of nausea and abdominal pain during BC as well as a lower number of previous ICs was associated with higher STAI-S. These findings can be interpreted as a vicious circle where co-morbid GI-symptom specific anxiety predisposes to impaired tolerance during BC whereas symptoms during BC lead to an increased nervousness in the moments prior to IC. Therefore, it would be intriguing to see whether measures taken to reduce anxiety could lead to improved tolerance.

This is a case–control study that carries its own limitations in terms of bias. In addition, all the questionnaires used are subjective and carry a risk of recall bias because they were given to patients prior to endoscopy and they were not filled in during symptom development. However, we tried to limit the confounding factors by blinding the endoscopists and by ensuring the best matching possible. Further, this is a cross-sectional study, not permitting any conclusion about temporal order or causality of the associations.

In conclusion, for the first time, we were able to demonstrate that disease activity in IBD as well as endoscopic inflammation were not associated with inadequate bowel preparation or nausea during cleansing. However, a higher GI-specific anxiety and co-morbid anxiety were associated with impaired tolerance to bowel preparation. Conversely, nausea and abdominal pain are associated with higher anxiety immediately prior to endoscopy, suggesting a vicious circle. Further studies to improve BC tolerance by making use of measures aiming at reducing anxiety are of interest.

**Conflict of interest**


**Acknowledgment**

**Guarantor of the article:** Talat Bessissow

All authors have made substantial contribution to the conception and design of the study, or acquisition of data, or analysis and interpretation of data, as well as to drafting of article or revising it critically for important intellectual content and they approved the final version of the manuscript.

**Author contributions:** TB contributed to the study design, data collection, statistical analysis, interpretation of data, and writing of the draft manuscript. CAVK participated in the study design, data collection, statistical

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**Table 6** Association between disease activity and psychological factors in IBD patients.

<table>
<thead>
<tr>
<th></th>
<th>HBI</th>
<th>Mayo score</th>
<th>SES-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson's r a</td>
<td>P value</td>
<td>Pearson's r a</td>
</tr>
<tr>
<td>VSI</td>
<td>0.51 b</td>
<td>0.0001</td>
<td>0.10</td>
</tr>
<tr>
<td>HADS-anxiety</td>
<td>0.17</td>
<td>0.19</td>
<td>−0.18</td>
</tr>
<tr>
<td>HADS-depression</td>
<td>0.28</td>
<td>0.025</td>
<td>0.03</td>
</tr>
<tr>
<td>STAI-S</td>
<td>0.28</td>
<td>0.025</td>
<td>−0.09</td>
</tr>
</tbody>
</table>


a Pearson correlation coefficients.

b r > 0.40: Pearson correlation coefficient of moderate magnitude, remains significant after Bonferroni correction for multiple testing.
analysis, and interpretation of data. LVO helped in the study design, performed the statistical analysis and participated in the interpretation of data, writing of the draft manuscript and critical revision of the manuscript. MF participated in the data collection, interpretation of data, and critical revision of the manuscript. SV helped in the study design, data collection, and critical revision of the manuscript. All authors read and approved the final submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.j.crohns.2013.04.011.

References