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Title: Improvement in constipation and diarrhea is associated with improved abdominal pain in patients with functional bowel disorders

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Abstract

Introduction: Abdominal pain is a bothersome and lifestyle limiting symptom in patients with functional bowel disorders. It is associated with decreased quality of life in affected individuals, as well as significant annual healthcare expenditure. Knowledge of specific factors that predict improvement in abdominal pain in those with functional bowel disorders is thus far limited.

Methods: Consecutive patients presenting for outpatient care at a major academic medical center between October 2017 and March 2020 completed an electronic symptom survey prior to initial clinic visit, and again after 3 months. The Rome IV questionnaires for functional dyspepsia,

irritable bowel syndrome, functional constipation, and functional diarrhea were all included. Additionally, all subjects completed the Patient Reported Outcomes Measurement Information System (PROMIS) Anxiety, Depression, and sleep disturbance questionnaires. Patients with a diagnosis of a Rome IV functional gastrointestinal disorder without any organic cause for symptoms were identified based on both chart review as well as survey response data. Univariable and multivariable analysis was used to assess predictors of improved abdominal pain after 3 months.

Results: 180 patients with a mean age of 45.3 years were included in the final analysis. 78.3% of patients were female, and 77.2% met Rome IV criteria for irritable bowel syndrome. On multivariable analysis, improvement in constipation and diarrhea were both independent predictors of improved abdominal pain after 3 months.

Conclusion: Improvement in constipation and diarrhea both predicted improvement in abdominal pain, suggesting that addressing these factors is central to the management of abdominal pain in functional gastrointestinal disorders.

Keywords: Abdominal pain, irritable bowel syndrome, functional dyspepsia, constipation, diarrhea, sleep disturbance, anxiety

Introduction:

Abdominal pain is a cardinal symptom of Irritable Bowel Syndrome (IBS)(1), and has been cited as being among its most bothersome symptoms(2). It is associated with decreased quality of life(3), and has been shown to have a larger impact on quality of life and daily

activities than predominant bowel habit in IBS patients(4). Increased abdominal pain severity is also associated with increased healthcare expenditure(5). A recent US epidemiological study estimated that there were a total of 2.7 million annual ambulatory visits for IBS or chronic abdominal pain, with 1181 annual visits per 100,000 US individuals for chronic abdominal pain(6).

Abdominal pain is a challenging symptom to manage, as its etiology is usually multifactorial, and can include bloating(7), fecal loading/constipation(8), and visceral hypersensitivity(9,10). Thus far, there are few treatments specifically targeted at management of abdominal pain. While the majority of research in abdominal pain in adult patients is in the area of IBS, abdominal pain is commonly seen in other conditions like functional diarrhea(11) and functional constipation(12). Tricyclic antidepressants (TCAs) are often used for treating IBS patients in whom pain is a predominant symptom, and while they have evidence for efficacy, they are often associated with side effects(13). A recent systematic review and network meta analysis of commonly utilized treatments in IBS demonstrated that TCAs, peppermint oil, and antispasmodic medications were more effective than placebo for abdominal pain in IBS, but noted that the number of included participants was small, and that many of the underlying studies were at high risk of bias(14). While antispasmodic medications are frequently used for treating abdominal pain, the most recent American College of Gastroenterology guideline recommends against the use of this drug class for treatment of global IBS symptoms(15). Various trials examining secretagogue laxatives(16,17) and prescription antidiarrheals(18,19) have also demonstrated improvement in abdominal pain symptoms, though in clinical practice, these medications are more often prescribed for altered bowel habit.

Given the bothersome nature of abdominal pain, its impact on quality of life and healthcare utilization, and the lack of trials specifically assessing for factors associated with its improvement, there exists a clear impetus for reaching a better understanding of how it can be ameliorated in clinical practice. Our aim in this study, therefore, was to prospectively study patients presenting to gastroenterology clinic at a tertiary care center to identify factors that were predictive of improvement in abdominal pain symptoms over a 3 month period of time.

Methods

Study Sample

Patients presenting to the outpatient Center for Functional Bowel Disorders and Gastrointestinal Motility at Beth Israel Deaconess Medical Center in Boston, Massachusetts between October 2017 and March 2020 completed an electronic symptom survey at their initial visit (baseline), and after 3 months (3-month follow-up). Data was collected via Research Electronic Data Capture (REDCap), a HIPAA compliant, free, secure, web-based application. Ethics approval was obtained from the institutional review board. Written consent was obtained from all patients agreeing to participate in the data repository. Patients were considered eligible if they met Rome IV diagnostic criteria for a functional gastrointestinal disorder or if they were clinically diagnosed by a gastroenterologist, and not found to have an alternative organic cause for their symptoms within 6 months of their initial visit (based on chart review).

Questionnaires

The Rome IV questionnaires for functional dyspepsia, IBS, functional constipation, and functional diarrhea were all asked of patients at baseline. Patients were classified as having these conditions based on previously established Rome IV diagnostic criteria(20,21), which must be fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis.

The Patient Reported Outcomes Measurement Information System (PROMIS) scale is a National Institutes of Health set of tools used to provide information on patient outcomes in a variety of fields. Patients completed the PROMIS Belly Pain, Constipation, Diarrhea, Anxiety, Depression, and Sleep Disturbance questionnaires before their initial visit and at 3 months. The PROMIS abdominal pain questionnaire asks 5 questions on abdominal pain frequency, severity, and day-to-day impact, each scored on a 1-5 scale. A sixth question asked subjects to list all possible areas with abdominal pain (out of 9 total). The associated score was then aggregated, and transformed to a t-score, with a score of 50 representing the mean in the US general population, and a change in score of 10 points reflecting a single standard deviation change. A 0.5-0.6 standard deviation change was cited in one study as representing the minimally important difference for the PROMIS GI symptom scales(22). The constipation module contained 9 questions (all scored on 1-5 scale) on frequency and bothersomeness of constipation, straining, rectal pain, and incomplete evacuation. The diarrhea questionnaire contained 6 questions asking about frequency and bothersomeness of loose stools and fecal urgency, all scored on a 1-5 scale(23). At their 3 month follow-up visit, patients were asked to list medications utilized. We categorized these medications into one of 14 classes, listed in Supplemental Table 1.

The data that support the findings of this study are available from the corresponding author (VR) upon reasonable request.

Statistical Analysis

Statistical analysis was performed used Stata 13.0 (Statacorp, College Station, TX, USA). Descriptive statistics such as mean with standard deviation (SD) are reported. Univariable analysis was then performed to assess for correlation between change in abdominal pain score and baseline variables (age, sex, abdominal pain score, constipation score, diarrhea score, anxiety score, depression score, sleep disturbance score, presence of IBS, and presence of functional dyspepsia), as well as correlation between change in abdominal pain score and change scores in other variables (constipation score, diarrhea score, anxiety score, depression score, and sleep disturbance score). Multivariable analysis using generalized linear regression was then performed with change score in abdominal pain as dependent variable and the other change scores noted above as independent variables, while adjusting for potential confounders age, sex, baseline abdominal pain score, and presence of IBS and functional dyspepsia.

Results:

This study included 180 patients with functional GI disorders with mean age of 45.3. Over 3/4 of subjects were female, and met Rome IV Criteria for IBS (Table 1). Nearly half met Rome criteria for Functional Dypsepsia. Subjects in this study had baseline abdominal pain score of 59.1 on the PROMIS questionnaire (US population mean of 50), with mean improvement of 3.6 points over the following 3 months. Mean baseline constipation score was 55.9, with mean

improvement of 2.1 points over the following 3 months. Mean baseline diarrhea score was 54.4, with mean improvement of 2.3 points over the following 3 months (Table 1, Figure 1).

Medications utilized

A total of 121 patients received some sort of pharmacotherapy. A list of all the medication classes and number of patients utilizing each medication class is noted in Supplemental Table 1. We specifically examined those patients on medications primarily aimed at controlling pain symptoms (i.e. antispasmodics and neuromodulators), and those on medications without known pain modulating effects aimed at treating excessive bowel frequency (i.e. antidiarrheal or bile acid sequestrant) or decreased bowel frequency (i.e. osmotic or stimulant laxative). 44 patients were on an osmotic or stimulant laxative, and not on any medication aimed at treating pain. The mean change in pan score among these patients was -3.7 (SD 9.1). 11 patients were on an antidiarrheal or bile acid sequestrant, and not on any medication aimed at treating pain. The mean change in pain score among these patients was -3.7 (SD 11.5). 16 patients were on an antispasmodic or neuromodulator, and mean change score among these patients was -2.1 (SD 9.5). The change scores in these three groups were not significantly different (ANOVA p value 0.18).

Univariable analysis

Change in diarrhea (β 0.23, p = 0.002) and constipation (β 0.23, p = 0.01) scores demonstrated significant correlation with change in abdominal pain, with improvement in both symptoms associated with an improvement in abdominal pain. Baseline diarrhea (β -0.02, p = 0.77) and constipation (β -0.04, p = 0.62) scores were not associated with change in abdominal pain. Baseline anxiety (β -0.10, p = 0.12) and depression (β -0.03, p = 0.65) were not significantly associated with change in abdominal pain, but change in anxiety (β 0.26, p = 0.007) did show a significant correlation, with improvement in anxiety associated with improvement in abdominal pain. Similarly, baseline sleep disturbance (β -0.004, p = 0.94) was not correlated with change in abdominal pain, but improvement in sleep disturbance (β 0.23, p = 0.038) did correlate with improvement in abdominal pain. Higher baseline abdominal pain (β -0.28, p < 0.001) was also correlated with improvement in abdominal pain (Table 2).

Multivariable analysis

On multivariable regression controlling for age, sex, baseline abdominal pain, underlying IBS, and underlying functional dyspepsia, we assessed whether change scores in anxiety, depression, sleep disturbance, constipation, and diarrhea were independent predictors of change in abdominal pain. On this analysis, improvement in constipation (β 0.22, p = 0.016) and diarrhea (β 0.21, p = 0.004) were both independent predictors of improvement in abdominal pain. Presence of IBS (β 3.85, p = 0.033) and increased baseline abdominal pain score (β -0.35, p < 0.001) were also independent predictors of improved abdominal pain. None of the other variables correlating with change in abdominal pain on univariable analysis were independent predictors of change in abdominal pain on multivariable analysis (Table 3).

Discussion

In this prospective study of 180 patients at an academic center specializing in functional gastrointestinal disorders, we found that improvement in constipation and diarrhea were both independent predictors of improved abdominal pain, as was higher baseline abdominal pain. Improvement in anxiety and sleep were also correlated with improved abdominal pain on univariable analysis, but were not independent predictors on multivariable analysis.

Prior studies have provided conflicting data as to whether improvement in underlying constipation and diarrhea predict improvement in abdominal pain. Prior studies of polyethylene glycol plus electrolytes in IBS-C(24) and ondansetron in IBS-D(25) demonstrated improvement in bowel frequency endpoints, but not in abdominal pain endpoints, with pharmacologic therapy compared with placebo. However, clinical trials of other prescription medications like linaclotide(16), plecanitide(17), alosetron(18), and eluxadoline(19) did demonstrate concomitant improvement in bowel frequency or consistency and abdominal pain, mirroring the findings of our study.

Among these studies, multiple possible mechanisms for concomitant improvement in pain and underlying abnormal bowel habit have been posited. Among agents for constipation predominant IBS, proposed mechanisms for pain improvement include repair of tight junctions and reduced visceral hypersensitivity with lubiprostone(26,27), and the possible antinociceptive effect of guanylate cyclase-C receptors activated by linaclotide and plecanitide(16,17). Decreased fecal loading represents another possible mechanism for improvement in pain, as IBS patients are known to be hypersensitive to intraluminal distension(28). Additionally, as

previously noted, bloating is associated with worsened pain severity in IBS(7), and is thought to represent a mechanical phenomenon in those with constipation(29). Constipated patients may associate bloating with pain(8), and indeed secretagogue laxatives have been shown to improve symptoms of both bloating as well as pain(16,27,30). The mechanism of pain improvement in diarrhea predominant IBS is less clear. Eluxadoline and alosetron have both been shown to reduce pain in diarrhea predominant IBS(18,19), an effect thought to be mediated by agonism of u-opioid receptors and 5-HT3 receptors in the case of these two medications, respectively(31). The fact that improvement in constipation and diarrhea both independently predicted improvement in abdominal pain suggests that even among patients with pain (rather than abnormal bowel habit) as the predominant symptom, treatment of underlying abnormal bowel habit remains an important aspect of treatment. The fact that there were no significant differences in change in pain score between those patients treated with medications targeted mainly at underlying bowel habit (i.e. osmotic or stimulant laxatives, antidiarrheals), and those targeted more at underlying pain (i.e. antispasmodic or neuromodulator medications) seemingly supports this conclusion as well.

Baseline abdominal pain was also an independent predictor of improvement in abdominal pain. This finding is in line with those of prior studies that have demonstrated that higher baseline pain was a predictor of treatment response in IBS. Those with higher levels of baseline abdominal pain and bloating were found to be more likely to respond to lubiprostone when compared to placebo(32), utilizing a composite endpoint that included improvement in abdominal pain. Higher baseline abdominal pain was also a predictor of improved abdominal pain with placebo treatment in constipation predominant IBS(33). A study of linaclotide also noted that the effect of the medication on pain was most pronounced in those with “severe” or very severe” pain at baseline(16). It has previously been demonstrated that IBS patients with increased baseline symptom severity were less likely to report response to global “adequate” or “satisfactory” symptom relief endpoints, but had significantly greater symptom improvement based on IBS symptom severity score (IBS-SSS)(34,35). This may in part represent some regression to the mean in those patients with higher baseline levels of abdominal pain at the start of the study.

Improvement in anxiety and improvement in sleep disturbance were both correlated with improvement in abdominal pain on univariable analysis, but were not independent predictors of change in abdominal pain on multivariable analysis. This likely reflects the fact that the treatments utilized in the gastroenterology clinic were more targeted towards treating abnormal underlying bowel habit rather than underlying sleep disturbance or psychological comorbidity. Indeed, the magnitude of mean change in constipation and diarrhea scores was greater than the magnitude of mean change in anxiety and sleep disturbance scores (Figure 1). Had there been greater improvement in anxiety and sleep disturbance scores among study subjects, it is possible that these two variables may also have been independent predictors of improved abdominal pain. A larger sample size may also have more clearly elucidated whether improvement in anxiety and sleep disturbance predicted improvement in abdominal pain. Indeed, psychological comorbidities are known to play a role in the pathogenesis of IBS. Negative emotions are thought to impact the processing of visceral sensory stimuli(36), and baseline psychological distress has been shown to correlate with symptom severity in IBS(34). Anxiety and depression have both been associated with pain in other conditions as well, including inflammatory bowel disease(37) and gastroparesis(38). Similarly, sleep disturbance has been shown to be common in a multitude of GI disorders(39,40)(41), and poorer sleep quality has been associated with abdominal pain symptoms in IBS(42,43). A recent pilot study of behavioral therapy for insomnia in IBS patients demonstrated a significant improvement in sleep quality, as well as a trend towards improvement in as well as IBS severity (measured by the IBS-SSS scale) and abdominal pain (measured using the PROMIS questionnaire)(45).

In this large, prospective study utilizing validated survey instruments, we demonstrated that improvement in constipation and diarrhea symptoms predicted improvement in abdominal pain in patients with functional GI disorders (including over 75% of patients with IBS). This suggests that effective management of so-called peripheral factors may represent an important component for managing abdominal pain in IBS patients. Potential weaknesses of this study include its reliance on self reported patient data for abdominal pain and predictors that were analyzed in this study. Additionally, this study only collected follow-up data at 3 months, and a longer period of follow-up to assess the durability of pain improvement in patients whose underlying psychological comorbidities and abnormal bowel function is successfully managed. Finally, a future study with a larger number of patients would also allow for subgroup analysis

based on the type of underlying functional GI disorder. While meeting criteria for IBS was a predictor for improvement in abdominal pain, we were unable to perform further subgroup analysis in this study, due to there being only a small number of patients who did not meet criteria for IBS. Nonetheless, we believe that the findings of this study carry important clinical implications, suggesting that treating underlying bowel habit should represent an early treatment goal in patients with functional bowel disorders and abdominal pain.

Table 1 – Patient Demographics (N = 180)

Age (mean, (SD))	45.3 (17.2)
Female (%)	78.3%
Baseline abdominal pain score*	59.1 (10.3)
Baseline constipation score*	55.9 (8.7)
Baseline diarrhea score*	54.4 (9.7)
Baseline anxiety score*	55.6 (10.4)
Baseline depression score*	49.4 (9.9)
Baseline sleep score*	52.7 (9.6)
Irritable Bowel Syndrome (%)**	77.2%
Functional Diarrhea (%)**	6.5%
Functional Constipation (%)**	19.1%
Functional Dyspepsia (%)**	46.1%

* PROMIS scale; population mean 50, range 0-100

**Per Rome IV criteria

Table 2 - Univariable regression analysis

	Coefficient*	P value	95% Confidence Interval
Age	0.05	0.24	[-0.03, 0.13]
Sex	-0.08	0.90	[-3.4, 3.2]
Baseline abdominal pain	**-0.28**	**<0.01**	**[-0.41, -0.16]**
Baseline constipation	-0.04	0.62	[-0.19, 0.12]
Change in constipation*	**0.23**	**0.01**	**[0.05, 0.42]**
Baseline diarrhea	-0.02	0.77	[-0.16, 0.11]

Change in diarrhea*	**0.23**	**<0.01**	**[0.09, 0.37]**
Baseline anxiety	-0.10	0.12	[-0.23, 0.03]
Change in anxiety*	**0.26**	**0.01**	**[0.07, 0.45]**
Baseline depression	-0.03	0.65	[-0.17, 0.10]
Change in depression*	0.12	0.26	[-0.09, 0.33]
Baseline sleep	-0.004	0.94	[-0.14, 0.13]
Change in sleep*	**0.23**	**0.04**	**[0.01, 0.44]**
Rome IBS	0.45	0.78	[-3.7, 2.8]
Rome Functional dyspepsia	-0.07	0.96	[-2.8, 2.6]

*Positive coefficient indicates that negative change in a parameter (i.e. reduction in constipation score) is associated with greater reduction in pain

Table 3 – Multivariable regression analysis

	Coefficient*	P value	95% Confidence Interval
Age	0.02	0.538	[-0.05, 0.10]
Sex	0.62	0.701	[-2.57, 3.81]
Irritable Bowel Syndrome	**3.85**	**0.033**	**[0.32, 7.38]**
Functional Dyspepsia	1.07	0.450	[-1.72, 3.88]
Baseline Abdominal pain	**-0.35**	**<0.001**	**[-0.50,-0.20]**
Change in Anxiety score*	0.13	0.208	[-0.07, 0.33]
Change in Depression score*	-0.02	0.833	[-0.24, 0.19]
Change in Sleep*	0.14	0.199	[-0.07, 0.34]
Change in Constipation*	**0.22**	**0.016**	**[0.04, 0.40]**
Change in Diarrhea*	**0.21**	**0.004**	**[0.07, 0.35]**

*Positive coefficient indicates that negative change in a parameter (i.e. reduction in constipation score) is associated with greater reduction in pain

Figure 1: Change in PROMIS score, 3 month follow-up (0-100 scale, US population mean 50, standard deviation 10)

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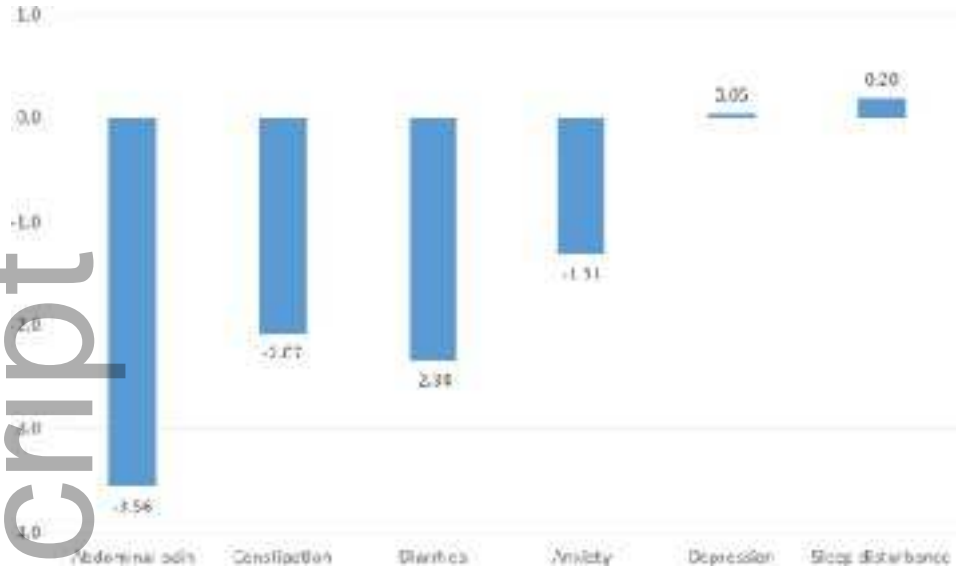

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