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Number of retained radiopaque markers on a colonic transit study does not correlate with symptom severity or quality of life in chronic constipation

DR Kyle Staller, MD, MPH^{1,2,3,*}, DR Kenneth Barshop, MD^{4,*}, Ashwin N Ananthakrishnan, MD, MPH^{1,3}, and Braden Kuo, MD, MSc^{1,2}

¹Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School Boston, MA

²Center for Neurointestinal Health, Massachusetts General Hospital, Boston, MA

³Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA

⁴Department of Medicine, Brigham and Women's Hospital, Boston, MA

Abstract

Background: Ingestion of radiopaque markers (ROM) is frequently used to determine colonic transit in chronic constipation. Although 20% of retained markers at 5 days defines slow-transit constipation, some clinicians use the number of retained markers to determine disease severity.

Methods: We assembled a cross-sectional cohort of patients presenting for evaluation of chronic constipation who underwent transit testing by ROM and completed validated symptom severity and quality of life (QOL) measures. We performed a correlation analysis to determine whether there was an association between number of retained markers and symptom severity and QOL.

Key Results: Among 159 patients undergoing evaluation for chronic constipation, there was poor correlation between the number of retained markers and symptom severity ($R=0.09$, $P=0.25$) and quality of life. Among the 55 patients with slow-transit constipation defined by 5 retained markers retained on Day 5, there were similarly poor correlations between symptom severity ($R=0.17$, $P=0.21$) and quality of life ($R=0.07$, $P=0.60$). Excluding patients with irritable bowel syndrome and outlet obstruction by balloon expulsion testing did not materially alter our results, nor did a multivariable analysis controlling for demographic and psychiatric confounders.

Corresponding author: Kyle Staller, MD, MPH, Division of Gastroenterology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, P: +1-617-724-6038, F: +1-617-724-6832, kstaller@mgh.harvard.edu.

*authors share first authorship

AUTHORSHIP STATEMENT

Guarantor of article: KS

Specific author contributions:

KS and BK planned and designed the study. KS and KB collected and analyzed the data; KS drafted the manuscript; all authors interpreted the results and contributed to critical review of the manuscript.

KS had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors approved the final version of the article, including the authorship list.

DISCLOSURES

KS has received research funding from Astra-Zeneca and Gelesis. BK and has received research funding from GSK, Vibrant, and Gelesis and consulted for Medtronic and Ironwood. AAA and KB report no disclosures.

Conclusions and Inferences: Among patients with chronic constipation, number of retained markers on a ROM colonic transit study does not correlate with measures of symptom severity or QOL. Clinicians should be cautious about over-interpreting ROM transit testing.

Graphical Abstract

Abbreviated abstract: Retention 20% of retained markers at 5 days defines slow-transit constipation in a radiopaque marker (ROM) study, but some clinicians use the number of retained markers as a surrogate for disease severity. We found no correlation between number of retained ROMs and symptom severity or quality of life in a cohort of patients presenting for evaluation of chronic constipation. The results of this study serve as a caution against the over-interpretation of ROM transit testing in chronic constipation.

Keywords

chronic constipation; Sitz marker study; severity; slow-transit constipation

INTRODUCTION

Affecting approximately 16% of the population with a direct medical cost in excess of \$200 million in the US alone, constipation is common, costly, and one of the most frequent reasons to seek care from a gastroenterologist. Initial symptom-driven treatment options include fiber and/or over-the-counter laxatives before moving to more specialized physiologic testing with the goal of establishing physiologic subtypes including slow transit and pelvic floor dysfunction (1).

Current guidelines recommend the identification and treatment of patients with pelvic floor dysfunction before moving on to an assessment of colonic transit because a substantial proportion of patients with pelvic floor dysfunction have evidence of slowed colonic transit. In practice, colonic transit testing via ingestion of radiopaque markers followed by a plain abdominal x-ray is simpler and more palatable to many patients; thus, colonic transit testing is likely more frequently performed in the community prior to anorectal manometry.

Work from our group previously demonstrated no correlation between the accumulation of markers in the distal colon on x-ray and likelihood of outlet obstruction constipation despite

common perception otherwise (2). Similarly, many clinicians are thought to consider an increasing number of retained markers to correlate with more severe constipation despite lack of evidence otherwise. We therefore sought to determine the relationship between the number of retained markers on a colonic transit study and a validated measure of constipation symptom severity among patients presenting for evaluation of constipation at a tertiary referral center. Evidence linking symptom scores and retained markers could provide a reasonable means of identifying patients with severe, potentially treatment-refractory disease earlier in their evaluation.

MATERIALS and METHODS

We assembled a cross-sectional cohort population of consecutive (18 years old) patients with chronic constipation presenting for anorectal manometry (ARM) at a tertiary referral hospital (Massachusetts General Hospital) (MGH) from February 2014 to November 2016. Patients were referred for testing by both internal and external gastroenterologists for the physiologic assessment of chronic constipation. Patients presenting for fecal incontinence or proctalgia were excluded from the analysis. Patients completed a series of validated questionnaires assessing Rome III diagnosis, symptom severity, quality of life, and anxiety and depression. From this population, patients were excluded if they did not undergo concomitant colonic transit testing (our primary exposure) or were missing information on symptom severity (our primary outcome). All data were assembled by two authors (KS and KB).

Colonic transit assessment

The primary predictor of interest for this study was the number of retained radiopaque markers on a Day 5 plain abdominal film. Colonic transit was assessed by means of the Hinton method(3), where an abdominal film was obtained five days after observed ingestion of 24 radiopaque markers in a gelatin capsule (Sitzmarks capsules, Konsyl Pharmaceuticals, Easton, MD, USA). Retention of five or more markers on imaging was defined as slow colonic transit. Anatomic location of retained markers in the colon was determined by radiologist interpretation of the plain abdominal film using a hierarchical system from right to left where patients with any markers in the left or rectosigmoid colon would still be classified as “right colon” if they had retained markers in the right colon as well and patients with markers in the rectosigmoid colon would only be classified as “rectosigmoid” if there were no retained markers in the right or left colon. Patients were advised to stop all medications that could alter colonic motility, especially laxatives (both prescription and over-the-counter).

We stratified our cohort into patients with markers remaining in the rectosigmoid colon, left colon, and right colon as well as those with markers localized throughout the colon or no retained markers. This methodology of describing marker location was consistent with a previous study by our group (2). Further stratification was performed to exclude patients with outlet obstruction as defined by a prolonged balloon expulsion time as part of the anorectal manometry protocol. We determined outlet obstruction by means of timed balloon expulsion testing of a 50 mL water-filled balloon inserted in the rectum while the patient is

on the commode (4). We dichotomized this variable into normal (≤ 2 minutes) or prolonged (>2 minutes) as per established standards (5).

Assessment of patient characteristics, symptom severity, and quality of life

All patients completed a standardized battery of validated psychometric questionnaires prior to ARM. Constipation-specific questionnaires included the Rome III Constipation Module for classification of patients with irritable bowel syndrome (IBS) and functional constipation (FC) and the Hospital Anxiety and Depression Scale (HADS), a validated instrument for the detection of anxiety and depression in the outpatient setting scored from 0 to 21 for anxiety and from 0 to 21 for depression.(6) Scores ≤ 8/21 for both depression and anxiety are considered diagnostic with a sensitivity and specificity of approximately 0.80 (7).

The primary outcome was correlation between number of retained markers and symptom severity as measured by the Patient Assessment of Constipation Symptom Questionnaire (PAC-SYM)(8), a 12-term measure of constipation symptom severity (minimum score 0, maximum score 48) divided into three subscales of Abdominal symptoms, Rectal symptoms, and Stool symptoms. A secondary outcome was correlation between number of retained markers and the Constipation-Related Quality of Life measure (CR-QOL)(9), a constipation-specific measure of quality of life (minimum score 19, maximum score 90) with four domains addressing Social Impairment (scored 6–30), Distress (scored 6–30), Eating Habits (scored 3–15), and Bathroom Attitudes (scored 4–20).

Statistical analysis

Continuous variables were summarized using means and standard deviations, while categorical variables were expressed as proportions. We compared characteristics and responses to survey instruments of patients with no retained markers vs. those with retained markers. For the discrete outcomes, univariate comparisons were made using the Fisher's exact test and continuous outcomes were compared using a T-test. The Shapiro-Wilk test was used to confirm normality of our data. For our primary outcome, we determined the correlation between number of retained markers and PAC-SYM score and CR-QOL score using Pearson correlation to determine correlation coefficients (R values). We divided the number of retained markers into quartiles and created a multivariable model to assess the relationship between quartile of retained markers and symptom severity (PAC-SYM score) after adjustment for age, sex, presence of IBS (By Rome III module), and depression (by HADS). We also performed sensitivity analyses looking at the effect of excluding patients with a Rome III diagnosis of IBS and those with a prolonged balloon expulsion time on ARM.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined by a two-sided p-value of 0.05. All authors had access to the study data and reviewed and approved the final manuscript. The study was approved by the Institutional Review Board at Massachusetts General Hospital (Protocol# 2014P001464).

RESULTS

We identified a total of 326 patients who underwent anorectal manometry at Massachusetts General Hospital for chronic constipation symptoms between February 2014 and November 2016. Of these, 161 patients did not have recent colonic transit testing and 6 were missing information on symptom severity (PAC-SYM scores), thus leaving 159 patients for inclusion in our final analysis. Patients with any retained markers on colonic transit testing were likely to be older (49.1 vs. 40.5 years, $P<0.0001$) but were otherwise similar in regards to sex distribution, body mass index, presence of irritable bowel syndrome, anxiety, depression, and likelihood of pelvic floor dysfunction as assessed by balloon expulsion time compared to those without retained markers (Table 1). Additionally, there were no significant differences in constipation severity or quality of life as assessed by the PAC-SYM (1.83 vs. 1.88, $P>0.05$) and CR-QOL (49.6 vs. 51.2, $P>0.05$) respectively, between patients with retained markers and those with no retained markers.

For our primary outcome, there was poor correlation between the number of retained markers and symptom severity ($R=0.09$, $P=0.25$) (Figure 1) and quality of life ($R=0.06$, $P=0.46$) (Table 2). Among the 55 patients with slow-transit constipation defined by 5 markers retained on Day 5, there were similarly poor correlations between symptom severity ($R=0.17$, $P=0.21$) and quality of life ($R=0.07$, $P=0.60$) (Table 3).

We performed additional sensitivity analyses excluding patients with irritable bowel syndrome ($n=62$ without IBS, $R=0.02$, $P=0.87$) and those with outlet obstruction as measured by prolonged balloon expulsion time ($n=92$ without outlet obstruction, $R=0.14$, $P=0.18$), which also demonstrated poor correlation between number of retained markers and constipation symptom severity. We also divided the number of retained markers in quartiles and created a multivariable model to assess the impact of quartile of retained markers on symptom severity. After adjustment for age, sex, presence of IBS, and depression by multiple linear regression analysis, those in highest quartile of retained markers had similar symptom severity scores compared to those in the lowest quartile of retained markers ($\beta=0.08$ (-0.21 – 0.38), $P=0.59$).

We also assessed the impact of marker location on symptom severity in the 88 patients for whom location data could be determined by radiologist assessment. As above, this was done in a hierarchical fashion from right to left. There was no significant difference between symptom severity score among patients with markers retained in any region of the colon: right colon ($n=27$, 1.76 vs. 1.89, $P=0.41$), left colon ($n=41$, 1.91 vs. 1.80, $P=0.46$), or rectosigmoid colon ($n=20$, 1.85 vs. 1.85, $P=0.98$). The latter analyses excluded those with markers in both the right and left colon. Among the 8 patients with markers distributed throughout the colon, there was no significant difference in symptom severity compared to those with markers localized to only one segment of the colon (1.71 vs. 1.86, $P=0.54$).

DISCUSSION

In this cross-sectional study of 159 patients presenting for evaluation of constipation at a tertiary academic center, we found no correlation between number of retained markers on a

colonic transit study and symptom severity or quality of life on validated symptom surveys despite controlling for demographics, psychiatric comorbidities, outlet obstruction, and presence of irritable bowel syndrome.

To put these findings in the context of the literature, our observation that symptom severity does not increase with the number of retained radiopaque markers on a colonic transit builds upon prior work by Hinton et al (3). In this original study validating this method of colonic transit analysis, only two of the normal subjects had 20% of the markers retained at 5 or more days, thus establishing the normal values used today. Our findings are novel in that the number of retained markers beyond the 20% threshold has not—to our knowledge—been evaluated. Previous studies attempting to correlate symptom severity and physiology found that patients with normal colonic transit reported higher symptom severity than those with slow-transit constipation, and even higher symptom severity in patients with visceral hypersensitivity compared to those with slow-transit and pelvic floor dysfunction (10). Thus, there may be a U-shaped relationship between transit and symptom severity such that those with few retained markers represent a proportion of patients with visceral hypersensitivity, while those with many retained markers may have more severe symptoms secondary to colonic dysfunction. Indeed, others have demonstrated a weak, negative correlation ($R = -0.26$) between colonic transit time and level of psychological distress (11).

Additional literature exists in colonic transit studies utilizing the Metcalf method, which allows for the calculation of segmental transit times from serial ingestions of radiopaque markers and serial x-rays (12). Although our study did not use this method, we found no correlation between marker location on the plain film and symptom severity or quality of life. As we used the Hinton method for colonic transit assessment (where a single abdominal radiograph is taken 5 days after capsule ingestion), the meaning of a spot film with accumulation of markers at specific colonic locations should be interpreted with caution, but are similar to a prior study demonstrating no association between segmental colonic transit and abdominal pain or bloating in patients with IBS (13).

Importantly, colonic transit testing utilizing radiopaque markers measures only one aspect of colonic sensorimotor function. Among patients with confirmed slow-transit constipation, Singh et al demonstrated significant pathophysiological heterogeneity when patients underwent colonic manometry (14). More than 40% of slow-transit patients demonstrated no identifiable abnormalities while 26% had colonic neuropathy and 32% had colonic myopathy. Poor correlation between GI transit and symptoms is well established among patients with functional dyspepsia, where the severity of delayed emptying on gastric scintigraphy is a poor predictor of symptom severity (15).

Additional limitations include the cross-sectional design of this study, where causation cannot be clearly ascertained, and we cannot exclude the possibility that unmeasured confounders may explain our failure to observe a correlation between symptoms and number of retained markers. Secondly, our patient population was derived from a tertiary referral center, where the population seeking care are more likely to have refractory disease that is not reflective of the consulting population at large. Finally, there is the inherent human error among patients required to abstain from laxatives and simultaneously ensure correct timing

between the ingestion of the capsule and the abdominal plain film—leading to potential issues with the reproducibility of a single colonic transit study (16).

Relative strengths of the current study include a robust psychometric and physiologic characterization of this population with the ability to measure symptom severity, quality of life, and adjust for psychiatric disease and irritable bowel syndrome. Additionally, we were able to account for the presence of pelvic floor dysfunction, which is an important confounder of colonic transit studies in that pelvic floor dysfunction is known to be associated with slow-transit constipation (17, 18). By failing to demonstrate a correlation between symptom severity and the number of retained markers on a colonic transit study, we suggest that clinicians not overinterpret the meaning of physiologic testing in functional GI disease, where our pathophysiologic understanding fails to account for significant heterogeneity.

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KEY MESSAGES

- Retention 20% of retained markers at 5 days defines slow-transit constipation in a radiopaque marker (ROM) study, but some clinicians use the number of retained markers as a surrogate for disease severity.
- We found no correlation between number of retained ROMs and symptom severity or quality of life in a cohort of patients presenting for evaluation of chronic constipation.
- The results of this study serve as a caution against the over-interpretation of ROM transit testing in chronic constipation.

Figure 1:
Scatter plot of retained marker number versus symptom severity score (PAC-SYM global score)

Table 1:

Demographic, medical, and symptom characteristics of patients with constipation undergoing colonic transit testing stratified by presence of any residual colonic markers

	No retained markers	Any retained markers	P-value
Demographics/comorbidities	----	----	----
N	67 (42.1%)	92 (57.9%)	----
Age (SD)	40.5 (16.1)	49.1 (15.6)	<0.001
Female sex (%)	60 (89.6%)	80 (87.0%)	0.81
Body mass index (SD)	24.5 (5.5)	24.0 (5.6)	0.58
Irritable bowel syndrome (%) ^a	40 (61.5%)	57 (64.8%)	0.74
Prolonged balloon expulsion time ^b	29 (44.6%)	35 (38.5%)	0.51
Anxiety (%)	68 (100%)	97 (100%)	1.00
Depression (%)	13 (19.4%)	26 (28.3%)	0.26
Symptom/QOL measures	----	----	----
Constipation symptom severity (PAC-SYM)	1.88 (0.84)	1.83 (0.66)	0.66
Abdominal symptoms subscore	2.22 (1.04)	2.13 (0.95)	0.55
Rectal symptoms subscore	1.05 (1.09)	0.96 (0.80)	0.54
Stool symptoms subscore	2.10 (0.99)	2.09 (0.86)	0.94
Constipation-specific quality of life (CR-QOL) ^c	51.2 (18.0)	49.6 (15.3)	0.56
Distress subscale	21.7 (6.1)	21.3 (6.2)	0.73
Social impairment subscale	9.0 (5.7)	8.5 (5.4)	0.63
Eating subscale	9.7 (4.0)	10.3 (3.8)	0.36
Bathroom subscale	11.0 (8.5)	9.8 (4.8)	0.29

^a Six patients were missing data on presence of irritable bowel syndrome

^b Defined as balloon expulsion time > 2 minutes, 3 patients missing data

^c Eight patients were missing data on CR-QOL

Table 2:

Correlations between marker number and constipation symptom severity and quality of life

	<i>Correlation coefficient ^a</i>	<i>P-value</i>
Symptom Severity (PAC-SYM)	0.09	0.25
Abdominal symptoms	0.03	0.75
Rectal symptoms	0.05	0.54
Stool symptoms	0.10	0.22
Quality of Life (CR-QOL)	0.06	0.46
Distress	0.08	0.36
Social impairment	0.08	0.33
Eating	0.03	0.70
Bathroom	0.02	0.81

^aCorrelation coefficients calculated using Pearson method given normally-distributed data for PACY-SYM and CR-QOL

Table 3:

Correlations between marker number and constipation symptom severity and quality of life in patients with slow transit ^a.

	<i>Correlation coefficient^b</i>	<i>P-value</i>
Symptom Severity (PAC-SYM)	0.17	0.21
Abdominal symptoms	0.07	0.59
Rectal symptoms	0.07	0.62
Stool symptoms	0.21	0.13
Quality of Life (CR-QOL)	0.07	0.60
Distress	0.09	0.54
Social impairment	0.10	0.46
Eating	0.15	0.29
Bathroom	−0.05	0.74

^a Slow transit defined as 5 markers remaining on an abdominal x-ray 5 days after ingestion of a capsule containing 24 radiopaque markers (N=55)

^b Correlation coefficients calculated using Pearson method given normally-distributed data for PACY-SYM and CR-QOL