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# Changes in the Frequency of Constipation and Opioid Prescription at the Time of Referral to Outpatient Palliative Care

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## Abstract

**Objective:** Primary objective was to examine if there is a difference in Patient-Reported Constipation (PRC) before and after receiving an educational intervention about constipation among Advanced Cancer Patients (ACP).

**Methods:** This was a prospective randomized trial which ACP were assessed for PRC before and after randomization to receive educational materials about constipation. Patients were recruited at the time of consultation at outpatient Supportive Care Center.

**Results:** The study was stopped due to lower frequency of constipation than expected. Fifty-nine patients participated in the study. The median age (IQR) was 58 (51-66), 39 (66%) were female and most common cancer type was lung (25%). Only 21/59 (36%) were constipated according to modified ROME III criteria. Rate of strong opioids use and morphine equivalent daily dose were significantly lower than the previous study (70% vs 88.0%, p=0.004; median MEDD 37.5 vs 60, p=0.0039).

**Significance of the Results:** Constipation in this population was less frequent than the past. Opioid usage before palliative care consult decreased significantly. Future studies about constipation in ACP should be conducted in patients who are reporting constipation. More research is necessary to better characterize the association between MEDD and constipation.

**Keywords:** Advanced Cancer; Constipation; Opioid; Palliative Care; Patient Outcome Assessment; Prescription

## Introduction

Constipation is defined as infrequent or difficult defecation with reduced number of bowel movements, which may or may not be abnormally hard, with increased difficulty or discomfort [1]. If untreated constipation can cause distressing symptoms such as abdominal pain, nausea, vomiting, anorexia, delirium and psychological distresses [1-3]. Severe constipation may lead to subsequent life threatening complications such as bowel obstruction or perforation [4]. Opioid analgesics are major contributors to constipation in cancer patients [5]. Constipation may affect up to 90% of ACP taking opioids [1,6-8]. Our previous study [9] found a frequency of constipation of 50% in patients arriving for a palliative care consult. Along with routine assessments and the appropriate use of laxatives, patient education is central in managing and preventing constipation in ACP [10].

The main objective of this study was to examine if there is a difference in Patient-Reported Constipation (PRC) before and after receiving an educational intervention about constipation among ACP. Secondary objectives were to compare PRC to objective assessment of constipation by modified Rome III criteria and to obtain preliminary data on changes in PRC with two ways of educational intervention - educational video and fact sheet information. We hypothesized that there would be an increase in

the severity of PRC after receiving an educational intervention among ACP.

## Methods

### Study Design

The Institutional Review Board of the MD Anderson Cancer Center and the Committee for The University of Texas Health Science Center at Houston approved this protocol. This was initially a prospective randomized controlled trial in the outpatient Supportive Care Center at M.D. Anderson Cancer Center. The clinical end point was patient-reported perception of constipation (PRC) among ACP. ACP were assessed for PRC before and after randomization to either an educational video describing symptoms of constipation and importance of regular bowel movement or a fact sheet which the information is exactly the same. The original protocol estimated the expected frequency of constipation to be 50% based on prior literature [1,9]. This resulted in a sample size calculation of 150 patients to provide a power of 0.8. These patients were to be randomized to two different educational interventions regarding constipation.

### Patient Eligibility, Enrollment and Study Procedures

Patients with diagnosis of advanced cancer; age ≥ 18 years; able to speak English; have no clinical evidence of cognitive impairment were recruited at the time of consultation. Patients with a diagnosis of inflammatory bowel disease (i.e. Crohn's disease or ulcerative colitis); complete or partial bowel obstruction; had a bowel ostomy were excluded. The palliative care outpatient population was specifically chosen because the constipation was highly prevalent in this setting as reported in previous studies [1,6-9].

Patient's demographic (age, gender, cancer diagnosis, stage and ECOG performance status) were collected. Patients were asked to rate their PRC, randomized either to an educational video or a fact sheet about constipation, rate their PRC again after receiving the educational material and lastly, complete the Modified Rome III questionnaire. Opioid and laxative consumption were collected from the medication history. The Morphine Equivalent Daily Dose (MEDD) was calculated using an equianalgesic conversion table [11-14]. We calculated the Laxative Equivalent Daily Dose (LEDD) using the number of laxatives and dose (e.g., the minimal dose of one laxative would have a score of one; the minimal dose of two laxatives or twice the minimal dose of one laxative would have a score of two) [9].

## Assessment Tools

### The Modified Rome III criteria [9]

The original ROME III criteria [15] diagnoses functional constipation and has been taken to be indicators of the severity of constipation. Because Rome III was developed for the diagnosis of chronic constipation, we decided to use the Modified Rome III criteria to apply to screening ACP for current constipation as we had done in our previous study [9].

### Patient-Reported Numeric Constipation Scale (PRC) [9]

This patient-reported tool used to assess bowel function commonly used in hospice and palliative care programs and was recently used in our previous study. It consists of 0 to 10 numeric scale (where 0 represents no constipation, and 10 is worst imaginable constipation). An anchor of two weeks was chosen to coincide with the modified Rome III assessment.

### Statistical Analysis

The variables of interest included rate of opioid use, MEDD and LEDD. Data was summarized using standard descriptive statistics such as mean, standard deviation, median, Interquartile Range (IQR) and range for continuous variables; and frequency and proportion for categorical variables. Association between categorical variables was examined by Chi-Squared test or Fisher's exact test whichever appropriate. To better understand the changes in opioids and laxative use over time, we included data from a previous constipation study conducted in the same outpatient setting. Wilcoxon rank-sum test was used to examine the difference in continuous variables between two groups. All computations were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

### Results

Although initially a randomized controlled trial, the study was closed early after 59 patients were accrued (enrolled May 2015-August 2015) due to lower frequency of constipation than expected. This affected the sample size required to test the hypothesis to be much larger and the duration of the study would be excessively long. A total of 76 patients were eligible and approached. of these, 59 patients (78%) agreed to participate in the study. Patient characteristics, frequency of constipation as defined by modified ROME III criteria, strong opioid use, MEDD and LEDD of the current and previous study are summarized in Table 1. In this study, only 36% (21/59) of patients were constipated, as compared

to 50% (50/100) in the previous study. Rate of strong opioids use, MEDD and LEDD are significantly lower in the current study (70% vs 88.0%, p=0.004; median MEDD 37.5 vs 60, p=0.0039; and median LEDD 0 vs 2, p=0.0067).

| Patient Characteristics | N (%) | | p-value |
|---|---|---|---|
| | Current study N=59 | Previous study[7] N=100 | |
| **Age** (years), median (Q1–Q3) | 58 (51-66) | 57 (49–65) | 0.59 |
| **Female** | 39 (66) | 63 (63) | 0.69 |
| **Married** | 35 (59) | 77 (77) | **0.0127** |
| **Highest education level** | | | **<0.0001** |
| High school or below | 3 (5) | 34 (34) | |
| Any college undergraduate education | 32 (56) | 54 (55) | |
| Any advanced postgraduate education | 22 (39) | 11 (11) | |
| Missing | 2 | 1 | |
| **Cancer diagnosis** | | | 0.0669 |
| Respiratory | 15 (25) | 18 (18) | |
| Breast | 14 (24) | 15 (15) | |
| Gastrointestinal | 10 (17) | 12 (12) | |
| Gynecologic | 6 (10) | 9 (9) | |
| Head and neck | 6 (10) | 4 (4) | |
| Genitourinary | 3 (5) | 10 (10) | |
| Hematologic | 2 (3) | 6 (6) | |
| Dermatologic | 0 (0) | 15 (15) | |
| Others | 3 (5) | 11 (11) | |
| **ECOG Performance Status** | | | 0.18 |
| 0 | 0 (0) | 3 (3) | |
| 1 | 19 (32) | 38 (41) | |
| 2 | 32 (54) | 35 (38) | |
| 3 | 8 (14) | 17 (18) | |
| Missing | 0 | 7 | |

**Table 1:** Patient Characteristics of Current and Previous study [7].

| Variables | Study | | p-value |
|---|---|---|---|
| | Current (N=59) | Previous (N=100) | |
| Constipated: Modified ROME III | 21 (35.6%) | 50 (50%) | 0.0775 |
| Strong Opioid Use | 41 (69.5%) | 88 (88%) | **0.0040** |
| MEDD (Median, IQR)[1,2] | 37.5 (0, 80) | 60 (30, 185.25) | **0.0039** |

| | | | |
|---|---|---|---|
| LEDD (Median, IQR)[1] | 0 (0, 4) | 2 (0, 4.5) | **0.0067** |

[1]Abbreviations: MEDD = Morphine equivalent daily dose; LEDD = Laxative equivalent daily dose;

IQR = Interquartile range

[2]MEDD of the previous study was not equal to those reported because of the change in calculation of MEDD which the previous study used conversion ratio of 1 (mg/day to mg/day) for Hydrocodone and 3.6 (microgram/hr to mg/day) Fentanyl transdermal patch, while in this study we used ratio of 1 and 1.5 (mg/day to mg/day) for Hydrocodone <40 and ≥40 mg/day respectively, and 2.5 (microgram/hr to mg/day) for Fentanyl transdermal patch [12,14].

**Table 2:** Frequency of Constipation, Strong Opioid Use, Morphine Equivalent Daily Dose and Laxative Daily Dose.

Table 2 shows that the MEDD and LEDD are not significantly different between patients with and without constipation in the current trial, while in the previous study, both were significantly higher in patients with constipation. The MEDD among the constipated patients in this study was similar to the MEDD of those without constipation in the previous study (median 45 mg/day for both groups, p=0.1648). The sensitivity and specificity of PRC (pre-intervention) using ≥ 3 as a cutoff point in this study were 86% and 71% compared to 84% and 62% in the previous study.

## Discussion

We observed that the patients were reporting a lower than expected frequency of constipation, therefore the study was closed early. The constipation rate according to modified ROME III criteria in this patient group was 36%, less frequent as compared to our hypothesis and previous studies which reported constipation among advanced cancer patients of 40% up to 90% [1,7,8].

Number of patients receiving strong opioids has decreased. Furthermore, they were receiving less than two-thirds of the dose of opioids they were using before. This change might be due to less use of strong opioids by primary oncologists before referring patients to palliative care. One likely contributor to this is the change to schedule 2 for hydrocodone by the United States Food and Drug Administration [13,16], which occurred around October 2014. The reason why the MEDD in patients with and without constipation in current study were not significantly different is possibly because patients were receiving uniformly low opioid doses. The MEDD among the constipated patients in this study was similar to the MEDD of those without constipation in the previous study. This suggests that MEDD might not be the major factor for constipation in the current study. Constipation in cancer patients is by nature, a multi-factorial syndrome [1]. It has various causes other than opioids such as anticholinergic drugs, lack of food intake, dehydration, decreased function and metabolic disturbances. Taken together, our study suggests that MEDD of more than 45 mg/day may be associated with constipation in ACP. More research is necessary to better characterize the association between MEDD and constipation. Similar to our previous study, using a cutoff of PRC ≥ 3/10 resulted in a good level of sensitivity and specificity for constipation. There was no significant difference between PRC before and after the educational intervention but that was not expected because frequency of constipation was lower than expected and affected the power to detect a difference.

## Conclusion

Constipation was still relatively frequent in our cancer patients, but less frequent than in the past. Opioid usage before palliative care referral decreased significantly. These findings could be related to the changes in patterns of opioid prescription after the U.S.FDA announcement of re-scheduling the hydrocodone. Future constipation studies in ACP should be conducted in patients who are reporting constipation or receiving MEDD of > 45 mg. More research in this area is needed.

### Author Disclosure Statement

No competing financial interests exist.

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