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Use of an ACE inhibitor or angiotensin receptor blocker is a major risk factor for dehydration requiring readmission in the setting of a new ileostomy

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Abstract

Purpose—Diverting ileostomies help prevent major complications related to anastomoses after colorectal resection but can cause metabolic derangement and hypovolemia, leading to readmission. This paper aims to determine whether angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use increased the risk of readmission, or readmission specifically for dehydration after new ileostomy creation.

Methods—Retrospective analysis of patients undergoing diverting ileostomy at a tertiary-care hospital, 2009–2015. Primary outcome was 60-day readmission for dehydration; secondary outcomes included 60-day readmission for any cause, or for infection obstruction.

Results—Ninety-nine patients underwent diverting ileostomy creation, 59% with a primary diagnosis of colorectal cancer. The 60-day readmission rate was 36% (n = 36). Of readmitted patients, 39% (n =14) were admitted for dehydration. Other readmission reasons were infection (33%) and obstruction (3%). The majority (64%, n = 9) of patients readmitted for dehydration were taking either an ACEi or an ARB. Compared to patients not readmitted for dehydration, those who were readmitted for dehydration were more likely to be on an ACEi or an ARB (11/85, 13% vs. 9/14, 64%). After controlling for covariates, ACEi or ARB use was significantly associated with risk of readmission (p <0.0001, odds ratio = 13.56, 95% confidence interval 3.54–51.92,). No other diuretic agent was statistically associated with readmission for dehydration.

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Compliance with ethical standards This study was approved by the Columbia University Medical Center (CUMC) Institutional Review Board with waiver of informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

Conclusions—ACEi and ARB use is a significant risk factor for readmission for dehydration following diverting ileostomy creation. Consideration should be given to withholding these medications after ileostomy creation to reduce this risk.

Keywords

Diverting ileostomy; Readmission; Dehydration; Angiotensin-converting enzyme inhibitor; Angiotensin receptor blocker

Introduction

Readmission after colorectal surgery is a common problem and is associated with significant cost [1, 2]. Such readmissions have drawn increasing scrutiny since the Centers for Medicare and Medicaid Services (CMS) introduced the Hospital Readmissions Reduction Program (HRRP) in 2012, which levied financial penalties against hospital reimbursements for excess risk-adjusted 30-day readmission rates [3, 4]. Multiple studies have identified ileostomy creation as an independent risk factor for readmission after colorectal surgery [1,2, 5–7]. Dehydration and metabolic disarray secondary to high ileostomy output are leading indications for readmission after ileostomy creation [8, 9]. Several centers have recently reported significant reduction in readmission rates after ileostomy creation, following the implementation of standardized post-operative care pathways; in addition to in-hospital measures, these efforts have focused on maintaining adequate hydration in the post-discharge setting [10, 11].

The pathogenesis of high ileostomy output remains poorly understood. Research by Huber et al. demonstrated that plasma mineralocorticoid levels are elevated in patients in the weeks following ileostomy creation, suggesting that hyperactivity of the renin-angiotensin-aldosterone system (RAAS) is part of the normal compensatory response to stoma losses [12, 13]. More recent work by Malsure et al. has found that the amiloride-sensitive epithelial sodium channel (ENaC), which is present in intestinal mucosa and is regulated by RAAS, is critical to maintaining the bowel's absorptive capacity [14]. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are commonly prescribed anti-hypertensive medications that target RAAS by reducing the kidney's ability to reabsorb water and salt. We hypothesized that use of such medications after ileostomy creation may increase risk of readmission by inhibiting the renal and intestinal mechanisms responsible for fluid homeostasis.

This study examines the association between the use of ACEi and ARB and the risk of 60-day readmission for dehydration in patients undergoing colorectal surgery with diverting loop ileostomy creation.

Methods

This study was approved by the Columbia University Medical Center (CUMC) Institutional Review Board with waiver of informed consent. Patients undergoing elective colorectal surgery with creation of diverting loop ileostomy at CUMC between 2010 and 2015 were identified from a prospectively collected colorectal divisional outcome database. Patients

who underwent emergency surgery or elective surgery by other surgical divisions at CUMC, who had a prior ileostomy, or who were diverted via jejunostomy were excluded. Clinical and pathologic data were retrieved from review of the medical record; variables retrieved included patient baseline demographics, comorbidity, medication usage, and post-operative outcome. Patients were considered to be taking an ACEi or ARB post-operatively if that medication was listed in their chart at the time of their pre-operative clinic visit, and if instructions to resume that medication were noted in their discharge records.

The primary outcome was readmission for dehydration within 60 days of discharge. Secondary outcomes included 60-day readmission for any cause, or for infection or obstruction. Dehydration was considered the primary indication for readmission when at least two of the following conditions were met: (1) “dehydration,” “hypovolemia,” or “high output stoma” noted in the medical record as the primary indication for readmission; (2) laboratory abnormalities of either blood urea nitrogen (BUN) > 20 or serum creatinine (SCr) > 0.3 above pre-operative levels; (3) administration of resuscitative intravenous fluids upon re-presentation; and (4) reported ileostomy output > 1500 cm^3/24 h immediately prior to readmission, AND there was no other complication, such as intra-abdominal infection, that could otherwise account for these findings.

Continuous variables are presented as mean with standard deviation (SD) and were evaluated with Student’s *t* test; ordinal variables were evaluated with Spearman’s rank correlation coefficient; and categorical variables were evaluated with Pearson’s Chi-squared test or Fisher’s exact test, as appropriate. Two-tailed p values < 0.05 were considered to be statistically significant. Multiple logistic regression models were constructed to determine whether ACEi or ARB use, or any use of any other diuretic medication, was independently associated with risk of 60-day readmission, or risk of 60-day readmission for dehydration. Potential explanatory covariates adjusted for included age; sex; comorbidity, including diabetes and renal insufficiency; American Society of Anesthesiologists (ASA) physical status grade; indication for index operation; history of prior abdominal operation; and surgical approach. Stepwise selection was used to select covariates that were significant at the $p < 0.20$ level. Statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA).

Results

Ninety-nine patients were eligible for inclusion in this study. Patient demographic characteristics, medical comorbidity, and diuretic medication use are given in Table 1. The mean age of patients was 51.8 years (SD, 19.4 years), and 48 patients (48%) were female. The most common indication for ileostomy creation was temporary fecal diversion at the time of resection of colorectal cancer ($n = 58$, 59%). Eleven patients (11%) had a pre-operative diagnosis of diabetes mellitus, and four patients (4%) had a diagnosis of renal insufficiency; no patients had a diagnosis of end-stage renal disease requiring dialysis. Twenty patients (20%) were determined to be taking either an ACEi or an ARB post-operatively; a further nine patients (9%) were found to be taking a loop diuretic. Forty-five patients (45%) had previously undergone an abdominal operation.

The overall 60-day readmission rate following creation of a diverting loop ileostomy was 36% (n = 36). Mean time to readmission was 4 weeks. Of these readmitted patients, 14 (39%) were admitted for dehydration; thus, 14% of the total cohort was readmitted for dehydration. Other leading indications for readmission included infection (n = 12, 33%) and obstruction (n = 2, 6%). Indications for readmission are given in Table 2.

In a univariable analysis, ACEi or ARB use and prior abdominal operation were both significantly associated with readmission for dehydration (p = 0.03 and p < 0.001, respectively). After adjusting for covariates, both ACEi and ARB use (p <0.0001, OR 13.56, 95% CI 3.54–51.92) and prior abdominal operation (p = 0.04, OR 4.26, 95% CI 1.05–17.28) remained significantly associated with risk of readmission for dehydration. Most patients (n = 9/14, 64%) readmitted for dehydration were taking an ACEi or ARB. Compared to patients not readmitted for dehydration, those who were readmitted for dehydration were significantly more likely to be taking an ACEi or an ARB (13 vs. 64%, unadjusted OR 13.56, p <0.0001). Put another way, patients who undergo loop ileostomy creation and resume ACEi or ARB therapy after surgery have a 64% chance of readmission for dehydration, compared with only a 13% chance of readmission for dehydration among patients not taking ACEi or ARB therapy after surgery. Loop diuretic use was not associated with risk of admission for dehydration (p = 0.47).

In a separate unadjusted analysis performed for readmission for any cause, prior abdominal operation, history of diabetes mellitus, and loop diuretic use were significantly associated with risk of 60-day readmission for any cause (p = 0.02, p = 0.047, and p = 0.047, respectively); ACEi or ARB use was not significantly associated with risk of readmission (p = 0.052). After adjusting for covariates and stepwise selection, prior abdominal operation remained significantly associated with risk of readmission (p = 0.02, odds ratio (OR) 3.00, 95% confidence interval (CI) 1.20–7.47). Results of univariable and multivariable analyses are given in Tables 3 and 4, respectively.

Discussion and conclusion

Readmission due to dehydration after ileostomy creation remains a leading complication after colorectal surgery. Bliss et al. recently reported that the median cost of readmission for electrolyte disorders and fluid imbalance after colectomy was $4261 [2]; such unplanned costs have come under increasing scrutiny in the contemporary era of quality care metrics and bundled reimbursements. There is a growing consensus that these readmissions are not only costly but are also avoidable [7], and that improved inpatient coaching and outpatient follow-up care may reduce their incidence [10, 11]. Despite the increased attention paid to this subset of readmissions, however, the underlying pathogenesis of high ileostomy output and resultant dehydration remains unclear.

This study finds that ACEi or ARB use is significantly associated with increased risk of dehydration requiring readmission following creation of a diverting loop ileostomy. The findings presented here are novel and suggest that resumption of ACEi or ARB therapy in the peri-operative period may place such patients at increased risk of dehydration. Thus, the decision to resume such medications in the postoperative setting should not be taken lightly.

These results confirm much of the recent work regarding risk of readmission following ileostomy creation. The 60-day readmission rate of the present series (36%) is similar to that reported by Nagle et al. during an overlapping patient accrual period (35%) [10]; the rate of readmission for dehydration (14%) mirrors those reported by Nagle (15.5%) and Paquette et al. (17%) [9], as well. Taken together, these results suggest that dehydration remains a leading indication for readmission after ileostomy creation.

Post-operative care pathways appear to offer a preliminary solution to this problem. In an attempt to improve patients' ability to care for their ileostomy after discharge, Nagle et al. instituted an intensive post-ileostomy care pathway at their institution. Under the supervision of specially trained wound and ostomy care nurses, patients are encouraged to care for their new ostomies while still in the hospital, including emphasizing adequate hydration, recording oral intake and ostomy output, emptying and changing the ostomy appliance, and observing the appearance of the ostomy and surrounding skin. Importantly, the pathway recruits ancillary providers, including floor nurses and patient care technicians, to assist and educate patients in this process. Following implementation of this program, Nagle et al. reported that the rate of readmission for dehydration after ileostomy creation at their institution fell from 15.5 to 0% [10]. However, the findings presented here and elsewhere suggest that, despite increasing awareness of the risk of dehydration after ileostomy creation, and the growing acceptance of post-operative care pathways, high ostomy output leading to dehydration remains a common cause for readmission. Future efforts to reduce readmission and renal complication will likely need to address the causes of high ostomy output, in addition to volume replacement.

This study is the first of its kind to identify ACEi or ARB use as an independent risk factor for dehydration requiring readmission following ileostomy creation. Patients taking ACEi or ARB in the post-operative setting are significantly more likely to be readmitted for dehydration than patients not taking ACEi or ARB (64 vs. 13%, OR 13.56, $p < 0.0001$). ACEi or ARB use may reduce the bowel's absorptive capacity by disrupting the RAAS, thereby leading to increased ostomy output. Patient-focused efforts to increase intake in this setting may not adequately compensate for large volume losses. Accordingly, patients who have been prescribed these medications should be identified in the pre-operative setting, and the treating surgeon should discuss the risks and benefits of resuming them post-operatively with the patient's medical doctors. In the absence of a strong indication, it may be prudent to hold such medications with monitoring, or prescribe alternative anti-hypertensive agents, over the lifespan of a temporary ileostomy. It is conceivable that the use of classical diuretic agents, including loop and thiazide diuretics, may also contribute to dehydration after ileostomy creation; however, these medications do not have a well-defined effect on intestinal absorptive capacity.

Our multivariable analysis additionally identifies prior abdominal surgery as an independent risk factor for readmission due to dehydration ($p = 0.02$). This finding is unexpected and to the best of our knowledge has not been reported elsewhere in the literature. The mechanism for such an association is unclear; however, it is known that repeat abdominal surgery predisposes patients to post-operative ileus. We hypothesize that ileus transiently impairs the absorptive capacity of the small bowel, and that resolution of ileus may be associated with

increased ileostomy output, akin to the polyuric phase of renal recovery that follows acute kidney injury. Patients unable to match their oral intake with increased ileostomy output after ileus may thus be prone to readmission for dehydration.

The strengths of this study include its strict inclusion and exclusion criteria, which limit the heterogeneity of the study population; the use of a prospectively collected divisional outcome database; the relatively short accrual period; and the magnitude of the odds ratio. Potential limitations of the present series include the small sample size, which was restricted in part by low divisional case volume between 2010 and 2012, and the single-center nature of the study population. Additionally, this study's ability to distinguish ACEi or ARB prescription from actual medication use is limited, given its retrospective design; however, the design arguably measures the potential degree of harm in a real-world setting (as would an effectiveness trial), rather than in ideal conditions (i.e., an efficacy trial).

This study demonstrates that ACEi or ARB use increases the risk of dehydration requiring readmission after ileostomy creation. Patients who resume these medications after ileostomy creation are at significantly higher risk for readmission for dehydration than patients not taking either medication. A significant percentage of patients undergoing colorectal surgery are prescribed these medications for blood pressure control, and surgeons who create ileostomies should be aware of these risks. Future efforts to optimize ileostomy-specific care pathways should include careful examination of post-operative medication plans, ideally in consultation with both the surgical and medical teams.

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Table 1

Patient baseline characteristics. Overall cohort (n = 99)

Age (mean [SD])	**51.8(19.4)**
Female sex, no.	48
Diagnosis, no.	
IBD	27
Cancer	57
Prior operation, no.	45
Surgical approach, no.	
Laparoscopic	55
Open	43
ASA, no.	
I	1
II	43
III	51
IV	4
Comorbidities, no.	
Diabetes mellitus	11
CKD	4
Diuretic use, no.	
Loop	9
ACE/ARB	20

SD, standard deviation; *IBD*, inflammatory bowel disease; *ASA*, American Society of Anesthesiologists physical status grade; *CKD*, chronic kidney disease; *ACEi/ARB*, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker

Table 2

Indications for readmission

Cause	Number of patients readmitted (no., %)
Total readmissions	36 (100)
Dehydration	14 (38.9)
Infection	12(33.3)
Other	8 (22.2)
Bowel obstruction	2 (5.6)

Table 3

Univariable analysis of factors associated with risk of readmission, and of readmission for dehydration

Explanatory covariates	Overall cohort (*n* = 99)	No readmission for dehydration (*n* = 85)	Readmission for dehydration (*n* = 14)	*p* value	No readmission (*n* = 63)	Any readmission (*n* = 36)	*p* value
Age (mean, [SD])	51.8 (19.4)	50.9 (19.5)	57.3 (19.1)	0.3	52.1 (20.3)	51.3 (18.1)	0.4
Female sex (no., %)	47 (47.5%)	39 (46.3%)	8 (58.3%)	0.441	28 (44.4%)	19 (52.9%)	0.454
Diagnosis, no., %							
IBD	27 (27.3%)	24 (28.2%)	3 (21.4%)	0.596	17 (27.0%)	10 (27.8%)	0.932
Cancer	57 (57.7%)	50 (58.3%)	7 (53.9%)	0.761	40 (63.5%)	17 (47.1%)	0.118
Prior operation, no., %	45 (45.5%)	35 (41.2%)	10 (71.4%)	0.04*	23 (36.5%)	22 (61.1%)	0.02*
Surgical approach, no., %							
Laparoscopic	55 (55.6%)	48 (56.5%)	7 (50.0%)	0.618	36 (57.1%)	16 (45.7%)	0.398
Open	43 (43.4%)	36 (42.4%)	7 (50.0%)		27 (42.9%)	20 (54.3%)	
ASA, no., %							
I	1 (1.0%)	1 (1.2%)	0 (0.0%)	0.406	0 (0.0%)	1 (2.8%)	0.12
II	43 (43.4%)	39 (45.9%)	4 (28.6%)		31 (49.2%)	12 (33.3%)	
III	51 (51.5%)	41 (48.2%)	10 (71.4%)		31 (49.2%)	20 (55.6%)	
IV	4 (4.0%)	4 (4.7%)	0 (0.0%)		1 (1.6%)	3 (8.3%)	
Comorbidities, no., %							
Diabetes mellitus	11 (11.5%)	8 (9.6%)	3 (23.1%)	0.157	4 (6.6%)	7 (20.0%)	0.047*
CKD	4 (4.0%)	3 (3.5%)	1 (7.1%)	0.525	1 (1.6%)	3 (8.3%)	0.101
Diuretic use, no., %							
Loop	9 (9.1%)	7 (8.2%)	2 (14.3%)	0.466	3 (4.8%)	6 (16.7%)	0.047*
ACE/ARB	20 (20.2%)	11 (12.9%)	9 (64.3%)	<0.001*	9 (14.3%)	11 (30.6%)	0.052

*Values significant at $p < 0.05$

SD, standard deviation; *IBD*, inflammatory bowel disease; *ASA*, American Society of Anesthesiologists physical status grade; *CKD*, chronic kidney disease; *ACEi/ARB*, angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Table 4

Independent risk factors for readmission due to (a) dehydration and (b) any cause

Risk factor	Odds ratio	95% conf. interval	*p* value
a			
Prior operation	4.26	1.05–17.28	0.04 *
ACEi/ARB	3.56	3.54–51.92	<0.0001 *
b			
Prior operation	3.00	1.20–7.47	0.02 *
Diabetes mellitus	2.89	0.66–12.72	0.2
Loop diuretic	3.68	0.80–16.97	0.1
ACEi/ARB	1.80	0.57–5.77	0.3

* Values significant at $p < 0.05$

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker