



Research Article

The Effects of Ondansetron on Prolonged Postoperative Ileus in Colorectal Surgery Patients

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Abstract

Background: The use of 5-HT₃ receptor antagonists such as ondansetron in the postoperative colorectal patient is ever increasing. Limited data exists on the effects of ondansetron use on Prolonged Postoperative Ileus (PPI), and to the best of the authors' knowledge no studies have investigated its effects in colorectal bowel resection with primary anastomosis. The authors' aim to evaluate whether ondansetron delays return to bowel function in this patient population.

Methods: Retrospective chart reviews were carried out on all patients who underwent colorectal resection with primary anastomosis between 1 January 2017 and 30 April 2018. Markers for return to bowel function included time to passage of flatus, and bowels opening. Variables included ondansetron use, total dose, and use in conjunction with metoclopramide.

Results: In the 103 patients assessed, mean days to BO for ondansetron use and no ondansetron use was 4 and 4, respectively. Mean days to PF was 3 and 2, respectively. No significant difference existed in return to bowel function in patients who used ondansetron. Total dose of ondansetron had no significant effect on return of bowel function.

Discussion: In the moderate sample size studied, and in keeping with other antiemetics previously studied in the literature, ondansetron did not show any significant effect on the return to bowel function after colorectal resection surgery with primary anastomosis. Limitations included the retrospective nature of the study, and a standardised postoperative medication and recovery regimen may be of use in future prospective studies to eliminate further confounding factors.

Introduction

Antiemetics are widely used in the postoperative colorectal surgery patient, both in the treatment of Postoperative Nausea And Vomiting (PONV) and in the ongoing symptomatic relief of nausea that can be experienced after bowel resection in colorectal surgery. There is little in the literature investigating the effects of the newer 5-HT₃ receptor antagonists and their effect on the recovery of colorectal patients post bowel resection surgeries, in particular if they play a role in Prolonged Postoperative Ileus (PPI) and delaying

the return to normal bowel function. Various medications have been studied for their effects on PPI, including metoclopramide [1-3], Gastrografin® [4], erythromycin [3,5], neostigmine, enteral naloxone, tegaserod, and alvimopan [2]. Davison et al. found that metoclopramide had no statistically significant effect on reducing PPI [1]. Biondo et al. assessed the role of Gastrografin® in the recovery of PPI in elective colorectal surgery patients and found no statistically significant effect [4]. Smith et al found no effect of erythromycin on postoperative ileus in colorectal patients [5]. Maehara et al. postulated that 5-HT₃ receptor antagonists should

be therapeutically useful agents against PPI after mouse models with intestinal manipulation induced PPI showed restoration of gastrointestinal transit after administration of a 5-HT₃ receptor antagonist [6]. Other smaller scale studies have assessed the effects of 5-HT₃ receptor antagonists on bowel that had not undergone surgical manipulation and have found no effect [7], increased mean whole-gut transit time in a 10 patient comparative group [8], and increased left colonic transit time [9]. To the best of the authors' knowledge, there have been no studies to date assessing the effect of the 5-HT₃ receptor antagonist ondansetron on PPI. With the growing preference to prescribe the newer 5-HT₃ receptor antagonist agents such as ondansetron during the postoperative recovery period in colorectal patients, the authors felt it was important to investigate the effects of ondansetron on PPI.

Methods

Retrospective chart reviews were carried out on all

colorectal patients who underwent bowel resection surgery with primary anastomosis during the period of 1 January 2017 to 30 April 2018. Data was collected on age, gender, ASA classification, operation, days to Passage of Flatus (PF), days to Bowels Opening (BO), dosage of ondansetron given on each postoperative day, and other antiemetics administered. Markers used to assess for return to bowel function included time (days) to PF and BO. Variables assessed were presence of ondansetron use, dose of ondansetron, and the use of ondansetron in conjunction with metoclopramide.

Results

Demographics

Retrospective review yielded 103 patients. 48.5% (n=50) were male, and 51.5% (n=53) female, with an average age of 42.2 years (range 19-92 years). A breakdown of patient demographics can be seen in Table 1.

Total Patients	Male			Female		
103	50			53		
	Age					
	<50 years	51-60 years	61-70 years	71-80 years	81-90 years	>91 years
	17	20	24	27	14	1
	ASA Classification					
	ASA 1	ASA 2		ASA 3	ASA 4	
	2	58 including ASA 2E (4)		41 including ASA 3E (3)	2 including ASA 4E (1)	

Table 1: Patient demographics.

The most common colorectal bowel resection with primary anastomosis procedure was the laparoscopic right hemicolectomy (33%, n=34), followed by laparoscopic high anterior resection (27%, n=28). Table 2 depicts the type of resection and laparoscopic or open nature of the surgical procedure that made up the patient population.

Resections	
Laparoscopic Right Hemicolectomy	34
Laparoscopic Extended Right Hemicolectomy	7
Laparoscopic Left Hemicolectomy	2
Laparoscopic Anterior Resection	4
Laparoscopic High Anterior Resection	28
Laparoscopic Low Anterior Resection	7
Open Right Hemicolectomy	6
Open Left Hemicolectomy	1
Open Anterior Resection	5
Open High Anterior Resection	2
Subtotal Colectomy	6
Total Colectomy	1

Table 2: Breakdown of bowel resection surgeries that constituted the study population.

Data Analysis

Analysis of data was performed through survival methods. Days to BO and days to PF were used as indicators for bowel function. As there were no censored observations recorded in this data the survival times (days to return of bowel function) are completely observed. First, Kaplan-Meier plots (Figure 1a,b) are used to estimate the distribution of time (days) to return of bowel function for patients who used and those who did not use ondansetron after surgery. From the figure it appears that the distribution of times to return of bowel function (BO, PF) are statistically equivalent for using and not using ondansetron. Comparatively, these results did not change noticeably when ondansetron was used in conjunction with metoclopramide (Figure c).

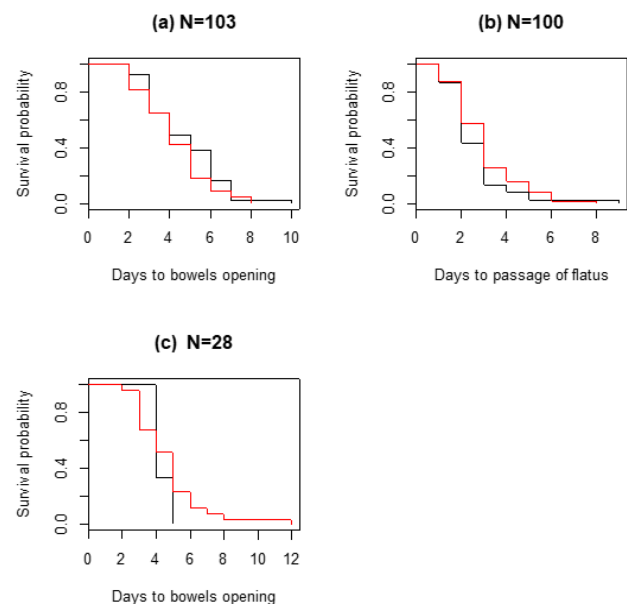


Figure 1: Kaplan-Meier (KM) curves for time (days) to BO and PF stratified by using and not using ondansetron. N denotes number of patients. Black line: not using ondansetron, red line: using ondansetron. In (a) and (b) ondansetron is used independently while in (c) ondansetron is used in the presence of metoclopramide. Survival times are completely observed.

Table 3 shows the median number of days to return of bowel function (BO, PF) following colorectal resection surgery with primary anastomosis. Also presented in Table 3, the log-rank test was applied to verify the graphical results in Figure 1. Results of the p-values of this test depicts that no significant difference exists when comparing the duration to return of bowel function across patients who used ondansetron and those who did not use ondansetron. Furthermore, the authors investigated the total dose

(mg) of ondansetron and its effect on the duration to return of bowel function using a Weibull accelerated failure time model. In this model the total dose is specified as a continuous covariate and its effect is examined using a measure termed the Event Time Ratio (ETR), also known as acceleration factor [10]. From the results in Table 3 it is apparent that total dose of ondansetron has no significant effect on bowel function after colorectal resection with primary anastomosis.

Days to bowels opening			
	Median (days)	ETR	p-value
Not using Ondansetron (N=37)	4		0.20 ^a
Using Ondansetron (N=66)	4		
Total dose		1.00	0.52 ^b
Days to passage of flatus			
Not using Ondansetron (N=37)	2		0.20 ^a
Using Ondansetron (N=63)	3		
Total dose		1.01	0.29 ^b
Days to bowels opening (Ondansetron in the presence of metoclopramide)			
Not using Ondansetron (N=3)	4		0.6 ^a
Using Ondansetron (N=25)	5		
Total dose		1.00	0.43 ^b

^aP-value for log-rank test, ^bp-value for ETR from the accelerated failure time model, ETR > 1.0 indicates that total dose increases time (days) to bowel opening/ passage of flatus, ETR < 1.0 indicates that total dose decreases time to bowel opening/passage of flatus, ETR=1.0 indicates that total dose has no effect on bowel opening/passage of flatus. P-value < 0.05 is statistically significant.

Table 3: Effects of no ondansetron use, ondansetron use, and total dose of ondansetron used on return to bowel function after colorectal resection with primary anastomosis.

Complications

Complications in the study series are outlined in Table 4. Patients with complications were not excluded from our case series, as there did not appear to be a direct relationship between the severity of complication and return to bowel function. The average days to BO in this group was 4.5, and average days to PF was

Complication	Resection	Management	Age	ASA	Days to BO	Days to PF
Bowel ischaemia (Rectum/Anus)	Laparoscopic High Anterior Resection	Operative; Defunctioning	82	2	2	2
Anastomotic leak	Laparoscopic Extended Right Hemicolectomy	Non-operative; Antibiotics	79	3	7	6
Urinary Tract Infection	Laparoscopic Right Hemicolectomy	Non-operative; Antibiotics	92	3	7	3
Aspiration Pneumonia	Subtotal Colectomy	Non-operative; ICU, antibiotics	56	1	7	3
	Laparoscopic High Anterior Resection	Non-operative; Antibiotics	53	2	4	1
Renal Failure	Open right hemicolectomy	Non-operative	90	4E	7	3

Table 4: Summary of patient complications in the study population.

Discussion

In line with other antiemetics previously studied in the literature, the authors found there to be no statistically significant effect of ondansetron on return to bowel function after colorectal bowel resection surgery with primary anastomosis. With the literature lacking in the assessment of the effects of ondansetron on PPI, the authors felt it was important to carry out this study with the ever increasing use of ondansetron in the postoperative period. Limitations included the moderate population study size and the retrospective nature of the study. While the presence of other antiemetics was controlled for, other variables in the postoperative colorectal patient are many. The authors' institution does not follow a standardised analgesia regimen for postoperative colorectal patients, and a prospective study may allow standardisation of opioid intake and exclusion of patients with higher opioid requirements, therefore facilitating elimination of this as a possible confounder. Similarly, the authors' institution did not have a formalised enhanced recovery after surgery protocol that all patients were enrolled in during the study period, which would also aid in identifying and eliminating confounding patients from the study population that may have had a slower recovery and would be beneficial in future prospective studies.

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