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Does alvimopan enhance return of bowel function in laparoscopic gastrointestinal surgery? A meta-analysis

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Abstract

Background Postoperative ileus (POI) remains a major impediment in patient recovery and leads to longer lengths of stay at the hospital, readmission rates, and hospital costs. Alvimopan, a mu-opioid receptor antagonist, lowers POI incidence following open gastrointestinal surgery, however, little is known about its role on POI prevention among patients undergoing laparoscopic gastrointestinal surgery.

Methods A comprehensive search of PubMed/MEDLINE, Scopus, CINAHL, and Cochrane databases was performed (December 2014). Meta-analysis was performed using the Mantel-Haenszel (fixed effects) model with odds ratio (OR) to assess prevention of POI and hospital readmission.

Results Five studies were included in the final analysis. Pooling 4 of 5 studies, there was over a 75% relative risk reduction in POI development when patients were given alvimopan compared to placebo (OR 0.24, 95%CI 0.12-0.51, P=0.02). The number needed to treat with alvimopan to prevent one POI episode was 11 patients. There was a modest reduction in the length of hospitalization between 0.2 and 1.6 days. There did not appear to be a difference in frequency of 30-day readmission rate among the alvimopan group compared to placebo (OR 1.15, 95%CI 0.54-2.45, P=0.62).

Conclusion Overall, there was a 75% relative risk reduction in POI development among patients undergoing laparoscopic gastrointestinal surgery. However, there did not appear to be a significant reduction in all-cause 30-day readmission rate or length of hospitalization. Future studies will need to address which subset of patients undergoing laparoscopic gastrointestinal surgery will benefit most from alvimopan.

Keywords Alvimopan, laparoscopic gastrointestinal surgery, postoperative ileus

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Introduction

Postoperative ileus (POI), defined as the transient cessation of coordinated bowel motility after surgical intervention, is a common complication following gastrointestinal surgery [1]. Incidence following open versus laparoscopic colectomy has been reported to be 31% and 21%, respectively [2]. POI remains a major impediment in patient recovery and leads to longer lengths of stay, readmission rates, and hospital costs [3,4].

The etiology of POI is thought to be multifactorial involving sympathetic neural reflexes, local and systemic inflammatory mediators and changes in many neural and hormonal influences [5]. Surgical factors such as longer operations, increased blood loss, increased bowel manipulation and open surgeries also contribute to higher incidences of POI [6,7]. Laparoscopic surgery is thought to lead to lower incidences of POI due to decreased bowel manipulation, blood loss, and less sympathetic activation. However, while studies have shown that laparoscopic surgery leads to shorter durations of POI of approximately 1 day, POI is still present regardless of the surgical approach [8,9].

Another contributing factor to POI is the use of opiates postoperatively for pain control. Opiates exert an analgesic effect by acting as opiate receptor agonists within the central nervous system. However, opiates also affect peripheral nerve terminals such as those in the enteric nervous system in the

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Conflict of Interest: None

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gastrointestinal tract. This leads to gut dysmotility, decreased fluid secretion and sphincter dysfunction, which presents as constipation, hard stools, and incomplete evacuation [10]. Alvimopan is an orally administered mu-opioid receptor antagonist that does not cross the blood-brain barrier at clinically relevant doses. It therefore can negate the effect of opiates on the bowel while not affecting the analgesic properties [11].

Multiple randomized controlled studies, meta-analyses and a Cochrane review have been performed showing the beneficial effect of alvimopan in lowering the incidence and duration of POI following open gastrointestinal surgery [12-19]. Following these results, alvimopan was approved by the Food and Drug Administration in 2008 for prevention of POI following major open abdominal surgery in the United States.

While the efficacy of alvimopan in reducing POI in open gastrointestinal surgery has been proven; no systematic review or meta-analysis to date has reported the effect of alvimopan exclusively in laparoscopic gastrointestinal surgery. This meta-analysis studies whether the opioid receptor antagonist, alvimopan, is effective in reducing POI and readmission rates in patients undergoing laparoscopic gastrointestinal surgery.

Materials and methods

Literature search

A comprehensive literature search was performed from multiple databases in the English language. First, multiple databases, including MEDLINE/PubMed, Cochrane databases, CINAHL, Scopus, and Google Scholar were searched in December, 2014. Search terms included "Alvimopan and abdominal surgery," "Alvimopan and laparoscopic surgery," and "Alvimopan and postoperative ileus". If data was incomplete, missing, or required clarification, authors were contacted.

Data extraction

All studies on adult patients that compared the use of alvimopan to placebo with respect to prevention of POI among patients who underwent laparoscopic colorectal surgeries were included. Two reviewers (SM & DLN) independently assessed the trials and extracted the appropriate data included in the analysis. Any disagreements were evaluated and settled by consensus or a third party (MLB).

Study quality assessment

The quality of studies was assessed using the Effective Public Health Practice Project model [20]. This scale assesses study quality as strong, moderate, or weak based upon criteria ratings for selection bias, study design, confounders, blinding, data collection methods, withdrawal and dropout descriptions, intervention integrity, and analysis. The quality of the study is based upon how many weak ratings per category (≥2 weak ratings = weak, one weak rating = moderate, and no weak ratings = strong).

Statistical analysis

Meta-analysis for the effects of alvimopan compared to placebo with respect to prevention of POI was performed. The results were reported using odds ratio (OR) with Mantel-Haenszel fixed effects model. Heterogeneity was analyzed by calculating the I^2 measure of inconsistency and was considered significant if $P<0.10$ or $I^2 >50\%$. If heterogeneity was statistically significant, a sensitivity analysis was utilized to examine for heterogeneity when certain studies were excluded from the analysis. Statistical analysis was performed using RevMan 5.1 (Review Manager, Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Publication bias was assessed by funnel plots. Significance was set at $P<0.05$.

Results

Study selection

The initial literature search identified a total of 38 articles and abstracts (Fig. 1). Of the 38 citations found, we excluded 30 duplicate articles, reviews, or assessments that did not exclusively look at laparoscopic surgical technique outcomes with alvimopan use. Among the 8 remaining articles identified, three studies by Wang *et al* [8], Absher *et al* [21], and Delaney *et al* [22] were excluded because their primary endpoints did not include the incidence of POI or 30-day readmission. A total of five studies [23-27] ultimately met our inclusion criteria and were included in the meta-analysis, which compared the effectiveness of alvimopan versus placebo in reducing POI and readmission rates in patients undergoing laparoscopic gastrointestinal surgery.

Study details

The details of the five included studies are summarized in Table 1 [23-27]. The total number of patients across the five studies was 626. In all studies, alvimopan was administered at a standard dose of 12 mg orally preoperatively and 12 mg b.i.d. postoperatively for maximum of 15 doses [22]. All studies but Abodeely *et al* [23-27] mentioned the use of standard perioperative recovery pathways and had similar discharge criteria.

Four of five studies included the incidence of POI as a primary endpoint [23-26]. All 4 studies had similar definitions of POI. Insertion of a nasogastric tube was a primary component of the definition of POI in 3 of 4 studies (Abodeely *et al*, Barletta

Table 1 Summary of studies included in the meta-analysis

Author	Study type	Dates of surgery	Location	No. of patients	Types of surgery	Alvimopan dosing	Mean length of hospitalization	Definition of POI	Overall quality paper
Abodeely *et al* 2011	Prospective	10/2008 – 12/2009	RI, USA	33	Laparoscopic right colectomy with primary anastomosis	12 mg preoperatively; 12 mg twice daily postoperatively until POD 7 or first bowel movement	Alvimopan: 4.63 days Placebo: 5.88 days	Insertion of NGT	Strong
Barletta *et al* 2011	Retrospective	11 month period, unspecified year	AZ, USA	133	Laparoscopic segmental colectomy with primary anastomosis	12 mg preoperatively and 12 mg b.i.d. post-operatively for up to 15 in-hospital doses	Alvimopan: 3.9 days Placebo: 3.7 days	3 episodes of vomiting over 24 h, cessation of oral diet, need for NGT within 5 days of surgery	Moderate
Itawa *et al* 2011	Retrospective	01/2007 – 01/2010	MD, USA	165	Laparoscopic segmental colectomy with primary anastomosis	12 mg preoperatively and 12 mg b.i.d. postoperatively for up to 15 in-hospital doses	Alvimopan: 2.81 days Placebo: 4.36 days	Delay of return of bowel function for 36-48 h postoperatively that could not be attributed to organic cause, usually accompanied by abdominal distention and nausea	Moderate
Obokhare *et al* 2011	Retrospective	02/1009 – 11/2009	Ohio, USA	200	Laparoscopic segmental colectomy with primary anastomosis	12 mg preoperatively and 12 mg b.i.d. post-operatively until return of bowel function, discharge from hospital or maximum of 7 days	Alvimopan: 3.63 days Placebo: 3.78 days	Lack of gastrointestinal function with 3 days post operatively, insertion of NGT secondary to abdominal distention, nausea, vomiting	Moderate
Whelpley *et al* 2011	Prospective	01/2008 – 10/2009	VA, USA	95	Laparoscopic partial small or large bowel resection with primary anastomosis	12 mg preoperatively and 12 mg b.i.d. post-operatively until discharge from hospital or maximum of 7 days	Alvimopan: 3.2 days Placebo: 4.3 days	Not evaluated	Strong

POD, post-operative day, POI, post-operative ileus; NGT, nasogastric tube

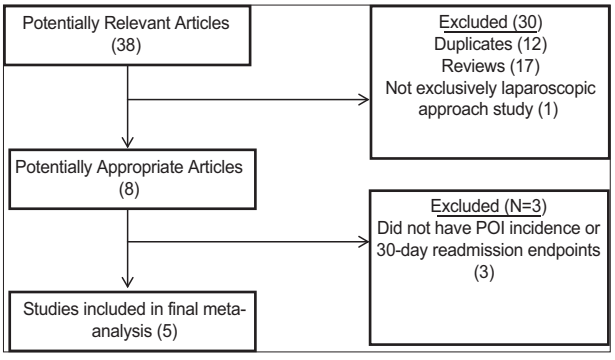

Figure 1 Algorithm demonstrating the article search
POI, post-operative ileus

et al, and Obokhare *et al*) [23,24,26]. Itawa *et al* [25] definition of POI was the least explicit and was defined as delay of return of bowel function for 36-48 h postoperatively that could not be attributed to organic cause, usually accompanied by abdominal distention and nausea.

Using the Effective Public Health Practice Project model [20] the studies were given an overall rating (Table 1). All five studies were unblinded prospective or retrospective control trials. The studies by Abodeely *et al* [23] and Whelpley *et al* [27] were given a rating of strong, given their prospective design, and the remaining 3 retrospective studies [24-26] were given a rating of moderate.

Prevention of POI

Four of five studies reported rates of POI among patients who underwent laparoscopic colorectal surgery who received alvimopan compared to placebo or no therapy [23-26] (Fig. 2). Pooling these 4 studies totaling 531 patients, the rate of POI among patients in the alvimopan group was 3.07% compared to 12.18% in the placebo group. Overall, there was nearly a 75% relative risk reduction in the development of POI when patients were given alvimopan compared to placebo (OR 0.24, 95%CI 0.12-0.51, P=0.02). The number needed to treat with alvimopan to prevent one POI episode

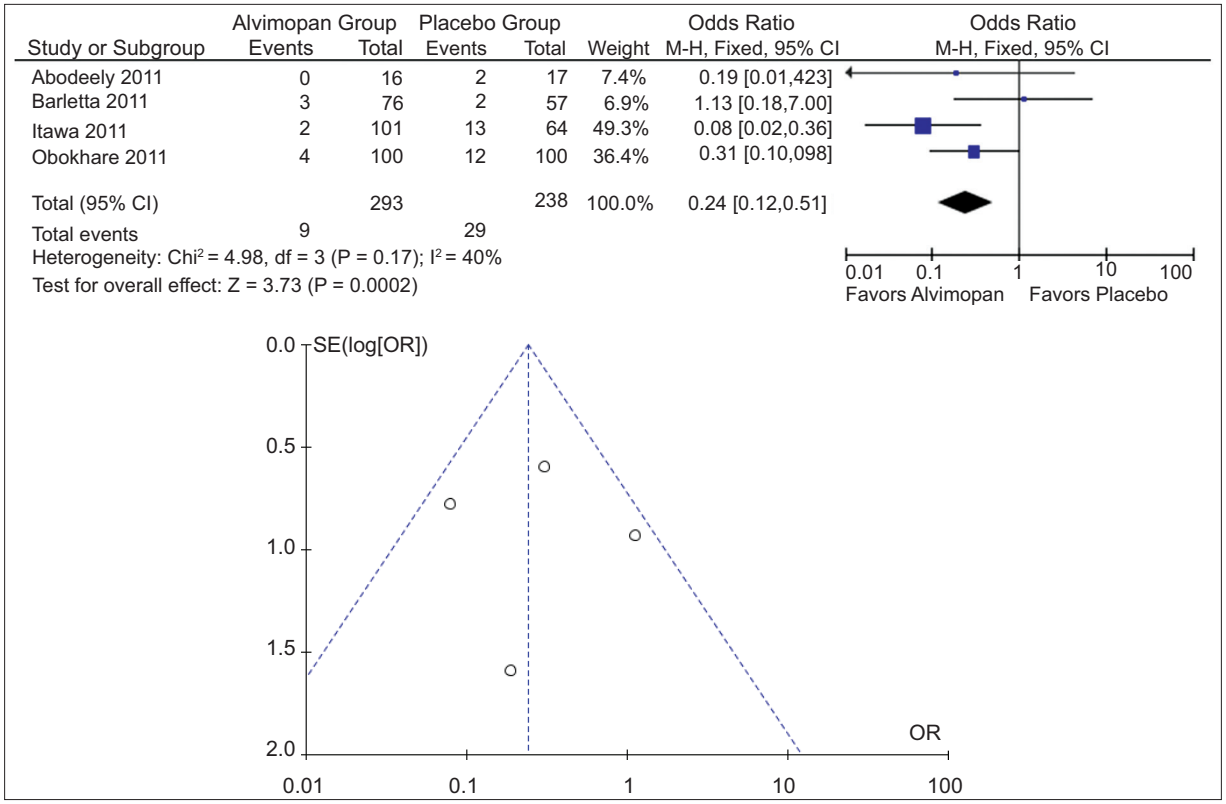

Figure 2 Forest plot of alvimopan compared to placebo for the prevention of post-operative ileus

was 11 patients. There was no statistically significant heterogeneity (I^2<50%).

Length of hospitalization

All 5 included studies evaluated the length of hospitalizations among patients who received alvimopan compared to placebo or no therapy. Four of 5 studies [23,25-27], except the one by Barletta *et al*, demonstrated a reduction in length of hospitalization between 0.2 and 1.6 days among patients on alvimopan compared to placebo. Despite multiple attempts to pool the studies together to truly define the trend for length of hospitalization, there remains a statistically significant heterogeneity (I^2>80%).

30-day hospital readmission rate

Four of 5 studies evaluated the frequency of all-cause hospital readmission within the first 30 days from hospital discharge (Fig. 3) [23,25-27]. There did not appear to be a difference in the frequency of readmission within 30 days of hospital discharge among the alvimopan group compared to placebo (OR 1.15, 95%CI 0.54-2.45). There was no statistically significant heterogeneity (I^2<50%).

Discussion

Up to 20% of patients undergoing laparoscopic gastrointestinal surgery will develop POI, which leads to increased morbidity, longer lengths of hospital stay, readmission rates, and overall cost of care [2-4]. Recent data have even reported an increase in length of hospital stay of up to 5 days with an added cost of more than $8000 when POI occurs [2]. Many strategies have been introduced to reduce the incidence of this postoperative complication such as the peripherally acting opioid receptor antagonist alvimopan. Though the role of alvimopan in prevention of POI among patients undergoing open abdominal surgery with an overall reduction length of stay. In a recent meta-analysis, Vaughan-Shaw et al demonstrated that there was nearly a 1.5-fold reduction in length of hospitalization among patients undergoing open abdominal surgery [19]. Unfortunately, the role of alvimopan in POI prevention and effect on length of hospitalization in laparascopic colorectal surgery remains largely undefined.

In this meta-analysis, pooling a total of 531 patients undergoing laparoscopic gastrointestinal surgery, we are the first to demonstrate that patients who were given alvimopan at the standard dose have a 75% relative risk reduction in the development of POI compared to those given placebo. Overall, the number needed to treat to prevent a single episode of POI among patients undergoing laparoscopic surgery was eleven

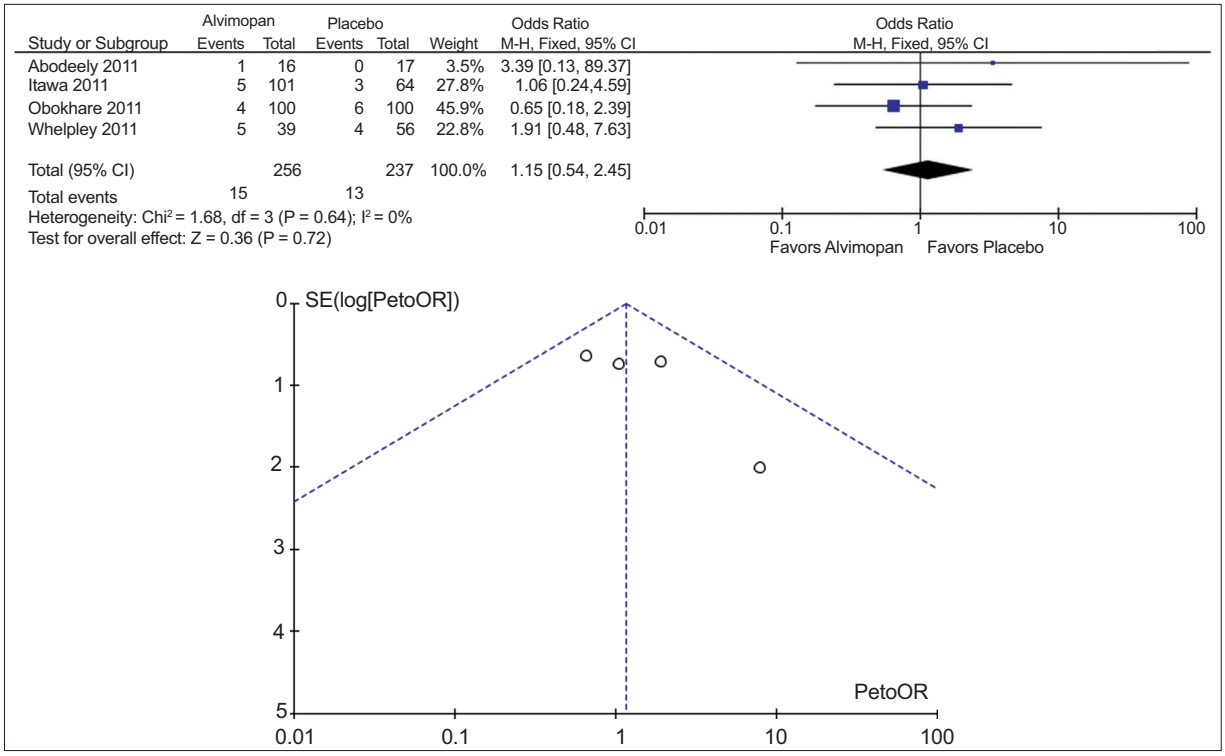

Figure 3 Forest plot evaluating the effect of alvimopan on 30-day readmission

Summary Box

What is already known:

- Postoperative ileus (POI) remains a major impediment in patient recovery and leads to longer lengths of stay at the hospital, readmission rates, and hospital costs
- Alvimopan, a mu-opioid receptor antagonist, lowers POI incidence following open gastrointestinal surgery

What the new findings are:

- There was an over 75% relative risk reduction in POI when patients were given alvimopan compared to patients not receiving alvimopan (OR 0.24, 95%CI 0.12-0.51, P=0.02)
- The number needed to treat with alvimopan to prevent one POI episode was 11 patients
- There was a modest reduction in the length of hospitalization in the alvimopan group, but there was no difference in the frequency of the 30-day readmission rate

patients. Furthermore, across the indexed studies, we found a reduction in length of stay between 0.2 to 1.6 days. Though the length of stay does not appear to be significant, previous studies do suggest that even a small reduction in length of stay can result in a tremendous impact on overall burden of the healthcare system, reduction in cost of care, and improvement of patient's overall quality of life [2,24].

Prior studies have shown that POI accounts for more than one-third of readmissions [2,28] and therefore, a lower incidence of POI should theoretically lead to lower rates of 30 day readmission. Interestingly, while the incidence of POI was decreased in our study, the 30-day all-cause readmission rates did not change in frequency in the patients given alvimopan as compared to those who received placebo or no therapy. Our contradictory finding is likely attributed to the fact that the studies included in this meta-analysis did not fully document the primary reason for hospital readmission, which are likely readmissions for postoperative complications other than POI (ie, venous thromboembolism, pneumonia, wound infection etc).

There are several limitations to our meta-analysis. First, the definition of POI is not uniform across the indexed studies and the diagnosis was largely based on clinical parameters. Second, while all studies included the endpoint of length of hospital stay, the data could not be pooled from the studies because of significant statistical heterogeneity. Therefore, the influence of alvimopan on length of stay among patients undergoing laparoscopic colorectal surgery remains debated. Future studies will need to define if the introduction of alvimopan is truly cost-savings with regards to marginal reduction in length of stay of 5-38 h. Third, the studies included in this meta-analysis do not address which subset of patients undergoing laparascopic surgery may benefit most from alvimopan

therapy (i.e., patients on chronic narcotics therapy and elderly) as it may not be cost-effective to introduce alvimopan in all subset of patients.

In conclusion, alvimopan appears to be effective in reducing POI in patients undergoing laparoscopic gastrointestinal surgery, with a relative risk reduction of over 75%. Additionally, prior studies have shown that alvimopan is well tolerated and is not associated with any adverse events or serious side effects [15-17]. Therefore, the standard dose of alvimopan should be considered in patients undergoing laparoscopic gastrointestinal surgery, particularly in patients at high risk for POI, including male gender, preoperative use of narcotics, older age, elevated body mass index, low preoperative albumin, history of respiratory comorbidity and peripheral vascular disease, and operation lasting ≥3 h [29,30]. Future studies will need to address the cost-effectiveness of empiric introduction of alvimopan among all patients undergoing laparoscopic gastrointestinal surgery versus selective administration only to high-risk patients with regards to POI prevention, length of hospitalization, hospital readmission, and quality of life.

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