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Alvimopan combined with enhanced recovery strategy for managing postoperative ileus after open abdominal surgery: a systematic review and meta-analysis

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ABSTRACT

Background: To assess the efficacy and safety of alvimopan in conjunction with enhanced recovery strategy, compared with this strategy alone, in management of postoperative ileus in patients undergoing open abdominal surgery.

Methods: Electronic databases were comprehensively searched for relevant randomized controlled trials. We were interested in doses of 6 and 12 mg. The efficacy end points included the time to recovery of full gastrointestinal (GI) function (a composite end point measured by the time to first toleration of solid food [SF] and the time to first passage of stool, GI-2), the recovery of upper (SF) or the lower (the time to first bowel movement, BM) GI function, and the length of hospital stay (the time to discharge order written). Safety end points included GI-related, non-GI–related, and serious adverse events. These parameters were all analyzed by RevMan 5.3 software.

Results: Nine randomized controlled trials involving 4075 patients were enrolled in this study. The pooled results showed that alvimopan significantly decreased the time to GI-2 recovery (6 mg, hazard ratio [HR] = 1.45, $P < 0.00001$; 12 mg, HR = 1.59, $P < 0.00001$), BM (6 mg, HR = 1.54, $P < 0.00001$; 12 mg, HR = 1.74, $P = 0.0002$), and the time to discharge order written (6 mg, HR = 1.37, $P < 0.00001$; 12 mg, HR = 1.34, $P < 0.00001$) compared with the placebo group. However, SF was significantly reduced in 6 mg group (HR = 1.23, $P = 0.008$) rather than 12 mg group (HR = 1.14, 95% confidence interval 1.00, 1.30, $P = 0.04$). The incidence of some GI-related and serious adverse events were significantly lower in the alvimopan group than the placebo group, and the dose of 12 mg was superior to 6 mg in this regard.

Conclusions: Alvimopan can accelerate recovery of GI function (especially for the lower GI tract), shorten the length of hospital stay, and reduce postoperative ileus-related morbidity without compromising opioid analgesia in an enhanced recovery setting.

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Introduction

Postoperative ileus (POI), a transient cessation of coordinated bowel motility, occurs to some extent after all major abdominal operations.[1] Generally, gastrointestinal (GI) motility should return to normal within 2 or 3 d after surgery, otherwise POI should be suspected.[2–6] Clinically, POI is characterized by nausea, vomiting, and bowel distension, accompanied by lacking of bowel sounds, bowel movements, and flatus.[7] Besides the abdominal discomfort, the POI also potentially increases postoperative pain, delays oral intake, leads to poor wound healing, and prolongs hospitalization, and thus significantly increase in health care costs.[5]

The causes of POI are multifactorial, which include surgical trauma, bowel manipulation, spinal–intestinal neural reflexes, sympathetic hyperactivity, secretion of inflammatory mediators, effects of endogenous opioids secreted within the GI tract, and exogenous opioids used for anesthesia and analgesia.[1,6,8,9] The treatment strategies for POI are equally varied. For nonpharmacologic treatment, epidural anesthesia, laparoscopic procedure, and sham feeding all have some effect on decreasing the duration of POI.[5,6,9–13] Regarding pharmacologic treatment, because of poor efficacy or serious potential adverse events (AEs),[10] there was no drug approved by the United States Food and Drug Administration (FDA) for POI until alvimopan was approved on May 20, 2008.[14]

Enhanced recovery after surgery (ERAS), also namely fast-track protocol, is a multimodal perioperative care pathway that uses various evidence-based interventions, such as providing dedicated preoperative counseling, adopting standard anesthetic protocol, restrictive perioperative fluid management, and early postoperative mobilization and feeding.[15] The ERAS programs attenuate the surgical stress response, decrease complications, maintain the postoperative physiological function, and accelerate recovery in patient undergoing major surgery, especially for open abdominal surgeries.[16] It has been proved that the ERAS could shorten the length of hospital stay and reduce health costs without affecting the patient safety.[17]

Alvimopan, an oral, highly selective and peripheral μ-opioid receptor antagonist, is absorbed poorly from the GI tract and does not readily cross the blood-brain barrier.[18] Therefore, alvimopan may relieve GI inhibition by competing with exogenous and endogenous opiates located in the GI tract without compromising postoperative analgesia. Although the results favored alvimopan across previous randomized controlled trials (RCTs)[19–27] and pooled studies,[28–30] the statistical significance, dose–response, and especially ileus-related morbidity were still somewhat inconsistent. Meanwhile, a previous study,[27] which was included by a meta-analysis[29] and a Cochrane review[30] published several years ago, reported the efficacy results using the risk ratio rather than the hazard ratio (HR), and the HR was generally used in other included studies. Another meta-analysis[28] published in 2012 just reported the efficacy of 12 mg alvimopan for patients undergoing bowel resection (BR) and only enrolled three RCTs.[20,21,25] Recently, some new RCTs[22,24] including different kinds of surgeries[19] have been completed, and one of them[19] explored the safety of alvimopan after increasing the dosage to 15 mg twice a day. Therefore, we aim to further assess the efficacy and safety of alvimopan combined with enhanced recovery strategy at doses of 6 and 12 mg compared with the strategy alone for the treatment of POI in patients after open abdominal surgery. Moreover, to decrease clinical heterogeneity, a subgroup analysis was also performed to investigate the efficacy of alvimopan for patients with different abdominal surgeries.

Methods

Eligibility and exclusion criteria

The following were eligibility criteria: (1) adult patients (age ≥18 y), who were generally healthy or had well-controlled systemic disease, scheduled to undergo open abdominal surgery and receive postoperative opioid-based pain management; (2) RCTs comparing 6 or 12 mg alvimopan doses with identical placebos; (3) reporting at least one end point that interested us; (4) mentioned at least one enhanced recovery strategy, such as removal of nasogastric tube (NGT) no later than noon on postoperative Day 1, liquid diet and ambulation on postoperative Day 1, and solid food by postoperative Day 2. The following were exclusion criteria: (1) any other condition known or suspected to be associated with an increased risk of postoperative morbidity, pregnancy, or patients who received a course of opioid analgesics more than 1 wk before surgery; (2) non-RCTs, open-label clinical trials, reviews, and trials published only as abstracts.

Searching strategy

The electronic database MEDLINE (1946–2015) and Embase (1974–2015) *via* Ovid, Cochrane Central Register of Controlled Trials (1948–2015), and China Biology Medicine disc (1978–2015) were independently searched by two authors (Liang-Liang Xu and Xiao-Qin Zhou). Before electronic searching, a sophisticated search strategy for each identified database was designed, complying with the advice given in Cochrane Handbook.[31] "abdom$ surgery," "paralysis," "ileus," "adynam$," "opioid receptor antagonist$," "avimopan," "entereg," and "ADL 8-2698" were used as key words; in addition, test words such as "colon surgery," "rectal surgery," and "postoperative ileus" were combined. Furthermore, the references of included trials and previous meta-analysis were scanned for more studies.

Study selection and data extraction

Two investigators (Xu and Zhou) independently assessed the titles and abstracts of the searched results. Full texts of potentially eligible studies were then screened to identify the final included studies. In the case of missing data, we contacted the original investigators to request relevant information. For each included study, we extracted the selection criteria, participant's characteristics, type and duration of surgery, outcome measures, AEs, and other data.