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Review

Effect of alvimopan on accelerates gastrointestinal recovery after radical cystectomy: A systematic review and meta-analysis

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HIGHLIGHTS

- Intestinal related complications are common in the patients undergoing radical cystectomy.
- Alvimopan significantly accelerates recovery of gastrointestinal function in patients performed radical cystectomy.
- Alvimopan reduces the length of stay after radical cystectomy.

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ABSTRACT

Purpose: The aim of the study was to evaluate the efficacy of alvimopan on accelerates gastrointestinal recovery after radical cystectomy.

Methods: We searched for all studies investigating alvimopan for bladder cancer patients undergoing radical cystectomy in Pubmed, Web of Knowledge, and the Cochrane Central Search Library. A systematic review and meta-analysis were performed. All studies that compared alvimopan with control group for patients undergoing radical cystectomy were included. Studies with overlapping or insufficient data were excluded. No language restrictions were made. Efficacy was assessed by the time to first toleration of clear liquids, first toleration of solid food, first bowel movement and length of stay.

Results: Our searches identified 5 studies, including 613 patients. A total of 294 (47%) patients took alvimopan. On meta-analysis, alvimopan reduced time to first toleration of clear liquids (HR 1.34, 95% CI 1.19 to 1.51, $p < 0.001$), first toleration of solid food (HR 1.22, 95% CI 1.11 to 1.34, $p < 0.001$), first bowel movement (HR 1.27, 95% CI 1.12 to 1.43, $p < 0.001$) and length of stay (HR 1.17, 95% CI 1.10 to 1.25, $p < 0.001$).

Conclusions: This meta-analysis has shown that alvimopan significantly accelerates recovery of gastrointestinal function and reduces the length of stay in patients performed radical cystectomy. More large scale, multicenter randomized controlled studies are needed before final clinical recommendations can be made.

1. Introduction

Radical cystectomy (RC) is a common treatment for muscle-invasive bladder cancer. In recent years, the perioperative morbidity and mortality have significantly reduced because a series of modifications in surgical technique and perioperative care have been made, but complication rates remain as high as 60% [1,2]. Intestinal related complications are common in the majority of patients undergoing RC and are associated with longer length of stay (LOS) [3]. In recent years, accelerated recovery programs have significant improved post cystectomy outcomes. “Fast track” regimens, which were proposed by Wilmore and Kehlet, aimed at reducing postoperative intestinal related complications [4]. The reduction of LOS after RC within an accelerated recovery programs is widely reported [5,6]. However, postoperative ileus (POI) remains a common complication prolonging LOS after RC [7]. POI refers to a temporary impairment in bowel function and characterized by obstipation, vomiting, bowel distension and intolerance of oral intake.

Alvimopan is a peripherally restricted μ-opioid receptor

Abbreviations: RC, radical cystectomy; LOS, length of stay; POI, postoperative ileus; RCT, randomized controlled trial; CCS, case–control study; GI, gastrointestinal; CI, confidence intervals.

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antagonist. There are several randomized control studies have shown that alvimopan accelerates bowel function recovery in patients undergoing abdominal surgery [8–10]. There are also several studies reports of its effectiveness in RC [11,12]. The objective of this meta-analysis is to evaluate the effectiveness of alvimopan in accelerates bowel function recovery and reduces LOS after radical cystectomy.

2. Methods

In accordance with the PRISMA guidelines [13], a systematic review of the literature was performed in February 2015 using Pubmed, Web of Knowledge, and the Cochrane Central Search Library. Search terms used included bladder cancer, bladder neoplasms, cystectomy, and alvimopan. All abstracts and review articles on this topic were reviewed; references of original studies were identified by manual search.

The following criteria were used for study selection: (1) Randomized controlled trial (RCT) or case–control study (CCS) were included, 2) patients diagnosed with bladder cancer and treated with RC, 3) Postoperative patients were divided into alvimopan group and control group (untreated or placebo). Studies with overlapping or insufficient data were excluded. No language restrictions were made.

The outcomes include recovery of gastrointestinal (GI) function and LOS. Recovery of GI function included a comprehensive assessment of upper GI and lower GI recovery. Upper GI recovery refers to ingested solid food without significant nausea or vomiting, lower GI recovery refers to first bowel movement [14]. Recovery of GI function was assessed by time to first toleration of clear liquids, first toleration of solid food and first bowel movement in our study. Time to first toleration of clear liquids or solid food was measured from the postoperative day (POD) 1 to the day ingested clear liquids or solid diet without significant nausea or vomiting. LOS was measured from the POD 1 to the day of hospital discharge order was written.

The quality of RCT study was assessed by Jadad scale [15]. The CCSs studies were assessed by the Newcastle-Ottawa Scale, scores 5 to 9 were considered high quality, and scores <5 were low quality [16]. The effect measures estimated were hazard ratio (HR) with 95% confidence intervals (CI). The temporal data was extracting from all the five studies for meta-analysis and the log HR and SE was calculated [17]. As patients in these studies have different risk profiles and inclusion criteria, HR were combined with the Mantel–Haenszel chisquared method using random effect models. HR > 1 represented a benefit in recovery of GI or a reduction in LOS favoring the alvimopan group, whereas HR < 1 represented benefit favoring the non-alvimopan group. All of these analyses were implemented in STATA 11.0 statistical software. (Stata Corp, College Station, TX, USA).

3. Results

3.1. Study characteristics

78 studies were identified from the database. We excluded 73 articles, resulting in 5 articles for analysis [11,12,18–20]. There studies included 1 RCTs, 4 CCSs that met our inclusion criteria. (Table 1) The characteristics of the included trials were described in Table 2.

3.2. Recovery of GI function

Three studies reported time to first toleration of clear liquids [11,18,19]. Two studies reported reduced time to clear liquids with alvimopan. One study reported there was no difference between the two groups in time to clear liquids. The pooled analysis showed a significantly shorter time to clear liquids in the alvimopan group compared with control group (Random-effect model; HR 1.34, 95% CI 1.19 to 1.51, $p < 0.001$). (Fig. 1) There was no statistical heterogeneity between the trials ($p = 0.41$; $I^2 = 0\%$).

Four studies reported time to first toleration of solid food [11,12,18,19]. All the four studies reported reduced time to first toleration of solid food with alvimopan. The pooled analysis showed a significantly quicker first toleration of solid food in the alvimopan group compared with control group (Random-effect model; HR 1.22, 95% CI 1.11 to 1.34, $p < 0.001$). (Fig. 2) There was no statistical heterogeneity between the trials ($p = 0.60$; $I^2 = 0\%$).

Three studies reported time to first bowel movement [12,18,19]. All the three studies reported reduced time to first bowel movement with alvimopan. The pooled analysis showed a significantly shorter time to first bowel movement in the alvimopan group compared with control group (Random-effect model; HR 1.27, 95% CI 1.12 to 1.43, $p < 0.001$). (Fig. 3) There was no statistical heterogeneity between the trials ($p = 0.43$; $I^2 = 0\%$).

3.3. Length of stay

Five studies reported LOS [11,12,18–20]. Four studies reported reduced LOS in alvimopan group. One study reported there was no difference between the two groups in LOS. The pooled analysis showed a significantly reduced LOS in the alvimopan group compared with control group (Random-effect model; HR 1.17, 95% CI 1.10 to 1.25, $p < 0.001$). (Fig. 4) There was no statistical heterogeneity between the trials ($p = 0.76$; $I^2 = 0\%$).

4. Discussion

POI is a common complication after radical cystectomy and associated with increased postoperative complications and LOS. Activation of opioid receptors could prolong POI [21]. alvimopan is selectively compete with peripheral opioid receptors in the GI. It does not cross the blood brain barrier, thus preventing antagonism of the central receptor [22,23]. Alvimopan has been proved accelerated GI recovery in patients performed laparotomy in many studies. In a randomized double-blind study, alvimopan showed accelerated GI function recovery in patients undergoing open laparotomy [24]. In another large scale randomized study, alvimopan showed accelerated GI tract recovery, and reduced POI in patients undergoing bowel surgery [25].

In all the five literature, alvimopan was well-tolerated and accelerated GI function recovery. The pooled analysis showed a significantly shorter time to clear liquids, solid food and first bowel movement in the alvimopan group compared with control group. A significantly reduced LOS was observed in the alvimopan group when compared with control group.

POI is associated with increased costs. Three studies in our analysis compared the costs between the two groups. Manger et al. reported the costs of alvimopan administration were $32,443, the cost benefit of administration over control was $40,604 ($p < 0.001$), institution of routine perioperative alvimopan had reduced costs by $7062 per hospitalization (20% reduction) [11]. The costs were included direct variable, overhead, and fixed variable costs in their study. Vora et al. also reported average costs were significantly lower in the alvimopan group per hospitalization than the non-alvimopan groups ($825 vs $1515, respectively) [19]. In their study, the costs were included the net cost of alvimopan use and subsequent reduction in length of stay. In the randomized controlled study, the mean difference in POI related costs was significantly lower in alvimopan group than placebo ($p = 0.04$) [26].