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Original article

Effects of goal-directed fluid therapy on enhanced postoperative recovery: An interventional comparative observational study with a historical control group on oesophagectomy combined with ERAS program

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SUMMARY

Background and aims: The Enhanced Recovery after Surgery (ERAS) program has been proposed as a postoperative recovery-enhancing strategy. We frequently apply the Modified-ERAS program following oesophagectomy. This study aims to elucidate the impact of goal-directed fluid therapy (GDT) for the perioperative management of oesophageal cancer on the postoperative recovery of patients undergoing oesophagectomy.

Methods: This is an interventional before-after comparative observational study conducted at Kanagawa Cancer Centre, Japan. Patients who underwent elective oesophagectomy for oesophageal cancer were recruited. Group H (retrospectively collected) received intraoperative and postoperative management consisting of fluid administration without haemodynamic monitoring and the M-ERAS program, while Group S prospectively received management consisting of GDT and the M-ERAS program. The primary endpoint was the speed of gastrointestinal functional recovery, while secondary endpoints were the level of postoperative mobilisation, incidence of complications, postoperative length of hospital stay (LOS), and nutritional status after discharge.

Results: The proportion of patients who completely egested Gastrografin by postoperative day 4, the level of postoperative mobilisation, and achievement ratio for a 100-m walk on the first postoperative attempt were significantly higher in Group S than in Group H ($P = 0.034$, $P = 0.0197$, and $P < 0.0001$, respectively). No significant differences were observed in the postoperative LOS and incidence of complications within 30 days between the groups. The serum albumin levels at 6 months after discharge was higher in Group S than in Group H ($P = 0.0002$).

Conclusions: The GDT-ERAS program enhanced postoperative gastrointestinal recovery and mobilisation, as well as postoperative nutritional status and protein synthesis. The program did not affect either postoperative LOS or the incidence of complications.

Trial registration: UMIN registration number: UMIN000013705, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000015999.

1. Introduction

In Northern Europe, the Enhanced Recovery after Surgery (ERAS) program was proposed as a postoperative recovery-enhancing strategy [1,2]. In 2009, the modified ERAS (M-ERAS) program, which is an ERAS program modified for the Japanese

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healthcare system, was introduced to the Department of Gastrointestinal Surgery at Kanagawa Cancer Centre, and we have previously reported the safety and outcomes of the M-ERAS program [3–5]. Because of the highly invasive nature of oesophagectomy for oesophageal cancer, we apply the M-ERAS program following nearly all of the surgeries, in which enteral feeding and ambulation are started as early as postoperative day (POD) 1. However, in some cases, the ambulation program must be discontinued, typically because of regurgitation of enteral nutrition to the oesophagus caused by impaired intestinal peristalsis, abdominal distension, adverse reactions to analgesics, difficulty in standing due to orthostatic hypotension, and unsteady walking.

Fluid management based on the ERAS program is thought to provide favourable outcomes achieved by balanced fluid therapy, in which fluid administration is restricted both intra- and postoperatively to the degree that it does not cause dehydration [1,2]. It has been reported that hypovolaemia causes increases in morbidity, including circulatory failure, renal failure, tachycardia, bowel dysfunction, and anastomotic leakage, whereas fluid overload causes increase in morbidity like respiratory insufficiency, bowel dysfunction due to intestinal oedema, and anastomotic leakage [6]. Goal-directed therapy (GDT) is an approach to manage patients' haemodynamics by appropriately administering fluid, vasoactive agents, and inotropes according to the values of cardiac output and other haemodynamic indices. It has been shown in a meta-analysis that GDT accelerates postoperative recovery of gastrointestinal function [7]. In 2015, Feldheiser et al. issued a consensus statement on anaesthetic management combined with the ERAS program for patients undergoing gastrointestinal surgery and strongly recommended GDT for patients with high risks and/or with extensive intravascular fluid losses due to bleeding [8]. The present study aimed to elucidate the effects of intraoperative and postoperative GDT on recovery of gastrointestinal function and ambulation achievement after oesophagectomy in patients treated using the M-ERAS program. Furthermore, its long-term effects on nutritional status after hospital discharge were also analysed.

2. Materials and methods

The present study was approved by the Institutional Review Board of Kanagawa Cancer Centre (chaired by Shigeki Motomura, M.D.) (Study-63), registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN registration number: UMIN000013705), and conducted after disclosure of information. The subjects were patients who were scheduled to undergo elective oesophagectomies for oesophageal cancer via thoracotomy or laparotomy in combination with the M-ERAS program at our centre, all of whom gave the written consent. The inclusion criteria were patients aged 20 years or older who were classified as class I or II by the American Society of Anesthesiologists Physical Status (ASA-PS) scale. The exclusion criteria were as follows: patients with a history of ischaemic heart disease or cerebrovascular disorder, impaired coagulability, renal dysfunction (estimated creatinine clearance $\leq$20 mL/min or on-going haemodialysis), severe anaemia requiring blood transfusion before surgery, and/or difficulty in walking before surgery. The reason for excluding these patients was because we actively wanted to try and test GDT with Hydroxyethyl starch (Voluven, Fresenius-kabi Japan, Tokyo, Japan). They are not excluded from M-ERAS protocol in our routine practice. The control group consisted of historical data for patients who had undergone oesophagectomies and had been managed with the M-ERAS program between June 30, 2012, and June 29, 2013 (Group H). All patients who met the inclusion criteria and did not meet the exclusion criteria were consecutively enrolled. We installed a new haemodynamic monitor in July of 2013, but for the next 10 months until April 2014, the use of the monitor and the fluid therapy management procedure were left to the discretion of individual physicians. From May 1, 2014 to April 30, 2015 the patients of the study group (Group S) were prospectively and consecutively enrolled and underwent oesophagectomy in combination with the GDT-M-ERAS program (standardised program), which was an M-ERAS program combined with intraoperative and postoperative fluid management (GDT) using a haemodynamic monitor.

The present study was designed as an observational study comparing data with and without the intervention. The primary outcome was the recovery speed of gastrointestinal function. Because there was no preceding report describing the same assessment method as used in this study, we empirically determined the sample size to be the estimated number of patients available for enrolment within one year, considering the acceptable sample size for an exploratory study. The secondary outcomes were the success rate of the postoperative ambulation program, incidence of complications, length of postoperative hospital stay (LOS), total volume of intraoperative fluid administration, volume of postoperative fluid administration, and nutritional status after discharge.

2.1. M-ERAS program

The major components of the M-ERAS program are shown in Table 1. In 2014, GDT was instituted for intraoperative and postoperative fluid management. In the basic postoperative analgesic regimen epidural analgesia was used in most patients in both groups using the same protocol (0.2% ropivacaine 200 mL, physiological saline 80 mL, and fentanyl 1000 μg. A total of 300 mL of solution was administered at 4 mL/h). For additional analgesia in Group S regular administration of acetaminophen and as-needed basis administration of nonsteroidal antiinflammatory drugs (NSAIDs) have replaced the conventional regimen of regular administration of NSAIDs and as-needed basis intravenous injection of fentanyl 1A (Table 1). In both Group S and H, a silicone thoracic drainage catheter was placed on the posterior lung surface and removed when the amount of drained fluid decreased to $\leq$300 mL/day.

2.2. Primary outcome

The recovery rate of postoperative gastrointestinal function was assessed by daily changes in Gastrografin (GG) location on abdominal radiographs. An enterostomy was performed during surgery. On the day of surgery (POD 0), the patients were managed with positive-pressure ventilation under anaesthesia and sedation with dexmedetomidine and propofol in the intensive care unit (ICU). On POD 1, the analgesic and sedative medications were discontinued, and the patients were extubated after weaning from ventilation. A mixture of 10 mL distilled water and 10 mL GG was injected into the enteral fistula in a single shot. One hour later, after confirming that the GG in the small intestine was migrating by abdominal radiography, enteral feeding was started. Abdominal radiography was performed at 9:00 a.m. on POD 1, 2, and 4, with the patient in the supine position. The location of the migrating front of GG was classified into the following 7 levels: the small intestine, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, or complete elimination from the body (no residue in the intestine). In all patients, enteral feeding was started at an infusion rate of 20 mL/h. This rate was doubled each day until the targeted amount of energy intake was reached. When adverse reactions, such as diarrhoea or vomiting, were observed, we did not increase the feeding rate, nor did we use intestinal peristalsis-promoting agents or purgatives.

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