Editorial Commentary

Does perioperative administration of glutamine, fiber and oligosaccharide (GFO) improve perioperative immune conditions and reduce early postoperative surgical stress after esophagectomy?

Hirotoshi Kikuchi, Hiroya Takeuchi

Department of Surgery, Hamamatsu University School of Medicine, Hamamatsu, Japan

Correspondence to: Hiroya Takeuchi, MD, PhD. Department of Surgery, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan. Email: takeuchi@hama-med.ac.jp.

Provenance: This is an invited article commissioned by the Section Editor Shuangjiang Li (Department of Thoracic Surgery and West China Medical Center, West China Hospital, Sichuan University, Chengdu, China).

Comment on: Abe T, Hosoi T, Kawai R, *et al.* Perioperative enteral supplementation with glutamine, fiber, and oligosaccharide reduces early postoperative surgical stress following esophagectomy for esophageal cancer. Esophagus 2019;16:63-70.

Submitted May 08, 2019. Accepted for publication May 21, 2019.
doi: 10.21037/jtd.2019.05.62
View this article at: http://dx.doi.org/10.21037/jtd.2019.05.62

Esophagectomy with two- or three-field lymphadenectomy plays a major role in achieving locoregional control in the treatment strategies for resectable thoracic esophageal cancer. Recent advances in surgical technique with newly developed surgical instruments and perioperative management with a multidisciplinary approach have improved the short-term outcomes of esophagectomy for esophageal cancer (1,2). However, esophagectomy remains a highly invasive procedure that can lead to severe postoperative complications (3). Therefore, further development of both operative procedures and perioperative approaches is needed in the management of esophageal cancer to improve esophagectomy outcomes.

Perioperative nutritional therapy has been reported to reduce postoperative complications, accelerate recovery after surgery and preserve host defense mechanisms against microbes in patients undergoing gastroenterological surgery (4). A dietary supplementation product enriched with glutamine, dietary fiber and oligosaccharide (GFO) reportedly has potential to decrease the severity of intestinal mucosal injury in human and rat models (5,6). In GFO, glutamine, one of the major fuel sources for intraepithelial lymphocytes (IELs) and intestinal epithelial cells, is thought to enhance IEL function (5). Dietary fiber and oligosaccharide are prebiotics that enhance the growth and functions of gut flora, activate gut immunity and improve the restoration of bowel function, leading to the control of diarrhea and a decreased incidence of bacterial translocation (6,7). In Japan, a commercial enteral GFO supplementation product (GFO®; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) is available and often used for the perioperative management of patients undergoing gastroenterological surgery. However, effects of perioperative GFO administration on postoperative outcomes have not been well investigated.

In a recent report, Abe *et al.* retrospectively analyzed the data of 326 thoracic esophageal cancer patients who underwent radical transthoracic esophagectomy, of which 189 received perioperative GFO administration (GFO group) and 137 did not (control group), and explored the impact of perioperative GFO administration on short-term postoperative outcomes and postoperative complications using a propensity score matching analysis (8). In the GFO group, GFO at 3 packs/day was administered orally or transluminally for 5 days before surgery, and via a feeding catheter or orally from 4 hours after surgery to postoperative day 14. After matching the baseline characteristics, the duration of the systemic inflammatory response syndrome (SIRS) seen after surgery was significantly shorter in the GFO group compared with the

control group (0.74±1.43 *vs.* 1.52±0.19, P=0.002). In the analysis of postoperative laboratory parameters, the CRP value on postoperative day 2 was significantly lower in the GFO group compared with the control group (P=0.007), and the lymphocyte/neutrophil ratio (L/N ratio) had significantly recovered in the GFO group on postoperative day 3 (8).

Although this study was retrospectively conducted at a single institute and there are some limitations, the results suggested the following possible effects of perioperative GFO administration; the early recovery from postoperative immunosuppressive conditions, the reduction of the postoperative excessive inflammatory response, and the shorter duration of SIRS after esophagectomy. Of note, in this study oral or transluminal nutrition supplementation with IMPACT® (AJINOMOTO Pharma, Tokyo, Japan) was performed for 5 days before surgery in both the control and GFO groups. In addition, enteral feeding with IMPACT® was initiated 4 hours after surgery at 250 mL/day and was increased gradually to 1,500 mL/day by day 4, and Racol RF® (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) at 2,000 mL/day was given on postoperative day 5 in both groups. The validity of early enteral nutrition after esophagectomy has been reported in previous studies, which showed a shorter duration of SIRS and lower incidence of postoperative infection including pneumonia in patients treated with early enteral nutrition (9-11). Despite the aggressive perioperative nutritional support for all patients in both the control and GFO groups that would have favorable effects on the postoperative immune conditions after esophagectomy, additional perioperative GFO administration appeared to further improve postoperative immune conditions resulting in a significantly shorter duration of SIRS in the GFO group in the study by Abe *et al.* (8). As GFO® contains 36 kcal, 3.6 g protein, 0 g fat, 6.0 g carbohydrates, 5.0 g alimentary fiber, 0.5 mg Na, 1.45 g galactosyl-sucrose and 3.0 g glutamine per pack, a 5-day preoperative administration of GFO® at 3 packs/day does not seem to significantly improve the nutritional status of patients. Thus, perioperative administration of GFO appeared to affect patients' postoperative immune condition in a nutrition-independent manner.

Although this study showed the feasibility of perioperative administration of GFO in esophageal cancer patients undergoing esophagectomy, mechanisms underlying the shorter duration of SIRS after esophagectomy and the favorable postoperative laboratory data in the GFO group have not been assessed in the study. Because GFO consists of glutamine, dietary fiber and oligosaccharide, it might function as a fuel source for IELs and intestinal epithelial cells, and as prebiotics in the gut as mentioned above. Via such biological mechanisms, GFO might suppress bacterial translocation after esophagectomy even in patients routinely treated with perioperative enteral nutrition. These hypotheses will hopefully be validated in future studies, for instance by measuring intestinal permeability or bacterial ribosomal RNA.

Although it remains unknown whether perioperative GFO administration modifies the contents and functions of gut flora to prevent postoperative bacterial translocation, perioperative administration of GFO appears to have the potential to improve postoperative systematic immunosuppressive conditions after esophagectomy perhaps by maintaining the perioperative immune conditions in the gut in a nutrition-independent manner. A multicenter prospective randomized controlled trial is desired to evaluate the favorable effects of perioperative GFO administration on early postoperative surgical stress after esophagectomy.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Booka E, Takeuchi H, Kikuchi H, et al. Recent advances in thoracoscopic esophagectomy for esophageal cancer. Asian J Endosc Surg 2019;12:19-29.
2. Watanabe M, Okamura A, Toihata T, et al. Recent progress in perioperative management of patients undergoing esophagectomy for esophageal cancer. Esophagus 2018;15:160-4.
3. Takeuchi H, Miyata H, Gotoh M, et al. A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. Ann Surg 2014;260:259-66.
4. Fukatsu K. Role of nutrition in gastroenterological surgery. Ann Gastroenterol Surg 2019;3:160-8.
5. Takechi H, Mawatari K, Harada N, et al. Glutamine protects the small intestinal mucosa in anticancer drug-

induced rat enteritis model. J Med Invest 2014;61:59-64.
6. Iyama S, Sato T, Tatsumi H, et al. Efficacy of Enteral Supplementation Enriched with Glutamine, Fiber, and Oligosaccharide on Mucosal Injury following Hematopoietic Stem Cell Transplantation. Case Rep Oncol 2014;7:692-9.
7. Chun H, Sasaki M, Fujiyama Y, et al. Effect of enteral glutamine on intestinal permeability and bacterial translocation after abdominal radiation injury in rats. J Gastroenterol 1997;32:189-95.
8. Abe T, Hosoi T, Kawai R, et al. Perioperative enteral supplementation with glutamine, fiber, and oligosaccharide reduces early postoperative surgical stress following esophagectomy for esophageal cancer. Esophagus 2019;16:63-70.
9. Kobayashi K, Koyama Y, Kosugi S, et al. Is early enteral nutrition better for postoperative course in esophageal cancer patients? Nutrients 2013;5:3461-9.
10. Xiao-Bo Y, Qiang L, Xiong Q, et al. Efficacy of early postoperative enteral nutrition in supporting patients after esophagectomy. Minerva Chir 2014;69:37-46.
11. Wang G, Chen H, Liu J, et al. A comparison of postoperative early enteral nutrition with delayed enteral nutrition in patients with esophageal cancer. Nutrients 2015;7:4308-17.

Cite this article as: Kikuchi H, Takeuchi H. Does perioperative administration of glutamine, fiber and oligosaccharide (GFO) improve perioperative immune conditions and reduce early postoperative surgical stress after esophagectomy? J Thorac Dis 2019;11(6):2215-2217. doi: 10.21037/jtd.2019.05.62

