ORIGINAL PAPER

Nagoya J. Med. Sci. **82**. 33–37, 2020
doi:10.18999/nagjms.82.1.33

A prospective trial to evaluate treatment effects of a β-hydroxy-β-methylbutyrate containing nutrient for leakage at the anastomotic site after esophagectomy

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ABSTRACT

Anastomotic leakage after esophagectomy is associated with prolonged hospitalization and increased medical cost. Additionally, it sometimes leads to a fatal condition and impaired postoperative quality of life. During the process of wound healing, β-hydroxy-β-methylbutyrate (HMB) is important for collagen biosynthesis. An open-label prospective intervention trial has been designed to evaluate the treatment effect of an enteral nutrient containing HMB with arginine and glutamine (Abound, Abbott Japan Co., Ltd.) for leakage at the anastomotic site after esophagectomy. Patients in whom leakage at the anastomotic site developed within 14 days after esophagectomy are eligible and Abound (24 g) is administered for 14 days through an enteral feeding tube. The target sample size is 10. The primary endpoint is duration between diagnosis and cure of leakage. Surgical procedure, safety, length of fasting, drainage placement and hospital stay, and nutritional status are determined as secondary endpoints. A historical control consisting of 20 patients who had leakage at the anastomotic site after esophagectomy between 2005 and 2018 at Nagoya University Hospital is compared with enrolled patients.

Keywords: esophagectomy, leakage at the anastomotic site, β-hydroxy-β-methylbutyrate

INTRODUCTION

Esophagectomy has been recognized as a complicated surgical procedure that is associated with frequent and serious postoperative complications.[1] Leakage at the anastomotic site remains a significant clinical challenge following esophagectomy with digestive tract reconstruction, with reported incidence rates of approximately 10% of cases, even in high-volume centers.[2,3] Additionally, preoperative radiotherapy reportedly leads to a significant increase in the leakage

Received: April 24, 2019; accepted: May 20, 2019

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at the anastomotic site.[4,5] Besides medical cost burden increased by medical treatments and prolonged hospitalization, leakage at the anastomotic site is a major cause of mortality. Thus, it is an important challenge to enhance cure of leakage at the anastomotic site in the field of digestive surgery.[6]

Collagen biosynthesis is essential for the wound healing process.[7] For accumulation of collagen at the wound, two dietary semi-essential amino acids, arginine and glutamine are absolutely necessary.[8] β-hydroxy-β-methylbutyrate (HMB) is a metabolite of leucine and has been reported to enhance a deposition of collagen in the wound, inhibits muscle proteolysis, and accelerate synthesis of proteins via mTOR pathway.[9] Further, xhibits anti-inflammatory and anticatabolic effects of HMB may be associated with suppression of excessive inflammation at the wound.[7] It has been demonstrated that enteral administration of nutrients containing HMB, arginine and glutamine were effective to treat patients with severe trauma and bedsores.[10] In the field of digestive surgery, Okamoto et al reported that preoperative administration of arginine, glutamine, and HMB had no preventive effect on leakage at the anastomotic site after esophagectomy.[11] However, no evidence is available regarding its treatment effects on leakage at the anastomotic site after esophagectomy.

We herein introduce the study protocol of a prospective clinical trial to evaluate the treatment effect of a nutrient containing HMB, arginine and glutamine for patients who experience leakage at the anastomotic site after esophagectomy.

METHODS

Study design

This trial has been designed as an open-label, single arm prospective study and fully conforms to the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects ethical guidelines. The study protocol has been approved by the Nagoya University Certified Review Board (approval nummber N0003) and registered in the Japan Registry of Clinical Trials (jRCT) as jRCTs041190018 (https://jrct.niph.go.jp/).

Eligibility and exclusion criteria

Patients who met all the following criteria are eligible for this study: patients who underwent reconstruction of the digestive tract after esophagectomy for esophageal cancer and diagnosed as a leakage at the anastomotic site within 14 days after surgery, aged ≥20 years, Performance Status <2, and patients with an enteral nutrition tube. Key exclusion criteria include severe pneumonia, sepsis, patients who underwent or require a second surgery and leakage at closed stumps (e.g. jejunum and duodenum).

Treatment

The nutritional components in a pack (24g, 79 kilocalories) of Abound (Abbott Japan Co., Ltd., Tokyo, Japan) are as follows: HMB 1.2 g, L-arginine 7 g, L-glutamine 7 g, carbohydrate 7.9 g, and calcium 300 mg.[12] A pack of Abound is diluted in 240–360 ml and administered for 14 days through an enteral feeding tube twice a day. Oral food intake, parenteral nutrition and other enteral nutrients are not prescribed. The criteria for cure of leakage are as follows: no fistula detected in contrast inspections from drainage tubes or digestive tract, and no abscess detected using a CT scan (Figure 1).

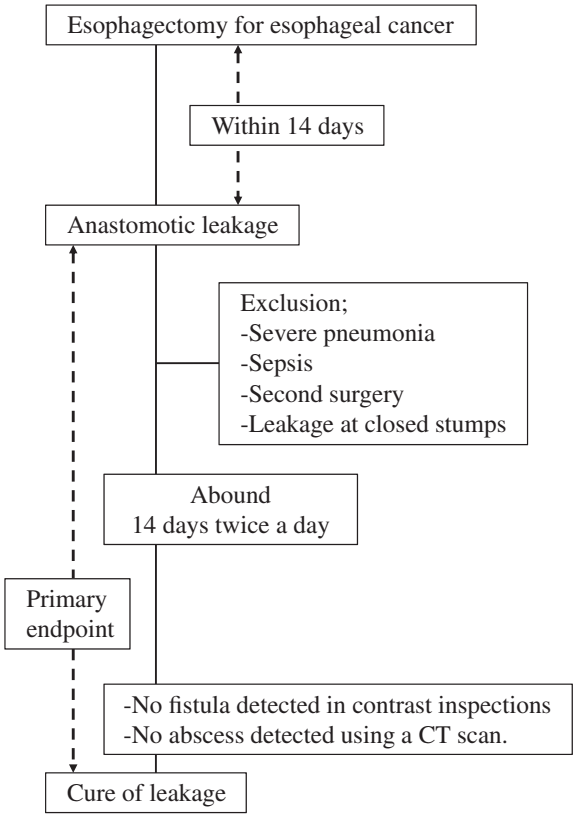

Fig. 1 A flow-chart of treatment

Investigation items

Following data are collected from medical records: age, sex, height, body weight, performance status, intraoperative findings, perioperative clinical course, blood data, pathological findings and imaging data.

Historical controls and study endpoints

Twenty patients were selected as historical controls (Table 1). All 20 patients met the eligibility criteria and underwent esophagectomy between 2005 and 2018. The primary endpoint of this trial is duration between diagnosis and cure of leakage at the anastomotic site. Surgical procedure, safety, length of fasting, drainage placement and hospital stay, and nutritional status are analyzed as the secondary endpoints.

Estimation of a target sample size

In the historical controls, the mean length of time from diagnosis to cure of leakage at the anastomotic site was 31.7 ± 23.3 (standard deviation: SD) days. From a previous study, patients treated by preoperative Abound and had leakage at the anastomotic site after esophagectomy spent 13.5 ± 14.3 (SD) days for treatment of leakage.[11] Considering this data, the threshold and expected duration between diagnosis and cure of leakage were determined 31.7 days and 13.5 days, respectively. To achieve a power of 90% and α-error at 0.05 (one-sided significance

Table 1 Clinical characteristics of the historical controls (n=20)

Variables	
Age, median (range)	66 (48–83)
Sex (male/female)	19/1
Preoperative body mass index, mean ± SD	21.0 ± 4.0
Neoadjuvant treatment (%)	9 (45%)
Number of field dissected	
2-field dissection	7
3-field dissection	13
Operative time (min), mean ± SD	565 ± 146
Intraoperative blood loss (ml), median (range)	418 (31–1478)
Length of treatment of anastomotic leakage (days), mean ± SD	31.7 ± 23.3

SD, standard deviation.

level of 95%), seven patients would be required. Considering some possible dropouts, we set the sample size at 10.

Statistical analysis

The Fisher's exact test is used to compare categorical variables between enrolled patients and historical controls. The Mann-Whitney test is employed to compare continuous variables. Adjustment with a multivariable analysis is planned. Statistical analysis of the data was performed using JMP13 software (SAS Institute, Inc., Cary, NC). A statistically significant difference is indicated by $P < 0.05$.

DISCUSSION

Leakage at the anastomotic site after esophagectomy has a certain persistence.[3,13] The standard treatment of leakage at the anastomotic site consists of control of local infection, appropriate drainage, and digestive tract decompression. Surgeons have experienced cases with persistent leakage because of impaired wound healing even when treated properly. This condition always impede social rehabilitation of patients and intensify the medical cost burden.[14] Moreover, aggravating leakage at the anastomotic site may result in an increased risk of fatal status, for example empyema formation and sepsis.[4] If an effective tool of nutritional support is proposed by this clinical trial, it provides significant benefits in patient management and medical costs by a shortening treatment period of leakage at the anastomotic site after esophagectomy.

ACKNOWLEDGMENTS

Masahide Fukaya, Kazushi Miyata, Chie Tanaka, Daisuke Kobayashi and Michitaka Fujiwara contribute to collection of clinical data. Masahiko Koike and Mitsuro Kanda designed the study. Kenta Murotani contributes to all statistical analyses. Masamichi Hayashi, Suguru Yamada and Goro Nakayama revised the manuscript. Yasuhiro Kodera and Masato Nagino supervised the project.

CONFLICT OF INTEREST

Nothing to declare.

FUNDING SOURCE

Self funding.

REFERENCES

1) 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(2):259–266.
2) Martin LW, Swisher SG, Hofstetter W, et al. Intrathoracic leaks following esophagectomy are no longer associated with increased mortality. *Ann Surg*. 2005;242(3):392–399;discussion 399–402.
3) Derogar M, Orsini N, Sadr-Azodi O, et al. Influence of major postoperative complications on health-related quality of life among long-term survivors of esophageal cancer surgery. *J Clin Oncol*. 2012;30(14):1615–1619.
4) Kassis ES, Kosinski AS, Ross P Jr, et al. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg*. 2013;96(6):1919–1926.
5) Goense L, van Rossum PS, Ruurda JP, et al. Radiation to the gastric fundus increases the risk of anastomotic leakage after esophagectomy. *Ann Thorac Surg*. 2016;102(6):1798–1804.
6) Kanda M, Tanaka C, Kobayashi D, et al. Proposal of the coagulation score as a predictor for short-term and long-term outcomes of patients with resectable gastric cancer. *Ann Surg Oncol*. 2017;24(2):502–509.
7) Hsieh LC, Chien SL, Huang MS, et al. Anti-inflammatory and anticatabolic effects of short-term beta-hydroxy-beta-methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit. *Asia Pac J Clin Nutr*. 2006;15(4):544–550.
8) Williams JZ, Abumrad N, Barbul A. Effect of a specialized amino acid mixture on human collagen deposition. *Ann Surg*. 2002;236(3):369–374;discussion 374–365.
9) Kuhls DA, Rathmacher JA, Musngi MD, et al. Beta-hydroxy-beta-methylbutyrate supplementation in critically ill trauma patients. *J Trauma*. 2007;62(1):125–131;discussion 131–122.
10) Imai T, Matsuura K, Asada Y, et al. Effect of HMB/Arg/Gln on the prevention of radiation dermatitis in head and neck cancer patients treated with concurrent chemoradiotherapy. *Jpn J Clin Oncol*. 2014;44(5):422–427.
11) Okamoto K, Ninomiya I, Hirose A, et al. Effectiveness of the specialized amino acid supplement consisting of CaHMB, L-arginine and L-glutamine (Abound™) for the treatment of anastomotic leakage after esophagogastrostomy. *JSPEN*. 2017;32:983–987.
12) Kanda M, Tanaka C, Murotani K, et al. Editors' Choice Efficacy of enteral nutrients containing beta-hydroxy-beta-methylbutyrate, glutamine, and arginine for the patients with anastomotic leakage after gastrectomy: study protocol of a multicenter phase II clinical trial. *Nagoya J Med Sci*. 2018;80(3):351–355.
13) Viklund P, Lindblad M, Lu M, et al. Risk factors for complications after esophageal cancer resection: a prospective population-based study in Sweden. *Ann Surg*. 2006;243(2):204–211.
14) Karampinis I, Ronellenfitsch U, Mertens C, et al. Indocyanine green tissue angiography affects anastomotic leakage after esophagectomy. A retrospective, case-control study. *Int J Surg*. 2017;48:210–214.