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Efficacy of enteral nutrients containing β -hydroxy- β -methylbutyrate, glutamine, and arginine for the patients with anastomotic leakage after gastrectomy: study protocol of a multicenter phase II clinical trial

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ABSTRACT

Anastomotic leakage is a major cause of prolonged hospitalization after gastrectomy and sometimes leads to fatal complications, such as abdominal abscess and sepsis. Arginine, glutamine, and β -hydroxy- β -methylbutyrate (HMB) are indispensable for biosynthesis of collagen, which plays an important role in the process of wound healing. However, treatment effects of amino acid supplements containing HMB on the healing process of anastomotic leakage after gastrectomy remain unclear. We designed an open-label, multicenter, phase II clinical trial to evaluate the therapeutic efficacy of an enteral amino acid supplement consisting of arginine, glutamine, and HMB (Abound, Abbott Japan Co., Ltd., Tokyo, Japan) in patients with anastomotic leakage after gastrectomy. Patients who are diagnosed with anastomotic leakage within 14 days after gastrectomy are eligible for this trial and the target sample size is 20. A pack of Abound is administered twice a day for 2 weeks. The primary objective of this clinical trial is to determine the length of time between diagnosis and cure of anastomotic leakage. The secondary endpoints include the safety of Abound, duration of drainage placement and fasting, postoperative hospital stay, surgical procedure, and blood test data. Variables are compared between enrolled patients and a historical control consisting of 20 patients who underwent gastrectomy between 2004 and 2016 at Nagoya University Hospital. We herein describe the study design and the concept in this protocol paper.

Keywords: Nutrition for anastomotic leakage

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INTRODUCTION

Gastrectomy is not only the mainstay of treatment for resectable gastric cancer as indicated in the Japanese gastric cancer treatment guidelines, but is also performed as palliative surgery in patients who suffer from persistent bleeding and stenosis.¹⁾ Because digestive tract anastomosis is mandatory after gastric resection, all patients are at risk of anastomotic leakage.²⁾ Besides the financial problem associated with prolonged hospitalization and medical treatments, anastomotic leakage may lead to abscess formation causing sepsis which may eventually be the cause of mortality.³⁾ Based on the Japanese National Clinical Database, the incidence of anastomotic leakage after distal gastrectomy and total gastrectomy was reported to be 2.1% and 4.5%, respectively.^{4,5)} Therefore, important clinical issues in the field of gastroenterological surgery are how to accelerate healing of anastomotic leakage and prevent aggravation.

Biosynthesis of collagen plays an important role in the process of wound healing.⁶⁾ Arginine and glutamine are dietary semi-essential amino acids that are conditionally indispensable for increased accretion of muscle mass and accumulation of wound collagen. β -hydroxy- β -methylbutyrate (HMB) is a naturally occurring metabolite of the essential amino acid leucine and has been reported to have multiple functions.^{6,7)} Previous studies have indicated that supplement of HMB inhibits muscle proteolysis, enhances collagen deposition in wounds, and stimulates protein synthesis through the mTOR pathway.⁸⁾ Additionally, HMB supplementation has some anti-inflammatory and anticatabolic effects, possibly contributing to suppression of excessive inflammation around the wound.⁹⁾ The efficacy of enteral administration of amino acid supplements consisting of arginine, glutamine, and HMB has been evaluated in patients with bedsores and severe trauma, and those undergoing esophagectomy. However, treatment effects of amino acid supplements containing HMB on the healing process of anastomotic leakage after gastrectomy remain unclear.^{7,8,10)}

In this article, we outline the study protocol of a prospective phase II trial. This trial was designed to examine the therapeutic efficacy of an enteral amino acid supplement consisting of arginine, glutamine, and HMB (Abound; Abbott Japan Co., Ltd., Tokyo, Japan) in patients with anastomotic leakage after gastrectomy.

METHODS

Trial design and registration

A single-arm, open-label, prospective, phase II trial was designed to evaluate the effect of administration of Abound on the course of anastomotic leakage after gastrectomy. The study protocol, which conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects, was approved by the Institutional Review Board of Nagoya University (No. 2017-0309). The protocol was registered in the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as UMIN000028945 (<http://www.umin.ac.jp/ctr/index.htm>).

Eligibility of patients

The eligibility criteria were as follows: (1) age of 20 years or older, (2) preoperative Eastern Cooperative Oncology Group Performance Status 0–2, (3) patients who were capable of oral intake before surgery, (4) patients who were treated by gastrectomy with reconstruction of the digestive tract for gastric cancer, (5) patients who are diagnosed with anastomotic leakage within 14 days after gastrectomy, (6) patients who tolerate placement of transnasal enteral nutrition

tubes, and (7) patients who have given written informed consent. The main exclusion criteria include sepsis, leakage at closed stumps of the duodenum or jejunum, patients requiring the second surgery, and patients who underwent preoperative chemotherapy.

Interventions

The nutritional components of Abound are shown in Table 1. After enrollment, a pack of Abound is administered twice a day for 2 weeks using transnasal enteral nutrition tubes. A package of Abound is recommended to be diluted by 240–360 ml of water. No other enteral nutrients are allowed during administration of Abound. No prescriptions on oral food intake and intravenous nutrition are provided in the study protocol. Anastomotic leakage is considered as being cured when following criteria is fulfilled; no leakage of a contrast medium in digestive tract contrast inspections, no fistula in contrast inspections from drainage tubes, no active intra-abdominal abscess in CT scan, and resumption of oral intake. After resumption of oral intake, Abound can be administered orally.

Table 1 Nutritional components of Abound

Amount: 24g per package	
L-Arginine	7 g
L-Glutamine	7 g
β -hydroxy- β -methylbutyrate	1.2 g
Carbohydrate	7.9 g
Calcium	300 mg
Calories	79 kcal

Study parameters

Patients' demographics, performance status, physical data, perioperative clinical course, intraoperative findings, results of imaging diagnostics, and pathological data are collected from medical records and entered in the case report forms. Blood test data, including the blood cell count, chemistry, and coagulation factors, are collected before surgery, at the trial registration, and 7 and 14 days after administration of Abound. Considering that the incidence and extent of anastomotic leakage may differ between total gastrectomy and distal gastrectomy, a subgroup analysis according to surgical procedure will be conducted.

Historical controls

Data of 20 patients who underwent gastrectomy between 2004 and 2016 at the Nagoya University Hospital and met all of the eligibility criteria were used as historical controls. The background of the historical controls is shown in Table 2. There is a potential concern that the collecting period of the historical controls is relatively long as 13 years.

Endpoints

The primary objective of this clinical trial is the length of time between diagnosis and cure of anastomotic leakage. The secondary endpoints include safety of Abound, duration of drainage tube placement and fasting, postoperative hospital stay, whether any surgical procedure was performed before the leakage was healed, and blood test data.

Table 2 Characteristics of 20 patients in the historical control group

Variables	
Age, median (range)	71 (49–85)
Sex (male/female)	10/10
Preoperative body mass index, mean \pm SD	22.3 \pm 4.2
Type of gastrectomy	
Total gastrectomy	9
Proximal gastrectomy	5
Distal gastrectomy	6
Operative time (min), mean \pm SD	264 \pm 42
Intraoperative blood loss (ml), median (range)	247 (10–1080)
Length of treatment of anastomotic leakage (day), mean \pm SD	25.6 \pm 8.6

SD, standard deviation.

Sample size

The mean length between diagnosis and cure of anastomotic leakage in the historical controls was 25.6 ± 8.6 (standard deviation; SD) days. In a previous report by Okamoto *et al.*, the treatment period of anastomotic leakage in patients who had preoperative administration of Abound and experienced anastomotic leakage after esophagectomy was 13.5 ± 14.3 (SD) days. Taking these data into account, we determined that the threshold and expected length of time between diagnosis and cure of anastomotic leakage in the present trial would be 25.6 days and 13.5 days, respectively. Fourteen patients would be required to achieve a power of 90% with a one-sided significance level of 95% and α -error at 0.05. Taking possible dropouts (mainly due to the second surgery) into consideration, the target sample size was set at 20 patients.

Statistical analysis

Comparisons of continuous variables between enrolled patients and historical controls are performed using the Mann–Whitney test t-test. The Fisher's exact test is used to compare categorical variables. Adjustment using multivariable analysis is also planned. Results are presented in delta values with the 95% confidence interval between two time points. A P value < 0.05 is considered to indicate statistical significance. Statistical analysis of the data is performed using a JMP software program (version 11, SAS Institute, Inc., Cary, NC).

DISCUSSION

The standard strategies to treat anastomotic leakage include appropriate drainage, intestinal tract decompression, and control of local infection.⁴⁾ However, even when treated properly, surgeons sometimes experience cases with persistent leakage due to impaired wound healing, and eventually a prolonged treatment period.^{11,12)} Persistent leakage can increase risks of serious conditions, such as intraabdominal hemorrhage and sepsis. Additionally, leakage disturbs patients' social rehabilitation and increases the burden of medical costs. If effective nutritional support, which can shorten the treatment period of anastomotic leakage after gastrectomy, is proposed by the results of the present trial, it will lead to great benefits for management of patients, medical safety, and medical economy.

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CONFLICT OF INTEREST

None declared.

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