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Original article

Efficacy of preoperative amino acid supplements on postoperative physical function and complications in open heart surgery patients: A study protocol for a randomized controlled trial

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ABSTRACT

Background: Elderly patients undergoing cardiac surgery often show poor nutritional status, muscle wasting, and sarcopenia, which are reported to affect postoperative functional recovery and incidence of complications. Amino acids are essential in maintaining nutritional status, synthesizing muscle protein, and promoting beneficial energy balance of the heart muscle. β-Hydroxy β-methylbutyric acid (HMB) is a leucine metabolite known to increase muscle protein synthesis and inhibit protein catabolism; it has been used to more effectively support patients with muscle wasting due to wearing diseases. However, the efficacy of amino acid administration comprising HMB in patients undergoing open heart surgery remains unclear. This study aims to examine whether preoperative short-term aggressive amino acid administration helps support postoperative recovery of physical function and prevent complications.
Methods: This is a single-center prospective randomized controlled trial (UMIN000030490). Patients aged ≥65 years who will be hospitalized for medical examination before cardiac surgery will be recruited. The participants will be randomly assigned to the experimental or control group. The experimental group will be administered with an amino acid supplement with HMB 1200 mg, L-glutamine 7000 mg, and L-arginine 7000 mg once or twice per day depending on the degree of renal dysfunction, for 14–28 days preoperatively. The control group will not receive any nutritional intervention. The main outcome will be a change in the 6-min walking test distance pre- and postoperatively as a sign of functional recovery. Secondary outcomes such as the incidence of complications; physical, nutritional, and psychological states; mortality; and length of hospital stay will also be evaluated.
Conclusion: This clinical study will determine the effects of preoperative short-term oral amino acid supplementation with HMB, L-glutamine, and L-arginine on postoperative physical function in elderly patients undergoing cardiac surgery.

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Introduction

As a result of extension of life expectancy and increase in prevalence of cardiovascular diseases associated with aging, the demand for open heart surgery in the elderly population is increasing in Japan [1,2]. Malnutrition is commonly observed in elderly patients with heart failure (HF) or undergoing cardiac surgery, which is often associated with sarcopenia. It is also gaining global attention because of its strong association with increased mortality in patients with HF [3–7]. Previous reports have shown that preoperative nutritional status and sarcopenia are associated with long-term cardiovascular outcomes, and affect postoperative functional recovery and incidence of complications in cardiac surgery [8–10]. Moreover, another study showed that preoperative administration of oral immune-enhancing nutritional supplement (L-arginine, ω3 polyunsaturated fatty acids, and yeast RNA) for patients who were scheduled to undergo coronary artery bypass improved preoperative immune function, decreased perioperative interleukin-6 levels, and reduced the incidence of postoperative infections [11]. Based on this evidence, preoperative nutritional support is increasingly recognized as being clinically relevant in patients undergoing cardiac surgery [9].

Protein intake was expected to increase the amount of skeletal muscle in elderly people. However, a recent randomized clinical trial revealed that a protein intake of 1.3 g/kg/day in older adults did not increase the lean body mass, which represents the total muscle amount or improve muscle performance and physical function [12]. Meanwhile, taking the supplement of amino acids (AA), the monomers of proteins, seems to be more effective in improving muscle condition than protein intake. AA are biologically essential for growth, development, and homeostasis in an organism. Recently, some of them have received much attention because of their varied effectual functions in promoting protein synthesis, regulating immunity, and reducing inflammation. A previous study revealed that an AA supplement, which consisted of β-hydroxy β-methylbutyric acid (HMB), L-glutamine, and L-arginine, shortened the healing time of diabetic foot ulcers [13]. This result is probably a consequence of not only the promotion of protein synthesis but also the repression of infection and well-regulated immune responses brought about by the supplement.

HMB is a leucine metabolite, known to have anabolic effects in muscle proteins and inhibit protein degradation, and has been used to support patients with muscle wasting due to wearing diseases, such as acquired immunodeficiency syndrome (AIDS), cancer, and chronic obstructive pulmonary disease (COPD) [14]. HMB has been shown to have favorable effects on skeletal muscles by facilitating muscle protein synthesis through the upregulation of anabolic signaling and downregulation of catabolic signaling. The mechanisms previously reported were that HMB induced (1) the stimulation of mammalian target of rapamycin pathway, (2) stimulation of growth hormone and insulin-like growth factors-1 pathway, (3) mitochondrial biogenesis, (4) inhibition of protein degradation via suppression of ubiquitin proteasome and autophagy-lysosome systems, and (5) proliferation of satellite cells [14]. Many studies investigated the beneficial effects of HMB on healthy subjects and the patients who suffered wearing diseases, such as AIDS, cancers, and COPD. Thus, we anticipate that the pretreatment of HMB in elderly patients undergoing cardiac surgery would improve their skeletal muscle condition preoperatively, which could promote rapid physical function recovery postoperatively.

We also intend to provide a certain amount of L-glutamine and L-arginine with HMB. Arginine has beneficial effects in improving the function of cardiovascular system due to its nitric oxide-producing ability, which reduces platelet aggregation and blood viscosity, improves blood flow, and helps repair vascular injury [15,16]. Glutamine is produced from glutamate and ammonia by glutamine synthetase and has various positive effects, notably stimulation of protein synthesis, support of immune function, and protection of the gut from atrophy and injury under various stress conditions [17].

Hence, we anticipate that the AA supplement consisting of HMB, L-glutamine, and L-arginine would have pleiotropic effects of improving nutrition, muscle condition, immunity, and cardiovascular function, in elderly patients undergoing cardiac surgery. This study aims to investigate the effects of preoperative oral AA supplementation on postoperative physical function and various postoperative outcomes in elderly patients undergoing open heart surgery.

Materials and methods

Study design

This study (URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000034773. Unique identifier: UMIN000030490) is a single-center, prospective, randomized, open label, controlled trial to elucidate the effects of preoperative short-term AA administration on loss of physical function postoperatively, as well as surgical complications, nutritional and psychological status, and length of hospital stay. Fig. 1 presents the study flowchart. The primary outcome will be the rate of change in the 6-min walking distance (6MWD) pre- and postoperatively. The changes in 6MWD between pre- and post-surgery in the patients might be affected by their pre- and post-operative cardiac condition. Thus, we planned that the patients would be well randomized and equally divided into the two groups in order to minimize the impact of cardiac condition on changes in 6MWD. The study will be conducted according to the guidelines of the Declaration of Helsinki and is approved by the Ethics Committee of Kobe University (approval no. 30002). Written informed consent will be obtained from all patients.

Recruitment and eligibility

All patients hospitalized in Kobe University Hospital will be recruited when they are admitted for preoperative medical examination after completion of all baseline measurements. Two or more cardiologists or cardiac surgeons will determine whether patients are eligible to guarantee safety in the study. Table 1 lists the inclusion and exclusion criteria. Exercise capacity and muscle strength were reduced approximately 20% from the baseline during the postoperative period regardless of the basal cardiac diseases or etiology [7], patients aged ≥65 years who will be hospitalized for medical examination before cardiac surgery will be recruited. Patients aged ≥65 years will be recruited and screened based on the protocol, and those who are willing to participate and able to comply with AA supplementation will be considered for inclusion. Once registered, Kobe University Hospital Clinical & Translational Research Center will manage and monitor the data.

Interventions

The study population will be randomly assigned in a 1:1 ratio to receive either oral AA supplementation (Abound®, Abbott, Abbott Park, IL, USA) [18–20] or no nutritional intervention at open labels (Fig. 1). One pack of Abound® (24 g) consists of HMB (1.2 g/24 g), L-glutamine (7 g/24 g), and L-arginine (7 g/24 g). Patients without chronic kidney disease will receive a pack of Abound® twice per day, whereas patients with chronic kidney disease [30 mL/min/

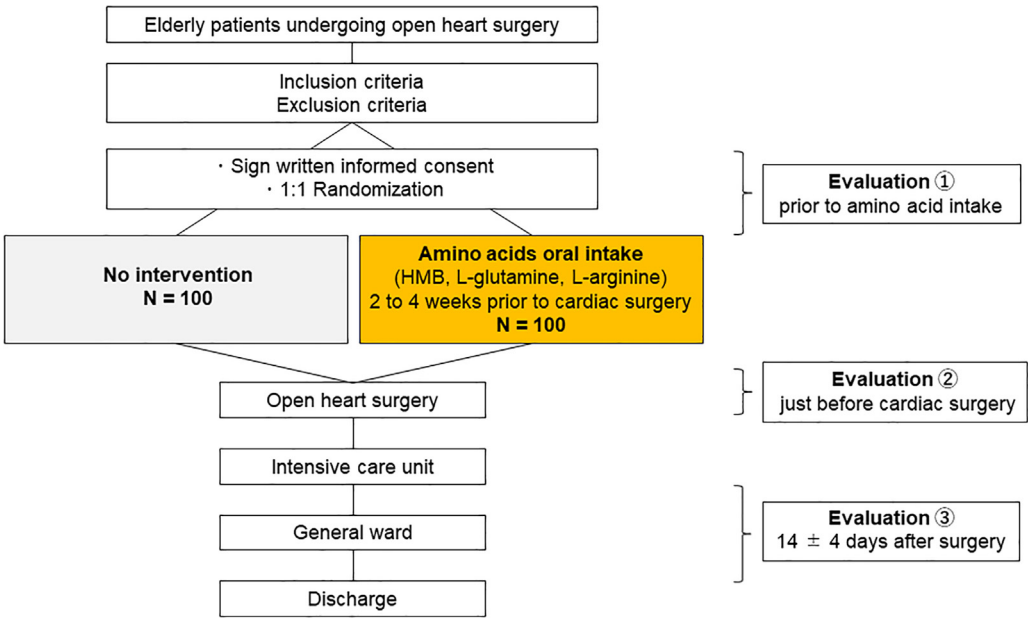

Fig. 1. Flow chart of the study.
HMB, 3-hydroxy 3-methyl butyrate.

Table 1
Inclusion and exclusion criteria of the study.

Inclusion criteria
1. Patients aged 65 years and older
2. Patients undergoing open heart surgery
3. Sign written informed consent prior to participating in the study
Exclusion criteria
1. Patients with unstable heart failure condition (BNP levels > 500 pg/mL)
2. Patients with severe kidney disease (eGFR < 30 mL/min/1.73 m^2)
3. Patients with severe liver dysfunction (T-Bil > 2.0 mg/dL)
4. Patients with oral intake difficulty
5. Patients with disorders of branched-chain amino acid metabolism
6. Patients who cannot perform 6 min walking test
7. Patients who take amino acids supplements prior to randomization
8. Participation in any clinical research study evaluating another investigational drug or therapy within 4 months prior to randomization
9. Patients judged by the investigator to be ineligible for some other reason

BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; T-Bil, total bilirubin.

1.73 m^2 < estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2] will receive a pack of Abound® per day for 14–28 preoperative days.

Assessing the compliance rate of supplement intake

Patients in the experimental group will be required to manually record their progress daily in a prescribed form during the intervention period to confirm compliance with AA supplementation. Patients whose compliance rate is <50% will be considered dropped out.

Outcomes

We will perform various assessments in three different serial times to clarify the efficacy of AA supplementation as shown in Fig. 1 and Table 2.

Table 2
Assessments in three different serial times.

Timing	Evaluation ① Prior to amino acid intake	Evaluation ② One day before cardiac surgery	Evaluation ③ 14 ± 4 days after surgery
Blood sampling	○	○	○
Physical function			
6 min walking test			
Handgrip strength	○	○	○
Knee extensor muscle strength			
Body composition	○	○	○
Short physical performance battery (SPPB)[a]	○	○	○
International physical activity questionnaire	○	○	
Food frequency questionnaire	○	○	○
Hospital anxiety and depression scale	○	○	○
Health-related quality of life	○	○	○
Compliance rate of Abound®		○	
Surgical complications			
Cardiac complication			
Lung complication			○
Renal injury			
Liver complication			
Surgical site infection			

[a] SPPB consists of three tests that involve walking speed, chair stands, and standing balance.

Primary outcome

The difference of changes in 6MWD between pre- and post-surgery.

Secondary outcomes

The secondary outcomes are as follows:

1. Difference in the incidence of postoperative complications.
2. Difference in changes in nutritional status between evaluation 1 and 2 and evaluation 2 and 3.
3. Difference in the change in physical function [grip strength, knee extensor muscle strength, body composition, short physical performance battery (SPPB) score, and physical activity estimates] between evaluation 1 and 2 and evaluation 2 and 3.
4. Difference in psychological and health status between evaluation 1 and 2 and evaluation 2 and 3.
5. Difference in changes in inflammatory status between evaluation 1 and 2 and evaluation 2 and 3.
6. Difference in hospital mortality.
7. Difference in the length of hospital stay.
8. Difference in the length of ICU stay.

Assessment of physical function

The 6MWD is a submaximal exercise test used for the assessment of functional capacity [21]. It was performed according to the American Thoracic Society guidelines in a 30 m-long, straight corridor under the guidance of a physiotherapist. Handgrip strength was measured with a grip strength dynamometer (T.K.K.5401®; Takei Scientific Instruments Co., Ltd., Niigata, Japan). Knee extensor muscle strength was measured using a handheld dynamometer (MicroFET2®; Hoggan Health Industries, Salt Lake City, UT, USA). Testing was performed for both legs at the maximum isometric contraction. To assess the body composition, bioelectrical impedance data for each patient will be obtained using the InBody S10® (BioSpace Japan, Tokyo, Japan) device. The SPPB was used to measure the physical performance and consists of three tests that involve walking speed, chair stands, and standing balance. We will assess and estimate the physical activity using the International Physical Activity Questionnaire. All the patients will start postoperative rehabilitation on the first day after the surgery in accordance with the Japanese Circulation Society guidelines for rehabilitation in patients with cardiovascular disease [22].

Assessment of surgical complications

Cardiac complications include the use of assisted circulation apparatus, myocardial infarction, HF, fatal arrhythmia, supraventricular arrhythmia, and cardiac tamponade. Lung complications include prolonged intubation (>48 h), reintubation, pneumonia, and tracheotomy. Renal injury is defined as the need for renal replacement therapy. Liver complication is defined as the need for treatment for liver injury. These complications will be recorded for 14 days postoperatively. Surgical site infections, such as deep wound infection that affected the sternum, muscles, and/or mediastinum and required antibiotic treatment and/or surgical debridement, during 30 days postoperatively will also be evaluated.

Blood sampling

Blood samples will be collected after an overnight fast and used to determine complete blood count, hemoglobin, albumin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, bilirubin, blood urea nitrogen, creatinine, eGFR, brain natriuretic peptide, electrolytes, C-reactive protein, glycated hemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, interleukin-6, lactate dehydrogenase, retinol-binding protein, total cholesterol, total protein, transferrin, transthyretin, tumor necrosis factor-α, and uric acid. The plasma samples were obtained after blood samples were centrifuged at 4 °C for 10 min at 3000 rpm and were stored at −80 °C for future exploratory research.

Assessment of nutritional, psychological, and health states

Habitual dietary intakes will be recorded using the food frequency questionnaire. We perform standard nutrition education for all the participants at evaluation 1 as shown in Table 2 to maintain protein intake according to eGFR. Patients without chronic kidney disease (eGFR > 60 mL/min/1.73 m^2) will be instructed to take protein 1.2 g/kg/day, whereas patients with chronic kidney disease (30 mL/min/1.73 m^2 < eGFR < 60 mL/min/1.73 m^2) will be instructed to take protein 0.8 g/kg/day. Abound® is not taken into account of these directed protein intakes. Albumin, lymphocyte, transthyretin, retinol-binding protein, and transferrin levels will also be measured to indicate the nutritional status. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). The HADS is a self-report questionnaire, which has been validated as a screening instrument to assess the presence or severity of anxiety disorders and symptoms of depression. HADS psychological score produces two scales: one for anxiety (HADS-A) and another for depression (HADS-D). To assess the health status, health-related quality of life will be investigated using the Japanese version of the Medical Outcomes Study, a 36-item Short-Form General Health Survey Version 2.0 (SF-36; v2).

Ethics

All participants must provide written informed consent upon enrollment, and the study will be conducted according to the guidelines of the Declaration of Helsinki. This study is approved by the Ethics Committee of Kobe University (approval no. 30002).

Statistical considerations

The sample size was calculated with referring to the previous paper [23] and our unpublished data. We hypothesized that following AA supplementation, there will be 6MWD improvement changes of 25 m (standard deviation 60 m). Significance level and power were set at 0.05 and 0.8, respectively. We then predict that nine patients will drop out and 100 patients per group will be included. The primary population for analysis is defined as all randomized patients identified according to the intent-to-treat analysis. Statistical analyses will be performed using the R software version 3.1.0 (http://www.r-project.org/), JMP version 10 (SAS Institute, Cary, NC, USA), and Prism version 7.0 (GraphPad Software; San Diego, CA, USA). The Shapiro–Wilk test will be used to determine whether the data were normally distributed. Results will be expressed as mean ± standard error of the mean or mean ± standard deviation for normally distributed data and median ± interquartile range (25th–75th percentiles) for non-normally distributed data. To evaluate the effectiveness of the intervention, we will investigate changes in pre- and post-surgery 6MWD scores and other outcome data between AA supplementation and control groups. The significance of differences between the two groups will be evaluated using two-tailed Student's *t*-test for normally distributed data or Mann–Whitney *U* test for non-normally distributed data. Fisher's exact test or chi-square test will

be used to compare categorical variables. For all tests, a p-value of <0.05 will be considered to indicate statistical significance.

Randomization

Randomization will be requested by the research investigators and will be performed by an independent researcher throughout the study to facilitate data management. Block randomization will be conducted according to a computer-generated allocation sequence with a varying block size. The randomization is stratified by (1) age and (2) sex.

Safety monitoring

Data safety and monitoring will be conducted by an independent Data Safety and Monitoring Board. Any serious adverse events will be registered as part of the data collection. Safety is observed throughout the study and will be evaluated through medical examination and laboratory data at evaluations 2 and 3. The Data Safety and Monitoring Board works independently from the funder and has no competing interests.

Results

The first patient was enrolled in this study in July 2018. The planned end date for the trial will be March 2021. If found to be efficacious, the AA supplement comprising HMB, L-glutamine, and L-arginine may be considered suitable for future standard intervention for improving postoperative outcomes. The results of the study will be disseminated via scientific forums including peer-reviewed publications and presentations at national and international conferences.

Discussion

This trial aims to investigate the effectiveness of AA supplement comprising HMB, L-glutamine, and L-arginine on postoperative physical function and other postoperative outcomes. The study will focus on elderly patients who are considered to potentially have sarcopenia and malnutrition. We hypothesize that our AA interventions will have favorable effects on not only the nutritional status but also postoperative general condition, systemic inflammation, wound healing, physical function, psychological status, which may shorten the length of hospital stay and prevent mortality in patients undergoing open heart surgery.

To our knowledge, no reports have described the effects of preoperative AA intervention in elderly patients undergoing open heart surgery. This prospective study with large number of participants could detect significant and meaningful differences in outcomes. The second strength is that this study includes several exhaustive and multifaceted outcomes including nutritional status by rapid turnover protein, inflammatory cytokines, body composition, habitual dietary intake, physical function and performance, muscle strength, and psychosocial factors. Thus, our study will show further possibility and limitations of nutritional supplementation in patients undergoing open heart surgery. The third strength is that this is an Asian cohort study. Because Japan is the front-runner of super-aged societies, elderly and malnourished patients are becoming a serious public health problem. Thus, the clinical significance of 6MWD changes according to our supplementation must help support postoperative recovery and prevent long-term mortality and morbidities.

This is an ongoing and recently recruiting trial. We believe that this clinical study will present novel insights addressing the effects of oral AA supplementation, comprising HMB, L-glutamine, and L-arginine in patients undergoing open heart surgery.

Conclusion

This is a single-center, randomized, open label trial that aims to evaluate the clinical efficacy of preoperative AA supplement, comprising HMB, L-glutamine, and L-arginine on postoperative physical function and complications in elderly patients undergoing open heart surgery. The result of the trial will provide insights into a novel preoperative management of elderly patients undergoing open heart surgery.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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