Peripheral vein infusions of amino acids facilitate recovery after esophagectomy for esophageal cancer: Retrospective cohort analysis

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HIGHLIGHTS

- Radical resection for esophageal cancer is a highly invasive procedure.
- Enteral feeding has been used in postoperative period for esophagectomy.
- Peripheral vein infusion of amino acids is effective for post esophagectomy.

ARTICLE INFO

ABSTRACT

Background: To investigate the efficacy of amino acid administration via peripheral veins in addition to conventional enteral feeding following esophagectomy.
Materials and methods: Retrospective analysis of data pertaining to 33 patients with esophageal cancer who underwent radical esophagectomy and satisfied the required nutrition control. Patients were divided into the amino acid group (n = 17) and control group (n = 16). Primary outcomes were albumin (Alb) and prealbumin (PreAlb) levels, urinary 3-methylhistidine/creatinine (3-MeHis/Cre) ratios, nitrogen balance, and weight; postoperative complications were noted as secondary outcomes.
Results: Alb levels were significantly higher in the amino acid group on postoperative day (POD)-14 (3.4 ± 0.3 vs. 3.1 ± 0.4 mg/dL in the control group, $p = 0.018$) and at 1 month after surgery (3.8 ± 0.4 vs. 3.5 ± 0.3 mg/dL, $p = 0.045$). No significant differences were observed in PreAlb and urinary 3-MeHis/Cre rates between the treatment groups. Body weights at 3 months postoperatively were decreased by 6% and 3% in the control and amino acid groups, respectively.
Conclusion: Peripheral venous administration of amino acids soon after surgical stress is an effective method for nutritional control.

1. Introduction

Radical resection for esophageal cancer involves extensive dissection and lymphadenectomy in the neck, chest, and abdomen. The procedure is invariably associated with damage to the mediastinum [1]. Optimal perioperative respiratory and circulatory management and proactive nutritional control during the early postoperative period can reduce the incidence of complications.

Highly invasive procedures, such as esophagectomy, tend to alter the energy dynamics in the body [1], i.e., endogenous energy is consumed from the breakdown of skeletal muscle induced by stress hormones and cytokines. In addition, the requirement of extracorporeal energy is reduced, including that from enteric and intravenous nutrition [2]. Therefore, excessive nutritional administration during the early postoperative period frequently induces adverse events (AEs), such as infections due to increased blood sugar, immunocompromised patients [3]. Guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN), published in 2009 [4], recommend initiation of enteral nutrition within 24–48 h of the start of intensive care with gradual increase in dose to reach the target dose over the next 48–72 h [4]. Under conditions of insufficient enteral nutrition by day 7 from the start of

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care, ASPEN also recommends initiation of intravenous feeding [4]. The guidelines from The European Society for Clinical Nutrition and Metabolism (ESPEN), published in 2009 [3], recommends initiation of intravenous feeding within 24—48 h in cases where normal nutrient intake is not achieved for at least 3 days because of intolerance or the presence of contraindications to enteral feeding [3]. Although the total recommended energy doses are similar in ASPEN and ESPEN, ASPEN recommends enteral feeding, whereas ESPEN recommends intravenous feeding, despite being predicated on enteral feeding.

In recent years, enteral feeding has primarily been used in the early postoperative period after esophagectomy [5,6]. Postoperative enteral feeding through jejunostomy or gastrostomy after esophagectomy with gastric tube reconstruction is known to reduce the incidence of postoperative complications, such as infection and malnutrition [6]. Although postoperative weight loss is unavoidable in the long term because of lack of oral feeding, an improvement in nutritional intake during the early postoperative period may minimize malnutrition in the first few months postoperatively. Nutritional intake that does not fully meet the requirement for carbohydrate-based energy due to intravenous feeding is acceptable during the early postoperative period [3,4]. However, there is no consensus regarding the doses of proteins and amino acids, which are essential for maintenance of skeletal muscle and for *in vivo* energy production.

In this study, we assessed the changes in nutritional indicators during transvenous administration of amino acids via conventional enteral feeding during perioperative and early postoperative periods in esophagectomy patients.

2. Materials and methods

2.1. Materials

Data from consecutive 110 esophageal cancer patients who received radical esophagectomy with two or three field lymphadenectomy from 2008 to 2012 were collected. Inclusion criteria were as follows: (1) histological diagnosis of esophageal cancer; (2) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0—2, and (3) provision of written consent. Exclusion criteria were preoperative factors which had need for increase or decrease of volume of infusion and enteral feeding as follows: (1) active infection prior to surgery, (2) 85 years or older, (3) congestive heart failure, (4) demonstrated abnormal electrolyte metabolism, (5) obstructive uropathy, (6) high degree of hepatorenal failure, (7) severe diabetes, (8) allergy to cow's milk protein, (9) active double cancer.

2.2. Surgical procedure

The surgical procedure consisted of subtotal esophagectomy, two or three-field lymph node dissection in the chest and abdomen or in the neck, chest, and abdomen, and gastric tube reconstruction via the posterior mediastinum route using right-sided thoracoscopic or right thoracotomy, laparotomy, and bilateral cervical approaches.

2.3. Nutritional control

1) Preoperative nutrition control

Food was withheld from all patients from 2 days prior to the operation, and fasting (no food or liquid) was initiated from 21 h prior to the operation. Two days prior to the operation, subjects were administered a 5% sugared acetic acid Ringer's solution

(30—40 mL/kg/day). No immune-enhancing diets were given during the preoperative period.

2) Postoperative nutrition control

Patients were divided into two groups by postoperative peripheral venous infusion solutions; Subjects who were administered vitamin B1, sugar, electrolytes, and amino acid solutions were assigned to the amino acid group, whereas those with a 10% sugar maintenance solution were assigned to the control group (Compositions of infusion solutions are presented in Supplementary Table 1).

Enteral feeding was administered with a 5% glucose solution from the jejunostomy on postoperative day 1. After confirming the absence of issues with jejunostomy, subjects were administered a semidigestion nutrition agent at 5 kcal/kg on postoperative day 2, 10 kcal/kg on postoperative day 3, and 25 kcal/kg on postoperative days 4—7 (Supplementary Fig. 1).

In addition, peripheral venous nutrition was administered to a total energy intake of 15 kcal/kg on postoperative days 1—3 and 10 kcal/kg on postoperative days 4—7. Furthermore, amino acids were administered to patients of the amino acid group at 1.0 g/kg on postoperative days 1—3 and at 0.7 g/kg on postoperative days 4—7. All Subjects started ingestion after postoperative day 8 and peripheral venous nutrition was discontinued concomitantly.

Table 1
Patient characteristics.

		Intervention group (n = 17)	Control group (n = 16)	p value
Age[a]		62	64.5	0.40[b]
Gender	male	14	13	0.64[c]
	female	3	3	
Preoperative weight [kg][d]		60.6	58.8	0.67[e]
Body mass index[d]		21.9	22.2	0.82[e]
Location of the lesion	Ut	3	1	0.51[b]
	Mt	10	10	
	Lt	3	5	
	Ae	1	0	
Depth of tumor invasion	T1	5	7	0.33[b]
	T2	3	3	
	T3	8	6	
	T4	1	0	
Lymph node metastasis	N0	10	8	0.43[c]
	N1	7	8	
Distant organ metastasis	M0	17	16	–
	M1	0	0	
Stage	IA	4	5	0.98[b]
	IB	1	1	
	IIA	5	2	
	IIB	3	4	
	IIIA	6	4	
Preoperative therapy		8	9	0.85[c]
Operative technique	thoracotomy	4	4	0.75[c]
	thoracoscopic	13	12	
Operative time [min][d]		649	639.5	0.92[e]
Operative bleeding [ml][d]		199	176.5	0.44[e]
% ideal body weight[d] (range)		99.7 (79.8—115.9)	100.9 (70.4—139.8)	0.82[e]
malnutrition	normal	13	11	0.79[b]
	mild	3	3	
	moderate	1	2	
	severe	0	0	

Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus.
[a] Median.
[b] Mann—Whitney's test.
[c] Yates-corrected c-square.
[d] Mean.
[e] Student's *t*-tt.

Enteral feeding was administered to a total ingested energy of 30 kcal/kg/day, and were decreased when necessary, according to ingestion states (Postoperative nutrition control protocol is shown in Supplementary Fig. 1).

2.4. Outcome variables

1) Primary outcomes were albumin (Alb), prealbumin (PreAlb), urinary 3-methylhistidine/creatinine ratio (3-MeHis/Cre), and nitrogen balance. Alb levels were assessed preoperatively and on postoperative days 1, 4, 8, and 14 and at 1 and 3 months after surgery. PreAlb levels were determined as rapid turnover proteins preoperatively and on postoperative days 1, 4, 8, and 14. 3-MeHis/Cre levels in urine were determined on postoperative days 1, 4, and 7 as an indicator of muscle protein metabolism. Mean values were compared between the two groups, and percentage rate of change from preoperative values were calculated for each group. Nitrogen balance was determined from 24 h urine samples collected on postoperative days 1—7.

2) Secondary outcomes were body weight and postoperative complications. Body weights were measured preoperatively, on postoperative days 8 and 14, and at 1 and 3 months after surgery. Percentage rate of change in body weight from preoperative level was compared between the groups. Data on incidence

of pneumonia, enteritis, sepsis, anastomotic leakage, and surgical site infections (SSI) were extracted. Pneumonia was diagnosed based on observation of infiltrative shadows on chest radiographs accompanied by fever, or by positive sputum cultures for non-indigenous bacteria. Enteritis was diagnosed by detection of non-indigenous bacteria in stool cultures accompanied by fever or diarrhea.

3) Blood biochemistry

Blood urea nitrogen (BUN) and sugar levels were determined biochemically as nutritional indicators. BUN was determined preoperatively, on postoperative days 1, 4, 8, and 14, and at 1 and 3 months after surgery. Subsequently, percentage rates of changes from preoperative values were compared between groups. Percentage rates of changes in blood sugar levels from preoperative values were compared between groups on postoperative days 1, 4, 8, and 14.

2.5. Statistical analyses

Comparisons of background factors were made using Mann—Whitney U test or chi-square test. Nutritional metrics and blood biochemistry data are presented as means ± standard errors of the mean. Differences between treatment and control groups were
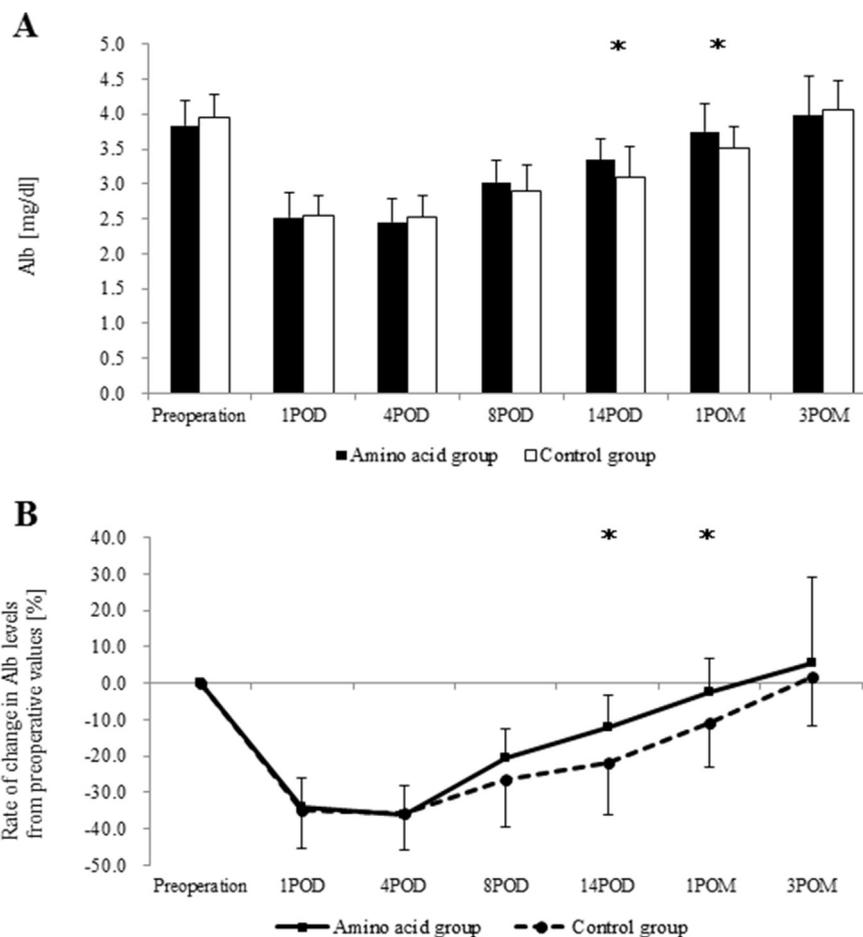
Fig. 1. Albumin levels and rate of change from preoperative values. (A) Albumin levels, (B) Rate of change in albumin levels from preoperative values. Significant differences in Alb levels were observed between the two groups on postoperative day 14 (amino acid group, 3.4 ± 0.3 mg/dL; control group, 3.1 ± 0.4 mg/dL; $p = 0.018$) and at 1 month postoperatively (amino acid group, 3.8 ± 0.4 mg/dL; control group, 3.5 ± 0.3 mg/dL; $p = 0.045$). Although Alb levels decreased in all patients by 35% by postoperative day 1, rates of changes did not differ significantly between the two groups. However, Alb levels were closer to preoperative values in the amino acid group (−12.3 ± 8.8%) than in the control group (−21.9 ± 14.2%, $p = 0.026$) on postoperative day 14 and at 1 month postoperatively (amino acid group, −2.4 ± 9.2%; control group, 10.9 ± 12.2%; $p = 0.031$). POD, postoperative day; POM, postoperative month; *, $p < 0.05$.

identified using Student's t-test and were considered significant when $p < 0.05$. Statistical analyses were performed using SAS statistical analysis software (JMP® 10).

3. Results

3.1. Patient background

Among the 110 patients with esophageal cancer who underwent radical esophagectomy with two- or three-field lymphadenectomy from 2008 to 2012, 50 patients met the preoperative criteria. Thirty-three of these 50 patients received the treatment and achieved satisfactory nutritional control. Of the 17 cases excluded from the data analysis, nine cases had incomplete enteral feeding; these included five patients with lymphatic fistula/chylothorax, one with jejunostomy obstruction, one in whom jejunostomy was not constructed, one with acute pancreatitis, and one who experienced difficulty with enteral feeding because of severe diarrhea. In eight patients, the infusion solutions had to be changed to maintain circulatory control.

Out of the 33 patients, 17 belonged to the amino acid group and 16 to the control group. No significant baseline differences with respect to age, male: female ratio, preoperative weight, body mass index, primary tumor site, tumor invasion, lymph node metastasis, distant metastasis, progression, preoperative treatment, procedure,

operative time, and intraoperative blood loss were observed between the groups (Table 1).

3.2. Primary outcomes

Significant differences in Alb levels were observed between two groups on postoperative day 14 (amino acid group, 3.4 ± 0.3 mg/dL; control group, 3.1 ± 0.4 mg/dL; $p = 0.018$; Fig. 1A) and at 1 month postoperatively (amino acid group, 3.8 ± 0.4 mg/dL; control group, 3.5 ± 0.3 mg/dL; $p = 0.045$; Fig. 1A). Although Alb levels decreased in all patients by 35% by postoperative day 1, rates of changes did not differ significantly between two groups. However, Alb levels were closer to preoperative values in the amino acid group ($-12.3 \pm 8.8\%$) than in the control group ($-21.9 \pm 14.2\%$, $p = 0.026$) on postoperative day 14 and at 1 month postoperatively (amino acid group, $-2.4 \pm 9.2\%$; control group, $10.9 \pm 12.2\%$; $p = 0.031$; Fig. 1B).

PreAlb levels were decreased by 40% at postoperative day 1 in all patients and the rate of change did not differ significantly between two groups (Fig. 2A and B). However, the rate of change was positive on postoperative day 8 in the amino acid group ($5.1 \pm 21.8\%$), but remained negative in the control group ($-12.3 \pm 24.9\%$; $p = 0.041$; Fig. 2B).

Although levels of urinary 3-MeHis/Cre were increased in both groups on postoperative day 4, these were similar on days 7 and 1. No significant differences in urinary 3-MeHis/Cre levels or rates of
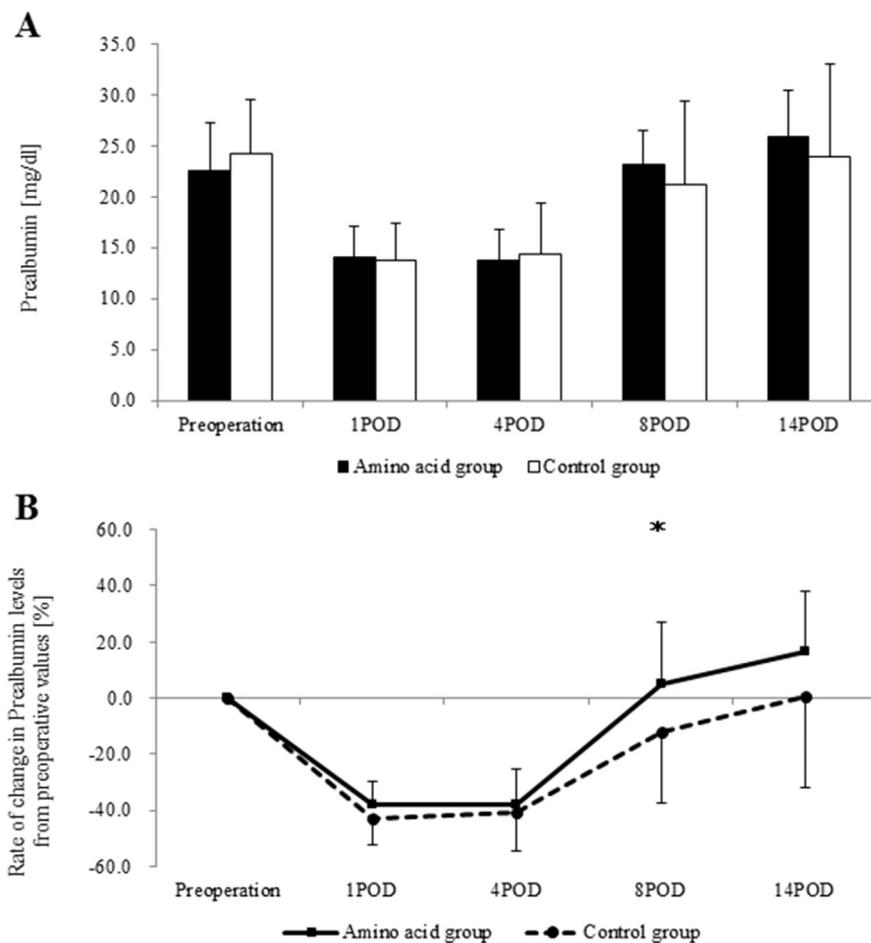
Fig. 2. Prealbumin levels and rate of change from preoperative values. (A) Prealbumin levels, (B) Rate of change in prealbumin levels from preoperative values. PreAlb levels were decreased by 40% at postoperative day 1 in all patients and the rate of change did not differ significantly between the two groups. However, the rate of change was positive on postoperative day 8 in the amino acid group ($5.1 \pm 21.8\%$), but it remained negative in the control group ($-12.3 \pm 24.9\%$; $p = 0.041$). POD, postoperative day; POM, postoperative month; *, $p < 0.05$.

changes were observed between two groups (Fig. 3A and B).

Nitrogen balance values were positive from postoperative day 1 to postoperative day 7 in the amino acid group, but were positive after postoperative day 4 in the control group (Fig. 4).

3.3. Secondary outcomes

Mean body weight was decreased by 3% at postoperative day-14 in both groups. Three months after surgery, body weights were found decreased by 3% and 6% in the amino acid and the control groups, respectively (Fig. 5).

Postoperative complication rates did not differ significantly between the two groups (six patients in the amino acid group (35.3%) versus four in the control group (25.0%) ($p = 0.52$).

3.4. Blood biochemistry

Although BUN levels were significantly higher in the amino acid group than those in the control group on postoperative day-4 (amino acid group, 15.1 ± 4.0 mg/dL; control group, 8.6 ± 2.8 mg/dL; $p < 0.001$) and day-8 (19.4 ± 3.9 mg/dL and 12.9 ± 4.5 mg/dL, respectively; $p = 0.001$), these values were similar in both groups at 3 months (13.5 ± 3.6 mg/dL and 13.0 ± 4.2 mg/dL, respectively; $p = 0.773$; Supplementary Fig. 2). Blood sugar levels did not significantly differ between the two groups until postoperative day-14 (Supplementary Fig. 3).
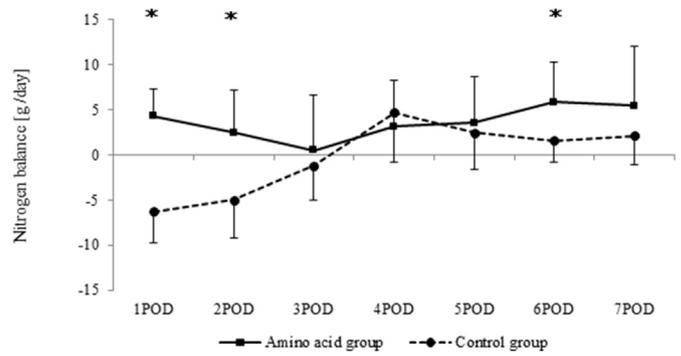
Fig. 4. Nitrogen balance. Nitrogen balance values were positive from postoperative day 1−7 in the amino acid group, but they were positive after postoperative day 4 in the control group. POD, postoperative day; *, $p < 0.05$.

4. Discussion

It has been thought that breakdown and catabolism of muscle protein can be limited by enteral or intravenous feeding that meets total energy requirements of patients during high-level post-surgical stress [7]. However, recent studies show that fat and muscle protein are catabolized following release of stress hormones and cytokines in response to high degrees of surgical stress, supplying
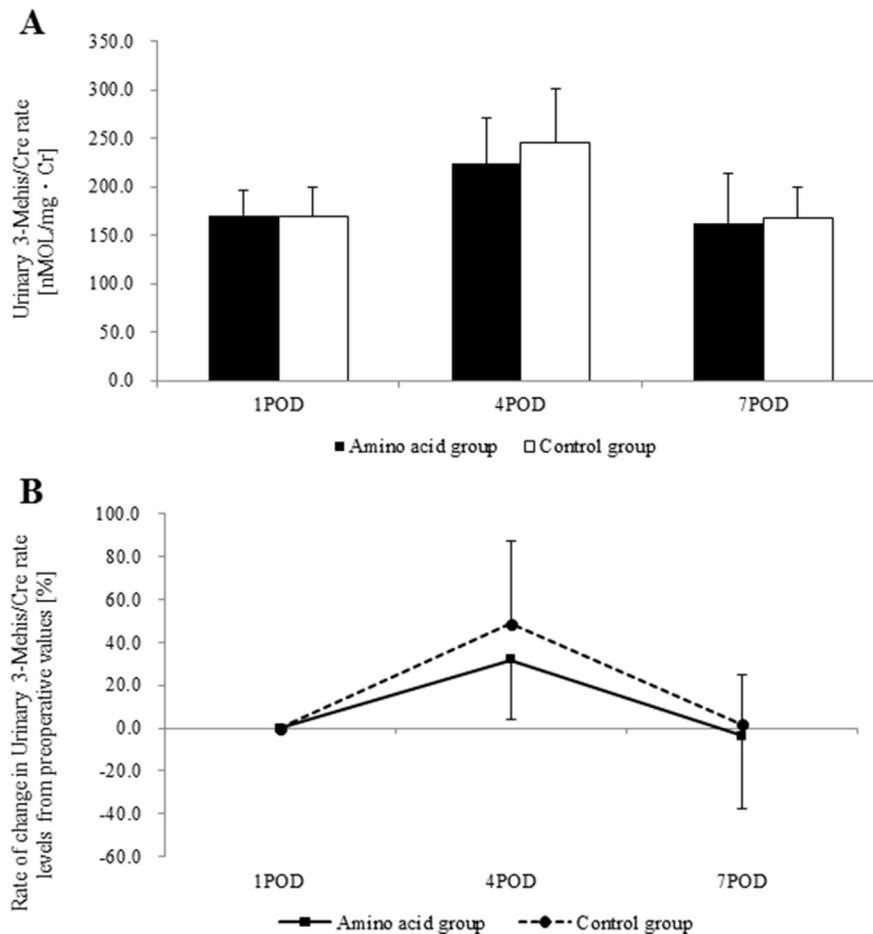
Fig. 3. Urinary 3-Mehis/Cre rate and rate of change from postoperative day 1 value. (A) Urinary 3-Mehis/Cre rate, (B) The rate of change of Urinary 3-Mehis/Cre rate levels from postoperative day 1 value. Urinary 3-MeHis/Cre levels were increased in both groups on postoperative day 4 and they were similar on days 7 and 1. No significant differences in urinary 3-MeHis/Cre levels or rates of changes were observed between the two groups. POD, postoperative day.
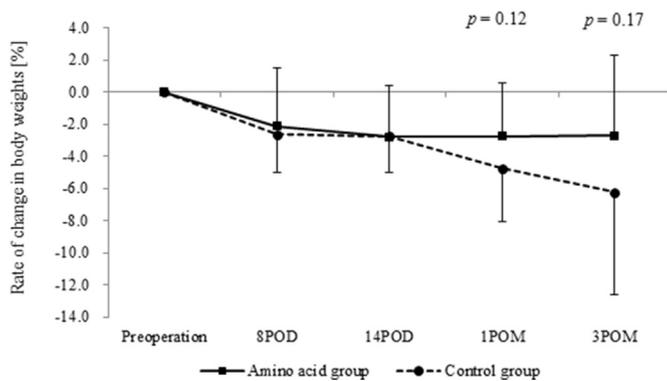
Fig. 5. Rate of change in body weight from preoperative values. Mean body weights were decreased by 3% at postoperative day 14 in both groups. However, they were decreased by 3% and 6% in the amino acid group and the control group, respectively, at 3 months after surgery. POD, postoperative day; POM, postoperative month.

the body with endogenous energy. Hence, the administration of exogenous nutrition that is equivalent to total energy consumption induce a relative surplus of energy and may trigger AEs such as hyperglycemia after highly invasive surgery. Therefore, nutrition therapy may adversely affect recovery from surgical stress [2]. Under these conditions, carbohydrate, proteins, and lipids are catabolized, and most of the energy is derived from skeletal muscle proteins [8] following catabolism of branched chain amino acids (BCAAs). Although protein synthesis and catabolism are enhanced in skeletal muscle under conditions of high surgical stress, catabolism exceeds synthesis, leading to protein loss and amino acid release [9,10]. Thus, the present nutrition strategy was designed to suppress protein catabolism and limit the loss of muscle.

Enteral feeding is generally used for nutritional control during the perioperative period in esophageal cancer patients [6] and is associated with a low risk of postoperative complications [11–14]. Usually, intravenous feeding is concurrently used with enteral feeding during early postoperative periods within 7 days in esophagectomy patients according to the guidelines of ASPEN and ESPEN. In this study, we assessed the effects of intravenous amino acid supplementation in these periods, within 7 days, after esophagectomy. In terms of intravenous glutamine supplementation, it has been reported that central venous nutrition with an abundance of glutamine during the postoperative period reduced postoperative infection rates and improved inflammatory responses in gastrointestinal cancer patients [15]. Meanwhile, Marton et al. demonstrated that perioperative glutamine supplementation had no influence on morbidity, mortality, and postoperative inflammatory response after esophagectomy [16]. As little is known of the effects of intravenous amino acid supplementation during recovery from surgical stress on early postoperative period, we assessed the effects of intravenous amino acid supplementation via peripheral veins, following radical esophagectomy for esophageal cancer patients.

No significant differences in urinary 3-Methi/Cre levels or rates of changes were observed between control and amino acid supplemented patients, indicating that catabolism of muscle protein [17,18] could not be controlled by intravenous administration of amino acids (Fig. 4). Skeletal muscle protein is degraded in the postsurgically stressed body, and it results in negative nitrogen balance. Nitrogen balance is normalized when the precedence of protein synthesis over degradation after recovery from starvation state by nutrition therapy [18]. In our study, as normalization of nitrogen balance was observed on postoperative days 3–4 in the control group, we considered this period representative of the

transition from protein degradation to protein synthesis. In the amino acid group, nitrogen balance remained positive from postoperative days 1–7 (Fig. 5). Accordingly, the present data indicate that nitrogen balance was maintained by addition of amino acids until postoperative day 7.

Interestingly, Alb levels and rates of changes were significantly higher in the amino acid group on postoperative day 14 and at 1 month postoperatively. In terms of the rapid turnover protein, the rate of change in PreAlb levels was higher in the amino acid group than that in control group on postoperative day 8, and tended to be higher on postoperative day 14. In addition, the rate of preoperative body weight loss remained comparatively low in the amino acid group at 1 and 3 months postoperatively, although no significant differences in postoperative body weights were found between the two groups. These data indicate that intravenous supplementation with amino acids in addition to enteral feeding during the early postoperative period did not produce immediate effects; however, subsequent protein resynthesis was improved after the initial period of muscle protein degradation by esophagectomy.

In this study, no significant increases in postoperative complications, including hyperglycemia, were observed.

5. Conclusion

Hence the present results demonstrate that peripheral venous administration of amino acids in addition to enteral following high surgical stress is an extremely effective method of nutritional control.

Author contribution

Masafumi Konosu performed the studies, data analyses, and drafted the manuscript; Takeshi Iwaya revised the article critically; Yuji Akiyama helped in data interpretation; Yoshihiro Shioi, Fumitaka Endo analysed the data; Hiroyuki Nitta, Koki Othuka, Keisuke Koeda supervised the study; Yusuke Kimura and Akira Sasaki conceived the study and participated in the design and coordination of the study.

Conflicts of interest

All authors declare no conflict of interest related with employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding, individually.

Guarantor

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Consent

All study participants provided informed written consent prior to study enrollment.

Registration of research studies

Research registry 1513.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amsu.2017.01.016.

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