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Original

Effect of Preoperative Carbohydrate and Amino Acid Infusion on Postoperative Counter-Regulatory Hormone in Patients Undergoing Elective Thoracoscopic Esophagectomy

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Abstract: Compared with the conventional open surgery, thoracoscopic esophagectomy results in decreased thorax destruction, fewer postoperative complications, and shorter hospitalisation. However, preoperative fasting causes hyperglycemia, prompting attempts to improve postoperative hyperglycemia by preoperatively administering carbohydrate orally or intravenously. Herein, we examined the effect of preoperative carbohydrate and amino acid infusion on counter-regulatory hormone levels in patients undergoing elective thoracoscopic esophagectomy. The glucose and amino acid (GA) group (n = 12) were infused with a low concentration of sugar accelerant and amino acid, and the control (GAF) group (n = 12) was infused with a sugar-free extracellular fluid, until entering the operating room. We evaluated plasma catecholamine 3 fractions, cortisol, and glucose, as well as 3-methylhistidine in the urine. Adrenaline levels were significantly higher in the GAF group (263.0 ± 201.8 μIU / ml) than in the GA group (114.7 ± 127.0 μIU / ml) at the end of the surgery ($P = 0.042$), and at postoperative day (POD) 1 (200.8 ± 137.4 vs. 80.5 ± 64.3 μIU / ml; $P = 0.013$). The noradrenalin level was also significantly higher in the GAF group (517.9 ± 523.6 μIU / ml) than in the GA group (254.3 ± 205.4 μIU / ml) at POD1 ($P = 0.028$), as was the cortisol level (20.0 ± 10.6 μIU / ml vs. 10.2 ± 8.0 μIU / ml; $P = 0.015$). No significant differences were observed between the two groups in levels of blood glucose or 3-methylhistidine in the urine. Preoperative glucose-amino acid administration improved catabolism suppression in this study.

Key words: esophageal cancer, preoperative carbohydrate and amino acid infusion, catecholamine fractions, counter-regulatory hormone

Introduction

Catabolism due to surgical stress can result in proteolysis, lipolysis, glycogenolysis, and gluconeogenesis, facilitating hyperglycemia[1]. Postoperative hyperglycemia delays wound healing, increases the risk of infection and other complications, and increases hospital stays, with the

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Table 1. Infusion formulation composition

	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	SO_4^{2-}	Ace tate$^-$	Lac tate$^-$	Cit rate^{3-}	P	Zn	Glucose	Total amino acid	Calorie
	mEq / l									mmol / l		g / l		kcal / l
BFLUID®	35	20	5	5	35	5	16	20	6	10	5	75	30	420
Veen-F®	130	4	3	−	109	−	28	−	−	−	−	−	−	−

resultant infection and other complications being potentially life-threatening[2–5]. Because hyperglycemia is facilitated by preoperative fasting, clinicians in Europe have undertaken trials of preoperative oral or intravenous administration of a carbohydrate to prevent or improve postoperative hyperglycemia[6–10]. Postoperative counter-regulatory hormone administration has also been tried in the past; however, reports of how preoperative carbohydrate–amino acid administration affects the postoperative counter-regulatory hormone are rare. Therefore, we examined the effect of preoperative carbohydrate and amino acid infusion on postoperative counter-regulatory hormone in patients undergoing elective thoracoscopic esophagectomy.

Patients and methods

Patients

The clinical trial ethics review committee of Showa University Hospital approved this study, and all patients provided informed consent. This study included 24 patients scheduled to undergo thoracoscopic esophagectomy in the left lateral decubitus position and gastric tube reconstruction from January 2011 to June 2012. Patients with diabetes or impaired glucose tolerance, congestive heart failure, azotemia, severe renal failure, or amino acid metabolism disorders were excluded.

Random allocation was performed by the envelope method, and patients were divided into two groups. The GA group was infused with a low concentration of sugar accelerant and amino acid (BFLUID®, Otsuka Pharmaceutical Co., Ltd.) in 2,000 ml, and the GAF group was infused with sugar-free extracellular fluid (Veen-F Inj., Kowa Co., Ltd.) in 2,000 ml, from 19:00 following the evening meal until the time of entering the operating room on the following day (Table 1).

Anesthesia

A unified method of anesthesia was given; whereby an epidural catheter was inserted before the induction of anesthesia, which involved the administration of remifentanil (0.1–0.5 μg / kg / min) and sevoflurane (1%–2%). After 1 h of surgery, an epidural continuous infusion of 0.2% anapein in 100 ml + morphine hydrochloride at 0.14 mg / kg at a rate of 4 ml / h was initiated. The intraoperative infusion was unified with the sugar-free extracellular fluid given to both the GA and GAF groups.

Postoperative infusion

The postoperative infusion was unified as follows:

-Surgery day : the amount of heat was 420 kcal and moisture content was 3.0 ml / kg / h, and was appropriately increased or decreased.

After the surgery, the sugar-free extracellular fluid was infused. At 0:00, the remaining sugar-less extracellular fluid was discarded, and an infusion of BFLUID® (1,000 ml) commenced.

-Postoperative day 1 : the amount of heat was 420 kcal and moisture content was 2.5 ml / kg / h, and was appropriately increased or decreased.

A BFLUID® infusion (1,000 ml) + sugar-free extracellular fluid (necessary amount of water) was administered.

-Postoperative day 2 : the amount of heat was 840 kcal and moisture content was 2.0 ml / kg / h, and was appropriately increased or decreased.

A BFLUID® infusion (2,000 ml) + sugar-free extracellular fluid (necessary amount of water) was administered.

-Postoperative day 3 : the amount of heat was 1,120 kcal and moisture content was 2.0 ml / kg / h, and was appropriately increased or decreased.

An ELNEOPA® No. 1 infusion (2,000 ml) + sugar-free extracellular fluid (necessary amount of water) was administered.

-Postoperative day 4 : the amount of heat was 1,120 kcal and moisture content was 2.0 ml / kg / h, and was appropriately increased or decreased.

An ELNEOPA® No. 1 infusion (1,000 ml) + sugar-free extracellular fluid (necessary amount of water) was administered.

Blood examination

Blood was collected on the day before surgery (①, the day before surgery), before entering the operation room (②, surgery day), at the end of the thoracic cavity operation (③, after the thoracic operation), at the end of the surgery (④, after operation), and on the mornings of the first day after surgery (⑤, POD1), third day after surgery (⑥, POD3), and fifth day after surgery (⑦, POD5).

Urine samples were collected for 24 h, two days before the surgery (①, before the surgery), during the surgery (④, after operation), and after the surgery until 24:00 of the surgery date from (⑤, POD1) (Fig. 1).

Statistical analysis

Catecholamine and cortisol are the basic materials of gluconeogenesis by decomposing proteins and fats ; hence, we evaluated catecholamine and cortisol. 3-methylhistidine is a metabolite of arginine, lysine, and histidine without being recycled for protein synthesis and is excreted in the urine. It is possible to evaluate the degree of catabolism and use it as an indicator of the turnover of muscle protein[11–14]. We thus measured blood glucose and the urinary concentration of 3-methylhistidine. We set the above evaluation items and examined the impact of the

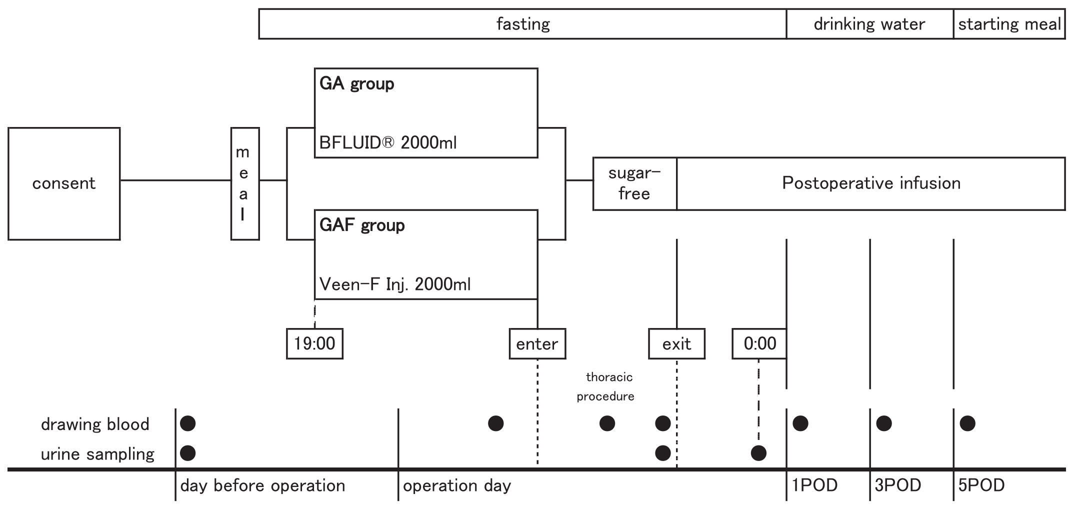


Fig. 1. Examination schedule, showing the points of infusion in both groups of patients and the points of drawing blood and sampling urine

Table 2. Patient characteristics and surgical outcomes

	GAF group (n = 12)	GA group (n = 12)	*P* value
Male / Female	11 / 1	5 / 7	0.027*
Age	64.4 ± 4.4	60.2 ± 9.1	0.445
Height (cm)	162.5 ± 9.2	162.4 ± 4.8	0.984
Weight (kg)	56.7 ± 9.7	54.6 ± 7.5	0.612
BMI (kg/m^2)	21.3 ± 3.0	20.6 ± 1.8	0.572
Stage (I / II / III / IV)	3 / 2 / 6 / 1	6 / 3 / 3 / 0	
Thoracic cavity Operation time (min)	242.7 ± 45.2	218.8 ± 80.6	0.438
Amount of bleeding (ml)	321.6 ± 284.0	150.4 ± 93.4	0.537

preoperative carbohydrate-amino acid administration on postoperative counter-regulatory hormone, as well as the presence of any postoperative inflammation and complications. Data analysis and the numbers are presented by the mean ± standard deviation. Statistical analysis was conducted using JSTAT 9.3, after performing an f-test (a test of normality) to test for differences between the groups, and a t-test (normal distribution) or Mann-Whitney U test (non-normal distribution). $P < 0.05$ was considered statistically significant.

Results

1) Patient characteristics and surgical outcomes

This study analyzed 24 patients. Three surgeons that were surgery technology certified in the area of esophagus malignant diseases by the Japan Endoscopic Surgery Society performed the surgery. There were more female patients in the GA group than in the GAF group, and a significant difference was observed in the male-to-female ratio calculated using Fisher's exact test; $P = 0.027$ (Table 2).

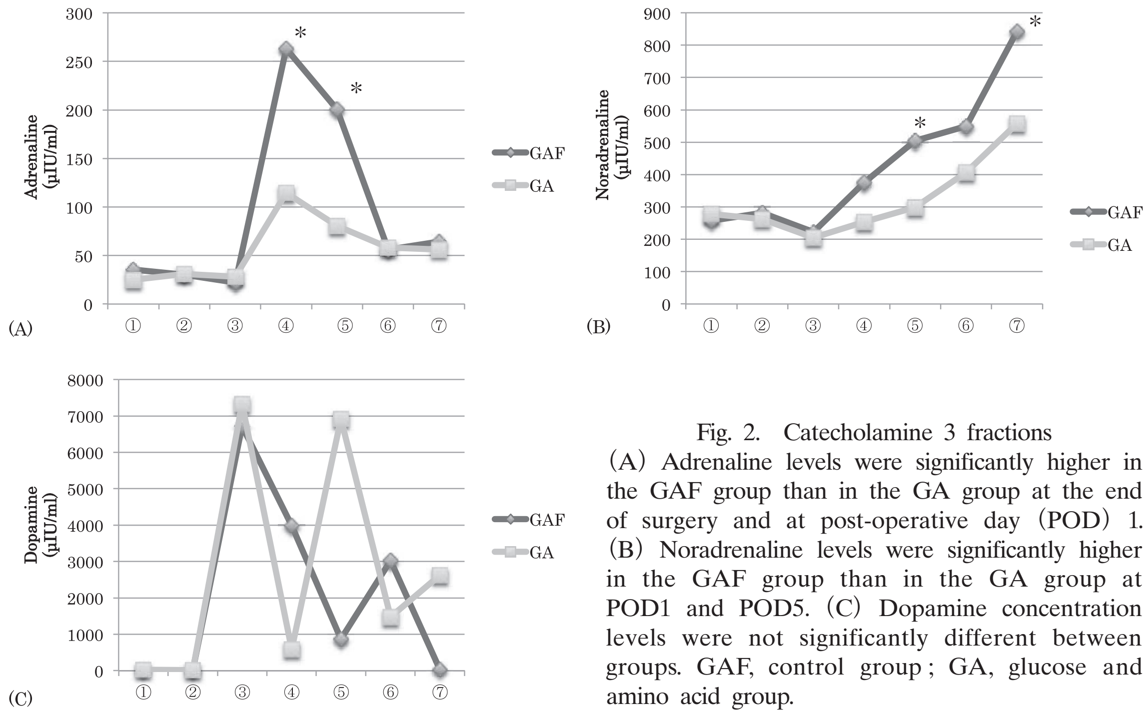


Fig. 2. Catecholamine 3 fractions
(A) Adrenaline levels were significantly higher in the GAF group than in the GA group at the end of surgery and at post-operative day (POD) 1. (B) Noradrenaline levels were significantly higher in the GAF group than in the GA group at POD1 and POD5. (C) Dopamine concentration levels were not significantly different between groups. GAF, control group ; GA, glucose and amino acid group.

2) Catecholamine 3 fractions

The adrenaline level was significantly higher in the GAF group (263.0 ± 201.8 μIU / ml) than in the GA group (114.7 ± 127.0 μIU / ml) at the end of the surgery and at POD1 (200.8 ± 137.4 μIU / ml vs. 80.5 ± 64.3 μIU / ml ; Fig. 2A).

The noradrenaline level was significantly higher in the GAF group than in the GA group at POD 1 and POD 5 (517.9 ± 523.6 μIU / ml vs. 254.3 ± 205.4 μIU / ml and 843.2 ± 313.8 μIU / ml vs. 558.4 ± 234.4 μIU / ml, respectively ; Fig. 2B).

There was no significant difference in the dopamine level between the groups (Fig. 2C).

3) Cortisol

Cortisol level at the end of the chest cavity operation was significantly higher in the GA group (5.0 ± 2.3 μIU / ml) than in the GAF group (9.3 ± 7.3 μIU / ml). However, at POD1 it was significantly higher in the GAF group (10.2 ± 8.0 μIU / ml) than in the GA group (20.0 ± 10.6 μIU / ml) (P = 0.015) (Fig. 3).

4) Blood glucose

The blood glucose level increased during the surgery and decreased after the surgery in both groups ; however, the differences between groups were not significant (Fig. 4).

5) Urinary 3-methyl histidine

The urinary 3-methyl histidine level decreased postoperatively in both groups, but not significantly (Fig. 5).

6) White blood cell count, CRP value, total protein value, albumin level, and urea nitrogen value

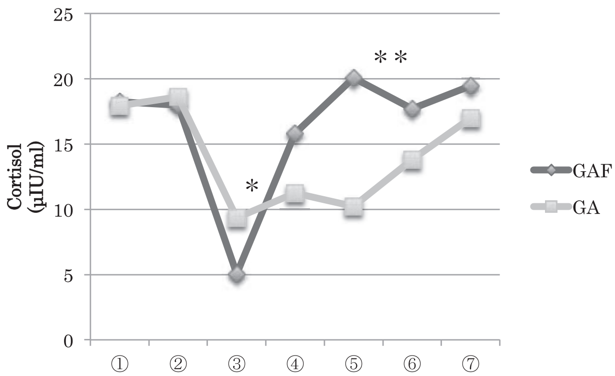


Fig. 3. Cortisol
Cortisol level was significantly higher in the GA group than in the GAF group after the thoracic operation. The level was significantly higher in the GAF group than in the GA group at post operative day (POD) 1. GAF, control group ; GA, glucose and amino acid group.

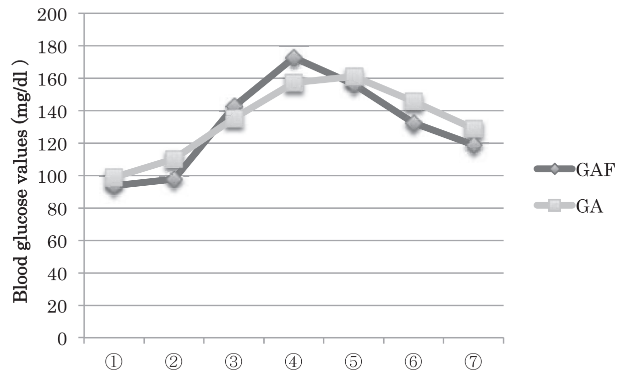


Fig. 4. Blood glucose
Blood glucose levels increased during surgery and decreased after the surgery. However, no significant difference between the groups was observed. GAF, control group ; GA, glucose and amino acid group.

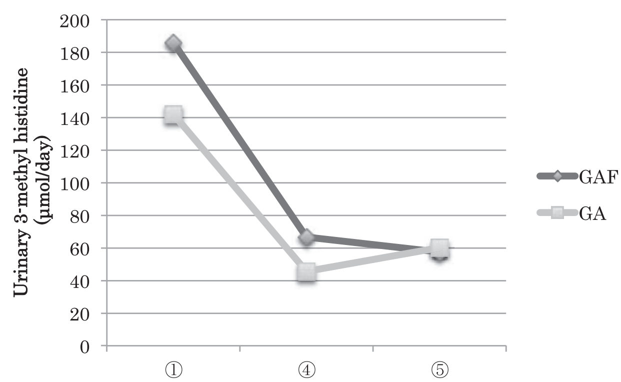
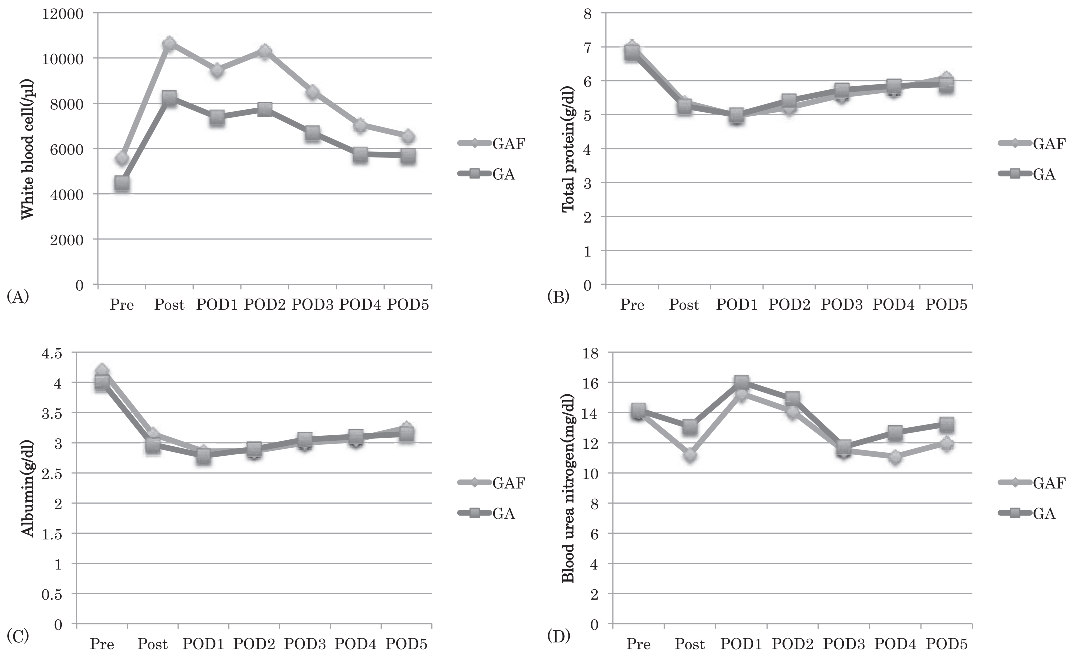


Fig. 5. Urinary 3-methyl histidine
Urinary 3-methyl histidine levels decreased after surgery and there were no significant differences between groups. GAF, control group ; GA, glucose and amino acid group.

The laboratory data are depicted as follows : the day before the surgery ①, and after the surgery ②, POD1 ③, POD2 ④, POD3 ⑤, POD4 ⑥ and POD5 ⑦, there were no significant differences between groups in white blood cell count (Fig. 6A), total protein level (Fig. 6B), albumin level (Fig. 6C), or urea nitrogen level (Fig. 6D). At POD2, the CRP level (Fig. 6E) was significantly higher in the GAF group (11.9 ± 4.0 μIU / ml) than in the GA group (8.2 ± 3.1 μIU / ml), and at POD3, the CRP value was significantly higher in the GAF group (10.7 ± 4.0 μIU / ml) than in the GA group (6.2 ± 3.5 μIU / ml).

7) Complications

Complications requiring reoperation did not occur in either group, and there were no significant differences between groups regarding the incidence of complications. Pneumonia, pneumothorax, lymphatic edema, and anemia were observed in each patient in the GAF group. Pneumonia was observed in two patients in the GA group.



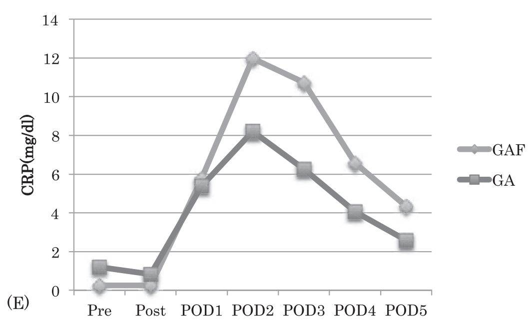


Fig. 6. White blood cell count, CRP, total protein, albumin, and blood urea nitrogen
No significant differences were observed between groups in white blood cell count (A), total blood protein level (B), blood albumin level (C), or blood urea nitrogen level (D); however, blood CRP levels were significantly higher in the GAF group than in the GA group at post-operative day (POD) 2 and POD3 (E). GAF, control group; GA, glucose and amino acid group.

Discussion

Cholecystectomy patients administered preoperative carbohydrates have demonstrated an improved postoperative hyperglycemia compared to those not receiving such preoperative treatment[6, 15]. However, cardiac surgery patients do not exhibit the same improvement following the preoperative administration of carbohydrates[16–18]. Based on the fact that similar differential effects have been observed with such preoperative treatment, we decided to investigate the outcomes in esophageal cancer patients.

As the half-life of catecholamine is a few minutes[19], it is believed to be an indicator of surgical stress[20]. In addition, more than 60% of systemic glucose is produced by gluconeogenesis following fasting for 22 hours[21]. Thus, because protein is converted into an amino acid by catecholamine, and fat is converted to glycerol and fatty acids by cortisol, catecholamines and cortisol are considered to be indicators of catabolism[21]. In this study, both adrenaline and noradrenaline levels were higher in the group of patients given preoperative carbohydrate-amino acid by infusion compared to the control group not given such infusion. Adrenaline was restored to approximately preoperative levels by POD3, and noradrenaline in both groups was higher than the preoperative levels even at POD5. Moreover, the results suggested an advanced invasive state persisting after surgery and that the preoperative carbohydrate–amino acid administration contributes to catabolism suppression. However, there was also a high level of variability in dopamine levels, making the evaluation between groups somewhat difficult, and some of the patients receiving intravenous dopamine during and after the surgery might have had an effect on these results. Lower cortisol levels in the GA group than in the GAF group indicated that the preoperative administration of carbohydrate–amino acids appeared to contribute to the suppression of catabolism.

As 3-methyl-histidine is excreted in the urine without being recycled for protein synthesis and the turnover to muscle protein, it can be used as an indicator of catabolism[11, 12]. The level of 3-methylhistidine in the urine was expected to remain high postoperatively in the present study cohort, although it was lower than the pre-operative levels in both groups, with no significant difference between groups. Therefore, the degree of protein catabolism was seemingly not different between the GAF and GA groups. Moreover, no significant difference was observed between the groups in blood glucose value or urinary 3-methylhistidine, confirming that evaluating the effect of the counter-regulatory hormone could be valid.

Our findings indicated that the preoperative administration of glucose–amino acids contributed to catabolism suppression. And the high level of catecholamine in the patients, even for the procedure of thoracoscopic esophagectomy, suggested extensive surgical invasion of the patients. Although surgery for esophageal cancer is the most invasive surgery of the digestive region, thoracoscopic esophagectomy has exhibited decreased thorax destruction compared with conventional open surgeries, minimal postoperative complications, and shorter hospital stays. High levels of CRP may indicate the occurrence of complications in such patients, and in this study, CRP levels were higher in the GAF group at POD2 and POD3, but the overall incidence of complications was low and there was no difference in the occurrence of complications between groups. This study only targeted patients undergoing thoracoscopic esophagectomy and future studies should compare results across open surgical patients. Finally, our findings indicate that the preoperative carbohydrate and amino acid infusion has a positive impact on postoperative outcomes.

Conflict of interest disclosure

The authors have no conflict of interest to declare.

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