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식도암 환자에서 아이보-루이스 식도절제술 시행 후 영양지원 평가

박수진[1] · 이영미[1] · 이유정[2*]
[1]삼성서울병원 약제부, [2]강원대학교 약학대학

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Evaluation of Postoperative Nutrition Support after an Ivor-Lewis Esophagectomy in Patients with Esophageal Cancer

Su Jin Park[1], Young Mi Lee[1], and Yu Jeung Lee[2]*
[1]*Department of Pharmacy, Samsung Medical Center, Seoul, South Korea*
[2]*College of Pharmacy, Kangwon National University, Chuncheon, South Korea*

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Objective: Undernutrition is common amongst esophageal cancer patients and therefore appropriate nutrition support is critical. Nevertheless, the effectiveness of enteral nutrition (EN) versus parenteral nutrition (PN) is still controversial. The aim of this study was to investigate the effect of EN and PN on the nutritional state and the length of hospital stay for patients who underwent an Ivor-Lewis (IL) esophagectomy. **Method:** A retrospective clinical analysis was performed that utilized the electronic medical records of patients who underwent IL esophagectomy during a 3-year period between January 2010 and December 2012 at a tertiary teaching hospital located in Seoul, Korea. The EN group and PN group were analyzed by comparing the nutrition supply, postoperative complications, length of hospital stay, and weight variation. **Results:** After an IL esophagectomy, the complication rate between the EN group and PN group was insignificant and the length of hospital stay was significantly shorter for the PN group compared to the EN group (14 vs. 16 days, respectively; $p<0.001$). At the time of discharge, those in the PN group lost less weight postoperatively ($p=0.003$). **Conclusion:** PN may be considered as safe nutrition support for esophageal cancer patients who underwent an esophagectomy.

□ Key words - nutrition support, Ivor-Lewis esophagectomy, EN, PN, esophageal cancer

INTRODUCTION

Esophageal cancer has the sixth highest prevalence rate amongst males worldwide, with a relatively higher incidence rate in Asia and Africa compared to that of the U.S.[1)] Undernutrition occurs in 60~85% of esophageal cancer patients and increases the mortality rate.[2)] Ivor-Lewis (IL) esophagectomy is a procedure used to approach and to remove a tumor located in the lower part of the esophagus. Compared to transhiatal esophagectomy, which was the more common approach used in the past, an IL esophagectomy has lower mortality and provides better oncological clearance, which makes it the preferred procedure in recent times.[3,4)] After an IL esophagectomy, 6-8 days of fasting is necessary, and typically the surgical site is checked for leakage on postoperative day (POD) 7 before beginning oral feeding. Thus, nutrition support is necessary because it is difficult to supply the calculated calorie need during the 7 days post-surgery.[5,6)] The two modes of nutrition support are enteral nutrition (EN) and parenteral nutrition (PN). Generally when PN is utilized, the occurrence rate of complications associated with the central venous catheter, metabolism, and infection are high. Therefore, if the gastrointestinal tract is functional, the EN approach should be considered first.[6,7)] Since

Correspondence to : Yu Jeung Lee
College of Pharmacy, Kangwon National University, Chuncheon-si, Gangwon-do 200-701, South Korea
Tel: +82-33-250-6913, Fax: +82-33-255-7865
E-mail: yujeung@kangwon.ac.kr

patients who undergo an esophagectomy often show severe weight loss that could lead to other complications, some researchers have suggested that all patients have a jejunostomy feeding tube inserted for EN after an esophagectomy.[8] However, other reports indicate that there is no significant clinical advantage (length of hospital stay, mortality rate, etc) for patients who receive jejunostomy feeding tubes placed after esophagectomy for EN.[9] In fact, a recent study has shown that after esophagectomy, PN and EN had similar nutritional state changes and complication rates[10], and therefore some clinicians do not insert jejunostomy feeding tubes and instead rely on PN for nutrition support.

After an esophagectomy, nutrition support for esophageal cancer patients is necessary in order to supplement undernutrition, but studies investigating which method of nutrition supply is most advantageous for these patients have been inadequate. Therefore, this study examined the effect of EN and PN on nutritional state, length of hospital stay, and weight variation for esophageal cancer patients who underwent an IL esophagectomy.

METHODS

Study subjects

A retrospective clinical analysis was performed utilizing the electronic medical records of patients who underwent IL esophagectomy during the 3-year period between January 2010 and December 2012 at the Samsung Medical Center, which is a 2000-bed tertiary teaching hospital located in Seoul, Korea.

1) Inclusion criteria

a. Esophageal cancer patients (Diagnosis code: C15, malignant neoplasm in esophagus)[11] who signed a consent for release of information

b. Patients who underwent an IL esophagectomy during the study period

2) Exclusion criteria

a. Patients with metastatic, recurrent forms of esophageal cancer

b. Patients with other cancers, such as stomach, colorectal, or lung cancer

c. Patients with organ dysfunctions, such as liver dysfunction or renal insufficiency

Data collection

The list of patients who underwent an esophagectomy from 2010 to 2012 was obtained from the Department of Medical Records at the Samsung Medical Center. Amongst them, patients who underwent an IL esophagectomy were selected as subjects for the study, and patients who met any of the exclusion criteria were excluded. Patients who had a jejunostomy feeding tube inserted during the IL esophagectomy were assigned to the EN group and patients who did not have a jejunostomy feeding tube inserted were assigned to the PN group. Nutrition supply, postoperative complications, and length of hospital stay were compared between the two groups. This retrospective study was approved by the Institutional Review Board (IRB) at the Samsung Medical Center.

Definitions

1) Fasting (nil per os; NPO)

No food or liquid by mouth

2) PN group

A jejunostomy feeding tube was not inserted during the IL esophagectomy, and during the fasting period sufficient nutrition was provided with PN.

3) EN group

A jejunostomy feeding tube was inserted during the IL esophagectomy, and during the fasting period nutrition was provided with EN and supplemented with PN.

4) Basal Energy Expenditure (BEE)

The Harrison Benedict Equation was used for the calculation.[7]

5) Total Calorie Need (TCN)

Basal Metabolic Rate* Stress Factor (1.2)* Activity Factor (1.2) = TCN for 1 day.[7]

6) Length of hospital stay

Total days of hospital stay, from hospitalization date to discharge date

7) Length of hospital stay after surgery

From the surgery date to discharge date. Normally, patients were admitted 1-2 days prior to the esophagec-

tomy and began fasting the day before surgery, but some patients were admitted more than 3 days prior to surgery for diagnosis and examination independent of the severity of the disease. To eliminate potential bias, the length of hospital stay after surgery was separately analyzed.

8) Length of hospital stay subgroup analysis

Exclusion of patients who were admitted more than 3 days prior to surgery from the total length of the hospital stay

Statistical analysis

Independent t-test, chi-squared test, or Fisher's exact test were used to analyze the baseline characteristics of study subjects. To compare the postoperative nutrition supply of the PN group with the EN group, a Mann-Whitney test was performed. After surgery, the complication rate of the two groups was compared using Fisher's exact test and chi-squared test. Length of hospital stay and weight variations were analyzed using the Mann-Whitney test and independent t-test, respectively. SPSS® version 12.0 (SPSS Inc., Chicago, USA) was utilized for statistical analysis. Statistical level of significance was defined as $p<0.05$.

RESULTS

Baseline characteristics of study subjects

During the length of the study, the number of patients who were admitted to the hospital's intensive care unit (ICU) after the esophagectomy was 518, of which 373 signed the consent for release of information. After excluding 69 patients with metastatic, recurrent forms of esophageal cancer, 27 patients with other forms of cancers, and 20 patients with organ dysfunction, 257 patients were left. Of these patients, 190 were included in the analysis that had undergone an IL esophagectomy. The PN and EN groups had 153 and 37 patients, respectively (Fig. 1).

Baseline characteristics of study subjects did not show any statistically significant differences. The average age of patients in the PN and EN groups was 63.1 and 65.5 years, respectively. Males accounted for 93.7% of the study subjects, and 97.4% of patients had squamous cell carcinoma (Table 1).

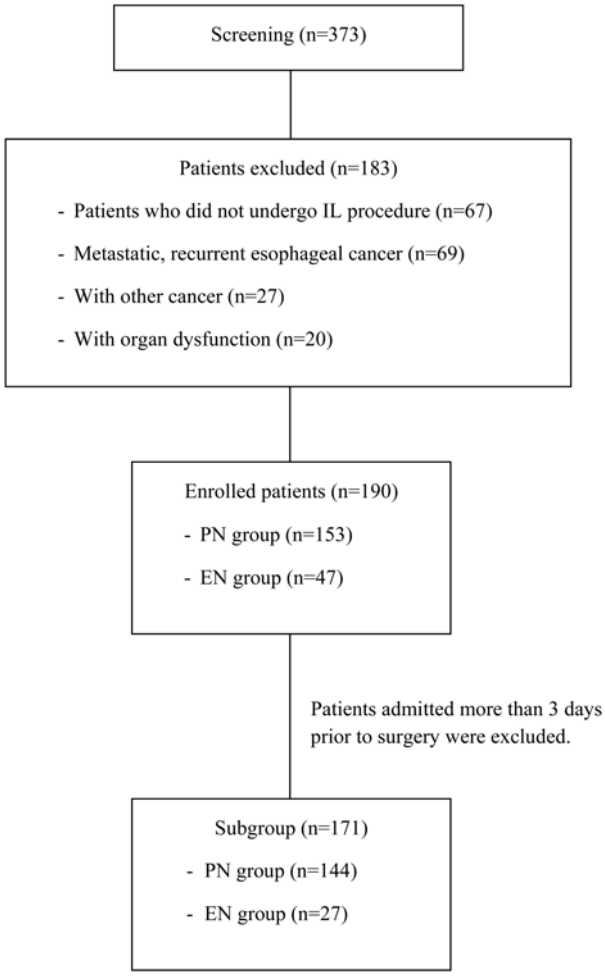

Fig. 1. Patient flow chart.

Supplied calorie count

The fasting period showed a non-normal distribution; the median values for the PN and EN group were 8 days and 4 days, respectively ($p<0.001$). BEE and total calorie need (TCN) of the two groups were not statistically different. The calorie need was approximately 30 kcal/kg/day for both groups. The day after surgery was designated as day 1, and the supplied calorie count of day 2 for the PN group was 31.2 kcal/kg/day, which was higher than that of the EN group, which was only supplied 24.9 kcal/kg/day ($p<0.001$). On POD 6, the supplied calorie count for the EN group was 35.7 kcal/kg, which was higher than that of the PN group, which received 33.2 kcal/kg ($p=0.019$). The 6-day average of supplied calorie count after surgery for the two groups was not significantly different. Both groups

Table 1. Characteristics of study subjects.[a]

Characteristics	Nutrition support type		Total (n=190)	p-value
	PN (n=153)	EN (n=37)		
Age (years)	63.1 (7.6)	65.5 (7.2)	63.6 (7.6)	0.081[b]
Sex, n (%) : male	145.0 (94.8)	33.0 (89.2)	178.0 (93.7)	0.254[c]
Height (cm)	165.0 (6.5)	163.6 (6.8)	164.7 (6.5)	0.233[b]
Weight (kg)	63.7 (9.2)	63.9 (11.3)	63.8 (9.6)	0.918[b]
BMI (mg/m^2)	23.4 (2.7)	23.8 (3.5)	23.5 (2.9)	0.458[b]
BMI group, n (%)				
Underweight	3 (2.0)	2 (5.4)	5 (2.6)	
Normal	105 (68.6)	21 (56.8)	126 (66.3)	0.294[c]
Overweight	41 (26.8)	13 (35.1)	4 (28.4)	
Obesity	4 (2.6)	1 (2.7)	5 (2.6)	
Histologic type, n (%)				
Squamous cell carcinoma	149 (97.4)	36 (97.3)	185 (97.4)	0.666[c]
Adenocarcinoma	2 (1.3)	1 (2.7)	3 (1.6)	
Others	2 (1.3)	0 (0.0)	2 (1.1)	
Neoadjuvant chemotherapy, n (%)	8 (5.2)	1 (2.7)	9 (4.7)	1.000[c]
Medical history, n (%)				
Diabetes mellitus	19 (12.4)	2 (5.4)	21 (11.1)	0.379[c]
Hypertension	56 (36.6)	12 (32.4)	68 (35.8)	0.705[d]
Cardiovascular disease	7 (4.6)	1 (2.7)	8 (4.2)	1.000[c]

Abbreviations: BMI (body mass index); EN (enteral nutrition); PN (parenteral nutrition).
[a]Values of continuous variables are expressed as mean (SD, standard deviation), unless otherwise noted. [b]Independent t-test. [c]Fisher's exact test. [d]χ^2-test.

were supplied with more than the calculated calorie need, but both groups did not show any significant differences when calorie need was compared with supplied calorie count (Table 2).

Postoperative complication rate and length of hospi-

Table 2. Comparison of nutrition support between the PN group and the EN group.[a]

	Nutrition support type		Total (n=190)	p-value[b]
	PN (n=153)	EN (n=37)		
Duration of NPO (day)	8.0 (7.0-28.0)	4.0 (4.0-11.0)	8.0 (4.0-28.0)	<0.001
BEE (kcal/day)[‡]	1341.0 (934.1-1762.6)	1291.0 (940.0-1768.5)	1339.2 (934.1-1768.5)	0.420
TCN (kcal/day)[§]	1931.0 (1345.1-2538.1)	1859.0 (1353.5-2546.6)	1928.4 (1345.1-2546.6)	0.420
TCN (kcal/kg/day)[§]	30.3 (27.4-40.3)	29.9 (26.0-34.8)	30.2 (26.0-40.3)	0.161
Daily provided calorie, (kcal/kg/day)				
Day 1	33.3 (5.8-45.9)	32.1 (15.9-47.0)	33.1 (5.8-47.0)	0.140
Day 2	31.2 (9.1-47.9)	24.9 (7.3-37.2)	29.6 (7.3-47.9)	<0.001
Day 3	32.6 (10.0-59.1)	31.8 (14.7-41.8)	32.5 (10.0-59.1)	0.250
Day 4	33.4 (13.6-52.6)	34.1 (13.0-46.2)	33.4 (13.0-52.6)	0.947
Day 5	33.6 (11.2-52.6)	33.0 (10.7-47.7)	33.5 (10.7-52.6)	0.915
Day 6	33.2 (8.1-59.1)	35.7 (20.2-54.2)	33.5 (8.1-59.1)	0.019
Mean of Day 1-6, (kcal/kg/day)	32.9 (18.5-50.6)	32.4 (13.6-43.2)	32.8 (13.6-50.6)	0.572
Provided calorie/TCN (%)	107.8 (62.0-140.0)	108.5 (50.0-130.0)	107.9 (50.0-140.0)	0.863

Abbreviations: BEE (basal energy expenditure); EN (enteral nutrition); NPO (nil per os); PN (parenteral nutrition); TCN (total calorie need).
[a]Values are expressed as median (range), unless otherwise noted. [b]Mann-Whitney test.

Table 3. Complications during hospitalization.

	Nutrition support type		Total (n=190)	p-value
	PN (n=153)	EN (n=37)		
Surgical complications, n (%)				
Arrhythmia	14 (9.2)	1 (2.7)	15 (7.9)	0.310[a]
Pneumonia	4 (2.6)	1 (2.7)	5 (2.6)	1.000[a]
Anastomosis site leakage	2 (1.3)	2 (5.4)	4 (2.1)	0.171[a]
Pleural effusion	8 (5.2)		8 (4.2)	0.358[a]
Wound problem	5 (3.3)		5 (2.6)	0.585[a]
Vocal cord palsy	4 (2.6)	1 (2.7)	5 (2.6)	1.000[a]
Others	2 (1.3)	3 (8.1)	5 (2.6)	0.052[a]
Any complications listed above	37 (24.2)	8 (21.6)	45 (237)	0.832[b]
Respiratory difficulty, n (%)	4 (2.6)	3 (8.1)	7 (3.7)	0.135[a]
Delayed gastric emptying, n (%)	2 (1.3)	2 (5.4)	4 (2.1)	0.171[a]
C-line related complications, n (%)	1 (0.7)		1 (0.5)	1.000[a]

Abbreviations: EN (enteral nutrition); PN (parenteral nutrition).
[a]Fisher's exact test. [b]χ^2-test.

tal stay

After the esophagectomy, the most common complications included arrhythmia, pneumonia, and respiratory failure, and the difference in complication occurrence rate between the groups was insignificant (Table 3). The length of total hospital stay for the PN group was significantly shorter than that of the EN group (14 vs. 16 days, respectively; p<0.001). The PN group also showed a significantly shorter length of hospital stay after surgery (p<0.001). After excluding patients who were hospitalized more than 3 days prior to surgery, the length of hospital stay for the PN group was significantly shorter than that of the EN group (14 vs. 15 days, respectively; n=171; p=0.005). The length of ICU stay was also significantly shorter for the PN group compared to the EN group (3 vs. 4 days, respectively; p=0.012) (Table 4).

Weight variation on POD 10 and on discharge date

Weight variation between the two groups on POD 10 was not significantly different (p=0.187). On the other hand, weight variation on the discharge date was greater for the EN group (p=0.003). On the discharge date, 24 patients from the PN group (15.7%) and 18 patients from the EN group (48.6%) lost more than 5% of their body weight (p<0.001) (Table 5).

DISCUSSION

Table 4. Comparison of length of hospital stay between the PN group and the EN group.[a]

	Nutrition support type		Total (n=190)	p-value[b]
	PN (n=153)	EN (n=37)		
Length of hospital stay (day)				
Total hospital stay	14.0 (11.0-34.0)	16.0 (13.0-47.0)	15.0 (11.0-47.0)	<0.001
Postoperative hospital stay	12.0 (9.0-32.0)	13.0 (11.0-38.0)	12.0 (9.0-38.0)	<0.001
ICU stay	3.0 (2.0-15.0)	4.0 (2.0-16.0)	3.0 (2.0-16.0)	0.012
	Subgroup[c] - Nutrition support type		Total	p-value[b]
	PN (n=144)	EN (n=27)	(n=171)	
Length of hospital stay (day)				
Total hospital stay	14.0 (11.0-34.0)	15.0 (13.0-29.0)	14.0 (11.0-34.0)	0.005
ICU stay	3.0 (2.0-15.0)	4.0 (3.0-16.0)	3.0 (2.0-16.0)	0.015

Abbreviations: EN (enteral nutrition); ICU (intensive care unit); PN (parenteral nutrition).
[a]Values are expressed as median (range), unless otherwise noted. [b]Mann-Whitney test [c]Patients admitted more than 3 days prior to surgery were excluded.

Table 5. Comparison of weight variation between the PN group and the EN group.[a]

	Nutrition support type		Total (n=190)	p-value
	PN (n=153)	EN (n=37)		
Weight variation on POD 10				
Amount of weight variation, kg (%)	0.0 (3.3)	-0.8 (2.9)	-0.2 (3.2)	0.187[b]
Weight variation group, n (%)				0.525[c]
Loss of ≥ 5%	9 (5.9)	1 (2.7)	10 (5.3)	
Change less than 5%	132 (86.3)	35 (94.6)	167 (87.9)	
Gain of ≥ 5%	12 (7.8)	1 (2.7)	13 (6.8)	
Weight variation at discharge				
Amount of weight variation, kg (%)	-2.2 (3.4)	-4.0 (2.8)	-2.5 (3.4)	0.003[b]
Weight variation group, n (%)				<0.001[c]
Loss of ≥ 5%	24 (15.7)	18 (48.6)	42 (22.1)	
Change less than 5%	125 (81.7)	19 (51.4)	144 (75.8)	
Gain of ≥ 5%	4 (2.6)	0 (0.0)	4 (2.1)	

Abbreviations: EN, enteral nutrition; PN, parenteral nutrition; POD, postoperative day.
[a]Values of continuous variables are expressed as mean (SD, standard deviation), unless otherwise noted.
[b]Independent t-test. [c]Fisher's exact test.

Compared to EN, PN has a higher rate of complication that can lead to liver dysfunction and hyperglycemia. Therefore, guidelines in the U.S. and Europe recommend EN when possible before resorting to PN.[5,6] However, the studies that substantiate these guidelines included not only esophageal cancer patients who underwent esophagectomy but other patients as well.

A study published in 2011 in Japan reviewed the effects of PN and EN on immune function, nutritional state, and inflammatory response in 30 adult esophageal cancer patients who had received an esophagectomy. After esophagectomy, 15 patients received nutrition via PN, and these patients were given 2000 kcal/day. The remaining 15 patients had a jejunostomy feeding tube inserted and were given 10 mL/hr as the initial amount, which increased gradually each day to a total of 60 mL/hr via EN. Using 5% or 10% dextrose in water, 2000 kcal/day was supplied at POD 4. Oral feeding was initiated on POD 8. Serum albumin and C-reactive protein (CRP) levels were measured on POD 1, 3, and 7, and did not show any statistically significant differences between the groups.[10] On the other hand, a different study involving 154 esophageal cancer patients reported that after surgery, EN reduced the rate of fatal complications.[12] EN was supplied via a nasojejunal tube, and 2000 kcal/day was set as the target calorie count. This result contrasts with the results of the aforementioned study, as the postoperative rate of total complications did not show any statistically significant difference between the groups (p=0.50). When two fatal complications, surgical site leakage and pneumonia, were analyzed together, the rate was statistically higher for the PN group compared to the EN group (30.6 vs. 15.7%, respectively; p=0.02). When surgical site leakage rate and pneumonia rate were analyzed separately, however, the rate of each complication did not show any statistically significant difference between the groups (surgical site leakage: p=0.17; pneumonia p=0.26). In addition, the length of hospital stay was significantly shorter for the EN group compared to the PN group (16 vs. 19 days, respectively; p=0.04), which contrasts with our current study. One difference is that 30% of the patients in the second study had stage IV patients and included all types of esophagectomy as well patients who had received neoadjuvant chemotherapy. Therefore, there is a possibility that more patients in the present study had less progressive forms of the disease. The fact that length of hospital stay for both groups was longer than this study also supports this notion.

There are several difficulties with utilizing EN after an esophagectomy. First, for the first 3-4 days, sufficient calorie and protein cannot be given, since nutrition supply must be gradually increased. Second, there is difficulty in

supplying nutrition as well as some aspiration risk. Third, EN has many complications, including diarrhea and flatulence. For these reasons, clinicians prefer to utilize PN after surgery.

One previous study measured the BEE of esophageal cancer patients who underwent an esophagectomy.[13] In that study, indirect calorimetry was used to measure BEE of 8 healthy adults and 8 patients who underwent an esophagectomy. Measurements were taken prior to surgery and on POD 7 as well as POD 14. Prior to surgery, the BEE of the experimental group was higher than the control group (23.3±2.1 vs. 20.4±1.6 kcal/kg/day, respectively). However, when the Harris-Benedict equation (HB equation) was used to compare the two groups, the values did not differ significantly. The measured BEE on POD 7 and POD 14 increased (27.3±3.5 and 23.7±5.07 kcal/kg/day, respectively). The measured BEE on POD 7 was 1.17 times higher than the value calculated using HB equation. Esophageal cancer patients who underwent an esophagectomy were found to have hypermetabolism. Therefore, based on the findings, the investigators of the study recommended a nutrition supply of 33 kcal/kg/day, which is obtained by multiplying the BEE with the active factor of 1.2-1.3, for patients undergoing an esophagectomy.

This study only examined calorie supply for up to 6 days after surgery, because the exact measurement of calorie supply was difficult to obtain from POD 7 when oral feeding began. The average of supplied calories for the 6 days was 32.8 kcal/kg/day, which is similar to the value found in the aforementioned study. However, the calorie supply was calculated using a standardized method and did not reflect nutritional state, weight, or disease state of each patient. The total supplied calories per day was 2000-2400 kcal/day, which was similar for all patients. As a result, it is likely that overweight patients received relatively lower supplied calories per kilogram, whereas underweight patients received relatively higher supplied calorie per kilogram. This implies that underweight patients may have a higher rate of complications arising from the over supplementation of calories.

Patients in the PN group began receiving nutrition on the day after surgery (day 2 of ICU stay), and administering nutrition via PN for newly admitted patients in the ICU remains controversial. A study published in 2011 indicated that if patients begin PN too soon after ICU admission, their dependence on an artificial respirator is longer and their infection-related complication rate is higher.[14] However, for patients who underwent an esophagectomy, there was a higher tendency of severe weight loss after surgery, which prompted clinicians not to delay PN. In addition, a recent study has shown that starting PN soon after ICU admission has advantages both in the length of artificial respirator use and muscle/fat tissue loss, which further supports starting PN the day after surgery.[15]

There were several limitations to this study. First, this study only included patients who underwent an IL esophagectomy from a single general hospital location. In addition, since patients with metastatic, recurrent esophageal cancer were excluded from the study, it is difficult to apply the results to all esophageal cancer patients. Lastly, the number of patients in the two groups differed greatly and complications involving hyperglycemia and electrolyte imbalance were not considered.

In conclusion, this study confirmed that PN and EN as nutrition supply methods do not have significantly different complication rates following an IL esophagectomy. The length of hospital stay was shorter and weight loss at discharge was lower for the PN group. Therefore, PN may be considered as a safe method of nutrition support after an esophagectomy for esophageal cancer patients.

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