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Randomized Controlled Study to Evaluate the Efficacy of a Preoperative Respiratory Rehabilitation Program to Prevent Postoperative Pulmonary Complications after Esophagectomy

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Key Words
Esophageal cancer · Rehabilitation · Clavien-Dindo classification · Utrecht pneumonia scoring system · Pulmonary complications

Abstract
Background/Aims: Patients with postoperative pulmonary complications after esophagectomy often have increased mortality. The purpose of the study was to examine the efficacy of preventing postoperative pulmonary complications by an intensive preoperative respiratory rehabilitation (PR) program for esophageal cancer patients. ***Methods:*** This study was a prospective randomized controlled study. Thirty patients in the PR group and 30 patients in the no preoperative respiratory rehabilitation (NPR) group were included. The PR group received preoperative rehabilitation for more than 7 days, while the NPR group did not receive any preoperative rehabilitation. All patients underwent postoperative rehabilitation from the first postoperative day. The postoperative pulmonary complications were evaluated using the Clavien-Dindo classification (CDC) and the Utrecht Pneumonia Scoring System (UPSS). ***Results:*** The CDC grade in the PR group was significantly lower than that in the NPR group ($p = 0.014$). The UPSS score in the PR group was significantly lower than that in the NPR group at postoperative day 1 ($p = 0.031$). In the multivariate analysis, NPR was an independent risk factor for postoperative pulmonary complications greater than CDC grade II (OR: 3.99, 95% CI: 1.28–12.4, $p = 0.017$). ***Conclusions:*** This study showed that the intensive PR program was capable of reducing the postoperative pulmonary complications in esophageal cancer patients.

Introduction

Esophagectomy is the optimal treatment for patients with resectable esophageal cancer. However, thoracic, abdominal and cervical surgical procedures during esophagectomy are often associated with high incidences of postoperative pulmonary complications due to surgical invasion. The incidence of postoperative pulmonary complications related to esophagectomy has been reported to range from 30 to 60% [1]. These complications in-

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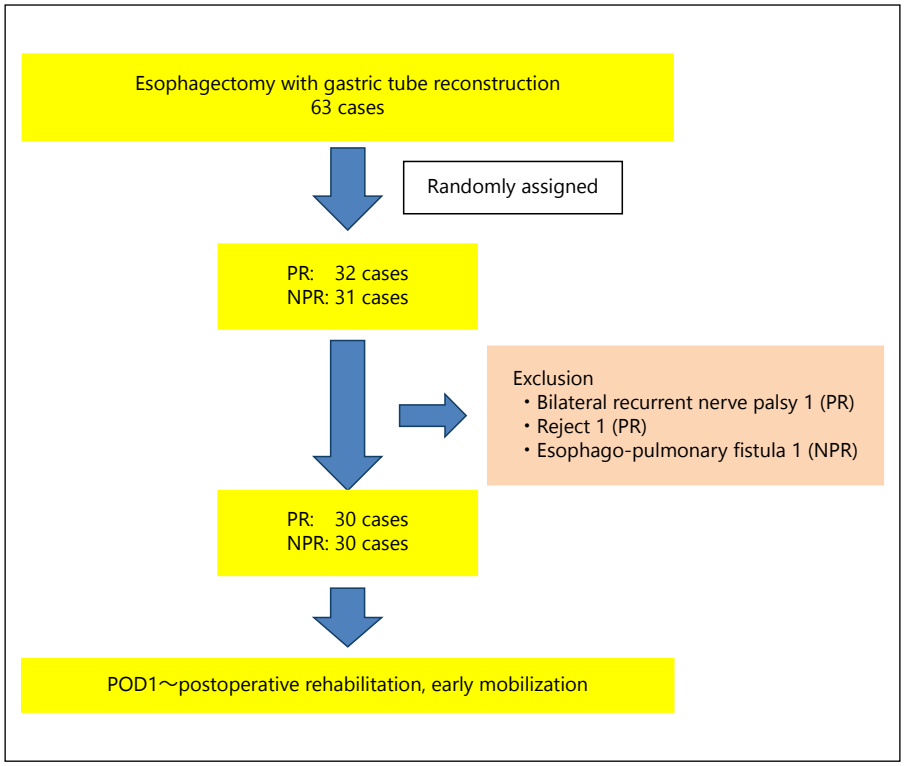

Fig. 1. The classification of patients. PR = Preoperative rehabilitation; NPR = non preoperative rehabilitation.

crease the mortality rate, prolong the hospital stay and contribute to additional medical costs [2]. Furthermore, a previous study demonstrated that the postoperative complications after esophagectomy correlated with a poor long-term survival [3]. The authors reported that the most likely cause was that patients who developed pneumonia died of unrelated causes to esophageal cancer after discharge from the hospital more frequently than those who did not develop pneumonia.

Recently, perioperative respiratory rehabilitation has been performed before thoracic surgery [4], cardiovascular surgery [5] and abdominal surgery [6] in order to prevent postoperative pulmonary complications. Previous groups have recommended intensive preoperative respiratory rehabilitation (PR) for patients undergoing thoracic surgery [7, 8]. This PR program is able to reinforce the respiratory muscle strength, lung volume and diaphragmatic excursion [9]. However, the clinical efficacy of PR is unclear for patients with esophageal cancer who undergo esophagectomy. Therefore, the aim of this study was to clarify the efficacy of PR for reducing respiratory complications after esophagectomy as evaluated through the use of the Clavien-Dindo classification (CDC) [10] and the Utrecht Pneumonia Scoring System (UPSS) [11].

Materials and Methods

Study Design

This study was a prospective randomized controlled study performed at Fukuoka University Faculty of Medicine from April 2011 to December 2014. The classification of the patients is shown in the Figure 1, and a total of 63 patients with esophageal cancer who underwent esophagectomy with gastric tube reconstruction participated in this study. The patients were randomly assigned to a PR group or a no preoperative respiratory rehabilitation (NPR) group by opening a sealed envelope. Three patients, including one patient who refused to participate in the trial, 1 patient who suffered from postoperative bilateral recurrent nerve palsy and 1 patient who underwent emergency surgery for an esophago-pulmonary fistula, were excluded. The PR group received PR for more than seven days, while the NPR group did not receive any PR. All of the patients underwent postoperative rehabilitation from the first postoperative day to the day of discharge. Even though the patients were under intubation in the intensive care unit during the postoperative phase, all patients completed the exercises for the program to the best of their abilities. The mortality, morbidity and postoperative pulmonary complications were investigated. The primary endpoint of this study was the incidence of postoperative pulmonary complications in patients with esophageal cancer who underwent esophagectomy.

Written informed consent was obtained from all included patients. This study was approved by the Institutional Review Board (No.11–7-04) and was registered in the UMIN CTR (UMIN No. 000006216) for clinical trials.

The Intensive PR Program

The intensive PR protocol consisted of the following exercises: (i) respiratory muscle and thoracic cage stretching to increase lung compliance; (ii) deep inspiration training and deep diaphragmatic breathing. The patient laid down on a flat surface. Then the patient placed one hand on his upper chest and the other just below the rib cage, which allowed the patient to feel his diaphragm move while breathing. The patient breathed in slowly through the nose so that the stomach moves against the hand. The patient then tightened his stomach muscles, letting them fall inward as he exhaled through pursed lips; (iii) efficient coughing and huffing with vigorous contraction of the abdominal muscles to improve expectoration; (iv) muscle strength exercises for the lower limbs and abdominal muscles. This muscle strength exercise leads to loading on the lower limbs and abdominal muscles using a weight; and (v) biking on an ergometer for 20 min. The volume of the load was modified depending on the patient's background. The PR program during the hospital stay was carried out for 60 min daily on weekdays under the supervision of a physical therapist in the rehabilitation center.

Evaluation of the Respiratory Function

The respiratory function, including FVC, FEV1, FEV1%, and peak flow (PEF), were measured using an Easy One™ device (Fukuda Denshi, Japan). Each value was measured in triplicate and the highest value obtained was considered for the analyses. The respiratory function was evaluated on the admission day.

Surgical Procedures and Perioperative Management

The current-smoking patients were educated to stop smoking preoperatively for at least 3 weeks. All patients underwent esophagectomy with gastric tube reconstruction. Initially, esophagectomy was performed using posterolateral thoracotomy or video-assisted thoracic surgery. All patients were administered 250 mg of methylprednisolone and 12.5 mg/h of sivelestat sodium hydrate intravenously during the intraoperative period. On postoperative days (POD) 1 and 2, 125 mg of methylprednisolone were given intravenously. The stomach wall was created under laparotomy. A gastric emptying procedure was not performed. A 28Fr thoracic drainage tube was detained in the right intrathoracic space. A feeding jejunostomy tube was inserted for postoperative nutritional support. A nasogastric tube was not used. All patients were admitted to the intensive care unit after surgery. In our protocol, the tracheal tube was removed on POD1. Early rehabilitation, which consisted of positioning, respiratory muscles and thoracic cage stretching, deep diaphragmatic breathing, coughing and huffing and early mobilization from POD1, was permitted under the supervision of a physiotherapist. From POD1, the patient was kept in a sitting and upright position while in bed. From POD2 onward, the patient began to walk around the ward. Oral care was provided by a dentist and nurse. Enteral nutrition through the feeding jejunostomy catheter was started on POD1. During surgery, the patients received epidural analgesia. Oral intake was typically started on POD7 after a radiological evaluation.

Evaluation of Postoperative Pulmonary Complications

Postoperative pulmonary complications were evaluated using both the CDC and UPSS. The UPSS was evaluated on POD1–4. The UPSS consists of readily available clinical parameters including temperature, white blood cell count, and chest radiographs. The maximum daily temperature was used. Morning laboratory results were used to determine the white blood counts. The directed reports were used to interpret the chest radiographs (table 1) [11].

Table 1. The Utrecht Pneumonia Scoring System

Diagnostic determinant	Range	Score
Temperature °C	≥36.1 and ≤38.4	0
	≥38.5 and ≤38.9	1
	≥39.0 and ≤36.0	2
Leukocyte count $\times 10^9$/l	≥4.0 and ≤11.0	0
	<4.0 or >11.0	1
Pulmonary radiography	no infiltrate	0
	diffused (or patchy) infiltrate	1
	well-circumscribed infiltrate	2

Statistical Analysis

Each variable was presented as the mean ± standard deviation. Differences among groups were evaluated by performing an analysis of variance or a nonparametric analysis for data having a skewed distribution. Each group was compared using the t test, Fisher's exact test and the Mann-Whitney U test. The pStage, CDC score, and UPSS were evaluated according to the Mann-Whitney U test, and a logistic regression analysis was used for the multivariate analysis.

We found that the rate of postoperative pulmonary complications over CDC grade II was approximately 60% in the NPR group over the last decade in our department. Therefore, we hypothesized a postoperative pulmonary complication rate in the PR group of approximately 20%. The required sample size was 56 patients (28 per group) for a two-sided hypothesis with alpha set at 0.05 and 80% power.

All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria) [12]. More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics. p values <0.05 were considered to be statistically significant.

Results

The details of the patients and their surgical characteristics of both groups are presented in table 2. The groups were similar in terms of their demographics and comorbidities. There were no statistically significant differences in the respiratory function, the rate of open thoracotomy or the Brinkman index between the PR and NPR groups.

Table 2. Characteristics of patients

Factor	PR (n = 30)	NPR (n = 30)	p value
Sex (%)			
Male	24 (80.0)	23 (76.7)	0.99
Female	6 (20.0)	7 (23.3)	
Age, years	68.33±7.64	65.90±9.50	0.28
PS* score (%)			
0	27 (90.0)	28 (93.3)	0.65
1	3 (10.0)	2 (6.7)	
ASA** score (%)			
1	24 (80.0)	26 (86.7)	0.50
2	6 (20.0)	4 (13.3)	
Tumor location (%)			
Ut	5 (16.7)	6 (20.0)	0.99
Mt	15 (50.0)	14 (46.7)	
Lt	8 (26.7)	7 (23.3)	
Ae	2 (6.7)	3 (10.0)	
Pathological findings			
Squamous	26 (86.7)	28 (93.3)	0.48
Adeno	3 (10.0)	1 (3.3)	
Basaloid	1 (3.3)	0 (0.0)	
Endocrin	0 (0.0)	1 (3.3)	
pStage (%)			
0	3 (10.0)	2 (6.9)	0.45
I	7 (23.3)	7 (24.1)	
II	11 (36.7)	8 (27.6)	
III	6 (20.0)	9 (30.0)	
IVa	2 (6.7)	4 (13.8)	
IVb	1 (3.3)	0 (0.0)	
Positive history of smoking (%)			
Yes	22 (73.3)	24 (80.0)	0.761
No	8 (26.7)	6 (20.0)	
Brinkmann index***			
median	600	562.5	0.97
History of drinking (%)			
Yes	29 (96.7)	26 (86.7)	0.35
No	1 (3.3)	4 (13.3)	
Body mass index, kg/m^2	21.77±2.71)	20.91±2.53	0.21
Diabet mellitus (%)			
Yes	1 (3.3)	2 (6.7)	0.99
No	29 (96.7)	28 (93.3)	
Liver disease (%)			
Yes	0 (0.0)	4 (13.3)	0.11
No	30 (100.0)	26 (86.7)	
Coronary artery disease (%)			
Yes	1 (3.3)	2 (6.7)	1
No	29 (96.7)	28 (93.3)	
Preoperative chemotherapy (%)			
Yes	13 (43.3)	15 (50.0)	0.80
No	17 (56.7)	15 (50.0)	
Preoperative radiation (%)			
Yes	3 (10.0)	5 (16.7)	0.71
No	27 (90.0)	25 (83.3)	
FEV1.0	2.28±0.59	2.27±0.66	0.96
FEV1.0	72.94±9.20	71.99±8.06	0.67
FVC	3.15±0.82	3.01±0.65	0.48
PEF	359.49±149.96	315.71±120.03	0.22
Prognostic nutrition index	48.62±2.95	48.00±5.43	0.59
Thoracotomy			
Thoracoscopic	23 (76.7)	21 (70.0)	0.77
Open	7 (23.3)	9 (30.0)	
Anastomosis (%)			
FEEA*	14 (46.7)	14 (46.7)	0.06
EEA**	5 (16.7)	0 (0.0)	
Hand sewn	11 (36.7)	16 (53.3)	
Reconstruction root (%)			
Poststernal	20 (66.7)	21 (70.0)	0.86
Antesternal	6 (20.0)	4 (13.3)	
Interthoracic	4 (13.3)	5 (16.7)	
Blood loss, ml	541.50±439.84	597.00±421.73	0.62
Operative time, min	576.53±105.83	578.60±160.79	0.95
Intraoperative fluid balance, ml/kg/h	5.98±3.49	6.31±3.42	0.71
Number of lymph node dissection	27.00±14.41	29.59±14.4	0.51

* Performance status; ** American Society of Anesthesiologists; *** Brinkmann index; the number of cigarettes smoked per day multiplied by the number of years of smoking.

Intensive PR was well-tolerated by all patients with no adverse events. All patients in the PR group were able to complete the program.

No in-hospital mortality was observed in the present series. Regarding postoperative pulmonary complications, a total of 60 cases were distributed as follows according to the CDC: grade I, 34/60; grade II, 18/60; grade IIIa, 2/60; grade IIIb, 6/60; grade IV, 0/60; and grade V, 0/60. Patients with CDC grades IIIa and IIIb were found to have hypoxia due to the postoperative amount of sputum in the bronchus. The CDC grade in the PR group was significantly lower than in the NPR group according to the Mann-Whitney U test (p = 0.014) (table 3). The UPSS scores were significantly lower in the PR group than in the NPR group on POD1 according to the Mann-Whitney U test (p = 0.031) (table 4). In the univariate analyses,

Table 3. The evaluation of Clavien-Dindo classification

Factor	PR (n = 30)	NPR (n = 30)	p value
CDC score (%)			
I	22 (73.3)	12 (40)	0.014
II	5 (16.7)	13 (43.3)	
IIIa	2 (6.7)	0 (0.0)	
IIIb	1 (3.3)	5 (16.7)	
VI	0 (0.0)	0 (0.0)	
V	0 (0.0)	0 (0.0)	

Table 4. The evaluation of the Utrecht Pneumonia Scoring System

Factor	PR (n = 30)	NPR (n = 30)	p value
UPSS score POD1 (%)			
0	20 (66.7)	13 (43.3)	0.031
1	10 (33.3)	12 (41.4)	
2	0 (0.0)	4 (13.8)	
3	0 (0.0)	1 (3.4)	
UPSS score POD2 (%)			
0	8 (26.7)	11 (36.7)	0.87
1	21 (70.0)	15 (50.0)	
2	1 (3.3)	3 (10.0)	
3	0 (0.0)	1 (3.3)	
UPSS score POD3 (%)			
0	8 (26.7)	15 (50.0)	0.13
1	21 (70.0)	13 (43.3)	
2	1 (3.3)	1 (3.3)	
3	0 (0.0)	1 (3.3)	
UPSS score POD4 (%)			
0	24 (80.0)	22 (73.3)	0.51
1	6 (20.0)	7 (23.3)	
2	0 (0.0)	0 (0.0)	
3	0 (0.0)	1 (3.3)	

the incidence of postoperative pulmonary complications over CDC grade II was significantly higher in the NPR group than in the PR group (p = 0.018), and the incidence of a UPSS score greater than 1 point on POD1 was significantly higher in the open thoracotomy group than in the thoracoscopic group (p = 0.008). According to a multivariate logistic regression analysis, NPR was found to be an independent risk factor for postoperative pulmonary complications over CDC grade II (odds ratio (OR): 3.99, 95% confidence interval (CI): 1.28–12.4, p = 0.017) (table 5). Open thoracotomy was found to be an independent risk factor for postoperative pulmonary complications according to a UPSS score of more than 1 on POD1 (OR: 7.16, 95% CI: 1.63–31.5, p = 0.0092) (table 6).

Table 5. Multivariate analysis of the risk factor for postoperative pulmonary complication over grade II according to CDC

Factor	OR	95% CI	p value
NPR	3.32	1.1–10.0	0.033
Open thoracotomy	1.47	0.37–5.81	0.58
Brinkmann index >800	0.63	0.18–2.15	0.46
FEV1%, <70%	3.04	0.82–11.3	0.097
Recurrent nerve palsy	1.03	0.30–3.56	0.96
Intraoperaive fluid balance >8 ml/kg/h	1.17	0.28–4.95	0.83

Table 6. Multivariate analysis of the risk factor for postoperative pulmonary complication over 1 score according to UPSS on POD1

Factor	OR	95% CI	p value
NPR	2.57	0.80–8.25	0.11
Open thoracotomy	7.16	1.63–31.5	0.009
Brinkmann index >800	0.76	0.21–2.68	0.67
FEV1%, <70%	2.06	0.54–7.83	0.29
Recurrent nerve palsy	1.73	0.50–6.0	0.39
Intraoperaive fluid balance >8 ml/kg/h	1.06	0.24–4.66	0.94

In other postoperative complications, anastomotic leakage occurred in 17 (28.3%), chylothorax in 6 (10%), and recurrent nerve palsy in 18 (30%) patients. There were no statistically significant differences between the PR group and the NPR group regarding the rate of anastomotic leakage (36.7 vs. 20%, respectively, p = 0.25), chylothorax (6.7 vs. 6.7%, respectively, p = 0.99) and recurrent nerve palsy (30 vs. 30%, respectively, p = 0.99).

Discussion

Respiratory complication is one of the common events after esophagectomy, with a reported incidence rate of up to 60% [1]. Respiratory failure due to pulmonary complications remains the major cause of postoperative morbidity and mortality after esophagectomy [1]. In our institution, 230 patients with esophageal cancer underwent esophagectomy with gastric tube reconstruction between April 2000 and March 2011. The rate of pulmonary complications over CDC grade II after esophagectomy was approximately 60%.

In this study, the CDC grade for postoperative pulmonary complications in the PR group was significantly low-

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er than in the NPR group. In the multivariate analysis, NPR was found to be an independent risk factor for postoperative pulmonary complications over grade II according to the CDC. These findings suggest that PR could reduce the incidence of postoperative pulmonary complications. In addition, the UPSS scores were significantly lower in the PR group than in the NPR group on POD1. In the multivariate analysis, open thoracotomy was found to be an independent risk factor for postoperative pulmonary complications greater than 1 point according to the UPSS on POD1, but not on POD2–4. Consequently, we speculate that the surgical stress of open thoracotomy may elevate the UPSS score on POD1. Furthermore, the volume of sputum expectoration by the PR program could decrease the UPSS score on POD2–4. As a result, we believe that intensive PR prevented postoperative pulmonary complications greater than CDC grade II.

Various factors have been suggested to result in pulmonary complications, including advanced age, a history of smoking, cirrhosis, diabetes, an abnormal chest radiograph, previous lung disease, spirometric or nutritional parameters, blood loss, blood transfusion, low serum albumin level, adjuvant oncologic therapy, performance status, inadequate postoperative analgesia, and disease stage [13–18]. Recently, a prospective RCT demonstrated for the first time the benefits of a minimally invasive approach for esophageal cancer on pulmonary complications [19]. This approach led to better outcomes regarding the amount of blood loss, postoperative pain intensity and postoperative recovery time compared with traditional surgery. Another study suggested that perioperative steroid therapy was effective for inhibiting the release of inflammatory mediators, such as interleukin (IL)-6 and IL-8, and decreasing the rate of postoperative pulmonary complications after esophageal cancer surgery [20]. It was also reported that pathogens present in preoperative dental plaque are risk factors for postoperative pneumonia following esophagectomy [21]. However, in this study, the rate of video-assisted thoracic surgery was not significantly different between the two groups. All patients were administered methylprednisolone, and perioperative oral care was provided by a dental surgeon.

Thus far, no prospective RCT has evaluated the efficacy of an intensive PR program in patients with esophageal cancer. Only one retrospective study has been reported [22]. In this previously reported study, 100 patients who underwent esophagectomy were retrospectively analyzed. The PR group, which included 63 patients, received sufficient PR of more than 7 days. The NPR group, which included 37 patients, received PR for less than 6 days or none at all. The result for the rates of postoperative pulmonary complications was 6.4 and 24.3% in the PR group and NPR group, respectively. However, the previous retrospective study included a period-background, which could lead to some bias in the results. Therefore, we performed a prospective RCT that had a higher evidence level and defined the NPR group as the group that did not receive any preoperative rehabilitation.

Concerning the evaluation method for the pulmonary complications, there has also been no standardized and global classification. The lack of a uniform definition of pneumonia has led to large variations in the pneumonia rates in the literature. In our study, postoperative pulmonary complications were evaluated using the CDC and UPSS. The CDC is a valuable tool that enables objective and detailed documentation, as well as defined grades of the severity of postoperative complications [10]. The UPSS was designed as a new clinical scoring system to define pneumonia following esophagectomy for cancer by van der Sluis et al. [11]. The UPSS is estimated using temperature, the leukocyte count and pulmonary radiography findings.

Preoperative inspiratory muscle training from PR programs is used to increase the respiratory muscle strength and endurance, and several studies have demonstrated the benefits of such programs. Riganas et al. reported a 28% increase in the inspiratory muscle strength after 6 weeks of inspiratory muscle training [23]. Several groups [4, 5] have also reported a significant increase in the inspiratory muscle strength between the second and fourth weeks of preoperative inspiratory muscle training. In this study, the mean period of PR was 15.1 days. Therefore, we consider this period of PR to be sufficient for reducing the rate of postoperative pulmonary complications.

Patients undergoing upper abdominal and thoracic surgery have a decreased postoperative VC, which leads to a VA/Q mismatch and contributes to the development of hypoxemia [24]. Thus, the incidence rate of postoperative pulmonary complications is substantially higher for thoracic and upper abdominal surgery than for lower abdominal surgery. This may be explained by diaphragmatic dysfunction. Therefore, the PR program may demonstrate beneficial effects and improve the respiratory muscle strength. PR, especially early mobilization, may improve the functional outcomes and cognitive and respiratory conditions, thereby reducing the risks of venous stasis and deep vein thrombosis. This can be helpful in preventing postoperative pulmonary complications such as atelectasis, reducing the need for painkillers, improving recovery and avoiding neuromuscular complications [25].

There are a few limitations associated with this study. One of the limitations of this study is that only the value of the PEF was evaluated as an indicator of the respiratory muscle strength. In future studies, the influence of the respiratory muscle strength on pulmonary complications should be evaluated. Another limitation is that the impact of PR appears to influence only minor lung infiltrates that do not require more treatment than antibiotic therapy, because there was no mortality and only a few major complications (greater than CDC grade IIIa) in either group.

Conclusion

PR was effective for reducing the incidence of postoperative pulmonary complications in patients with esophageal cancer undergoing esophagectomy with gastric tube reconstruction.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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