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Original Article

Activity of plasma thrombin and balance of Th17/Treg in esophageal cancer patients with pulmonary infection after esophagectomy and the influence of personalized nursing on these patients

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Abstract: Objective: To investigate the activity of plasma thrombin and the balance of helper T cell 17 (Th17)/regulatory T cell (Treg) cells in esophageal cancer patients with pulmonary infection after esophagectomy, and explore the influence of personalized nursing on these patients. Methods: In this retrospective study, we analyzed the clinical data of 110 esophageal cancer patients who underwent radical esophagectomy in the Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute between May 2017 and September 2019. According to whether or not these patients had postoperative pulmonary infection, they were assigned to the infection group (n=51) and the non-infection group (n=59). Pathogens were identified using an automatic microbial identification and analysis system. Activity of plasma thrombin and Th17/Treg ratio were compared between the two groups. Based on the difference in nursing methods, patients in the infection group were further divided into the control group (n=23) and the experimental group (n=28). Patients in the control group received routine nursing, while patients in the experimental group received personalized nursing. Self-rating anxiety scale (SAS) scores, self-rating depression scale (SDS) scores, pulmonary function parameters, like forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio, and Freiburg quality of life assessment (FLQA) scores in both the control group and the experimental group before and after intervention were compared. Results: After radical esophagectomy, 46.36% of the esophageal cancer patients suffered from pulmonary infection. Additionally, 64 pathogens were isolated from 51 patients in the infection group. Among these pathogens, 67.19% pathogens were gram-negative bacteria, 29.69% pathogens were gram-positive bacteria, and 3.13% pathogens were fungi. Compared with the non-infection group, the proportion of Treg in the infection group was significantly reduced, while activity of plasma thrombin, the proportion of Th17, and Th17/Treg ratio were significantly increased (all $P<0.001$). SAS and SDS scores in both the control group and the experimental group after intervention were significantly lower than those before intervention. Moreover, changes in the experimental group were more significant than those in the control group (all $P<0.05$). Pulmonary function parameters, like FEV1, FVC, and FEV1/FVC ratio in both the control group and the experimental group after intervention were significantly higher than those before intervention. What's more, changes in the experimental group were more significant than those in the control group (all $P<0.05$). FLQA scores in social function, psychological function, physical function, and material life in the experimental group on the day of discharge were significantly increased when compared with the control group (all $P<0.01$). Conclusion: Gram-negative bacteria are the essential pathogens inducing pulmonary infection after esophagectomy; increased activity of plasma thrombin and immune system dysfunction are observed in patients with postoperative pulmonary infection; personalized nursing can alleviate patients' negative emotions, and improve their pulmonary function and quality of life.

Keywords: Esophageal cancer, pulmonary infection, thrombin, Th17/Treg ratio, personalized nursing

Introduction

Radical esophagectomy is the primary treatment for patients with esophageal cancer. However, the postoperative mortality of esophageal cancer is higher than other malignant tumors observed in the digestive system. It was reported that the 30-day and 90-day postoper-

ative mortality of esophageal cancer was 1.1% and 2.1%, respectively [1]. Pulmonary infection is a common complication of esophagectomy. Also, in esophageal cancer patients, it is the main cause for postoperative mortality. The incidence of pulmonary infection after esophagectomy is as high as 27.8% [2]. Therefore, postoperative nursing plays an important role in the reduction of postoperative pulmonary infection, improvement of prognosis, and decline of mortality. With the improvement of living standards, people have higher requirements for nursing care and quality. It means that routine nursing can no longer meet the needs of patients. The most evident characteristic of personalized nursing is its emphasis on individual patient differences. In other words, suitable nursing is formulated based on each patient's actual condition. In recent years, personalized nursing has been widely applied in many clinical departments [3].

In current clinical practice, pulmonary infection after esophagectomy is mainly diagnosed through sputum culture. Auxiliary diagnosis, like dynamic detection of procalcitonin (PCT), is also used. However, it takes a long time to perform sputum culture. Accordingly, optimal treatment timing is missed. Chen et al. reported that the 72-hour PCT change rate is more sensitive and specific in the diagnosis of pulmonary infection after esophagectomy, with a critical value of 2 ng/mL [4]. However, there is no uniform criterion for the critical value of PCT. Some scholars believe that it is better to set the critical value of PCT at 2.6 ng/mL [5].

Thrombin not only participates in pathophysiological processes such as blood coagulation and wound healing, but also plays a critical role in the infiltration, metastasis, and pulmonary infection of malignant tumors [6]. The imbalance of helper T cell 17 (Th17)/regulatory T cell (Treg) can cause an abnormal immune response, which in turn leads to the occurrence and development of various diseases. It is confirmed that Th17/Treg imbalance is related to the occurrence of various pulmonary diseases such as lung cancer and pulmonary fibrosis [7, 8]. However, the number of reports on pulmonary infection is only a handful. In this study, we explored the type of pathogens, activity of plasma thrombin, and Th17/Treg ratio in esophageal cancer patients with pulmonary infection after esophagectomy. Furthermore, we investigated the influence of personalized nursing on negative emotions, pulmonary function and quality of life in these patients.

Materials and methods

General information

The clinical data of 110 esophageal cancer patients who underwent radical esophagectomy in the Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute from May 2017 to September 2019 were retrospectively analyzed. These data were all exported from the electronic medical record system of the Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute. Based on whether or not these patients suffered from postoperative pulmonary infection, they were assigned to the infection group (n=51) and the non-infection group (n=59). Baseline data were shown in **Table 1**. This study was approved by the Ethics Committee of Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute.

Diagnostic criteria: Patients cough and had purulent sputum; wet rales could be heard in the lungs; patients' chest X-ray showed lung invasive changes or lung inflammatory lesions; patients with body temperature above 38.0°C; patients had counts of more than 15×10^9/L white blood cell; patients had positive sputum bacterial culture. Patients met at least 3 of the above criteria were confirmed with postoperative infection [9].

Exclusion criteria: Patients who merely underwent surgical exploration of esophageal cancer; patients woh had thoracoscopic surgery; patients who received esophageal cancer exfoliation; before operation, patients were diagnosed with pulmonary edema or emphysema by both chest X-ray and lung CT; patients with severe heart, lung, kidney or other important organ dysfunction or failure; patients who had incomplete clinical data.

Methods

According to the difference in nursing methods, patients in the infection group were further assigned to the control group (n=23) and the experimental group (n=28). Patients in the con-

Table 1. Baseline data ($\bar{x}$ ± sd)

Group	Infection group (n=51)	Non-infection group (n=59)	χ^2/t	P
Gender (n)			0.099	0.753
Male	27	33		
Female	24	26		
Age (years)	50.5±4.4	49.6±6.2	0.887	0.377
BMI (kg/m^2)	23.35±3.20	22.89±4.11	0.659	0.511
Pathological type (n)			1.075	0.584
Squamous cell carcinoma	45	54		
Adenocarcinoma	5	3		
Others	1	2		
TNM staging (n)			0.914	0.339
Stage I-II	28	27		
Stage III-IV	23	32		
Operation time (min)	167.69±22.57	172.10±18.89	1.101	0.273
History of long-term smoking (n)			0.061	0.805
With	23	28		
Without	28	31		
History of alcoholism (n)			1.017	0.313
With	12	19		
Without	39	40		

trol group received routine nursing, which consisted of cleaning of the respiratory tract, detection of pulmonary function, and timely administration of antibacterial drugs following the doctors' advice.

In the experimental group, patients received personalized nursing: (1) Help to keep breathing smooth. Measures such as back-patting, atomization inhalation, postural drainage, and neck tracheal pressing to stimulate cough and sputum were taken after surgery to maintain smooth breathing. Fiberoptic bronchoscopy was used to aspirate sputum and artificial respirators was provided to maintain breathing, if necessary. (2) Psychological counseling. The incidence of postoperative pulmonary infection in elderly patients was high. In addition, various body functions of these patients were reduced. As a result, they were prone to negative emotions like nervousness and anxiety. Psychological counseling was provided for these patients. They were comforted and encouraged to eliminate their negative emotions, enhancing their confidence in defeating the disease. Patients were thereby more willing to actively cooperate with medical staff in the follow-up treatment, which was pretty beneficial for the promotion of postoperative recovery. (3) Drainage tube care. Patients were informed of preventing folding and bending of the drainage tube after surgery. Drainage volume and color of chest cavity were closely observed. Analgesic treatment was provided for patients with obvious postoperative pain.

Outcome measures

Main outcome measures: Respiratory secretions of patients in the infection group were collected, and pathogens were identified with an automatic microbial identification and analysis system (Biolog, Inc, USA, origin: USA). S. aureus ATCC25923, Pseudomonas aeruginosa ATCC-27853, and Escherichia coli ATCC25922 were quality control strains. These strains were purchased from the National Center for Clinical Laboratories (NCCL). A volume of 6mL of fasting venous blood was collected from patients in the infection group and the non-infection group within 2 d of infection. Thereafter, 3 mL of the blood was treated with sodium citrate anticoagulant, and centrifuged at 3000 rpm for 10 min. Plasma was then obtained. Quantitative measurement of plasma thrombin was performed using the chromogenic substrate method (The kit was procured from Shanghai Sun Biotechnology Co., Ltd., China product number:

Table 2. Distribution of pathogens (n, %)

Pathogens	Number of strains (n)	Proportion (%)
Gram-positive bacteria	19	29.69
Staphylococcus aureus	7	10.94
Streptococcus pneumoniae	7	10.94
Hemolytic Streptococcus	3	4.69
Staphylococcus epidermidis	2	3.13
Gram-negative bacteria	43	67.19
Klebsiella pneumoniae	17	26.56
Pseudomonas aeruginosa	10	15.63
Acinetobacter baumannii	7	10.94
Escherichia coli	4	6.25
Stenotrophomonas maltophilia	2	3.13
Neisseria meningitides	2	3.13
Others	1	1.56
Fungi	2	3.13
Candida albicans	2	3.13
Total	64	100.00

EY47583, origin: China). The other 3 mL of blood was let naturally coagulate, and centrifuged as before. The amount of Th17 (The kit was purchased from Beijing Lvyuan Bode Biotechnology Co., Ltd., China, product number: 560484, origin: Germany) and Treg (The kit was procured from Beijing Fubo Biotechnology Co., Ltd., China, product number: 560762, origin: Germany) cells in both the infection group and the non-infection group were measured by flow cytometer (Beckman, USA, type: Navios, origin: USA). Th17/Treg ratio was then obtained.

Secondary outcome measures

Levels of anxiety and depression, which were respectively assessed by self-rating anxiety scale (SAS) and self-rating depression scale (SDS), were compared between the control group and the experimental group before and after intervention. The higher the SAS score was, the more severe the anxiety. Similarly, the higher the SDS score was, the more severe the depression.

Pulmonary function, which was measured using a pulmonary function tester (Jaeger, Germany, type: MasterScreen PFT, origin: Germany), was compared between the control group and the experimental group before and after intervention. Changes of pulmonary function parameters like forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were recorded. FEV1/FVC ratio was then calculated.

Freiburg quality of life assessment (FLQA) was used to evaluate the life quality of patients in both the control group and the experimental group on the day of discharge. The assessment was composed of 4 aspects, including social function, psychological function, physical function, and material life. The higher the FLQA score was, the better the quality of life [10]. FLQA was performed by patients on the day of discharge. The recovery rate was 100%.

Statistical methods

All data were analyzed using SPSS statistical software version 20.0. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Independent sample t test was used for inter-group comparison, while paired t-test was applied for before-after comparison within the same group. The enumeration data were expressed as number/percentage (n, %); comparison was conducted with chi-square test. The difference was statistically significant when the *P* value was less than 0.05.

Results

Baseline data

Among the 110 esophageal cancer patients who received esophagectomy, 51 patients suffered from postoperative pulmonary infection, accounting for 46.36%. There was no significant difference concerning baseline data such as gender, age, body mass index (BMI), pathological type, TNM staging, operation time, history of long-term smoking, and history of alcoholism between the infection group and the non-infection group (all P>0.05). See **Table 1**.

Distribution of pathogens

In total, 64 pathogens were isolated from 51 patients with postoperative pulmonary infection. As shown in **Table 2**, 43 pathogens were gram-negative bacteria, accounting for 67.19%; 19 pathogens were gram-positive bacteria, accounting for 29.69%; 2 pathogens were fungi, accounting for 3.13%. Klebsiella pneumoniae and Pseudomonas aeruginosa were the main gram-negative bacteria, accounting for 26.56% and 15.63%, respectively; Staphylococcus aureus and Streptococcus pneu-

Table 3. Activity of plasma thrombin and balance of Th17/Treg ($\bar{x}$ ± sd)

Group	Plasma thrombin (U/L)	Th17 (%)	Treg (%)	Th17/Treg ratio
Infection group (n=51)	116.56±14.39	3.19±0.54	2.97±0.27	1.10±0.25
Non-infection group (n=59)	63.39±8.84	1.50±0.28	5.20±0.38	0.31±0.12
T	23.687	20.125	35.823	20.560
P	<0.001	<0.001	<0.001	<0.001

Note: Th17: helper T cell 17; Treg: regulatory T cell.

Table 4. SAS and SDS score ($\bar{x}$ ± sd)

Group	Time	SAS score	SDS score
Experimental group (n=28)	Before intervention	50.50±4.39	48.87±4.75
	After intervention	41.08±5.70$^{***,\#\#\#}$	40.20±4.40$^{***,\#\#\#}$
Control group (n=23)	Before intervention	49.89±5.02	49.10±5.29
	After intervention	46.68±4.90*	45.60±5.20*

Note: SAS: self-rating anxiety scale; SDS: self-rating depression scale. Compared with before intervention, *P<0.05, ***P<0.001; compared with the control group after intervention, $^{\#\#\#}$P<0.001.

Table 5. Pulmonary function ($\bar{x}$ ± sd)

Group	Time	FEV1 (L)	FVC (L)	FEV1/FVC
Experimental group (n=28)	Before intervention	1.44±0.39	1.98±0.52	56.30±5.49
	After intervention	2.12±0.52$^{***,\#\#}$	2.78±0.61$^{***,\#}$	61.04±3.78$^{***,\#}$
Control group (n=23)	Before intervention	1.40±0.41	2.02±0.44	56.11±4.50
	After intervention	1.77±0.41**	2.45±0.48**	58.76±4.10*

Note: FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity. Compared with before intervention, *P<0.05, **P<0.01, ***P<0.001; compared with the control group after intervention, $^{\#}$P<0.05, $^{\#\#}$P<0.01.

moniae were the essential gram-positive bacteria, both accounting for 10.94%. See **Table 2**.

Activity of plasma thrombin activity and balance of Th17/Treg

Compared with the non-infection group, the proportion of Treg in the infection group was significantly decreased, while activity of plasma thrombin, the proportion of Th17, and Th17/Treg ratio were significantly increased (all P<0.001). See **Table 3**.

SAS and SDS score

SAS and SDS scores in both the control group and the experimental group after intervention were significantly lower than those before intervention. The changes in the experimental group were more significant than the control group (all P<0.05). See **Table 4**.

Pulmonary function

Pulmonary function parameters like FEV1, FVC, and FEV1/FVC ratio in both the control group and the experimental group after intervention were significantly higher than those before intervention. The changes in the experimental group were more significant than the control group (all P<0.05). See **Table 5**.

FLQA scores

FLQA scores in social function, psychological function, physical function, and material life in the experimental group on the day of discharge were significantly increased when compared with the control group (all P<0.01). See **Figure 1**.

Discussion

The incidence of pulmonary infection in esophageal cancer patients after radical esophagectomyis is high [11, 12]. Postoperative pulmonary infection is caused by many factors. Elderly patients, operation time over 3 h, postoperative ventilator-assisted breathing above 2 h, difficulty in swallowing and severely im-

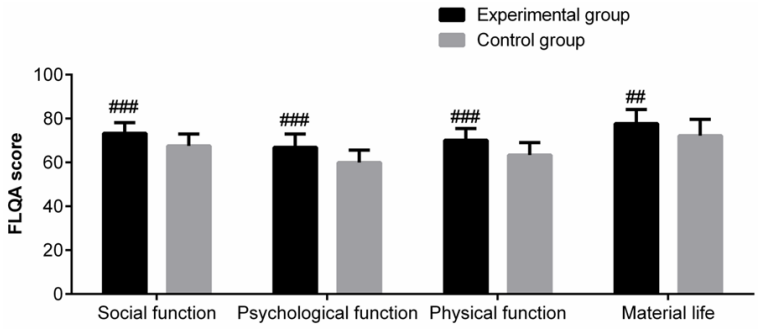

Figure 1. Comparison of FLQA scores. FLQA: Freiburg quality of life assessment scale. Compared with the control group, ##P<0.01, ###P<0.001.

paired pulmonary function are all factors that can increase the risk of postoperative pulmonary infection [13]. In our study, the incidence of postoperative pulmonary infection was as high as 46.36%.

Immune function of patients with esophageal cancer is reduced. These patients are thereby prone to be invaded by pathogens. Combined with factors like long-term bed rest and increased respiratory secretions in esophageal cancer patients, pulmonary infection is induced [14]. Our results of pathogen analysis showed that gram-negative bacteria were the main pathogens inducing pulmonary infection in esophageal cancer patients after radical esophagectomy, accounting for 67.19%; gram-positive bacteria were the secondary pathogens, accounting for 29.69%; fungi were the least pathogens. Klebsiella pneumoniae and Pseudomonas aeruginosa were the main gram-negative bacteria, while S. aureus and Streptococcus pneumoniae were the primary gram-positive bacteria. Therefore, before the results of pathogen analysis come out, antimicrobial therapy could be applied empirically on the basis of distribution of pathogens.

It was reported that mutations in G20210A and C399T genes could promote the invasion and metastasis of esophageal cancer. This might be closely related to the increased activity of plasma thrombin, which was induced by mutations in G20210A and C399T genes [15]. Here, our results displayed that the content of plasma thrombin in the infection group was significantly higher than that in the non-infection group, denoting that the activity of plasma thrombin in patients with pulmonary infection after esophagectomy was increased when compared with patients without pulmonary infection after esophagectomy. Patients with postoperative pulmonary infection were in a hypercoagulable state. Thus, they were prone to thromboembolism [16]. However, further research is needed to verify whether it was related to postoperative recurrence of esophageal cancer. Under normal physiological conditions, the pro-inflammatory response of Th17 and anti-inflammatory response of Treg are in a dynamic balance. If the balance of Th17/Treg is dysregulated, patients are prone to suffer from autoimmune diseases, ischemic diseases, and infectious diseases and so on [17-19]. Th17/Treg imbalance may be involved in the pathogenesis of lung diseases like chronic obstructive pulmonary disease (COPD) [20, 21]. In our study, the proportion of Treg in the infection group was significantly decreased when compared with the non-infection group, while the proportion of Th17 and Th17/Treg ratio were significantly increased, suggesting that patients with postoperative pulmonary infection are accompanied by Th17/Treg imbalance and immune system disorders. Imani et al. also reported that Th17/Treg imbalance played an important role in the immune pathogenesis of various lung diseases [22].

Elderly patients are more prone to postoperative pulmonary infection on account of the increased respiratory secretions and decreased pulmonary function. In addition, most patients are nervous and anxious after the reduction of body function. Personalized nursing is a patient-oriented nursing model. It means that the unique differences between patients are valued. In order to meet the diversified needs of patients as much as possible, different nursing plans are formulated based on each patient's actual condition and various needs, and different nursing measures are carried out [23]. Personalized nursing has been widely applied in pediatrics, orthopedics, obstetrics, major surgery, and other departments. Anderson et al. reported that personalized nursing could effectively control the risk of asthma in children [24]. Moreover, Armstrong et al. reported that personalized nursing could help to improve pul-

monary function of patients with chronic lung diseases, which was consistent with our results [25]. In our study, SAS and SDS scores in the experimental group after intervention were significantly decreased when compared with the control group, while pulmonary function parameters, like FEV1, FVC, FEV1/FVC ratio, and FLQA scores were significantly increased. These results indicate that personalized nursing is beneficial to the alleviation of negative emotions like anxiety and depression, and help create improvements in pulmonary function and quality of life. However, the number of cases in this study is small. Additionally, the correlation analysis between postoperative prognosis and the above outcome measures is not performed due to the lack of follow-up. The correlation analysis will be performed in subsequent study.

In summary, the main pathogen in pulmonary infection after esophagectomy is gram-negative bacteria. For patients with postoperative pulmonary infection, activity of plasma thrombin is high, and the immune system is dysregulated. Personalized nursing can help to alleviate patients' negative emotions, improve their pulmonary function and quality of life.

Disclosure of conflict of interest

None.

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