Efficacy of Prophylactic Antibiotic Use in Preventing Post-bronchoscopy Pneumonia in Lung Cancer Patients

Naoki HAYAMA, Hiroto TAKIGUCHI, Keito ENOKIDA, Shigeaki HATTORI, Genki TAKAHASHI, Tomoe TAKEUCHI, Jun TANAKA, Yukihiro HORIO, Katsuyoshi TOMOMATSU, Kyoko NIIMI, Yoko ITO, Tsuyoshi OGUMA and Koichiro ASANO

Division of Pulmonary Medicine, Department of Medicine, Tokai University School of Medicine

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Objective: Post-bronchoscopy pneumonia can affect the prognosis of lung cancer patients. This prospective study examined the efficacy of prophylactic antibiotics for lung cancer patients at high-risk of post-bronchoscopy pneumonia, determined by our prediction score, using three risk factors: age 70 years or older, current smoking, and central tumors visualized on CT.
Methods: Patients with lung cancer who underwent diagnostic bronchoscopy between June 2018 and March 2020 with a score of 2 points or higher were enrolled. Sulbactam/ampicillin was administered intravenously within one hour prior to bronchoscopy, followed by oral clavulanate/amoxicillin for three days. We used the data of lung cancer patients who underwent diagnostic bronchoscopy between April 2012 and July 2014 and exhibited a score of 2 or higher as the historical control.
Results: Post-bronchoscopy pneumonia occurred in none of the 24 patients in the prophylaxis group and in 17 of 144 patients in the control group, with no significant difference in the incidence of pneumonia between the two groups.
Conclusions: Antibiotic prophylaxis can be effective and safe for the patients high-risk of post-bronchoscopy pneumonia. A multicenter prospective study to examine the effects of prophylactic antibiotics in high-risk patients is feasible with a modest number of participants.

Key words: bronchoscopy, antibiotics, prophylaxis, lung cancer, risk prediction score

INTRODUCTION

Flexible fiberoptic bronchoscopy is a generally safe procedure widely used for the diagnosis of various respiratory diseases, including lung cancer. However, this technique is associated with some complications such as bleeding, pneumothorax, fever, and pneumonia, which could be severe [1]. We previously reported that post-bronchoscopy pneumonia occurred at a rate of 4.1–6.3% in two independent cohorts of patients with lung cancer. In more than half of the patients who developed pneumonia, it resulted in serious consequences such as the discontinuation or delay of cancer treatment or death [2]. Therefore, appropriate risk assessment and effective prophylaxis of post-bronchoscopy pneumonia are important prior to bronchoscopy.

Prophylactic antibiotic use is recommended for the prevention of infective endocarditis or surgical site infection. However, whether prophylactic antibiotics are beneficial for patients undergoing bronchoscopic examinations remains controversial [3–5]. In our retrospective study, in which 18% of patients received oral β-lactam antibiotics immediately after bronchoscopy, we did not find any significant benefits of antimicrobial prophylaxis [2]. The British Thoracic Society guideline for bronchoscopy does not recommend the use of prophylactic antibiotics for the prevention of infective endocarditis and pneumonia [1].

The benefits of prophylactic antibiotic use can be maximized when applied to high-risk patients. Therefore, prophylactic antibacterial agents to prevent surgical site infection are recommended only in surgical interventions at sites with bacterial contamination, such as gastrointestinal perforation and dirty trauma [6–8]. Moreover, current guidelines recommend administering prophylactic antimicrobial agents before the skin incision but not after the surgical incision is closed [9]. Therefore, administration of antimicrobial agents immediately before the procedure targeting high-risk patients may reduce the incidence of post-bronchoscopy pneumonia and improve the outcome of lung cancer patients.

To identify patients at high-risk for post-bronchoscopy pneumonia, we extracted three major risk factors based on the results of multiple variable logistic regression analysis: age 70 years or older, current smoking, and central tumors visualized on thoracic computed tomography (CT) scans. Subsequently, we created a pneumonia prediction score by allocating one point for each factor and validated its accuracy [2]. The prevalence of post-bronchoscopy pneumonia in the two cohorts was 0% for the cases with 0 points of the

Koichiro ASANO, Division of Pulmonary Medicine, Department of Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-93-0381 E-mail: ko-asano@tokai-u.jp

score, 2.9–3.7% for those with one point, and 9.7–13.4% for those with two or three points. The area under the receiver operating characteristic curve was 0.713–0.735, indicating that the pneumonia prediction score had a good discriminative ability for identifying high-risk patients [2].

Herein, we conducted a preliminary prospective single-center, single-arm study to evaluate the efficacy of prophylactic antibiotics in lung cancer patients at high-risk of post-bronchoscopy pneumonia for the design of future multi-center trials.

MATERIALS AND METHODS

Patients

This study was conducted between June 2018 and March 2020. Patients with lung cancer who underwent diagnostic bronchoscopy at Tokai University Hospital in Japan and presented with post-bronchoscopy pneumonia prediction scores of 2 points or more were enrolled. Patients with penicillin hypersensitivity were excluded from the study. One-hundred and forty-four patients who underwent diagnostic bronchoscopy between April 2012 and July 2014 at our hospital and were diagnosed with lung cancer with a prediction score of 2 points or more were used as the historical control group.

This study was approved by the Institutional Review Board of Tokai University Hospital (17R-191). The investigation conforms with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients before their enrollment in the study.

Prophylactic antibiotic treatment

Within one hour preceding bronchoscopy, 1500 mg sulbactam/ampicillin was administered intravenously over 30 min. After bronchoscopy, 500 mg of amoxicillin and 125 mg of clavulanate was administered orally three times a day for three days.

Bronchoscopy

Bronchoscopy was performed by experienced pulmonologists, including at least one specialist certified by the Japan Society for Respiratory Endoscopy. Local laryngopharyngeal anesthesia was performed with 1% lidocaine, and premedication with intramuscular injection of pentazocine, hydroxyzine pamoate, and atropine sulfate or intravenous injections of midazolam and pethidine were administered. We used flexible fiberoptic bronchoscopes, BF-1T260 and BF-P260 (Olympus Corporation, Tokyo, Japan), with intra-tracheobronchial injections of 1% lidocaine for local anesthesia. After observing the bronchial lumen, a transbronchial biopsy was performed using biopsy forceps or a guide sheath kit, followed by bronchial lavage with 20 mL saline.

Definition of post-bronchoscopy pneumonia

Clinical symptoms and body temperature were recorded daily from the day after bronchoscopy to the first hospital visit. Post-bronchoscopy pneumonia was diagnosed when body temperatures of over 37˚C persisted for 24 hours or more, accompanied by either an exacerbation of respiratory symptoms or the appearance of new opacities on chest radiography or CT.

Statistical analyses

Data are presented as median values (ranges) or counts and percentages. Data were analyzed using Mann-Whitney's *U*-test and Fisher's exact test for quantitative and categorical variables. P values < 0.05 were considered statistically significant. Sample size calculation was performed with an α error of 0.05, β error of 0.2, and a sample size of 1 : 1. We used the Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA) for the analysis.

RESULTS

Patient characteristics

Thirty patients were enrolled in this study. Six patients were excluded: four with insufficiency or withdrawal of consent, one with an error of antibiotic treatment, and one with non-malignant disease. All feasible cases received a designated dose of sulbactam/ampicillin and clavulanate/amoxicillin. There were no adverse events due to antibiotic treatment. The characteristics of the twenty-four patients and the historical controls are summarized in Table.

The median age, distribution of post-bronchoscopy pneumonia score, and histology of lung cancer were consistent between the two groups. In the historical control group, there were significantly more men than in the prophylaxis group, and the ratio of current smokers and patients at less advanced clinical stages (stage I or stage II) were significantly higher. In the prophylaxis group, no patients with stage I or II disease were included.

Effect of prophylactic antibiotics

There were no patients with a fever (temperatures of over 37˚C) persisting for 24 hours or more in the prophylaxis group. One patient in the prophylaxis group, a 69-year-old woman with squamous cell carcinoma (clinical T4N1M0, stage IIIA) presented with exacerbation of sputum and appearance of new opacities on chest radiography. She received additional antibiotic treatment with intravenous piperacillin/tazobactam and recovered without experiencing serious consequences. Therefore, the incidence rate of post-bronchoscopy pneumonia in the prophylaxis group was 0.0% per protocol and 4.2% in patients who received therapeutic antibiotics.

Pneumonia after bronchoscopy occurred in 17 patients (11.8%) in the historical control group. There was no significant difference in the incidence of pneumonia between the two groups (Figure, $p = 0.14$–0.47). When patients with stage III/IV disease alone were analyzed, the difference between the incidences of post-bronchoscopy pneumonia in the prophylaxis group (0.0%–4.2%) and in the control group (17.6%) was more significant ($p = 0.02$–0.12).

Power analysis was performed with an α error of 0.05, β error of 0.2, and a sample size of 1 : 1. The number of patients required to confirm the efficacy of prophylactic antibiotic treatment to prevent post-bronchoscopy pneumonia was 61–199 subjects in each group. If enrollment is limited to cases of advanced cancer, the number could be reduced to 39–84 per group.

Table Characteristics of the prophylaxis and historical control groups

Characteristic – no.		Historical control n = 144	Prophylaxis group n = 24	p-value
Median age, year (range)		74 (36–84)	74 (65–80)	
Sex, Male/Female		124/20	14/10	< 0.01*
PBP score[#]	2	127	19	
	3	17	5	
Smoking status	Never smoked	11	3	
	Former smoker	51	14	
	Current smoker	82	7	< 0.05*
Median pack-year smoked (range)		47 (0–175)	46 (0–141)	
Histology	Adenocarcinoma	44	4	
	Squamous cell carcinoma	53	6	
	Small cell carcinoma	24	7	
	Others[&]	23	7	
Clinical stage, Ⅰ / Ⅱ / Ⅲ / Ⅳ /unknown		25/25/36/55/3	0/0/13/11/0	< 0.01*
Post-bronchoscopy pneumonia		17 (11.8%)	0–1[##] (0.0–4.2%)	0.14–0.47*, ##

[#]post-bronchoscopy pneumonia prediction score, [&]Others included large cell carcinoma, pleomorphic carcinoma, adenosquamous carcinoma, carcinoid, and unclassified tumor; [##]including one case that did not meet the criteria of pneumonia per protocol but required therapeutic antibiotic treatment; *Fisher's exact test

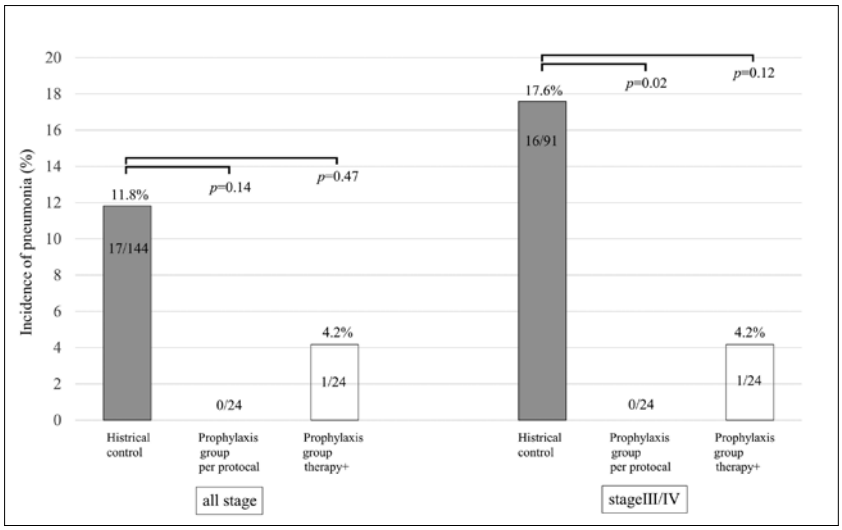

Figure Incidence of post-bronchoscopy pneumonia in the historical control and prophylaxis groups. Prophylaxis group per protocol: post-bronchoscopy pneumonia that met the protocol criteria, prophylaxis group therapy + : post-bronchoscopy pneumonia that did not meet the criteria of pneumonia per protocol but received therapeutic antibiotics.

DISCUSSION

This preliminary study demonstrated that the incidence of post-bronchoscopy pneumonia in patients with higher prediction scores may be reduced to less than 5% with the prophylactic use of antimicrobial agents administered immediately before the procedure and during the following three days. The predicted sample size to confirm the benefit of prophylactic treatment in high-risk populations is modest and feasible.

Prophylactic antibiotic use during bronchoscopy is not recommended, even in patients at high-risk of infective endocarditis in the current guidelines of the British National Institute for Health and Care Excellence and the British Thoracic Society [1, 10]. Indeed, there are reports that prophylactic antibiotics are not effective in preventing the onset of post-bronchoscopy pneumonia throughout bronchoscopy for any lung disease [3, 11]. However, a randomized controlled trial showed that prophylactic azithromycin is effective in preventing pneumonia after bronchoscopy in patients with lung cancer [5]. The incidence of respiratory tract infection was 2.9% in the no-antibiotic treatment group and 0.7% in the azithromycin group (p

= 0.06) [5]. Kitami *et al.* reported that cancerous lungs with cavitary lesions or central necrosis had a high-risk of developing lung abscesses after bronchoscopy, and prophylactic antibiotics suppressed the appearance of lung abscesses in these patients [12].

Another problem associated with prophylactic antibiotic use for diagnostic bronchoscopy is the low frequency of post-bronchoscopy pneumonia [4, 5, 13–16]. As mentioned, azithromycin treatment reduced the incidence of respiratory tract infection from 2.9% to 0.7% [5]; however, the number needed to treat (NNT) was 45. Using the pneumonia prediction score that includes older age, current smoking, and central lesions of lung cancer, we identified high-risk populations with high reproducibility and reduced the NNT to 9. Considering the high rate of dire outcomes of post-bronchoscopy pneumonia, such as delay of cancer treatment or death, prophylactic antibiotic use can be justified. Other studies have identified endobronchial lesions as a risk factor for post-bronchoscopy pneumonia [4, 5, 17]. Our previous study also identified endobronchial lesions as a risk factor for post-bronchoscopy pneumonia [2]; however, we chose to use the central lesion of lung cancer on chest images so we could evaluate the risk associated with bronchoscopy before engaging in the procedure.

Previous reports on the prevention of post-bronchoscopy pneumonia started with antibiotics after bronchoscopy [5, 11]. However, prophylactic antibiotic administration should be performed 60 min before the start of the procedure, as recommended for the prevention of infective endocarditis or surgical site infection [9]. Therefore, in this study, intravenous administration of antibacterial agents was completed by the time bronchoscopy was started. Additional antibiotics was administered orally for three days after bronchoscopy, since the site of bronchoscopy was considered to correspond to a "contaminated" wound defined by the U.S. Center for Disease Control and Prevention [6]. Amoxicillin or ampicillin was used because of its efficacy against oral bacteria [18] and because it is less expensive than intravenous azithromycin. The incidence of pneumonia was 0.0–4.2% in the prophylaxis group and 11.8% in the control group, which is compatible with the results of the subpopulation analysis in the previous report. Kanazawa *et al.* demonstrated that the incidence of pneumonia in patients with endobronchial stenosis due to lung cancer was 14.8% without prophylactic antibiotics and 3.0% with azithromycin treatment [5]. Furthermore, our approach limiting antibiotic prophylaxis to the high-risk cases selected by the pneumonia prediction score would be beneficial to suppress the emergence of resistant strains by excessive use of antimicrobial agents.

In conclusion, the incidence of post-bronchoscopy pneumonia is relatively high in lung cancer patients with higher pneumonia prediction scores. Antibiotic prophylaxis can be effective and safe for the high-risk patients. A multicenter prospective study to examine the effects of prophylactic antibiotics in high-risk patients is feasible with a modest number of participants.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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