ORIGINAL ARTICLE

Clinical impact of early bronchoscopy in mechanically ventilated patients with aspiration pneumonia

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ABSTRACT

Background and objective: A handful of studies have reported that bronchoscopies influence the clinical outcome of mechanically ventilated patients with aspiration pneumonia. The purpose of the present study is to elucidate the therapeutic role of early bronchoscopy in patients with aspiration who are mechanically ventilated.

Methods: A retrospective cohort study was conducted via medical record review from 2003 through 2013 in a tertiary hospital. All the diagnoses of pneumonia were supported by the probability of aspiration and consolidation of dependent areas confirmed by computed tomography. Patients who underwent bronchoscopy within 24 h after intubation were categorized as the early bronchoscopy group and the others as the late bronchoscopy group. We compared the demographics, clinical parameters and outcomes between the two groups.

Results: Of the 154 patients who were included, the early bronchoscopy group (n = 93) showed significantly lower in-intensive care unit (ICU) mortality and 90-day mortality (in-ICU: 4.9% vs 24.6%; 90-day: 11.8 vs 32.8%) regardless of the initial empirical antibiotics. In addition, their sequential organ failure assessment score on day 7 tended to decrease more rapidly. Among the survivors, patients in the early bronchoscopy group were extubated earlier with a higher success rate, had a shorter length of mechanical ventilation and had a shorter ICU stay. The early bronchoscopy was associated with lower 90-day mortality in multivariate analysis (odds ratio: 0.412; 95% confidence interval: 0.192–0.883).

Conclusions: Early bronchoscopy could benefit the clinical outcomes of mechanically ventilated patients with aspiration pneumonia.

INTRODUCTION

Aspiration is a process whereby material from the oropharynx and stomach enter the larynx or lower respiratory tract; it is reported to occur in 10.3% of patients who are diagnosed with community-acquired pneumonia and 30% of patients with pneumonia who are admitted from a long-term care facility.1 Approximately 90% of patients in intensive care units (ICU) also experience aspiration events at least once during their ICU stay.2

Aspiration pneumonia is an infectious and inflammatory process of microorganisms, which colonize in the aspirated materials. It has been demonstrated that bronchoscopy accompanied with bronchoalveolar lavage (BAL) is helpful for patients with aspiration-induced lung injury in order to reveal causative organisms and determine the appropriate
duration of antibiotic treatment.\textsuperscript{3,4} It is also known that the initial administration of appropriate antibiotics can lower the mortality rate in these patients.\textsuperscript{5,6}

To date, no studies have reported whether the timing of bronchoscopy could influence clinical outcome of an aspiration pneumonia. One study in ventilator-associated pneumonia (VAP) patients reported that late therapeutic bronchoscopy, which was performed 24 h after initiation of antibiotics, did not decrease the mortality rate.\textsuperscript{7} Another study of VAP noted that diagnostic BAL did not improve clinical outcomes because clinicians could not obtain microbiological information from bronchoscopy early enough to change antibiotics and improve survival.\textsuperscript{8}

The aim of this study was to elucidate the therapeutic role of early bronchoscopy, which was performed within 24 h after intubation, in patients with aspiration who were mechanically ventilated in a medical ICU. We hypothesize that early bronchoscopy in itself may improve clinical outcomes, including mortality and hospital course, in these patients.

**METHODS**

**Study populations**

A retrospective cohort study was conducted via medical record review from 2003 through 2013 in a single tertiary teaching hospital. Over a period of 10 years, we reviewed 926 patients who had pneumonia with classic symptoms or signs of aspiration who required mechanical ventilation (MV) in a medical ICU. After thorough review, 706 patients who had pulmonary diseases other than aspiration pneumonia were excluded. In addition, 26 patients who had comorbidities, such as acute coronary syndrome, valvular disease or pulmonary embolism, were excluded; another 12 patients who did not undergo a chest computed tomography (CT) for diagnosis of pneumonia were excluded. Finally, 28 patients without a bronchoscopy within 7 days after intubation were excluded. The remaining 154 patients were divided into early bronchoscopy (EB) group (bronchoscopy ≤24 h after intubation) and late bronchoscopy (LB) group (bronchoscopy >24 h after intubation). They were followed for 90 days from intubation (Fig. 1).

We recorded the number of repeat bronchoscopies for the 7 days after intubation. We also reviewed patient baseline clinical characteristics, including age, gender, body mass index, Eastern Cooperative Oncology Group performance status, comorbidities and recent history of nursing home residence, as well as those who received a nasogastric tube, percutaneous endoscopic gastrostomy tube or tracheostomy tube. We classified the type of pneumonia, aspiration probability and the ICU admission source. The initial acute physiology and chronic health evaluation (APACHE) II scores, lung injury score (LIS), clinical pulmonary infection score (CPIS) and sequential organ failure assessment (SOFA) score were calculated.\textsuperscript{9–11} The time interval from intubation to ICU admission, initial medical care department, and whether the patient was admitted on a holiday or weekend were reviewed. A previous history of aspiration and the aspiration probability were defined differently in this study. A previous history of aspiration denoted whether an aspiration event occurred, while aspiration probability was based on swallowing dysfunction, defined as follows:\textsuperscript{12} certain probability with direct observation, probable probability with previously diagnosed swallowing dysfunction, and suspicious probability with possibility of swallowing dysfunction.

**Assessment of clinical outcomes**

We established the primary outcome as all-cause mortality in the ICU or within 90 days. We divided the cause of death into two categories: death by respiratory causes, such as acute respiratory distress syndrome (ARDS); and death by non-respiratory causes, such as septic shock or cardiogenic shock. The duration of MV, length of stay in the medical ICU, change

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**Figure 1** Flow chart of patient enrolment. CT, computed tomography; ICU, intensive care unit.
of LIS, CPIS and SOFA score, successful extubation, and tracheostomy during hospitalization were analysed, as well as other clinical outcomes.

In addition, we determined which causative pathogens were detected and the appropriateness of antibiotic use based on results from quantitative BAL culture; this determination is a key factor for decreasing the mortality rate of patients with pneumonia.6 If no pathogen was found, the patients with escalation of antibiotics were classified in the initially inappropriate empirical antibiotic group, and those without escalation of antibiotics were classified in the initially appropriate empirical antibiotic group.

Statistical analysis
We analysed binary outcome variables with Pearson’s chi-squared test or Fisher’s exact test; continuous outcome variables were analysed with the Student t-test. We estimated survival rate with the Kaplan–Meier analysis and compared the results using a log–rank test. We also analysed the LIS, SOFA score and CPIS on days 0, 3 and 7 with repeated measurements of analysis of variance (ANOVA) to determine the clinical course for the initial 7 days. After Mauchly’s test of sphericity, multivariate tests of repeated measurements of ANOVA were performed. Finally, we performed univariate and adjusted multivariate analysis according to Cox proportional hazards regression model for binary and continuous outcome variables. Before Cox regression analysis, we performed linear regression analysis to determine collinearity between variables by calculating variance inflation factors (VIF). We used the statistical software SPSS 19.0 (SPSS Inc, Chicago, Illinois, USA) for all analyses.

Ethics
The Institutional Review Board of the Seoul National University Bundang Hospital has approved this retrospective study and waived the need for informed consent to have access to patient records (IRB No. B-1312-232-105).

RESULTS
Baseline characteristics of the study populations
The EB group comprised 93 (60.4%) of the 154 patients. Their median age was 75 years (range: 19–92), and 77 (82.8%) were male. The time interval from intubation to bronchoscopy was 11.3 ± 8.0 h in the EB group. Comparison of the two groups revealed that most of demographic data were not significantly different, except the history of diabetes mellitus (Table 1).

Clinical features of aspiration pneumonia at intensive care unit admission
The analyses of the type of pneumonia, aspiration probability, admission source, initial clinical severity scores (i.e. APACHE II score, LIS, CPIS and SOFA score), initial PaO2/FiO2 ratio, time interval from intubation to ICU admission and initial department of admission showed no differences between the groups. However, patients in the LB group tended to be admitted on a holiday or weekend (P < 0.001; Table 2). In addition, a larger number of patients who had bronchoscopy occurred more than once in the first week were in the EB group (P = 0.009).

Causative pathogens from BAL culture results were found in 60 (64.5%) of 93 EB patients and 37 (60.7%) of 61 LB patients who underwent bronchoscopy within the initial 7 days. The choice for initial empirical antibiotics was not different between the two groups (Supplementary Table S1). Based on culture results, the patients who initially received appropriate empirical antibiotics were 33 (55.0%) of 60 patients in the EB group and 14 (36.8%) of 39 patients in the LB group (P = 0.080). After additional analysis based on medical records of antibiotic administration in patients without detected pathogens, patients who received initially appropriate empirical antibiotics were 52 (55.9%) of 93 patients in the EB group and 26 (42.6%) of 61 patients in LB group, and there was also no significant difference between the two groups (P = 0.107; Table 2).

All-cause mortalities
All-cause mortality was different between the two groups (ICU and by day 90; Table 3). Six (4.9%) patients in the EB group and 15 (24.6%) in the LB group died in the ICU (P = 0.001); 11 (11.8%) in the EB group and 20 (32.8%) in the LB group had died by day 90 (P = 0.002). Although relatively more patients in the LB group died from ARDS than those in the EB group, no significant difference in the causes of death between the two groups was found. Kaplan–Meier analysis and log–rank test for the probability of survival from intubation through 90 days showed an improved survival rate in the EB group (P = 0.001; Fig. 2).

Secondary outcomes
The duration of MV and length of stay in ICU were shorter, and the successful extubation rate was higher in the EB group. In contrast, more patients underwent a tracheostomy during hospitalization and were discharged with a home ventilator in the LB group. In the analysis of LIS, SOFA score and CPIS for the first week, all scores decreased more rapidly in the EB group; in particular, the change of SOFA scores was statistically significant (P = 0.028; Fig. 3).

Univariate and multivariate analysis
Univariate analyses showed that EB was associated with patient survival (Supplementary Table S2). In addition to undergoing EB, admission on a holiday or weekend and initial appropriateness of empirical antibiotics were statistically related with mortality. They were found not to have collinearity with early bronchoscopy in VIF that was less than 1.3. Initial APACHE II score, LIS and SOFA score were different between survivor and non-survivor groups. After
multivariate analysis with adjustment of all parameters related to survival, we found that EB significantly increased the survival rate (odds ratio: 0.412; 95% confidence interval: 0.192–0.883; Table 4).

**DISCUSSION**

This study showed that EB may improve clinical outcomes in patients with mechanically ventilated aspiration pneumonia whose diagnosis is supported by CT in dependent areas. This result was still statistically significant after adjusting some variables affecting mortality.

The overall benefit of diagnostic bronchoscopy for microbiology in regard to the clinical outcome of pneumonia is well known. A recent study reported that bronchoscopic toilet could lower the incidence of pneumonia, length of stay and mortality in ICU patients with a tracheostomy. Other studies suggested that bronchoscopy in pneumonia with inhalation injury could help decrease the ICU length of stay, hospital costs and even mortality by resolving airway occlusion. Moreover, refractory asthma and pulmonary alveolar proteinosis patients may benefit from bronchoscopy by removing immunological airway material. These studies implied that therapeutic bronchoscopy may benefit patients with pneumonia or pneumonitis by reducing airway inflammation. In the same context, bronchoscopy, especially done earlier, for aspiration pneumonia in the ICU may also have a beneficial effect on clinical outcome by removing aspirated inflammatory and contaminated material.

Time differences in the performance of bronchoscopy would more likely depend on the ICU’s availability of resources, such as equipment or human, rather than individual patient’s medical condition. The EB and LB groups presented with different characteristics at admission, such as admission on a holiday or weekend. Because of the time required to activate the on-call bronchoscopy team and lack of in-house doctors and nurses, admission on a holiday or weekend delayed the performance of bronchoscopy. This finding concurs with a previous report, which showed that a weekend ICU admission was associated with increased mortality.

In Kaplan–Meier analysis, early mortality within 14 days of admission showed no difference between the EB and LB groups; however, late mortality within 90 days of admission reached statistically significant
difference. We reviewed the clinical courses of patients with late mortality and found that they had a stable period and abruptly proceeded to respiratory failure or septic shock. With an analysis of overall mortality from day 15 to day 90, 17 patients in the LB group died of respiratory failure ($n = 12$; 70.6%) and septic shock ($n = 4$; 23.5%). It is thought that the mortality of those patients may be caused by ventilator-associated complications or hospital-acquired secondary infections because MV duration

| Table 2  | Clinical features of aspiration pneumonia at ICU admission |
|----------|----------------------------------------------------------|
|          | EB ($n = 93$)   | LB ($n = 61$)   | $P$-value |
| Classification |                |                | 0.176     |
| CAP       | 50 (53.8%)     | 26 (42.6%)     |           |
| HAP (including HCAP) | 43 (46.2%) | 35 (57.4%)     |           |
| Aspiration probability |              |                | 0.523     |
| Certain   | 13 (14.0%)     | 9 (14.8%)      |           |
| Probable  | 48 (51.6%)     | 26 (42.6%)     |           |
| Suspected | 32 (34.4%)     | 26 (42.6%)     |           |
| Admission source |            |                | 0.148     |
| Emergency room | 60 (64.5%) | 33 (54.1%)     |           |
| Ward      | 31 (33.3%)     | 23 (37.7%)     |           |
| Other sources* | 2 (2.2%) | 5 (8.2%)       |           |
| Initial APACHE II score | 25.5 ± 6.4 | 26.2 ± 6.2 | 0.525 |
| Initial LISb | 1.76 ± 0.52 | 1.79 ± 0.61 | 0.772 |
| Initial SOFA scorec | 9.76 ± 2.71 | 9.56 ± 2.91 | 0.661 |
| Initial CPISd | 6.89 ± 1.35 | 6.70 ± 1.47 | 0.406 |
| PaO$_2$/FiO$_2$ ratio at intubation | 207.2 ± 91.5 | 209.4 ± 104.0 | 0.894 |
| Time interval from intubation to ICU admission (h) | 2.0 ± 4.1 | 3.6 ± 7.7 | 0.147 |
| Initial admission department | | | 0.228 |
| Internal medicine | 70 (75.3%) | 38 (62.3%) |           |
| Surgical departments | 11 (11.8%) | 11 (18.0%) |           |
| Other departments* | 12 (12.9%) | 12 (19.7%) |           |
| Admission on holiday or weekend | 5 (5.4%) | 29 (47.5%) | <0.001 |
| Frequency of bronchoscopy for first week | | | 0.009 |
| ≤1 | 58 (62.4%) | 50 (82.0%) |           |
| ≥2 | 35 (37.6%) | 11 (18.0%) |           |
| Identification of causative pathogen | 60 (64.5%) | 37 (60.7%) | 0.627 |
| Detected pathogens on BAL | | | 0.851 |
| Staphylococcus aureus | 17 (28.3%) | 9 (23.7%) |           |
| Klebsiella pneumoniae | 13 (21.7%) | 11 (28.9%) |           |
| Pseudomonas aeruginosa | 10 (16.7%) | 8 (21.1%) |           |
| Streptococcus pneumoniae | 7 (11.7%) | 2 (5.3%) |           |
| Acinetobacter baumannii | 3 (5.0%) | 2 (5.3%) |           |
| Other speciesf | 10 (16.7%) | 6 (15.8%) |           |
| Initial appropriateness of empirical antibiotics | | |           |
| Only patients with detected pathogens in BAL cultureg | 33 (55.0%) | 14 (36.8%) | 0.080 |
| Patients with and without detected pathogens in BAL culture | 52 (55.9%) | 26 (42.6%) | 0.107 |
| De-escalation of empirical antibioticsf | | | 0.742 |
| Yes | 28 (46.7%) | 16 (43.2%) |           |
| No | 32 (53.3%) | 21 (56.8%) |           |

*Other sources included intermediate care units and other hospitals.

*bWe had one missing value; 60 patients in the LB group were analysed.

*cWe had two missing values; 59 patients in the LB group were analysed.

*dWe had one missing value; 60 patients in the LB group were analysed.

*eOther departments included neurology, rehabilitation and emergency medicine.

*fOther species included Enterobacter, Escherichia coli, Citrobacter sp., Stenotrophomonas sp. and Enterococcus sp.

*gThe rate of initially appropriate empirical antibiotics use was analysed in 60 patients in the EB group and 37 patients in the LB group in whom pathogens were detected in BAL culture.

*hDe-escalation of antibiotics is a proper change to antibiotics with less extensive spectrum according to microbiological results. The rate of de-escalation of empirical antibiotics was analysed in 60 patients in the EB group and 37 patients in the LB group in whom pathogens were detected in BAL culture.

APACHE, acute physiology and chronic health evaluation; BAL, bronchoalveolar lavage; CAP, community-acquired pneumonia; CPIS, clinical pulmonary infection score; EB, early bronchoscopy; HAP, hospital-acquired pneumonia; ICU, intensive care unit; LB, late bronchoscopy; LIS, lung injury score; SOFA, sequential organ failure assessment.
or ICU length of stay was prolonged, rather than by aspiration pneumonia itself.\textsuperscript{19–21} Therefore, the role of early bronchoscopy for improving clinical outcomes might result from the reduction of MV duration or ICU length of stay, thus resulting in less secondary complications.

There was a tendency towards a difference in appropriateness of empirical antibiotic therapy between the two study groups; however, the difference was not statistically significant. The criteria for the choice of empirical antibiotic therapy cannot be significantly different between doctors in a tertiary hospital. Actually, we found minimal difference in the usage of antibiotic agents (Supplementary Table S1).

There are some limitations to this study. First, this study is a single-centre, retrospective, cohort study. However, we reviewed 10 years of medical records, which contained all the patients admitted after this centre opened. Second, the 154 patients did not represent all patients with aspiration pneumonia. Instead, we assessed whether the patients had an aspiration tendency, symptoms of bacterial pneumonia and CT findings that favoured aspiration pneumonia. Therefore, the results of this study could only be applied to a limited population. Third, ideally, the time interval from the aspiration event to initiation of antibiotics should be compared between the two groups because it would affect the prognosis of pneumonia. We could not obtain adequate information from retrospective chart reviews to determine the exact onset of aspiration pneumonia. However, the antibiotic administration process in the emergency department or ward would not be significantly different between two groups. Instead, we reviewed the time interval from intubation to ICU admission, which represents the time interval from respiratory failure to ICU care.

In conclusion, early bronchoscopy could benefit the clinical outcomes of mechanically ventilated patients with aspiration pneumonia. Further large-scaled, randomized control trial is needed to establish

### Table 3 Clinical outcomes between the early and late bronchoscopy groups

|                        | EB (n = 93) | LB (n = 61) | P-value |
|------------------------|------------|------------|---------|
| ICU mortality          | 6 (4.9%)   | 15 (24.6%) | 0.001   |
| 90-day mortality       | 11 (11.8%) | 20 (32.8%) | 0.002   |
| Cause of death         |            |            | 0.110   |
| Respiratory causes     | 6 (6.5%)   | 15 (24.6%) |         |
| ARDS                   | 1 (1.1%)   | 1 (1.6%)   |         |
| VAP                    | 5 (5.4%)   | 14 (23.0%) |         |
| Non-respiratory causes | 5 (5.4%)   | 5 (8.2%)   |         |
| Septic shock           | 2 (2.2%)   | 4 (6.6%)   |         |
| Cardiogenic shock      | 1 (1.1%)   | 1 (1.6%)   |         |
| failure                | 1 (1.1%)   | 0          |         |
| Unknown\textsuperscript{†} | 1 (1.1%) | 0          |         |
| Successful extubation  | 83 (89.2%) | 35 (57.4%) | <0.001  |
| Mechanical ventilation duration (days)\textsuperscript{‡} | 7.1 ± 5.6 | 17.7 ± 20.0 | 0.004   |
| Tracheostomy during hospitalization | 33 (35.5%) | 36 (59.0%) | 0.004   |
| ICU stay (days)        | 9.8 ± 8.2  | 22.9 ± 27.8 | 0.001   |
| Discharge with home ventilator | 5 (5.4%) | 14 (23.0%) | 0.001   |

\textsuperscript{†}One patient with an unknown cause of death slept well throughout the night without any events, and his wife checked his condition at 4 AM. He was found dead at 7 AM. Although we could not clearly determine the cause of death, it was assumed that the patient has expired from an underlying disease, amyotrophic lateral sclerosis.

\textsuperscript{‡}Mechanical ventilation durations were calculated only in patients who had successful extubation: 83 patients in the EB group and 35 patients in the LB group.

ARDS, acute respiratory distress syndrome; EB, early bronchoscopy; ICU, intensive care unit; LB, late bronchoscopy; VAP, ventilator associated pneumonia.

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Figure 2 Kaplan–Meier curve for probability of survival from time of intubation through 90 days between patients who underwent early bronchoscopy and late bronchoscopy. (—) Early bronchoscopy; (—) late bronchoscopy.
the therapeutic role of early bronchoscopy in these populations.

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Figure 3 Analysis of sequentially measured LIS, CPIS and SOFA scores. LIS was evaluated in 41 patients in the early bronchoscopy group and 46 patients in the late bronchoscopy group; P = 0.280. CPIS was evaluated in 72 patients in the early bronchoscopy group and 55 patients in the late bronchoscopy group; P = 0.218. SOFA score was evaluated in 72 patients in the early bronchoscopy group and 54 patients in the late bronchoscopy group; P = 0.028. CPIS, clinical pulmonary infection score; D0, time of intubation; D3, third day after intubation; D7, seventh day after intubation; LIS, lung injury score; SOFA, sequential organ failure assessment. Early bronchoscopy; (—) late bronchoscopy.
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**Supplementary Information**

Additional Supplementary Information can be accessed via the online version of this article at the publisher’s website:

Table S1 The choice of initial empirical antibiotics.

Table S2 Univariate analysis to assess risk factors for 90-day mortality.