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Safety of Research Bronchoscopy in Critically Ill Patients

Sarah E.W. Prebil, MD[1], **Joel Andrews, RN, BSN**[2], **Sushma K. Cribbs, MD, MSc**[2,3], **Greg S. Martin, MD, MSc**[2], and **Annette Esper, MD, MSc**[2]

[1]University of Minnesota, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Minneapolis, MN

[2]Emory University, Division of Pulmonary, Allergy and Critical Care Medicine, Atlanta, GA

[3]Pulmonary Medicine, Department of Veterans Affairs Medical Center, Atlanta, GA

Abstract

Objective—Bronchoscopy and bronchoalveolar lavage are common procedures in intensive care units, however no contemporaneous safety and outcomes data have been reported, particularly for critically ill patients.

Design—Retrospective analysis of prospectively collected data from teaching hospital adult intensive care units.

Interventions—One hundred mechanically ventilated patients with severe sepsis, septic shock, acute lung injury and/or acute respiratory distress syndrome underwent bronchoscopy with unilateral bronchoalveolar lavage (BAL). Data collected included demographics, presence of sepsis or acute lung injury, PaO_2 to FiO_2 ratio, PEEP, APACHE score, SOFA score, and peri-procedural or post-procedural complications.

Results—Men comprised 51% of the patients; 81% of patients were black and 15% were white. The mean age was 52 (SD ± 16) years. The mean APACHE score was 22 (± 7.5) while the median SOFA score was 9 (IQR 5–12). Ten patients (10%) had complications during or immediately after the procedure. Hypoxemia during or immediately after the BAL was the most common complication. 90% of complications were related to transient hypoxemia; while bradycardia and hypotension each occurred in one patient. Age, female gender and higher PEEP were associated with complications.

Conclusions—Bronchoscopy with BAL in critically ill patients with sepsis and ALI is well tolerated with low risk of complications, primarily related to manageable hypoxemia.

Corresponding author: Annette M. Esper, M.D., MSc, 49 Jesse Hill Jr Drive, SE, [FOB], Atlanta, GA 30303, Phone: (404) 616-0148, Fax: (404) 616-8455, aesper@emory.edu.

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Keywords

bronchoscopy; bronchoalveolar lavage; complications; critically-ill; mechanically-ventilated

INTRODUCTION

Bronchoscopy and bronchoalveolar lavage (BAL) are common procedures in intensive care units; however, the safety and complication rates in mechanically-ventilated patients have not been reported since the early 1990's. Since that time, research in critically ill patients has increased and therefore more procedures are done for the sole purpose of clinical and translational research.

Earlier studies addressing the safety of bronchoscopy included patients who underwent bronchoscopy with BAL and protected-specimen brush for diagnostic purposes, or a combined patient population who had a procedure for either diagnostic or research purposes [1–3]. The complications reported included significant hypoxemia, cardiac arrhythmias, hypotension, bleeding and pneumothorax. In these studies, hypoxemia was reported as SaO_2 <90% and hypotension as mean arterial pressure <60 mm Hg. The rates of these complications or adverse events ranged from 2% to 40% [1–5]. All of these studies concluded that while bronchoscopy with BAL is usually well tolerated in critically ill patients, attention to procedural safety and guidelines are imperative [1, 2].

Given the non-contemporaneous nature of informative studies, we aimed to examine the safety of bronchoscopy for research purposes in critically ill, mechanically ventilated patients in current intensive care unit (ICU) settings.

METHODS

Sites and Patient Selection

Patients were screened daily for the presence of severe sepsis and/or or acute lung injury (ALI), and then enrolled into one or more clinical studies that required performing a bronchoscopy. Specifically, one study was an observational study of patients with severe sepsis or septic shock[6] and the other study was a randomized control trial of albumin vs. hetastarch in patients with acute respiratory distress syndrome (ARDS)[7]. Patients were enrolled from the adult ICUs at Grady Memorial Hospital, Emory University Hospital and Emory University Hospital Midtown from May 2009 to September 2012. Consent for study participation was obtained by the principal investigator, co-principal investigators, or designated research assistants.

Inclusion criteria

Patients were eligible if they were mechanically ventilated and met the criteria either for ALI or ARDS, or severe sepsis or septic shock. The presence of ALI or ARDS was based on the American-European consensus clinical definitions of ALI and ARDS [8]:

1. PaO_2 / FiO_2ratio ≤ 200 (ARDS) or ≤ 300 (ALI)

2. Bilateral infiltrates on chest x-ray
3. No clinical evidence of congestive heart failure
4. PAOP ≤ 18 mm Hg, if a pulmonary arterial catheter is present.

The definitions of severe sepsis and septic shock were based on the ACCP/SCCM criteria for sepsis [9]:

1. Patients met at least two of the following criteria for systemic inflammatory response syndrome: a) temperature >38° C or, <36° C; b) white blood cell count $>12\times10^9$/L or $<4\times10^9$, or presence of >10% bands/immature neutrophils; c) respiratory rate >20 breaths/minute; d) heart rate >90 beats/minute.
2. Clearly defined or suspected source of infection.
3. Criteria for severe sepsis: sepsis associated with organ dysfunction manifest by alterations in respiratory, cardiovascular, renal, metabolic, or hepatic function.
4. Septic shock was defined as meeting at least one of the following: a) systolic blood pressure <90 mm Hg or >40 mm Hg drop for >1 hour; b) the requirement for vasopressor therapy, excluding dopamine at a dose <4 mcg/kg/min;

Exclusion Criteria

Patients were not eligible for enrollment in the study if there was no informed consent, they were pregnant, they were less than 18 years old, or expected survival was ≤ 72 hours. In addition, patients with head injury were excluded in one study.

Procedure

Exclusion criteria for bronchoscopy were known or suspected intracranial hypertension, active hemodynamic instability, or an FIO_2 requirement of > 0.90. Flexible fiberoptic bronchoscopy was performed within 24 hours of enrollment with BAL performed in one lung segment (right middle lobe) with instillation of 120–200 mL of normal saline. Topical lidocaine was administered into the endotracheal tube 10 minutes prior to the procedure and the FiO_2 was increased to 100%. During the procedure, intravenous sedation was used as needed and the patient's vital signs, oxygenation and ventilator parameters were continuously monitored.

Data Collection

Study personnel (research nurses, coordinators, and assistants) collected the following data on study subjects: demographics, comorbid conditions, medication history, ventilator settings (e.g. tidal volume, respiratory compliance), severity of illness measures (APACHE, SOFA, lung injury score), duration of mechanical ventilation, and vital status at ICU and hospital discharge. Data was entered into a secure, HIPAA-compliant, web-based database for subsequent analysis. We classified the following as reportable complications: 1) severe hypoxemia requiring increased ventilator support during or immediately after the procedure (based on pulse oximetry), 2) severe arrhythmias requiring intervention or premature termination of the procedure, 3) severe bleeding requiring intervention, 4) hypotension

requiring intervention with additional intravenous fluids or vasopressors, 5) pneumothorax, or 6) death.

Institutional Review Board Approval

All of the personnel involved in the screening and patient identification part of this study completed the course on *Human Subjects Education and Responsible Conduct of Research* sponsored by the Emory University Human Investigations Committee of the Institutional Review Board. The study protocol was reviewed and approved by the Emory University Institutional Review Board and the Grady Hospital Research Oversight Committee.

Statistical Analysis

Descriptive statistics are presented as mean ± standard deviation (SD) or if not normally distributed, as median and interquartile (25%–75%) range (IQR). Ninety-five percent confidence intervals were calculated where appropriate. Univariate comparisons between patients who did and did not develop complications were calculated and evaluated for statistical significance at an alpha of 0.05 using a chi-squared test for categorical variables and a two-sample t-test for continuous variables.

RESULTS

Characteristics of Patient Population

One-hundred bronchoscopies with BAL were performed on critically ill patients for research purposes. Men comprised 51% of the patients; 81% of patients were black, 15% were white, and 4% were of other ethnicities (Table 1). The mean age of the cohort was 52 (SD16) years. ALI was present in 67% of this population and severe sepsis was present in 91%. The mean APACHE score was 22 (SD 7.5) while the median day 1 SOFA score was 9 (IQR 5–12). Hospital mortality for the cohort was 38%. The median PaO_2 to FIO_2 ratio was 218 (IQR 146–313). The average amount of lavage fluid instilled was 188 mL, with an average return of 79 mL.

Types of Complications

Ten percent [95% CI 4–16%] of patients had complications during or immediately after the procedure. Hypoxemia during or immediately after the bronchoscopy with BAL was the most common complication, and occurred in 9 patients (9%); 1 patient (1%) had bradycardia and 1 patient (1%) had hypotension. The duration of desaturation was not noted. Clinically significant hypoxemia (SaO_2 <90%), occurred in 6 (6%) of the patients; 4 patients had a SaO_2between 80%–89% and 2 patients had a SaO_2 ≤80%. Only 2 patients required increased PEEP and/or FIO_2 due to hypoxemia, while the other episodes of hypoxemia were transient and improved spontaneously or after suctioning. Bronchoscopy had to be prematurely terminated in one patient due to persistent hypoxemia.

Characteristics of patients stratified by the presence of complications

Females comprised 80% of the patients with complications (Table 2). The mean age was 41 years (SD 11) and all of the patients were black. The mean APACHE score was 20 (SD 7.5)

with a median SOFA of 6 (IQR 0–11). Eleven percent [95% CI 6–19] of sepsis patients had a complication compared to 14% [95% CI 7–24] of ARDS patients. The median PaO_2 to FIO_2 was 195 (IQR 113–276). The hospital mortality in the complication group was 10%.

In the group of patients who did not experience complications related to bronchoscopy with BAL, 55% of the patients were male, the mean age was 54 (SD16) years and 78% were black. The mean APACHE score was 22 (SD7.6) and median SOFA was 9 (IQR 7–12). The median PaO_2 to FIO_2 was 228 (IQR 146–313). The hospital mortality in this group was 41%.

In comparing patients with and without complications, the complications group was comprised of a majority of females, 80% vs. 45%, p = 0.04. (Table 2). Patients with complications from bronchoscopy with BAL were significantly younger than patients without complications (41 years vs. 54 years, p = 0.01). There was no difference in the presence of shock or ALI between patients with and without complications. PaO_2/FIO_2 was not associated with complications, while there was a trend towards increased complications in patients requiring higher levels of PEEP (p=0.097). Mortality was higher in the group without complications compared to those with complications (41% vs. 10%, p=0.06), although not statistically significant. There was no difference in hospital length of stay or ventilator free days between patients with and without complications.

DISCUSSION

Bronchoscopy with BAL is a common procedure in the ICU utilized for both clinical and research purposes. As more research on critically ill patients is conducted, more research bronchoscopies will be performed in this group of patients. This study is the first to systematically review the performance and safety of bronchoscopy specifically for research purposes in critically ill patients, specifically in patients with severe sepsis or ARDS. In our cohort, 100 bronchoscopies were performed on critically ill patients with severe sepsis, ALI or both, and resulted in a complication rate of 10%. This was mostly attributed to clinically significant hypoxemia in 6% of patients, and with 1 instance each of bradycardia and hypotension.

Hertz et al [1] examined ninety-nine critically ill, mechanically ventilated patients who underwent bronchoscopy with BAL for diagnostic purposes. They reported that none of their patients had complications severe enough to necessitate premature termination of the procedure, with a modest 2% risk of hypotension, and no severe hypoxemia or arrhythmias. In our cohort of severe sepsis and lung injury patients, one procedure had to be terminated because of persistent hypoxemia.

Another study from Steinberg [3] was conducted on 110 critically ill, mechanically ventilated patients with ARDS who underwent bronchoscopy with BAL. They reported clinically significant hypoxemia (SaO_2 <90%) in 4.5% of patients and hypotension in 3.6% of patients. There were no prolonged episodes of hypoxemia in their cohort of patients. Our rate for hypoxemia was higher while the rate of hypotension was comparable; however, there may have been differences in the patient populations with respect to illness severity

that explain the differences in rate of hypoxemic complications. It is unclear what percentage of patients in the Steinberg had sepsis as their ARDS risk factor. Furthermore, patients with hypotension did not undergo bronchoscopy, while 30% of patients in the current study who underwent bronchoscopy had septic shock. The frequency of hypoxemia may be related to the volume of fluid instilled or the volume recovered. Certain groups recommend delivery of 100ml to 240ml of total fluid in 20–60ml aliquots [10]. It is unclear whether a larger volume of fluid instilled results in more hypoxemia. In the current study, those without complications had more fluid instilled than those patients with complications (191ml ± 32 vs 158ml ±40, p=0.01). There was no significant difference in volume of return during lavage between patients with and without complications.

There are two studies that have been done in research-only populations, one in chronic obstructive pulmonary disease patients and one in asthma patients. Hattotuwa et al [11] conducted 98 bronchoscopies on 57 patients, none of whom were critically ill or mechanically ventilated. Sixty-eight bronchoscopies included endobronchial biopsy and BAL and thirty bronchoscopies performed biopsy alone. They reported 5 adverse events: one patient with bronchospasm and 1 patient with a pneumothorax (both occurring in the group that underwent biopsy and BAL) and 3 episodes of hemoptysis (2 in the BAL only group) which did not require intervention. Elston et al [12] performed 273 bronchoscopies on 159 asthmatic research patients (228 endobronchial biopsies with BAL, and 45 endobronchial biopsies alone). They report a 12.5% adverse event rate which included bronchospasm, pleuritic chest pain, bleeding and shortness of breath; only 2 patients had to be admitted for their complications. Although bronchoscopy may be associated with adverse events, these two studies indicate that research bronchoscopy in patients with COPD and asthma is well tolerated and is not associated with significant adverse events that require specific intervention or prolonged morbidity.

When comparing patients with and without complications in our current study, we found both younger age and female gender to be associated with complications. The reason for this finding is unclear. Gender and age have not been previously reported as significant risk factors for bronchoscopy. In fact, bronchoscopy has been shown to be well tolerated in both the elderly and the young [13]. The sample size of our study may explain these findings. Furthermore, all the patients with complications were black which is not surprising since the majority of the study population were black. It is unlikely that race alone is a risk factor for bronchoscopy complications.

The strength of this study is its systematic reporting of bronchoscopy-related complications in a contemporaneous and specifically-defined population of critically ill patients with sepsis and ALI. Importantly, with these data the patients and their surrogates providing informed consent for this procedure can be accurately informed about the current risks of bronchoscopy with BAL. For safety purposes, we have chosen to conservatively present all complications, regardless of impact on the procedure or patient-centered outcomes, resulting in a 10% rate of complications. The majority of complications were related to transient hypoxemia, and only 1 episode resulted in premature termination of the procedure. The duration of desaturation was not recorded for mild episodes of hypoxemia, which were managed by the primary ICU team. This is a potential weakness of our study.

The primary limitation of this study is the sample size, which is limited by the frequency of research bronchoscopy in critically ill patients even in a large multi-institutional study. A larger sample size would permit more confidence in the reported complications, and potentially permit the capture of rare complications not seen in this study. Also, despite the inherent flaws of retrospective analyses, it should be noted that the data for this study were collected prospectively.

CONCLUSION

Bronchoscopy with BAL in critically ill patients with sepsis and ALI is well tolerated with a 10% complication rate primarily related to transient hypoxemia. Furthermore, 1% of procedures may require premature termination due to complications. Age, female gender and higher PEEP were associated with complications, which were not associated with longer duration of ventilation, hospital stay or mortality. These data are useful as a current examination of the safety of bronchoscopy in a large population of critically ill patients, to optimally inform the consent process for subjects and their surrogates.

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References

1. Hertz MI, Woodward ME, Gross CR, Swart M, Marcy TW, Bitterman PB. Safety of bronchoalveolar lavage in the critically ill, mechanically ventilated patient. Critical care medicine. 1991; 19(12):1526–1532. [PubMed: 1959373]
2. Montravers P, Gauzit R, Dombret MC, Blanchet F, Desmonts JM. Cardiopulmonary effects of bronchoalveolar lavage in critically ill patients. Chest. 1993; 104(5):1541–1547. [PubMed: 8222821]
3. Steinberg KP, Mitchell DR, Maunder RJ, Milberg JA, Whitcomb ME, Hudson LD. Safety of bronchoalveolar lavage in patients with adult respiratory distress syndrome. The American review of respiratory disease. 1993; 148(3):556–561. [PubMed: 8368623]
4. Katz AS, Michelson EL, Stawicki J, Holford FD. Cardiac arrhythmias. Frequency during fiberoptic bronchoscopy and correlation with hypoxemia. Archives of internal medicine. 1981; 141(5):603–606. [PubMed: 7224740]
5. Raoof S, Mehrishi S, Prakash UB. Role of bronchoscopy in modern medical intensive care unit. Clinics in chest medicine. 2001; 22(2):241–261. vii. [PubMed: 11444110]
6. Esper AMKJ, Ward L, Brown LA, Hart CM, Martin GS. Severe Sepsis Attenuates PPARy activity. American Journal of Respiratory and Critical Care Medicine. 2011; 183:A3867.
7. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Critical care medicine. 2005; 33(8):1681–1687. [PubMed: 16096441]
8. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. American journal of respiratory and critical care medicine. 1994; 149(3 Pt 1):818–824. [PubMed: 7509706]
9. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. Chest. 1992; 101(6):1644–1655. [PubMed: 1303622]

10. Baughman RP. Technical aspects of bronchoalveolar lavage: recommendations for a standard procedure. Seminars in respiratory and critical care medicine. 2007; 28 (5):475–485. [PubMed: 17975775]

11. Hattotuwa K, Gamble EA, O'Shaughnessy T, Jeffery PK, Barnes NC. Safety of bronchoscopy, biopsy, and BAL in research patients with COPD. Chest. 2002; 122(6):1909–1912. [PubMed: 12475825]

12. Elston WJ, Whittaker AJ, Khan LN, Flood-Page P, Ramsay C, Jeffery PK, Barnes NC. Safety of research bronchoscopy, biopsy and bronchoalveolar lavage in asthma. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 2004; 24(3): 375–377.

13. Hehn B, Haponik EF. Flexible bronchoscopy in the elderly. Clinics in chest medicine. 2001; 22(2): 301–309. viii. [PubMed: 11444113]

Highlights

- Bronchoscopy is a common procedure used for clinical and research purposes in the critically ill.
- Bronchoscopy in critically ill patients with sepsis and ARDS is well-tolerated.
- The most common complication encountered during bronchoscopy is mild transient hypoxemia.
- Age, female gender and higher PEEP were associated with more complications.

Table 1

Patient characteristics of entire cohort.

N	100
Age (Mean, SD)	52 (16)
Gender (% male)	51
Race	
White (%)	15
Black (%)	81
Other (%)	4
APACHE (Mean, SD)	22 (8)
SOFA (Median, IQR)	9 (6–12)
Severe Sepsis (%)	91
Acute Lung Injury (%)	67
PEEP (Median, IQR)	5 (5–10)
PaO2 to Fi02 ratio (Median, IQR)	218 (146–313)
Mortality (%)	38

Table 2

CHARACTERISTICS OF PATIENTS STRATIFIED BY THE PRESENCE OF A COMPLICATION

	Complication	No Complication	p-value
N	10	90	
Age (Mean, SD)	41 (11)	54 (16)	0.01
Gender (% male)	20	55	0.04
Race			0.26
White (%)	0	17	
Black (%)	100	78	
Other (%)	0	5	
APACHE (Mean, SD)	19 (7.5)	22 (7.6)	0.39
SOFA (Median, IQR)	6 (0–11)	9 (7–12)	0.062
Severe Sepsis (%)	100	90	0.29
Acute Lung Injury (%)	90	65	0.11
PEEP (Median, IQR)	10 (8–10)	5 (5–10)	0.097
PaO2 to Fi02 ratio (Median, IQR)	195 (113–276)	228 (146–313)	0.37
Infusion of vasopressors (%)	10	32	0.15
Mortality (%)	10	41	0.06