Respiratory Medicine 140 (2018) 71–76

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease

Joseph Cooley[a,*], Rick Balestra[b], Alejandro A. Aragaki-Nakahodo[c], Danielle N. Caudell Stamper[c], Thitiwat Sriprasart[d], Zulma Swank[a], Robert P. Baughman[c], Sadia Benzaquen[c]

[a] Department of Internal Medicine, University of Cincinnati Medical Center, USA
[b] Providence Health & Services of Oregon and Southwest Washington, Division of Pulmonary and Critical Care Medicine, USA
[c] Division of Pulmonary, Critical Care and Sleep Medicine, University of Cincinnati Medical Center, USA
[d] Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

ARTICLE INFO

Keywords:
Bronchoscopy
Diffuse parenchymal lung disease
Interstitial lung disease
Safety
Transbronchial lung cryobiopsy

ABSTRACT

Introduction: Transbronchial lung cryobiopsy (TBLC) has become a popular option for tissue diagnosis of interstitial lung disease (ILD), however reports vary regarding the safety of this procedure. Herein, we evaluate the safety of transbronchial cryobiopsy in hospitalized patients, comparing adverse events to outpatient procedures.
Methods and measurements: This is a single center, retrospective chart review of all TBLC performed for suspected ILD between November 2013 and March 2017. Biopsies were performed by a board certified interventional pulmonologist or interventional pulmonology fellow using a two-scope technique.
Results: One hundred fifty-nine cryobiopsies were performed for the diagnosis of ILD. Rates of adverse events are as follows: pneumothorax 11%, persistent air leak 1.3%, moderate-severe bleeding 3.8%, ICU transfer within 48 h 3.1%, and all cause 30-day mortality 1.9%. No deaths were attributed to the procedure. Comparing adverse events between hospitalized patients and outpatients, rates of pneumothorax were 24% vs 9.9%, persistent air leak 5.9% vs 0.7%, ICU transfer 12% vs 2.1%, and 30-day mortality 5.9% vs 1.4%. However, no differences were statistically significant.
Conclusion: Practitioners should recognize that while cryobiopsies are a high-yield, safe, and cost-effective alternative to surgical lung biopsy, not all procedures carry the same risk profiles. Hospitalized patients may have a greater propensity for pneumothorax, persistent air leak, transfer to the ICU, and 30-day mortality.

1. Introduction

The use of cryoprobes for bronchoscopic purposes was first reported in 1977 [1], but in the past decade transbronchial lung cryobiopsy (TBLC) has emerged as an option for obtaining lung tissue. It has been especially useful for diagnosis of interstitial lung disease (ILD) when a diagnosis cannot be established with non-invasive techniques. Current guidelines recommend surgical lung biopsy (SLB) for tissue diagnosis of ILD [2–5], however SLB requires hospitalization, a post-procedural chest tube, and carries a variable post-operative mortality based on urgency of procedure [6,7].

TBLC provides a safer and more cost-effective option for tissue diagnosis [8,9]. However, recent publications have cautioned about high rates of adverse events [10]. In our experience over nearly three and a half years, we observed that hospitalized patients tended to incur more frequent complications. In effort to help delineate factors that predispose patients to adverse events, we compared the safety of TBLC between hospitalized patients (inpatients) and outpatients with suspected ILD.

2. Methods

We performed a retrospective review of consecutive patients referred to the interventional pulmonology service for tissue diagnosis of suspected ILD between November 2013 and March 2017 at the University of Cincinnati Medical Center (IRB # 2015–2392). Data on a portion of the patients has been reported previously [7,11,12]. Inclusion criteria were age greater than 18 years, referral to interventional pulmonology service for tissue diagnosis of suspected ILD, and absence of a previous definitive diagnosis. All patients had computed tomographic (CT) abnormalities indicative of an interstitial pulmonary process. Patients in the intensive care unit were excluded, as nearly all met clinical criteria for acute respiratory distress syndrome (ARDS) and had a high rate of adverse events inherent to their condition. Patients

* Corresponding author. 234 Goodman St ML0781, Cincinnati, OH, 45219, USA.
E-mail address: cooleyjc@ucmail.uc.edu (J. Cooley).

https://doi.org/10.1016/j.rmed.2018.05.019
Received 16 January 2018; Received in revised form 23 May 2018; Accepted 24 May 2018
Available online 25 May 2018
0954-6111/ Published by Elsevier Ltd.

previously on anticoagulation or antiplatelet agents were included in the study, with cessation of these medications left to the discretion of the interventional pulmonologist. Usual practice is to continue aspirin, discontinue clopidogrel 7 days prior to procedure, and discontinue oral anticoagulants 5 days prior to procedure. Informed consent was obtained and patients subsequently underwent flexible fiberoptic bronchoscopy with TBLC.

All procedures were performed by a board certified interventional pulmonologist, or an interventional pulmonology fellow under guidance of an interventional pulmonologist, using a two-scope technique, described below. All procedures were performed in an identical manner: under general anesthesia with spontaneous ventilation through a laryngeal mask airway (LMA) or an endotracheal tube (ETT) in a bronchoscopy suite utilizing fluoroscopy. Two therapeutic bronchoscopes (Olympus XT 180, Tokyo, Japan) with a 2.8 mm working channel were utilized, with a 1.9 or 2.4 mm cryoprobe (Erbe, Tübingen, Germany). After December 2015, the activation time was standardized to the time necessary to form a 13 French iceball in room temperature saline for the 1.9 mm cryoprobes, or a 16 French iceball for 2.4 mm cryoprobes. Prior to December 2015, freezing time was determined by the pulmonologists' preference, usually 5–8 s. To obtain each biopsy, the cryoprobe was advanced into a segmental airway and guided to the outer third of the lung under fluoroscopic guidance. After meeting resistance, the cryoprobe was withdrawn approximately 0.5–1 cm and freezing was activated. The bronchoscope and cryoprobe were then withdrawn en-bloc, with rapid insertion of a second bronchoscope that was advanced and wedged into the biopsied segment to control bleeding. Bronchoalveolar lavage (BAL) is routinely performed, but additional interventions, such as endobronchial ultrasound guided biopsy (EBUS), endobronchial forceps biopsy, and transbronchial forceps biopsy were performed per the pulmonologists' discretion.

Immediately after the procedure, chest ultrasound and/or chest radiography was obtained to evaluate for pneumothorax. After outpatient procedures, patients were monitored for approximately 2 h in the recovery area prior to discharge. Inpatients were observed in the recovery area for approximately 1 h before returning to their hospital room.

Formalin fixed samples were used to prepare hematoxylin and eosin slides, which were reviewed by a pulmonary pathologist. Each pathology report was reviewed for specimen number, location, largest biopsy diameter, presence of pleura, histologic description, and diagnosis. Final histologic diagnoses were categorized as definite, possible, and non-diagnostic. A diagnosis was considered definite when pathologic features of a distinct pulmonary disease were present; possible when pathologic features of more than one pulmonary disease were present; and non-diagnostic when no distinct pathologic features were present.

A consensus diagnosis was determined by multidisciplinary discussions involving pulmonologists, chest radiologists and pulmonary pathologists. Consensus diagnosis required that pathology be categorized as definite or possible, and that a single definitive consensus diagnosis was established after multidisciplinary discussions. Diagnostic yield was defined as the proportion of cryobiopsy procedures that resulted in a consensus diagnosis.

Patient charts were reviewed in detail for at least 30-days post-procedure. Adverse events were defined as any of the following within 30 days after the procedure: pneumothorax, persistent air leak (> 5 days), moderate-severe bleeding (grade 3 or 4), and death. ICU transfer within 48 h of the procedure was also considered an adverse event.

Bleeding was classified as follows: (adapted from Yarmus et al. and Du Rand et al.)[13,14]

Grade 0 Traces of blood not requiring suctioning
Grade 1 Bleeding only requiring suctioning and hemostatic wedging for up to 2 min (two 1-min cycles)
Grade 2 Bleeding requiring hemostatic wedging for 3 min or more
Grade 3 Bleeding requiring topical instillation of epinephrine or ice cold saline
Grade 4 Bleeding requiring hemodynamic support, transfusion of blood products, selective mainstem intubation, bronchial blocker, hospital admission, or surgical intervention.

We defined moderate bleeding as grade 3, and severe as grade 4.

Comparisons were done by Student's t-tests, Wilcoxon rank-sum tests, chi-squared or Fisher's exact tests. Data were expressed as means ± standard deviation with the range, or as counts and percentages. Analysis was performed using SAS®, version 9.4 (SAS Institute; Cary, NC).

Table 1
Adverse events.

	OP	IP	Total
Pneumothorax	9.9%	24%	11%
Chest Tube	7.7%	18%	8.8%
Persistent Air Leak	0.7%	5.9%	1.3%
Moderate-Severe Bleeding	4.2%	0%	3.8%
Admission to ICU within 48 h	2.1%	12%	3.1%
30-day mortality	1.4%	5.9%	1.9%
Timing of Mortality (days post-procedure)	9	9	9

3. Results

A total of 159 cryobiopsy procedures were performed for the diagnosis of ILD: 142 as an outpatient, 17 as an inpatient. Adverse events are summarized in Table 1. Rates of most adverse events were higher for inpatients compared to outpatients, though none of these reached statistical significance. This included pneumothorax (24% vs 9.9%, $p = 0.11$), persistent air leak (5.9% vs 0.7%, $p = 0.20$), admission to the ICU within 48 h of the procedure (12% vs 2.1%, $p = 0.09$), and 30-day mortality (5.9% vs 1.4%, $p = 0.29$). Moderate-severe bleeding occurred in 3.8% of cases, all of which were outpatients.

Of the 17 inpatients, 15 were hospitalized for respiratory failure, 1 for fatigue, and another for acute kidney injury. The latter 2 were found to have abnormal chest imaging and with respiratory symptoms, prompting further evaluation. Basic clinical data are reported in Table 2, comorbidities and medications in Table 3, chest CT findings in Table 4, and procedure details in Table 5. We compared all variables listed in Tables 2–5 between outpatients and inpatients, which revealed statistically significant differences for the following: ASA scores (2.8 vs 3.1, $p = 0.03$), nodules on CT (71% vs 41%, $p = 0.03$), diagnosis of HIV (0.71% vs 12%, $p = 0.03$), history of transplant (0.71% vs 18%, $p = 0.004$), current use of corticosteroids (30% vs 71%, $p = 0.003$) and antibiotics (2.8% vs 65%, $p < 0.0001$). There were no significant differences in procedural variables among levels of care (outpatient vs inpatient). Twenty-eight percent of outpatients required home oxygen, averaging 0.73 L by nasal cannula. Comparatively, 18% of inpatients required home oxygen, averaging 0.53 L by nasal cannula. However, on the day of the procedure 71% of inpatients required supplemental oxygen, averaging 2.4 L by nasal cannula.

Presence of pleura on the cryobiopsy pathology report was the only variable from Tables 2–5 associated with pneumothorax ($p = 0.0001$). All 4 with pleura were outpatients and subsequently developed a pneumothorax. Pneumothorax rate and freezing time were not significantly different before standardization of freezing time (9.0%, 6.11 s, respectively) and after (14%, 6.14 s, respectively). One inpatient pneumothorax was recognized 24 h post-procedure, while the rest were discovered within 2 h of the procedure. For patients with a pneumothorax, the most common histologic findings were non-diagnostic (4), non-specific interstitial pneumonia (NSIP, 3), organizing pneumonia (2), and non-caseating granulomas (2). The most common consensus diagnoses in patients with pneumothorax were non-diagnostic