COMPLICATIONS FOLLOWING TRANSBRONCHIAL BIOPSY: THE ROLE OF CRYOBIOPSY IN THE INCIDENCE OF POSTOPERATIVE PNEUMOTHORAX

COMPLICACIONES POST BIOPSIA TRANSBRONQUIAL: EL PAPEL DE LA CRIOBIOPSIA EN LA INCIDENCIA DE NEUMOTÓRAX POSTOPERATORIO

COMPLICAÇÕES APÓS BIÓPSIA TRANSBRÔNQUICA: O PAPEL DA CRIOBIOPSIA NA INCIDÊNCIA DE PNEUMOTÓRAX NO PÓS-OPERATÓRIO

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Transbronchial lung cryobiopsy is one of the diagnostic methods for interstitial lung disease. Today its use has grown greatly. It is a less invasive method and with good diagnostic performance, but it has complications. Pneumothorax is one of the most frequent.

Our work intends to determine its incidence and the need to perform a pleural drain as part of treatment.

Key Concepts

A) Current Knowledge:

- Transbronchial biopsies are widely performed to obtain histopathological diagnosis of focal and diffuse lung diseases.
- Overall diagnostic yield of conventional fluoroscopic transbronchial forceps biopsy varies widely in different series.
- Transbronchial cryobiopsy was developed as a high-diagnostic yield and safe approach.
- Pneumothorax is a frequent complication following transbronchial biopsies.

B) What This Paper Contributes to Our Knowledge:

- Transbronchial cryobiopsy has a higher incidence of postoperative pneumothorax when compared to forceps biopsy.
- Even though transbronchial cryobiopsy offers a better diagnostic yield, its association with a higher rate of pneumothoraces should be carefully considered when indicating and performing this procedure.

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Resumen:

Introducción: La criobiopsia pulmonar transbronquial (TBCB) se ha convertido en una alternativa diagnóstica a la biopsia pulmonar quirúrgica, principalmente en la enfermedad pulmonar intersticial. A pesar de su naturaleza menos invasiva y de un mayor rendimiento diagnóstico, se han descrito algunas complicaciones asociadas, como el neumotórax. En pocas oportunidades se ha comparado la TBCB y la biopsia transbronquial con fórceps (TBFB). El objetivo del presente estudio es evaluar la incidencia de neumotórax después de TBFB y TBCB y la necesidad de drenaje pleural.
Métodos: Estudio retrospectivo de pacientes que se sometieron a TBCB y TBFB, específicamente aquellos que desarrollaron neumotórax postoperatorio.
Resultados: Se realizaron un total de 181 biopsias pulmonares transbronquiales. Sesenta y tres (35%) fueron TBFB y 118 (65%) fueron TBCB. Tres pacientes en el grupo TBFB (5%) presentaron neumotórax postoperatorio, mientras que 16 pacientes (14%) presentaron neumotórax en el grupo TBCB (p 0,051). El análisis univariado reveló una asociación estadísticamente significativa entre el diagnóstico preoperatorio de fibrosis y un mayor riesgo de neumotórax postoperatorio después de TBCB (p 0.027), mientras que otras variables no arrojaron un resultado significativo.
Conclusión: Aunque se necesitan más estudios comparativos de alto volumen, este documento destaca la relevancia del neumotórax después de la TBCB. Esto deriva en una fuerte necesidad de protocolos de procedimientos claramente estandarizados para TBCB y una evaluación cuidadosa de sus complicaciones versus su rendimiento diagnóstico.

Palabras clave: *biopsia; drenaje; fórceps; pulmón; neumotórax*

Abstract:

Introduction: Transbronchial lung cryobiopsy (TBCB) has emerged as a diagnostic alternative to surgical lung biopsy mostly in interstitial lung disease. Despite its less invasive nature and reported higher diagnostic yield, some associated complications have been described, such as pneumothorax. Moreover, a comparison between TBCB and transbronchial forceps biopsy is seldomly made. The aim of the present study is to evaluate the incidence of pneumothorax following TBFB and TBCB and the need for pleural drainage.
Methods: Retrospective study of patients who underwent transbronchial forceps biopsy or transbronchial lung cryobiopsy, specifically those who developed postoperative pneumothorax.
Results: A total of 181 transbronchial lung biopsies were performed. Sixty-three (35%) were TBFB and 118 (65%) were TBCB. Three patients in the TBFB group (5%) presented postoperative pneumothorax, while 16 patients (14%) presented pneumothorax in the TBCB group (p 0,051). The univariate analysis revealed a statistically significant association between the preoperative diagnosis of fibrosis and a higher risk of postoperative pneumothorax following TBCB (p 0.027), while other variables did not yield a statistical significance.
Conclusion: Even though more high-volume comparative studies are needed, this paper highlights the relevance of pneumothorax following TBCB. This derives in a strong need for clearly standardized procedure protocols for TBCB and careful evaluation of its complications vs. its definitive diagnostic yields.

Keywords: *biopsy; drainage; forceps; lung; pneumothorax*

Resumo

Introdução: A criobiopsia pulmonar transbrônquica (TBCB) surgiu como uma alternativa diagnóstica à biópsia pulmonar cirúrgica principalmente na doença intersticial pulmonar. Apesar de sua natureza menos invasiva e maior rendimento diagnóstico relatado, algumas complicações associadas foram descritas, como o pneumotórax. Além disso, raramente é feita uma comparação entre TBCB e biópsia de pinça transbrônquica. O objetivo do presente estudo é avaliar a incidência de pneumotórax após TBFB e TBCB e a necessidade de drenagem pleural.
Métodos: Estudo retrospectivo de pacientes submetidos à biópsia de fórceps transbrônquico ou criobiopsia pulmonar transbrônquica, especificamente aqueles que desenvolveram pneumotórax pós-operatório.
Resultados: Foram realizadas 181 biópsias pulmonares transbrônquicas. Sessenta e três (35%) eram TBFB e 118 (65%) eram TBCB. Três pacientes no grupo TBFB (5%) apresentaram pneumotórax no pós-operatório, enquanto 16 pacientes (14%) apresentaram pneumotórax no grupo TBCB (p 0,051). A análise univariada revelou associação estatisticamente significante entre o diagnóstico pré-operatório de fibrose e maior risco de pneumotórax pós-operatório após TBCB (p 0,027), enquanto outras variáveis não apresentaram significância estatística.
Conclusão: Embora sejam necessários mais estudos comparativos de alto volume, este artigo destaca a relevância do pneumotórax após o TBCB. Isso deriva de uma forte necessidade de protocolos de procedimento claramente padronizados para o TBCB e de uma avaliação cuidadosa de suas complicações versus seu rendimento diagnóstico definitivo.

Palavras-chave*: biópsia; drenagem; pinça; pulmão; pneumotórax*

INTRODUCTION

Nowadays, transbronchial forceps biopsy (TBFB) is widely performed to obtain histopathological diagnosis of focal and diffuse lung diseases, especially when the suspected interstitial lung pathology is likely to have a peribronchovascular or centrilobular location [(1)].

Although the introduction of imagenologic guidance improved the diagnostic yield of TBFB, the overall diagnostic yield of conventional fluoroscopic TBFB varies from 18% to 75% depending on the characteristics of the underlying lung disease [(2)]. The small size of the biopsy specimen (median size 5mm), and the high probability of crush artifacts, limit the role of TBFB [(3)].

Therefore, surgical lung biopsy is required when the pattern on high resolution computed tomography is indeterminate or suggests an idiopathic interstitial pneumonia. While the advent of video-assisted thoracoscopic surgical biopsy has made this procedure much safer, it is still associated with significant complications and contraindications in certain patients.

Consequently transbronchial lung cryobiopsy (TBCB) was developed in 2009 in response to the need for a less invasive, more efficient, high-diagnostic yield and safe approach [(3)].

Both TBFB and TBCB are associated with postoperative complications such as bleeding and pneumothorax. Even though is has been described that TBCB when compared with TBFB, increases the diagnostic yield, there is also a concomitant reported increase in the risks of significant bleeding (1-4% to 14.2%) and pneumothorax (from 0.7%-2% to 9.4%) [(4)].

Pneumothorax as a complication of transbronchial biopsy brings about the need for a longer hospital stay and further invasive procedures such as pleural drainage in order to manage said complication. However, scientific evidence comparing pneumothorax incidence after TBFB and TBCB is limited.

The aim of the present study is to evaluate the incidence of pneumothorax following TBFB and TBCB and the need for pleural drainage. Secondarily, the purpose of the study is to identify risk factors for postoperative pneumothorax after TBCB.

METHODS

Design and Ethics

This is a single-cohort, retrospective analysis of a prospectively maintained database. Data for all adult patients (> 18 years old) undergoing TBFB and TBCB at the Interventional Pulmonology Unit of the Hospital Italiano de Buenos Aires between June 2013 and June 2018 were reviewed.

TBFB was performed in patients with suspected lung pathology that is located beyond the cartilaginous airways that may include elements of the small airways of the distal bronchial tree, the alveolar space, the vasculature, and lymphatic structures immediately surrounding the alveoli (i.e. sarcoidosis, Langerhans cell histiocytosis, pulmonary alveolar proteinosis, lipoid pneumonia, eosinophilic pneumonia, drug-induced pneumonitis, pulmonary infiltrates in the immunocompromised host, pulmonary nodule or mass, lymphangitic malignancy).

TBCB was performed in patients with a preoperative clinical and imagenological suspected diagnosis of indeterminate diffuse parenchymal lung disease, with a heterogeneous and patchy involvement of lung parenchyma.

Informed consent was obtained for all patients before each procedure and the Hospital Italiano Ethics Committee gave ethical approval to perform this study.

Study Aims

Primary endpoint was to assess the incidence of pneumothorax following TBFB and TBCB. Secondary endpoints were to evaluate the need for pleural drainage after the diagnosis of postoperative pneumothorax associated with TBFB and TBCB and to identify risk factors for postoperative pneumothorax after TBCB.

Procedure techniques

TBFB and TBCB were performed by a team of professionals composed of two interventional pulmonologists and one thoracic surgeon. Both procedures were performed via flexible bronchoscopy under general anesthesia with mechanical ventilation through a laryngeal mask or an endotracheal tube in an operating room utilizing fluoroscopy guidance. Careful study of a prebronchoscopy CT scan is useful in determining the best pulmonary segment to access for biopsy. Number of biopsies sought or obtained per case varied from 1 to 6, with three biopsies per case being most common.

TBFB technique

After a careful airway examination is performed, the pulmonary segment of interest is intubated with the tip of the bronchoscope, and the pulmonary forceps are passed through the working channel of the bronchoscope. As the forceps are visualized entering the pulmonary subsegment, the fluoroscopy unit may be activated to visualize the forceps as they enter the distal segments of the lung. To biopsy the lung periphery, the forceps should be gently advanced in the closed position until resistance is encountered. Next, the forceps are withdrawn approximately 1 cm, and the command is given to open the forceps jaws. The forceps are then advanced halfway to the area where resistance was encountered, and the forceps jaws are closed. With the fluoroscopy unit still activated, the forceps are retracted with firm, continuous pressure to allow the biopsy specimen to be removed from the surrounding lung parenchyma. The lung parenchyma should be watched on the fluoroscopy monitor for retraction during the collection of the biopsy sample. If there is excessive resistance, or extensive retraction of the lung parenchyma during sampling, the forceps should be opened to release the lung tissue, and the biopsy procedure should be restarted. After a sample is obtained, the forceps are removed from the working channel of the bronchoscope, and the biopsy is placed in formalin [(5)].

TBCB technique

The cryoprobe is advanced through the working channel of the bronchoscope into the peripheral lung and then activated for several seconds, causing surrounding parenchyma to rapidly freeze and adhere to the cryoprobe tip. The bronchoscope and cryoprobe with attached frozen biopsy are then removed en-bloc from the airway; this is necessary because the cryobiopsy is significantly larger than the working channel of the bronchoscope and thus cannot be extracted through this channel. Cryoprobe tip with frozen biopsy are then submerged in saline to rapidly thaw and release the biopsy from the cryoprobe, which is then removed from the working channel as the bronchoscope is re-introduced into the airway. Resulting biopsies tend to be 7–10 mm in greatest dimension, significantly larger than traditional forceps biopsies, and notably lack crush artifact [(6)].

Variables Analyzed

Variables collected included patient demographics (age, gender), patient medical history (chronic obstructive pulmonary disease, pulmonary fibrosis diagnosed by multislice computed tomography, smoking, prior lung surgery) type of procedure (TBFB, TBCB), lung biopsy site (right superior lobe, right inferior lobe, medial lobe, left superior lobe, left inferior lobe, multiple sites, lingula), number of biopsy samples per procedure, presence of postoperative pneumothorax, need of pleural drainage as treatment of pneumothorax, time of hospital days after initial procedure (days).

Postoperative pneumothorax was diagnosed through intraoperative fluoroscopy or a routinely performed chest X-ray carried out immediately after the initial procedure.

Pleural drainage was performed by inserting 12 French catheters (Ring-McLean Cook®) using the Seldinger technique with local anesthesia under tomographic guidance.

Statistical Analysis

Categorical variables are described using percentages. Continuous variables are expressed as means and standard deviation (SD) for symmetrically distributed, and median and interquartile interval (IQI) for non-symmetrically distributed data. The primary endpoint of the study was the presence of postoperative pneumothorax following TBFB and TBCB. Variables potentially associated to postoperative pneumothorax after TBCB were compared using Chi-square test. Statistical analyses were performed using STATA version 13 (StataCorp LP, TX). A p value < 0.05 was regarded as significant.

RESULTS

Between June 2013 and June 2018, 181 transbronchial lung biopsies were performed at the Hospital Italiano de Buenos Aires. Sixty three (35%) were TBFB and 118 (65%) were TBCB. The patients who underwent transbronchial lung biopsies were 78 females (43 %) and 102 males (57 %), with a median age of 67 years old (SD 13). Patient and biopsy characteristics according to type of procedure are listed in Table 1. It is worth noting that the lengthy hospital stay in some cases was related to prior hospitalization due to acute respiratory failure and underlying diseases.

Three patients in the TBFB group (5%) presented postoperative pneumothorax, while 16 patients (14%) presented pneumothorax in the TBCB group. Even though this represents a clinically relevant descriptive difference, it presented no statistical significance (p 0.051). The univariate analysis revealed a statistically significant association between the preoperative diagnosis of fibrosis and a higher risk of postoperative pneumothorax following TBCB (p 0.027). The biopsy specimens > 3 (p 0.181), COPD (p 0.677), smoking (p 0.293), sex (p 0.839), history of prior lung surgery and lesion location did not significantly influence the risk of pneumothorax in our analyses.

Table 1. Patient and procedure characteristics

	TBFB (n = 63)	TBCB (n = 118)
Gender, male #	41 (65)	62 (53)
Age, years °	70 ± 10	65 ± 12
Smoking #	32 (51)	52 (44)
COPD #	7 (11)	13 (11)
Fibrosis * #	1 (1)	14 (12)
> 3 samples #	19 (30)	91 (78)
Biopsy site #		
SRL	19 (30)	20 (17)
ML	7 (11)	2 (2)
IRL	9 (14)	25 (21)
SLL	18 (29)	5 (4)
ILL	7 (11)	19 (16)
Lingula	3 (5)	43 (37)
Multiple	0 (0)	3 (3)
Hospital stay, days °	4 ± 20	10 ± 24
Biopsy result #		
Normal	28 (44)	51 (44)
Neoplastic	28 (44)	35 (30)
Fibrosis	1 (2)	11 (9)
Insufficient	3 (5)	4 (3)
Others	3 (5)	16 (14)
Postoperative pneumothorax a	3 (5)	16 (14)

n (%); ° Median ± SD. * Preoperative presumptive diagnosis according to computed tomography.

COPD, chronic obstructive pulmonary disease; SRL, superior right lobe; ML,

DISCUSSION

Transbronchial forceps biopsy is performed to diagnose focal and diffuse lung diseases. TBFB was first reported by Anderson et al. in 1965 using a rigid bronchoscope in a small series of 13 patients [(7)]. Afterwards, TBFB was successfully performed through a flexible bronchoscope [(8)], leading to its widespread use until this day, with the assistance of different forms of imagenologic guidance (fluoroscopy, ultrasound, or electromagnetic navigation).

TBFB is often the biopsy procedure of choice when the suspected interstitial lung diseases is likely to have a peribronchovascular or centrilobular location and when a diagnosis can be made from small samples of lung tissue [(1)]. Examples of centrilobular diseases include sarcoidosis, hypersensitivity pneumonitis, lymphangitic carcinomatosis, eosinophilic pneumonia, and alveolar proteinosis. TBFB is less likely to be helpful when the pattern on high resolution computed tomography is indeterminate or suggests an idiopathic pulmonary fibrosis.

Limitations of TBLB include small specimen size (0.1–0.8 cm), sampling errors, and artifacts, thus lowering its diagnostic yield in certain cases [(9)]. Consequently, due to a significantly larger size of tissue sample, surgical lung biopsy is sometimes favored over traditional transbronchial forceps biopsy. However, this well-established sampling procedure is associated with higher morbidity and mortality [(10)]. Transbronchial lung cryobiopsy (TBCB) was developed in response to the need for a less invasive, more efficient and safe approach.

While cryotherapy dates back to the 19th century when it was used in a limited manner for control of local pain, since that time, many advances have occurred, eventually resulting in the use of cryotherapy in pulmonary medicine, through the application of rapid freeze-thaw cycles. For several years, cryotherapy was employed for the purpose of treating central airway obstruction (of benign or malignant etiology), early superficial tumors, removal of foreign bodies, control of bleeding, or removal of granulation tissue (which might form inside an endobronchial stent or at sites of anastomosis). In 2009, Babiak introduced the use of a cryoprobe for the purpose of obtaining lung biopsies during flexible bronchoscopy [(3)].

Even though they are less invasive, these procedures are not without complications. It has been reported that estimates of the risk of pneumothorax associated with transbronchial biopsy typically range from 0 to 5%, with higher rates reported in mechanically ventilated patients [(11)]. The purpose of this study was to evaluate the incidence of pneumothorax following TBFB and TBCB and the need for pleural drainage. Similarly to the published literature, with an incidence of 5% and 14%, pneumothorax was more frequent after TBCB than TBFB. Fifty percent of the patients with pneumothorax after TBCB required pleural drainage in our series.

Recent published articles report an incidence of pneumothorax after TBCB from 10 to 37% [(12–15)]. Meanwhile, reported estimates of pneumothorax after TBFB varies from 4 to 8% [(16–18)]. It has been reported that the risk of pneumothorax following TBCB was increased when samples were taken from different sites, from the upper lobes and it was also related with the number of samples, presence of emphysema and the lung function impairment [(16,19,20)]. Some authors highlight the lack of procedural standardization for transbronchial lung biopsy as the reason for a high incidence of complications. The type of anesthesia, procedural airway management, cryoprobe size, biopsy number, use of navigational guidance, ideal patient population, and biopsy location are heterogeneous in the reports published to date [(21)]. In our study, prior presumptive diagnosis of fibrosis was associated with a higher risk of postoperative pneumothorax following TBCB. This was probably confounded to some degree by the fact that idiopathic pulmonary fibrosis is one of the most frequent lung pathologies for which transbronchial biopsy is performed. However due to the relatively low amount of pneumothoraces in our series, a multivariate or logistic regression was not carried out to assess this fact.

The present study has certain limitations. On one hand, the difference between the incidence of pneumothorax in TBCB and TBFB had no

statistical significance with a p value of 0.051. Even though this could be attributed to an inherent variability of the statistical method it could also be argued that the lack of statistical significance is due to the small number of patients in the study sample. On the other hand, mainly due to the retrospective nature of the study, selection bias may have been incurred taking into account that patients were knowingly selected to undergo TBCB or TBFB according to previous medical history and imaging studies. A prospective randomization would have been ideal. However, ethical and methodological issues may arise from this approach.

To the authors' knowledge, this one of the first reports of the incidence pneumothorax after TBFB and TBCB in a single center. Even though more high-volume comparative studies are needed, this paper highlights the relevance of pneumothorax following TBCB. This derives in a strong need for clearly standardized procedure protocols for TBCB and careful evaluation of its complications vs. its definitive diagnostic yields.

Limitations of liability: The responsibility of the present work is only of the authors.

Originalidad del trabajo

Este artículo es original y no ha sido enviado para su publicación a otro medio de difusión científica en forma completa ni parcialmente.

Cesión de derechos

Los participantes de este trabajo ceden el derecho de autor a la Universidad Nacional de Córdoba para publicar en la Revista de la Facultad de Ciencias Médicas y realizar las traducciones necesarias al idioma inglés.

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