УДК 616.24-076

Сравнительное исследование диагностической эффективности чрезбронхиальной биопсии легких, трансбронхиальной биопсии лимфоузлов средостения под контролем эндосонографии в верификации саркоидоза 2 стадии

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Comparative study for diagnostic yield of TBLB and EBUS and their combination in verification of sarcoidosis II

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Резюме

Несмотря на 10-летнюю историю трансбронхиальной аспирационной биопсии лимфоузлов средостения и более 50-летнюю — чрезбронхиальной биопсии легкого, доказательств полезности их комбинации или последовательности недостаточно до сих пор. Цель: сравнить диагностическую эффективность TBLB, EBUS и их комбинации для верификации саркоидоза 2 стадии. Дизайн: проспективное нерандомизированное исследование с последовательным включением пациентов с января по декабрь 2018 г. Критерии включения: пациенты старше 18 лет с выявленной патологией в КТ грудной клетки, подозрительной на саркоидоз 2 стадии: сосуществование легочной диссеминации и средостенной лимфаденопатии и с показанием для верификации. Критерии исключения: ранее подтвержденный диагноз без инвазивной процедуры, противопоказания к бронхоскопии и общей анестезии или неспособность дать согласие. **Материалы и методы исследования.** В исследование было включено 100 пациентов. Пациенты были разделены на три группы: группа 1 (TBLB) — 50 человек, группа 2 (EBUS) — 35 человек, группа 3 (комбинация TBLB и EBUS) — 15 человек. TBLB и EBUS-TBNA были выполнены опытной командой в соответствии с имеющимися рекомендациями. Все диагнозы были поставлены в соответствии с национальными рекомендациями. Статистический анализ: использовался лицензионный программный пакет статистического анализа SPSS Statistics 10.0 и Excel-2010 (Microsoft). Чтобы определить значимость различий P в сопоставимых значениях, мы использовали методы таблиц сопряжения — сравнительный анализ проводился с использованием критерия χ^2 или точного критерия Фишера. **Результаты:** окончательная патология: саркоидоз — 75 (75,0%), туберкулез — 13 (13,0%), другая патология —

12 (12,0%). Общая чувствительность в группах 1, 2 и 3 составила 78,0, 80,0 и 93% соответственно (p<0,05). **Заключение:** у пациентов с КТ-признаками, подозрительными на наличие саркоидоза 2 стадии (сосуществования легочной диссеминации и средостенной лимфаденопатии) EBUS-TBNA должен быть первым методом диагностического вмешательства.

Ключевые слова: чрезбронхиальная биопсия легкого, TBBL, ультразвуковая бронхоскопия, EBUS-TBNA, саркоидоз, диссеминированный процесс.

Summary

Despite the 10 years of history of EBUS and more then 50 years of TBLB, the evidence of the usefulness of their combination or sequence are not enough till now. The aim: to compare the diagnostic efficacy of TBLB, EBUS and their combination in verification of sarcoidosis II. Design**:** a prospective non-randomized trial with consecutively enrolled patients from January 2018 till December 2018. Inclusion's criteria: Patients older than 18 years with the revealed pathology in the chest CT: suspicion of sarcoidosis II (coexistence of pulmonary dissemination and mediastinal lymphadenopathy). Exclusion's criteria: previously confirmed the diagnosis without the invasive procedure, contraindications to bronchoscopy and general anesthesia or inability to consent. **Material and methods:** 100 patients were enrolled in the trial. Patients were divided into 3 groups: group 1 (TBLB) — 50 patients, group 2 (EBUS) — 35 patients, group 3 (TBLB and EBUS) — 15 patients. TBLB and EBUS-TBNA were performed by the experienced team according to available guidelines. All diagnoses were made according to the national recommendations. Statistical analysis: the licensed software package of statistical analysis SPSS Statistics 10.0 and Excel-2010 (Microsoft) were used. In order to determine the significance of P differences of comparable values, we used the methods of pairing tables — a comparative analysis was carried out using the Chi-square test or Fisher's exact test. **Results:** final pathology: sarcoidosis — 75 (75.0%), tuberculosis — 13 (13.0%), other pathology — 12 (12.0%). Overall sensitivity in Group 1, Group 2 and Group 3 was 78.0%, 80.0% and 93% respectively (p<0,05). The sensitivity for sarcoidosis: 87.0%; 85.0% and 92.9%, in Group 1, Group 2 and Group 3, respectively. **Conclusion:** in patients with CT-signs of suspicion of sarcoidosis II the EBUS-TBNA should be the first-choice method of diagnostic intervention.

Keywords: TBBL, EBUS-TBNA, sarcoidosis, lung dissemination

Summary

Differential diagnosis of pathology of lungs and mediastinal lymph nodes remains the huge problem till now. The frequency of clinical mistakes is high and can achieve 60%. The diagnostic pause can be counted by many years [1]. Difficulties of diagnosis are connected with the fact that often radiological, molecular biological, bacteriological data are not enough to establish a diagnosis. Due to the lack of specificity of noninvasive methods, in mostly cases, the verification of the diagnosis is obligative. Historically, most spread methods are videothoracoscopic biopsy or videomediastinoscopy. But sometimes, the surgical procedures can be complicated. The frequency of complication's rate depends from an institution's experience, but estimated as 5% [2, 3].

More than 50 years ago the method of transbronchial lung biopsy (TBLB) was invented in the clinical practice. The history of the endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) counts more than 10 years [4].

At the same time, there are still unresolved questions of the sequence of application of one or another method of verification, depending on the CT.

The aim of our study was to evaluate the diagnostic yield of bronchoscopic methods in the verification of pathology in the cases of the coexistence of pulmonary dissemination and mediastinal lymphadenopathy.

Material and methods

Patients were older than 18 years with the revealed pathology in the chest CT suspicion of sarcoidosis II (coexistence of pulmonary dissemination and mediastinal lymphadenopathy) and with an indication for tissue verification. 100 consecutive patients were enrolled in the study. All 3 groups: group 1 (TBLB) — 50 patients, group 2 (EBUS) — 35 patients, group 3 (TBLB and EBUS) — 15 patients, respectively. There were 43 females and 57 males. The age of patients ranged from 19 to 79 years, the median age was 54 years. All patients were admitted in the clinic without the clinical signs of the disease.

The decision to obtain tissue for diagnostic purposes was made in a discussion between members of the multispecialty-team. The previous diagnostic evaluation consisted of a conventional evaluation (medical history, physical examination, and laboratory tests) with computed tomography of the chest. Exclusion criteria were previously confirmed a diagnosis without the invasive procedure, contraindications to bronchoscopy and general anesthesia or inability to consent.

This trial was approved by the local ethics committee and written informed consent was obtained from every patient.

This was an investigator-initiated, unblinded, prospective, non-randomized trial. Nodal aspirates and histologic lung biopsies were sent to the local pathologist for pathologic assessment. In addition, tissue samples were routinely sent for culture and polymerase chain reaction for mycobacterium tuberculosis testing.

For patients without a conclusive diagnosis after bronchoscopy the video-thoracoscopy (VATS) was done.

The final diagnosis was established according to national guidelines:

1) tuberculosis of lungs or mediastinal lymph nodes — the detection of granuloma with caseous necrosis or DNA of Mycobacterium tuberculosis or positive results of Bactec MGIT-960 in the diagnostic material [5];
2) sarcoidosis — the decision of the multidisciplinary team by the detection of the granuloma without caseous necrosis in the diagnostic material and results of clinical and laboratory examination [6].

The diagnosis after 3-months follow-up was considered the reference standard.

Diagnostic procedures

TBLB. Before the TBLB together with the radiologist, the biopsy site was determined — as the zone of the most pronounced changes according to CT. Procedures were performed with Pentax videoendoscopes under a fluoroscopic guide. At least, 3 pieces of lung tissue were taken during the procedure. The range of pieces was 3–11. The technique of the biopsy was well described in the guideline [7].

The first biopsy specimen, placed in saline, was sent for PCR-RT examination and Bactec MGIT-960. Subsequent biopsies were immediately fixed in 10% formalin solution for further histological examination.

EBUS-TBNA. EBUS-TBNA was performed by the technique, which was previously described by us [8].

The number of punctures of lymph nodes — 3. In all cases the 2 groups were punctured 7 and 4R, according to IASLC, 2009 [9]. EBUS specimens were examined by histology, PCR-RT and Bactec MGIT-960.

Combination of the two method. The one and other methods were done on different days (first day — TBLB and second day — EBUS-TBNA) by the technique, which was described earlier.

Statistical analysis. The licensed software package of statistical analysis SPSS Statistics 10.0 and Excel-2010 (Microsoft) was used. In order to determine the significance of P differences of comparable values, we used the methods of pairing tables — a comparative analysis was carried out using the Chi-square test or Fisher's exact test. The investigation of the diagnostic efficacy in Group 1 and 2 was done by the calculation of its main criteria: sensitivity, specificity and accuracy.

Results and discussion

Mean duration of the procedure was 30 minutes for TBLB (range, 15–45) vs 35 minutes for EBUS-TBNA (range, 15–55). All procedures of transbronchial lung biopsy were done under local anesthesia vs all EBUS-TBNA under general anesthesia. Transbronchial lung biopsies were performed under fluoroscopic guidance in 50 of 50 patients.

The complication's rate was — 3%. There were 3 pneumothoraxes (6.0%) in Group 1 was revealed after the TBLB. In all cases chest tube was inserted and lung was expanded. There were no complications in Group 1 and 2 ($p<0.05$).

Final diagnosis. In 78 (78.0%) from 100 patients the diagnosis was done after the bronchoscopic methods. In 22 (22.0%) the cases the VATS were done.

The structure of the diagnosis which was confirmed in patients is in table 1.

In the group of «other» diagnosis were: 1 — bronchiolitis, 11 — Unclassifiable idiopathic interstitial pneumonia.

The overall diagnostic yield of the bronchoscopic method consisted of 78% — the diagnostic yield in the Group 1,2 and 3 in table 2.

The difference between the sensitivity of the three approaches was significant.

We compared the diagnostic yield of the three methods for the diagnosis of the sarcoidosis — the results in table 3.

The sensitivity of all methods in the diagnosis of sarcoidosis is high and approximately equal. According to the diagnostic yield of each method in the diagnosis of tuberculosis, due to a small number in G3, the compare

Table 1

The structure of the final diagnosis in the patients

Diagnosis	Overall (n=100)	Group 1 (n=50)	Group 2 (n=35)	Group 3 (n=15)
Sarcoidosis	75 (75.0%)	31 (62.0%)	30 (85.7%)	14 (93.3%)
Tuberculosis	13 (13.0%)	9 (18.0%)	3 (8.6%)	1 (6.7%)
Other diagnosis	12 (12.0%)	10 (20.0%)	2 (5.7%)	0

Table 2

The sensitivity in the Group Group 1, 2 and 3

Group	Sensitivity	p
Group 1	78.0%	<0.05
Group 2	80.0%	
Group 3	93.0%	

Table 3

Diagnostic yield for the diagnosis of the sarcoidosis in Group 1, 2 and 3

Diagnosis	Sensitivity	Specificity	Accuracy	p
Group 1	87.0%	100.0%	92.0%	>0.05
Group 2	85.0%	100.0%	82.0%	
Group 3	92.9%	100.0%	93.3%	

was done only between Group 1 and Group 2. There was sensitivity: 77% vs 100%, but without statistical power.

This trial was the first prospective study, which was compared the diagnostic yield of the two bronchoscopic methods of the verification in cases of coexistence of pulmonary dissemination and mediastinal lymphadenopathy. The main difference of this trial vs previously reported GRANULOMA trial, because is the criteria of inclusion was taken only CT-scan dates and only patients with suspicion to Sarcoidosis II were enrolled [10].

The point of interest of this study — is the trial was done in the country of a high burden of the Tuberculosis. Tuberculosis was the second diagnosis, which was found in the structure of the final diagnosis. We got different results vs our previous report [8]. It can be explained, that in this trial we enrolled the patients with the coexistence of lung dissemination and mediastinal lymphadenopathy vs previous inclusion's criteria — only mediastinal lymphadenopathy.

Transbronchial lung biopsies achieve the good results of the diagnostic yield. The overall sensitivity (78%) in our study is within the range as reported in the literature (80–90%) [11–13].

Combination use of the TBLB and EBUS-TBNA achieved the highest diagnostic yield. But in all cases the EBUS was informative in patients of Group 3, when the TBLB was negative. This discordance can be explained by the small number of participants in Group 3.

The sensitivity of the TBLB for the sarcoidosis is equal to the EBUS. In cases of sarcoidosis 2, the same results were achieved in the other study [10].

The complication's rate of the TBLB is significantly higher, than in the EBUS group. This has a good correlation with the literature [14, 15].

Several limitations of this trial are known. First, this is a non-randomized trial. Second, conventional blind TBNA was not included in the protocol.

But despite these limitations, the results could be reviewed as a basis to a decision of the choice of method of the verification in patients with coexistence of pulmonary dissemination and mediastinal lymphadenopathy. An additional trial should be done.

Conclusion

In patients with suspicion to Sarcoidosis II (coexistence of pulmonary dissemination and mediastinal lymphadenopathy), the EBUS should be the first option, as a diagnostic procedure.

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Поступила в редакцию 04.03.2019 г.

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