THE EFFICACY OF ENDOBRONCHIAL VALVE THERAPY IN COMPLEX TREATMENT OF BRONCHO-PLEURAL FISTULAS

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Lung diseases represent the leading causes of mortality as well in Europe as in the whole world [1]. Pneumonia, tuberculosis, chronic obstructive pulmonary disease (COPD) accounted for 9.5 mln deaths worldwide (1/6 of global total) [2]. Broncho-pleural fistulas (BPF) are among severe complications of respiratory system diseases [3]. BPF is associated with high mortality rates – from 25% to 67% [28]. The data of study series carried out from 2000 showed that BPF is observed in approximately 5-7% of patients after surgery (for TB, lung cancer, etc.). Treatment of choice for these complications generally are: conservative therapy (thoracentesis, chest tube insertion) and (or) surgery. However, after prolonged infection empyema develops, which significantly complicates surgical treatment and worsens its effectiveness. There are a few data about alternative methods of treatment BPF in modern literature, the implementation of bronchoscopy methods (namely the use of endobronchial valve- EBV) is becoming most popular in the complex treatment of these complications during the last decade [8]. Despite increasing popularity, bronchoscopic methods does not meet yet evidence-based scientific standard. There are also scarce and in most cases controversial data about the efficacy of these treatment methods. Therefore, the aim of our investigation was the assessment of the efficacy of endobronchial valve (EBV) therapy in the complex treatment BPF.

Material and methods. The presented study has been carried out in several centers of Georgia (basically in the National Center for Tuberculosis and Lung Diseases).

The study group was selected according to the following criteria - Inclusion criteria. Patients with BPF, who underwent endobronchial valve therapy only and signed the informed consent to participate in the study. Exclusion criteria: Severe and urgent cardiovascular conditions, prescription of anticoagulation therapy during 5 days before the intervention, refusal to participate in the study. According to these criteria, 30 patients were included in the study group: the mean age was 38.0 (Standard deviation (SD) -13.8 years, male patients were 28 (93.3%), female - 2 (6.7%)].

The corresponding control group was selected according to the following criteria - Inclusion criteria.Patients with BPF, who underwent conservative therapy by multiple thoracentesis, chest tube insertion and also surgery, and signed the informed consent to participate in the study. Exclusion criteria were the same as in the study group. According to these criteria 28 patients were included in the – control group: mean age - 50.4 (SD-12.0) years, male patients were 25 (89.29%), female - 3 (10.71%)]. EBV therapy has been carried out by combined using the rigid (Friedel) and flexible (Olympus and Pentax) bronchoscopes. The intervention was performed in the surgery unit under general anesthesia. The patients were intubated by rigid (Friedel) bronchoscope by tubes of various sizes (usually: N11, N12, and N13). EBV therapy has been performed by valves of Medlung Ltd [9]. After EBV therapy patient stayed in the intensive care unit (ICU) for 24 hours. The quality of life in study and control groups has been studied by the Saint George Respiratory Questionnaire (SGRQ) [10]. The SGRQ consists of three domains: Symptoms – effects of respiratory symptoms; Activities – activities caused or reduced by breath problems; addresses the patient's current state (i.e. how they are these days). The activity score measures disturbances to daily physical activity. Effects - The impacts score covers a range of disturbances of psycho-social function. A Total score summarizes the impact of the disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 representsthe worst possible health status and 0 indicates the best possible health status. Statistical Analysis performed by software SPSS 22.0. T- and χ^2-tests have been used for continuous and categorical variables. The criterion of the rejection of the null hypothesis was – $p<0.05$.

Results and discussion. As was mentioned above, 30 patients were included in the study group. Non-TB pyothorax with BPF was diagnosed in 12 (40%) cases, TB was in remained 18 (60%) cases. BPF in the left lung was identified in 16 (53.3%) cases and in the right lung - in 14 (46.7%) cases. Comorbidities (hepatitis B and C, HIV, diabetes mellitus type 2) were reported in 3cases (10.0%). In 16 (53.33%) patients BPF was developed after surgery, while in 6 (20.0%) patients - after chest tube insertion and/or multiple thoracentesis. 28 patients were included in the control group. Non-TB Pyothorax with BPF was diagnosed in 6 s (21.43%) cases, TB was in remained 22 (78.57%) cases. BPF in the left lung was identified in 13 (46.43%) cases, and in the right lung in 14 (53.57%) cases. Comorbidities (hepatitis B and C, HIV, diabetes mellitus type 2) were reportedin in 2 (7.14%) cases. In 10 (35.71%) patients BPF was developed after surgery, while in 7 (25%) patients - after chest tube insertion and/or multiple thoracentesis. BPF closure after EBV intervention in the study group was in 28 cases from 30 and in 19 cases from 28 in the control group. Respectively the relapse cases after EBV intervention or surgery showed that 2 (6.7%) cases were identified in the study group and 9 (32.14%) cases – in the control group. Difference between groups was statistically significant ($\chi^2 = 6.1163$; $p=0.0134$, Fig. 1). The duration of the pre-surgery period in the study group was significantly lower, 0.89 (SD - 1.45) days compared to the control group, 11.04 (SD -17.0) days. The mean value of hospital delay after EBV intervention was 8.0 (SD - 14.1) days, the corresponding value in the control group was 36.9 (SD - 47.4) days (the difference was significant $p=0.0023$, Fig. 2). The mean duration of the chest tube insertion in the study group after EBV therapy - 2.6 (SD - 1.7) days. Analogous values in control group was 18.4(SD - 20.2) days ($p=0.0001$).

The assessment of the quality of life by SGRQ in study and control groups showed that the total SGRQ score was decreased significantly during 6 months from 65.38 to 42.26 ($p<0.001$), i.e. by 23.12. The total SGRQ score in the control group was not decreased significantly during 6 months (from 63.6 to 58.4, p=NS). The dynamics for symptom domain was also significant - 27.6($p=0.008$), for activity domain - 31.5 ($p<0.001$), for impact domain - 17.0($p=0.011$).

BPF still remains one of the hazardous complications of respiratory diseases [11].The two critically important components (points) for treatment tactics are the time of BPF onset and the defect size. Large bronchial defects are caused massive isch-

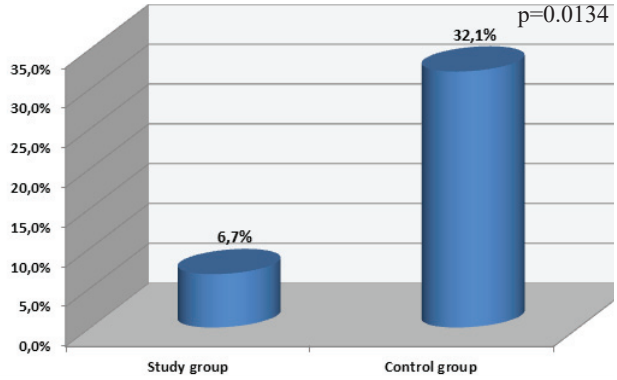

Fig. 1. Percentages of relapse cases in the study (n=30) and the control (n=28) groups

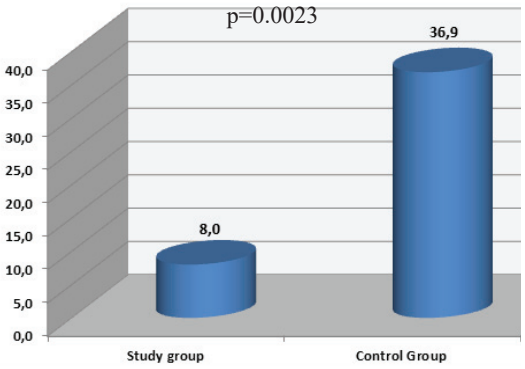

Fig. 2. The mean values of hospital delay after EBV intervention (Study group) and surgery (Control group)

emic bronchial necrosis and may represent the condition harmful for life [12]. They require wide surgical intervention due to the weakness of tissues. Smaller bronchial damages are better managed by conservative and endoscopic methods. They can be considered as an alternative to surgery. Sometimes, the clinical conditions of patients with BPF are not favorable for surgical intervention. In other words, patients with "late" identified BPF became severe due to prolonged infection, empyema develops, which significantly complicates surgical treatment and worsens its effectiveness. It is the reason for the attempts to carry out endoscopic methods for BPF closure. However, we have not significant evidence and yet EBV therapy is considered as supporting. The BPF closure does not mean healing from empyema and it requires the specific treatment. The latter is better managed in the conditions without microbial contamination. Literature data confirm that EBV therapy is one of these methods. Our results enrich the existing data and indicate the necessity of further investigation.

Conclusion. EBV therapy revealed high efficacy in the treatment of BPF. Compared to traditional methods, such as conservative therapy (thoracentesis, chest tube insertion) and surgery it was expressed by significantly lower frequency of relapses, lower duration of chest tube insertion, and lower duration of hospital delay.

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SUMMARY

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carried out by combined using the rigid (Friedel) and flexible (Olympus and Pentax) bronchoscopes. EBV therapy has been performed by valves of Medlung Ltd.The quality of life in study and control groups has been studied by the Saint George Respiratory Questionnaire (SGRQ). Statistical analysis performed by software SPSS 22.0.

BPF closure after EBV intervention in the study group was in 28 cases from 30 and in 19 cases from 28 in the control group. Respectively the relapse cases after EBV intervention or surgery showed that 2 cases (6.7%) were identified in the study group and 9 cases (32.14%) – in the control group. Difference between groups was statistically significant (χ^2=6.1163; p=0.0134).

The duration of the pre-surgery period in the study group was significantly lower, 0.89 (SD - 1.45) days compared to the control group, 11.04 (SD -17.0) days. The mean value of hospital delay after EBV intervention was 8.0 (SD - 14.1) days, the corresponding value in the control group was 36.9 (SD - 47.4) days (the difference was significant p=0.0023).

The mean duration of the chest tube insertion in the study group after EBV therapy - 2.6 (SD - 1.7) days. Analogous values in control group was 18.4 (SD - 20.2) days (p=0.0001).

The assessment of the quality of life by SGRQ in study and control groups showed that the total SGRQ score was decreased significantly during 6 months from 65.4 to 42.3 (p<0.001), i.e. by 23.1. The total SGRQ score in the control group was not decreased significantly during 6 months (from 63.6 to 58.4, p=NS). The dynamics for symptom domain was also significant -27.6 (p=0.008), for activity domain -31.5 (p<0.001), for impact domain -17.0 (p=0.011).

EBV therapy revealed high efficacy in the treatment of BPF. Compared to traditional methods, such as conservative therapy (thoracentesis, chest tube insertion) and surgery it was expressed by significantly lower frequency of relapses, lower duration of chest tube insertion, and lower duration of hospital delay.

Keywords: Broncho-pleural fistula, Endobronchial valve, Saint George Respiratory Questionnaire.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ КЛАПАННОЙ БРОНХОБЛОКАЦИИ В КОМПЛЕКСНОМ ЛЕЧЕНИИ БРОНХОПЛЕВРАЛЬНОЙ ФИСТУЛЫ

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Целью исследования явилась оценка эффективности эндобронхиальной клапанной терапии в комплексном лечении бронхоплевральной фистулы. Исследование проводилось в Национальном центре туберкулеза и легочных заболеваний. Наблюдались 30 пациентов с бронхоплевральной фистулой (БПФ), которым проведена клапанная бронхоблокация. Средний возраст больных составил 38,0±13,8 г., пациентов мужского пола было 28 (93,3%), женщин - 2 (6,7%). Контрольную группу составили 28 пациентов с БПФ, которым проводилась консервативная терапия с дренированием плевральной полости и хирургическое лечение. Обследованные пациенты подписали информированное согласие на участие в исследовании. Эндобронхиальная клапанная (ЭКБ) терапия проведена комбинированным применением жесткого (Friedel) и гибких (Olympus и Pentax) бронхоскопов и клапанами компании Medlung Ltd. Качество жизни оценивалось посредством опросника Saint George Respiratory Questionnaire (SGRQ). Закрытие бронхо-плевральной фистулы в исследуемой группе произошло в 28 случаях из 30, в контрольной группе в 19 случаях из 28. Соответственно, рецидив после интервенции в исследуемой группе проявился в 2 (6.7%) случаях и в 9 (32.1%) – в контрольной группе. Разница между группами статистически достоверна (χ^2=6.1163; p=0.0134). Продолжительность предопеорационного периода в контрольной группе составила 11.0 (SD -17.0) дней. Показатель преинтервенционного периода был достоверно ниже в исследуемой группе - 0.9 (SD 1.5) дней (p<0.001). Средняя величина срока госпитализации в исследуемой группе составила 8.0 (SD- 14.1) дней, соответствующая величина в контрольной группе - 36.9 (SD47.4) дней (разница достоверна p=0.0023). Средняя продолжительность дренирования плевральной полости в исследуемой группе после ЭКБ терапии составила 2.6 (SD1.7) дней, в контрольной группе - 18.4 (SD20.2) дней (p=0.0001). Исследование качества жизни по опроснику SGRQ показало, что суммарный показатель SGRQ в исследуемой группе в течение 6 месяцев достоверно уменьшился с 65.38 до 42.3 (p<0.001), т.е. на 23.1, в контрольной группе - недостоверно уменьшился с 63.6 до 58.4 (p=NS). Динамика для домена симптомов была достоверной - 27.6 (p=0.008), для домена активностей - 31.5 (p<0.001), для домена влияний - 17.0 (p=0.011). ЭКБ терапия выявила высокую эффективность в лечении бронхоплевральной фистулы в сравнении с традиционными методами, т.е. консервативным лечением (пунктирование и дренирование плевральной полости) и хирургическим вмешательством, что выразилось в достоверном снижении: частоты рецидивов, продолжительности дренирования плевральной полости и сроков госпитализации.

რეზიუმე

სარქვლოვანი ბრონქობლოკაციის ეფექტურობა ბრონქოპლევრული მარგულის კომპლექსურ მკურნალობაში

დ.ჭყონია, კ.ვაჭარაძე, თ.მსხალაძე

ტუბერკულოზისა და ფილტვის დაავადებათა ეროვნული ცენტრი, თბილისი, საქართველო

კვლევის მიზანს წარმოადგენდა სარქვლოვანი ბრონქობლოკაციის ეფექტურობის შეფასება ბრონქოპლევრული მარგულის კომპლექსურ მკურნალობაში.

კვლევა ჩატარდა ტუბერკულოზისა და ფილტვის დაავადებათა ეროვნული ცენტრის ბაზაზე. საკვლევი ჯგუფი შედგა 30 პაციენტისგან ბრონქოპლევრული მარგულით, რომელთაც ჩაუტარდა სარქვლოვანი ბრონქობლოკაცია (სბ). პაციენტების საშუალო ასაკი - 38,0±13,8 წ., მათ შორის მამაკაცი იყო 28 (93,3%), ქალი - 2 (6,7%). საკონტროლო ჯგუფი შედგებოდა 28 პაციენტისგან, რომელთაც ჩაუტარდა კონსერვატული მკურნალობა მრავალჯერადი პლევრის ღრუს პუნქციებით (თორაკოცენტეზი), პლევრული ღრუს დრენირებითა და ქირურგიული ჩარევით. პაციენტებისაგან მიღებული იყო ინფორმირებული თანხმობა კვლევაში მონაწილეობაზე. სბ ჩატარდა რიგიდული (Friedel) და დრეკადი (Olympus და Pentax) ბრონქოსკოპების კომ-

ბინირებული გამოყენებით და Medlung Ltd ენდობრონქული სარქველებით. ცხოვრების ხარისხი შეფასდა სენტ ჯორჯის რესპირაციული (Saint George Respiratory Questionnaire (SGRQ) კითხვარით.

ბრონქოპლევრული მარგული საკვლევ ჯგუფში დაიხურა 30-დან 28 შემთხვევაში, ხოლო საკონტროლო ჯგუფში - 28-დან 19 შემთხვევაში. შესაბამისად, რეციდივების რაოდენობამ საკვლევ ჯგუფში შეადგინა 2 (6.7%), ხოლო საკონტროლო ჯგუფში - 9 (32.1%). ჯგუფებს შორის განსხვავება სტატისტიკურად სარწმუნოა (χ^2=6.1163; p=0.0134). წინასაოპერაციო პერიოდის ხანგრძლივობამ საკონტროლო ჯგუფში შეადგინა 11.4 (SD17.0) დღე. წინა-სბ პერიოდის ხანგრძლივობა სარწმუნოდ მცირე იყო საკვლევ ჯგუფში - 0.9 (SD1.5) დღე (p<0.001); სტაციონარში დაყოვნების საშუალო მაჩვენებელმა საკვლევ ჯგუფში შეადგინა 8.0 (SD 14.1) დღე, შესაბამისმა მაჩვენებელმა საკონტროლო ჯგუფში შეადგინა 36.9 (SD 47.4) დღე (განსხვავება სარწმუნოა p=0.0023). პოსტინტერვენციული პლევრის ღრუს დრენირების საშუალო ხანგრძლივობა საკვლევ ჯგუფში სბ-ის თერაპიის შემდგომ იყო - 2.6 (SD 1.7) დღე. საკონტროლო ჯგუფში კი 18.4 (SD 20.2) დღე (p=0.0001). ცხოვრების ხარისხის კვლევამ SGRQ კითხვარით აჩვენა, რომ ჯამური SGRQ ქულა საკვლევ ჯგუფში ინტერვენციის ჩატარებიდან 6 თვის შემდეგ სარწმუნოდ შემცირდა 65.4-დან 42.3-მდე (p<0.001), ე.ი. 23.1-ით. ჯამური SGRQ ქულა საკონტროლო ჯგუფში არასარწმუნოდ შემცირდა 63.6-დან 58.4-მდე (p=NS). სიმპტომების დომენის დინამიკა იყო სარწმუნო -27.6 (p=0.008), აქტივობების დომენის -31.5 (p<0.001) და გავლენების დომენის -17.0 (p=0.011).

სბ თერაპიამ გამოავლინა მაღალი ეფექტურობა ბრონქოპლევრული მარგულის კომპლექსურ მკურნალობაში ტრადიციულ მეთოდებთან (პლევრის ღრუს პუნქცია და დრენირება) და ქირურგიულ მკურნალობასთან შედარებით, რაც გამოიხატა რეციდივების სიხშირის, პლევრული ღრუს დრენირების ხანგრძლივობისა და ჰოსპიტალში დაყოვნების სარწმუნო შემცირებაში.

DIRECT-ACTING ANTIVIRALS FOR HEPATITIS C DO NOT AFFECT THE RISK OF DEVELOPMENT OR THE OUTCOME OF HEPATOCELLULAR CARCINOMA

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HCV infection and its complications (hepatocellular carcinoma, decompensate cirrhosis) is a substantial public health burden. According WHO's Global Hepatitis Report [17], there are 1.7 million newly register cases every year and 400 000 death by related complications. Among them 137000 is a liver cancer patients, developed secondary after HCV infection [25]. Hepatocellular carcinoma (HCC) is an aggressive disease. It is the sixth most commonly diagnosed tumor and the fourth leading cause of cancer death in the world (841,000 new cases, 782,000 deaths annually). Incidence of liver cancer in male is 3 times higher. Therefore, it ranks second in terms of cancer deaths for males [1].

One of the main causes of the hepatocellular carcinoma (HCC) is a chronic hepatitis C induced liver cirrhosis. Effects of the different anti-hepatitis C virus treatment options on the epidemiology of HCC and its prognosis is conflicting and not fully understood [23]. Several author reports reduced risk of HCC during viral eradication therapy by Interferon (IFN)-based regimens, but some researchers show increasing incidence of the HCC recurrence after direct-acting antiviral (DAA) treatment, however these controversies based on different treatment options, measured parameters and observed groups and mainly derived from small series and observational studies [9,12,15,16,21,22].

In 2015 "Nationwide hepatitis C elimination program" was lunched in Georgia. According the protocol, patients with HCC also receives antiviral treatment [8,13]. Based on this 5-year experience, we study effect of the different DAA therapy regiments on the incidence or recurrence of HCC and its prognosis.

Material and methods. Research [# PhD_F_17_33] has been supported by Shota Rustaveli National Science Foundation of Georgia (SRNSFG). The protocol had obtained approval from the Ethics Committee of TSU Aleqsandre Natishvili Institute of Morphology and complied with the ethical guidelines of the 2013 Declaration of Helsinki (WMA - declaration of Helsinki – ethical principles for medical research involving human subjects). All patients gave their written informed consent to participate in the study.

Overall, 408 patients were recruited in Georgian-French Joint Hepatology Clinic HEPA between April 2015-March 2016. The selection criteria were as follows: 1. age 50-65 years; 2. liver fibrosis level F3-F4 or cirrhosis at least 15 years of disease history; 3. HCV positive diagnosed by PCR method, whatever the level of viral load and genotype ; 4. absence of previous complications of cirrhosis (ascites, gastrointestinal bleeding or HCC; 5. Child-Pugh class A or B; and 6. absence of severe extrahepatic disease. Their past medical history, essential clinical and biological parameters were recorded.

Clinical monitoring and management of adverse events were performed at regular base. The patients were seen by physicians every 6 months, and the essential clinical and biological data were recorded. Ultrasound examinations with Doppler were performed every 6 months. If mass lesions were detected by ultrasound, a diagnostic procedure using contrast-enhanced imaging (computed tomography scan or magnetic resonance imaging) and/or guided biopsy was performed according to the 2011 American Association for the Study of Liver Diseases

Guidelines [2]. A diagnosis of HCC was thus established by either histological examination or based on noninvasive crite-