ORIGINAL ARTICLE

The impact of co-existing comorbid diseases on long-term mortality in bronchoscopic lung volume reduction

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ABSTRACT

Aim Emphysema is a lung disease in which alveolar capillary units are destroyed supporting tissue lost. Bronchoscopic lung volume reduction (BLVR) is a novel treatment for emphysema. Several comorbidities have been reported to coexist in patients with chronic obstructive pulmonary disease (COPD). The aim of this study was to evaluate comorbidities of patients with severe emphysema who underwent BLVR and association of these comorbidities with mortality.

M**ethods** Between January 2011 and December 2017 the records of severe emphysema patients who underwent endobronchial valve (EBV) or lung volume reduction coil (LVRC) placement were reviewed retrospectively.

Results There were 37 patients who received EBV therapy and 29 received LVRC therapy. There were no significant differences in the demographic and clinical characteristics between two groups before the treatment. There were seven deaths (10.6%) over the period of twelve months following the BLVR treatment. All deaths occurred in patients with at least one comorbid condition. Mortality was increased in the presence of comorbidities (14.3% vs 0%, respectively; p=0.099), and it was significantly increased in the presence of multiple comorbidities (18.5% vs 0%; p=0.059). The mortality rate was higher (37.5% vs 10.5%) in the LVRC comparing to the EBV treatment group in the presence of multiple comorbid conditions, albeit not reaching statistical significance (p=0.099).

Conclusion The presence of more than one comorbidity in patients who underwent the LVRC treatment are associated with significant increase of mortality. For patients with severe emphysema who have more than one comorbidity, EBV is a better choice than LVRC.

Key words: coil, comorbidity, COPD, endobronchial valve, emphysema

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Original submission:
22 May 2019;
Revised submission:
13 August 2019;
Accepted:
26 August 2019
doi: 10.17392/1043-20

Med Glas (Zenica) 2020; 17(1):73-78

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a serious public health issue that affects approximately sixty-five million people across the globe and causes the deaths of three million people annually. Currently ranked fourth among the leading diseases causing death, it is predicted that it will ascend to third place by the year 2030 (1). Emphysema, comprising more than 30% of COPD patients, is characterized by lasting damage of the airways distal to the terminal bronchioles. The development of dyspnoea in COPD patients is mainly caused by lung hyperinflation secondary to emphysema.

Current medical treatment of emphysema encompasses modalities such as smoking cessation, beta-2 agonists, anticholinergic drugs, oral/inhaled steroids, oxygen treatment and pulmonary rehabilitation (2,3). However these treatment modalities have a limited effect on ameliorating lung hyperinflation, the main objective of treatment. The efficiency of Lung Volume Reduction Surgery (LVRS) in lessening lung hyperinflation has been evaluated in the NETT study (3). The frequency of early postoperative complications with LVRS and its high mortality rate led to the development of less invasive bronchoscopic lung volume reduction (BLVR) treatments, even though LVRS resulted in significant clinical improvement (4).

One important issue that has an impact on the natural history of COPD, particularly on its symptomatology along with its morbidity and mortality is the presence of comorbidities. Studies show that the treatment of COPD with coexisting comorbid disorders can be improved by a multidisciplinary team-based approach (5).

There are multiple studies addressing the prevalence of comorbidities, their contribution to mortality, and the burden these add to the management of COPD patients. Similarly, there is a multitude of studies concerning BLVR therapies (6-10). We are not aware of any studies in the medical literature that have examined the relationship between mortality and/or the presence or prevalence of comorbidities in patients that underwent BLVR therapy.

In the current study we aimed to investigate the effect on mortality of BLVR therapy when performed in predominantly (severe) emphysema phenotype COPD patients with comorbidities.

PATIENTS AND METHODS

Patients and study design

The records of severe emphysema patients who underwent endobronchial valve (EBV) or lung volume reduction coil (LVRC) placement as a part of BLVR therapy were retrospectively reviewed between January 2011 and December 2017.

The records of the patients included the age, gender, smoking history, comorbid diseases, pulmonary function test results and effort capacities. Comorbid diseases were determined by reviewing detailed patient records and evaluation of the last twelve months of prescribed drugs from the database of the Social Security Institution. Patients whose comorbidities could not be clearly determined and those who had a follow-up of less than twelve months following BLVR procedure were excluded from the study.

Approval of the Ethics Committee of the Karabuk University Faculty of Medicine was obtained.

Methods

The EBV placement was done using a flexible bronchoscope (BF-1TQ180 Olympus, Tokyo, Japan) with a working channel of 2.8 mm under conscious sedation with midazolam. Thin slice high resolution computerised tomography (HRCT) imaging and quantitative lung perfusion scintigraphy were used to choose the target lobe. The selected target lobe was subsequently preoperatively assessed by Chartis collateral ventilation system (Pulmonx, Redwood City, CA, USA), and the EBV was placed to all segments or subsegments (of the target lobe) detected to have no collateral ventilation (Zephry Tm EBV, Pulmonx Inc., Redwood, CA, USA). A chest x-ray was routinely obtained 2 hours following the procedure, or immediately in patients with respiratory symptoms. Patients without complications who were stable after 4 hours of observation were sent home to return for a control chest x-ray 24 hours later.

All LVRC procedures were done under general anaesthesia and under fluoroscopic guidance. Thin slice HRCT and quantitative lung perfusion scintigraphy were used to choose the target lobe in patients who met the selection criteria. Following the patients' intubation the bronchial system of the tar-

get lung lobe was assessed and the coils (Coil, PneumRx Inc. Mountain View, California, USA), after being straightened before the procedure with a special system, were placed under fluoroscopy into the subsegmental airway at approximately 3 cm distance from the pleura. A posteroanterior chest x-ray was routinely obtained 2 hours following the procedure or immediately in patients with respiratory symptoms. Patients with symptoms were given prophylactically systemic steroids against foreign body reaction for 7 days and were admitted to hospital for a period of 3 to 5 days.

Statistical analysis

Data obtained in the study were expressed as mean ± standard deviation (SD) for continuous variables and as numbers and percentages (%) for categorical variables. The Kolmogorov-Smirnov test was used to test if continuous variables were normally distributed. When comparing defined groups, $\chi 2$ test or Fisher's Exact Test was used for categorical variables and Student-t test for Mann Whitney-U test was used for continuous variables depending on the premac sence or absence of normal distribution. A $p < 0.05$ was used as the cutoff for statistical significance.

RESULTS

The data of 76 patients with severe emphysema who received BLVR therapy were retrospectively evaluated. Nine patients whose follow-up period was less than twelve months and one patient who died following the procedure were excluded; the remaining 66 patients' data were used in the study. There were 37 patients who received EBV therapy and 29 patients who received LVRC therapy; 59 (89.6%) patients were males (average age of 62.7±7.3). The average age of male and female patients was 62.4±6.9 and 65.8±10.3, respectively (p=0.245).

Five patients from the LVRC group and only one from the EBV group received bilateral procedure. There were no significant differences in the demographic and clinical characteristics of the EBV and LVRC groups before treatment (Table 1). One patient died on the eighth day following LVRC therapy secondary to massive haemoptysis. Out of sixty-six study patients, 17 had no comorbidities, while 49 had at least one comorbid condition (Table 2).

Table 1. Baseline demographics and clinical characteristics of the patients with endobronchial valve (EBV) and lung volume reduction coil (LVRC) treatment

Characteristic	EBV treatment (n=37)	LVRC treatment (n=29)	p
Age (years)	62.5±8.0	63.0±6.5	0.799
Females/Males (No)	6/31	1/29	0.120
Pack year smoking	47.6±20.3	54.6±40.8	0.379
FEV1 (L)	0.77±.22	0.80±.18	0.606
FEV1 (% predicted)	28.1±8.0	28.2±7.8	0.998
FVC (L)	2.37±.66	2.29±.56	0.596
FVC (% predicted)	67.8±16.3	64.5±21.2	0.467
FEV1/FVC (%)	33.7±7.2	35.6±9.5	0.349
TLC (L	7.71±1.21	8.32±2.19	0.161
TLC (% predicted)	129.9±24.2	8.32±2.19	0.698
RV (L)	5.09±1.14	5.92±2.12	0.064
RV (% predicted)	231.4±58.5	254.6±82.6	0.195
RV/TLC (%)	65.8±7.5	68.1±17.4	0.513
DLCO (mmol/min/kPa)	10.32±4.64	12.00±6.21	0.330
DLCO (% predicted)	40.5±16.4	48.8±23.9	0.204
DLCO/VA (mmol/min/kPa/L)	52.3±20.9	65.9±30.4	0.106
6MWD (m)	265.8±132.8	255.6±101.6	0.745

FEV1, forced expiratory volume in 1 s; FVC, functional vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, diffusing capacity divided by the alveolar volume; 6MWD, 6 min walking distance;

Table 2. Comorbidity rates of the patients with endobronchial valve (EBV) and lung volume reduction coil (LVRC) treatment

	No (%) of patients		
No of comorbidities	EBV treatment	LVRC treatment	Total
None	6 (16.2)	11 (37.9)	17 (25.8)
Single	12 (32.4)	10 (34.5)	22 (33.4)
Multiple	19 (51.4)	8 (27.6)	27 (40.8)
Total	37 (100)	29 (100)	66 (100)

Table 3. Baseline demographics and clinical characteristics of the patients with and without comorbidities

Characteristics	With comorbidity (n=49)	No comorbidity (n=17)	p
Age (years)	63.3±7.7	61.5±6.1	0.379
Females/Males (No)	6/43	1/16	
Pack year smoking	49.9±28.4	55.1±38.8	0.564
FEV1 (L)	.77±.21	.81±.17	0.537
FEV1 (% predicted)	28.2±8.6	28.3±5.6	0.968
FVC (L)	2.31±.63	2.42±.59	0.542
FVC (% predicted)	66.2±19.4	67.0±17.3	0.879
FEV1/FVC (%)	34.4±8.9	35.0±7.0	0.817
TLC (L)	7.80±1.86	8.62±1.16	0.095
TLC (% predicted)	128.9±30.3	139.7±28.3	0.191
RV (L)	5.30±1.83	6.03±1.11	0.130
RV (% predicted)	234.7±71.0	266.8±65.1	0.108
RV/TLC (%)	66.0±15.0	69.7±6.2	0.337
DLCO (mmol/min/kPa)	10.84±5.34	11.20±5.50	0.854
DLCO (% predicted)	43.7±18.6	45.0±25.6	0.859
DLCO/VA (mmol/min/kPa/L)	61.9±29.1	53.0±20.3	0.359
6MWD (m)	261.3±117.9	260.1±129.3	0.974

FEV1, forced expiratory volume in 1 s; FVC, functional vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, diffusing capacity divided by the alveolar volume; 6MWD, 6 min walking distance;

The demographic and clinical characteristics of both groups before treatment were similar (Table 3). On the other hand, the prevalence of comorbidities in the EBV group was significantly higher (63.3% vs 36.7%; p=0.045) (Table 4). The most commonly encountered comorbidities were cardiovascular diseases.

Table 4. Comorbid disease incidence in the patients with endobronchial valve (EBV) and lung volume reduction coil (LVRC) treatment

Comorbidity diseases	EBV treatment	LVRC treatment
CVD	30 (76.9)	9 (23.1)
Pulmonary diseases	6 (85.7)	1 (14.3)
GID	5 (52.5)	3 (37.5)
Endocrinological / metabolic diseases	8 (50)	8 (50)
Neurological / psychiatric disorders	7 (53.8)	6 (46.2)
Urological diseases	6 (75)	2 (25)
Other*	3 (50)	3 (50)

*2 case with glaucoma, 1 case with rheumatoid arthritis
CVD, cardiovascular diseases; GID, gastrointestinal diseases

Pulmonary comorbidities included minimal bronchiectasis in contralateral lung in three patients, resected lung cancer more than five years prior in two, and tracheobronchomalacia in two patients (Figure 1). Similarly, the number of patients with multiple comorbidities was significantly higher in the EBV group (67.9% vs 32.1%; p=0.022).

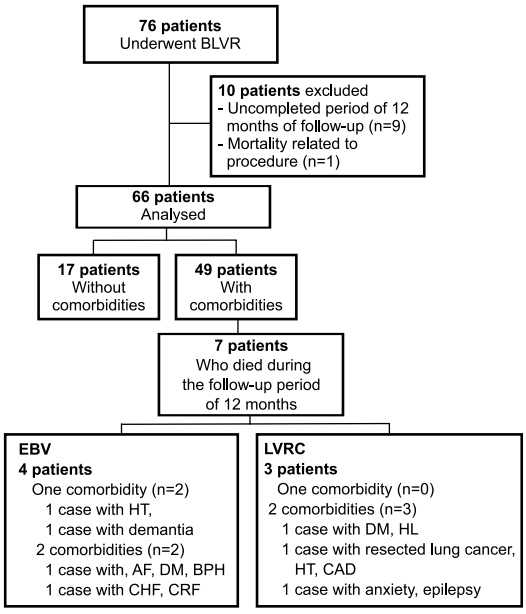

Figure 1. Mortality rate of patients who underwent BLVR and relation with comorbidities were shown in trial profile
BLVR, bronchoscopic lung volume reduction; EBV, endobronchial valve, LVRC, lung volume reduction coil; HT, hypertension; HL, hyperlipidaemia; AF, atrial fibrillation; DM, diabetes mellitus; BPH, benign prostate hypertrophy; CHF, congestive heart failure; CAD, coronary artery disease; CRF, chronic renal failure;

There were seven deaths (10.6%) over the period of twelve months following BLVR treatment. All deaths occurred in patients with at least one comorbid condition, suggesting that mortality was increased in the presence of comorbidities (14.3% vs 0%; p = 0.099), and it was significantly increased in the presence of multiple comorbidities (18.5% vs 0%; p=0.059).

Four of the deaths occurred in EBV patients and three in LVRC patients. The causes of death were determined as pulmonary in five (end-stage respiratory failure in three, pneumonia of the treated lung in one, pneumonia in the contralateral lung in one and extrapulmonary in two (acute kidney injury requiring dialysis in one myocardial infarction in one) patients. Mortality rates were similar between the two BLVR treatment groups, without a statistically significant difference (p=0.951). Regarding the choice of BLVR procedure and its impact on mortality in patients with coexisting comorbid diseases, a significant difference between the two groups was not found (p=0.717). The mortality rate was higher (37.5% vs 10.5%) in the LVRC comparing to EBV treatment group in the presence of multiple comorbid conditions, albeit not reaching statistical significance (p=0.099).

DISCUSSION

The analysis of the prevalence and the impact of the coexisting comorbidities on mortality in 66 patients with advanced emphysema treated with EBV and LVRC showed that the presence of comorbidities in advanced emphysema patients treated with BLVR could increase mortality. Also, it was found that the presence of multiple comorbidities in patients treated with LVRC increased mortality further.

Proinflammatory processes, oxidative stress and sedentary lifestyle are potential biologic mechanisms linking COPD with comorbidities (11). Over the past years some studies have focused on the relation between the dominant COPD phenotype, COPD severity and the presence of comorbid diseases. Camiciolotti et al. reported that 347 of 422 COPD patients (84%) had at least one comorbidity with hypertension (HT) and peripheral vascular diseases are prevailing comorbidities among both emphysema-dominant and airway-dominant COPD patients (11). On the other hand, a meta-

analysis of studies about COPD and comorbidities reported that the prevalence of comorbid conditions ranged from 36% to 90% (12). The prevalence of comorbid conditions in our study was 74.2%. It should be noted that our patients were a selected group with severe phenotype COPD who were eligible for BLVR therapy. Similarly to other reports our results showed that the most common comorbid diseases that accompany COPD were cardiovascular diseases.

Data regarding the presence of comorbidities in COPD patients continue to emerge (13-16). Additionally, there is a gradual increase in the amount of information about therapeutic lung volume reduction methods in patients with advanced stage emphysema (17). Despite published data, they appear to be insufficient to formulate recommendations either about disease management strategies or for the determination, evaluation and management of comorbid conditions (13).

From this standpoint, we think that studies conducted on BLVR treatment of patients with severe emphysema underestimate the importance of comorbidities when discussing issues of treatment, effectiveness, safety and complications. Supporting this view is the lack of similar studies in the medical literature. When selecting patients for BLVR, patients should be thoroughly questioned for comorbidities for deciding whether or not to treat the patient.

The results of the first study comparing BLVR to standard medical treatment in COPD were presented in the VENT study by Sciurba et al. in 2010, including similar criteria for EBV treatment to the criteria in our study, whereas in their exclusion criteria they listed ‘’unstable cardiac conditions’’ among comorbid diseases. The results of the study did not show a difference in mortality between the two groups, while complications such as haemoptysis and COPD exacerbation leading to hospitalization were seen more frequently in the EBV treatment arm (6).

The STELVIO study that evaluated the one-year outcome of 64 patients without collateral ventilation who were treated with EBV reported only two deaths. One patient died of respiratory failure on the 58th day, while the second died of myocardial infarction on the 313th day following treatment. The comorbidity status of the patients who died was not specified (18). Fiorelli et al. in their study on the long-term follow-up results of their patients treated with EBV, have reported 27% (9 of 33 patients) 5-year death rate and the causes of death were lung cancer (n=6), myocardial infarction (n=2) and end-stage respiratory failure (n=1). This study did not share any information about the pre-treatment of comorbid conditions of the deceased patients (19). In our study, four patients treated with EBV died. All deceased patients had at least one comorbid disease, which was also valid for patients who died (n=3) among those treated with LVRC. The causes of death were of pulmonary origin in five, and of extrapulmonary origin in two cases.

The LVRC treatment is an effective procedure for BLVR. Similar to studies about EBV treatment, studies comparing standard treatment methods with LVRC treatment have generally evaluated the effects on pulmonary function tests, effort capacity and dyspnea scores and do not provide data about comorbidities (10, 20- 21).

Our study is the first one focusing on the presence of comorbid conditions and their relationship to mortality in patients with emphysema treated with BLVR. In addition, unlike previous studies that compared patients undergoing BLVR treatments with patients receiving standard medical therapy, we compared patients treated with EBV with patients treated with LVRC. Despite the fact that patients treated with EBV had an increased number and prevalence of additional diseases, they had a lower mortality rate. Because of this finding, we suggest that EBV treatment might be the procedure of choice in the presence of multiple comorbidities. However, it is difficult to make a clear conclusion because of the small number of cases. In addition, there are some important limitations of our study, such as the retrospective study and lack of a control group followed by medical treatment without BLVR. In the evaluation of the weight of comorbidity, the history and prescribed drugs were used. We are aware that it is roughly possible to detect comorbidities with the used drugs, but that was not enough. It would be better to use the Charlson comorbidity index or comorbidity-polypharmacy score, but since this was a retrospective study, it was not possible. For all these reasons, we think that our findings should be supported by a larger series and prospective studies.

This study has shown that the presence of comorbidities in COPD patients with severe emphysema who had undergone a BLVR procedure and the presence of more than one comorbidity in the patients, who had undergone LVRC treatment, were associated with significantly increased mortality. We suggest that EBV should be preferred in place of coil, especially in the presence of two or more comorbid diseases.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATION

Conflicts of interest: Nothing to declare

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