AABIP JOURNAL CLUB

A MULTICENTER RANDOMIZED CONTROLLED TRIAL OF ZEPHYR ENDOBRONCHIAL VALVE TREATMENT IN HETEROGENEOUS EMPHYSEMA (LIBERATE)

AJRCCM / Nov 2018

THE CLINICAL QUESTION

Are Zephyr valves effective and safe at 12 months follow-up when used for endobronchial lung volume reduction in patients with heterogeneous emphysema with little to no collateral ventilation in the treated lobes?

TAKE HOME MESSAGE

This is the first trial to demonstrate improvement in lung function, exercise capacity, dyspnea and quality of life in patients with emphysema and negative collateral ventilation who underwent EBV placement at 12 months follow-up.

The improvements are of the same magnitude as those seen after LVRS but with less mortality and morbidity. Further long-term validation of these benefits is still pending. The rate of pneumothorax was considerable and associated with 4 deaths. A thoughtful multidisciplinary approach to patient selection, determination of target lobe, and management of potential life-threatening pneumothoraces are key for good outcomes.

BACKGROUND

- COPD is the 3rd leading cause of mortality in the U.S. Hyperinflation as a result of emphysema leads to dyspnea and predisposes patients to exacerbations.
- Lung volume reduction surgery (LVRS) reduces hyperinflation and improves lung function, dyspnea, exercise tolerance, and long-term survival in very highly selected patients (upper lobe predominant emphysema and low exercise performance on CPET). LVRS is underused due to its invasiveness, increased perioperative morbidity and mortality, and narrow patient eligibility criteria.
- Lobar deflation using EBV reduces hyperinflation and mimics the mechanisms of LVRS. Prior studies showed that only patients with complete fissures and complete lobar occlusion had meaningful clinical improvement. This was valid for both heterogeneous and homogeneous severe emphysema patients with less morbidity than LVRS. All these studies included a control arm, and subjects were followed for 3 or 6 months.

STUDY DESIGN

- Type of trial: Multicenter, randomized controlled trial
- Randomization: Patients underwent 2:1 allocation random assignment after confirmation of negative collateral ventilation using the Chartis System.
- N: 190 patients

- Study groups: There were 2 study groups: EBV plus standard medical management (EBV group, n=128 patients) vs. standard of care medical management alone (SoC group, n= 62 patients)
- Settings: 24 sites (which included 18 U.S. centers)
- Enrollment: 909 patients consented, 719 excluded, 190 randomized to either EBV or SoC
- Follow up: Up to 12 months
- Primary outcome: Percentage of patients in the EBV group at 1-year post-procedure who had an improvement in post-bronchodilator FEV1 of ≥15% compared with that in the SoC group.

POPULATION

Inclusion criteria
- Age 40 to 75 years
- BMI < 35 kg/m2
- COPD stable with < 20mg prednisone (or equivalent) daily.
- Nonsmoking for 4 months prior to screening interview
- Completed a supervised pulmonary rehabilitation program or is regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than 6 months prior
- FEV1 between 15% and <45% of predicted value at baseline exam
- Post-rehabilitation 6MWD between 100 and 500 meters at baseline exam
- Current Pneumococcus and Influenza vaccination
- Little or no collateral ventilation (CV-) as determined using the Chartis System during bronchoscopy

Exclusion criteria
Uncontrolled COPD/bronchitis
- Clinically significant (> 4 tablespoons/day) sputum production or clinically significant bronchiectasis
- ≥2 COPD exacerbations requiring hospitalization or ≥2 **pneumonia episodes in the last year at screening**

Concern of malignancy
- Unplanned weight loss >10%
- Pulmonary nodule requiring surgery as noted by chest X-ray or CT scan.

Cardiac/vascular conditions
- MI or CHF within 6 months of screening. LVEF < 45% in recent echocardiogram (3 months prior)
- **Uncontrolled pulmonary hypertension (PASP >45 mm Hg) or evidence of cor pulmonale in a recent echocardiogram (3 months prior)**
- **Unable to safely discontinue anticoagulants or antiplatelets for 7 days**
- Arrythmias including resting bradycardia (<50 beats/min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT. Also includes dysrhythmia that might pose a risk during exercise or training

Pulmonary conditions that required or might require surgery
- Prior lung transplant, LVRS, bullectomy or lobectomy
- HRCT within 3-months of screening date with the following:
  - Parenchymal destruction score > 75% in all three right lobes or both left lobes
  - Emphysema heterogeneity score <15%
  - Large bullae encompassing >30% of either lung

PFT outside severity range of obstruction or diffusion capacity, or ruling out hyperinflation and/or air trapping
- Post-bronchodilator FEV1 <15% or > 45% of predicted value
- TLC <100% predicted
- RV >175% predicted
- DLCO <20% predicted
- 6MWD < 100 meters or > 450 meters

Other lab tests
PaCO2 < 45 mm Hg or > 50mm Hg on room air
Presence of alpha-1 anti-trypsin deficiency
Plasma cotinine level greater than 13.7 ng/ml (or arterial carboxyhemoglobin >2.5% if using nicotine products) at screening
Baseline Characteristics (No significant differences in all variables, except in COLD stage, which was higher in the SoC group)
- EBV group: Age 64 +/-6.8, on continuous oxygen 35.9%, COLD stage III and IV in EBV group was 42% and 57% respectively, compared to 25% and 74% in the SoC group
- EBV group: Emphysema score at target lobe 70.0±8.5. Post FEV1 (L) 0.76±0.25, TLC (%) 133.5±21, RV (%) 224.5±42, DLCO (%) 34.6±11, and 6MWD test (m) 311±81

OUTCOMES

Primary outcomes:
There was a ≥15% increase in post-bronchodilator FEV1 at 12 months post-procedure favoring the EBV group (47.7% vs 16.8% in the SoC group), with a between group absolute difference of 31.0% (95% CI, 18.0-43.9%; P<0.001; intention-to-treat).

Secondary outcomes:
The secondary outcomes included differences between EBV and SoC groups in the absolute change at 12 months in FEV1, SGRQ, and 6MWD. All these outcomes improved in favor of the EBV group and were statistically significant. They were observed as early as 45 days and persisted to at least 12 months.
- Increase of FEV1 (L): EBV (0.104±0.2) vs SoC (-0.003±0.1)
- Increase of 6MWD (m): EBV (12.98±81) vs SoC (-26.3±81)
- Decrease of SGRQ (points): EBV (-7.55±15) vs SoC (-0.50±15)

Adverse events (AE):
The EBV group had a significant number of earlier AEs. The most concerning was the rate of pneumothorax that was associated with death in 4 cases (4 definitely, 1 probably related). All the pneumothorax-related deaths occurred in patients who were not treated in the most diseased lobe.
- **EBV group, early AEs (<45 days): Pneumothorax (n=34, 26.6%), COPD exacerbation (n=10, 7.8%), death (n=4, 3.1%), respiratory failure (n=2, 1.6%).The SoC group had a higher incidence of longer-term AEs, except for pneumothorax (EBV group n=8, 6.6% vs 0 in the SoC group)**
- **Control group, longer term AEs (45 days to 12 months). The most common was COPD exacerbation (n=19, 30.6% vs n=28, 23% in the EBV group)**
- **In the both EBV and SoC groups, the rate of pneumonia increased as a longer-term AE (n=7, 5.7% and n=5, 8.1% respectively)**

COMMENTARY

This is a multicenter randomized controlled trial (2:1 allocation), homogeneously well-matched groups that adhered to a very strict protocol and had the longest follow-up to date (12 months) in patients undergoing EBV for BLVR. The primary end-point (≥15% increase in FEV1) represented a higher minimal clinically important difference (MCID) cut off when compared to prior EBV studies.

Study Limitations and Potential for Bias:The very strict study protocol did not allow expansion to patients with homogeneous disease, led to a high rate of screening, and prevented bronchoscopy for valve revision in those patients who might have benefited from it.

Research question: Do the initial benefits observed at 12 months for patients who underwent bronchoscopic LVR with the Zephyr EBV persist at years 3 and 5?

FUNDING

The study was funded by PulmonX, the manufacturer of the valve used in this study.

SUGGESTED READING

1. Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). Am J Respir Crit Care Med. 2017 Dec 15;196(12):1535-1543
2. Sciurba FC, Ernst A, Herth FJF, Strange C, Criner GJ, Marquette CH,et al. VENT Study Research Group. A randomized study ofendobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-1244.
3. Criner GJ, Cordova F, Sternberg AL, Martinez FJ. The NationalEmphysema Treatment Trial (NETT) Part II: lessons learned about lungvolume reduction surgery. Am J Respir Crit Care Med 2011;184-881-893.

ARTICLE CITATION

Criner GJ, Sue R, Wright S, Dransfield M, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). Am J Respir Crit Care Med. 2018 Nov 1;198(9):1151-1164.

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