A randomized clinical trial of lung volume reduction surgery versus best medical care for patients with advanced emphysema: a two-year study from Canada


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of lung volume reduction surgery (LVRS) in patients with advanced emphysema. The surgical technique was standardised. A preoperative high resolution computed tomographic scan and a ventilation-perfusion scan were used to determine target areas that were resected through a median sternotomy. Approximately 20 to 30% of the total lung volume was removed and the staple line was buttressed with either bovine pericardium or polytetrafluoroethylene to reduce postoperative air leaks.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with advanced emphysema who met the inclusion criteria. The inclusion criteria were:

- disabling dyspnoea, defined as a Chronic Respiratory Disease Questionnaire (CRQ) dyspnoea score of less than 5;
- age between 40 and 79 years;
- postbronchodilator forced expiratory volume in 1 second (FEV1) ≤ 40% predicted;
- diffusing capacity ≤ 60%;
- total lung capacity ≥ 120% or residual volume ≥ 200%; and
- able to attend rehabilitation.

The exclusion criteria were:

- the presence of significant ischaemic heart disease, peripheral vascular disease or neuromuscular disease;
- pulmonary hypertension (systolic > 50 mmHg or mean > 35 mmHg);
- excessive corticosteroid therapy (prednisone > 10 mg/day);
- malnutrition (body mass index < 20 kg/m2) or obesity (body max index > 30 kg/m2);
- previous thoracotomy,
solitary bullae (bulla > 20% of hemithorax);
concurrent malignancy,
chronic bronchitis (daily sputum production > 3 months per year);
hypercapnia (Pco2 > 55 mg Hg); or
asthma (increase in FEV1 > 20% and > 200 mL postbronchodilator).

**Setting**
The setting was secondary care. The economic study was carried out in five Canadian centres.

**Dates to which data relate**
The resource use and effectiveness data were gathered prospectively for 2 years after patient enrolment in the study (July 1997 to January 2001). Canadian 2004 prices were used to compute costs.

**Source of effectiveness data**
The effectiveness evidence was derived from a single study.

**Link between effectiveness and cost data**
The costing was undertaken prospectively on the same patient sample as that used for the effectiveness study.

**Study sample**
The authors estimated a required sample size of 350 patients. The sample size calculation was based on a two-tailed type I error rate, alpha of 5% with a power of 90%, and a clinically important difference of 0.10 over the 2-year period. Sixty-two patients completed pulmonary rehabilitation and were candidates for randomisation. Thirty-two patients were randomised to surgery and 30 to BMC.

**Study design**
This was a prospective, blinded, randomised controlled study that was based on five hospitals in Canada. The follow-up period was 2 years. At the 2-year follow-up, 3 patients randomised to the LVRS group did not undergo surgery. All scheduled outcome measures for one of these 3 patients were obtained and included in the surgical cohort results.

**Analysis of effectiveness**
The analysis was conducted on an intention to treat basis. The primary health outcomes considered were:
mortality,
pulmonary function and blood gases,
activity level assessed by the 6-minute walk test (6MWT), and
the scores of the disease-specific CRQ and the generic Medical Outcomes Survey Short-Form (SF-36).
The authors did not compare the demographic characteristics of the groups at baseline.

**Effectiveness results**
The overall 2-year mortality was similar in each arm of the study. There were 5 deaths (16%) in the LVRS arm and 4 (13%) in the BMC arm, (p=0.935).

The difference between the groups at 2 years in all four domains of the CRQ achieved statistical significance: dyspnoea (1.14, 95% confidence interval, CI: 0.33 to 1.95; p=0.008), fatigue (0.90, 95% CI: 0.04 to 1.76; p=0.0414), mastery (1.00, 95% CI: 0.13 to 1.87; p=0.0261) and emotional function (0.87, 95% CI: 0.09 to 1.64; p=0.0308).

Of the 10 domains, only the physical domain was both clinically important and statistically significant at the 2-year assessment (26.42, 95% CI: 11.3 to 41.5; p=0.0016).

Over the 2-year study, 29 of the 32 (91%) surgical patients had a measurable increase in their FEV1 after LVRS, while 10 of the 30 (33%) patients treated medically showed an improvement in their FEV1, (chi-squared 22.62, p<0.0001; Fisher exact, p2<0.0001).

Patients in the surgical arm showed an improvement in quality-adjusted FEV1 of 267 mL, (p=0.0013), compared with patients in the medical arm.

There were no significant changes in arterial blood gas measurements over the 2-year study and no significant changes in the patients in the medical arm.

Twenty-two of the 32 patients (69%) in the surgical arm had a measurable increase in their 6MWT while 10 (31%) deteriorated.

Eight of the 30 (27%) patients in the medical arm had a measurable increase in their 6MWT while, 22 (73%) deteriorated as the 2-year study progressed, (chi-squared 10.98, p<0.0009; Fisher exact, p2<0.0011).

Clinical conclusions
The results of the study indicated that LVRS in addition to BMC improves pulmonary function, exercise activity, and quality of life in selected patients with advanced emphysema.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). The utilities were obtained from the Health Utility Index (HUI3). The HUI3 difference between intervention arms over the 2-year study period was expressed in QALYs gained.

Direct costs
The cost/resource boundary adopted for the study was that of a third-party payer. Broad expenditure areas included surgery, hospitalisation, rehabilitation, oxygen and outpatient visits (emergency room visits, nonprotocol specialist visits and nonprotocol investigations). Most of the resource quantities used were reported separately from the unit costs. Discounting was not reported. The price weights for hospital resources were provided by a large Ontario Case Costing Project teaching hospital. The costs of physician services were taken from the Ontario Schedule of Benefits. The unit costs for drugs were derived from the Ontario Drug Benefits Schedule. The price year was 2004.

Statistical analysis of costs
The costs were treated stochastically. Non-parametric bootstrap methods were used to calculate a 95% interval for the incremental cost-effectiveness.

Indirect Costs
No indirect costs were included.
Currency
Canadian dollars (CAD) were used in the economic analysis.

Sensitivity analysis
No areas of uncertainty were identified or investigated.

Estimated benefits used in the economic analysis
LVRS patients were found to have 0.21 more QALYs than BMC patients over a 2-year time horizon.

Cost results
The authors reported a mean cost related to the index of hospitalisation of CAD 33,622 per patient in the LVRS group and CAD 0 per patient in the BMC group. This included a mean of CAD 4,684 for surgical costs (including bronchoscopy and/or tracheotomy) and CAD 29,938 for hospitalisation costs.

The total mean cost over the 2-year period was CAD 49,776 in the surgery group and CAD 21,657 in the BMC group. This resulted in an incremental cost of LVRS of CAD 28,119 (95% CI: 5,756 to 22,362).

Synthesis of costs and benefits
The incremental cost-utility ratio, computed by dividing the incremental cost of LVRS patients (CAD 28,119) by their incremental QALYs (0.21), was CAD 133,900 per QALY (95% CI: 26,000 to undefined).

Authors' conclusions
Lung volume reduction surgery (LVRS) in addition to best medical care (BMC), including pulmonary rehabilitation, provides meaningful physiologic changes that reduce a patient's dyspnoea, and improve quality of life. The cost is high but comparable to other expensive treatment modalities currently available.

CRD COMMENTARY - Selection of comparators
The comparator was explicitly reported, and the reason for its choice was clear; BMC represented standard practice in Canada. You should decide if the comparator selected represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The clinical study was a randomised controlled trial. It appears to have been reasonably well conducted so bias should be minimal. However, the authors stated that it was underpowered for the primary outcome and did not compare demographic characteristics at baseline. Appropriate statistical analyses were conducted and the results were clearly presented. The authors adopted mortality, pulmonary function and blood gases, activity level assessed by the 6MWT, and the scores of the disease-specific CRQ and SF-36 as measures of effectiveness. These appear to have been valid measures.

Validity of estimate of measure of benefit
QALYs were the measure of benefits used in the economic analysis. This appears to have been a valid measure of benefit. Moreover, the use of QALYs enables comparisons of the study results across different interventions.

Validity of estimate of costs
The study was conducted from the perspective of a third-party payer and relevant cost categories were included for this perspective. The resource quantities were reported separately, thus enhancing the reproducibility of the study to other settings. Sensitivity analyses were not performed in order to assess uncertainty.
Other issues
The authors stated that, although the study was underpowered for its primary outcome, it was well-powered for the other outcomes assessed. The authors compared their results with those of other studies, finding them generally to be in agreement. The cost estimates are likely to be specific to Canada, but the detailed resource use description may help transferability to other settings. Also, a summary measure of benefits such as QALYs enables comparisons with other studies and technologies necessary to help decision-makers in the allocation of resources.

Implications of the study
The results of the study support the provision of LVRS in addition to BMC in patients with advanced emphysema.

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