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Exercise training for people following lung resection for non-small cell lung cancer – A Cochrane systematic review

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ABSTRACT

Objectives: To determine the effects of exercise training on exercise capacity, health-related quality of life (HRQoL), lung function (forced expiratory volume in one second (FEV_1)) and quadriceps force in people who have had a recent lung resection for non-small cell lung cancer (NSCLC).
Data sources: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, SciELO and PEDro up to February 2013.
Review methods: We included randomised controlled trials (RCTs) in which study participants with NSCLC, who had recently undergone lung resection, were allocated to receive either exercise training or no exercise training. Two review authors screened and identified the studies for inclusion.
Results: We identified three RCTs involving 178 participants. On completion of the intervention period, exercise capacity, as measured by the six-minute walk distance, was statistically greater in the intervention group compared to the control group (mean difference (MD) 50.4 m; 95% confidence interval (CI) 15.4–85.2 m). No between-group differences were observed in HRQoL (standardised mean difference (SMD) 0.17; 95% CI −0.16–0.49) or FEV_1 (MD −0.13 L; 95% CI −0.36–0.11 L). Differences in quadriceps force were not demonstrated on completion of the intervention period.
Conclusions: Evidence from our review suggests that exercise training may potentially increase the exercise capacity of people following lung resection for NSCLC. The findings of this review should be interpreted with caution due to disparities between the studies, methodological limitations, some significant risks of bias and small sample sizes.

Introduction

Lung cancer is an important problem worldwide. Data from 2008 indicate that lung cancer is the most commonly diagnosed cancer in men and the fourth most commonly diagnosed cancer in women [1,2]. Mortality from lung cancer is high, with a five-year survival of 14%, making it the leading cause of death from malignancy in developed countries such as Australia [3], the United States of America (USA) [2] and the United Kingdom (UK) [4]. Non-small cell lung cancer (NSCLC) is the most common lung cancer, accounting for approximately 85% of all cases [5]. Survival from NSCLC is considerably better than for small cell lung cancer (SCLC). Approximately 40% of people with NSCLC who undergo complete lung resection of the primary tumour survive 5 years [6]. In contrast, for people with SCLC, metastasis is common at the time of diagnosis and lung resection is rarely an option. Thus the median survival ranges from 313 to 388 days [7].

Since the early 2000s, there has been an increased interest in outcomes other than survival for people diagnosed with NSCLC. Notably, people with this condition who require lung resection perceive physical debility as a far more important and undesirable outcome than pulmonary complications such as lung collapse and pneumonia [8]. Earlier work has demonstrated impairments in exercise capacity in people with lung cancers [9]. The reasons for this are likely to be multifactorial. Tumours in the lungs are thought to disrupt pulmonary mechanics and gas exchange [10] resulting in weight loss, anorexia, anaemia, protein catabolism and muscle wasting [11,12]. Dyspnoea and fatigue are also common and likely to result in the adoption of a sedentary lifestyle

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[13], which serves to further compromise exercise capacity because of skeletal muscle and cardiovascular deconditioning. Treatment for lung cancer compounds the decrements in exercise capacity. Compared with pre-operative measures, the peak rate of oxygen uptake (VO_{2peak}) has been shown to be reduced by 13% and 28% 6 months following lobectomy and pneumonectomy, respectively [14]. Adjuvant therapy such as chemotherapy initiates a 'deconditioning storm' that further reduces the capacity to deliver or utilise oxygen and substrate during exercise, thereby contributing to exercise intolerance [15]. The peak rate of oxygen uptake is an objective measure of exercise capacity which is inversely associated with mortality in both healthy individuals [16,17] and individuals with different medical conditions [18,19] including people who have been diagnosed with NSCLC [20]. Specifically in this population, for each increase of 1 $mL\,kg^{-1}\,min^{-1}$ in VO_{2peak} all-cause mortality is reduced by 4% [20].

Another important outcome for people with lung cancer is health-related quality of life (HRQoL). At the time of diagnosis, people with lung cancer present with impaired HRQoL and considerable psychological distress, such as feelings of anxiety and depression [21,22]. People who have received lung resection have demonstrated short-term (4 months) and long-term (4 years) impairments in HRQoL. These impairments were of similar magnitude to those reported by people who have undergone coronary bypass grafting [23]. Pertaining to differences between surgical techniques (i.e. video-assisted thoracoscopic surgery versus open thoracotomy), Aoki et al. [24] demonstrated that HRQoL scores did not differ significantly between groups at 3 or 12 months after surgery.

Lung function has consistently been shown to decrease after lung resection for NSCLC, regardless of the surgical technique [25,26]. Measures such as the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC) and the single breath diffusing capacity for carbon monoxide (D_{L}-CO) are negatively affected by thoracic surgery and demonstrate limited recovery at 3–6 months after lung resection. Compared with pre-operative measures, Bolliger et al. [27] reported a reduction in FEV_1, FVC, TLC and D_LCO of 11%, 11%, 12% and 8%, respectively, 3 months after lobectomy. Significant deficits persisted with reductions of 9%, 7% and 10% in FEV_1, FVC and TLC, respectively, 6 months following lobectomy. Of note, a decreased FEV_1 has been associated with early mortality following lung resection for lung cancer [28,29].

Finally, skeletal muscle loss and weakness appears to be the most significant clinical event in cancer cachexia [30] and is associated with decreased overall HRQoL, physical function and fatigue [31]. Specifically, people with thoracic cancers have been shown to have a trend to produce lower peak torque and work (in watts) for both the quadriceps and hamstrings group of muscles, compared to matched healthy people [32].

Exercise training was the intervention for this systematic review. Training included aerobic or strengthening (resistance) exercise. Preliminary data have shown that supervised exercise training is feasible, safe and may confer benefits in exercise capacity [33–36] and HRQoL [34] for people following lung resection for NSCLC. The role of exercise training is well established in many chronic respiratory conditions, including chronic obstructive pulmonary disease (COPD) [37], interstitial lung disease [38] and asthma [39]. There is especially strong evidence for people with COPD. In this population, Cochrane reviews have shown that exercise training improves exercise capacity and HRQoL [37,40] as well as reduces symptoms of dyspnoea and fatigue [37]. There is also evidence to suggest a reduction in healthcare utilisation and a survival benefit [37,40]. The mechanisms underlying improvements in exercise capacity and reductions in dyspnoea on exertion relate to a reduction in exercise-induced lactic acidosis due to improved skeletal muscle oxidative capacity [41,42]. Previous studies have shown that exercise training confers gains in fatigue and HRQoL in people with other forms of cancer, such as prostate and breast cancer [43,44]. We hypothesise that exercise training will also be advantageous in people following treatment for lung cancer.

The results of this study have the capacity for an immediate and direct impact on clinical practice. If exercise training is shown to be effective for people following lung resection for NSCLC, it will provide a strong evidence base to promote the referral to existing pulmonary rehabilitation programmes. This review will also identify the strengths and limitations of the studies in this area, as well as gaps in the literature. Therefore, the results will be of use when designing future randomised controlled trials (RCTs) to determine to effect of exercise training in this population.

This paper is based on our Cochrane review [45] published in *The Cochrane Library*, issue 7, 2013 (see www.thecochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and also in response to comments and criticisms. Therefore the Cochrane Library should be consulted for the most recent version of the review.

Objectives

The primary aim of this study was to determine the effects of exercise training on exercise capacity in people following lung resection (with or without chemotherapy) for NSCLC. The secondary aims were to determine the effects on other outcomes such as HRQoL, lung function (FEV_1), peripheral muscle force, dyspnoea and fatigue as well as feelings of anxiety and depression.

Methods

Types of studies

This review included RCTs in which the study participants were allocated to receive either exercise training or no exercise training following lung resection for NSCLC. Studies and abstracts published in any language were eligible for inclusion.

Primary outcomes

This primary outcome was any measure of exercise capacity including VO_{2peak} and the six-minute walk distance (6MWD).

Secondary outcomes

1. HRQoL (e.g. the Medical Outcomes Study Short Form 36 General Health Survey (SF-36), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 (EORTC-C30) and the St. George's Respiratory Questionnaire (SGRQ)).
2. Lung function (FEV_1).
3. Force-generating capacity of the quadriceps (e.g. measures of quadriceps muscle force).

Search methods for identification of studies (electronic searches)

Trials were identified using electronic bibliographic databases including the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2013, issue 2 of 12), MEDLINE (via PubMed) (1966 to February 2013), EMBASE (via Ovid) (1974 February 2013), SciELO (The Scientific Electronic Library Online) (1978 to February 2013) and PEDro up to February 2013 (Physiotherapy Evidence Database) (1980 to February 2013).