Physical Benefit of Postoperative Exercise Training on Lung Cancer Patients Comorbid with COPD: A Randomized Controlled Trial

Zhonghua Yu (1850549417@qq.com)
Sichuan University West China Hospital https://orcid.org/0000-0001-6424-8759
Guosheng Xie
Sichuan University West China Hospital
Hongchen He
Sichuan University West China Hospital

Research Article

Keywords: Lung cancer, postoperative rehabilitation, physical function, lung function

Posted Date: September 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-810116/v1

Abstract

Background: The prognosis of lung cancer is heavily affected by the comorbidity of chronic obstructive pulmonary disease. The aim of this trial is to investigate whether postoperative exercise training can improve physical function and lung function of lung cancer patients comorbid with chronic obstructive pulmonary disease.

Methods: Both groups were given standard postoperative rehabilitation for one week. After that, oxygen therapy (if needed) and nebulization were given to control group, while patients in exercise group started to participate in exercise programs on the basis of receiving oxygen therapy and nebulization as same as in control group. The exercise programs consisted of 24 training sessions. Cardiopulmonary exercise test and 6-minute walk test were used to assess the physical capacity. Data in pulmonary function test like force vital capacity and forced expiratory volume in first second were used to assess the overall lung function.

Results: In both groups, the functional status and the result of pulmonary function test decreased from baseline to endpoint. But after surgery and intervention program, both the maximal oxygen consumption in Cardiopulmonary Exercise Test and walking distance in 6-Minute Walk Test in exercise group were significantly better than control group [13.09(±1.46) mL/kg/min vs 11.89(±1.38) mL/kg/min, P=0.033; 297(46) m vs 243(43) m, P=0.041]. FVC and FEV1 in exercise group were better than control group, but the differences didn't meet statistically significant level [1.76(±0.19) L vs 1.60(±0.28) L, P=0.084; 1.01(±0.17) L vs 0.96(±0.21) L, P=0.467].

Conclusions: Postoperative exercise training program can facilitate recovery of functional capacity of lung cancer patients with comorbidity of chronic obstructive pulmonary disease. Postoperative lung function appears superior in patients who participated in exercise training, only fails to reach a statistically meaningful level.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2100042867, Registered 13 May 2021, https://www.chictr.org.cn/index.aspx.

Highlights

1. Effect of postoperative exercise on physical function and lung function in lung cancer patients comorbid with chronic obstructive pulmonary disease was examined;
2. Double-blind randomized controlled trial design and intention-to-treat analysis was used;
3. Postoperative exercise was found to improve physical function significantly for lung cancer patients comorbid with chronic obstructive pulmonary disease;
4. Lung function also improved, but didn't reach a significant level.

Background

Chronic obstructive pulmonary disease (COPD) is an important comorbidity of lung cancer. Chronic obstructive pulmonary disease has been found to be an independent risk factor of lung cancer, estimated to affect about 55% of lung cancer patients worldwide[1]. The prognosis of lung cancer is heavily affected by this comorbidity. Higher rates of postoperative pulmonary complications (PPCs) and poorer survival outcomes in lung cancer patients are associated with chronic pulmonary obstructive disease[2]. Surgical resection remains the best treatment option for lung cancer patients of early stage[3]. Surgical operation for lung cancer comorbid with chronic pulmonary obstructive disease can be challenging as chronic pulmonary obstructive disease may increase postoperative morbidities and decrease survival rate[4]. Even in patients with early-stage chronic pulmonary obstructive disease, the prevalence of postoperative pulmonary complications is higher than in patients with normal spirometry[5].

Fatigue and shortness of breath are the two most frequently mentioned postoperative complications, related to decreased physical capacity and pulmonary function[6]. The beneficial effects to reduce fatigue as well as dyspnea and enhance recovery of postoperative rehabilitation has been studied recently[7–9]. Postoperative rehabilitation programs consisting of exercise training are considered effective for unselected lung cancer patients in 2 systematic reviews[10, 11]. But whether postoperative exercise is beneficial to lung cancer patients comorbid with COPD remains unknown. This category of patients happens to make a big component of all lung cancer patients who are expected to have worse physical function and lung function and slower recovery after surgery than patients with normal spirometry. So the aim of this trial is to investigate whether postoperative exercise training can improve physical function and lung function of lung cancer patients comorbid with chronic obstructive pulmonary disease.

Methods

This clinical study was a prospective, randomized controlled trial applying assessor blinding and intention-to-treat analysis. The study was ratified by the Ethics Committee of West China Hospital, Sichuan University (No.201264), and was carried out in accordance with the Declaration of Helsinki. It was registered at Chinese Clinical Trial Registry (ChiCTR2100042867). This trial was conducted from February 01, 2021 to April 30, 2021 in West China Hospital, Sichuan University, which is responsible for the integrity and conduct of the current study.

The participant inclusion criteria were: 1) patients aged above 18-year old; 2) patients with proven or suspected lung cancer waiting for resection surgery; 3) the diagnosis including chronic obstructive pulmonary disease (forced expiratory volume in 1 second [FEV1]80% of the predicted value and FEV1 /forced vital capacity [FVC] ratio0.7). The exclusion criteria were: 1) uncontrolled respiratory or cardiovascular disease; 2) mental or psychiatric disease; 3) unable to participate in exercise (e.g. lower limb bone fracture or hemiplegia) 4) thoracic surgery medical history before this trial.

After inclusion and exclusion, eligible patients were required to sign informative consents. Consenting participants were randomized to an exercise group (EG) and a control group (CG) by a nurse who was not involving in the later intervention and data collection process using a random number table generated by computer.

Lung cancer patients with normal spirometry are usually hospitalized for no more than 1 week after surgery. But for those comorbid with chronic pulmonary obstructive disease, the surgeons considered it risky to let those patients go home just after this short period and so transferred them to the Rehabilitation Medicine Center for ongoing postoperative rehabilitation and care.

After surgery, patients in both groups were given standard postoperative rehabilitation for one week in the surgery department, which included early mobilization, cough and deep-breath technique teaching, supplemental oxygen therapy and nebulization. After the first week with participant being transferred to the Rehabilitation Medicine Center and settled in two separate wards, patients in control group received oxygen therapy (if needed) and nebulization as before, while patients in exercise group started to participate in exercise programs on the basis of receiving oxygen therapy and nebulization as same as in control group.

The exercise program consisted mainly of aerobic training. Exercise group patients were asked to ride on cycle ergometers (Schiller, 911S/L) for 30 minutes each session, twice daily, six days weekly. The exercise intensity was set at 20% of heart rate reserve (HRR) at the beginning, and gradually increased to 60%-70% of heart rate reserve. Before each training session, participants had a 5-minute warmup. This 30-minute training can be break down into two 15 minutes or three 10 minutes depending on patients' need, with interval rest less than 5 minutes. Supplemental oxygen was available during exercise if needed. When patients feel dizziness, moderate chest discomfort and breathing difficulty, or peripheral oxygen saturation dropping for more than 4 degrees during exercise, they should stop that training session. The exercise program was adapted from exercise training guidelines for cancer survivors by American College of Sports Medicine and revised[12]. It lasted two weeks for each participant.

Outcome measurements

Baseline and endpoint tests were carried out 3 days before surgery (baseline) and 1day after end of exercise program (endpoint). Cardiopulmonary exercise test (CPET) and 6-minute walk test (6MWT) were used to assess the physical capacity[13, 14]. Higher maximal oxygen consumption (peakVO_2) in cardiopulmonary exercise test and longer walking distance in 6-minute walk test means better functional capacity. Data in pulmonary function test (PFT) like force vital capacity (FVC) and forced expiratory volume in first second (FEV1) were used to assess the overall lung function[15, 16].

The primary outcomes were the change in physical capacity, and the second outcomes were the change in pulmonary function test.

Statistical methods

Sample size was calculated on G*power software (Version 3.1.9.2) with α=0.05 and statistical power=0.80, which gave 56 as minimum sample size[17]. In consideration of a 20% dropout rate, 70 was determined as a proper sample size to generate statistically significant difference between groups.

Statistical software SPSS version 23.0 (SPSS, Inc., Chicago, IL) was used for data processing, and Kolmogorov-Smirnov test for distribution pattern. Continuous data were presented as mean and standard deviation (SD), while categorical data as frequency (percentage). Intergroup differences were analyzed by a two-sided unpaired *t*-test, Mann-Whitney *U* test, or $\chi 2$ test where appropriate. All statistical tests were two sided and conducted at the 5% significance level.

Results

Study Population

The flowchart of this trial was showed in Figure 1. A total number of 96 patients diagnosed with both lung cancer and chronic pulmonary obstructive disease were screened for eligibility, of which 70 provided consents. After randomization, there were 34 in control group and 36 in exercise group. Six participants dropped out after exercise program, 1 in control group because of self-unwillingness, 5 in exercise group because of postoperative pain interacting with training. The remaining 31 patients in exercise group all completed 24 training sessions. All 70 patients went through baseline assessment, while only 64 undergone endpoint assessment.

Demographic data was showed in Table 1. The two groups didn't have significant difference regarding to gender, age, body mass index, marriage status, education length, history of cardiovascular disease, history of chronic obstructive pulmonary disease, COPD stages and preoperative anti-cancer treatment. In both groups, the age of participants was 68.9 ± 6.1 years old, with oldest 84 and youngest 55. Twenty participants (28.5%) were female and the average length (standard deviation) of chronic obstructive pulmonary disease history is 12.3 ± 2.4 years.

Surgical characteristics were summarized in Table 2. The surgery type and resection sites didn't differ significantly, neither did ventilation parameters during surgery procession and postoperatively.

Primary outcome

The functional status and the result of pulmonary function test from baseline to endpoint were shown in Table 3 and Table 4. Compared with baseline assessment, functional capacity parameters declined significantly in both groups. But after surgery and intervention program, both the peakVO_2 in cardiopulmonary exercise test and walking distance in 6-minute walk test in exercise group were significantly better than control group [13.09(±1.46) mL/kg/min vs 11.89(±1.38) mL/kg/min, P=0.033; 297(46) m vs 243(43) m, P=0.041].

Secondary outcome

Declines in lung function test also occurred after surgery in both group. Still, FVC and FEV1 in exercise group were better than control group, but the differences didn't meet statistically significant level [1.76(±0.19) L vs 1.60(±0.28) L, P=0.084; 1.01(±0.17) L vs 0.96(±0.21) L, P=0.467].

Discussion

This study demonstrates that short-term postoperative exercise training program can facilitate recovery of functional capacity of lung cancer patients with comorbidity of chronic obstructive pulmonary disease. Postoperative lung function appears superior in patients who participated in exercise training, only fails to reach a statistically meaningful level. To our knowledge, this is the first randomized controlled trial investigating the effect of postoperative exercise on lung cancer patients comorbid with chronic pulmonary obstructive disease.

Surgical resection causes a 15–30% decrease in VO_2 peak, and the presence of chronic pulmonary obstructive disease may decrease VO_2 peak further[18]. Perioperatively speaking, the reduction in cardiopulmonary exercise test and 6-minute walk test results of both groups were obvious in both groups as the data above showed. But comparison between groups suggests that patients in exercise group had substantially less decrease in physical capacity. Before our study, Edvardsen et al. reported that high-intensity endurance and strength training can induce clinically significant improvements in peak oxygen uptake, and functional fitness[19]. Salhi et al. reported that rehabilitation program in patients with lung cancer significantly improved exercise capacity, and muscle strength[20]. The current trial extends their findings to reach a conclusion that lung cancer patients comorbid with chronic pulmonary obstructive disease can also gain physical benefit from postoperative exercise training.

The comparison of lung function test between groups from baseline to endpoint showed an improvement of clinical data, but that failed to reach statistically significant level. This result coincided with another trial investigating the effect of postoperative exercise plus inspiratory muscle training on lung cancer patients, in which respiratory muscle strength didn't improve to a significant level after intervention, but the trend was favorable[21].

There are some limitations of our study. First, chronic pulmonary obstructive disease is not the only comorbidity that may interfere with the recovery of postoperative lung cancer patients. Future studies should enlarge the high risk patient group, like those with coronary disease and emphysema. Second, although participants in two groups were hospitalized in two separate wards, the communication between groups was still impossible to be totally prohibited. Sample contamination is possible, leading to a reduced inter-group difference.

Compared with patients with normal spirometry, lung cancer patients comorbid with COPD are usually expected to have a longer recovery process, worse exercise tolerance and dyspnea more frequently in doing daily activities. These patients usually have a longer postoperative hospital stay. Even so, if the patients leave the surgery department and directly go home, the postoperative recovery and adaptation may be greatly delayed, and eventually resulting in decreased quality of life. Postoperative rehabilitation exercise training can improve patients' physical fitness and accelerate the postoperative recovery process. At the same time, it can also improve lung function to a certain extent. Postoperative rehabilitation exercise training is demonstrated to help lung cancer patients comorbid with COPD to return to their preoperative living or working state.

Postoperative rehabilitation is underestimated by medical staff working with lung cancer patients, and the evidence regarding it is very scarce, compared with preoperative rehabilitation which is heavily studied in recent years. Not just for patients of high risk, patients who were considered to be low risk before operation may still have the possibility to develop very serious complications postoperatively. Postoperative rehabilitation can serve as s remedy and improve this situation.

Conclusion

Postoperative exercise training program can facilitate recovery of functional capacity of lung cancer patients with comorbidity of chronic obstructive pulmonary disease. Postoperative lung function appears superior in patients who participated in exercise training, only fails to reach a statistically meaningful level.

Declarations

Acknowledgements

We acknowledge Professor Quan Wei, Dr Pengming Yu as well as Dr Daxing Zhu.

Authors' contributions

ZHY conceived of and led the study. ZHY and GSX drafted the original grant proposal and trial protocol. HCH designed the process evaluation and the data management and the Statistical Analysis Plan. ZHY wrote the manuscript. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study was ratified by the Ethics Committee of West China Hospital, Sichuan University (No.201264), and necessary consents were obtained from all participants.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding

The authors received no funding support from any person, groups or organizations.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Carr LL, Jacobson S, Lynch DA*, et al.* Features of COPD as Predictors of Lung Cancer. Chest, 2018, 153(6): 1326-1335.
2. Wang W, Dou S, Dong W*, et al.* Impact of COPD on prognosis of lung cancer: from a perspective on disease heterogeneity. Int J Chron Obstruct Pulmon Dis, 2018, 13: 3767-3776.
3. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med, 2020, 41(1): 1-24.
4. Hopkins RJ, Ko J, Gamble GD*, et al.* Airflow limitation and survival after surgery for non-small cell lung cancer: Results from a systematic review and lung cancer screening trial (NLST-ACRIN sub-study). Lung Cancer, 2019, 135: 80-87.
5. Kim ES, Kim YT, Kang CH*, et al.* Prevalence of and risk factors for postoperative pulmonary complications after lung cancer surgery in patients with early-stage COPD. Int J Chron Obstruct Pulmon Dis, 2016, 11: 1317-1326.
6. Barnes H, See K, Barnett S*, et al.* Surgery for limited-stage small-cell lung cancer. Cochrane Database Syst Rev, 2017, 4: CD011917.
7. Quist M, Sommer MS, Vibe-Petersen J*, et al.* Early initiated postoperative rehabilitation reduces fatigue in patients with operable lung cancer: A randomized trial. Lung Cancer, 2018, 126: 125-132.
8. Sommer MS, Vibe-Petersen J, Staerkind MB*, et al.* Early initiated postoperative rehabilitation enhances quality of life in patients with operable lung cancer: Secondary outcomes from a randomized trial. Lung Cancer, 2020, 146: 285-289.
9. Maeda K, Higashimoto Y, Honda N*, et al.* Effect of a postoperative outpatient pulmonary rehabilitation program on physical activity in patients who underwent pulmonary resection for lung cancer. Geriatr Gerontol Int, 2016, 16(5): 550-555.
10. Sommer MS, Staerkind MEB, Christensen J*, et al.* Effect of postsurgical rehabilitation programmes in patients operated for lung cancer: A systematic review and meta-analysis. J Rehabil Med, 2018,

50(3): 236-245.

11. Ni HJ, Pudasaini B, Yuan XT*, et al.* Exercise Training for Patients Pre- and Postsurgically Treated for Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis. Integr Cancer Ther, 2017, 16(1): 63-73.
12. Schmitz KH, Courneya KS, Matthews C*, et al.* American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc, 2010, 42(7): 1409-1426.
13. Voorn MJJ, Franssen RFW, Verlinden J*, et al.* Associations between pretreatment physical performance tests and treatment complications in patients with non-small cell lung cancer: A systematic review. Crit Rev Oncol Hematol, 2021, 158: 103207.
14. Ha D, Mazzone PJ, Ries AL*, et al.* The Utility of Exercise Testing in Patients with Lung Cancer. J Thorac Oncol, 2016, 11(9): 1397-1410.
15. Muller DC, Johansson M, Brennan P. Lung Cancer Risk Prediction Model Incorporating Lung Function: Development and Validation in the UK Biobank Prospective Cohort Study. J Clin Oncol, 2017, 35(8): 861-869.
16. Warkentin MT, Lam S, Hung RJ. Determinants of impaired lung function and lung cancer prediction among never-smokers in the UK Biobank cohort. EBioMedicine, 2019, 47: 58-64.
17. Peddle-McIntyre CJ, Singh F, Thomas R*, et al.* Exercise training for advanced lung cancer. Cochrane Database Syst Rev, 2019, 2: CD012685.
18. Jones LW, Peddle CJ, Eves ND*, et al.* Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer, 2007, 110(3): 590-598.
19. Edvardsen E, Skjonsberg OH, Holme I*, et al.* High-intensity training following lung cancer surgery: a randomised controlled trial. Thorax, 2015, 70(3): 244-250.
20. Salhi B, Haenebalcke C, Perez-Bogerd S*, et al.* Rehabilitation in patients with radically treated respiratory cancer: A randomised controlled trial comparing two training modalities. Lung Cancer, 2015, 89(2): 167-174.
21. Brocki BC, Andreasen JJ, Langer D*, et al.* Postoperative inspiratory muscle training in addition to breathing exercises and early mobilization improves oxygenation in high-risk patients after lung cancer surgery: a randomized controlled trial. Eur J Cardiothorac Surg, 2016, 49(5): 1483-1491.

Tables

Table 1. Demographic data and Clinical Characteristics between groups.

	Control Group (n=34)	Exercise Group (n=36)	P-value
Male sex	25□73.5□	25□69.4□	0.407
Age (years)	69.4□4.9□	68.5□4.23□	0.438
BMI (kg/m^2)	23.6□2.3□	24.3□1.6□	0.182
Married	23□67.6□	26□72.2□	0.139
Education length (years)	3.5□1.6□	3.2□1.4□	0.597
Diabetes mellitus	6□17.6□	7□19.4□	0.848
Coronary artery disease	5 (14.7)	6 (16.7)	0.792
Hypertension	18 (52.9)	20 (55.6)	0.624
Peripheral arterial disease	6 (17.6)	9 (25.0)	0.201
COPD history (years)	11.3□3.9□	12.8□3.5□	0.231
Stages of COPD			0.212
GOLD I	6(17.6)	9(25.0)	
GOLD II	23(67.6)	20(55.6)	
GOLD III	5(14.7)	7(19.4)	
GOLD IV	0(0.0)	0(0.0)	
Preoperative treatment	5□14.7□	8□22.2□	0.109

BMI: body mass index. COPD: chronic obstructive pulmonary disease. GOLD: consensus of the Global Initiative for Chronic Obstructive Lung Disease, with classification of COPD stages I-IV based on ratio of FEV1 to predicted value.

Table 2. Surgical Characteristics and Perioperative Data

	Control Group (n=34)	Exercise Group (n=36)	P-value
Resection sites			0.533
Segmentectomy	9(26.5)	13(26.1)	
Lobectomy or bilobectomy	24(70.6)	22(61.1)	
Pneumonectomy	1(2.9)	1(2.8)	
Surgery types			0.571
VATS	24(70.6)	27(75.0)	
Thoracotomy	10(29.4)	9(25.0)	
Duration of surgery, min	187 (51)	195 (47)	0.312
Duration of anesthesia, min	273 (72)	285 (80)	0.341
VT during TLV, mL/kg PBW	7.9 (1.8)	8.3 (1.7)	0.207
PEEP during TLV, cm H_2O	5 (1)	5 (2)	0.839
FIO_2 during TLV, %	54 (11)	56 (14)	0.428
VT during OLV, mL/kg PBW	6.0 (1.5)	6.3 (1.8)	0.302
PEEP during OLV, cm H_2O	6 (1)	6 (2)	0.697
FIO_2 during OLV, %	63 (16)	67 (21)	0.171
PaO_2 /FIO_2 on POD1, %	34 (15)	31 (17)	0.209

VT, tidal volume; TLV, two-lung ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; FIO_2, fraction of inspiratory oxygen; OLV, one-lung ventilation; POD1, first postoperative day; PaO_2/FIO_2, ratio of partial oxygen pressure to inspiratory fraction of oxygen.

Table 3. Functional status and result of pulmonary function test of baseline assessment.

	Control Group (n=34)	Exercise Group (n=36)	P-value
CPET (mL/kg/min)	16.13(1.69)	16.72(1.86)	0.391
6MWT (m)	351(52)	366(57)	0.305
FVC (L)	2.16(0.49)	2.02(0.35)	0.152
FEV1 (L)	1.32(0.27)	1.24(0.21)	0.744

CPET: cardiopulmonary exercise test. 6MWT: 6-minute walk test. FVC: forced vital capacity in pulmonary function test. FEV1: forced expiration volume in first second in pulmonary function test.

Table 4. Functional status and result of pulmonary function test of endpoint assessment.

	Control Group (n=33)	Exercise Group (n=31)	P-value
CPET (mL/kg/min)	11.89(1.38)	13.09(1.46)	0.033
6MWT (m)	243(43)	297(46)	0.041
FVC (L)	1.60(0.28)	1.76(0.19)	0.084
FEV1 (L)	0.96(0.21)	1.01(0.17)	0.467

CPET: cardiopulmonary exercise test. 6MWT: 6-minute walk test. FVC: forced vital capacity in pulmonary function test. FEV1: forced expiration volume in first second in pulmonary function test.

Figures

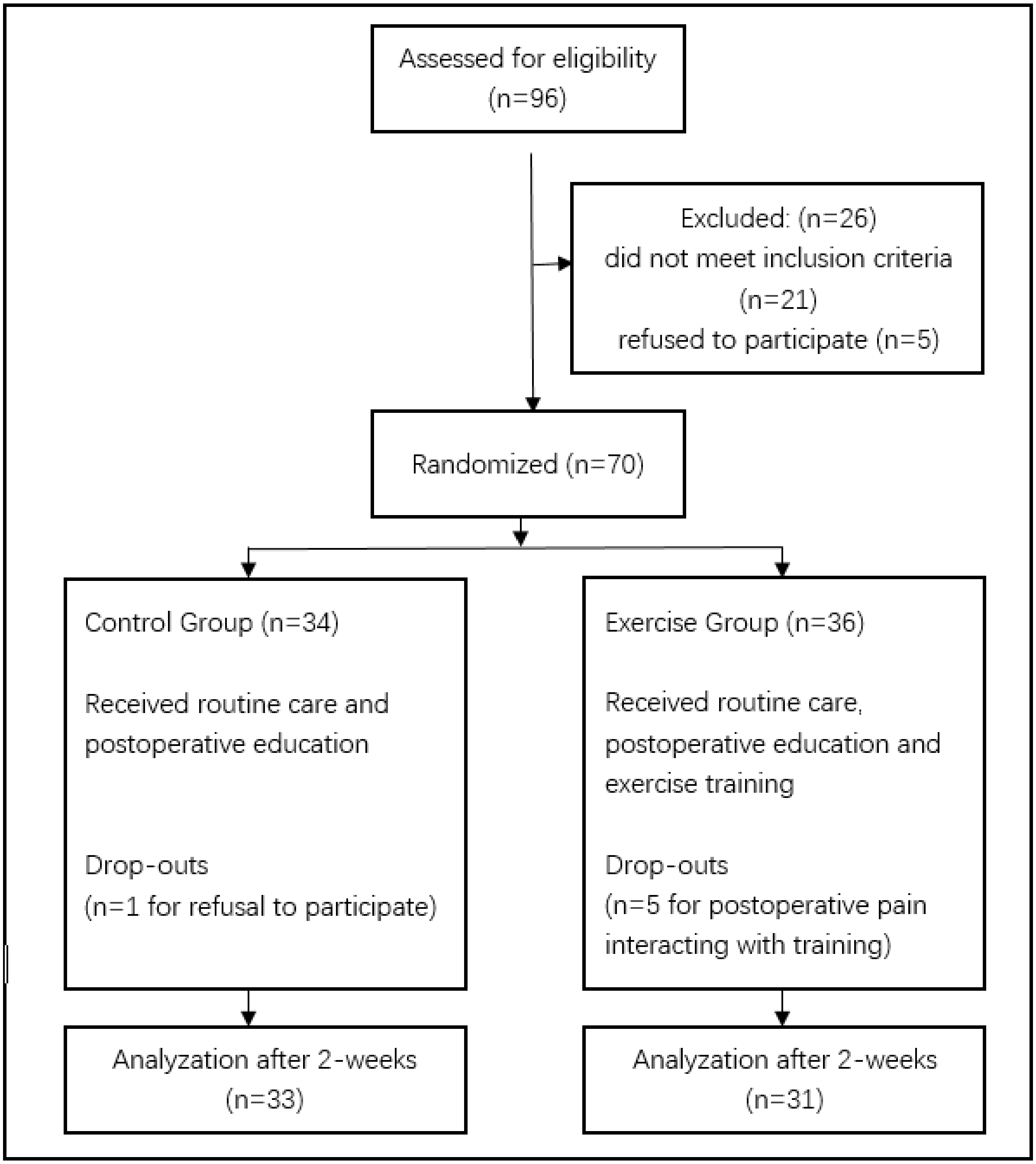

Figure 1

Flowchart of the study.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc