P: ISSN No. 2231-0045 RNI No. UPBIL/2012/55438 VOL.-8, ISSUE-4 May -2020
E: ISSN No. 2349-9435 Periodic Research

Effects of Supervised Exercise Training on Cardiopulmonary Functions and Quality of Life Outcomes in Breast Cancer Patients; Randomized Controlled Trial

Paper Submission: 15/05/2020, Date of Acceptance: 26/05/2020, Date of Publication: 28/05/2020

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Abstract

Background: Breast is the commonest site of cancer in females. With new advanced and more efficient surgical and medical treatments the survival rate has improved. The adverse effects of cardiotoxic nature of adjuvant therapies results in depreciated cardio pulmonary capacity and worsening quality of life.

Purpose: To determine the effects of exercise training on cardiopulmonary function and quality of life in stage II and III breast cancer survivors who had completed surgery (modified radical mastectomy-MRM), chemotherapy and are currently on radiation therapy.

Methods: 30 Breast cancer patients were randomly assigned to an exercise (n=15) or control (n=15) group. The exercise group received exercise training thrice a week at initiating intensity of 13 RPE upto 15 RPE in time frame of 4 weeks. The control group did not train but was at conventional treatment as at DHRC. The primary outcomes were changes in peak oxygen consumption and overall quality of life from baseline to post intervention. Peak VO_2 was assessed by submaximal exercise Half mile walk test and quality of life by using SF-36 questionnaire.

Results: All 30 patients completed the trial. The baseline values for peak VO_2 (p=0.656), PCS (p=0.582) and MCS (p=0.389) scores of quality of life did not differ between groups. Peak VO_2 increased in exercise group and decreased in control group [mean difference of 3.509ml/kg/min; CI=95%; p<0.001]. PCS and MCS increased in exercise group and decreased in control group [mean difference of 10.86 and 14.78 respectively with CI=95% and p<0.001].

Conclusion: Exercise training had beneficial effect on cardiopulmonary function and overall quality of life in breast cancer females.

Keywords: Breast Cancer, Exercise Therapy, Peak VO_2, Quality of Life.

Introduction

Breast cancer is a disease[1] of high prevalence requiring intense and extended treatments[2]. Advances in technology and the valued efficiency of cancer treatments have significantly increased the survival rates. However the impact of cancer therapy is not restricted to diseased cells but also causes lethal effects on healthy tissues. Cardiopulmonary capacity may be compromised in survivors because of pathology of the disease, curative regimen and weight gain due to inactivity and bed rest. Compromised cardiopulmonary capacity reduces Quality of life[3, 4] and can cause premature death[5, 6, 7] .

Over time, the different stages and phases of cancer, varying from diagnosis to treatment and post treatment, have been associated with psychological impairments such as anxiety and depression[12], reduced self efficacy[13], sleep disorders, distress, and difficulty coping[14]. Cancer treatment is also associated with side effects like fatigue, nausea and weight gain. Whether fatigue has more psychological, physical, or combined consequences, patients' associate it with a high rank of mutilation in daily living and, therefore, a low quality of life[11]. The

occurrence of reduced aerobic capacity and physical performance are some physiological mechanisms expected as a side effect of anti cancer treatment[11, 14]. These physiological mechanisms may be aggravated by the inactivity resulting from the advice of bed rest and to down scale activities also adding to the muscle wasting phenomena. A low activity pattern may lead to more muscle deconditioning and disuse atrophy, which in turn may aggravate the feelings of fatigue. In fact a vicious circle may occur and account for the persistence of reduced quality of life in the longer term[14].

Once post mastectomy patients start with their chemotherapy or radiotherapy sessions; there starts a procedure that is a cause of sacrifice on patient's cardio pulmonary front. This is due to presence of cardio toxic drugs used in chemotherapy and the patients exposure to radiations in radiotherapy. Also patient experiences the dehydration like condition when taking adjuvant treatment. All these factors sum up to further worsening of quality of life and reduce functional capacity. Exercises can attenuate many of these side effects. Physical exercise is reported to be beneficial for cancer patients because it is aimed at improving functional capacity and muscle strength and at decreasing cancer related fatigue, which may in turn contribute to a better overall quality of life.

Many researches did in past have provided initial evidences for practicability and efficacy of exercise training within safe limits in patients with breast cancer[8, 9]. Few studies, however, have been randomized controlled trials[8]. Overall, sparse is knowledge about the eventuality of exercise training on cardiopulmonary functions and quality of life in these patients. The role of exercise training in recovery during and after treatment may be particularly important, the comparison of which has been shown in many studies; proving the effect in both groups but more in during treatment groups[10].

The exercises for health benefits and rehabilitation after breast cancer [REHAB][8] trial is a randomized controlled experimental design, designed to drive the outcomes of supervised exercise training on cardiopulmonary functions and quality of life in breast cancer patients who had completed their surgery and chemotherapy following with radiotherapy with or without hormone therapy. In our present study we targeted to see the effects of supervised exercise training in breast cancer with Indian population scenario in mind. As mentioned earlier patients of breast cancer are under emotional, physical and social pressure as well. In India a financial burden is added along with more than half the patients. So therefore it became important for us to study the effects of supervised exercise training with a protocol designed such to provide the maximum benefit for women going through with their cancer adjuvant treatment. With an experimental hypothesis that the exercise training will improve the cardiopulmonary function and quality of life in breast cancer patients we proceed further with study. We also considered the importance of adherence to exercises and patients time management, hence keeping it in mind we framed the protocol for 4 weeks duration which is also the requisite for radiotherapy treatment sessions. The present study aimed at utilization of aerobic and resistance training along with flexibility exercises for our patients and anticipating the positive effects on them.

Methodology

Setting and Participants

The trial was conducted at Dharamshila Hospital and Research Centre (DHRC) after taking ethical board approval for the trial.

Thirty histologically confirmed stage II and III breast cancer females with no evidence of recurrence; completed surgery (MRM) atleast one month ago and upto 6 months, completed chemotherapy and on current radiotherapy; age between 40 to 60 years; minimum high school educated; non smoking status were recruited. Participants having any known cardiac disease, severe lymphedema, BMI above 30, thyroid condition, uncontrolled hypertension, diabetes or any other contraindications to exercise were excluded.

Table 1.Demographic Characteristics Of Subjects

	Group 1 (n=15)	**Group 2 (n=15)**
Variables	Mean±SD	Mean±SD
Age	49.3 ±6.8	50.2 ± 6.2
BMI	26.5±3.0	25.4±3.0

Study Design and Recruitment

The study was a prospective, single blinded randomized controlled trial. Subjects were recruited from radiotherapy unit of DHRC and randomization into groups were done by using a computer generated random number chart. Two groups viz group 1 experimental n group 2 control were formed. The measured variables were peak VO_2 and quality of life on SF-36 scale.

Instrumentation

Exercise equipments with vital monitorswere used in physitherapy setup. Borg's scale was used to measure the exertion level on scale of 6-20 as RPE. Quality of life was assessed on questionnaire SF-36 QOL[37]. SF-36 includes one multi item scale that assesses eight health concepts.

Protocol and Procedure

Consent of all patients was obtained in writing. Demographic data, weight and height and complete relevant medical history were recorded in data collection forms. For measuring the baseline scores; patients were asked to fill SF-36 QOL questionnaire, the peakVO_2 was measured by recording the time taken by patient to cover the distance of half a mile. All dependent variables were measured at baseline and then post 4 weeks. The detailed procedure of obtaining the dependent variables and the exercise training method for experimental group is as follows.

Group 1

All the patients in this group were explained the training protocol. Patient's blood pressure, hydration status of body and any kind of edema or edematous changes of ipsilateral upper limb were

constantly monitored throughout the session. Exercise session started with warm up phase of 5 – 10 minutes which included walking, slow jogging. The next round started with aerobics and strengthening exercises. Patients were instructed to maintain exertion level at 10 on 6-20 point RPE scale initially for 5 minutes and then attain the intensity corresponding to the 13 at RPE scale. The intensity of exercises progressed from 13 in first week to 15 at RPE scale by fourth week. The last 10 minutes were alloted for cool down period of slow walking. The exercise training was given thrice a week for 4 weeks at alternate days. If patient faced discomfort at any point during the session, or presented the signs of deteriorating lymphedema then session was terminated immediately or if patient happened to miss on any session for any unavoidable reasons then it was rescheduled for some other day. SF-36 was used for QOL measurements.

Group 2

The baseline measurements were taken. Patients of control group that presented with mild to moderate lymphedema were managed as per the protocol of hospital. They were treated with stroking massage in upward direction with three layer bandaging and in cases of restricted shoulder range of motion (possibly due to post surgical scarring), flexibility exercises were performed.

Post 4 weeks reading of both the groups were taken in similar fashion as for baseline.

Data Analysis

We statistically analyzed the data using Statistical Package for Social Sciences (version 15.0, SPSS, Chicago, IL, USA). The dependent variables for statistical analysis were peak oxygen consumption (pVO_2), PCS and MCS summary scores of quality of life. To compare the 4 week exercise training effect in group 1 and no exercise training effect in group 2 on pVO_2 measured by half mile walk test and quality of life measured by generic questionnaire SF – 36

Paired t test was used for intra (within) group analysis and Independent / Unpaired t test was used for inter (between) group analysis. The descriptive variables were expressed as mean ± standard deviation. The data was analyzed at 95 % confidence interval and the results were considered statistically significant when significance level (p value) was ≤ 0.05.

Result

The demographic characteristics of subjects of both the group is shown in table 1.

Peak Oxygen Consumption

In group 1, the mean of baseline (pVO_20) was 19.19 ± 2.51ml/kg/min and that of group 2 was 19.55 ± 1.85ml/kg/min. On performance of independent t testing no significant difference between the baseline readings of the two groups were found. This showed that both the groups were homogenous and there was no baseline difference between two groups.

Comparing the pVO_2 within the group 1 between baseline (pVO_20) and post 4 weeks of intervention (pVO_21) table 2 and from the difference $dpVO_2$ (pVO_20-pVO_21) = -2.33 ± 0.94 implied that there was statistically significant improvement in pVO_2. When paired t-test was performed to compare pVO_2 within the group, t = - 9.522, (df = 14, p< 0.05). Figure 1. Comparing the pVO_2 within the group 2 between baseline (pVO_20) and post 4 weeks (pVO_21) table 2 and the difference between two readings $dpVO_2$ = 1.19 ± 1.07, which implies that the oxygen consumption for the patients of group 2 who all does not underwent exercise training of 4 weeks decreased as compared to their baseline values. When paired t-test was performed to compare pVO_2 within the group, t = 4.305, (df = 14, p<0.05). Figure 2. When statistically compared the effects of exercise in group 1 and no exercise in group 2 post 4 weeks on peak oxygen consumption using the Independent t test, the result was found to be significant with t = 3.652, df = 28, p < 0.05. Table 3, Figure 3

Quality of life

The baseline measurement of quality of life summary scores of SF – 36 i.e. PCS (physical component scores) and MCS (mental component scores) of group 1 was PCS0 = 41.75 ± 3.26 and MCS0 = 35.37 ± 5.04, and that of group 2 was calculated out to be as PCS0 = 41.17 ± 2.38 and that of MCS0 = 33.62 ± 5.89. The difference between the baseline data of quality of life of two groups was statistically insignificant which means the two groups were homogenous and comparable

In group 1 when comparing the baseline and post intervention data for PCS and MCS scores of quality of life table 2 and from the difference dPCS (PCS0 – PCS1) that was – 6.77 ± 2.82 and that of dMCS (MCS0 – MCS1) was – 8.57 ± 5.03, it was implied that the statistically significant improvement occurred in both physical as well as mental component scores of SF – 36 in individuals of group 1 post 4 weeks of exercise training. Paired t test when performed, t (PCS) = -9.319, df=14, p<0.05 ; t (MCS) = -6.599, df=14, p<0.05. Figure 1. In group 2 when comparing the baseline (PCS0 and MCS0) and post intervention (PCS1 and MCS1) data for PCS and MCS scores of quality of life table 2 and from the dPCS (PCS0 – PCS1) which was found out 4.0867 ± 2.3892 and that of dMCS (MCS0 – MCS1) was 6.2200 ± 3.88517, it appeared that the physical and mental component scores of quality of life based on SF – 36 were statistically significant on the down scale in control group. Paired t test when performed, t (PCS) = 6.625, df=14, p<0.05 ; t (MCS) = 6.200, df=14, p<0.05. Figure 2. When statistically compared the effects of exercise in group 1 and no exercise in group 2 post 4 weeks on quality of life PCS using the independent t test, the result was found to be statistically and significantly different with t=8.278, df=28, p<0.05 and that on MCS results were different with t=8.330, df=28, p<0.05. Table 3 and Figure 3.

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Table 2. Intra (Within) Group Comparison

Dependent Variables	Group 1			Group 2		
	Baseline	Post 4 weeks	P	Baseline	Post 4 weeks	P
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
pVO_2	19.1873±2.5091	21.5073±2.5576	.0001	19.55±1.8462	18.3607±2.1431	.001
PCS	41.753±3.2546	48.527±3.6578	.0001	41.173±2.3762	37.087±3.9078	.0001
MCS	35.37±5.037	43.94±5.9251	.0001	33.62±5.894	27.4±4.9016	.0001

Table 3. Inter Group Comparison

Dependent Variables	Baseline			Post 4 weeks		
	Group 1	Group 2	P	Group 1	Group 2	P
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
pVO_2	19.1873±2.5091	19.55±1.8462	.656	21.5073±2.5576	18.3607±2.1431	.001
PCS	41.753±3.2546	41.173±2.3762	.582	48.527±3.6578	37.087±3.9078	.0001
MCS	35.37±5.037	33.62±5.894	.389	43.94±5.9251	27.4±4.9016	.0001

*PCS: Physical component score
*MCS: Mental component score

Discussion

The primary aim of this study was to elucidate the cardiopulmonary functions measured as peak oxygen consumption and the quality of life of breast cancer patients post surgery and during their adjuvant therapy by supervised exercise training. In support of our proposed hypothesis, we achieved that administered exercise training had beneficial effects on changes in peak oxygen consumptions and overall quality of life. The main findings of the present study targeted the 4 weeks of supervised exercise training in group 1 versus no exercise training in group 2 in breast cancer survivors during radiotherapy treatment.

Figure1. Baseline and post 4 week comparison of dependent variables group 1

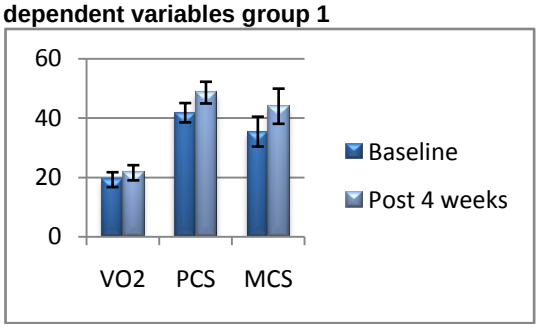


Figure 2. Baseline and post 4 week comparison of dependent variables group 2

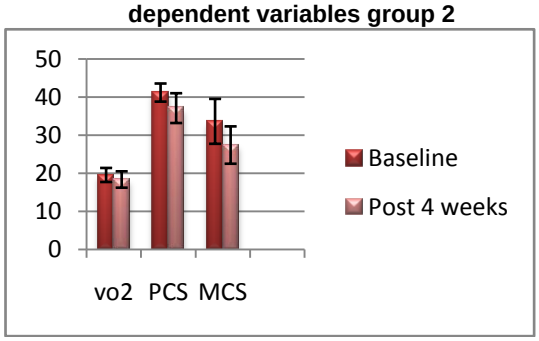
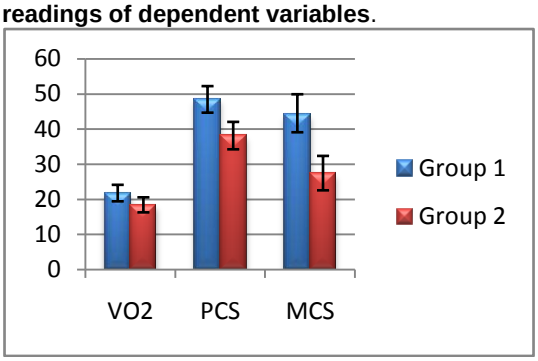


Figure 3. Inter group comparison of post 4 week readings of dependent variables.



On statistical analysis there was no difference between the demographic characteristics and baseline readings of dependent variables of the two groups. Both groups were homogenous. When compared the post 4 week readings with their baseline readings respectively of both the groups, it was found that there existed a significant difference in pVO_2 and quality of life scores. Where group 1 showed improvement of both the functions, at the same time group 2 exhibited the downfall of the same variables as compared with their respective baseline data. Our trial merits a comment. The randomized control design added to the strengths of the trial, a high exercise adherence rate, constancy and minimal loss to follow up which eventually led to null dropouts were other potential advantages of the study. Short exercise intervention with no long term follow up might appear to be a limitation, but it was designed to increase the patient compliance and adherence to program. Keeping in mind the Indian scenario where availing complete medical facilities are considered a financial burden as well as wastage of earning time and hand for the middle class society, at this stage convincing female cancer patients to attend the exercise sessions is a difficult task. On the other side, patients are required to visit radiotherapy unit as a compulsory phase of treatment for at least a time span of one month (25 sessions minimum). Involving the patients into exercise program during this time

frame helped a lot to maintain patients' regularity and zero dropout conditions. Thereby supporting our plan of scheduling 4 weeks of exercise intervention. The major finding of our trial was that exercise training had a positive effect on pVO_2. It increased by 12.09% in the exercise group, where as it decreased by 6.08% in the control group. The magnitude of this treatment effect is comparable to that observed in previous studies[15]. Also it was found to be comparable to randomized trials of similar treatments in chronic heart failure and heart transplantation patients, that showed effects between 12% to 30% [16, 17, 18]. Researches in older women have shown that adjustment and reworking with skeletal muscles is also a determined mechanism involved in exercise training impelled improvements in peak VO_2 [19,20]. Skeletal muscle changes include rise in oxidative enzymes, capillary density and myoglobin concentrations. Muscle glycogen and adaptation of muscle fiber to a higher percentage of type 1 fibers[21] was also found associated. Improved peak oxygen consumption after exercise training is also coupled with an increased cardiac output and greater arterio-venous oxygen content difference[22]. It is therefore correctly assumed that both mechanisms contributed to the physiological adaptations observed in this trial. Exercise training has been shown to produce many positive physiological and psychological benefits[23]. Positive effects of exercise training oppose negative effects of cancer treatments, resulting in a "mirror effect."[24] Exercise has been reported to be effective to improve cardiovascular efficiency, increase cardiac output and stroke volume, decrease resting heart rate thereby lowering the exercise heart rate, and improve ventilation and transport of oxygen from the environment to the cell. These benefits have the potential to reverse cancer toxicities and minimize cancer treatment-related fatigue[24]. Using an animal model, Chicco et al [25] found novel evidence of a cardio protective exercise effect. The preservation of cardiac function coincided with the prevention of chemotherapy-induced activation of apoptotic signaling. Continuing, Chicco et al [26] and Hayward et al [27] found that exercise training preserved intrinsic cardiovascular function after the use of various chemotherapeutic agents. These protective effects were associated with an exercise-induced increase in endothelial nitric oxide synthase and myocardial heat shock protein content. These findings serve as a basis for future studies to explore the underlying mechanism and the therapeutic value of exercise training in cancer survivors undergoing or after cancer treatment.

The second main finding of our trial was that exercise training had a constructively worthy effect on overall quality of life. We found a change of 16.22% in physical functioning score and of 24.22% in mental function score of quality of life. We also found that the percentage of improvement in subject's psychological field of group 1 was about 24% as compared to the detriment of the same in control group by 18.5%. This can be explained as with the improvement in physical functioning, person attains higher levels of independency. Also many studies reported clinically relevant reductions in cancer related fatigue after completion of multidimensional rehabilitation program. And most of the reductions found were in domain of physical fatigue[28, 29]. Improved ADL and self confidence motivates patient to a better direction leading to a feeling of self enhancement. This definitely elevates patients' mental score. On the contrary, in the control group patients, the adjuvant therapy's side effect day by day deconditions the patient who is already on a sacrificed front in physical fitness. This correlates with deteriorating condition of patient psychologically also. Lack of physical fitness and strength is a common and grievous symptom of the cancer patients[30, 31, 32]. Few interventions have been shown to efficiantly treat both physical deconditioning and psychological stress.

Our finding is consistent with the expansion of research showing that exercise training can help manage physical and psychological stress in cancer survivors[11, 34, 35]. Consequently, exercise training is worth recognition as a primary treatment for both physical and psychological side effects of cancer therapy. The magnitude of changes in our trial in cardiopulmonary function is smaller and that of quality of life is almost comparable to those reported in other exercise trials involving breast cancer survivors during adjuvant therapy[9, 15]. It is not clear, however, this disparity in outcomes can be explained as the result of differences in the methodology of the trial. For example; difference in frequency and intensity of the prescribed exercise, adherence rates, measure of aerobic fitness and the duration of the trial. A clinical trial that can assess ideal time and method of an exercise intervention for survivors of breast cancer is justified in all aspect.

Several mechanisms including biological, psychological or social may explain the reformation of quality of life in cancer survivors that result from exercise training, cardiopulmonary adaptations, endorphins, concentration games, positive feedback and social interaction. With improved physical level of functioning and reduced fatigue, patients are encouraged to get back to their normal social life. Many studies have examined the mechanisms of change [36]. They found the correlation between the changes in cardiopulmonary functions and change in quality of life.

The limitations of the study were neither many nor major. The variation in different sub surgical procedures under Mastectomy was not controlled. Also the long term follow up would have yielded enhanced clinical relevance. Future research is needed to find out the optimal duration, intensity and mode of exercise training in breast cancer survivors for excavating the maximum benefit to counter the effects of cancer therapy with sufficient follow up.

Conclusion

It is concluded that exercises have beneficial effects both physiologically and psychologically in post operative breast cancer patients during their adjuvant therapy. Thus proving our experimental hypothesis

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