Original Article

Respiratory training efficacy on quality of life and functional capacity in patients with Leukemia

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ABSTRACT

Background: Leukemia, as a type of cancer that is treated with chemotherapy often encounters functional status limitations with pulmonary toxicity and decreased inspiratory muscle strength in the 3 phases of its treatment. Aim of the study: To assess the efficacy of respiratory training on functional capacity and quality of life in patients with leukemia .Material and methods: Forty men patients with leukemia, in the age range of 37.1 ± 4.89, underwent chemotherapy for at least one cycle. The patients, chosen from National Cancer Institute, Cairo (inpatient ward), were arbitrarily allocated into two groups. Study Group included 30 patients who received respiratory muscles training for 4 successive weeks, 5 sessions/week; and Control Group included 10 patients who acted as a control group on chemotherapy only. Data obtained from both groups regarding forced Maximum voluntary ventilation(MVV), 2 min walk test, Quality of life questionnaire (FACT-G) were statistically analyzed and compared. Results: After 4 weeks of training, the results of the study group showed that there was a significant increase in the MVV, 2min walk test distance, and FACT-G by 23.59%, 17.29% and 18.86%; respectively. While for the control group, the results showed significant decrease in the previous parameters assessed by 12.93%, 15.48% and 8.27%; respectively. Conclusion: It was concluded that respiratory muscle training can be performed in an attempt to minimize the consequent effects of respiratory muscle weakness, and preserve the functional capacity, and improve the quality of life in patients with leukemia receiving chemotherapy.

Keywords: Leukemia, chemotherapy, functional capacity, quality of life, respiratory training.

Introduction

Cancer is a type of disease which includes uncontrolled growth and expansion of abnormal cells. It has been estimated that about 1.7 million new cancer cases to be diagnosed in 2018. Also, the death rates and progress of cancer cases and their incidence would be increased. Adding to these, the risks leading cancer would also be increased that would provide socio-economical burden [1].

Leukemia is a fatal disease which is mostly found among people aged from 0 to 18 years old, including 25-35% of all tumors in this population. Based on cytology, immunohistochemistry and cytogenetics, Leukemia has been categorized as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) [2]. ALL includes 70-80% of the cases, and AML includes almost 15% of the cases [3].

Although Acute myeloid leukemia (AML) is the most widespread kind of leukemia in adults, its survival rate is the lowest among all leukemias. While, the survival rate has considerably improved in the younger age group, the prognosis in older patients is still very weak [4, 5].

Patients with AML often show various non-specific (generalized) symptoms. The symptoms can be weight loss, fatigue, fever, night sweats, and loss of appetite. In fact, these are not just the symptoms of AML, and mostly are resulted from some reasons other than leukemia [6].

Treating leukemia, like the other kinds of cancer, is a complex process. In most of the cases, in the standard procedure of the treatment, chemotherapy followed by a bone marrow transplant is applied [7].

Although CT is given to kill cancer cells, it damages normal cells, and cause significant side effects. The side effects vary depending on the particular CT drug, dosage, rout of

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administration and patient characteristics; while some people may experience very few side effects, others may experience more. Some CT side effects can be too severe which may require hospitalization [8].

In all types of cancer treated with chemotherapy, the group of side effects includes the ability of the patient to function at pre-cancer levels. In most of the cases, when the overall physiological and psychological functioning is decreased, further administration of treatment is stopped or slowed down, and this can result in low treatment outcomes. Among the common side effects of chemotherapy conducted on leukemia patients, it can be mentioned to debilitating fatigue, nausea, loss of body mass (development of cancer cachexia), anemia, and depression [7].

Patients with AML often suffer from poor health-related quality of life; symptoms like fatigue and Pulmonary Functions at baseline have been recognized as independent prognostic factors for overall survival that in several studies, there has been shown an improvement in both domains through treatment [9].

Patients suffering from cancer also encounter the risk of complications including pulmonary dysfunction. Pulmonary toxicity due to the chemotherapy or associated with radiotherapy may also cause interstitial lung injury during the initial stage until several months after the treatment and, in the late stage, the most widespread problem is lung fibrosis that has been associated with reduced lung volumes and capacities reflected on functional capacity of the patients [10].

In an attempt to seek alternatives to minimize the effects on weakness and/or respiratory muscle fatigue, in 1976, the first study was conducted to evaluate the effects of inspiratory muscle training in healthy individuals. Since then, the number of studies regarding inspiratory muscle training (IMT) has increased. As it proves to be effective in strength gain and respiratory muscle strength, leading to the reduction in dyspnea, improves the performance of activities of daily living (ADL) and reduces postoperative pulmonary complications [11].

Inspiratory muscle training (IMT) improves the strength and endurance of inspiratory muscles, functional exercise capacity, dyspnea and quality of life. It was found that in patients with inspiratory muscle weakness, adding IMT to a general exercise training program improved the maximum inspiratory pressure (MIP), and tended to improve the exercise performance [12].

Methods

Forty leukemic men patients with the age range of 37.1 ± 4.89, underwent chemotherapy for at least one cycle. The patients were chosen from National Cancer Institute, Cairo (inpatient ward). The patients were randomly allocated into two groups. Randomization was done by opening an opaque envelope which was prepared by an independent individual in which there were random numbers. 30 patients who were included in the study group received inspiratory muscles training for 4 successive weeks, 5 sessions/week; and 10 patients who formed the control group, just received chemotherapy.

The patients included in this study followed the criteria of: Leukemic men patients with the age range of 30 to 50 years. They were hemodynamically stable, and have been on chemotherapy at least one cycle as a treatment of malignant tumor. While the exclusion criteria included the patients who suffered from the metastasis of lung, ribs, mediastinal structure, Pulmonary pathology (e.g. acute respiratory distress syndrome or exacerbation of Chronic Obstructive pulmonary disease), Ruptured eardrum or any other condition of the ear, and the patients with marked elevated left ventricular end-diastolic volume and pressure, heart failure signs and symptoms, and the bed- ridden patients.

Ethical consideration included the patients' rights to know benefits, procedures and potential risks that were explained thoroughly to all the patients prior to signing an informed consent with explaining that the confidentiality was assured. The study was approved by the ethical committee of Faculty of Physical Therapy no. P.T.REC/012/001806 and the Institution Review Board of the National Cancer Institute no.201617032.4.

This study was registered in ClinicalTrials.gov Identifier: NCT03876834

Outcome measures: Both groups underwent an identical battery of tests: baseline (before training) after 4 weeks of exercise training program (after training). The evaluated parameters included (MVV) that was performed by spirometry maneuver, 2 min walk test distance as to assess the functional capacity of each patient enrolled in the study [13], and the Quality of life questionnaire (FACT-G).

The training program by using Threshold Inspiratory Muscle Training that was performed by the study group as follows, lasted for 20 minutes: The patients started breathing at a resistance equal to 30% of their maximal inspiratory pressure (MIP), measured at baseline [14].

The resistance was increased incrementally, based on the rate of perceived exertion (RPE) scored by the patient on the modified Borg Scale. If the RPE was less than 5, the resistance of the inspiratory threshold trainer was increased incrementally by 2cm $H2O$. The resistance did not change if the level of perceived exertion was rated from 6 to 8, and the resistance was decreased by 1 to 2 cm $H2O$ if the level of perceived exertion was rated 9 or 10 [15].

Then, the load was increased rapidly over the first 7 days up to 60–80% of the baseline MIP. The patients were allowed to take breaks during the training session in order to cough or to rest for a while when they felt fatigue. But the duration of these breaks was minimized in order to maintain the training stimulus [16].

Statistical analysis:

Descriptive statistics and t-test were conducted for comparing the mean age, weight, height, and BMI of both groups. The statistical analysis and comparison of MVV, 2 min walk test distance and FACT-G within each group and between both groups were done at baseline after 4 weeks of training with a level of significance of $p < 0.05$ for all the statistical tests. The statistical package for social studies (SPSS) version 19 for windows was used to obtain all the statistical measures.

Results

Table 1 shows the demographic data of the patients.

Table 1 : Demographic data of the patients enrolled in the study:

	Study Group	Control Group	MD	t- value	p- value	Sig
	$\bar{X}$ ± SD (SE)	$\bar{X}$ ± SD (SE)				
Age (years)	37.1 ± 4.89 (0.9)	37.8 ± 5.05 (1.6)	-0.7	-0.38	0.7	NS
Weight (kg)	74.06 ± 8.08 (1.47)	72.2 ± 8.96 (2.83)	1.86	0.61	0.54	NS
Height (cm)	171.8 ± 5.36 (0.97)	173.1 ± 5.36 (1.69)	-1.3	-0.66	0.51	NS
BMI (kg/m²)	25.2 ± 3.47 (0.63)	24.13 ± 3.16 (1)	1.07	0.85	0.39	NS

$\bar{X}$: Mean, SD: Standard Deviation, SE: Standard error, MD: Mean difference, value: Unpaired t value, p value: Probability value, NS: Non significant

Results of Maximum Voluntary Ventilation:

The mean ± SD MVV at baseline for the study group was 86.15 ± 21.9 L/min and that of the control group B was 83.64 ± 27.73 L/min, representing the mean difference between both groups to be 2.51 L/min. That showed that there was no significant difference in the MVV between both groups (p = 0.79). While the results showed that after weeks of training for the study group, the mean value was ± SD 106.48 ± 16.12 L/min, with the mean difference of -20.33 L/min. There was a significant increase in the MVV post treatment compared with pre treatment (p = 0.0001). After 4 weeks, for the control group, the mean ± SD MVV was 72.82 ± 22.8 L/min with the mean difference of 10.82 L/min. There was a significant decrease compared with its results at the baseline duration (p = 0.01). Also between the both groups, the mean difference was 33.66 which showed a significant difference in favor of the study group (Table 2, Fig.1).

Table 2: Statistical analysis for Maximum Voluntary Ventilation (MVV):

MVV (L/min)	Study Group	Control Group	MD	t- value	p- value	Sig
	$\bar{X}$ ± SD (SE)	$\bar{X}$ ± SD (SE)				
At Baseline	86.15 ± 21.9 (4)	83.64 ± 27.73 (8.76)	2.51	0.26	0.79	NS
Post-4 weeks	106.48 ± 16.12 (2.94)	72.82 ± 22.8 (7.21)	33.66	4.32	0.001	S
MD	-20.33	10.82				

% of change	↑23.59 %	↓12.93 %
t- value	-9.61	3.05
P-value	0.001	0.001
Sig.	S	S

$\bar{X}$: Mean, SD: Standard Deviation, SE: Standard error, MD: Mean difference t value: Unpaired t value, p value: Probability value, NS: Non significant

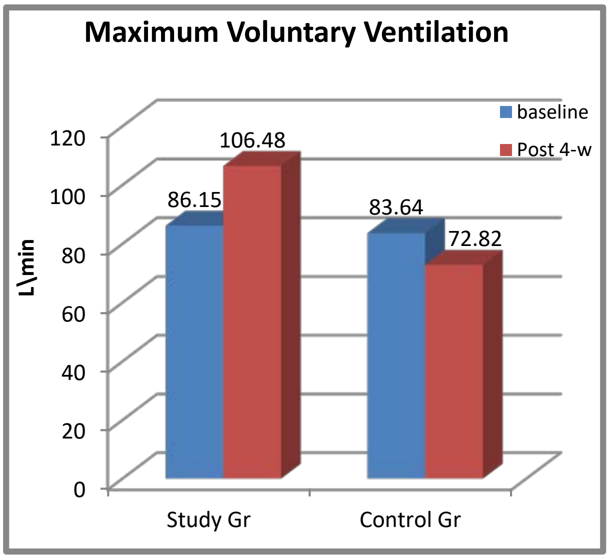

Figure 1 : Maximum Voluntary Ventilation for both groups

Results of 2-min.walk test distance:

The mean ± SD of 2 min walk test distance at baseline of the study and control groups was 115.44 ± 29.24 meters and 113.78 ± 28.84 meters; respectively. The mean difference between both groups was 1.66 meters. There was no significant difference in the 2 min walk test distance between them (p = 0.87). While the results after 4 weeks of training for the study group showed mean ± SD 135.41 ± 23 meters with the mean difference of -19.97 meters which indicated a significant increase in the 2 min walk test distance (p = 0.0001). For the control group, the results were different after 4 weeks, as the mean ± SD was 96.16 ± 38.2 meters with mean difference of 17.62 meters which showed a significant decrease in 2 min walk test distance (p = 0.03). The results of the comparison between the groups showed a mean difference between both groups of 39.25 meters with a significant increase in the 2 min walk test distance for the study group (p = 0.01) (Table 3, Fig.2).

Table 3: Statistical analysis for 2 min walk test distance:

	Study Group	Control Group	MD	t- value	p- value	Sig
	$\bar{X}$ ± SD (SE)	$\bar{X}$ ± SD (SE)				
At Baseline	115.44 ± 29.24 (5.33)	113.78 ± 28.84 (9.12)	1.66	0.15	0.78	NS
Post-4 weeks	135.41 ± 23.7 (4.32)	96.16 ± 38.2 (12.08)	39.25	3.05	0.01	S
MD	-19.97	17.62				

% of change	↑17.29 %	↓15.48 %
t- value	-6.4	2.43
P-value	0.0001	0.03
Sig.	S	S

$\overline{X}$: Mean, SD: Standard Deviation, SE: Standard error, MD: Mean difference
t value: Unpaired t value, p value: Probability value, NS: Non significant

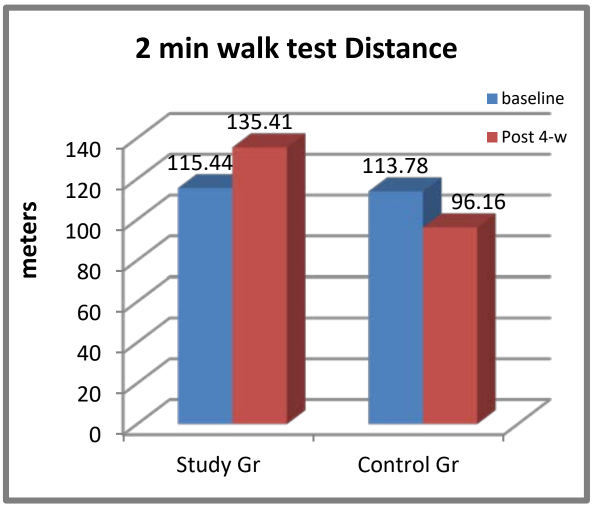

Figure 2: 2 min. walk Test Distance

% of change	↑18.86 %	↓8.27 %
t- value	-11.91	3.23
P-value	0.0001	0.01
Sig.	S	S

$\overline{X}$: Mean, SD: Standard Deviation, SE: Standard error, MD: Mean difference
t value: Unpaired t value, p value: Probability value, NS: Non significant

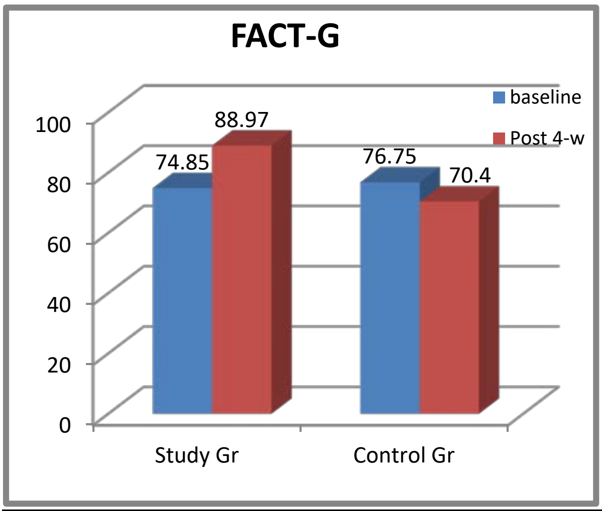

Figure 3: FACT-G

Results Quality of life questionnaire (FACT-G):

The mean ± SD FACT-G at the baseline for the study group was 74.85 ± 9.38, and for the control group was 76.75 ± 13.67 with the mean difference of -1.9 between both groups. There was no significant difference in the FACT-G between them (p = 0.62). After 4 weeks, the results showed mean ± SD as 88.97 ± 8.86 with the mean difference of -14.12, and there was a significant increase in the FACT-G for the study group (p = 0.0001). While the results for the control group was 70.4 ± 14.53, the mean difference was 6.35 with a significant decrease in the FACT-G (p = 0.01). The statistical analysis between both groups showed that the mean difference between both groups was 18.57, and there was a significant increase in the FACT-G for the study group compared to that of the control group after 4 weeks of the study duration (p = 0.003) (Table 4, Fig.3).

Table 4: Statistical analysis Quality of life questionnaire (FACT-G):

FACT-G	Study Group $\overline{X}$ ± SD (SE)	Control Group $\overline{X}$ ± SD (SE)	MD	t- value	p- value	Sig
At Baseline	74.85 ± 9.38 (1.71)	76.75 ± 13.67 (4.32)	-1.9	-0.4	0.62	NS
Post-4 weeks	88.97 ± 8.86 (1.61)	70.4 ± 14.53 (4.6)	18.57	3.81	0.003	S
MD	-14.12	6.35				

Discussion:

Fatigue is one of the most common symptoms of cancer and it has been manifested in the clinic as weakness and exercise intolerance. This factor not only hinders patients' quality of life (QOL), but also decreases their physical activity, causing limited treatment and heightened morbidity [17].

Cancer-related fatigue would affect all quality aspects of life negatively, and might increase the risk factor of decreased survival. It necessitates the engagement in physical activity which has been recommended by all cancer societies [18].

Eliminating cancer disparities in terms of socioeconomic status with other factors provoked a necessity to handle these side effects and correlate them to the patients' QoL as to support patients physically and psychologically and remove the barriers to preventive care, early detection, and optimal treatment to overcome the burden of long time of treatment [19].

The results of this study declared that the enrollment of cancer patients in the respiratory rehabilitation as a role to minimize the weakened effect due to cancer treatment represented in the MVV that was improved by 23.59% with a significant increase in the study group corresponded to a decreased percentage of change in the control group by 12.93% that reflected the increased respiratory muscle strength.

Concerning 2 min walk test distance, that assessed the functional capacity of the patients, the results revealed that in the study group, it was improved by 17.29%, while in the control group, it was decreased by 15.48% after 4 weeks of the study.

Regarding the health-related quality of life questionnaire FACT-G, it was found that FACT-G was changed by 18.86%, that was a significant increase in the FACT-G in the study group after the respiratory training compared with the control group that was changed by 8.27%.

The results of this study were supported by De Macedo et al, [11], who executed a quasi-experimental study on children treated for acute leukemia. Group A received inspiratory muscle training, and Group B was the control group. Their maximum respiratory pressure was examined. Based on the results, there was a significant improvement of 35% in the maximum inspiratory and expiratory pressures in group A at the end of the training along with a strong positive correlation between the used load levels and maximal inspiratory ($p< 0.0001$) and expiratory ($p= 0.0001$) pressures. They reported that Inspiratory muscle training could be effective for improving the inspiratory muscle strength in children treated for acute leukemia.

The improvement shown in the results of this study agreed with the conclusion of De Macêdo et al., [10] who stated that physical exercise tended to improve the maximal exercise capacity. IMT enhances the inspiratory muscle strength and endurance, functional exercise capacity, MIP, dyspnoea and quality of life.

Also, the results of this study coincided with the results of the study done by Rn [20] who investigated the effects of threshold inspiratory muscle training in patients suffering from lowered functional capacity after 8 weeks of inspiratory training, and it was found that the mean maximum inspiratory pressure was improved by 56.8%, the mean 6-minute walk test distance was improved by 21.8%, and the baseline dyspnoea index was increased from 4.48 ± 2.12 points to 9.0 ± 2.27 points. These data concluded that the threshold inspiratory muscle training could reduce patients' difficulties with respect to functional capacity and health-related quality of life.

It was declared by Schmidt [21], in cancer patients, the functional capacity testing was required as an objective and subjective measure of physical function due to the decreased inspiratory muscle strength which acts as a ventilator pump to the patients' functional status that came in accordance with the results of this study considering 2 min walk test distance that was used as an objective measure for the patients' functional status.

The results of this study confirmed choosing IMT to a study done by Mello et al.[22] who stated that a simple, inexpensive, home-based IMT program would result in clinically relevant increments of maximal functional capacity, associated with a reduction in muscle sympathetic nerve activity (MSNA) and improvement in the quality of life. Moreover, their results showed that the respiratory muscle training would improve exercise intolerance, neurovascular control, and cardiac sympathetic and parasympathetic regulation as the patients preferred to have biofeed back for their case.

The results of the current study were also supported by Taaffe et al., [23] who studied the effects of different exercise modalities on fatigue in cancer patients for 12 months. Randomised Controlled Trial to exercise targeting the musculoskeletal system (impact loading + resistance training; ILRT), the cardiovascular and muscular systems (aerobic + resistance training; ART), or to usual care/delayed exercise (DEL;) Encouraging fatigued patients to undertake exercise at adequate intensity, regardless of mode, were likely to help in reducing or attenuating the adverse effects of ADT on fatigue and vitality.

Four of the fifteen studies reported no statistically significant difference in post-test QoL between the intervention and control groups, whereas eight studies reported that exercise was statistically more beneficial to QoL than the control intervention. Campbell et al [24] assessed QoL using the FACT-G, FACT-B and the SWLS, although the FACT-G was identified as the most important. The FACT-G as the most important outcome indicated a statistically significant improvement in QoL pre-post test in the exercise group in comparison with the control group.

However, Mutrie et al [25] used the FACT-G as the major measure of QoL in addition to the FACT-B. The obtained results indicated no statistically significant differences between groups in the FACT-G, although the FACT-B demonstrated a statistically significant difference between groups post intervention in favour of the exercise arm [26].

Also, this study was confirmed by Stout et al., [27], based on this review, exercise interventions including therapeutic exercise, physical activity, strength training, aerobic conditioning, rehabilitative exercise, and stretching, etc. should be included in most cancer care plans. The exercise plan of care was perfectly designed in the context of known disease treatments, and anticipated side effects of treatment, and was overseen by a health care provider with specialized knowledge and skills in cancer-specific exercise and cancer rehabilitation. Exercise increases significant improvements in clinical, functional, and in some cases, survival outcomes, and it can be recommended in all kinds of cancer. Also, generally safe patients should be checked, and appropriate precautions should be taken. Actions should be taken to increase the uniformity in clinical trial reporting, develop clinical practice guidelines, and integrate exercise and rehabilitation services into the cancer delivery system are required.

Also the results were supported by the findings of the study done by Friedenreich et al., [28], that supported the emerging recommendations to increase the recreational physical activity after the diagnosis of cancer conditions that would enhance the health-related quality of life for cancer patients as to overcome the residual risk conditions related to chemotherapy and radiotherapy or even surgical procedures.

A systematic review demonstrated that patients with non-small cell lung cancer (NSCLC) could safely exercise before and after the cancer treatment. Results suggested that the patients with NSCLC before and after the treatment should be offered some forms of exercise training that appeared to be associated with positive benefits on exercise capacity and some domains of HRQL and symptoms. The published studies provided an excellent preliminary work [29].

Even for patients who underwent surgery, the results of the study done by Valkenet et al., [30] showed that pre- operative inspiratory muscle training decreased the incidence of pneumonia and length of hospital stay, but did not find any improvements in the quality of life.

Conclusion

Based on the results of this study, the adjunctive physical therapy modalities with its various effects has been recommended , which can help in supporting the maintenance of cancer patients' health-related quality of life in their long exhausting treatment stages which would aid in their rehabilitation with respecting to disparities.

Conflict of Interest

The authors declared no conflict of interest.

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