Investigating the Impact of Eight Weeks of Aerobic Training on Liver Enzymes and Hematological Profile in Children With Leukemia

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ABSTRACT

The objective of the evaluation was to study and determine the impact of eight weeks of aerobic training (AT) on liver enzymes and changes in hematological profile in children with leukemia. In this semi-experimental and applied study, 24 children in the age range of 7-10 years referring to hospital were randomly classified into two control (n=12) and experimental (n=12) groups. experimental group have eight-week AT with 40% to 70% of heart rate reserve, three sessions per week, the controls didn't exercise training program was observed in during the study. Liver enzymes such as Aspartate aminotransferase (AST) and alanine aminotransferase (ALT), Hemoglobin (Hb), White Blood Cells (WBC), platelets (PLT), and bilirubin were measured. Data analysis using a paired t-test and analysis of covariance was performed with SPSS software (version 18). The results showed that moderate-intensity AT had a significant effect on hemoglobin and liver enzyme levels and a significant increase in Hb ($p<0.05$) and significant reduction the ALT and AST ($p<0.05$), whereas there was no significant influence on WBC, ALT, and bilirubin ($p>0.05$). AT may accelerate the oxygen supply and reduce liver damage caused by medications in children diagnosed with leukemia without having corrupting effect on PLT, bilirubin, and safety factors.

Keywords: Aerobic training, Leukemia, Children, Liver Enzyme, Hematological profile

INTRODUCTION

There are four major types of leukemia. Acute lymphoblastic leukemia (ALL) is the most common type of leukemia that affects children. In ALL large numbers of white blood cells (WBC), that called blast cells, are released before they are ready (Eghbalian, Monsef, & Mousavi, 2009; Lago et al., 2021)

The prevalence of the disease is about 40 children in one million children under the age of 15, and each year about 2,000 new cases of ALL are reported in children in the United States (Kuehn et al., 2021). Leukemia is a common cancer in Iran and the prevalence of this disease is increasing (Farhood, Geraily, & Alizadeh, 2018). Cancer treatments include surgery, biological therapies (including immunotherapy and gene therapy), radiotherapy and chemotherapy (Najafi-Vosough et al., 2022). Complications of chemotherapy for children with ALL include an increase in liver enzymes (ALT and AST), fatty liver, abnormalities in blood coagulation factors, and an increase in bilirubin, as well as a decrease in WBC, ALT, and Hb (Belson, Kingsley, & Holmes, 2007). Anemia is one of the most important and common problems in patients undergoing chemotherapy (Boyadjiev & Taralov, 2000). Various studies have reported a high prevalence of anemia in patients receiving chemotherapy (Kitano et al., 2007; Wojtukiewicz et al., 2009) .

Most cancer patients who suffer from fatigue and muscle weakness are encouraged to rest and avoid exercise to reduce fatigue and improve pain symptoms (Courneya & Friedenreich, 2007). In recent decades, the use of exercise programs as an effective intervention to improve the quality of life of cancer patients has attracted the attention of scientists (Lin et al., 2021; Mujtaba, Mazhar, & Tanzeel, 2021). Many studies have been conducted on the effect of physical activity on various diseases (Courneya & Friedenreich, 2007) but there are limit studies about effect of physical activity on ALL. The first goal of cancer treatment is to eradicate the disease. If this initial goal cannot be met, the next objective was relieving sings and maintaining the quality of life for the rest of the patient's lifetime. Shamsoddini at al. (2015) research has shown that exercise has a significant effect on liver enzymes, to some extent the treatment of fatty liver in patients that have hepatic fat with nonalcoholic fatty liver disease and an increase in the number of WBC and RBC, and reduces the risk of immune diseases (Hashida et al., 2017; Moosavi-Sohroforouzani & Ganbarzadeh, 2016; Shamsoddini et al., 2015).

Numerous studies have shown that AT improves hemoglobin and red blood cell counts in individuals during treatment and after chemotherapy (Gasmi, Benaicha, Rouabhi, & Kebieche, 2021; Kazemi et al., 2009; Mittelman, 2003). Physical exercise as a therapy that can restore physical and functional capacities; however, it is essential to understand its effect and role in improving the symptoms of patients with ALL. There are few studies investigating the effect of AT on liver enzymes and hematological profile in children with leukemia. The question now is whether AT can have beneficial effects on the side effects of chemotherapy for children with leukemia?

METHODS

Subjects

The method of this research is applied and semi experimental. Statistical population of this study included all children with leukemia was admitted to charity supporting for children with cancer. A block randomization method with a block size of four was used to randomize patients. For this purpose, four sheets of paper were prepared. The letter I (under treatment with exercise program) was written on two sheets and the letter C (control group) was written on the other two sheets. The sheets were mixed together and then randomly drawn out one at a time for each patient without replacement until all four sheets were drawn. This method is repeated until all 24 patients were randomized. A block randomization method with a block size of four was used to randomize patients. For this purpose, four sheets of paper were prepared. The letter I (under treatment with exercise program) was written on two sheets and the letter C (control group) was written on the other two sheets. The sheets were mixed together and then randomly drawn out one at a time for each patient without replacement until all four sheets were drawn. This method is repeated until all 24 patients were randomized. The sample size was estimated to be 24 according to the single proportion equation with a 95%-confidence interval. Statistical sample include 24 children aged 7 to 10 years that referred to hospital for treatment and were divided randomly into two control (n=12) and experimental (n=12) groups.

In this study, the AT group performed exercises with an average intensity of 40 to 70% percent of heart rate (Naderifar, Mohammad khani Gangeh, Mehri, & Shamloo Kazemi, 2022).

The inclusion criteria included 7 to 10-year-old children with fatty liver disease who were confirmed by ultrasound with acceptable sensitivity and specificity and had undergone chemotherapy in the hospital. All people are in the remission phases of the disease. Exclusion criteria included chronic medical and orthopedic conditions that prevent exercise, use of beta-blockers, hemoglobin less than 8 g/dL, PLT less than 20,000(U/L), muscle fatigue and weakness, abnormal pulse rate, bone pain, chest pain, severe nausea or nausea during exercise, vomiting 24 to 36 hours before exercise, dizziness, lightheadedness, blurred vision, shortness of breath, and shortness of breath (Eghbalian, Monsef, Alam Ghomi, & Monsef, 2013).

The study protocol was approved by the human research Ethics Committees of the Research Ethics Committees of Shahid Beheshti University, Iran. This informed consent form was obtained from their parents.

In order to increase the validity of the research and prevent the effects of puberty and body size on the research findings, the 5-step Tanner Maturity Questionnaire was used to determine the maturity status and to measure anthropometric indicators (fat percentage, Height and weight). Blood samples were taken from the subjects before the first training session. All subjects were presented in laboratory at 9 to 11 morning. In order to evaluate the liver fat in the participants, sonography was used by a radiologist in all participants using the same equipment at hospital. Sonography of liver tissue was performed only before the test because one of the conditions for subjects to enter the plan was to have fatty liver. After the 8-week exercise training program, the participants were asked to repeat and perform the tests in the same manner and order. For

preventing the occurrence of the acute adverse effects of exercise training program, post-testing was performed 48 hours after the end of the training intervention.

All activities of the experimental group were performed in the occupational therapy hall of hospital under the supervision of oncology specialist, occupational therapist and master student of sports physiology. The control group did just their own daily routine exercises.

Aerobic Exercise Intervention

The subjects of the experimental group were first examined by sport medicine. After the approval of the relevant specialist to participate in the training session. The individuals participated in AT for eight weeks and three sessions per week. Each session lasting for 20–45 minutes, which was increased over time (Table 1). The AT consisted of three phases including warm-up, training and cool down. The participants were asked to warm up for a determined time (in the range 5–7 min), and then entered the main part of the exercise where AT using a treadmill, then after completing the exercise, the subjects cool down for 5 to 7 minutes.

Borg test and heart rate test were used to control the intensity of exercise, so that due to the young age of children, picture of Borg test was used and the target heart rate was 40 to 70% HR reserve. The first week of AT started with an intensity of 40–60% of the reserve heart rate and gradually increased during eight weeks, and in the last week the intensity of the AT reached between 55–70% of the reserve heart rate. To measure the target heart rate in each AT session, the reserve heart rate formula (% exercise intensity × (HRmax − HRrest) + HRrest) was used. Treadmill model (DIAMOND 5051) made in Korea was used for aerobic exercise. To measure the subjects' heart rate, a polar heart rate monitor made in China with a wrist monitor was used. Three sessions per week, each session lasting 20 to 45 minutes.

Table 1. Exercise protocol

Variable	First Week	Second Week	Third Week	Fourth week	Fifth week	Sixth Week	Seventh Week	Eighth week
Intensity of training	40–60 %HRR	40–60 %HRR	45–65 %HRR	45–65 %HRR	50–65 %HRR	50–65 %HRR	55–70 %HRR	55–70 %HRR
Time of training	20 Min	25 Min	25 Min	30 Min	35 Min	40 Min	45 Min	45 Min

Maximum heart rate was calculated using the formula (25): HRmax = age-220

Measurement of white cells and their separation

In the laboratory, the amount of neutrophils, monocytes and eosinophils was determined using microscopy and leukocyte formula. ethyl alcohol was used to prepare and fix the blood spread and then stained with ready-to-dye solutions available in the laboratory. In Bagisma staining, the cytoplasm of blue basophilic cells and the cytoplasm of acidophilic cells turn red and the nucleus of the cell turns purple. Immersion oil was used on the slides to count white blood cells and one hundred cells were counted in a zigzag pattern. This method of determining the type of white blood cells is

called the percentage of leukocyte formula, which in normal and adults includes: 50–70% neutrophils, 25–40% lymphocytes, 3–8% monocytes and 1–4% eosinophil's and less than 1% Is a basophil.

- **Hb:** To measure the amount of hemoglobin, a special kit for Monobind 1 and ELISA method was used.
- **ALT**: To measure the indicators, a platelet was made by Sysmex automated cell counter device model 1800 XT.
- **Bilirubin**: To measure bilirubin, spectrophotometric method was used with BT3000 device and Pars test kit.
- **Liver enzymes**: ELISA kit for aggregation of ALT and AST enzyme activity in AU400 chemical analyzer.

Statistical analysis

The Levene and Shapiro–Wilk tests were used to determine the equality of variances and normal distribution of the data, respectively. Data are represented as mean ± standard error (SD). The changes within each group were undertaken using paired t-tests. Statistical significance was accepted when $P<0.05$. Moreover, SPSS software version 18.0 (SPSS, Inc. Chicago, Illinois, USA) was used for data analysis. o determines whether exercise and medication (Experimental group) had a greater effect on AST enzyme or drug use alone (control group) the effect coefficient t was used.

RESULTS

In the experimental group the mean age, height and weight was 8.67±1.98 years, 133.58±8.73 cm, 33.59±9.57 kg, respectively. In the control group the average age, height and weight was 8.42±1.21 years, 130.04±6.21 cm, and 33.91±8.03 kg, respectively.

Table 2. Liver enzymes and hematological profile in children with leukemia

Groups	Variable	Pre mean ± SD	Post Mean ± SD	P-value
Experimental	AST (U/L)	93.33±13.71	48.92±11.81	<0.001
Control		92.92±16.05	68.67±30.11	0.026
Experimental	ALT (U/L)	102.75±13.05	57.75±19.84	<0.001
Control		103.83±13.79	79.75±24.70	0.002
Experimental	WBC ($\times 10^9$/L)	4.1±0.59	4.43±0.81	0.295
Control		4.22±0.80	4.15±0.52	0.840
Experimental	Hb (g/dL)	10.74±1.23	12.75±2.83	0.050
Control		10.77±1.72	10.56±1.40	0.693
Experimental	PLT (U/L)	255.75±56.42	262.50±33.38	0.707
Control		256.67±56.40	254.08±32.90	0.886
Experimental	Bilirubin(mg/L)	0.68±0.25	0.50±0.12	0.083
Control		0.61±0.26	0.59±0.18	0.817

AST: Aspartate aminotransferase, ALT alanine aminotransferase, WBC: white blood cell, Hb: hemoglobin, PLT: platelets, SD: Standard error,

There was no significant difference between the two groups in terms of height, weight, age and body mass index (P<0.05) and the two groups were homogeneous.

Also, the results of T-Test showed (Table 2) that there was not significant difference between pre-test and post-test in both control and experimental groups. There was significant difference between the pre-test and post-test in the change of AST, ALT and Hb in the experimental group (P≤0.05), while no significant difference was observed between the pre-test and post-test in the control group (P>0.05). To determine whether exercise and medication (Experimental group) had a greater effect on ALT enzyme or drug use alone (control group), the effect coefficient t was used. According to the calculations, the effect on ALT enzyme was 93.01% in the experimental group, and 58.77% in the control group. As shown, the effect of AT on ALT and AST enzymes reduction was greater. According to the calculations, the effect on AST enzyme was 86.18% in the experimental group and 23.23% in the control group. There was no significant difference in ALT and bilirubin between pre-test and post-test in the control and experimental groups.

DISCUSSION

The results showed those eight weeks of AT significantly reduced liver AST and ALT liver enzymes in children with leukemia. The results of the present study were consistent with the findings of Suzuki et al. (2006) and Davoodi (2012) studies. This can be due to the type of training, duration of training, age of the subject, clinical condition of the subject, and intensity of training. Studies show that exercise may modulate liver fat directly by altering liver fat oxidation (Lee, 1998). During exercise the increased O_2 demand of skeletal muscle is mainly matched by increasing muscle blood flow by increasing cardiac output, by modulating blood flow distribution among active and inactive organs, and by optimizing microcirculation (Welch et al., 2012). Aerobic activity may further reduce ALT and AST levels by reducing oxidative stress and inflammation (Shamsoddini et al., 2015). Moosavi-Sohroforouzani and Ganbarzadeh (2016) reported that AT effectively decreased the ALT and AST in patients with fatty liver disease. In addition, Ghamarchehreh et al. (2019), reported a significant reduction in ALT and AST levels after eight weeks of AT regardless of weight. It is noteworthy that few studies have focused on the role of aerobic and resistance exercises on ALT and AST levels in patients with leukemia. Changing the lifestyle, losing weight and exercising seem to be appropriate as the first line of treatment. The positive role of regular exercise training against liver injury, inflammation reduction, liver injury and fibrosis has been reported through macrophage filtration (Kawanishi et al., 2012). In this study, the results showed that eight weeks of AT has a significant effect on Hb in children with leukemia. This was consistent with the results of Rezaei Seraji et al., (2012). and Dimeo et al. (1997) studies. In the present study, it was observed that AT has significantly increased the resting Hb concentration of children 7 to 10 with cancer. These findings are inconsistent with the results of Françoise (Alijani Renani, Keikhai, Ghadimi Mahani, & Latifi, 2012; Charnay-Sonnek & Murphy, 2019; El-Sayed, Sale, Jones, & Chester, 2000). One of the possible reasons for the difference between the results of the present study and Françoise research is the age of the subjects. Because in the study, the elderly over 65 years were studied (Charnay-Sonnek & Murphy, 2019). It is noteworthy that from the age of 20, the production of red blood

cells and Hb decreases (Gligoroska et al., 2019). It seems that the main factor of this adaptation is the lack of tissue oxygen and the increase in the need for tissue oxygen, which is created by proper training stimuli. The results demonstrated that eight weeks of AT increased the number of platelets in the blood, but this increase was not significant. This increase may be attributed to the release of fresh platelets from the vascular bed of the spleen, bone marrow and other PLT stores in the body. It also stimulates the bone marrow to make new ALT. Eight weeks of aerobic exercise reduced the total bilirubin level of leukemia patients, but this decrease was neither significant compared to the pretest nor to the control group (Pfalzer, 1989). Health organizations worldwide advocate increased regular physical activity as a potent treatment of NAFLD and for the prevention of steatohepatitis and associated metabolic comorbidities. All kinds of exercise interventions (e.g., endurance and resistance exercise, a combination of both, or unstructured increase in daily physical activity) are effective in ameliorating NAFLD (Hoene et al., 2021). Lack of significant increase in plasma levels of plasma bilirubin can be attributed to a significant increase in total antioxidant capacity. The increase in post-match bilirubin is attributed to injuries caused by foot injuries and increased iron catabolism (Alavi, Dorostymotlagh, Mahmoodi, Jarollahi, & Chamari, 2007). Due to the moderate intensity of exercise and an increase in Hb in the exercise group, the decrease in bilirubin could be due to increased antioxidant capacity (Swift, Johannsen, Earnest, Blair, & Church, 2012). At any given capillary blood flow, the amount of O_2 unloaded from Hb to the cells of working muscle can be increased greatly by decreasing Hb-O_2 affinity (Mairbäurl, 2013).

The results showed that eight weeks of AT had no significant effect on the number of WBC in children with cancer. Moreover, Ag. Daud et al. (2019) reported that mean total leucocyte count increased significantly ($p<0.05$) immediately after exercise at all intensities and durations. Leukocytosis was the most obvious and consistent change that occurred during or after exercise (Neves et al., 2015). A precise definition of an individual's workload that consists of intensity and duration of exercise is crucial as it will affect blood viscosity and blood flow during and immediately after exercise (Mairbäurl, 2013). Some previous studies have showed that endurance training reduces hematocrit and increases hemoglobin with platelets (Belviranli, Okudan, & Kabak, 2017; Wardyn et al., 2008). However, most of the previous studies have reported that the changes in the number and distribution of leukocytes and their subclasses due to the exercise are temporary and unstable, and it is not clear to what extent these factors affect the immune system. In addition to platelets, bilirubin, and safety factors, lipid profile levels possible is suggested.

CONCLUSION

Eight weeks of AT may help prevent damage through decreasing serum levels of liver enzymes and significant increase in Hb, whereas there was no significant influence on WBC, PLT and bilirubin.

Conflict of interest: the authors declare that they have no conflicts of interest.

Informed consent: All participants provided written informed consent to participate in this study

Ethical approval: Ethical approval was IR.SBU.REC.1400.031

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