

Research article

Effects of a combined aerobic and strength training program in youth patients with acute lymphoblastic leukemia

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Abstract

Cure rates of youth with Acute Lymphoblastic Leukemia (ALL) have increased in the past decades, but survivor's quality of life and physical fitness has become a growing concern. Although previous reports showed that resistance training is feasible and effective, we hypothesized that a more intense exercise program would also be feasible, but more beneficial than low- to moderate-intensity training programs. We aimed to examine the effects of an exercise program combining high-intensity resistance exercises and moderate-intensity aerobic exercises in young patients undergoing treatment for ALL. A quasi-experimental study was conducted. The patients (n = 6; 5-16 years of age) underwent a 12-week intra-hospital training program involving high-intensity strength exercises and aerobic exercise at 70% of the peak oxygen consumption. At baseline and after 12 weeks, we assessed sub-maximal strength (10 repetition-maximum), quality of life and possible adverse effects. A significant improvement was observed in the sub maximal strength for bench press (71%), lat pull down (50%), leg press (73%) and leg extension (64%) as a result of the training (p < 0.01). The parents' evaluations of their children's quality of life revealed an improvement in fatigue and general quality of life, but the children's self-reported quality of life was not changed. No adverse effects occurred. A 12-week in-hospital training program including high-intensity resistance exercises promotes marked strength improvements in patients during the maintenance phase of the treatment for Acute Lymphoblastic Leukemia without side-effects. Parents' evaluations of their children revealed an improvement in the quality of life.

Key words: Acute lymphoblastic leukemia, child, strength training, pediatrics, quality of life.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer, accounting for 30% of all cancers diagnosed in children younger than 15 years of age (Linnet et al., 1999; Huang and Ness, 2011). Although ALL cure rates have considerably increased over the last decades, the quality of life (QOL) and physical fitness of survivors have become a growing concern (Lucia et al., 2005; Wolin et al., 2010).

Lucia et al. (2005) observed that decreased energy expenditure, impaired neuropsychological functions, gross and fine-motor disturbances, anthracycline-induced cardiotoxicity, sarcopenia, muscle weakness, osteoporosis, pain, paresthesia and reduced ankle range of motion are adverse effects often related to ALL treatment, to a

sedentary lifestyle and/or to the cancer itself. Accordingly, San Juan et al. (2008) recently showed that children receiving treatment against ALL present a lower functional capacity and QOL than healthy children. The same group also showed the benefits of in-hospital supervised exercise training in this population (San Juan et al., 2007a; 2007b). The authors submitted seven children (4-7 yr) to a 16-wk conditioning program that included both resistance and aerobic-type training. The results showed improvements in aerobic fitness and functional mobility. Moreover, there were modest but clinically relevant gains in strength for both upper and lower limbs. Taken together, these results indicate that exercise training constitutes a useful adjunct to the treatment of ALL (Lucia et al., 2005; Marchese et al., 2004; San Juan et al., 2007a; 2007b).

It is well known that high-intensity exercise depresses the immune function in adults (Koch et al., 2001), which could theoretically impose a risk to ALL patients, who are more prone to systemic infections than healthy people. In contrast, there are some data (Timmons, 2005) suggesting that chronic physical activity has little impact on immune function in a healthy pediatric population. Yet, no study has reported the safety of high-intensity resistance exercises in pediatric patients who are receiving treatment for ALL.

Therefore, the aim of this study was to investigate the efficacy and safety of an in-hospital exercise training program, which comprised high-intensity resistance exercises combined with moderate aerobic training in children and adolescents with ALL during the maintenance phase of their treatment. We hypothesized that this training program could promote significant strength gains without inducing any significant side effects in this population.

Methods

Patients

Eleven patients recruited from the Children's Institute took part in this study. The inclusion criteria for this study were: 1) children and adolescents (5-18 yr) during the maintenance therapy against low-risk or high-risk ALL; 2) time elapsed since the start of the treatment > 6 months; 3) preserved cardiac structure and function, as assessed by an echocardiogram, and 4) the absence of musculoskeletal disturbances that could limit participation in the exercise training program.

One patient, prior to initiating the training proto-

col, presented non-exercise-related haematemesis due to a gastric ulcer and had to be excluded. Another four patients withdrew from the study prior to the training protocol due to personal reasons. Thus, six patients initiated and completed the protocol and were included in the analyses. The patients' characteristics are shown in Table 1. Three patients were at high-risk and three were at low-risk. The patients with low-risk ALL were submitted to the GBTLI-99 protocol and those with high-risk were submitted to the PROP-II-97 protocol. The GBTLI-99 protocol (Brazilian Group of Childhood Leukemia Treatment) comprises the administration of mercaptopurine ($50 \text{ mg m}^{-2} \text{ day}^{-1}$) and methotrexate ($25 \text{ mg m}^{-2} \text{ week}^{-1}$). The patients also receive vincristine (1.5 mg m^{-2}) and dexamethasone ($3 \text{ mg m}^{-2} \text{ day}$) every 8 weeks until the 106th week. The PROP-II-97 protocol (Institutional Protocol of the University of São Paulo) comprises the administration of the following medications for 80 weeks: methotrexate ($2 \text{ g m}^{-2} \text{ week}^{-1}$) plus mercaptopurine ($75 \text{ mg m}^{-2} \text{ day}^{-1}$) for 3 weeks; cyclophosphamide ($250 \text{ mg m}^{-2} \text{ day}^{-1}$) for 4 consecutive days followed by etoposide ($250 \text{ mg m}^{-2} \text{ day}^{-1}$) for 3 consecutive days; teniposide (vumon) and citarabine ($300 \text{ mg m}^{-2} \text{ week}^{-1}$ and $250 \text{ mg m}^{-2} \text{ dose week}^{-1}$, respectively) for 3 weeks; citarabine ($1.5 \text{ g m}^{-2} \text{ day}^{-1}$) for 2 consecutive days and methotrexate ($40 \text{ mg m}^{-2} \text{ week}^{-1}$) with mercaptopurine for 6 weeks. After the 80th week, the patients are given methotrexate ($40 \text{ mg m}^{-2} \text{ week}^{-1}$) with continuous daily mercaptopurine, vincristine (1.5 mg m^{-2}) pulses every 6 weeks and dexamethasone ($3 \text{ mg m}^{-2} \text{ day}^{-1}$) for 7 days until the 120th week.

The study was approved by the General Hospital's Ethics and Committee Review Board. Before initiating the study, all of the subjects' parents provided a written informed consent after being provided with a complete verbal and written explanation about the study's objectives, as well as the risks and benefits that were involved.

Experimental design

A small prospective study with a quasi-experimental design was conducted. At the beginning of the trial, the patients were submitted to an echocardiographic and $\text{VO}_{2\text{max}}$ assessment. Then, they underwent a 12-week supervised training program, which combined high-intensity strength exercises with a moderate aerobic exercise. Although the trial focused on the effects of intensive resistance training, aerobic training was also included because it had previously been shown to benefit ALL patients (San Juan et al., 2007a; 2007b).

At baseline and after 12 weeks, the subjects were submitted to a sub-maximal dynamic strength assessment

through the use of the ten repetition-maximum test (10-RM). Hematological parameters, serum muscle enzymes, inflammatory markers and QOL were also determined at the same time frame.

$\text{VO}_{2\text{peak}}$ assessment

Heart rate was recorded at rest, during the effort, and during the recovery phase by means of simultaneous monitoring of 12 derivations (D1, D2, D3, AVr, AVl, AVf, V1, V2, V3, V4, V5, and V6). Arterial blood pressure was measured indirectly using an aneroid sphygmomanometer by the auscultatory method. The gas exchange and ventilatory variables were analyzed by using a breath-by-breath calorimetry system (Cortex - model Metalyzer III B, Leipzig, Germany).

The patients were submitted to an incremental treadmill test (Heck et al., 1985). In short, the protocol begins at a speed of $2.74 \text{ km hour}^{-1}$ and a 10% slope. After each three-minute stage, the workload is increased by a combination of treadmill speed and grade increments. Attainment of $\text{VO}_{2\text{peak}}$ was accepted when two of the following three criteria were met: an age-predicted maximal heart rate (Tanaka et al. 2001), a plateau in VO_2 , a respiratory exchange ratio > 1.1 , and a volitional exhaustion.

10-RM test

Dynamic strength was assessed through a sub-maximal strength test instead of the conventional one-repetition-maximum test (1-RM). According to San Juan et al. (2007b), the sub-maximal test appears to better reflect the gains in muscle strength that are associated with improvements in the functional ability to perform daily living tasks in children and adolescents with ALL.

The patients underwent 4-8 familiarization sessions before the 10-RM tests took place. Patients were considered familiarized when the variation between two consecutive tests was lower than 5%. The average period necessary to complete familiarization was 3 ± 1 weeks. Familiarization sessions consisted of a light warm-up, followed by the 10-RM test protocol.

The 10-RM is defined as the maximum strength capacity to perform ten repetitions until muscular fatigue. Prior to the test, a warm-up (i.e., 3 sets of 5 repetitions at 40–60% of the perceived 10-RM with a 1-min rest period) was performed. Thereafter, 3 to 5 separate single attempts were performed until the 10-RM was attained. The interval between each unsuccessful attempt was 4 min. patients were instructed to perform each exercise to acute muscular exhaustion. Any repetitions that were not

Table 1. Clinical characteristics of the patients.

Patient	Sex	Age (yrs)	Time of treatment (wks)	Risk factor	Treatment protocol	BMI (kg m^{-2})	BMI percentile*	$\text{VO}_{2\text{peak}}$ ($\text{ml kg}^{-1} \text{ min}^{-1}$)
I	F	11	116	High	PROP-II-97	19.5	50-75	33.1
II	M	6	45	Low	GBTLI-99	21.7	50-75	25.8
III	F	16	30	High	PROP-II-97	24.8	75-85	27.6
IV	F	14	98	High	PROP-II-97	16.1	75-85	31.4
V	F	9	91	Low	GBTLI-99	16.2	25-50	28.9
VI	M	6	78	Low	GBTLI-99	21.5	>95	18.1

F=female; M=male; PROP-II-97=treatment protocol for children with leukemia at high risk (see the methods section for more details); GBTLI-99=treatment protocol for children with leukemia at low risk (see the methods section for more details); BMI=body mass index. *according to National Center for Health Statistics percentiles.

performed with a full range of motion were discarded. The 10-RM tests were conducted for 4 exercises: bench press, lat pull down, leg press and leg extension.

Exercise training

The exercise program consisted of 12 weeks of supervised training. The exercise sessions occurred twice a week and lasted approximately 1 h per session. Training sessions consisted of a 10-min treadmill warm-up followed by 30 min of resistance training, 20 min of treadmill aerobic training and 5 min of stretching exercises. All sessions were monitored by one fitness professional and one physician. The exercise program was performed in a gymnasium located at the Rheumatology Division of the School of Medicine, University of Sao Paulo. An exercise session would be cancelled whenever the patient presented fever (temperature > 38°C/100.4°F), low blood platelet levels (< 50.000 per μ l), a neutrophil count lower than 500 cells per μ l, marked anemia (hemoglobin < 8 g/dl) or severe cachexia (i.e., weight mass loss > 35%).

The resistance training included five exercises for the main muscle groups: bench press, leg press, lat pull down, leg extension and seated row. Patients were required to perform 4 sets of 6-10-RM, except during the first week, when they performed only 2 sets of approximately 15-RM for each exercise as an adaptation to the high-intensity resistance training. Progression to greater resistance levels was implemented when the subject was able to perform 10 repetitions in the last training set for 2 consecutive workouts. Aerobic running intensity was set at the corresponding heart rate of approximately 70% of VO_{2peak} .

Quality of life

The QOL was assessed by the validated Brazilian PedsQL inventory (Klatchoian et al., 2008), which is a modular approach to measuring health-related quality of life in healthy children and adolescents and in those with acute and chronic health conditions. These inventories involve both a child self-report as well as parent proxy-reporting scales. The PedsQL included three domains, which were the generic core scale, the multidimensional fatigue scale and the cancer module. Items were reversed, scored and linearly transformed into a 0-100 scale, thus higher scores indicate a better quality of life (Varni et al., 1999).

Safety analyses

In order to determine the safety of the exercise training, the number of occurrences of bleeding, infections, erythrocyte and/or platelet transfusions and hospital admissions were assessed throughout the exercise training program. In addition, blood markers of inflammation (i.e., C-reactive protein levels and erythrocyte sedimentation rate), muscle damage (i.e., creatine phosphokinase and aldolase levels) and hepatic enzymes (i.e., alanine transaminase and aspartate transaminase) were measured.

Statistical analyses

The power of the analysis was calculated *post hoc* with the use of the G-Power software (version 3.1.2 – Universität Kiel, Germany). The analysis was conducted by

inputting the α error (0.05), sample size (6 subjects) and the effect sizes of the exercise training on muscle strength and quality of life in ALL patients obtained from the study. Calculation was based on a T-test for dependent means and the power obtained ($1 - \beta$ error) range from 0.95 to 0.70. Effect size (ES) for all dependent variables were estimated to determine the practical significance of the findings.

All data were expressed as mean \pm SD. Shapiro-Wilk test revealed that all data were normally distributed. Paired t-tests were used to analyze all the dependent variables. Pre-post pooled data of weight lifted in the four exercises (bench press + leg press + leg extension + lat pull down) were also examined in order to provide a broader view of strength changes. The alpha level was previously set at $p < 0.1$. The analyses were conducted using SPSS 14.0 software (SPSS Inc, Chicago, Illinois).

Results

A significant improvement was observed in the 10-RM bench press, lat-pull-down, leg-press and leg-extension as a result of the resistance training (Table 2). A similar trend was observed when the pooled data regarding total weight lifted was analyzed (ES: 1.48; $p = 0.0001$; Figure 1).

Table 2. Effects of exercise training on strength, as assessed by the 10 RM tests. Data are means (\pm SD).

	PRE (kg)	POST (kg)	Δ (%)
leg press	29.5 (13.7)	51.2 (12.9) ***	73
leg extension	10.5 (5.6)	17.2 (7.0) **	64
bench press	11.3 (5.5)	19.3 (5.8) ***	71
lat pull down	12.5 (6.1)	18.8 (7.6) *	50

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

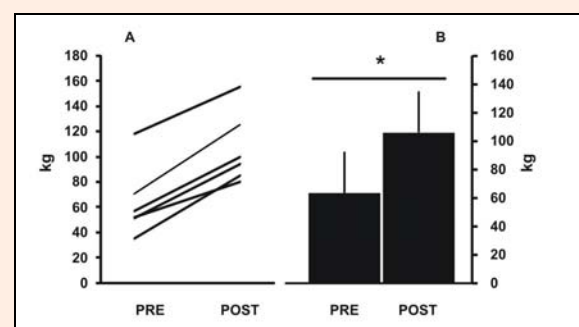


Figure 1. Individual (panel A) and mean (panel B) strength pooled data, as assessed by 10 RM, for lat pull down, bench press, leg extension and seated row (*PRE vs. POST statistically different; $p=0.004$).

Throughout the training period, there were no reports of pain, muscle injury, cramps, muscle soreness, eczemas, excessive exhaustion or any apparent exercise-related adverse episode. Furthermore, there was no occurrence of muscle bleeding, infections or hospital admission during the training period. No suppressions in hematological or alterations in biochemical blood parameters were observed as a consequence of the exercise training (data not shown). Regular physical examinations have

also revealed no abnormalities.

The parents' evaluations of their children revealed an improvement in the QOL in the generic domain as well as in the fatigue scale. On the other hand, parents' evaluation of QOL regarding the cancer module remained unaltered. Children's self-reported QOL was unchanged (Table 3).

Table 3. Quality of life, as assessed by PedsQL questionnaire (scores were transformed to a 0-100 scale. The higher the score, the better the reported quality of life). Data are means (\pm SD).

Domain	Reporter	PRE	POST
Cancer	Patient	62 (8)	67 (3)
	Parent	47 (16)	63 (12)
Fatigue	Patient	73 (14)	72 (10)
	Parent	57 (30)	83 (14) *
Generic	Patient	67 (14)	74 (9)
	Parent	55 (21)	79 (10)

* $p < 0.05$

Discussion

This study indicated that a 12-week exercise program involving high-intensity resistance exercises combined with aerobic training promotes marked strength improvements without any apparent adverse effect in children and adolescents during the maintenance phase of the ALL treatment. Importantly, we have reported an increase in the QOL of these patients as a consequence of an exercise training program, which was probably a consequence of the strength gain.

Exercise training has been shown to be an emergent, non-pharmacological intervention that may be able to counteract the short and long-term effects of the ALL treatment (i.e. muscle atrophy and muscle deconditioning) (San Juan et al., 2007a; 2007b; Wolin et al., 2010). However, only few studies have addressed the effects of exercise training on children with ALL (Marchese et al., 2004; San Juan et al., 2007a; 2007b). Despite the promising findings of low- to moderate-intensity training on aerobic fitness, functional mobility and strength (San Juan et al., 2007a; 2007b), we hypothesized that resistance training at a higher intensity could also lead to further strength gains without any adverse effects.

As expected, we observed a marked increase in sub-maximal dynamic strength in the patients as a result of the high intensity resistance training program. It is worth noting that the strength gains observed in the current study were largely greater than those seen by San Juan et al. (2007b) (e.g., a 70% vs. a 14% increase for the seated bench press). Notably, the greater intensity of resistance training used in the present study is likely to be responsible for the difference in these outcomes. While San Juan et al. (2007b) evaluated a resistance training program in which children completed one set of 8-15-RM for each exercise, we designed a resistance training program that consisted of 4 sets of 6-10-RM per exercise. Although not quantitatively determined, the training volume is indeed superior in our study. In fact, training volume seems to be an essential factor that leads to strength gain in children. Data by Faigenbaum et al. (1999)

showed only slight increments in strength in healthy children who underwent low-volume resistance training. Thus, since both the intensity and volume of resistance training were higher in our study, it is impossible to distinguish whether the greater strength gains were mainly related to the greater intensity, training volume or both. Further studies should address this topic.

Even though exercise has been shown to be effective, safety is still an issue regarding ALL patients. In adults, there is a consistent body of evidence showing that chronic exercise training improves the immune system function (Nieman, 2003), whereas acute bouts of intensive exercise lead to a marked immunosuppression (Dohi et al., 2001; Gleeson et al., 2004; Gleeson, 2007; Nieman, 2003). In contrast, children tend to be less susceptible to major exercise-induced perturbations to the immune system (Koch et al., 2001). Some authors (San Juan et al., 2007a; 2007b; 2008) have investigated the effects of exercise on the immune system of children with ALL. Overall, the outcomes have revealed that the pattern, magnitude and direction of the exercise-induced leukocytosis were comparable between youth patients with ALL and healthy children. Our results extend these findings to high-intensity exercise interventions even though studies with more patients are required to confirm or reject these findings.

Finally, we verified improvements only in the parents' evaluation of QOL for the generic domain and for the fatigue scale. As previously argued by others (Marchese et al., 2004; San Juan et al., 2007b), the lack of improvements in children's self-reported QOL might reflect a certain ceiling effect during the pre-training inventory, with the majority of children and parents minimizing their actual QOL problems.

The present study has some limitations. First, considering the putative risks inherent to a high-intensity exercise program in children and adolescents undergoing treatment against ALL, we prudently chose to conduct a small sample study before initiating a larger trial. For this reason, caution should be exercised in extrapolating the current findings to clinical practice. Despite the reduced number of participants, the large magnitude of our outcomes enables us to find statistically significant differences as a result of the intervention. Second, we were unable to design a control group. The lack of non-trained subjects can be attributed to the same reasons raised by San Juan et al. (2007b). Briefly, both ethical and practical factors hampered us from enrolling non-hospitalized children and adolescent patients to perform a long-term, in-hospital familiarization protocol without providing further training intervention. However, we strongly believe that the robustness of our familiarization protocol inhibited learning effects, thereby strengthening our quasi-experimental design.

Conclusion

We demonstrated that a 12-week exercise program including high-intensity resistance training is safe and able to substantially improve strength and quality of life, as reported by their parents, in youth patients receiving

treatment against ALL. Further, randomized controlled trials should investigate the long-term safety and efficacy of this mode of intervention in a larger ALL sample.

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Key points

- Patients with ALL present low muscle strength and poor quality of life.
- High-intensity resistance exercises combined with moderate-intensity aerobic exercise improved muscle strength and quality of life during the maintenance phase of ALL treatment.
- The exercise training program seemed to be tolerable and safe in ALL patients.

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