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Feasibility and Initial Effectiveness of Home Exercise During Maintenance Therapy for Childhood Acute Lymphoblastic Leukemia

Adam J. Esbenschade, MD, MSCI, Debra L. Friedman, MD, MS, Webb A. Smith, MS, Sima Jeha, MD, Ching-Hon Pui, MD, Leslie L. Robison, PhD, and Kirsten K. Ness, PT, PhD

Department of Pediatrics (Drs Esbenschade and Friedman), Vanderbilt University School of Medicine and the Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville TN; Departments of Epidemiology and Cancer Control (Mr Smith, Drs Robison and Ness) and Oncology (Drs Jeha and Pui), St. Jude Children's Research Hospital, Memphis, TN; Vanderbilt-Ingram Cancer Center (Dr Friedman), Nashville, TN

Abstract

Purpose—Children with acute lymphoblastic leukemia (ALL) are at increased risk of obesity and deconditioning from cancer therapy. This pilot study assessed feasibility/initial efficacy of an exercise intervention for ALL patients undergoing maintenance therapy.

Methods—Participants were children with ALL, age 5-10 years, receiving maintenance therapy, in first remission. A 6-month home-based intervention, with written and video instruction, was supervised with weekly calls from an exercise coach. Pre- and post-study testing evaluated strength, flexibility, fitness and motor function.

Results—Seventeen patients enrolled (participation 63%). Twelve (71%) finished the intervention, completing $81.7 \pm 7.2\%$ of prescribed sessions. Improvements 5% occurred in 67% for knee and 75% for grip strength, 58% for hamstring/low-back and 83% for ankle flexibility, 75% for the 6-minute-walk-test, and 33% for performance on the Bruininks-Oseretsky Test of Motor Proficiency Version 2.

Conclusions—This pilot study demonstrated that exercise intervention during ALL therapy is feasible and has promise for efficacy.

Keywords

acute lymphoblastic leukemia/therapy; children; exercise therapy; flexibility; motor skills; obesity; physical fitness; strength

Correspondence: Dr. Adam Esbenschade, Department of Pediatrics, Vanderbilt University School of Medicine and the Monroe Carell Jr. Children's Hospital at Vanderbilt, Division of Pediatric Hematology and Oncology, 2020 Pierce Avenue 397 PRB, Nashville TN, 37232. adam.esbenschade@vanderbilt.edu.

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INTRODUCTION AND PURPOSE

Cure rates for acute lymphoblastic leukemia (ALL), the most common type of childhood cancer, have now risen to over 85%,^{1, 2} resulting in a growing cohort of survivors who are at potential risk for long-term complications from ALL and its therapy. One of these complications is the development of components of the metabolic syndrome, which includes obesity, hypertension, dyslipidemia, and insulin resistance.^{3,4} Recent data have indicated that these metabolic changes manifest first while patients are still receiving therapy, particularly during maintenance, a two to three year time period that includes pulses of corticosteroid treatment.⁵⁻⁸ Thus, the period of maintenance therapy, when patients are also found to be deconditioned with decreased muscle strength,^{9, 10} appears optimal to develop a preventive intervention. The aim of this pilot study was to determine the feasibility and initial efficacy of an aerobic and strengthening exercise intervention program conducted during maintenance therapy among children treated for ALL.

METHODS

Participants

Participants for this pilot study were recruited from among children being treated for ALL. Eligible children were between 5 and 10 years old at enrollment, in first remission, and in the maintenance phase of chemotherapy with at least six months of treatment remaining. Each child approached had a modified Lansky score of at least 60 and medical clearance to participate. Parents/guardians provided written informed consent and participants 8 to 10 years old provided assent prior to enrollment.

Intervention

All participants in this pilot study received an intervention that included 6 months of ability specific, progressive stretching, strengthening and aerobic exercise. The exercise intervention was designed to address 7 common neuromusculoskeletal and fitness impairments seen during and following treatment for childhood ALL including: 1) impaired ankle range of motion, 2) distal lower extremity weakness, 3) proximal lower extremity weakness, 4) distal upper extremity weakness, 5) poor balance, 6) poor general fitness/coordination, and 7) poor aerobic fitness.¹¹

The exercise intervention included 5 main exercise groups for flexibility, ankle strengthening, leg strengthening, balance, and general fitness (Appendices 1 and 2, Supplemental Content 1 and 2). Participants were instructed to complete prescribed flexibility, strengthening and balance exercises 3 days per week, completing prescribed general fitness activities on 3 other days per week. Each workout took 30 to 45 minutes to complete. Weekly phone calls from an exercise coach (exercise physiologist, physical therapist, or study nurse) were made to answer participant and/or parent questions and to assess and progress the intensity and duration of the intervention. An assessment and progression of the intervention was also made during each medical clinic visit, approximately monthly. Participants were provided with necessary equipment for the prescribed exercises, detailed written and graphic instructions (Appendices 1 and 2,

Supplemental Digital Content 1 and 2), a videotape demonstrating each exercise (see Video, Supplemental Digital Content 3), and a log book (Appendix 3, Supplemental Digital Content 4) to record the exercise. Parents were given a supply of stickers and small toys to reward their children at their discretion.

Study measures

Feasibility—Feasibility was evaluated by determining the percentage of children enrolled among those who were eligible and approached, the percentage of children who remained on study, and the percentage of prescribed sessions completed among children who remained on study.

Effectiveness—Preliminary effectiveness of this intervention was evaluated by having participants complete both baseline and follow-up physical performance testing including measures of flexibility, strength, cardiopulmonary fitness and age specific motor performance. Height and weight were recorded and then converted into body mass index (BMI) using the formula weight (kilograms)/ height (meters).² Percentiles for BMI were calculated using age and gender-standardized growth population norms (based on the Centers for Disease Control and Prevention's Year 2000 growth charts).¹² A BMI >85th percentile adjusted for age and sex was considered overweight and >95th percentile was considered obese.¹²

General flexibility was evaluated with the sit and reach test. A yardstick was placed on a firm flat surface and tape placed across it at a right angle to the 15 inch mark. The participant sat with the yardstick between the legs which were extended at right angles to the taped line on the floor. The heels of the feet touched the edge of the taped line and were 10-12 inches apart. The participant reached forward with the hands in parallel as far as possible. The best value for 3 trials, in centimeters, at the most distant point of the fingertips was recorded and used for analysis.¹³⁻¹⁵

Ankle dorsiflexion passive range of motion was measured with a goniometer with the child sitting with the hips and knees in 90° of flexion using standard procedures.^{16,17} The maximum of 2 trials was used for analysis.

Isometric knee extension strength in Newton-meters (Nm) was measured with the subject seated in an adjustable straight-back chair. The pelvis and contralateral thigh were fixed with adjustable straps and the knee being tested flexed at 45°. The participant was instructed to exert a maximal voluntary force until their contraction was "broken." Resistance was applied by the examiner with a hand held myometer (Chatillion-Ametek, Largo, FL) held against the anterior surface of the leg, just above the medial malleoli.¹⁷ The contraction was repeated 3 times with each leg; the peak values from each leg were averaged for analysis. Handgrip strength in kilograms was measured using a hand held dynamometer (Jamar, Sammons Preston Rolyan, Nottinghamshire, UK). Participants were seated with the shoulder in 0-10° of flexion and the elbow in 90° of flexion. The forearm was positioned in neutral. Each participant completed 3 trials; the peak value from each hand was averaged for analysis.^{18,19}

The Bruininks-Oseretsky Test of Motor Proficiency Version 2 (BOT-2) Short Form was used to evaluate motor function. This norm-referenced instrument was designed to test gross and fine motor function, balance and strength in children and adolescents 4-21 years of age. Coefficients range from 0.95 to 0.96 for internal consistency reliability, and from 0.77-0.82 for test-retest reliability. The r-squared for inter-rater reliability is 0.98. Scores consistently increase with increasing age. The items were administered and scored according to the standardized procedures in the manual. Standard scores were used for analysis and range from 20 to 80 with a mean of 50 and a standard deviation of 10.²⁰

Cardiopulmonary fitness was evaluated with the modified six-minute walk test (6MWT).²¹ Children used a wheeled measuring device with an adjustable handle to motivate them to keep walking and to determine distance in meters. Children were instructed to walk as far as possible along a 20 meter course, without jogging or running, in 6 minutes. Stopping, slowing down, and resting against the wall during the test were allowed, but the distance covered at the end of 6 minutes was the time used. Encouragement was given in 1-minute intervals.

RESULTS

Feasibility

Among the 27 participants eligible and approached to participate in this study, 17 (63.0%) agreed to enroll and completed baseline testing. Among the 10 who declined participation, 4 reported being too busy, 3 were not interested in doing exercises, and 3 gave no reason. Children who declined participation were on average 6.0 ± 1.8 years of age, eight (80.0%) were male. Participants were similar in age to the non-participants (7.4 ± 2.0), 12 (70.6%) were male. Among the 17 enrolled participants, 12 (70.6%) completed the study. Of the 5 who did not complete the study, 3 withdrew because they were unable to incorporate the exercises into their daily routines, 1 did not return for the final appointment and 1 had leukemia relapse. Children primarily enrolled in this study in the fall and winter months. Those who dropped out were equally distributed across enrollment seasons. The 12 participants who completed the study completed $81.7 \pm 7.2\%$ of their prescribed exercise sessions.

Preliminary effectiveness

Physical performance measures prior to and after the 6-month intervention are provided in the Table. Overall, changes in flexibility, strength, age specific motor performance and cardiopulmonary fitness were positive, with the biggest percent changes in flexibility (81.4% for passive ankle dorsiflexion and 42.2% for the sit and reach test). Average handgrip strength improved by 16.9% and average distance walked in 6 minutes improved by 16.0%. Improvements of 5% or greater occurred in 67% for knee strength, 75% for hand grip strength, 58% for performance on the sit and reach test, 83% for ankle range of motion, 75% for the 6MWT, and 33% for age- and sex-specific standard scores on the BOT2-Short Form. BMI also decreased by a mean of 4.2 percentile points and there was maintenance or reduction in weight among 8 patients with weights above the 75th percentiles, with 4 achieving normal weight by the end of the intervention. Only 1 non-overweight subject

became overweight during the study. There were no associations between changes in BMI and strength parameters.

Family and coach responses

In addition to improvements in functional measures, children and parents generally reported that they enjoyed the exercise program and felt it was beneficial. Often, the entire family participated in the general exercise activity to encourage the child. Families universally expressed that the exercises were challenging during the weeks when the child's chemotherapy included dexamethasone and vincristine. The exercise coaches at the 2 sites reported that the program was easy to administer because it was well received by most children their families. Successful strategies for coaching included making the exercises a game and engaging siblings. Families who were the most engaged required the least amount of follow-up from the exercise coach.

DISCUSSION

Sustained exercise interventions in ALL patients during maintenance can be difficult to implement as they are often deconditioned and have not made exercise a priority. However over 75% of the patients that enrolled in this pilot study were at least 70% compliant with a 6-month exercise plan indicating feasibility. Furthermore, our results suggest that such an intervention will result in improvement of overall fitness. Of the patients who completed the study, half of the patients showed a 5% or greater improvement in at least 6 of the 7 metrics that were measured.

Many trials have evaluated exercise interventions in pediatric ALL patients, with differing sample sizes, methodology and measurement,^{11,22-37} which make it difficult to directly compare results. Among 14 recent trials, the exercise intervention was implemented at different stages in therapy including the first 6 months of therapy, maintenance therapy, throughout therapy, off therapy, and post stem cell transplant. Duration of the interventions range from less than 1 week to 2 years, with only 3 of the interventions 6 months or longer and some included adolescents >12 years of age. Enrollment rates ranged from 56%-100% and completion rates from 25% -100%, similar to our rates of 63% and 71% respectively.

The maintenance phase of ALL therapy has been shown to be a key time period that puts patients at risk for excessive weight gain.^{5,6,8} Previous studies were not able to show an improvement in BMI after an exercise intervention.^{24,25,29,31} In a study of 51 pediatric ALL patients randomized to a 2-year exercise program versus usual care, weight gain was similar in both groups during therapy, but those in the intervention group showed a more rapid decline in body fat 1 year off therapy.²² Our intervention resulted in an overall trend of weight maintenance or loss with many patients maintaining or losing weight. In contrast to previous studies,^{22,24,25,29,31} our exercise program was longer than most and included an exercise coach.

Among pediatric ALL patients receiving therapy, muscle strength capacity has been shown to be worse than that in matched healthy controls in 2 studies.^{10,33} In the current pilot study, leg strengthening exercises were specifically targeted, which resulted in clinically important

improvement (>5%) in knee extension in 75% of subjects. Although upper body strengthening was only targeted indirectly through general fitness exercises, a mean 17% improvement in hand grip was achieved among all participants. Our results demonstrating increases in muscle strength, measured by knee extension and grip, confirm those in other studies of short-term interventions, measured by knee extension strength,³³ seated bench press, seated tow, and seated leg press²⁹ and isometric muscle strength by dynamometer.²⁶ However, other small studies did not demonstrate improvements of muscle strength.^{24,25}

To improve overall fitness, we targeted flexibility exercises. The participants had modest gains on the sit and reach test with over half of subjects showing substantial improvements. The improvement in passive ankle dorsiflexion was even more impressive with a third improving by more than 100%. These data are in agreement with other small pilot studies demonstrating improvement in passive ankle dorsiflexion³³ and flexibility.³⁰ However, as with muscle strength, results are not consistent across studies, with several showing no differences in flexibility^{24,29} or even worsening over a 2-year intervention period.²² In a study by San Juan et al, although no difference was noted at the end of the 16-week intervention, improvement in passive ankle dorsiflexion was noted at a 20-week post intervention assessment.²⁹

In order to improve motor functioning, our study included several exercises to increase balance. However, the results were modest; only 1 patient had a large improvement (140%). Peripheral neuropathy is a well-described adverse effect of vincristine,^{38,39} a drug universally used during ALL therapy. Forty percent of patients in our pilot had documented neuropathy, which likely mitigated improvements in balance.

We sought to improve general fitness by a range of exercises such as jogging in place, 2-feet hopping, jumping jacks, jump and switch, hopscotch and jump rope. In general fitness, as assessed by the distance covered in the 6MWT, subjects showed a mean improvement of 71 meters, with 75% of subjects demonstrating substantial improvement. This supports findings of Marchese et al in their 16-week exercise intervention, although the differences between intervention and control subjects in their study did not reach statistical significance.³³

CONCLUSION

An important consideration in the design of any study is sustainability and an approach that is amenable to the broader target population. This study is significant in that it creates an exercise plan that can be completed at home without special equipment. The intervention includes the use of a trained exercise coach, familiar with oncology practice and the potential side effects of medications, so that program modifications can be incorporated into the plan when children are receiving chemotherapy agents that make exercise challenging. This was shown to be feasible with preliminary efficacy with a design that can be used across pediatric oncology centers. A larger prospective randomized efficacy study that includes a control group, thus taking into account improved fitness simply as a result of maturation or recovery from illness, is now warranted. Future research should include outcomes such as health-related quality of life and fatigue, which others have shown to be affected by exercise programs.^{27,29,30,33,35,36,40} Given the high prevalence of metabolic

syndrome observed in childhood ALL survivors,^{4,5,41-52} preventive interventions focused on increased physical fitness and maintaining a healthy weight need to be a priority. Effective approaches, initiated during ALL therapy, have the potential to prevent and ameliorate long-term cardiovascular complications that ultimately limit quality and quantity of life in these long-term survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Characteristics of study participants and study measures prior to and after six months of intervention

Sex	Age (years)	Compliance (%)	Body Mass Index Percentile	Knee extension strength (Nm)	Grip Strength (kg)	Sit and Reach (cm)	Passive Ankle Dorsiflexion (degrees)	6 minute walk distance (m)	BOT2-SF* Standard Score
1 Male	9	70.8 Pre-test	97.0	109.5	18.5	0.0	20.5	486.5	46.0
		Post-test	97.0	92.6	25.0	0.0	18.0	373.1	42.0
		Change (%)	0.0 (0.0)	-16.9 (-15.4)	6.5 (35.1)	0.0 (0.0)	-2.5 (-12.2)	-113.4 (-23.3)	-4.0 (-8.7)
2 Male	5	82.3 Pre-test	53.0	68.5	19.0	14.0	16.0	416.9	47.0
		Post-test	63.0	77.1	19.0	14.0	17.0	559.6	46.0
		Change (%)	10.0 (18.9)	8.6 (12.6)	0.0 (0.0)	0.0 (0.0)	1.0 (6.3)	142.7 (34.2)	-1.0 (-2.1)
3 Male	8	78.5 Pre-test	97.0	67.5	20.0	12.0	16.5	312.7	35.0
		Post-test	97.0	103.7	9.0	14.0	13.0	341.0	31.0
		Change (%)	0.0 (0.0)	36.2 (53.6)	-11.0 (-55.0)	2.0 (16.7)	-3.5 (-21.2)	28.3 (9.1)	-4.0 (-11.4)
4 Male	8	78.5 Pre-test	78.0	184.1	13.0	24.5	12.0	515.1	39.0
		Post-test	59.0	188.0	16.0	27.5	17.0	554.7	44.0
		Change (%)	-19.0 (-24.4)	3.9 (2.1)	3.0 (23.1)	3.0 (12.2)	5.0 (41.7)	39.6 (7.7)	5.0 (12.8)
5 Female	8	89.2 Pre-test	64.0	157.3	15.0	21.5	8.0	477.0	38.0
		Post-test	92.0	221.3	13.0	18.5	20.0	598.0	37.0
		Change (%)	28.0 (43.8)	64.0 (40.7)	-2.0 (-13.3)	-3.0 (-14.0)	12.0 (150.0)	121.0 (25.4)	-1.0 (-2.6)
6 Female	7	70.8 Pre-test	3.0	109.0	9.0	21.0	17.0	426.7	47.0
		Post-test	3.0	131.3	10.0	19.0	21.0	566.3	39.0
		Change (%)	0.0 (0.0)	22.3 (20.5)	1.0 (11.1)	-2.0 (-9.5)	4.0 (23.5)	139.6 (32.7)	-8.0 (-17.0)
7 Male	10	80.0 Pre-test	31.0	227.5	18.0	28.0	11.0	524.3	47.0
		Post-test	32.0	287.0	23.0	25.0	18.0	624.5	49.0
		Change (%)	1.0 (3.2)	59.5 (26.2)	5.0 (27.8)	-3.0 (-10.7)	7.0 (63.6)	100.2 (19.1)	2.0 (4.3)
8 Male	5	83.9 Pre-test	95.0	164.3	8.0	11.0	2.5	429.0	56.0
		Post-test	91.0	158.2	12.0	21.0	13.0	558.4	67.0
		Change (%)	-4.0 (-4.2)	-6.1 (-3.7)	4.0 (50.0)	10.0 (90.9)	10.5 (420.0)	129.4 (30.2)	11.0 (19.6)
9 Male	9	87.7 Pre-test	97.0	310.3	16.0	10.0	9.5	554.5	43.0
		Post-test	97.0	343.5	20.5	25.5	12.5	554.1	36.0
		Change (%)	0.0 (0.0)	33.2 (10.7)	4.5 (28.1)	15.5 (155.0)	3.0 (31.6)	-0.4 (-0.1)	-7.0 (-16.3)

Sex	Age (years)	Compliance (%)	Body Mass Index Percentile	Knee extension strength (Nm)	Grip Strength (kg)	Sit and Reach (cm)	Passive Ankle Dorsiflexion (degrees)	6 minute walk distance (m)	BOT2-SF* Standard Score
10 Male	5	76.9	97.0	176.0	9.0	8.5	12.5	415.8	40.0
		Pre-test							
		Post-test		187.5	13.0	29.0	18.0	554.2	96.0
		Change (%)	-36.0	11.5	4.0	20.5	5.5	138.4	56.0
11 Male	8	94.0	85.0	339.1	21.0	25.0	13.0	554.7	50.0
		Pre-test							
		Post-test	77.0	361.6	23.0	30.0	27.0	706.5	63.0
		Change (%)	-8.0	22.5	2.0	5.0	14.0	151.8	13.0
12 Male	5	87.7	83.0	192.1	6.0	29.5	9.0	573.0	56.0
		Pre-test							
		Post-test	61.0	139.2	8.5	31.0	20.0	554.7	56.0
		Change (%)	-22.0	-52.9	2.5	1.5	11.0	-18.3	0.0
Mean change ± SD (Mean % change)			-4.2±16.2	15.5±32.4	1.6±4.6	4.1±7.5	5.6±5.6	71.6±84.0	5.2±17.3
				(11.1)	(16.9)	(42.2)	(81.4)	(16.0)	(12.0)

* BOT2-SF: Bruininks-Oseretsky Test of Motor Performance Version 2, Short Form