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Effects of Physical Therapy Intervention for Children With Acute Lymphoblastic Leukemia

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Background. The purpose of this study was to examine the effects of physical therapy intervention in children with acute lymphoblastic leukemia (ALL). ***Procedure.*** Twenty-eight children aged 4–15 years were randomly assigned to an intervention or control group. The intervention group received five sessions of physical therapy and was instructed to perform an individualized home exercise program consisting of ankle dorsiflexion stretching, lower extremity strengthening, and aerobic exercise. ***Results.*** After 4 months children who received physical therapy intervention had significantly improved ankle dorsiflexion active range of motion and knee extension strength ($P < 0.01$). Differences were not found between the two groups for any of the other dependent variables. ***Conclusions.*** Physical therapy intervention for children with ALL receiving maintenance chemotherapy improved two body functions important for normal gait. Physical therapy programs initiated earlier in treatment and with greater emphasis on endurance activities may also improve stamina and quality of life (QOL). Pediatr Blood Cancer 2004;42:127–133.

Key words: exercise; leukemia; physical therapy

INTRODUCTION

As survival rates have increased for children with acute lymphoblastic leukemia (ALL), there is increasing attention to short-term complications and long-term outcomes from the cancer itself or the antineoplastic agents. Neuromuscular and musculoskeletal complications include pain, paresthesias, reduced deep tendon reflexes, muscle cramps, muscle weakness, reduced ankle dorsiflexion, impaired gross and fine motor performance, decreased energy expenditure, learning disabilities, avascular necrosis, osteopenia, and osteoporosis [1–17]. In a previous pilot study we showed that hand-held dynamometry and timed up and go (TUG), a functional mobility test, were reliable tools to assess strength and functional mobility in children with ALL [18]. Using these tools, we demonstrated that compared to age and gender matched peers, children with ALL were significantly weaker and had decreased functional mobility [18].

Despite documented complications involving range of motion, strength, endurance, and functional activities, there are no studies that evaluate the effects of a comprehensive physical therapy program including strengthening, stretching, aerobic activities and family consultation for children with ALL. Support for such a study comes from Wright et al. [19] who provided educational information regarding the risk for loss of ankle range of motion and the importance of activity and exercise during treatment. If the patients' ankle passive dorsiflexion decreased below 10° as measured with a goniometer an individualized intervention program was provided. This study showed that in children with ALL ankle active dorsiflexion decreased during medical treatment and improved following the completion of treatment [19]. The purpose of the present study is to determine if physical therapy intervention improves strength, range of motion, endurance, and quality of life (QOL) in children receiving maintenance chemotherapy.

MATERIALS AND METHODS

Patients

Children with ALL, 4–18 years of age, receiving maintenance therapy at The Children's Hospital of Philadelphia (CHOP) were eligible for this study. Children with a history of antecedent neurological, developmental,

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or genetic disorders and those currently receiving physical therapy intervention, were excluded. The Institutional Review Boards of CHOP and MCP Hahnemann University approved the study. Approval of physicians, consent from caregivers, and assent from patients were obtained. The children were stratified by their Children's Cancer Group (CCG) standard-risk or high-risk treatment groups and by whether they were in the first or second half of maintenance therapy. Then the primary investigator offered the children an envelope to select assignment into the intervention or control groups.

Instruments

A hand-held dynamometer (Nicholas Model 01160 Lafayette Instruments, P.O. Box 5729/3700 Lafayette, Indiana 47903) was used to measure knee extension strength and ankle dorsiflexion strength [20]. The children's body weight, taken on a standard scale, was used to normalize the strength values. A goniometer was used to measure ankle dorsiflexion active range of motion [21].

The timed up and down stairs (TUDS) test is a measure of the time needed to ascend and descend a set of steps [22]. The TUDS was used to measure functional mobility.

The 9 min run-walk test was used to measure maximal functional capacity and endurance of the cardiorespiratory system [23,24]. The children are instructed to walk or run as far as possible in 9 min with the objective to cover as much distance as possible.

The PedsQL version 3.0 is a health related QOL measure that incorporates a generic core and disease/symptom-specific modular approach for pediatric chronic health conditions [25]. The PedsQL was used in this study to measure QOL in children with ALL.

Procedure

One of two experienced physical therapists unaware of the children's group assignment performed the pre-test assessment and post-test assessment 4 months later. The assessments consisted of ankle dorsiflexion strength, knee extension strength, ankle dorsiflexion active range of motion, TUDS, 9 minute run-walk, and PedsQL measures. Assessments were performed at CHOP, a satellite clinic, or the child's home. Approximately 1 hr was required to perform the assessment.

The same therapist, under the same conditions and at the same location, performed the pre-test and post-test assessments in the same sequence. Knee extension strength was measured with the children positioned in prone with the knee flexed to 90° and the thigh stabilized. Ankle dorsiflexion active range of motion was measured with the children sitting with the knee flexed to 90° and the foot in neutral alignment.

The time it took the children to ascend and descend 12 stairs was measured with a stopwatch. The use of a railing while ascending and descending the stairs was permitted and kept consistent from pre-test to post-test. The distance the children traveled during the 9 min run-walk was measured to the nearest foot with a wheeled counter once the test was completed. The words of encouragement were kept consistent from pre- to post-test. Heart rates were measured before, immediately after, and 10 min after performing the 9 min run-walk test.

The children's hemoglobin levels were obtained from the medical records to observe changes in physiologic stability. The blood test levels were taken within 2 weeks of the pre- and post-test assessment sessions.

To ensure the two raters were consistent with the outcome measures throughout the study, we performed reliability testing on the pre-test measures on the sixth child and the post-test measures on the ninth child.

Intervention Procedures

The intervention program was based on activities the child and family enjoyed, review of the pre-test physical assessment, and observation of the child's mobility, walking, and running. Children in the intervention group received five sessions of physical therapy and participated in an exercise program at home. The five sessions lasted from 20 min to 1 hr and occurred immediately after the initial testing, and 2, 4, 8, and 12 weeks later. The therapist manually stretched and guided the children to assume specific positions to achieve proper body alignment while performing stretching and strengthening exercises. To identify an appropriate intensity and duration, the therapist also observed the children performing an aerobic activity while monitoring heart rate, respiratory rate, and work of breathing. Verbal report of the child's tolerance to exercise was used to modify the child's aerobic program if the exercise was not performed with the physical therapist. The children were given a log to record their exercise program. The therapist also maintained a log documenting the components of each child's intervention session.

Children and parents were also instructed on the performance of an individualized home exercise program. All exercises were functional exercises, that is, activities the children could incorporate into their daily routines based on consultation with parents and children. The program included bilateral ankle dorsiflexion stretching held for 30 sec, 5 days a week, three sets of ten repetitions of bilateral lower extremity strengthening 3 days per week, and aerobic fitness daily for 4 months. Children selected their own aerobic exercise such as walking, biking, or swimming. A written copy of the program with pictures was provided. They were instructed on the use of a Polar Pacer Heart Rate Monitor, (Polar Electro, Inc., 370 Crossways Park Drive, Woodbury NY 11797), to guide the intensity of the activity. Explanations of the contraindications to exercise were reviewed with each child and parent [26].

The control group received no instructions related to physical fitness and did not receive any physical therapy intervention. A consultative session was provided following the post-test assessment.

Data Analysis

Paired *t*-test and chi-square tests were used to compare the demographic characteristics of the intervention and control groups and to compare the mean scores of the patients to normative data for ankle dorsiflexion strength and knee extension strength.

A two-way analysis of variance (ANOVA), 2×2 (group $\times$ time), with repeated measures on the second factor time, was used to measure the effect of physical therapy for each dependent measure i.e., ankle dorsiflexor active range of motion, knee extension and ankle dorsiflexor strength (normalized by patients weight), 9 min run-walk, TUDS, and PedsQL. To determine if the groups differed from pre- to post-test, group by time interaction was examined with an acceptable alpha level of $P < 0.05$. Assumption of normality and homogeneity of variance were met with all dependent variables.

RESULTS

Among the 33 children who met the inclusion criteria, four parents declined participation, and one child was unable to complete the study. The 28 participants had a median age of 7.7 years. Table I shows there were no significant differences in clinical characteristics between the intervention and control group. In neither group did hemoglobin change significantly over the 4 months of the study.

Table II shows the mean outcomes for the control and intervention groups on all dependent variables. Intra-rater and inter-rater reliability for all measures ranged from r = 0.85 to 0.99. The intervention group pre-test median ankle active dorsiflexion range of motion was 6.0° and the range 0–20; the control group median was 10 and the range 2–20°. Children in the intervention group showed significant increases in ankle dorsiflexion active range of motion where the control groups remained stable between pre- and post-test assessments ($P < 0.01$)(Fig. 1). Knee extension strength for the children in the intervention group significantly increased where the control group remained stable from pre- to post-test, ($P < 0.01$) (Fig. 2). Children reported performing the ankle stretching exercise three times a week rather than the recommended five times; lower extremity strengthening exercises were performed three times a week as recommended.

There were no significant differences between groups for ankle dorsiflexion strength, TUDS, 9 min run-walk,

TABLE I. Clinical Characteristics of the Control and Intervention Groups

Group	Control group	Intervention group	*P*
Number of patients	15	13	0.56
Sex M:F	12:3	8:5	0.41
Age	8.3	7.5	
Median			
Mean	8.6	7.6	0.29
Range	5.1–15.8	4.3–10.6	
Time in maintenance			
First*	6	7	0.71
Second*	9	6	
Risk group			
Low	2	0	
Standard	9	10	0.36
High	4	3	

*First indicate the first half of maintenance therapy and second indicate the second half of maintenance therapy.

TABLE II. Pre- and Post-Test Outcomes for Control and Intervention Groups on Dependent Measures

	Control group			Intervention group			
	Pre-test	Post-test	Δ	Pre-test	Post-test	Δ	*P*
Hemoglobin (gm/100 ml)	12.4 ± 1.1	12.7 ± 1.3	+0.3	11.7 ± 1.3	11.7 ± 1.4	0.0	0.65
DAROM (degrees)	10.7 ± 5.6	9.8 ± 5.1	−0.9	8.5 ± 6.7	12.5 ± 6.3	+4.0	<0.01
DS (kg)	0.24 ± 0.1	0.22 ± 0.1	−0.02	0.24 ± 0.1	0.25 ± 0.1	+0.01	0.17
KE* (kg)	0.38 ± 0.1	0.37 ± 0.1	−0.01	0.34 ± 0.2	0.41 ± 0.2	+0.07	<0.01
TUDS (sec)	9.1 ± 3.2	8.6 ± 2.8	−0.5	10.2 ± 2.0	8.9 ± 2.7	−1.3	0.17
Run (ft)	3,323.3 ± 1167.5	3,304.5 ± 1233.0	−18.8	3,267.6 ± 628.4	3,647.2 ± 700.6	+379.6	0.25
Child C.	21.5 ± 11.9	14.53 ± 9.2	−6.97	17.7 ± 11.8	16.4 ± 12.8	−1.3	0.16
Parent C.	25.6 ± 13.4	20.9 ± 13.1	−4.7	25.0 ± 11.9	21.5 ± 14.0	−3.5	0.74
Child G.	21.3 ± 13.4	17.5 ± 10.7	−3.8	14.3 ± 10.2	15.0 ± 9.9	+0.7	0.39
Parent G.	18.2 ± 9.2	20.1 ± 11.5	+1.9	21.2 ± 11.8	16.3 ± 7.9	−4.9	0.07

All numbers except for the Δ=change score, and the *P*-value are mean and ±SD. C., cancer PedsQL; G., general PedsQL, extension; DAROM, dorsiflexion active range of motion; DS, ankle dorsiflexion strength (normalized by patients weight); KE, knee extension strength (normalized by patients weight); TUDS, timed up and down stairs.

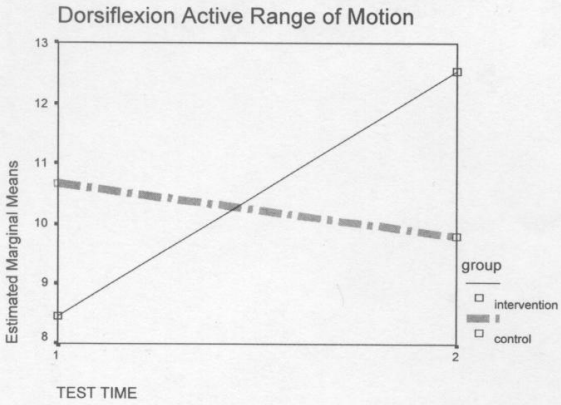

Fig. 1. Mean ankle dorsiflexion active range of motion from pre- to post-test for the intervention and control group.

child cancer PedsQL, child general PedsQL, parent cancer PedsQL, and parent general PedsQL from pre- to post-test. The children's reported frequency of aerobic exercise was daily, but they did not consistently maintain daily logs of activity and did not routinely use the heart monitor because it was inconvenient and uncomfortable.

Ankle dorsiflexion strength for both the intervention and control groups were significantly lower than normative values for healthy children for both the pre- and post-test measures ($P < 0.01$) [27]. Similarly, at pre-test, knee extension strength was significantly lower than the normative values for healthy children, tested in sitting [26] for both the intervention ($P = 0.01$) and control groups ($P = 0.02$). At post-test, knee extension strength for the control group was significantly lower than the normative values ($P < 0.01$), but the intervention group's knee extension strength was within the normal range ($P = 0.06$) (Table III).

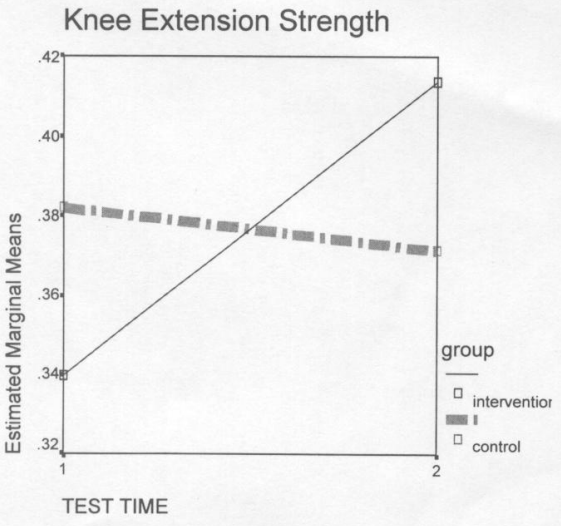

Fig. 2. Mean knee extension strength from pre- to post-test for the intervention and control group.

No child reported any negative effects from the exercises or experienced complications attributed to the physical therapy program. All but two children cooperated and participated in the testing measurements without difficulty. Both exceptions had femoral avascular necrosis that antedated the study. One child was unable to complete the study, as she needed crutches; the other was able to complete the study.

DISCUSSION

Both ankle dorsiflexion range of motion and knee extension strength are important functions for normal gait and navigating stairs. Both functions are impaired in patients with ALL [18,19]. The impairment is multifactorial: vincristine neuropathy, steroid myopathy, osteoporosis, weight gain, and reduced overall activity. In this study, the patients in the intervention group who received physical therapy demonstrated a significant increase in ankle dorsiflexion active range of motion compared with the control group. Normal ankle range of motion is 20° [28]. A patient must have the ability to passively dorsiflex the ankle 10° during the stance phase of gait and actively dorsiflex the foot to neutral (0°) during the swing phase of the gait cycle and up to 20° while ascending stairs [29,30]. The swing phase is the period in which the foot is in the air, prior to foot placement on the ground. Without adequate active ankle dorsiflexion range of motion the patient is going to compensate with other movements and possibly damage the integrity of the ankle structure. Active ankle dorsiflexion range of motion with the knee flexed is important to prevent tripping and falling because the foot must clear the ground when swinging the leg forward while walking and stair climbing. The knee is flexed to approximately 30–60° during the swing phase of the gait cycle and 90–100° during stair climbing prior to the foot placement on the step [29]. The improvement in ankle dorsiflexion active range of motion may be the result of the stretching exercises at least 3 days a week. It is still not known if stretching 5 days a week is better than 3 days per week.

Lower extremity strength is also required to safely ambulate and ascend and descend stairs. Knee extension strength is a key muscle group for both of these activities. During ambulation the knee extensors assist with advancing the lower leg during the swing phase of the gait cycle and as a stabilizer during the stance phase. Knee extension strength is critical when ascending and descending stairs to advance the body up onto a stair and to control the body during descent. Patients with ALL often have decreased proximal muscle strength due to taking corticosteroids and

TABLE III. Comparison Between Control and Intervention Groups Knee Extension Strength to Normative Values

Control group pre-test knee extension strength	Control group post-test knee extension strength	Normative values pre-test for the control group	Normative values post-test for the control group	Intervention group pre-test knee extension strength	Intervention group post-test knee extension strength	Normative values pre-test for the intervention group	Normative values post-test for the intervention group
212	176	139 ± 20	198 ± 42	90	117	120 ± 18	120 ± 18
105	128	139 ± 20	139 ± 20	45	65	139 ± 20	139 ± 20
125	159	211 ± 34	211 ± 34	157	240	181 ± 46	181 ± 46
157	77	139 ± 20	139 ± 20	91	114	136 ± 32	136 ± 32
64	65	120 ± 18	120 ± 18	53	51	119 ± 24	119 ± 24
128	139	139 ± 20	139 ± 20	26	90	120 ± 18	120 ± 18
49	56	119 ± 24	119 ± 24	164	188	119 ± 24	119 ± 24
241	219	211 ± 34	211 ± 34	159	154	136 ± 32	136 ± 32
230	226	296 ± 59	296 ± 59	50	57	139 ± 20	139 ± 20
95	122	120 ± 18	120 ± 18	117	137	139 ± 20	198 ± 42
45	45	120 ± 18	120 ± 18	61	79	120 ± 18	120 ± 18
59	74	119 ± 24	119 ± 24	49	91	198 ± 42	198 ± 42
111	106	136 ± 32	136 ± 32	34	34	91 ± 23	91 ± 23
110	117	120 ± 18	139 ± 20				
35	31	91 ± 23	91 ± 23				

All values are in newtons (N), normative values [27].

decreased activity. The patients in the intervention group demonstrated a significant increase in knee extension strength compared with the control group. However, the clinical meaningfulness of this gain is not known.

The lower extremity exercises that the intervention group integrated into their daily routine were performed by using the child's own body weight and gravity as the only resistance. The functional lower extremity strengthening program performed three times a week by the children was effective in significantly increasing knee extension strength. Hence the type and intensity of exercise chosen for strengthening knee extension was beneficial without the use of a weight-training program.

Significant findings were not identified in our study in the 9 min run-walk possibly because there was such a large standard deviation and a small sample size. The results may also reflect the wide range of endurance abilities in children with ALL or the level of training intensity may not have been high enough or adequately controlled considering the children did not wear the heart rate monitors. In addition, the intervention and control groups' activity levels were similar throughout the 4 month testing period. Thus the changes in ankle dorsiflexion active range of motion and knee extension strength can be attributed to the specific stretching and strengthening exercises versus the amount of aerobic activity the patients performed.

At post-test both the intervention and control groups were asked questions to document the types of activities performed during leisure and while at school. Eighty-two percent of the children in this study reported participating in gym class in school. Participation in routine aerobic activities, such as bike riding, swimming, and dancing ranged from once a week to daily in both the intervention and control groups. The intervention group was instructed to perform an aerobic activity each day as part of this study. The frequency for the intervention group's aerobic exercise program was reportedly performed on average 4 days per week, but this may not have been different than the usual physical activity reported by both groups. The control group did not receive any counseling about fitness or activity prior to or during the study by either the physical therapist at CHOP or others outside the hospital.

The children in the control group did not receive physical therapy intervention and did not have a significant increase or decrease in their abilities. Suggesting that during the maintenance phase of medical treatments, children with ALL do not improve or decrease motor and functional abilities possibly because the medical intervention is not as aggressive as it was in the previous months, thus allowing the children to enjoy more activity. This play time may be increased from previous months but by itself does not appear enough to significantly improve specific motor abilities such as ankle active dorsiflexion range of motion, knee extension strength or functional endurance.

The majority of children in this study scored within a poor range of exercise endurance ability, as measured by the 9 min run-walk, compared to normative data. More than 50% of all the children in the study, during pre- and post-test scored below the 25th percentile of the normative sample in the American Alliance for Health, Physical Education, Recreation and Dance Association Guidelines [23]. The association recommends a remedial individualized fitness program for all students who score below the 25th percentile [23]. Even though the children reported participating in many activities, several parents reported their children did not participate at their pre-treatment level of intensity or duration. The reason for the patients'

poor performance is not known but deconditioning is a possibility. The children while performing their activities may not be "exercising" at a high enough level to improve their endurance because in our study range of motion and strength improved but this did not impact their endurance. Thus, children may require more direct intervention to achieve significant gains in the area of endurance.

Health related QOL was measured in this study with the PedsQL. However, this tool did not reflect changes in health-related QOL for the children who received physical therapy. A ceiling effect had already occurred at pre-test with the majority of children and parents in this study reporting almost never to never having problems with the items on the PedsQL. The questions were asked in relation to the child and parent's perception of the frequency the child experienced problems, not how the child and parent perceived the quality in which the child performed the activities. A recommended alternative to the PedsQL is individualized outcomes for participation using goal attainment scaling [31]. Additionally, the study was not powered to detect a difference in QOL.

The results of this study provide direction for physical therapy service delivery for children with ALL. Some, but not all children with ALL have body function impairments, activity limitations, and participation restrictions. Hence, some children may require physical therapy with a greater frequency than proposed in this study and some children may not need therapy at all. All children would benefit from a comprehensive neuromuscular and musculoskeletal examination from a physical therapist knowledgeable in the subtleties that this specific patient population experiences. Prevention is the ultimate goal thus requiring timely referral and an intervention program the children and families will embrace.

This study presents a program of physical therapy intervention for children with ALL who were receiving chemotherapy. It showed that the intervention affected improvements in impairments of important body functions, specifically knee extension strength and ankle dorsiflexion active range of motion, a common impairment as a result of vincristine therapy. The results support structured physical therapy intervention. Future studies should address the following: (1) efficacy of physical therapy on children with ALL earlier in their treatment, (2) programs for a younger age group, (3) alternative means for measuring exercise intensity, (4) impact on quality of gait and running style, (5) increased frequency and intensity of intervention on activity and a greater emphasis on a child's participation in normal daily activities.

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