Benefits of Intrahospital Exercise Training after Pediatric Bone Marrow Transplantation

A. F. San Juan¹, C. Chamorro-Viña¹, S. Moral¹, M. Fernández del Valle¹, L. Madero², M. Ramírez¹, M. Pérez¹, A. Lucia¹

Affiliations
1 Department of Physiology, Universidad Europea de Madrid, Madrid, Spain
2 Department of Hematology and Bone Marrow Transplantation, Children’s Hospital Niño Jesús, Madrid, Spain

Abstract
The purpose of this study was to determine if an eight-week intrahospital supervised, conditioning program improves functional capacity and quality of life (QOL) in children (4 boys, 4 girls) (mean [SD] age: 10.9 [2.8] years [range: 8 – 16]) who have undergone bone marrow transplantation (BMT) for leukemia treatment within the last 12 months. A group of 8 age and gender-matched healthy children served as controls. The experimental group performed 3 weekly sessions of resistance and aerobic training inside an intrahospital gymnasium. A significant combined effect of group and time (p < 0.05) was observed for muscle functional capacity (Timed Up and Down Stairs [TUDS] test) and peak oxygen uptake (VO₂peak), i.e., with BMT children showing greater improvements than controls (VO₂peak at pre- and post-training of 25.9 (8.2) and 31.1 (7.6) mL/kg/min in diseased children). Muscle strength (6 RM test for bench and leg press and seated row) also improved after training (p < 0.05) in the BMT group. Concerning QOL, a significant combined effect of group and time (p < 0.05) was also observed for children’s self-report of comfort and resilience and for parents’ report of their children’s satisfaction and achievement. In summary, children who have received BMT experience physical and overall health benefits after a relatively short-term (8 weeks) supervised exercise training program.

Introduction
Bone marrow transplantation (BMT) following a high dose of chemotherapy is a potentially curative treatment for patients with severe hematological disorders, e.g., leukemia. This therapeutic tool is, however, associated with several transplant-related toxicities (particularly, altered cardiorespiratory function) which compromise full rehabilitation and result in early fatigue during physical activities of daily living and decreased quality of life (QOL) [3]. In survivors of childhood leukemia, BMT is associated with marked decreases in peak oxygen uptake (VO₂peak), a widely accepted index of functional capacity, health status and survival rate [20]. Previous reports have shown the benefits of exercise training in the physical capacity and overall health status of adults who have undergone BMT [5, 7 – 9, 29]. Considerably less research efforts have focused on pediatric populations receiving the same medical treatment. We recently reported positive results on very young children (≤ 7 years) in the last phase of treatment against leukemia (without BMT) who performed a supervised, intrahospital training program combining resistance and aerobic exercises [37, 38]. However, no study has specifically assessed the cardiopulmonary and neuromuscular effects of this type of intervention in children receiving BMT for leukemia treatment.

It was therefore the purpose of the present study to determine if an 8-week intrahospital supervised, conditioning program including both resistance and aerobic exercises [37, 38] and what is known to occur in healthy children [11 – 13, 32], we hypothesized that this type of program would have beneficial results and thus would be of clinical relevance.
Material and Methods

Patients
Before entering the study, informed consent was obtained from each participant’s parents and the study was approved by the local Human Investigations Committee and Review Board. A preliminary screening for subject selection was performed in the medical database of the Onco-Hematology Department at Children’s Hospital Universitario Niño Jesús (Madrid, Spain). A total of 40 medical records of children survivors of leukemia who had undergone BMT in the aforementioned hospital were examined. After the oncologist treating each patient provided consent, subjects were deemed eligible for the study if they met each of the following conditions: 1) survivors of childhood leukemia with time elapsed after BMT ≤ 12 months; 2) 8 – 16 yrs of age; 3) having no condition that could contraindicate vigorous physical activity, such as severe anemia (hemoglobin <8 g/dL), fever > 38 °C, or severe cachexia (loss of >35% premorbid body mass), platelet count lower than 50 × 10^9/µL, neutrophil count lower than 0.5 × 10^9/µL or anthracycline-induced cardiotoxicity [23]; 4) currently living with their parents in Madrid (Spain); and 5) having not participated in any type of exercise training program prior to the study.

Eight children (4 boys, 4 girls; age: 10.9 ± 2.8 [mean ± SD] years; height: 135.5 ± 25.6 cm; time post-transplantation: 8.9 ± 4.5 months [range: 2 – 12]) met all the abovementioned eligibility criteria and were included in the study. Their Tanner’s stage of maturation was I (n = 3), II (n = 3), III (n = 1) and IV (n = 1). Four children were survivors of acute lymphoblastic leukemia and four of acute myeloid leukemia. They had received haploidentical (n = 4) or allogeneic BMT (n = 4). Children with allogeneic BMT received daily immunosuppressive therapy (corticosteroids [6-metil-prednisolone] in three patients and mycophenolate in one patient) throughout the entire training period (see below) for the treatment of graft-versus-host disease. The latter is a multiorgan inflammation (e.g., scleroderma, esophagitis, biliary cirrhosis, sicca syndrome, polymyositis) that develops after allogeneic BMT [39]. One girl was also receiving treatment against osteopenia (calcium + estrogens).

A group of eight, nonathletic healthy children matched for age and gender (4 boys, 4 girls; age: 10.9 ± 2.6 years; height: 138.8 ± 16.4 cm) were selected as study controls. All lived with their parents in Madrid and had a socioeconomic status similar to the BMT group, i.e., they lived in the same part (~400 000 inhabitants) of Madrid (total population of 3.2 million).

Study protocol
The patients performed the same battery of tests (treadmill exercise, muscular strength [6 RM], functional mobility, passive and dynamic ankle range of motion and QOL questionnaires) before and after the exercise training program that is described below. For ethical and logistic reasons (particularly, long duration of the familiarization period inside an intrahospital setting), healthy controls only performed the tests in the Exercise Physiology Laboratory outside the Hospital (see below).

Setting
An intrahospital gymnasium designed to be used by children during anticancer treatment (Children’s Hospital Niño Jesús of Madrid, Department of Onco-Hematology and Bone Marrow Transplantation) [23] was the site where all training sessions, dynamic strength tests and Time Up and Go 3- and 10-m tests were performed (see below). Among other equipment, the intra-hospital gymnasium includes pediatric (specifically built for the body size of children) weight training machines (Strive Inc., Canonsburg, PA, USA) and bicycle ergometers (Rhyo Magnetic H490, BH Fitness Proaction, Vitoria, Spain). Treadmill tests, Timed Up and Down Stairs test and evaluation of passive and dynamic ankle range of motion (see below) were performed by all participants (patients + controls) in a University setting outside the Hospital (Exercise Physiology Laboratory and Facilities). Questionnaires on QOL were also administered to all subjects outside the Hospital.

Measurements at pre- and post-training
All children consumed their usual breakfast (cereals, milk and fruit juice) three hours before the test protocols described below. All performed a graded exercise test on a treadmill (Technogym Run Race 1400 HC; Technogym, Gambettola, Italy) for the determination of VO2peak and ventilatory threshold (VT). Each child performed at least one familiarization session prior to the actual treadmill test. Treadmill speed began at 1.0 km·h⁻¹ (or 1.5 km·h⁻¹ for the oldest participants) with a grade of 5.0%. Thereafter both treadmill speed and inclination were increased (by 0.1 km·h⁻¹ and 0.5%, respectively) every 15 s. Tests were terminated upon volitional fatigue of the children and/or when they showed loss of ability to maintain the required workload. During the tests, the children could not see their parents, but were given verbal encouragement by the investigators. Gas-exchange data were measured breath-by-breath using open circuit spirometry and specific pediatric face masks (Vmax 29C, Sensormedics, Yorba Linda, CA, USA). VO2peak and peak heart rate (HRpeak) were recorded as the highest value obtained for any continuous 20-second period [38]. The VO2 (ml·kg⁻¹·min⁻¹) at the VT was determined using the criteria of an increase in both the ventilatory equivalent of oxygen (VE·VO2⁻¹) and end-tidal pressure of oxygen (PetO2) with no increase in the ventilatory equivalent of carbon dioxide (VE·VCO2⁻¹) [38].

All treadmill tests were performed under similar environmental conditions (20 to 24°C, 45 to 55% relative humidity) and at the same time of the day (10:00 a.m. – 1:00 p.m.). Heart rate (HR) was continuously monitored during the tests from a twelve lead ECG (Quest Exercise Stress System, Burdick Inc., Milton, WI, USA).

In order to minimize the influence of a possible learning effect on strength tests (due to improvement of technique and coordination and/or diminishment of muscle inhibition) and thus to stabilize the initial test results, before the start of the study, all patients underwent a familiarization period. The familiarization period consisted of three 60-min sessions/week for a total of two weeks. Each session was preceded by a warm-up and ended with a cool-down of the same activities and duration used during the training period of the study. The body of each familiarization session consisted of two – three sets of one – three repetitions of the exercises (seated bench press, seated lateral row, seated leg press) used to evaluate muscular strength. Children were also familiarized (i.e., two – three repetitions) with the tests used to evaluate functional mobility (Time Up and Down Stairs test and 3- and 10-m Time Up and Go tests).
that are described below. Thus, any potential learning effect on the results of the variables determined should be minimal. Dynamic upper and lower-body muscle strength endurance were measured using a seated bench, seated lateral row, and seated leg-press machine (Strive Inc.), respectively. The six repetition maximum (6 RM) value was measured in kg and is described as the maximum strength capacity to perform six repetitions until momentary muscular exhaustion. The testing protocol consisted of three warm-up sets at 50, 70 and 90% of the perceived 6 RM separated by one-minute rest periods [21]. A two-minute rest period followed the last warm-up set after which a 6 RM attempt was made at 100–105% of perceived 6 RM depending upon the effort needed to perform the last warm-up set at 90% of the perceived 6 RM. If the first 6 RM attempt was successful, the resistance was increased 2.5–5% and after two minutes of rest, another 6 RM attempt made. If the second 6 RM attempt was successful, a second testing session was scheduled after 24 hours of rest. If the first 6 RM attempt was not successful, the resistance was decreased 2.5–5% and after 2 minutes of rest, another 6 RM attempt made. If the second 6 RM attempt was successful, the weight used was considered the 6 RM. If the second 6 RM attempt was not successful, another testing session was scheduled after 24 hours of rest. Each subject was instructed to perform each exercise to momentary muscular exhaustion. Any repetitions not performed with a full range of motion were not counted. To measure children’s functional mobility, we used the Time Up and Go (TUG) tests of 3- and 10 m and the Timed Up and Down Stairs (TUDS) test [15]. Both types of tests have been shown reliable and valid in healthy children and also in children with various diseases or disabilities [15,27]. The TUG tests of 3- and 10 m are measures of the time needed to stand up from a seated position in a chair, walk 3 and 10 m respectively, turn around, return to the chair, and sit down. For the TUDS test, the time it took to ascend and descend 12 stairs was measured [15]. All the children used a hand railing in the tests. The use of a railing while ascending and descending the stairs was allowed to diminish the risk of falling. Performance time in all the tests was measured by the same investigator with the same stopwatch to the nearest 0.1 s. A goniometer was used to measure ankle dorsiflexion passive and active range of motion (ROM). Ankle dorsiflexion passive (passive DF-ROM) and active (active DF-ROM) range of motion was measured with the children sitting with the knee flexed to 90° and the foot in neutral alignment [33]. The QOL of the children was assessed with the Child Report Form of the Child’s Health and Illness Profile-Child Edition (CHIP-CE/CRF) and Adolescent Edition (CHP-PE/AE), which is a self-report health status instrument for children [34,35] and of their parents rating of their children’s QOL [36]. The CHIP-CE/CRF includes five domains: Satisfaction (with self and health), Comfort (concerning emotional and physical symptoms and limitations), Resilience (positive activities that promote health), Risk Avoidance (risks behaviors that influence future health), and Achievement (social expectations in school and with peers). In our study, after obtaining permission from the authors and the corresponding institution (see Acknowledgements section), we used the Spanish version of the CHIP-CE and CHIP-AE, which has been shown to be valid in Spanish children [34]. Training intervention – exercise program All children in the BMT group followed an 8-week training program, consisting of three weekly sessions with a duration ranging from 90 min (in the first few weeks of the program) to 120 min (by the end of the program). The program was individually supervised (i.e., one instructor for every two children). A pediatrician was also present at each of the training sessions. Each session started and ended with a low intensity 15-min warm-up and cool-down period, respectively, consisting of cycle ergometer pedalling at very light workloads and stretching exercises involving all major muscle groups. The core portion of the training session was divided into strength and aerobic exercises. Strength training included 11 exercises engaging the major muscle groups (bench press, shoulder press, leg extension, press, leg curl, abdominal crunch, low back extension, arm curl, elbow extension, seated row, and lateral pull-down). For each exercise, the children performed one set of eight to 15 repetitions (total of ~ 20 s duration). Rest periods of one – two min separated the exercises. Stretching exercises of the muscles involved in the previous exercise were performed during the rest periods between exercises [1]. The load was gradually increased as the strength of each child improved. Aerobic exercises consisted of pedalling on a cycle ergometer, running, walking and “aerobic games” involving large muscle groups, i.e., jumping exercises, ball games, group games, etc. Aerobic and group games were necessary to maintain and improve the children’s adherence to the training program, i.e., by making every session different, the children’s compliance and retention of subjects was maintained. The duration and intensity of the aerobic training was gradually increased over the training period so that the subjects started with at least 10 min of aerobic exercises at 50% age-predicted maximum heart rate (HR max estimated as 220 – age) and progressed to at least 30 min of continuous exercise at ≥ 70% HR max by the end of the program. All children wore a portable HR monitor during the sessions to monitor their exercise intensity. Each child was evaluated by his/her oncologist every two weeks during the training period. These examinations included a thorough physical examination, complete hematological and biochemical blood analysis. All the children and their parents were instructed to follow the children’s usual nutritional habits throughout both the familiarization and training period. None of the children were taking any nutritional supplement during the entire duration of the project. Data analysis Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, USA). Mean values of all the variables at baseline were compared between both groups using independent t-tests (for parametric data) or Mann-Whitney U tests (for categorical data, i.e., QOL). In order to evaluate the combined effect of group and time in body mass, cardiorespiratory indices (VO2peak, HRpeak and VT), TUDS test and active and passive dorsiflexion, independent t-tests were used to compare the change in mean values over time (post-intervention minus pre-intervention) in training (BMT) and control groups. For the same purpose, the mean change over time (post-intervention minus pre-intervention) in BMT vs. control groups in QOL was compared using the Mann-Whitney U test. We have used the same statistical approach, which allows to minimize the risks of multiplicity of statistical analyses (and thus of having a p value < 0.05 due to chance alone) in previous training research on cancer survivors [17]. For those variables that were only measured in the BMT group (i.e., results of strength and TUG tests), we compared pre- vs. post-training values using paired t-tests. The level of signifi-
cance was set at 0.05 for all statistical analyses and results are expressed as mean ± SD.

Results

Body mass did not differ between groups at pre- (BMT: 33.5 ± 13.5 kg; controls: 32.5 ± 13.2 kg) or post-training (BMT: 34.2 ± 15.1 kg; controls: 35.8 ± 11.4 kg). No significant changes were observed over time in body mass within each group.

Adherence to training was above 70% in seven children, who had no health problem over the training period. Their hematological and biochemical blood parameters remained within normal limits and physical examinations revealed no abnormality. One child had some major health problems (pulmonary infection), which decreased her adherence to 50%.

Performance in the TUDS test at baseline was significantly lower in BMT children compared to controls (p < 0.05) although no difference was found for active or passive DF-ROM (Fig. 1). A significant combined effect of group and time was observed for the TUDS test (p < 0.05) whereas passive and active DF-ROM did not significantly improve over the study period in the training (BMT) group compared with healthy controls (p > 0.05) (Fig. 1).

Performance in the TUG tests significantly improved after training in the BMT group (p < 0.05) (Figs. 2 and 3). Mean values of VO2peak and VT at baseline were significantly lower in BMT children compared with controls (p > 0.05) (Figs. 2 and 3). A significant combined effect of group and time (p < 0.05) was found for VO2peak (mL/kg/min) whereas no change was observed in VT over the study period in the training (BMT) group compared with healthy controls (p > 0.05). No difference existed in HRpeak at baseline (p > 0.05) and no combined effect of group and time (p > 0.05) was found for this variable (Figs. 2 and 3).

Thus, the aforementioned improvement in VO2peak was solely attributable to the training program and not to possible differences in the effort level provided by the children before and after training.

A significant combined effect of group and time (p < 0.05) was observed for children’s self-report of comfort and resilience.
Discussion

Our study shows for the first time that a relatively short-length duration (8 weeks) intrahospital structured, supervised training program combining cardiorespiratory and resistance exercises positively affects changes in VO\textsubscript{2peak}, muscle strength, functional mobility and QOL in young children (< 16 yrs) survivors of leukemia who have recently undergone BMT for leukemia treatment. Many of these patients also receive aggressive immunosuppressive therapy after BMT (i.e., daily corticosteroids) for the prevention/treatment of graft-versus-host disease, a multiorgan inflammation that occurs after allogeneic BMT [39]. Our preliminary findings suggest that this subpopulation can safely undergo this type of supervised training in other hospitals of the world. Our findings are of special relevance given i) the frequent several transplant-related toxicities (e.g., altered cardiorespiratory function or graft-versus-host disease), which compromise full rehabilitation and result in early fatigue during physical activities of daily living [3, 41], and ii) the deleterious effects of immunosuppressive therapy associated with BMT (especially, aggressive corticosteroid therapy) on the ultrastructure and function of skeletal muscles, including declined myofibrillar mass, altered aerobic metabolism (due to decreased mitochondrial volume and/or mitochondrial myopathy), or reduced capillarization [18].

One potential limitation of our study comes from the fact that some degree of spontaneous improvement in children's fitness levels is to be expected after a certain period of time (e.g., a few months) has elapsed following BMT. This would artificially inflate the improvements we observed in their exercise capacity after the training program. The aforementioned limitation was minimized by the fact that the duration of post-transplant time did not surpass 12 months in our patients. Such a period of time

Table 1

<table>
<thead>
<tr>
<th>Domain</th>
<th>BMT Group</th>
<th>Control Group</th>
<th>Overall change in means</th>
<th>95 % CI for overall change in means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction</td>
<td>3.5 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 0.4</td>
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<tr>
<td>Comfort</td>
<td>3.8 ± 0.5</td>
<td>4.4 ± 0.6</td>
<td>4.6 ± 0.2</td>
<td>4.5 ± 0.2</td>
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<tr>
<td>Resilience</td>
<td>3.0 ± 0.6</td>
<td>3.4 ± 0.4</td>
<td>4.1 ± 0.3</td>
<td>3.9 ± 0.3</td>
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<tr>
<td>Risk avoidance</td>
<td>4.1 ± 0.3</td>
<td>4.2 ± 0.2</td>
<td>4.2 ± 0.4</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>Achievement</td>
<td>2.7 ± 1.0</td>
<td>2.5 ± 0.7</td>
<td>3.6 ± 0.4</td>
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</tbody>
</table>

Abbreviations: Pre (before intervention period), Post (after the intervention period), *Overall change in means* is the change (post minus pre means) for the training (BMT) group minus the change (post minus pre means) for the control group. Symbol: * p < 0.05 for the combined effect of group and time.

Table 2

<table>
<thead>
<tr>
<th>Domain</th>
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<th>Control Group</th>
<th>Overall change in means</th>
<th>95 % CI for overall change in means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction</td>
<td>3.4 ± 1.0</td>
<td>3.7 ± 1.0</td>
<td>4.0 ± 0.3</td>
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<tr>
<td>Comfort</td>
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<td>3.7 ± 0.8</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
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<tr>
<td>Resilience</td>
<td>3.6 ± 0.6</td>
<td>3.7 ± 0.6</td>
<td>3.8 ± 0.2</td>
<td>3.8 ± 0.2</td>
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<tr>
<td>Risk avoidance</td>
<td>4.1 ± 0.4</td>
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<td>3.9 ± 0.6</td>
<td>3.9 ± 0.5</td>
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<tr>
<td>Achievement</td>
<td>3.3 ± 0.9</td>
<td>3.7 ± 0.9</td>
<td>3.7 ± 0.2</td>
<td>3.7 ± 0.2</td>
</tr>
</tbody>
</table>

Abbreviations: Pre (before intervention period), Post (after the intervention period), *Overall change in means* is the change (post minus pre means) for the training (BMT) group minus the change (post minus pre means) for the control group. Symbol: * p < 0.05 for the combined effect of group and time.
is not long enough to allow for a total disappearance of post-transplant complications. For instance, lung function (i.e., lung volume and gas diffusion capacity) is still impaired, at least partly, one year after transplantation [24] and a total of 2 years might be necessary before lung complications totally disappear [14]. Cardiac abnormalities can persist for as long as – 3 years post-BMT [10]. In fact, the VO_2peak of BMT recipients is still decreased (i.e., 69% of predicted) at 6 years after transplantation [19].

The pre-training values of VO_2peak and VT of our patients (~26 mL O_2/kg/min and –18 mL O_2/kg/min, respectively) were clearly below those of the control group and also below the expected values for healthy children of the same age range, i.e., VO_2peak ~40 – 45 mL/kg/min [2] and VT > 25 mL/kg/min [4, 16, 25, 26] and similar to those previously reported in the same type of diseased population [10, 19, 20, 22]. After completion of the training program, patients’ VO_2peak values significantly improved, i.e., mean change of +5.2 mL/kg/min. Such a finding is of clinical significance as VO_2peak is an excellent indicator of health status and an independent predictor of mortality, i.e., an increase of only 3.5 mL/kg/min is associated with a 12% increase in survival rate in both healthy and diseased adults [31]. Of especial relevance was the fact that the aforementioned improvement in VO_2peak was obtained despite a relatively low adherence to training (~70%), i.e., considerably lower than that (>85%) reported by our group in children who had not received BMT and were training while undergoing maintenance treatment against leukemia (with a final improvement in their VO_2peak of +6 mL/kg/min) [38]. On the other hand, our findings are in agreement with previous studies on adult patients who had undergone BMT and gained significant improvements in their fitness level after aerobic [7] or strength exercise training [9].

The VT values in our patients (~18 mL·kg⁻¹·L⁻¹) were considerably lower than those previously reported in survivors of leukemia <13 years of age, i.e., ~24 mL/kg/mL [36]. The VT is a health indicator in diseased populations [30]. Exercise-induced improvements in this variable result in attenuation of breathlessness, improved exercise capacity at submaximal levels, and contribute to the well-being of patients during their daily activities [30]. Although we have previously observed improvements in the VT values of children with leukemia (not receiving BMT), after 16 weeks of supervised exercise training [38], in the present study, VT did not significantly improve after an 8-week training program. One potential explanation for the lack of improvement in patients’ VT might lie on the fact that an important amount of their endurance training was performed at intensities >70% HRmax whereas their VT corresponded to >60% HRmax. Longer (and possibly less intense) training programs and/or higher adherence to training would seem necessary to elicit significant gains in this variable.

Dynamic upper and lower-body muscle strength improved with training. The strength levels of our subjects are difficult to compare with those of other diseased children as muscle strength is not commonly measured in diseased children, included children who have undergone BMT, despite the importance of this variable. The pre-training strength values of our patients (aged 8–16 yrs) were higher than those reported by us using the same equipment and tests in children undergoing maintenance chemotherapy against leukemia [38]. Such a difference might be attributable to the higher age (and thus different maturity status) of the present subjects. The strength gains obtained in our patients after completing the 8-week training program (seated bench press: ~8%; seated row: ~18%; leg press: ~11%) were overall lower than those we previously reported in younger (<7 yrs) children with leukemia with a training intervention of the same duration (seated bench press: ~20%; seated row: ~20%; leg press ~9%) [37]. Such a difference may be attributed, at least partly, to the lower adherence to the training program in the present subjects (~70% vs. >85% in younger children with leukemia [37]). We chose to assess dynamic muscle strength endurance (six repetition maximum, 6 RM) instead of maximal dynamic strength (one repetition maximum, 1 RM) in order to obtain results of practical relevance for children, in whom maximal strength is not a main determinant of their ability to perform physical activities of daily living, which are mostly submaximal-strength tasks, e.g., climbing stairs, sitting and rising from a chair, outdoor activities, etc.

In line with previous research of younger children with leukemia [37, 38] we also found significant training-induced improvements in the TUDS, TUG-3-m and 10-m tests after the exercise program intervention, indicating a significant gain in muscle functional capacity and in tasks of daily living. On the other hand, passive and active DF-ROM did not significantly improve with training. This finding is in agreement with previous research on children with leukemia [38], though Marchese et al. [27] reported improvements in active DF-ROM after a 16-week physical therapy protocol. As opposed to the very low pre-training values of VO_2peak or muscle strength, the patients in the present study had sufficient DF-ROM at baseline for sustaining normal activities of daily living, such as normal gait patterns [42].

We found significant improvements in some of the main items of the children’s (comfort and resilience) and parents’ self-reported QOL (satisfaction and achievement) after the training intervention. This result is in apparent disagreement with previous research on younger children with leukemia showing a nonsignificant trend towards an improvement in QOL [27, 38]. Such lack of significance was attributed to a certain “ceiling effect” during the pre-training questionnaire, with the majority of children and parents minimizing their actual QOL problems before the training intervention, i.e., reporting having no problems with the items on the questionnaire (health status, satisfaction, etc.). The older age and maturity status of the present subjects might contribute to a more objective evaluation of their QOL before engaging the training program and thus to prevent the aforementioned “ceiling effect” that would minimize actual improvements in QOL.

Our findings do also emphasise the need for performing individualized, supervised training for children with leukemia, preferably in a hospital setting. Marchese et al. [27] studied the effect of a 16-wk physical therapy intervention program in children with leukemia combined with home-based exercises (aerobic training, stretching exercises). No significant improvements in indirectly estimated aerobic capacity (i.e., 9-min run-walk test) and functional mobility (i.e., TUDS test) were observed after this intervention. In contrast, our supervised intrahospital training program including both aerobic and strength training did induce significant improvements in directly measured maximal aerobic capacity (VO_2peak), muscle strength endurance and functional mobility (TUDS, TUG-3-m, TUG-10-m), suggesting the need for performing individually supervised training programs as the one used here (i.e., one instructor for every two children) instead of home-based training. The need for an individually supervised program to bring about maximal fitness gains is supported by...
previous research showing that an individually supervised strength training program results in significantly greater strength gains than a program involving instruction, but having the subjects perform the training on their own [28]. In summary, although more research using larger population groups is necessary to corroborate our preliminary findings, young children (8–16 years) who have recently (≤ 12 months) undergone bone marrow transplantation for the treatment of leukemia can safely undergo an in-hospital supervised, super- vised conditioning program. This program should include both aerobic and resistance exercise training to induce significant health benefits (improved aerobic fitness, muscle strength, functional mobility and important aspects of QOL) in only 8 weeks.

Acknowledgements

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