Functional Capacity of Children with Leukemia

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Abstract

The purpose of this study was to determine if the functional capacity and quality of life of children receiving treatment against acute lymphoblastic leukemia (ALL) is decreased compared to healthy age and gender-matched children. Functional capacity was assessed with a number of measurements as the peak oxygen uptake (V˙O2peak) and ventilatory threshold determined during a ramp treadmill test, functional mobility (Timed Up and Down Stairs test [TUDS]) and ankle dorsiflexion passive and active range of motion (passive and active DF-ROM, respectively). Quality of life (QOL) was determined with the Spanish version of the Child Report Form of the Child Health and Illness Profile-Child Edition (CHIP-CE/CRF). Fifteen children (9 boys, 6 girls; mean [SD] age: 6.8 ± 3.1 years) receiving maintenance therapy against ALL were studied and fifteen, nonathletic healthy children (9 boys, 6 girls; 6.9 ± 3.3 years) were selected as controls. The mean values of V˙O2peak and active DF-ROM were significantly (p < 0.05) lower in patients (25.3 ± 6.5 ml·kg−1·min−1 vs. 31.9 ± 6.8 ml·kg−1·min−1 in controls and 19.6 ± 8.0° vs. 24.1 ± 5.0°, respectively). Children’s self report of satisfaction (with self and health) (p < 0.05), comfort (concerning emotional and physical symptoms and limitations) (p < 0.01) and resilience (positive activities that promote health) (p < 0.01) were significantly decreased in patients with ALL. In summary, children receiving treatment against ALL have overall lower functional capacity and QOL than healthy children. However, their physical condition and health status are sufficiently high to allow them to participate in physical activities and supervised exercise programs.

Introduction

Previous research has shown that adult cancer patients and/or survivors commonly exhibit poor physical capacity, i.e., peak oxygen uptake (VO2peak) levels considerably lower (~ 50%) than predicted, which reflects, at least partly, the sedentary lifestyle habits of this population group [11]. Less research has focused on the physical capacity (e.g., expressed as VO2peak) of children with cancer. This is, however, an important topic given that outdoor physical activities play an important role in the daily routine of children; thus, impaired physical capacity can have a direct detrimental effect on their quality of life (QOL) [11]. Decreased QOL associated to a poor functional capacity has indeed been reported in survivors (i.e., who have successfully completed treatment) of childhood cancer, a fact that is attributable to various mechanisms related to the side effects of treatment as musculoskeletal and neuro-muscular complications, anthracycline-induced cardiotoxicity, sarcopenia and muscle weakness, or reduced ankle range of motion [12]. To the best of our knowledge, however, little research is available on the exercise capacity (i.e., VO2peak) of children during treatment against cancer. Thus, it would be interesting to assess if functional capacity is also significantly decreased in this population. If this was indeed the case, exercise training prescription would seem necessary during treatment (not only after successfully completing treatment) to improve the physical condition and QOL of children with cancer. This would aid in preventing poor physical condition from becoming a chronic problem and a self-perpetuating condition in the years that follow the completion of treatment.

It was therefore the purpose of this study to determine if the physical fitness (assessed with a number of measurements as VO2peak, ventilatory threshold, functional mobility and ankle range of
of age started at a treadmill speed of 1.0 km·h⁻¹ (or 1.5 km·h⁻¹ for the oldest participants) with an incline of 5.0%. Both treadmill speed and inclination were increased by (0.1 km·h⁻¹ and 0.5%, respectively) every 15 s. Children between 9 and 12 years started at a treadmill speed of 3.0 km·h⁻¹ with an incline of 1.0% and treadmill speed was increased by (0.1 km·h⁻¹) every 10 s to reach a speed between 7 and 9 km·h⁻¹. Thereafter, the treadmill incline was increased (by 0.5%) every 10 s. The tests were stopped upon volitional fatigue of the children and/or when they showed loss of coordination to maintain the required workload. All the children were verbally encouraged with no visual access to their parents during testing. Gas-exchange data were measured breath-by-breath using open circuit spirometry and specific pediatric face masks ($V_{\text{max}}$, 29C, Sensormedics, Yorba Linda, CA, USA). Peak oxygen uptake ($V_{\text{O2peak}}$) was recorded as the highest value obtained for any continuous 20-second period. Heart rate (HR) was continuously monitored during the tests from a twelve lead ECG. The workload eliciting the ventilatory threshold (VT) was determined using the criteria of an increase in both the ventilatory equivalent of oxygen ($V_{\text{E}}$-$V_{\text{O2}}$⁻¹) and end-tidal pressure of oxygen ($\text{PetO}_2$) with no increase in the ventilatory equivalent of carbon dioxide ($V_{\text{E}}$-$V_{\text{CO2}}$⁻¹) [10].

All the exercise 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 am – 1:00 pm) and all the children consumed their usual breakfast (cereals, milk and fruit juice) three hours before the tests.

### Functional and range of motion tests

To measure children’s functional mobility, we used the Timed Up and Down Stairs test (TUDS) [14]. This test has been shown reliable and valid in healthy children and also in children with various diseases or disabilities [7, 14 – 16]. All the children performed at least one previous familiarization session and used a hand railing while ascending and descending the stairs 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 range of motion (active DF-ROM) were measured with the children sitting with the knee flexed to 90° and the foot in neutral alignment [21]. Both measurements (active and passive DF-ROM) have been shown to be reliable in children with ALL [15].

### Children’s report of their health status:

Child report form of the child health and illness profile-child edition (CHIP-CE/CRF)

All the children and their parents completed a Child Report Form of the Child Health and Illness Profile-Child Edition (CHIP-CE/CRF) and Parents Report Form (CHIP-CE/PRF), which is a self-report health status instrument for children < 11 years old and their parents [25, 26]. 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 (risky behaviours 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, which has been shown to be valid in Spanish children < 11 years [23, 24].
Data analysis

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 12.0 software (SPSS Inc., Chicago, IL, USA). Differences in anthropometric variables, indices of cardiorespiratory fitness obtained during the exercise tests (\( \dot{V}O_2\)peak), functional mobility (TUDS test), ankle range of motion and QOL between controls and diseased children were assessed using the Mann-Whitney test. All the data are presented as mean ± SD. The level of statistical significance was set at \( p < 0.05 \).

Results

No differences were found between groups in anthropometric measures \( (p > 0.05) \) (Table 1). Except for a lower active-DF ROM in patients \( (p < 0.05) \), no other significant difference was found in functional and range of motion tests (Table 2). Mean values of \( \dot{V}O_2\)peak were lower in the ALL group than in controls \( (p < 0.05) \), but no other significant differences were encountered in the VT (Table 3).

Children’s self-report of satisfaction (with self and health) \( (p < 0.05) \), comfort (concerning emotional and physical symptoms and limitations) \( (p < 0.01) \) and resilience (positive activities that promote health) \( (p < 0.01) \) were significantly decreased in patients with ALL (Table 4). The parents’ score report for children’s comfort (Table 5) was significantly lower in ALL patients \( (p < 0.05) \), but no other significant difference was encountered in the other variables scored (Table 5).

Discussion

Our study shows that young children (“first decade of life”) receiving treatment against the commonest type of childhood cancer, i.e., LL, have overall decreased functional capacity (\( \dot{V}O_2\)peak and active-DF ROM) and QOL compared to healthy controls matched by age and gender. To the best of our knowledge, this is the first attempt to specifically assess such questions in this population.

We observed a lower mean \( \dot{V}O_2\)peak value in the diseased children compared to controls \( (~-6.6\ \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \text{ or } ~-21\%) \). This finding is of clinical relevance as this variable is widely considered as the single best indicator of aerobic physical fitness [27] and is a powerful predictor of mortality in both healthy and diseased individuals [3, 20], e.g., a ~3.5\( \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) reduction is associated with a 12% decrease in the survival rates of diseased people [20]. Our result is in agreement with previous data on children (mean age ≤ 13 yrs) survivors of ALL (mean of ~5 – 7 years posttreatment) [9,31,32] or on girl survivors of different types of malignancies [17]. A recent meta-analysis has indeed evidenced a mean \( \dot{V}O_2\)peak decrease of ~6 – 8\( \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in ALL survivors (age ranging from 7 to 19 yrs) [30]. On the other hand, the \( \dot{V}O_2\)peak values of our patients were lower than those previously reported in ALL survivors (34\( \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of an older age (7 to 21 yrs) [5]. Taken together, our findings and those of previous research suggest that the impairment of \( \dot{V}O_2\)peak in ALL survivors is a problem that starts in early phases of the life (~3 to 7 yrs of age), i.e., during the years in which treatment protocols

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Variable & ALL group & Control group \\
& \((n = 15)\) & \((n = 15)\) \\
\hline
Body mass (kg) & 26.4 ± 9.0 & 28.5 ± 13.3 \\
Height (cm) & 119.8 ± 14.8 & 126.9 ± 23.8 \\
Subscapular skinfold (mm) & 9.4 ± 4.9 & 7.3 ± 3.2 \\
Triceps skinfold (mm) & 12.7 ± 5.1 & 10.2 ± 5.9 \\
\hline
\end{tabular}
\caption{Mean ± SD values of anthropometric variables}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Variable & ALL group & Control group \\
& \((n = 15)\) & \((n = 15)\) \\
\hline
\( \dot{V}O_2\)peak \( (\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \) & 25.3 ± 6.5* & 31.9 ± 6.8 \\
\( \dot{V}O_2 \) at the VT \( (\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \) & 16.6 ± 4.6 & 19.9 ± 4.6 \\
\( \%\dot{V}O_2\)peak at the VT & 64.6 ± 12.4 & 62.6 ± 6.0 \\
\hline
\end{tabular}
\caption{Mean ± SD results of the ramp treadmill tests}
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\begin{table}[h]
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\begin{tabular}{|c|c|c|}
\hline
Domain & ALL group & Control group \\
& \((n = 15)\) & \((n = 15)\) \\
\hline
Satisfaction & 34.9 ± 4.6* & 38.6 ± 3.7 \\
Comfort & 39.8 ± 9.4** & 54.8 ± 2.3 \\
Resilience & 27.1 ± 5.7** & 33.0 ± 2.8 \\
Risk avoidance & 30.4 ± 5.8 & 33.4 ± 3.0 \\
Achievement & 25.5 ± 5.1 & 28.5 ± 3.3 \\
\hline
\end{tabular}
\caption{Mean ± SD score of children’s QOL}
\end{table}
(total duration of ~30 months) are usually applied to patients [22]. On the other hand, there appears to be no medical contra-indication other than those previously indicated in the Methods section (i.e., severe anemia [hemoglobin < 8 g/dL], fever > 38°C, or severe cachexia (loss of > 35% premorbid weight), platelet count lower than 50 × 10^9/µL, neutrophil count lower than or anthracycline-induced cardiotoxicity) for children undergoing maintenance therapy against ALL to engage in physical activities or exercise programs [12]. In fact, the VO_{2peak} levels of our diseased children were clearly above those levels necessary for independent living. The values of our diseased children were clearly above those levels necessary for independent living (~14 ml·kg^{-1}·min^{-1}) [28] and high enough to allow participation in physical activities. It follows that exercise interventions aiming to improve the cardiorespiratory fitness of these individuals should probably start as soon as possible, namely while they are receiving anticancer therapy.

This is an important consideration as the peak incidence of age of diagnosis for ALL is between 2 and 5 yrs [22] followed by approximately 30 months of therapy. Thus, the timing of the diagnosis and the length of the treatment coincides with a period of life during which it is important to establish sound physical activity habits since childhood activity patterns may “track” into adulthood [4,13]. The levels of physical activity are too low in young children receiving treatment against ALL probably due to an overprotective approach from parents, guardians and teachers [2]. Furthermore, the incidence of obesity is increased among survivors of ALL compared to healthy controls [30], a problem that is largely due to the low physical activity levels of the former [32].

Although statistical significance was not reached, the VO_{2} at which VT occurred tended to be reduced in our diseased children and was below the workloads at which VT usually occurs in healthy children, i.e., ≥20 ml·kg^{-1}·min^{-1} [19]. This is also an important consideration as the ventilatory threshold is a health indicator (that is, of sustainable exercise capacity) in both patients with chronic diseases and in deconditioned individuals [19]. Improvements in VT with supervised exercise training result in attenuation of breathlessness, improved exercise capacity at sub-maximal levels, and contribute to the well-being of patients during their daily activities [19].

In support for the need and safety of children receiving antican- cer therapy to enroll in exercise training programs is the fact that 1) our patients had sufficient levels of passive DF-ROM for sustaining normal gait patterns and functional activities [36], and 2) a measure of functional mobility, as in performance in the TUDS test, was not significantly altered in children with ALL. On the other hand, mean values of active DF-ROM were significantly lower in the latter than in controls, reflecting a weakening of ankle dorsiflexor strength, most likely due to the peripheral neuropathy which is a common side effect of treatment in this patient population [34,35]. Nevertheless, our patients showed higher values of active DF-ROM than those reported by Marchese and co-workers in children with ALL before and after a physical therapy protocol [15] and, most important, the impairment in active DF-ROM was not sufficient to influence normal gait and up-stairs patterns (i.e., no significant impairment in the TUDS test).

In the present study, important aspects of QOL as patients’ self-report of comfort (concerning emotional and physical symptoms and limitations), satisfaction (with self and health) and resilience (positive activities that promote health), and parents’ report of comfort, were significantly decreased compared to controls. These findings reflect, at least in part, an excessively protective approach by concerned parents, physicians, school teachers, which may alter the child’s perception of their actual capacity for physical activity, resulting in fear of overexertion or low self-confidence (self-efficacy) [17,18,33]. In this regard, previous pioneer research in the field of cardiac rehabilitation for adult cardiac patients has shown that low self-efficacy can negatively affect physical function. Low physical performance was positively associated with patients’ or relatives’ (wives) low self-efficacy [7,29]. For instance, participation in treadmill testing early after acute myocardial infarction is an effective means for reassuring spouses about the capacity of their partners to engage in physical activities with safety [29]. Similarly, the results of the present functional tests should reassure parents, guardians and school teachers about the capacity of young children with ALL to engage safely in physical activities. In summary, children receiving treatment against ALL have overall lower functional capacity (particularly, decreased VO_{2peak}) and quality of life than healthy children. However, their physical condition is sufficiently high to allow them to enrol in physical activities and supervised exercise programs. Future controlled studies should assess the effects of a supervised exercise program on the functional capacity and quality of life of children receiving treatment against ALL.

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