RAPID COMMUNICATION

Strength capacity in young patients who are receiving maintenance therapy for acute lymphoblastic leukemia: a case-control study

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INTRODUCTION

The treatment for children and adolescents with acute lymphoblastic leukemia (ALL) can lead to multiple adverse effects, including a poor physical capacity. Accordingly, several studies have reported that survivors of ALL may experience muscle weakness, even years following their remission.[1,2] However, it has not yet been determined whether patients who are currently receiving treatment for ALL present with impaired strength.

To date, only a single pilot study compared muscle strength in ALL with healthy controls.[3] Using an isometric strength assessment, the authors found that the ALL patients were weaker than their healthy peers. Importantly, the children with ALL demonstrated a progressive weakening from the initiation of delayed intensification phase through the next 28 days, suggesting that muscle strength may fluctuate during ALL treatment. Understanding the time course of treatment-induced muscle strength impairments can help to determine the timing of exercise training intervention,[3] which is known to benefit ALL patients.[4-6]

The present case-control study aimed to characterize muscle strength in children who were receiving maintenance therapy for ALL and to compare this strength to that of age-, gender-, and BMI-matched healthy controls.

METHODS

Subjects

Ten patients with ALL (ALL group) were recruited from the Children's Institute of the School of Medicine, University of São Paulo (São Paulo, Brazil). The inclusion criteria were the following: 1) children and adolescents (12-16 years of age) who were receiving maintenance therapy for high-risk ALL; 2) patients who had undergone more than six months of treatment; 3) patients with a preserved cardiac structure and function as assessed by an echocardiogram; and 4) patients with an absence of musculoskeletal disturbances that may preclude their participation in the strength assessment. The patients' characteristics are shown in Table 1. A group of ten age-, gender-, and BMI-matched healthy children were recruited using an advertisement and served as the control group (CTRL group). None of the patients were involved in a structured physical activity program for at least six months prior to testing, whereas the healthy children were only engaged in regular physical education classes (twice a week, 50 min per class). None of the participants had previous experience with the isokinetic strength test. The present study was approved by the institution's Ethics and Committee Review Board. The subjects' parents provided written informed consent after receiving a complete verbal and written explanation of the study's objectives and the associated risks and benefits.

One, one and eight of the patients in the ALL group were entered into the GBTLI–99, GBTLI–2009 and PROP-II-97 protocols, respectively. The GBTLI-99 protocol (Brazilian Group of Childhood Leukemia Treatment) included the administration of mercaptopurine (50 $mg/m^2/day^{-1}$) and methotrexate (25 $mg/m^2/week^{-1}$). The patients also received vincristine (1.5 mg/m^2) and dexamethasone (4 mg/m^2) for seven days. The GBTLI–2009 protocol included the administration of methotrexate (200 mg/m^2) every 21 days, leucovorin plus mercaptopurine pulses (100 $mg/m^2/day^{-1}$) for ten days, vincristine (1.5 mg/m^2) and predinisone (40 $mg/m^2/day^{-1}$) every four weeks for seven days. GBTLI–99 and GBTLI–2009 also included intrathecal chemotherapy with methotrexate, citarabine and dexamethasone every eight weeks until the 106th week. The PROP-II-97 protocol (Institutional Protocol of the University of São Paulo) included the administration of the following medications for 80 weeks: methotrexate (2 $g/m^2/week^{-1}$) plus mercaptopurine (75 $mg/m^2/day^{-1}$) for three weeks; cyclophosphamide (250 $mg/m^2/day^{-1}$) for four consecutive days followed by etoposide (250 $mg/m^2/day^{-1}$) for three consecutive days; teniposide and citarabine (300 $mg/m^2/week^{-1}$ and 250 $mg/m^2/dose/week^{-1}$, respectively) for three weeks; citarabine (15 $g/m^2/day^{-1}$) for two consecutive days and methotrexate (40 $mg/m^2/week^{-1}$) with mercaptopurine for six weeks. After the 80th week, the patients were given methotrexate (40 $mg/m^2/week^{-1}$) with continuous daily mercaptopurine and vincristine (1.5 mg/m^2) pulses every six weeks and dexamethasone (3 $mg/m^2/day^{-1}$) for seven days until the 120th week.

Isokinetic strength assessment

To assess the lower- and upper-limb isokinetic strengths, we measured the concentric knee and elbow flexion and the

Table 1 - Physical characteristics and treatment protocols for the patients in the ALL group.

Patient	Gender	Age (years)	Weeks elapsed since start of treatment	Risk factor	Treatment Protocol	BMI (kg/m^2)
1	F	12	116	High	PROP-II-97	19.5
2	F	12	115	High	PROP-II-97	18
3	F	13	30	High	GBTLI-2009	19.5
4	F	13	117	High	PROP-II-97	22.9
5	F	13	30	High	GBTLI-99	21.1
6	F	14	98	High	PROP-II-97	21.8
7	M	15	70	High	PROP-II-97	20.7
8	F	15	70	High	PROP-II-97	22.5
9	F	16	30	High	PROP-II-97	24.8
10	F	16	112	High	PROP-II-97	26.9
Mean		13.9	78.8	-	-	21.7
SD		1.5	37.8	-	-	2.65

All patients were at high risk.

extension strength using a calibrated isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, NY, USA). Before testing, the patients were familiarized with the procedures. The testing sessions were comprised of a standardized procedure that included a 2-min warm-up period on a cycle ergometer at moderate intensity. The patients were seated in the dynamometer's chair with 90° of hip flexion. The knee of the dominant leg was positioned near the apparatus' lever arm, and the anatomical axis of rotation of this joint was aligned with the dynamometer's rotation axis. The contact pad was placed approximately 3 cm superior to the medial malleolus with the foot in a plantigrade position. The range of motion was set from 90° of knee flexion to 10° of knee extension. For the elbow flexion/extension assessments, the dynamometer's power head was rotated to 30°. The limb rest-device was used to support the patient's arm with the elbow slightly beyond the end of the pad to allow for full extension. The elbow's axis of rotation was aligned to that of the dynamometer. The subject then gripped the handle bar in a neutral forearm position. The length of the attachment shaft was adjusted while moving through the range of motion so that the wrist was neither compressed nor stretched when gripped firmly to the handle bar. The range of motion for the elbow test was set at 100° from the fully extended position (with full extension = 0°).

During both of the tests (i.e., concentric knee and elbow flexion/extension), the patients were asked to perform five maximal repetitions to determine the peak torque (PT), normalized peak torque (PT/BW), total work (TW) and maximum work performed in a single repetition (Wmax). These values were recorded at 30 and 60°/sec for the elbow and knee, respectively. During the tests, the verbal encouragement was consistent and standardized.

The dynamometer was calibrated according to the manufacturer's calibration procedure. At the start of each test, a passive determination of the effects of gravity on the limb and lever arm was performed. Additionally, straps were used to minimize unwanted body movements. When lower-limb was tested, patients were instructed to keep their arms crossed at their chest.

Statistical analysis

Between-group comparisons of all of the strength parameters were performed using an unpaired Student's *t*-test. The data are expressed as mean ± standard deviation. Differences with $p \leq 0.05$ were considered to be statistically significant.

RESULTS

The children in the ALL group exhibited a decreased knee extension peak torque (PT) for the right (29.8%; $p = 0.05$) and left limbs (30.8%; $p = 0.02$), and a lower normalized peak torque (i.e., peak torque to body weight, PT/BW) than the CTRL group for the right (24.3%; $p = 0.05$) and left limbs (21.1%; $p = 0.06$) (Figure 1A and B). Additionally, the ALL group exhibited a higher degree of unbalance between the flexors and extensors than the CTRL group (for the right limb: $p = 0.05$; Figure 1A). The children in the ALL group also expended less total work during knee extension than their healthy peers (right limb: 25.1%, $p = 0.03$; left limb: 23.9%, $p = 0.02$). Additionally, the maximum amount of work that was performed during a single knee extension repetition was lower for the ALL group when compared to the CTRL group for the right (22.6%, $p = 0.04$) and left limbs (22.3%, $p = 0.008$) (Figure 1C and D). Moreover, the time-to-peak torque during the concentric knee flexion was significantly greater for the ALL group when compared to the CTRL group in the right (868 ± 299 *vs.* 594 ± 234 ms, respectively; $p = 0.03$) and left limbs (696 ± 256 *vs.* 542 ± 203 ms, respectively; $p = 0.05$). No differences were observed with regard to the time-to-peak torque during the concentric knee extension.

Our evaluation of the upper limbs revealed that the children in the ALL group exhibited a greater disparity in their left limb balance between the flexors and extensors when compared to the CTRL group (left limb: $p = 0.002$ Figure 2B). The total work expended by the elbow extensor was also less for the ALL group when compared to the CTRL group for the right (9.5%, $p = 0.04$, Figure 2C) and left limbs (9.4%, $p = 0.002$, Figure 2D). The time-to-peak torque during the concentric elbow flexion was significantly greater for the ALL group when compared to the CTRL group for the right (1627 ± 670 *vs.* 1164 ± 543 ms, respectively; $p = 0.02$) and left limbs (1723 ± 453 *vs.* 1157 ± 563 ms, respectively; $p = 0.02$). No differences were observed with regard to the concentric elbow extension values.

DISCUSSION

The aim of the present study was to characterize the muscle strength in children who were receiving maintenance

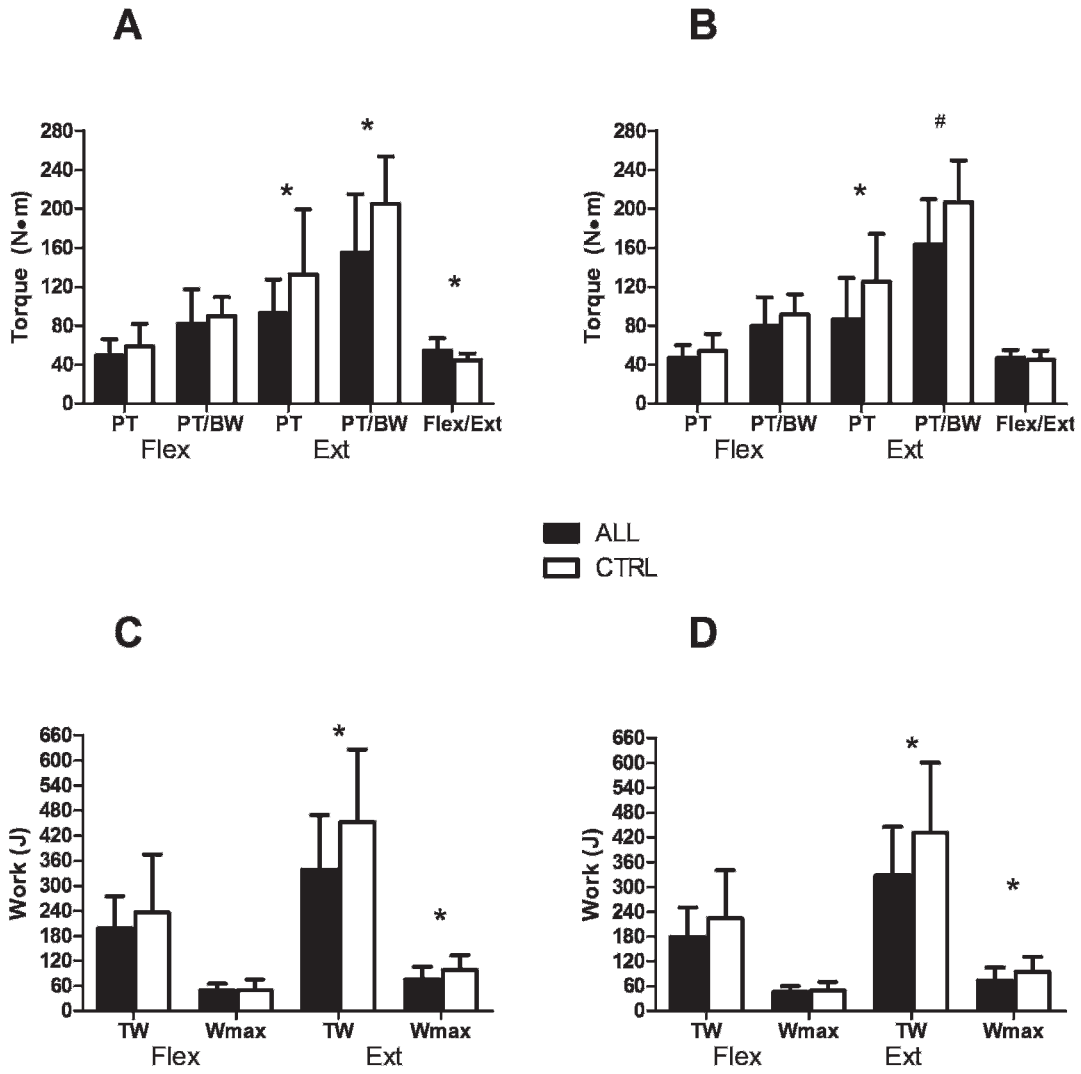

Figure 1 - Knee flexor and extensor isokinetic strength measurements for the right (panels A and C) and left (panels B and D) limbs. PT, peak torque; PT/BW, peak torque normalized to body weight; Flex/Ext, balance between flexors and extensors; TW, total work; Wmax, maximum work performed during a single repetition. *, $p \leq 0.05$ for between-group comparisons. #, $p = 0.06$ for between-group comparisons.

treatment for high-risk ALL. We observed that these patients generally presented with decreased muscle strength relative to their healthy control peers.

Although several studies have reported muscle weakness in long-term survivors of ALL,[1,2] there is a paucity of data regarding the time course of the strength impairment in this disease. Marchese et al[3] reported a decreased isometric strength and function in children with ALL early in their course of treatment, with the weakest muscle strength occurring on the 28th day of the delayed intensification phase. Our present data are consistent with the idea that muscle weakness is a relevant clinical manifestation in patients with ALL and further extend this notion to patients who are in the maintenance phase of ALL therapy.

It has been suggested that muscle weakness in patients with ALL is the result of several combined factors, such as impaired neuropsychological functioning, gross and fine motor disturbances, alterations in growth, cardiac and endocrine function, vincristine- and corticosteroid-induced muscle wasting, and hypoactivity, with the latter-most factor playing a key role in the decline in strength.[7] Accordingly, it seems reasonable to speculate that any reduction in daily-living activities would compromise the muscles of the lower limb, a notion that is supported by our observation of an impaired peak torque (both absolute and normalized) in the muscles of the lower but not upper limbs. In practical terms, it seems reasonable to recommend that lower-limb strengthening exercises must be incorporated in a training program for patients with ALL during the maintenance phase of their treatment.

Another noteworthy finding is the reduced time-to-peak torque that we observed in the upper and lower limb flexors. The ability to produce torque rapidly has been positively associated with balance and functionality in the elderly.[8] In children, there is evidence suggesting that knee-flexor peak torque is an important contributor to retaining balance following an induced forward sway, thereby reducing the time needed to stabilize the center of gravity.[9] Taken together, these data allow us to speculate that the higher time-to-peak torque for the

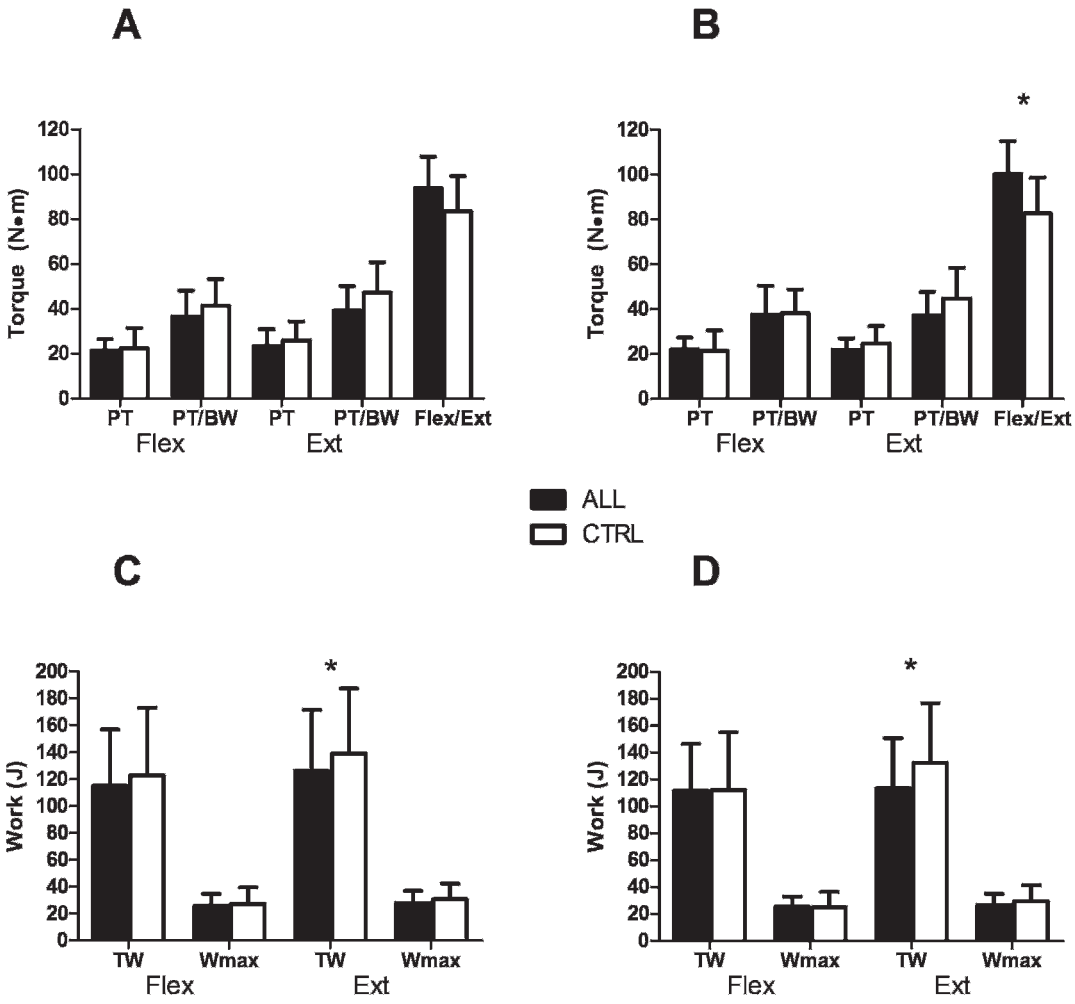

Figure 2 - Elbow flexor and extensor isokinetic strength measurements for the right (panels A and C) and left (panels B and D) limbs. PT, peak torque; PT/BW, peak torque normalized to body weight; Flex/Ext, balance between flexors and extensors; TW, total work; Wmax, maximum work performed during a single repetition. *, $p<0.05$ for between-group comparisons.

knee flexors may be implicated in the function and balance deficits that were previously observed in children with ALL.[3,10] Moreover, the total and maximal work that was produced during a single repetition were reduced in the upper and lower limbs, which partially explains why children with ALL are more prone to fatigue and weakness.[3,10]

It is important to note that the strength impairment was more evident for the extensor muscles than for the flexor muscles of the lower limb. Although these findings are difficult to reconcile, one may intuitively speculate that daily-living activities primarily involve the activation of the lower-limb extensor muscle groups. However, this idea cannot be extrapolated to the upper limbs, thus warranting further investigation into the causes of the impaired upper-limb extensor strength in ALL patients.

In conclusion, we report that children who are receiving maintenance treatment for ALL generally present with weaker isokinetic strength than their healthy counterparts. This finding further supports the prescription of exercise training programs that include strengthening exercises for patients with ALL, particularly during the maintenance phase of their therapy.

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