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Research Article

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The Effect of an Exercise Therapy Program on Physical Function in Patients Undergoing a Haematopoietic Progenitor Cell Transplantation: An Observational Study

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Abstract

Purpose: To observe the effect of a exercise therapy (ET) program on the physical capacity of patients undergoing a haematopoietic stem cell transplant (HSCT) 3 months after said intervention.

Methods: An observational study was carried out in patients who underwent a HSCT between September 2020 and August 2021. Patients were assessed before admission and 3 months after the transplant. The 30-second chair to stand test (30CST) was used to measure lower body resistance, and the timed up and go (TUG) was employed to assess functional mobility and detect balance and coordination problems. During admission, the patients completed the ET program developed at the hospital and based on the guidelines for ET after a HSCT from the Spanish Group for Transplantation and Cellular Therapy (GETH-TC).

Results: 34 patients were included. Three months after the HSCT, a decrease both in the number of 30CST repetitions from 11.58 ± 4.09 to 10.94 ± 3.54 ($p < 0.0001$) and in the time to perform the TUG from 9.86 ± 5.56 to 8.65 ± 3.30 seconds ($p < 0.0001$) was recorded.

Conclusions: An ET program starting with conditioning for a HSCT is safe, can improve coordination and balance, and serves to help mitigate the loss of muscle strength these patients tend to experience because of disease, the transplant process, and prolonged inactivity.

Implications for Cancer Survivors

The maintenance or improvement of strength and mobility may contribute to increased patient well-being and quality of life.

Keywords: Exercise therapy (ET); Haematopoietic stem cell transplantation (HSCT); Muscle strength; Coordination; Balance

Introduction

Hematopoietic stem cell transplantation (HSCT) is a therapeutic procedure used to treat multiple oncological or non-haematological and immunological pathologies as well as other aetiologies. After the administration of high-dose chemotherapy and/or radiotherapy (conditioning), haematopoietic progenitor cells obtained from bone marrow, peripheral blood, or umbilical cord blood are infused [1]. This transplant may be autologous (autoHSCT) when cells

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from the patient are employed, or allogeneic (alloHSCT) if the donor is different from the recipient, regardless of whether they are related to the patient or not. Transplantation, whether with curative intent or to consolidate the response achieved with prior chemotherapy, can be associated with multiple toxicities, with some of them, such as graft versus host disease (GVHD), also requiring immunosuppressive treatment, usually with high-dose corticosteroids [2]. Different studies have shown a reduction in the functional and physical capacities of these patients because of the disease itself, the transplant process, treatments received, and physical inactivity during hospital admission. Furthermore, because of this inactivity, there is an increased risk of complications such as decreased overall muscle capacity, impaired balance, decreased physical function, increased fragility [3], worsening lung function, and an increased risk of respiratory infections. Different physical and emotional symptoms such as fatigue and muscle weakness and depression, anxiety, fear, and frustration, respectively, add to the difficulties of post-transplant recovery [4]. Indeed, patients undergoing HSCT therapy usually experience a significant deterioration in their health status, especially among those receiving an alloHSCT. There are often significant changes in the clinical evolution of patients in the first 3 to 6 months after HSCT, the impact of which can be felt for many years [5,6]. Interventions that include exercise are known to have a beneficial effect on disease-related alterations, improving patient function and participation in the activities of daily living and work. Therefore, these interventions have the potential to help mitigate disability in cancer patients [7-10], and together with oncological treatments, are currently considered the new paradigm for improving patient survival and health-related quality of life (HRQoL) [11-14]. Indeed, aerobic activity, sometimes even as basic as walking, positively impacts HSCT patients [15]. Aerobic exercise training considerably improves health results and physical functioning in patients with lymphoma without interfering with medical treatments or responses to them, with an improvement in cardiovascular capacity [16]. The first time the positive effects of ET after an autoHSCT were demonstrated was in 1986 in work by Cunningham et al. [17]. However, it took until 2003 and 2006 to show the effects of physical activity in patients who had received an alloHSCT [18,19], with interventions performed on patients after their discharge from hospital. It was not until 2009 that Bauman et al. published the first study on the effects of ET in transplant patients through interventions completed during the conditioning phase and the immediate post-transplant period [20]. This study suggested that the use of individually designed programs based on performing daily practices are suitable for all types of patients undergoing HSCT. These authors argued that initiating exercise from the beginning of the acute phase of therapy can reduce patient immobility and improve HRQoL. In another study also conducted in 2009, a 4–6 week programme that also included the admission period for alloHSCT and incorporated multimodal exercise, relaxation, and education, demonstrated that a combination of such exercises is feasible, effective, and safe for these patients [21]. Thus, prescribing regular physical activity to patients can lead to better physical performance during the recovery period and a better perception of physical and emotional state, without posing additional risks [15,22,23]. Finally, systematic reviews have confirmed that exercise appears to have a beneficial effect on physical fitness, HRQoL, and fatigue compared to standard care in patients treated with a HSCT [14,24]. The best time to inform patients about the importance of physical exercise and for its implementation, is at the beginning of the transplant process, especially when patients did not perform adapted physical activity on a regular basis before the diagnosis of disease [7]. Physical exercise is safe, feasible, and beneficial for patients before, during, and after alloHSCT [25,26] and the optimal time for them to begin exercising is before the transplant [24,25,27-29]. Such interventions must be performed with the supervision of a physiotherapist, if the patient does not have any serious symptoms of bleeding or infections [30]. Moreover, professionals must also understand the specific details of the diagnosis and treatments each patient is receiving, as well as the most common associated toxicities [26]. For example, it is important for physiotherapists to know that a greater risk of fractures and cardiovascular events is associated with hormonal therapies, and which chemotherapies most frequently cause neuropathies, musculoskeletal morbidity, or cardiotoxicity, among others. For this reason, ET must be prescribed individually to avoid injuries or adverse events resulting from the disease characteristics of each patient [26]. In this context, in 2017, an ET program was launched at the Álvaro Cunqueiro Hospital (ACH) in Vigo (Galicia-Spain) for all patients undergoing HSCT. However, to date, we still do not have enough evidence to conclude which exercise prescription is the best for patients before or after HSCT. Given all the above, the objective of this current study was to analyse the effect of ET in patients undergoing HSCT at our centre.

Methodology

Setting

An observational, longitudinal prospective study with a pre-post design was carried out in patients treated by the Haematology Service at the ACH in Vigo (Galicia-Spain). These patients underwent HSCT between September 2021 and August 2022 and during admission they completed the ET program protocolised by the Physiotherapy Unit and Haematology Service at the Hospital.

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Participants

Inclusion criteria: patients admitted to the haematology ward in the ACH to undergo a HSCT, who were aged over 18 years, capable of complying with the therapeutic exercise programme autonomously and according to the indications of the physiotherapy team and haematology ward staff and had signed the informed consent to participation. Exclusion criteria: patients unable to follow instructions or consent to participation, or who did not give their consent to participate in the study. Elimination criteria: patients who, because of deterioration of their condition, were unable to continue with the therapeutic exercise program or who died before completing their participation in the program. As the objective of this study was to analyse the potential benefits of an ET program already integrated into the hospital's routine clinical practice, establishing a control group was not feasible. To deny access to the program was considered unethical, as it may provide significant benefits to patients. Thus, to compare our findings we searched the evidence available in the academic literature on the theoretical effect produced by onco-haematological disease and the HSCT process in these patients. Informed consent was obtained from al individual participants included in the study. Anonymity of the participants was maintained by the staff involved in the study. Study protocol and all associated documentation was approved by the Autonomous Ethics and Research Committee of Galicia (CEImG), with registration number CAEI 2020/022.

Outcome measures

The intervention began in the nursing consultation prior to admission for transplant. The patient was invited to perform the timed up and go (TUG) test [31-33] and the 30-second chair to stand test (30CST) [34,35]. In addition, variables including diagnosis, transplant type, age, and sex were also recorded. On the day of hospital admission, a physiotherapist interviewed the patients, assessed their physical condition, and planned the exercise programme they would complete based on the ET guide for HSCTs published by the Spanish Group for Transplantation and Cellular Therapy (GETH-TC) [36]. The patient attended daily to complete the exercises and, twice a week, if their physical condition had deteriorated because of the disease process, the plan was adapted and modified, as necessary.

Typical ET planning comprised respiratory exercises including diaphragmatic breathing, rib breathing, free upper limb flexion exercises (ULFEs) combined with deep breathing, free ULFE adduction/abduction exercises combined with deep breathing, and resistance exercises with and without weights to work the following muscle groups: biceps brachii, triceps brachii, pectoralis major/serratus major, triceps surae, psoas, and quadriceps/gluteus maximus. To adapt the intensity of the workload, dumbbells, elastic bands, and body weight was used. To regulate the exercises, the perception of effort was measured using the modified Borg scale [37,38]. This scale is graded from 1 to 10 and each patient was asked to reach level 4–5 for each muscle group, which corresponded to a perception of a 'somewhat hard' to a 'hard' effort. Series of repetitions were interspersed with rest periods. In cases where the physical capacity of the patient had deteriorated during admission, making it impossible for them to complete a continuous training session, two short training sessions per day were indicated, to the extent of the individual capabilities of the participants. The program also included aerobic work on a stationary bicycle, treadmill, stepper, or walking around the room or floor, depending on the moment and the ability of the patient to perform these types of exercise. During the last week of admission, instructions were given for performing exercises at home and the patient was encouraged to continue with the ET program, progressively increasing the time and intensity of these activities after hospital discharge. In order to compare results, 3 months after the HSCT, the same nurse collected data in the consultation identical to that recorded prior to admission.

Statistical analysis

First, we performed a descriptive analysis. We assumed that the quantitative variables had a non-parametric distribution and expressed these using the medians and interquartile ranges. The qualitative variables were represented as frequencies and percentages. Wilcoxon or Friedman tests were used to compare repetitions (30CST) and time (TUG) pre- versus post-intervention, depending on the number of categories for each variable. Depending on the number of groups of each variable, chi-squared or Fisher tests were used to compare stand-up support, sit-down support, walking destabilisation support, and turning destabilisation support pre- versus post-intervention. *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 19.0; IBM Corp., Armonk, NY).

Results

A total of 37 patients were invited to participate in the study; 3 patients refused to participate. Of the 34 patients included all of them completed the study by performing the scheduled test 3 months post-transplant. The clinical characteristics and demographics of all the participants are shown in table 1. By sex, slightly more men received a HSCT (55.9% male versus 44.1% female) and 73.5% of the patients underwent an autoHSCT. The main underlying diseases were multiple myeloma (41.2% of the included patients) and lymphoma (29.4%). Some 38.2% of the patients were in the 51–60 years age range, followed by 61–70 years (29.4%).

There was a significant decrease in the number of repetitions the patients were able to perform in the 30CST test, from 11.58 ± 4.09 repetitions before hospitalisation to 10.94 ± 3.54 3 months after the HSCT ($p < 0.0001$; table 2).

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Table 1: Clinical and demographic characteristics.

PATIENS				
			AutoHSCT	AlloHSCT
Patients [n (%)]		34 (100%)	25 (73,5%)	9 (26,5%)
Age [mean±sd]		53±10,31		
Sex	Female [n (%)]	15 (44,1%)	10 (29,4%)	5 (14,7%)
	Male [n (%)]	19 (55,9%)	15 (44,1%)	4 (11,8%)
Disease type	Leukaemia [n (%)]	6 (17,6%)	0	6 (17,6%)
	Lymphoma [n (%)]	10 (29,4%)	10 (29,4%)	0
	Multiple Myeloma [n (%)]	14 (41,2%)	14 (41,2%)	0
	Other [n (%)]	4 (11,8%)	1 (2,9%)	3 (8,8%)
Age range	21-30 [n (%)]	1 (2,9%)	0	1 (2,9%)
	31-40 [n (%)]	3 (8,8%)	1 (2,9%)	2 (5,9%)
	41-50 [n (%)]	7 (20,6%)	3 (8,8%)	4 (11,8%)
	51-60 [n (%)]	13 (38,2%)	11 (32,4%)	2 (5,9%)
	61-70 [n (%)]	10 (29,4%)	10 (29,4%)	0

Table 2: Number of chair-to-stand repetitions performed by the patients in 30 seconds.

30" CST			
	Rep. Before_Hospt.	**Rep. After_Hosp**	**P**
Total (n=34) [mean±sd]	11,58±4,09	10,94±3,54	**p<0,0001**
AutoHSCT (n=25) [mean±sd]	11,6±4,33	11,6±3,57	0,356
AlloHSCT (n=9) [mean±sd]	11,55±3,57	9,11±2,89	0,151
Leukaemia (n=6) [mean±sd]	12,33±4,08	8,16±3,12	0,058
Lymphoma (n=10) [mean±sd]	10,7±4,76	10,3±3,40	0,888
Multiple Myeloma (n=14) [mean±sd]	12,35±4,19	12,35±3,62	0,37
Other (n=4) [mean±sd]	10±1,63	11,75±1,70	0,141
Female (n=15) [mean±sd]	11,6±4,68	11,06±3,65	1
Male (n=19) [mean±sd]	11,57±3,70	10,84±3,54	0,775
21-30 years (n=1) [mean±sd]	8±0	10±0	
31-40 years (n=3) [mean±sd]	14±5,0	9,33±5,13	0,285
41-50 years (n=7) [mean±sd]	11,57±1,71	11,7±3,68	0,766
51-60 years (n=13) [mean±sd]	11,84±3,97	12,07±3,98	0,265
61-70 years (n=10) [mean±sd]	10,9±5,38	9,5±2,06	0,396

No significant values were found in any of the different subgroups studied and the number of repetitions had generally decreased by the end of the study. However, in some patient subgroups, these figures were maintained or had even increased. As an indication of frailty and coordination, the time patients needed to perform the TUG test generally decreased from before to after admission (9.86 ± 5.56 to 8.65 ± 3.30 seconds; $p < 0.0001$) and 3 months after the HSCT, significantly fewer incidents in which patients required support were reported; the number of times help was needed when standing up decreased from 10 to 6 ($p = 0.014$) and when sitting down from 9 to 6 ($p = 0.002$; table 3).

The subgroup analysis showed that the greatest decreases in time occurred in the autoHSCT group, with a significant reduction from 10.46 ± 6.33 to 8.39 ± 3.27 seconds ($p = 0.001$), with this group also showing a significant decrease in their need of support to sit (from 7 to 4 incidents; $p = 0.003$); the total number of incidents that occured while getting up, sitting down, or related to destabilisation also decreased from 17 to 9 in this group. In this subgroup only 1 case became destabilised while walking and turning in both the pre- and post-intervention tests (p = ---). According to the disease type, the execution time of the TUG reduced in all the groups except for leukaemia (all these patients received

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Table 3: The timed up and go test and number of times support or assistance was needed. The mean number of seconds needed to perform the test ± the standard deviation (*SD*) and number of participants who needed help. Abbreviations: A_lev_pr: help required to get up pre-admission; A_lev_pst: help required to get up post-admission; A_Sent_pr: help required to sit down pre-admission; A_Sent_pst: help required to sit down post-admission; D_Cam_pr: pre-admission walking imbalance; D_Cam_pst: post-admission walking imbalance; D_gir_pre: pre-admission rotation imbalance; D_gir_pst: post-admission rotation imbalance.

	TUG														
	Before_ Hosp.	After_ Hosp.	p	H_GUp_pr	H_GUp_ps	p	H_ SDw_ pr	H_ SDw_ ps	p	W_ Imb_pr	W_ Imb_ Ps	p	R_ Imb_pr	R_ Imb_ ps	p
	[mean±sd]	[mean±sd]		n	n		n	n		n	n		n	n	
Total(n=34)	9,86±5,56	8,65±3,30	P<0,0001	10	6	0,014	9	6	0,002	1	2	0,06	1	2	0,059
AutoHSCT (n=25)	10,46±6,33	8,39±3,27	0,001	8	3	0,081	7	4	0,003	1	1	p:---	1	1	p:---
AlloHSCT (n=9)	8,2±1,75	9,37±3,49	0,594	2	3	0,083	2	2	p:---	0	1		0	1	
Leukaemia (n=6)	7,97±1,95	10,08±4,14	0,116	1	2	0,333	1	2	0,333	0	1		0	1	
Lymphoma (n=10)	12,69±9,34	9,22±4,49	0,022	4	1	0,4	4	3	0,033	1	1	p:---	1	1	p:---
M. Myeloma (n=14)	9,04±2,67	7,96±2,15	0,03	4	2	0,176	3	1	0,214	0	0		0	0	
Other (n=4)	8,52±1,29	7,52±1,35	0,068	1	1	p:---	1	0		0	0		0	0	
Female (n=15)	10,87±7,91	8,73±3,69	0,036	3	2	0,081	3	2	0,029	1	1	p:---	1	1	p:---
Male (n=19)	9,07±2,54	8,59±3,06	0,116	7	4	0,117	6	4	0,071	0	1		0	1	
21-30 years (n=1)	6,48±0	6,5±0													
31-40 years (n=3)	8,76±1,96	8,76±1,96	0,593	0	1		0	1		0	0		0	0	
41-50 years (n=7)	8,01±1,65	8,66±4,01	0,374	2	2	p:---	2	1	0,222	0	1		0	1	
51-60 years (n=13)	8,91±2,79	7,73±1,97	0,023	3	2	0,127	3	1		0	0		0	0	
61-70 years (n=10)	13,06±9,12	9,99±4,15	0,139	5	1	1	4	3	0,048	1	1	p:---	1	1	p:---

an alloHSCT). In cases of lymphoma, there was a significant decrease in time from 12.69 ± 9.34 to 9.22 ± 4.49 seconds ($p = 0.022$). Furthermore, the number of patients who needed support when sitting decreased from 4 to 3 cases ($p = 0.033$). In patients with multiple myeloma, the decrease in time from 9.04 ± 2.67 to 7.96 ± 2.15 seconds ($p = 0.030$) was also significant. Similarly, in women the decrease in time from 10.87 ± 7.91 to 8.73 ± 3.69 seconds ($p = 0.036$) and reduction in the need for support to sit from 3 to 2 incidents ($p = 0.029$) was significant. By age group, in the 61- to 70-year-old group, there was a decrease in the time required to sit and a significant decrease in the need for help to sit ($p = 0.048$).

Discussion

The objective of this current study was to assess the effect of the ET program implemented at the HAC in Vigo on patients undergoing HSCT. Variations in the programme were specifically planned for each patient to adapt to their physical conditions and the evolution of the disease process during their admission. Because of the loss of physical capacity in this type of patient, starting from the time of their admission, we consider maintenance of similar results in the tests repeated 3 months after the HSCT to be a favourable result. The ET program aims to take advantage of the exercise routine acquired by patients during their admission, prolonging it after their discharge from hospital, based on the knowledge that individually prescribed aerobic exercise at home is an acceptable, safe, and potentially effective intervention to improve functioning, physical fitness, and fatigue in HSCT recipients [24,25,39]. Thus, this work serves as a starting point to understand the effect of exercise on these patients and to compare our results with similar previous studies. In our study, the patients showed a slight decrease in lower body strength 3 moths post-HSCT, reflected by the fact that the average number of 30CST repetitions they could perform was lower. This agrees with evidence reported in the scientific literature suggesting a loss in muscle mass in HSCT recipients [17,40-42]. The subgroup analysis showed

Comesana AC, et al., Arch Physiother Rehabil 2026
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minimal, insignificant variations with respect to the general result. This objective loss of strength seen in the patients did not correlate with an increase in fragility measured through the TUG test, a loss in functional capacity, or with the risk of falling. Nonetheless, in the TUG we observed a general decrease in the execution time, the number of incidents requiring support to get up or sit down (significantly so in both cases), and in imbalances. This decrease was maintained in practically all the subgroups studied and was significant in many of them. Thus, patients that had received an autoHSCT showed a decrease in the TUG result by more than 2 seconds and least needed support for sitting, with destabilised walking and turning remaining the same, thereby suggesting a decrease in fragility in this group. The decreased TUG time in lymphoma and multiple myeloma was also significant, with a reduction seen in the number of patients who needed support when sitting in the first case. In patients that had undergone an alloHSCT, we observed an increase in the TUG time and in the number of incidents in which aid was needed to help them sit, stand up, or maintain their balance. Elsewhere, Potiaumpai and Rothe demonstrated worsening in the TUG results in the first case and no significant changes in the latter among patients who underwent an autoHSCT. However, the data from our study suggest a decrease in fragility in these patients because they needed less support and showed fewer imbalances 3 months post-transplant. We did observe a slight increase in frailty in patients that underwent an alloHSCT transplant, mainly among those with acute leukaemia, which is consistent with the observations by Ueki et al. and Morishita et al., although to a lesser degree [30,40]. Ueki et al. reported a 45% incidence of falls in patients that had received an alloHSCT during the hospitalisation period and Morishita et al. reported a deterioration in balance as well as a decrease in physical capacity after an alloHSCT.

Thus, resistance and strength training seems to help mitigate the decreased mobility and improve the HRQoL of patients undergoing alloHSCT without posing additional risks [22], and that functional benefits are obtained with short-term physical training [23]. Considering the above and our data, we postulate that the early initiation of TE and its maintenance after discharge improved the physical capacity of patients that had received an autoHSCT and slowed the deterioration of those that had undergone an alloHSCT. We believe this reinforced the role of these programmes in improving the survival and HRQoL of patients undergoing HSCT. In our work, patient adherence to the programme was satisfactory given that there were no dropouts. This reinforces the commitment of patients enrolled in programmes they feel are centred on them. These results agree with those from other studies also carried out in these types of patients [25].

Limitations

It was not possible to use a control group in this work because the therapeutic exercise programme is part of the clinical practice for HSCTs and therefore, it would have been unethical to deprive some patients of said programme. In addition, the planned number of participants for the project was not reached because of delays in patient admissions given that the work was conducted after the COVID-19 pandemic period.

Advantages

Although it was impossible to establish a control group because of the aforementioned limitations, to avoid bias, the person who conducted the pre- and post-admission assessments was not part of the ET program carried out at the hospital.

Conclusion

An exercise therapy (ET) program starting with conditioning for HSCT is safe, can improve patient coordination and balance, and serves to stop the loss of muscle strength these patients experience because of the disease, the transplant process, and prolonged inactivity. Subsequent studies with a larger cohort size will be needed to confirm the positive results obtained in this work.

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Conflict of interests

None of the authors have any conflicts of interest regarding the conduct of this study to declare.

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