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ORIGINAL ARTICLE

Balance Function after Balance Exercise Assist Robot Therapy in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: A Pilot Study

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Objectives: This study compared the balance function in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT) with their balance function after subsequent training sessions with a Balance Exercise Assist Robot (BEAR). **Methods:** In this prospective observational study, inpatients who underwent allo-HSCT from human leukocyte antigen-mismatched relatives were enrolled from December 2015 to October 2017. Patients were allowed to leave their clean room after allo-HSCT and underwent balance exercise training using the BEAR. Sessions (20–40 min) were performed 5 days per week and consisted of three games that were performed four times each. A total of 15 sessions were performed by each patient. Patient balance function was assessed before BEAR therapy according to the mini-balance evaluation systems test (mini-BESTest), and patients were divided into two groups (Low and High) based on a 70% cut-off value for the total mini-BESTest score. Patient balance was also assessed after BEAR therapy. **Results:** Fourteen patients providing written informed consent fulfilled the protocol: six patients in the Low group, and eight patients in the High group. In the Low group, there was a statistically significant difference between pre- and post-evaluations in postural response, which a sub-item of the mini-BESTest. In the High group, there was no significant difference between pre- and post-evaluations in the mini-BESTest. **Conclusions:** BEAR sessions improve balance function in patients undergoing allo-HSCT.

Key Words: balance disorder; fall; hematopoietic stem cell transplantation; robotic rehabilitation

INTRODUCTION

Among the treatments used for patients with hematological malignancies, transplantation therapy has shown good outcomes. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been reported to reduce morbidity and extend life expectancy. In recent times, almost 50,000 patients have undergone allo-HSCT with improved survival rates.[1,2] However, deterioration in physical function and quality of life (QOL) and the appearance of general fatigue related to allo-HSCT treatment have been reported. During allo-HSCT treatment, deterioration in the physical function of patients may occur because of the underlying disease, chemotherapy before HSCT, and graft-versus-host disease after allo-HSCT. In addition, long-term therapy in a clean room can cause severe disuse syndrome, which manifests as decreased physical fitness[3] and decreased cardiopulmonary function.[4] Furthermore, the cumulative dose of steroids

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associated with the treatment has been related to physical deterioration.[5] These declines in physical function can continue after discharge from the hospital and may affect social activities, such as activities of daily living and the return to work.[6–8]

Patients that undergo allo-HSCT often experience falls during hospitalization. Ueki et al. reported that 50% of post-HSCT patients experienced one or more falls during hospitalization.[9] In addition, Morishita et al. evaluated balance function based on changes in the patient's center of pressure (COP) after allo-HSCT and found that balance function decreased after allo-HSCT.[10] Furthermore, some studies have described factors associated with an increased incidence of falls in patients hospitalized with bone marrow transplantation.[11–13] The prevention of falls is crucial in these patients because thrombocytopenia occurs after allo-HSCT, and falls may lead to serious bleeding injuries. Therefore, there is significant need for the development of a medical treatment and rehabilitation environment where falls can be prevented. Regarding the effect of rehabilitation on physical decline after allo-HSCT, improvements in muscle strength and walking ability have been reported.[14–16] A previous study reported that an interdisciplinary approach involving hematology–oncology and stem cell transplantation increased mobility and reduced the incidence of falls.[17]

In recent years, use of robots for rehabilitation of balance disorders has been reported.[18–20] Ozaki et al.[19,20] utilized a balance training robot known as the Balance Exercise Assist Robot (BEAR) in the rehabilitation of patients with balance disorders caused by spinal cord injury or central nervous system diseases, such as stroke. These patients demonstrated improved dynamic balance ability and strength in the lower extremities.[20] A study of elderly individuals found that a balance training robot improved dynamic balance ability and lower limb muscle strength when compared with treatments based on general exercise.[19] Another study reported that a balance training robot, the Hunova, improved balance function.[18] Furthermore, a robotic system, such as the BEAR, can provide appropriate exercise support for patients undergoing allo-HSCT. Given that the BEAR is controlled by an inverted pendulum system similar to the balance strategy used by human beings, it is anticipated that the use of the BEAR will allow for balance training that facilitates the acquisition of movement. The objective of this study was to investigate the changes in balance function in patients undergoing allo-HSCT by comparing balance function before and after use of the BEAR.

MATERIALS AND METHODS

Study Design

This study was a prospective, observational investigation of balance function among patients undergoing allo-HSCT.

Patients

Inpatients who underwent HSCT from human leukocyte antigen (HLA)-mismatched relatives, as reported in a previous study,[21,22] were enrolled in this study from December 2015 to October 2017. Patients with bone metastases or brain metastases were excluded. All patients were allowed to leave their clean room in the hospital after allo-HSCT. Written informed consent was obtained from all patients before inclusion into the study, and the study was conducted with the approval of the Facility Ethics Review Board (No. 1888).

Protocol

Patients began exercise with a physical therapist (sessions of 20–40 min per day, 5 days per week) prior to allo-HSCT and continued until they were discharged. The exercise program included stretching, resistance training, and endurance training. Patients in this study used the BEAR in addition to regular physical therapy. Before starting use of the BEAR, we evaluated outcome measurements (pre-evaluation). The function of the BEAR was explained to the patient, and a balance check was performed on the BEAR. Patients performed 20- to 40-min sessions, 5 days per week, each consisting of three games (tennis, ski, rodeo) that were performed four times each. After the completion of 15 BEAR sessions, we conducted a post-evaluation. The same therapist performed the pre- and post-evaluations without blinding.

Balance Exercise Assist Robot

We utilized the BEAR (Toyota Motor Corp., Japan) for balance exercises (**Fig. 1**).[19,20,23] The BEAR is equipped with two wheels with in-wheel-type motors, controlled by an inverted pendulum system and two footplates that incline separately, thereby maintaining a horizontal position when the rider banks the robot laterally; the robot also includes a safety harness for the rider. The BEAR moved according to the location of the COP; when the COP of the rider moved forward or backward, the BEAR also moved forward or backward; when the COP moved right or left, the BEAR moved in the counter direction; and when the COP remained in the center, the BEAR was stationary. The BEAR monitored the output of the images from the three games (tennis, ski, and rodeo). Patients practiced forward and backward movements

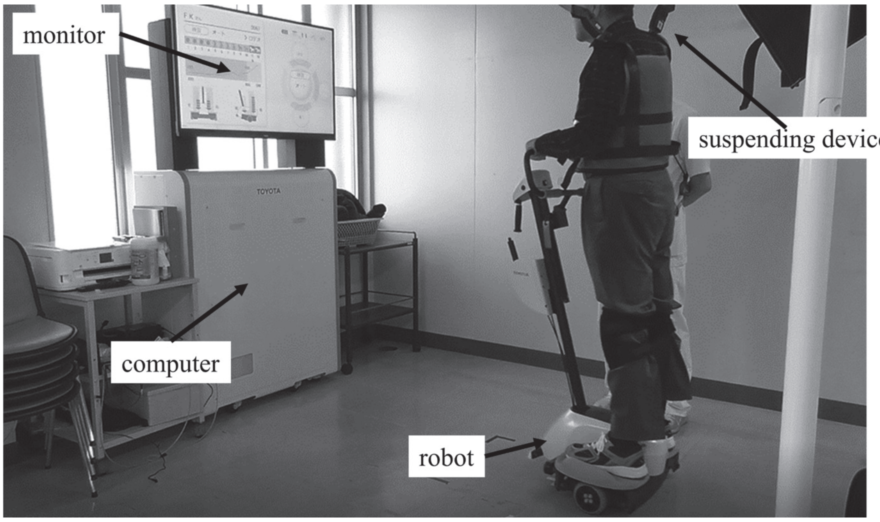

Fig. 1. Photograph of the Balance Exercise Assist Robot (BEAR) in use. The BEAR system includes a monitor, computer, suspending device, and robot.

in the tennis game and right and left movements in the ski game. The rodeo game exposed the patients to extra stimulation; that is, the movement of the BEAR was randomized and unpredictable while the patient attempted to remain at the center. The game level and difficulty were automatically adjusted according to the patient comfort level. In this study, we extracted the game-level transition from the initial game level to the final game level.

Mini-balance Evaluation Systems Test

We performed the mini-balance evaluation systems test (mini-BESTest) to evaluate balance function.[24–27] The mini-BESTest is a brief version of the balance evaluation systems test (BESTest),[28] and has four systems that include 14 items. We evaluated 0, 1, or 2 rating categories for each item and calculated the total score. The mini-BESTest comprises important balance functions of dynamic balance control, such as the capability of anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait, including cognitive function. Several studies have confirmed the reliability and validity of the mini-BESTest in patients with stroke, Parkinson's disease, or in geriatrics.[26,29] The results of the mini-BESTest were calculated to give a total score and each system score was expressed as a percentage.

Body Sway Testing

A twin gravicorder (G6100; Anima, Tokyo, Japan) force platform was used to measure body sway. The COP was measured as an index of statistical postural stability. The tasks were performed with a 20-Hz sampling rate under two conditions: eyes open or eyes closed. While barefoot or wearing thin stockings, patients were instructed to stand on a force plate and to keep their eyes either open or closed while maintaining a certain stance for 60 s. In the eyes-open condition, patients were asked to look at a small black circle that was 250 cm away from where they were standing. The total length of the COP, area of COP, root mean square of COP, and average velocity of COP were measured as parameters of conventional stationary analysis. The Romberg ratio was calculated as the area of eyes-open and eyes-closed conditions.

Berg Balance Scale

The Berg Balance Scale (BBS) is a comprehensive balance function battery that includes 14 items,[30] each of which has 5 categories (0–4) for a maximum total score of 56 points. The reliability and validity of the BBS have been verified in previous studies.

Timed Up-and-Go Test

The Timed Up-and-Go (TUG) test was used to evaluate gait and balance performance. A stopwatch was used to record the time taken for the patients to stand up from a chair and walk 3 m, turn a corner, walk back, and sit down again.

Physical Function

Physical strength was assessed by the handgrip and knee-extensor strength tests. The 10-m Walk Test was used as a measure of gait speed. All assessments were performed as

Table 1. Demographics and clinical characteristics of HSCT patients in both groups

		Low group (n=6)	High group (n=8)
Age (years)		48.5 (27–63)	42.5 (20–58)
Sex	Male/female	1/5	6/2
Height (cm)		160±4.8	165.6±6.7
Body weight (kg)		44.1±5.3	52.4±11.2
Hematological diagnosis	Acute myeloid leukemia	3	5
	Acute lymphoblastic leukemia	3	1
	Malignant lymphoma	0	1
	Myelodysplastic syndrome	0	1
Stem cell source	Peripheral blood stem cell	6	6
	Bone marrow	0	1
	Cord blood	0	1
Donor	HLA-mismatched/related	6	7
	HLA-mismatched/unrelated	0	1
Conditioning regimen	Myeloablative	0	0
	Reduced intensity	6	8
Stay in clean room (days)		80.0±36.0	50.6±9.1

Age is shown as median with range in parentheses. Height, Body weight, and Stay in clean room are shown as mean and standard deviation. Other data are shown as number.

previously described.[31–34]

Statistical Analysis

In this study, patients with low or high balance function were combined. The fall risk cut-off value was 70% of the total mini-BESTest.[29] Therefore, we divided patients into two groups: one group whose pre-evaluation score was less than 70% on the total mini-BESTest (Low group); the other group had scores that were higher than 70% on the total mini-BESTest (High group). Essentially, the Low group indicated patients with low balance function and the High group indicated patients with high balance function. We performed a *t*-test or the Wilcoxon test to compare the Low and High groups in terms of their clinical characteristics. Outcomes were also compared between pre- and post-evaluations in each group using the *t*-test or the Wilcoxon test. Statistical significance for the analysis was set at $P < 0.05$.

RESULTS

Demographics and Clinical Characteristics

In this study, 30 patients were recruited after providing written informed consent. Of these, 16 patients were excluded: 8 wished to receive only hematological therapy, 5 were discharged from our hospital, and 3 were not interested in using the BEAR. The remaining 14 patients were included in the analysis. There were 6 patients in the Low group and 8 patients in the High group. Demographics and clinical characteristics of the HSCT patients in both groups are summarized in **Table 1**. In the Low group, the median age of the patients was 48.5 years (1 male and 5 females). The hematological diagnoses included acute myeloid leukemia and acute lymphoblastic leukemia. The source of the hematopoietic stem cells was peripheral blood stem cells and the donor relationships were HLA-mismatched/related in the 6 patients. In the High group, the median age of the patients was 42.5 years (6 males and 2 females). Hematological diagnoses included acute myeloid leukemia, acute lymphoblastic leukemia, malignant lymphoma, and myelodysplastic syndrome. The source of the hematopoietic stem cells was peripheral blood stem cells in 6 patients, bone marrow in 1, and cord blood in 1. The donor relationships in the High group were HLA-mismatched/related in 7 patients and HLA-mismatched/unrelated in 1 patient. All patients in both groups underwent a conditioning regimen of reduced intensity. The average length of stay in the clean room was 80.0 days for the Low group and 50.6 days for the High group. There was no statistically significant difference in length of stay in the clean room between the groups [$P = 0.06$, 95% confidence interval (CI) = −59.7 to 0.96].

Table 2. Change of mini-BESTest in each group from before to after BEAR therapy

Mini-BESTest	Low group (n=6)				High group (n=8)			
	Pre	Post	P value	95% CI	Pre	Post	P value	95% CI
Total (%)	52.4±15.9	70.9±18.6	0.09	−3.8 to 40.7	88.8±11.2	92.0±8.3	0.54	−7.4 to 13.7
Anticipatory postural adjustments (%)	50.0±21.1	61.1±17.2	0.34	−13.7 to 35.9	91.7±23.6	89.6±15.3	0.84	−23.4 to 19.2
Postural responses (%)	11.1±13.6	55.6±25.1	0.003*	18.5–70.4	79.2±26.4	87.5±24.8	0.53	−19.1 to 35.8
Sensory orientation (%)	88.9±20.2	91.7±13.9	0.79	−19.5 to 25.1	93.7±8.6	95.8±7.7	0.62	−6.7 to 10.9
Stability in gait (%)	56.7±20.7	73.3±24.2	0.23	−12.2 to 45.6	90.0±9.3	93.8±5.2	0.33	−4.3 to 11.8

Pre, mini-BESTest evaluation before BEAR therapy; Post, mini-BESTest evaluation after BEAR therapy.
* Statistical significance (P<0.05)

Table 3. Change of secondary outcome measurements in both groups from before to after BEAR therapy

	Low group (n=6)				High group (n=8)			
	Pre	Post	P value	95% CI	Pre	Post	P value	95% CI
Grip power (kg)	10.6 ±4.2	12.7±4.5	0.43	−3.5 to 7.6	22.4±8.7	23.7±7.7	0.76	−7.5 to 10.1
Knee extensor (kg/BW)	0.21±0.07	0.29±0.21	0.38	−0.1 to 0.3	0.39±0.11	0.35±0.09	0.49	−0.15 to 0.07
10-m gait time (s)	9.6 ±1.9	8.9±1.5	0.50	−3.0 to 1.6	7.5±2.3	6.9±1.5	0.61	−2.7 to 1.6
TUG (s)	10.3 ±2.3	9.0±1.2	0.24	−3.7 to 1.0	7.2±1.8	6.7±1.6	0.54	−2.3 to 1.3
Dual task TUG (s)	11.7±1.6	10.5±1.5	0.20	−3.3 to 0.8	8.0 ±2.1	7.1±1.6	0.39	−2.8 to 1.2
FRT (cm)	24.6±5.2	24.2±6.5	0.90	−8.0 to 7.2	30.1±3.9	28.2±8.1	0.56	−8.7 to −4.9
Single-leg standing (s)	11.1±11.5	11.0±10.4	0.98	−14.2 to 13.9	21.9±8.3	24.7±4.8	0.43	−4.5 to 10.1
BBS (points)	49.7±5.9	52.7±3.3	0.30	−3.1 to 9.2	55.5±1.4	55.6±0.5	0.41	−1.0 to 1.3
Body sway testing								
Eyes open								
Length of COP (cm)	112.5±21.3	99.2±23.1	0.32	−41.9 to 15.3	69.7±34.5	60.0±30.7	0.56	−44.7 to 25.4
Area (cm^2)	4.5±1.9	5.4±1.4	0.39	−1.3 to 3.0	2.7±1.5	3.2±2.0	0.57	−1.4 to 2.5
RMS (cm)	0.82±0.2	0.91±0.13	0.37	−0.13 to 0.31	0.69±0.09	0.81±0.09	0.33	−0.14 to 0.39
Velocity (cm/s)	2.2±0.9	1.9±0.6	0.51	−1.3 to 0.7	1.5±0.4	1.3±0.5	0.36	−0.6 to 0.2
Eyes closed								
Length of COP (cm)	219.8±73.6	151.5±27.3	0.06	−139.7 to 3.0	98.4±58.3	97.6±57.1	0.98	−62.7 to 61.1
Area (cm^2)	8.2±3.4	5.8±2.7	0.21	−6.3 to 1.6	3.4±2.7	3.7±2.9	0.86	−2.8 to 3.3
RMS (cm)	1.01±0.23	0.87±0.19	0.29	−0.40 to 0.13	0.69±0.1	0.72±0.1	0.83	−0.26 to 0.32
Velocity (cm/s)	4.7±3.7	3.0±1.3	0.31	−5.2 to 1.8	2.1±0.8	2.2±1.0	0.96	−1.0 to 1.0
Romberg ratio (eyes closed/eyes open)	1.9±0.4	1.1±0.4	<0.01	−1.3 to −0.3	1.2±0.4	1.1±0.4	0.96	−0.4 to 0.4

Pre, evaluation before BEAR therapy; Post, evaluation after BEAR therapy; FRT, functional reach test; RMS; root mean square

Mini-BESTest

The fall risk cut-off point was set at a total mini-BESTest of 70%, and the patients were divided into the two groups according to this value (**Table 2**).[29] In the Low group, there were statistically significant differences between pre- and post-evaluations in postural response, whereas there was no statistically significant difference between pre- and post-evaluations in the mini-BESTest in the High group.

Secondary Outcome Measurements

The difference between pre- and post-evaluations for Romberg ratio was statistically significant in the Low group, but there was no statistically significant difference in other secondary outcome measurements (**Table 3**).

Game Level

For each game, the average game level increased with the number of games in both groups (**Fig. 2**). Within each group,

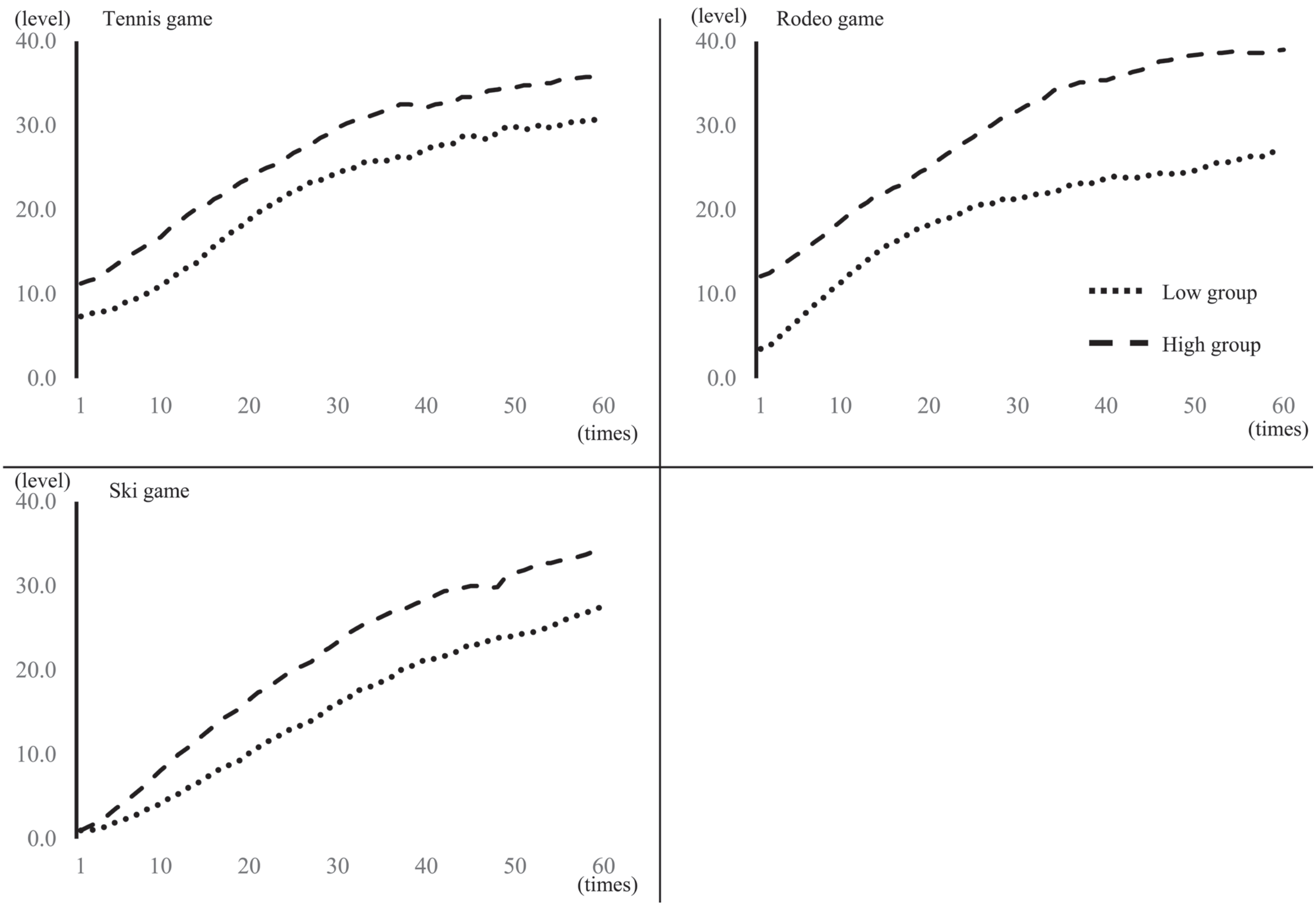

Fig. 2. Change of game level with increasing game experience for tennis game (upper left), ski game (lower left), and rodeo game (upper right). Dotted line, average level in Low group; dashed line, average level in High group.

the differences between initial and final game level were statistically significant for all games.

DISCUSSION

This study monitored changes in balance and physical function after BEAR use in patients who had undergone allo-HSCT. A previous study reported that the greatest impairment in such patients occurred at 90 days post allo-HSCT,[35] and balance function was impaired a few weeks post HSCT.[10] The physical function of patients following allo-HSCT was reported to recover to the same level as before allo-HSCT within approximately 1 year,[35] although trends in balance function remain unclear.

A previous study reported a minimal detectable difference (MDC) in the mini-BESTest score of cancer survivors of 8.5%.[24] We observed a 3.2% difference in the mini-BESTest scores between the pre- and post-evaluations in the High group. However, the difference in the mini-BESTest scores between the pre- and post-evaluations was 18.5% in the Low group. Therefore, the change in the mini-BESTest score in the Low group was meaningful in terms of the effects of the BEAR. In addition, there were statistically significant differences in the postural response between the pre- and post-evaluations in the Low group. Previous studies have assessed the effects of several interventions for postural response. Several perturbation methods have been used, such as pull perturbation on a treadmill or platform,[36–38] walking on a slippery ground surface[39–41] or surface change,[42,43] and ground surface translation during walking.[44,45] These previous studies reported that training with perturbation improved the fall-prevention reaction. In the present study, the BEAR included a perturbation game (Rodeo) in which the patients had to adapt to the robot's random movements. The robot's movements were unpredictable in terms of the direction and magnitude of the perturbation stimulus, and the success rate of the patients automatically adjusted the level of the next game. The Fitts and Posner model describes three stages (cognitive stage, associated stage, and autonomous phase) in motor learning skills.[46] During the early cognitive stage, the learner is highly dependent on visual feedback, whereas the learner is less dependent on visual feedback in the middle associated stage and the use of proprioceptive feedback increases. In use of the BEAR, the monitor enables visual recognition of movement. In addition, because the robot moves, the somatosensory system and proprioceptors are easily stimulated, thereby contributing to motor learning effects. Furthermore, the BEAR has an inverted pendulum control. Given that humans use inverted pendulum control to maintain a standing position, it is easy to generalize, even in an environment other than BEAR. Therefore, the patients in the Low group achieved the maximum effect from their efforts using the BEAR, with significant improvements in postural response.

We found no statistically significant changes in secondary outcome measurements in either group except for the Romberg ratio in the Low group. This effect may have been caused by the inability of the BEAR to provide sufficient load to induce changes in muscle strength. In a previous study, muscle activity during BEAR use was investigated in healthy subjects. The authors reported that the muscle activity in the thigh area was approximately 2% of the maximum voluntary contraction.[23] To improve muscle strength, high-load exercise of approximately 80% of one repetition maximum is generally used.[47] It has been reported that muscle strength can be improved by low-load exercise, but even during low-load exercise, the load is approximately 20% of one repetition maximum.[47] Therefore, the load on the muscle while using the BEAR was extremely low, and no change in muscle strength was observed. Conversely, there was a statistically significant difference in the Romberg ratio in the Low group. As we described previously, use of the BEAR stimulated the somatosensory system and proprioceptors, thereby allowing motor learning effects to be obtained. Therefore, the change in balance function from using the BEAR did activate motor control but did not alter muscle strength.

Study Limitations

This study has some limitations. The BEAR automatically adjusted the game levels for each patient, but only one level at a time. Therefore, in patients with high balance function, the game level was only increased by one game level at a time, even if the patient demonstrated an ability above the set game level. In these cases, it is possible that the exercise load was not optimal. However, as another limitation, some patients with lower stamina were unable to complete full BEAR sessions. Furthermore, given the lack of available space in clean rooms and the requirements of large floor area for the BEAR system, patients had to leave the clean room environment to use the BEAR. Unfortunately, almost all patients that were allowed to leave the clean room were discharged within 1 or 2 weeks and did not continue with BEAR therapy. Future studies should include a larger sample size and focus on structural improvement of the BEAR, such as decreasing its space requirements. For example, it would be desirable to develop balance training that could be performed in a sitting position using less expensive equipment such as home video game consoles so that even patients with poor balance function can participate. In addition, future studies should seek to identify the cause of prolonged stays in the clean room and the association with balance dysfunction in patients receiving allo-HSCT.

CONCLUSION

Balance training using the BEAR was effective for patients with balance dysfunction after allo-HSCT.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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