Development of an Evidence-Based Exercise Program for Patients Undergoing Hematopoietic Stem Cell Transplantation

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Abstract

PURPOSE

Although the efficacy of different exercise programs on different outcomes of hematopoietic stem cell transplantation (HSCT) patients have been examined, the details of process of exercise program development has not been described previously. In this study, we described the systematic development process of an evidence-based exercise program for HSCT patients.

METHODS

We developed the exercise program for HSCT patients using eight steps: (1) a literature review, (2) understanding patient characteristics, (3) first expert group discussion, (4) development of the first draft of the exercise program, (5) a pre-test, (6) second expert group discussion, (7) a pilot study, and (8) a focus group interview.

RESULTS

Through six systematic steps, tailored exercise program was developed based on patients' physical and hospital room conditions, which varies in intensity (three different intensities) and exercise positions (supine, sitting, and standing). Then, a pilot randomized trial was conducted on 21 patients with HSCT patients. The adherence rate to exercise program was 44.7% and significantly better timed up and go and symptom scale were seen in the exercise group compared than those of control group. Through the last step, three barriers and four facilitators of exercise during HSCT were identified.

CONCLUSION

A safe and feasible tailored unsupervised exercise program for patients during HSCT was developed and tested. In the future, the efficacy of the exercise program should be tested with RCT with implementation strategies to reduce exercise barriers and maximize facilitators of exercise identified in the current study.

Introduction

Although hematopoietic stem cell transplantation (HSCT) is a primary medical treatment option for patients with hematologic diseases such as leukemia, lymphoma, and multiple myeloma (1), it has many physiological and psychological side effects (1–4). Previous randomized controlled trials have reported that exercise improve physical function (5–7), fatigue (7, 8), depression (9, 10), anxiety (9), and quality of life (11) in patients receiving HSCT. However, the exercise programs described in previous studies have limited applicability to HSCT patients in real clinical settings in terms of different treatment processes and environments (e.g., isolation period, size of the hospital room, and access to exercise equipment and therapist). For example, aerobic exercises on a treadmill or stationary bike that were used in previous studies (5–7, 11–18), require space and equipment. Moreover, the supervised exercise programs (7, 15) (16–18) are difficult to implement in an isolated room due to limited access.

Intervention programs must be cautiously and carefully developed in clinical trials. Particularly for patients receiving intense treatment or with serious health conditions such as HSCT, a reliable intervention program which guarantees safety and feasibility is required. Evidence-based medicine involves integrating the clinical expertise, proficiency, and

judgment that individual clinicians acquired from clinical experience and practice, with the best available external clinical evidence from systematic research (19–21). Accordingly, we attempted to develop an exercise program for HSCT patients based on evidence from a systematic process used by An et al. (21). Here, we describe the development process of an evidence-based exercise program for patients receiving HSCT.

Methods

Study design and participants

In the current study, we developed an exercise program using 10 systematic steps developed by An et al. (21). We changed the order of the focus group interview from the original process and included only the first eight steps. The development process in this study included (1) a literature review, (2) understanding patient characteristics, (3) first expert group discussion, (4) development of the first draft of the exercise program, (5) a pre-test, (6) second expert group discussion, (7) a pilot study, and (8) a focus group interview (Fig. 1). Patients with hematologic disease receiving HSCT participated in this study. All study procedures were approved by the institutional review board and the research ethics committee of Severance Hospital (no. 4-2016-0676). Written informed consent was obtained from all participants.

Step 1. Literature review

The electronic online literature databases such as Embase, Pubmed, and CENTRAL were searched. To identify relevant studies, the following search terms were used: (hematopoietic stem cell transplantation OR bone marrow transplantation OR autologous transplantation OR allogeneic transplantation OR peripheral blood stem cell transplantation) AND (exercise OR physical activity (PA) OR training) AND (randomized controlled trial). Two investigators (KYA, MSY) independently filtered the references retrieved from the literature search by screening the titles and abstracts. The selected articles were re-filtered based on full-text review to identify relevant information. The articles were included if they met the following inclusion criteria: 1) published in English, 2) full-text article, 3) randomized controlled trial, 4) included inpatient exercise intervention, and 5) included patients with hematologic diseases receiving HSCT. The literature search adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement guidelines.

Step 2. Understanding patient characteristics

In this step, we collected data by observation, survey, interview, and physical assessment. An exercise therapist accompanied a hematologist on the daily ward rounds, and observed and recorded the changes in patient performance status from the treatment process by the Karnofsky Performance Status Scale (KPS) (22) for four weeks.

The patient survey was conducted to identify the PA level, performance status, exercise barriers, and exercise beliefs of HSCT patients. Pre-diagnosis and current PA level were assessed by the International PA Questionnaire short form (23), while exercise belief was assessed using the modified Exercise & Quality of Life Questionnaire (24). Exercise barriers were investigated using an open question and performance status was assessed by the KPS (22).

Participants were also interviewed about their exercise barriers and preferences, expected effects of exercise, and changes in physical and psychological condition according to treatment during the hospitalization. A face-to-face interview was conducted with trained research staff in an independent space to ensure participant comfort.

Range of motion at eight joints (i.e. neck, shoulder, elbow, wrist, trunk, hip, knee, and ankle) was assessed using goniometers and patient-perceived pain levels during each movement were recorded using the Wong-Baker Faces Pain Rating Scale (0–10) (25) .

Step 3. First expert group discussion

An expert group consisted of two hematologists, a nurse, and a fellow in hematology, and three exercise specialists including one professor in kinesiology. Patients' condition and physical functions, exercise goals, and precautions for exercise intervention were discussed.

Step 4. Development of the first draft of the exercise program

A draft version of the exercise program was developed based on the results of the step 1 to 3. First, possible resistance and stretching exercises for main muscle groups according to the anatomical motions of each joint were identified. Thereafter, the necessary and feasible exercises to meet the exercise goals were selected. Finally, the most appropriate exercises for HSCT patients varying intensities, ranging from extremely low to moderate, were included in the draft considering the patients' conditions, exercise precautions, and space availability.

Step 5. Pre-test

We tested the feasibility and safety of the draft program with three HSCT patients. Participants learned tailored exercises and were provided with an exercise brochure, exercise videos, and daily log book before they entered the isolated room (i.e. bio-clean room or laminar air flow room) for HSCT. The participants were asked to perform the exercise program for approximately three weeks while staying in the isolated room. The adherence to the program was recorded in the log book.

Step 6. Second expert group discussion

The expert group discussed the intensity, feasibility, safety, suitability, and effects of each exercise based on the results of the pre-test.

Step 7. Pilot randomized controlled trial (RCT)

A total of 21 participants with hematologic diseases who were initiating HSCT were recruited and randomly assigned to the exercise group or the usual care group in a 1:1 ratio using the permuted block design considering sex and transplantation type. Participants in the exercise group learned exercise program prior to admission to the isolated room and asked to perform the exercise program during their hospitalization. Printed information and video on exercise (<https://youtu.be/2TyjelwsrvU>) along with a daily log book were provided. Exercise specialists (KYA, MSY) visited the participants 2–3 times per week and encouraged participants to comply with prescribed exercise. Body composition, physical function, and symptoms were assessed before and after their stay in the isolated room. Blood transfusion volume and time to engraftment were obtained from each patient's electronic medical record.

Step 8. Focus group interview

We also collected qualitative data on the barriers and facilitators to completion of the exercise intervention during HSCT. A total of six participants in the exercise group of the pilot RCT participated in a face-to-face interview. All interviews were recorded and then transcribed and summarized by an interviewer, and the transcript and summary of the interview were confirmed by each participant to ensure their accuracy. The method of the qualitative data collection has been reported elsewhere (26).

Results

Step 1. Literature review

A total of 149 articles were initially found in the literature search and 18 articles (11 intervention programs) were included in the literature review. The literature search protocol is described in Fig. 2, and the characteristics of the exercise programs in the included articles are shown in Table 1.

Table 1
Characteristics and exercise programs of the selected studies

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Cunningham B.A. et al. (1986)	Three-arm RCT: exercise 3 times/week (EG3) vs. exercise 5 times/week (EG5) vs. control (CG)	30 marrow transplantation: EG3 = 10, EG5 = 10, CG = 10	EG: resistance exercise	Resistance exercise: biceps- triceps curl, bench press, shoulder retractors, straight leg raise, hip extension, hip abduction, sit up, knee extension; 30 min/session; 15 reps	Body weight: ↔ Arm muscle area: ↔ Temperature: ↔ Nitro balance: ↔ Creatinine excretion: ↓
Dimeo F. et al. (1997)	Two-arm RCT: exercise (EG) vs. control (CG)	70 patients underwent chemotherapy for auto-PBSCT: EG = 33, CG = 37	EG: daily aerobic exercise	Bed ergometer: 1 min, at least 50% of the cardiac reserve ×15 times, 1-min rest between bouts, 30 min/day, daily	Physical performance: CG↓ vs. EG Neutropenia: EG↓ vs. CG Thrombopenia: EG↓ vs. CG Platelet transfusion: EG↓ vs. CG Cardiologic examination: ↔ Pain severity: EX↓ vs. CG Duration of hospitalization: EG↓ vs. CG

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Mello M. et al. (2003)	Two-arm RCT: exercise (EG) vs. control (CG)	18 allo-BMT patients: EG = 9, CG = 9	EG: active exercise, muscle stretching, treadmill walking	<p>Active ROM exercise: shoulder, elbow, hip, knee and ankle</p> <p>Stretching: hamstring, triceps surae, quadriceps muscle.</p> <p>Treadmill walking: 5 sets of 3 min, 3-min rest between sets in the first week, 2 sets of 10 min with accelerated in the 6th week;</p> <p>daily, 40 min/session, HR < 70% of HR_{max}, 6 weeks</p>	Muscle strength: EG↑ vs. CG

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Kim S.D. & Kim H.S. (2005)	Two-arm RCT: exercise (EG) vs. control (CG)	35 allo-BMT patients: EG = 18, CG = 17	EG: bed exercise	<p>Bed exercise: preliminary exercise for 10 min, relaxation breathing for 10 min, finish exercise for 10 min</p> <p>Preliminary exercise: concentrate the attention on lower abdomen for 3 min, put left ankle on right knee for 3 min, put right ankle on left knee for 2 min, bend both knees for 2 min</p> <p>Finish exercise: rest and relax for 2 min, stroke hair and face for 2 min, rotate both ankles right and left for 2 min, stretch legs and arms for 2 min, stretch out on the bed for 2 min</p> <p>Every day, 30 min, 6 weeks</p>	Fatigue: EG↓ vs. CG

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Kim S.D. & Kim H.S. (2005)	Two-arm RCT: exercise (EG) vs. control (CG)	35 allo-BMT patients: EG = 18, CG = 17	EG: bed exercise	<p>Bed exercise: preliminary exercise for 10 min, relaxation breathing for 10 min, finish exercise for 10 min</p> <p>Preliminary exercise: concentrate on lower abdomen for 3 min, put left ankle on right knee for 3 min, put right ankle on left knee for 2 min, bend both knees for 2 min</p> <p>Finish exercise: rest and relax for 2 min, stroke hair and face for 2 min, rotate both ankles right and left for 2 min, stretch legs and arms for 2 min, stretch out on the bed for 2 min</p> <p>Every day, 30 min, 6 weeks</p>	<p>Anxiety: EG↓ vs. CG</p> <p>Depression: EG↓ vs. CG</p> <p>Leukocyte: EG↑</p>

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Kim S.D. & Kim H.S. (2006)	Two-arm RCT: exercise (EG) vs. control (CG)	35 allo-BMT patients: EG = 18, CG = 17	EG: bed exercise	<p>Bed exercise: preliminary exercise for 10 min, relaxation breathing for 10 min, finish exercise for 10 min</p> <p>Preliminary exercise: concentrate on lower abdomen for 3 min, put left ankle on right knee for 3 min, put right ankle on left knee for 2 min, bend both knees for 2 min</p> <p>Finish exercise: rest and relax for 2 min, stroke hair and face for 2 min, rotate both ankles right and left for 2 min, stretch legs and arms for 2 min, stretch out on the bed for 2 min</p> <p>Every day, 30 min, 6 weeks</p>	<p>Lymphocyte: CG↓ vs. EG</p> <p>T-cell subset: ↔</p>
DeFor T.E. et al. (2007)	Two-arm RCT: exercise (EG) vs. control (CG)	100 allo-HCT patients: EG = 51, CG = 49	<p>EG: structured walking regimen</p> <p>CG: no formal exercise</p>	<p>Treadmill walking: 2 times/day, at least 15 min during hospitalization; 1 time/day, 30 min after discharge</p>	<p>PA level: EG↑ vs. CG</p> <p>Karnofsky: ↔ in total population, CG↓ vs. EG in patients who received nonmyeloablative conditioning</p> <p>Physical and emotional well-being: EG↑ vs. CG, ↔ at 100 days post-transplant</p> <p>Length of hospital stay: ↔</p> <p>Survival: ↔</p>

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Jarden M. (2007)	Two-arm RCT: exercise (EG) vs. control (CG)	19 allo-HSCT patients (14 completed): EG = 8, CG = 6	EG: multimodal intervention of exercise, progressive relaxation, and psychoeducation CG: conventional care	Stationary cycling: 5 days/week, low to moderate intensity (50–75% HR _{max} , RPE 10–13, 5.5 MET), 15–30 min/session, rest intervals as needed, increase intensity and duration Stretching: 5 days/week (dynamic: 1–2 sets, 10–12 reps, static: 1 set, hold for 15–30 sec), 3.5 MET, 15–20 min/session Resistance training: 3 days/week, low to moderate intensity (1–2 sets, 10–12 reps, RPE 10–13, 3 MET), 15–20 min/session Progressive relaxation: 2 days/week, low intensity (RPE: 6–9, 2.5 MET), 20 min/session	Feasibility: 74% completed Exerciser group: 66% completed Adherence: 94% (cycling 86%, dynamic stretching 88%, resistance and relaxation 100%) Chest press: EG↑ vs. CG Leg extension: EG↑ vs. CG Right knee flex: EG↑ vs. CG Right elbow: ↔ VO _{2max} : ↔ Stair test: ↔

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Jarden M. et al. (2009)	Two-arm RCT: exercise (EG) vs. control (CG)	42 allo-HSCT patients: EG = 21, CG = 21	EG: multimodal intervention of exercise, progressive relaxation, and psychoeducation CG: conventional care	Stationary cycling: 5 days/week, low to moderate intensity (50–75% HR _{max} , RPE 10–13, 5.5 MET), 15–30 min/session, rest intervals as needed, increase intensity and duration Stretching: 5 days/week (dynamic: 1–2 sets, 10–12 reps; static: 1 set, hold for 15–30 sec), 3.5 MET, 15–20 min/session Resistance training: 3 days/week, low to moderate intensity (1–2 sets, 10–12 reps, RPE 10–13, 3 MET), 15–20 min/session Progressive relaxation: 2 days/week, low intensity (RPE: 6–9, 2.5 MET), 20 min/session	VO _{2max} : EG↑ Muscle strength: EG↑ Diarrhea (EORTC): EG↓ FACT-An: ↔ HADS: ↔ Self-reported PA: ↔

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Jarden M. et al. (2009)	Two-arm RCT: exercise (EG) vs. control (CG)	42 allo-HSCT patients: EG = 21, CG = 21	EG: multimodal intervention of exercise, progressive relaxation, and psychoeducation CG: conventional care	<p>Stationary cycling: 5 days/week, low to moderate intensity (50–75% HR_{max}, RPE 10–13, 5.5 MET), 15–30 min/session, rest intervals as needed, increase intensity and duration</p> <p>Stretching: 5 days/week (dynamic: 1–2 sets, 10–12 reps; static: 1 set, hold for 15–30 sec), 3.5 MET, 15–20min/session</p> <p>Resistance training: 3 days/week, low to moderate intensity (1–2 sets, 10–12 reps, RPE 10–13, 3 MET), 15–20 min/session</p> <p>Progressive relaxation: 2 days/week, low intensity (RPE: 6–9. 2.5 MET), 20 min/session</p>	Symptom: EG↓ vs. CG

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Baumann F.T., (2009)	Two-arm RCT: exercise (EG) vs. control (CG)	64 HSCT patients: EG = 32, CG = 32	EG: endurance + activities of daily living (ADL) training CG: standard care	Endurance: cycle ergometer, 7 times/week, goal: 10–20 min without interruption, watt load increased by 25 watt every 2 min until the patient reached a set heart rate (180 - age). Achieved watt load decreased by 20% and defined as patient's training intensity. ADL: strength, coordination, stretching, walking, ad stair climbing, 20–30 min/day, "slightly strenuous" or "strenuous" on the Borg scale.	Endurance: CG↓ vs. EG Strength: CG↓ vs. EG QOL (EORTC): ↔ Hematology: ↔

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Wiskemann J. et al. (2010)	Two-arm RCT: exercise (EG) vs. control (CG)	105 allo-HCT patients (80 completed): EG = 52, CG = 53	<p>EG: home-based exercise (1–4 weeks) before admission, supervised exercise after admission, home-based exercise after (8 weeks) discharge</p> <p>Endurance and resistance exercise using stretch bands</p> <p>CG: moderate PA recommendation, Telephone calls and visits in hospital as in EG</p>	<p>Endurance: 3–5 times/week, 20–40 min/session</p> <p>Resistance: 2 times/week</p> <p>20–40 min/session</p>	<p>Fatigue (MFI, POMS): CG↑ vs. EG</p> <p>Fatigue (EORTC): ↔</p> <p>Physical function (EORTC, HADS): EG↑ vs. CG</p> <p>Anxiety (HADS): EG↑</p> <p>Distress (HADS): EG↓</p> <p>Anger/hostility (POMS): EG↑ vs. CG</p> <p>Pain (EORTC): EG↓ vs. CG</p> <p>6-MWT: EG↑</p> <p>Lower-extremity strength: EG↑</p> <p>Pedometer step: ↔</p> <p>Coordination (balance): ↔</p>

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Baumann F.T. et al. (2011)	Two-arm RCT: exercise (EG) vs. control (CG)	47 allo-HSCT(33 completed, 14 deceased): EG = 17, CG = 16	EG: endurance + ADL training CG: standard care	Endurance: cycle ergometer, 7 times/week, goal: 10–20 min without interruption, watt load increased by 25 watt every 2 min until the patient reached a set heart rate (180 - age). Achieved watt load decreased by 20% and defined as patient's training intensity. ADL: strength, coordination, stretching, walking, and stair climbing, 20–30 min/day, "slightly strenuous" or "strenuous" on the Borg scale.	Endurance: CG↓ Strength: CG↓ Lung function: ↔ Weight: EG↓CG↓ Fatigue: CG↑ Physical function: EG↓CG↓ Emotional state: EG↑
Oechsle K. et al. (2014)	Two-arm RCT: exercise (EG) vs. control (CG)	48 auto-PBSCT: EG = 24, CG = 24	EG: supervised exercise, warm-up + endurance + resistance exercise + stretching	Endurance: bicycle ergometer, 5 times/week, 10–12 min/session, individually adjusted intensity Resistance: bridging, sit-ups, back and arm exercise using elastic band, 40–60% of 1RM, 16–25 reps, 2 sets, 5 times/week, 20 min/session	Physical performance: EG↑ CG↓ Oxygen consumption: EG↑ vs. CG Expiratory minute ventilation: EG↑ vs. CG QOL (physical function): EG↑ vs. CG Fatigue (cognition, psychosocial function): EG↓ vs. CG

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Wiskemann J. et al. (2013)	Two-arm RCT: exercise (EG) vs. control (CG)	105 allo-HCT patients (80 completed): EG = 52, CG = 53	EG: home-based exercise (1–4 weeks) before admission, supervised exercise after admission, home-based exercise (8 weeks) after discharge Endurance and resistance exercise using stretch bands CG: moderate PA recommendation, Telephone calls and visits in hospital as in EG	Endurance: 3–5 times/week, 20–40 min/session Resistance: 2 times/week 20–40 min/session	6MWT: EX unfit ↑ vs. EX fit All muscle strength group: EX unfit ↑ vs. EX fit Knee-extension: Unfit ↑ vs. control Hip-flexion: Unfit ↑ vs. control Elbow-extension: Unfit ↑ vs. control 6MWT: Unfit ↑ vs. control
Jacobsen P.B. et al. (2014)	Four-arm RCT: exercise (EG) vs. stress management (SM) vs. combination (COM) vs. usual care (CG)	711 auto- or allo-HCT patients: EG = 180, SM = 178, COM = 178, CG = 175	EG: walking SM: abdominal breathing + muscle relaxing + coping self-statements COM: exercise + stress management	Exercise goal: 20–30 min/session, 3–5 times/week, 50–75% of heart rate reserve, 180 days	PSC (+ 100 days): ↔ MCS (+ 100 days): ↔ Overall survival (+ 100 days): ↔ Days of hospitalization (+ 100 days): ↔ Distress (+ 100 days): ↔ Sleep quality (+ 100 days): ↔ Pain (+ 100 days): ↔ Nausea (+ 100 days): ↔

Author (year)	Design	Participants	Intervention	Exercise program details	Result
Bargi G. et al. (2016)	Two-arm RCT: inspiratory muscle training (IMT) group vs. control group (CG)	55 allo-HSCT patients (38 completed): IMT = 20, CG = 18	IMT: IMT at 40% of maximal inspiratory pressure (MIP) CG: IMT at 5% of MIP	30 min/day, 7 days/week, 40% of MIP, 6 weeks	MISWT: IMT ↑ vs. CG 6-MWT: IMT ↑ vs. CG Respiratory muscle strength: IMT ↑ vs. CG Depression: IMT ↓ vs. CG Dyspnea: IMT ↓ Fatigue: IMT ↓ Peripheral muscle strength: ↔ QOL: IMT ↑
Kuehl R. et al. (2016)	Two-arm RCT: exercise (EG) vs. control (CG)	153 allo-HCT patients: EG = 76, CG = 77	EG: endurance and resistance exercise CG: muscle relaxation program	5 times/week (3 supervised) during hospitalization Home-based 3–5 times/week after discharge (10-min phone call)	Adherence: 100% Determinants for exercise adherence: low physical fatigue, having children home during inpatient, endurance performance, controlling for emotional functioning after discharge Determinants for contamination: isometric muscle strength, physical fatigue
6MWT: 6-min walking test; allo-HCT, allogeneic hematopoietic cell transplantation; BMT, bone marrow transplantation; HSCT, hematopoietic stem cell transplantation; MISWT: Modified Incremental Shuttle Walking Test; PBSCT, peripheral blood stem cell transplantation; RM, repetition maximum; ROM, range of motion					

The literature review identified that the previous exercise programs included aerobic, resistance, breathing, core, and stretching exercises, and an elastic band, bare hand, or ankle weight were used for the resistance exercise and a stationary bike or treadmill walking was used for the aerobic exercise. Stretching was performed as a warm-up or cool-down exercise in most of the included studies.

Exercise intensity was 50–70% of the heart rate (HR) reserve or rate of perceived exertion (RPE) of 10–14. The intensity of the resistance exercise was 40–60% of 1 repetition maximum, an RPE of 10–16, or slightly strenuous to strenuous. Exercise duration was gradually increased in the range of 20–40 min/day. The range of exercise frequency was 3–7 days/week. Among 11 programs, seven were supervised interventions. We identified the possible type, intensity, and frequency of exercise that HSCT patients can perform.

Step 2. Understanding patient characteristics

A total of three HSCT patients were observed for four weeks. Their KPS scores were in the range of 20–70 depending on the treatment process and individual health condition. The patients who had KPS scores of 20–30 spent most of their time lying on the bed in the laminar air flow/bio-clean room. Participants initially stayed in the general room for about a week, followed by a stay in the laminar air flow or bio-clean room of about three weeks for chemotherapy, transplantation, and engraftment. After engraftment, they moved back to the general room and stayed there for one or two weeks before discharge. The room type (laminar air flow or bio-clean) is generally decided by transplantation type (autologous or allogeneic). Participants in the laminar air flow room were restricted from contacting with others and leaving the room to prevent infection. The patients in the bio-clean room have a caregiver in the room but the bed space is sterile and covered with plastic curtains to minimize contact with other people. The patients in the bio-clean room had to stay on the bed within the plastic curtain whenever possible except when going to the bathroom. Thus, the PA levels of the patients were extremely low. The results of the observation were summarized as follows: 1) exercise intensity should be started very low; 2) exercises that can be performed on the bed are required because of the limited ambulation; 3) an unsupervised exercise program was needed because of the limited contact; and 4) recovery of physical function, maintenance of muscle mass and range of motion, and improvement of psychological factors might be the primary goals of the exercise program.

A total of 15 HSCT patients were surveyed. The results of the patient survey are shown in Table 2. The mean current light PA time was shorter than the pre-diagnosis light PA. No participants had current moderate to vigorous PA and participants with multiple myeloma were the least active. The KPS score during chemotherapy was lower than those during pre-chemotherapy and the recovery period. Dry mouth, fatigue, drowsiness, numbness, and pain were the most common symptoms. All participants reported that they believed that exercise positively affects the recovery from HSCT.

Table 2
Participants' physical activity level and performance status

	Pre-diagnosis daily walking time (min/day)	Current daily walking time (min/day)	Karnofsky score (0 ~ 100)
Total (n = 15)	27.86 ± 38.47	1.74 ± 4.12	60.67 ± 13.35
Diagnosis			
Lymphoma (n = 7)	40.36 ± 51.87	3.02 ± 5.69	62.86 ± 16.04
Leukemia (n = 5)	23.65 ± 20.88	1.00 ± 2.24	62.00 ± 10.95
Multiple myeloma (n = 3)	5.71 ± 9.90	0	53.33 ± 11.55
Transplantation			
Auto (n = 8)	4.29 ± 8.57	0	50.00 ± 11.55
Allo (n = 3)	22.72 ± 19.89	6.67 ± 7.64	70.00 ± 10.00
Half allo (n = 4)	32.62 ± 31.48	0	60.00 ± 10.00
Treatment Process			
Pre-chemo (n = 4)	22.32 ± 21.65	1.54 ± 2.79	67.50 ± 15.00
Chemo (n = 1)	145.50 ± 0.00	0	50.00 ± 0.00
*Recovery (n = 10)	18.32 ± 22.24	2.00 ± 4.83	59.00 ± 12.87
*Recovery means status after outgoing from bioclean/laminar flow room			

A total of 14 participants completed the interview. We identified that participants experienced physical symptoms such as nausea, vomiting, exhaustion, and anemia during chemotherapy and recovery period as well as psychological distress due to loneliness and claustrophobia in the isolated room and wanted a daily exercise program because of boredom and loneliness. Additionally, the participants thought that resistance exercise, stretching, and stepping were appropriate during HSCT treatment and expected those exercises would help them maintain muscle mass, muscle strength, and physical fitness as well as improve their blood circulation. The exercise barriers included limited space, lack of information, decreased physical fitness, and the presence of medical tubes and intravenous lines. In particular, the patients with multiple myeloma reported bone-related problems such as dislocation and severe pain that were caused by osteolytic lesions at the shoulder or lower back. Participants additionally wanted an exercise program that featured: 1) reliable exercise information; 2) supervised exercise with an expert; 3) therapeutic exercise programs as a standard treatment; 4) tailored and modified exercise intensity according to individual daily condition; 5) exercises that could be performed in a limited space; 6) sufficient pre-exercise education before entering the isolated room; and 7) availability of self-exercise materials in the isolated room.

A total of nine participants participated in the measurement of the range of motion. Two participants with multiple myeloma were unable to complete the measurement because of osteolytic lesion-related problems. The other seven participants had full range of motion without any limitations or pain at all joints. This test identified that patients with multiple myeloma commonly had osteolytic lesions that limited their movement, while other HSCT patients did not have any limited movements for exercise.

Step 3. First expert group discussion

The hematologist (JWC) suggested different types of exercise for the three different hospital rooms because of different spaces and contact limitations, and for participants with multiple myeloma because of osteolytic lesions. The kinesiology professor (JYJ) suggested different intensities of the exercise program according to an individual's daily condition, and extra exercises to strengthen the joints of participants with multiple myeloma. He also suggested a daily exercise because the exercise intensity would be low. The exercise goal was deemed to be the maintenance of muscle mass, muscular fitness, walking ability, and cardiopulmonary function, all of which may decline due to lack of PA and immobilization in the isolated room. Aerobic exercise such as walking or biking was not included in the program due to the limited equipment and space. Instead, rest intervals between exercises were minimized to increase heart rate during exercise.

Step 4. Development of the first draft of the exercise program

The exercises included stretching, resistance exercises, and joint-specific exercises using body weight or an elastic band. The exercises were performed in three different positions (supine, sitting, and standing) according to patient condition (bad, normal, or good) and hospital room type (general, laminar air flow, or bio-clean room). Three extra joint exercises (shoulder, lower back, and knee) were included for patients with osteolytic lesions.

Step 5. Pre-test

A total of three participants participated in the pre-test: two in the bio-clean room and one in the laminar air flow room. Participants had no problem performing exercises following the instruction of the brochure and exercise videos. Participants reported that all exercises in the program were feasible and safe when their physical condition was good. However, they reported difficulty completing the prescribed exercises daily when their physical condition was poor, even though exercise prescribed to them was extremely low- or low-intensity exercise program which they could perform in the supine position. A lack of motivation and energy to comply with the prescribed exercise program were the most significant barriers to exercise. The participants reported that they laid on bed all day when their physical condition was extremely bad.

Step 6. Second expert group discussion

In the second expert group discussion, all expert group members agreed to use the first draft of the exercise program without changes for the next step.

Step 7. Pilot RCT

The results of pilot RCT are shown in Table 3. A total of 21 participants participated in this study. The average adherence to the exercise program was 44.7%. The time for 8-foot up-and-go ($p = 0.032$) and the symptom score ($p = 0.039$) were significantly increased in the control group while there is no significant change in the exercise group. Moreover, physical functions tended to decrease and blood transfusion volume and time to engraftment tended to be higher in the control group than the exercise group. There was no exercise-related complication reported in the exercise group. These results showed the safety and potential positive effects of the exercise program on the patients' health-related fitness, symptoms, and recovery-related variables. However, an advanced strategy to improve exercise adherence during HSCT was needed to optimize the effects of the exercise program.

Table 3
The effects of the exercise program on recovery from HSCT.

Exercise group (n = 10)					Control group (n = 11)				p value
Variables	n	Baseline	At discharge	Δ	n	Baseline	At discharge	Δ	
Body composition									
Weight(kg)	10	66.7 ± 17.0	64.4 ± 15.4*	-2.3 ± 2.6	10	58.8 ± 11.7	57.2 ± 11.9*	-1.6 ± 1.9	0.49
BMI(kg/m ²)	10	24.1 ± 4.6	23.0 ± 3.9*	-1.1 ± 1.5	10	22.8 ± 3.6	22.1 ± 3.7*	-0.6 ± 0.8	0.37
Muscle mass(kg)	10	25.5 ± 8.3	25.1 ± 7.7	-0.5 ± 1.3	10	23.2 ± 4.9	22.3 ± 4.5	-0.9 ± 1.9	0.55
Fat mass(kg)	10	19.9 ± 5.6	18.2 ± 4.4	-1.7 ± 2.4	10	15.8 ± 4.2	15.8 ± 6.3	0.0 ± 2.8	0.16
Fat percent(%)	10	30.3 ± 6.3	28.8 ± 5.2	-1.6 ± 3.3	10	26.7 ± 3.5	26.8 ± 6.8	0.2 ± 4.7	0.36
BMR(kcal)	10	1379.3 ± 295.8	1367.6 ± 276.3	-11.7 ± 49.2	10	1298.4 ± 173.6	1264.4 ± 158.2	-34.0 ± 69.9	0.42
Physical function									
2-min knee up(reps)	7	96.0 ± 15.1	91.6 ± 22.0	-4.4 ± 12.8	8	94.0 ± 14.9	72.9 ± 35.7	-21.1 ± 31.8	0.22
Sit and reach (cm)	9	1.6 ± 11.1	-5.4 ± 10.5	-7.0 ± 10.7	11	1.7 ± 15.4	-1.8 ± 14.2	-3.5 ± 10.0	0.47
Hand-grip strength(kg)	9	27.6 ± 13.2	27.1 ± 11.0	-0.5 ± 3.5	11	26.0 ± 8.3	24.3 ± 7.4	-1.8 ± 4.4	0.48
Chair stand(reps)	9	13.4 ± 3.8	14.0 ± 1.7	0.6 ± 3.0	10	13.3 ± 2.4	11.7 ± 4.4	-1.6 ± 3.5	0.17
8 foot up and go(sec)	9	6.1 ± 1.2	5.9 ± 0.7	-0.1 ± 1.0	10	7.0 ± 1.6	8.7 ± 2.1*	1.7 ± 2.1	0.030
Symptoms									
Symptom (0-130)	9	42.0 ± 23.1	54.2 ± 20.3	12.3 ± 17.4	10	31.7 ± 18.6	46.5 ± 23.3*	14.8 ± 19.3	0.77
Interference (0–60)	9	23.2 ± 18.3	29.8 ± 13.7	6.6 ± 14.9	10	24.6 ± 10.0	26.7 ± 19.4	2.1 ± 19.1	0.58
Recovery									
Platelet transfusion (ml)	10	987.2 ± 856.2			11	1243.8 ± 1208.8			0.59
Red blood cell transfusion (ml)	10	368.9 ± 428.1			11	807.3 ± 875.1			0.17
Platelet engraftment (day)	10	11.5 ± 6.9			11	12.9 ± 6.5			0.64

Exercise group (n = 10)					Control group (n = 11)				<i>p</i> value
Variables	n	Baseline	At discharge	Δ	n	Baseline	At discharge	Δ	
Abbreviation: N/A, not applicable; EG, exercise group; CG, control group									
<i>p</i> value for comparison of change of variables between exercise and control group									
* <i>p</i> < 0.05 vs. baseline.									

Step 8. Focus group interview

The result of this process has previously been reported (26). Through this process, three exercise barriers and four exercise facilitators were identified. The exercise barriers included physical barriers such as nausea, vomiting, sore throat, reduced appetite; psychological barriers such as decreased willpower and anxiety due to isolation; and environmental barriers such as neighboring patients' negative opinions about the exercise program and a lack of encouragement from the medical professionals. Exercise facilitators included the desire to exercise; easy, simple, and safe nature of the exercises; and the availability of detailed and reliable information about the importance and potential benefits of exercise from the medical professionals rather than an exercise therapist. Finally, the participants preferred the exercise program to be supervised by the exercise therapists rather than unsupervised.

Final exercise program

Despite the participants preferring a supervised program, the supervised sessions were provided only before the isolation period started due to limited access to the isolated room. Instead, a brochure including pictures of and instructions for each movement and online videos viewable by smartphone for self-managed sessions during the isolation. The exercise program is shown in Tables 4 and 5. The exercise program is daily and included stretching and resistance exercises using body weight in three different positions (i.e., lying down, sitting, and standing). The exercise intensity was classified as very low, low, or moderate, among which the participants were allowed to choose depending on their daily condition. The choice of the sitting or standing position was decided according to the room space. One to two sets of 10 repetitions for all isotonic exercise and 10 seconds for all isometric exercises and stretches were performed each day. If the participants had osteolytic lesions, they were prescribed extra exercises for the problematic joint. The daily maximum exercise time was less than 30 minutes, which was shorter than previous exercise programs considering the patients' low physical condition and daily exercise frequency.

Table 4
Contents of inpatient exercise program for HSCT patients

Exercise type		Detailed exercises
Stretching (very low intensity)		Lying neck and ankle stretching
		Lying shoulder circle
		Lying trunk rotation
		Lying hamstring stretching
		Lying hip joint stretching
		Lying thigh isometric exercise
Lying down resistance exercise (low intensity)		Lying neck bridge
		Lying band front raise
		Lying band arm curl
		Lying pelvic tilt
		Lying shoulder bridge
		Lying ball knee adduction
		Lying calf isometric exercise
Sitting resistance exercise (moderate intensity)		Sitting band row
		Kneeling wall push-up
		Crunch
		Straight leg bridge
		Side leg raise
		Sitting thigh isometric exercise
		Sitting calf isometric exercise
Standing resistance exercise (moderate intensity)		Standing band row
		Standing bed push-up
		Crunch
		Good morning and side band
		Standing hip exercise (abduction, flexion, and extension)
		Sit and stand
		Standing calf raise
Joint exercise	Shoulder	Lying band ex-rotation exercise
		Lying band in-rotation exercise
	Lower back	Pelvic tilt
		Shoulder bridge

Exercise type	Detailed exercises
Knee	Lying thigh isometric exercise
	Sitting isometric leg curl
HSCT, hematopoietic stem cell transplantation	

Table 5
Exercise program tailored to the patient's daily condition and room type

Room	Condition		
	Bad (very low)	Normal (low)	Good (moderate)
Laminar air flow room or General room	Stretching	Stretching and lying down resistance exercise	Stretching and standing resistance exercise
Bio-clean room	Stretching	Stretching and lying down resistance exercise	Stretching and sitting resistance exercise
Joint exercise ^a	Shoulder/lower back/knee exercise		
^a Patients with joint problems add exercise for each problematic joint			

Discussion

Although exercise is a safe intervention method, it can cause injury, tiredness, or even fainting in patients with poor health condition. Nevertheless, no reliable standardized exercise program for HSCT patients has been developed to date. This study introduced the development process of an evidence-based exercise program for HSCT patients, which is a modified version of the An et al.'s development process of the exercise program for postoperative colorectal cancer patients (21).

Through the literature review, we realized that medical environments for HSCT among different countries differ and that we needed a tailored program suitable for the Korean medical environment. In most previous studies, the participants performed aerobic exercise using a treadmill or stationary bike (5–7, 11–18) and participated in a supervised program (5–11, 14–18, 27). However, in the Korean medical environment, the use of a treadmill and stationary bike, and a supervised program were not available because of confined space and lack of access to the isolated room. For these reasons, we developed a suitable program for the Korean medical environment that included bed exercises requiring minimal exercise equipment and space. These findings suggest that the development of a tailored intervention program based on participant needs and study environments may be essential in different circumstances.

Low adherence to the exercise program was the most important limitation of this study. Previous studies (7, 15, 17, 28) reported 94% and 87% rates of exercise adherence with the supervised program, respectively. However, we were unable to use the supervised program because of the inaccessibility during the isolation period; thus, our adherence rate was much lower (45%). In the focus group interview, the participants mentioned poor physical and psychological conditions as exercise barriers; and the easy and simple nature of the exercises, and reliability of the information. Many

participants admitted that the exercise program was easy and simple to perform. Nevertheless, they may not be motivated when their physical and psychological conditions are extremely poor due to chemotherapy and HSCT.

Participants also reported a lack of motivation from medical professionals as an exercise barrier. According to the Theory of Planned Behavior, if they think their significant others want them to perform the behavior (subjective norm), they will have the intention to perform the behavior (29). Furthermore, Park et al. (30) showed that an oncologist's exercise recommendation with an exercise motivation package significantly increased exercise participation among breast and colorectal cancer patients. If not only exercise therapists but also medical professionals such as physicians or nurses provided exercise recommendations and encouragements, it might have been able to improve exercise adherence and show significant differences between groups.

Limitations of this study include the low exercise adherence rate, small sample size, and non-significant differences between groups in the feasibility study. Nevertheless, this study showed the detailed process of development of the exercise program for HSCT patients using evidence from the literature, expert opinions, patient feedback, and objective measures. Furthermore, this study demonstrated the potential of the developed program to improve the health-related fitness and recovery of HSCT patients. A randomized controlled trial using this evidence-based exercise program with additional support by medical professionals is required to validate its effects.

In conclusion, this study described the development process of an evidence-based exercise program for Korean HSCT patients. Despite evidence from the literature review, patient needs, and expert opinions, exercise adherence was low in the real clinical setting. To validate the effects of this evidence-based exercise program using a randomized controlled trial, strategies to improve exercise adherence involving medical professional cooperation is required. With improved adherence, this program is expected to benefit the physical and hematologic recovery of HSCT patients.

Declarations

Funding

This study was conducted without funding.

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

All study procedures were approved by the institutional review board and the research ethics committee of Severance Hospital (no. 4-2016-0676).

Consent to participate

Written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

JY Jeon, JW Cheong, MS Yu, and KY An participated in the study concept and design. JW Cheong and M Choi participated in participants recruitment. KY An had full access to all of the data in the study and participated in data analysis. KY An, MS Yu, and M Choi participated in data collection. KY An participated in the drafting of the manuscript. W Cho, M Choi, K Courneya, M Choi, JW Cheong, and JY Jeon participated in critical revision of the manuscript.

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References

1. Copelan EA (2006) Hematopoietic stem-cell transplantation. *N Engl J Med* 354(17):1813–1826
2. Wiskemann J, Huber G (2008) Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 41(4):321–329
3. Baker F, Zabora J, Polland A, Wingard J (1999) Reintegration after bone marrow transplantation. *Cancer Pract* 7(4):190–197
4. Hayes SC, Rowbottom D, Davies PS, Parker TW, Bashford J (2003) Immunological changes after cancer treatment and participation in an exercise program. *Med Sci Sports Exerc* 35(1):2–9
5. Oechsle K, Aslan Z, Suesse Y, Jensen W, Bokemeyer C, de Wit M (2014) Multimodal exercise training during myeloablative chemotherapy: a prospective randomized pilot trial. *Support Care Cancer* 22(1):63–69
6. Baumann FT, Zopf EM, Nykamp E, Kraut L, Schule K, Elter T et al (2011) Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention. *Eur J Haematol* 87(2):148–156
7. Wiskemann J, Dreger P, Schwerdtfeger R, Bondong A, Huber G, Kleindienst N et al (2011) Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation. *Blood* 117(9):2604–2613
8. Kim SD, Kim HS (2005) Effects of a relaxation breathing exercise on fatigue in haemopoietic stem cell transplantation patients. *J Clin Nurs* 14(1):51–55
9. Kim SD, Kim HS (2005) Effects of a relaxation breathing exercise on anxiety, depression, and leukocyte in hemopoietic stem cell transplantation patients. *Cancer Nurs* 28(1):79–83
10. Bargi G, Guclu MB, Aribas Z, Aki SZ, Sucak GT (2016) Inspiratory muscle training in allogeneic hematopoietic stem cell transplantation recipients: a randomized controlled trial. *Support Care Cancer* 24(2):647–659
11. Baumann FT, Kraut L, Schule K, Bloch W, Fauser AA (2010) A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. *Bone Marrow Transplant* 45(2):355–362
12. DeFor TE, Burns LJ, Gold EM, Weisdorf DJ (2007) A randomized trial of the effect of a walking regimen on the functional status of 100 adult allogeneic donor hematopoietic cell transplant patients. *Biol Blood Marrow Transplant* 13(8):948–955
13. Mello M, Tanaka C, Dulley FL (2003) Effects of an exercise program on muscle performance in patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant* 32(7):723–728

14. Dimeo F, Fetscher S, Lange W, Mertelsmann R, Keul J (1997) Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. *Blood* 90(9):3390–3394
15. Wiskemann J, Kuehl R, Dreger P, Schwerdtfeger R, Huber G, Ulrich CM et al (2014) Efficacy of exercise training in SCT patients—who benefits most? *Bone Marrow Transplant* 49(3):443–448
16. Jarden M, Baadsgaard MT, Hovgaard DJ, Boesen E, Adamsen L (2009) A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT. *Bone Marrow Transplant* 43(9):725–737
17. Jarden M, Hovgaard D, Boesen E, Quist M, Adamsen L (2007) Pilot study of a multimodal intervention: mixed-type exercise and psychoeducation in patients undergoing allogeneic stem cell transplantation. *Bone Marrow Transplant* 40(8):793–800
18. Jarden M, Nelausen K, Hovgaard D, Boesen E, Adamsen L (2009) The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial. *J Pain Symptom Manage* 38(2):174–190
19. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS (1996) Evidence based medicine: what it is and what it isn't. *Bmj* 312(7023):71–72
20. Sackett DL (1997) Evidence-based medicine. *Seminars in perinatology* 21(1):3–5
21. An KY, In Yang H, Kang DW, Courneya KS, Jeon JY. Development process of an evidence-based exercise program for post-operative colorectal cancer patients. *Support Care Cancer*. 2020;28(2):755 – 65
22. Mor V, Laliberte L, Morris JN, Wiemann M (1984) The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. *Cancer* 53(9):2002–2007
23. Chun MY (2012) Validity and reliability of korean version of international physical activity questionnaire short form in the elderly. *Korean J Fam Med* 33(3):144–151
24. Chung JY, Lee DH, Park JH, Lee MK, Kang DW, Min J et al (2013) Patterns of physical activity participation across the cancer trajectory in colorectal cancer survivors. *Support Care Cancer* 21(6):1605–1612
25. Garra G, Singer AJ, Taira BR, Chohan J, Cardoz H, Chisena E et al (2010) Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients. *Acad Emerg Med* 17(1):50–54
26. Yu MS, An KY, Byeon J, Choi M, Cheong JW, Courneya K et al (2020) Exercise barriers and facilitators during hematopoietic stem cell transplantation: a qualitative study. *BMJ Open* 10(9):e037460
27. Kim SD, Kim HS (2006) A series of bed exercises to improve lymphocyte count in allogeneic bone marrow transplantation patients. *Eur J Cancer Care (Engl)* 15(5):453–457
28. Jacobsen PB, Le-Rademacher J, Jim H, Syrjala K, Wingard JR, Logan B et al (2014) Exercise and stress management training prior to hematopoietic cell transplantation: Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. *Biol Blood Marrow Transplant* 20(10):1530–1536
29. Ajzen I (1991) The theory of planned behavior. *Organizational Behavior Human Decision Process* 50(2):179–211
30. Park JH, Lee J, Oh M, Park H, Chae J, Kim DI et al. The effect of oncologists' exercise recommendations on the level of exercise and quality of life in survivors of breast and colorectal cancer: A randomized controlled trial. 2015;121(16):2740–8

Figures

Figure 1

The exercise program development process

Figure 2

The literature search protocol