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ORIGINAL RESEARCH

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Effect and feasibility of the combination of branched chain amino acid and exercise therapy on muscle mass and echo intensity of muscle in orthopedic patients in a convalescent rehabilitation hospital: A crossover trial

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Abstract

Background and Aims: This study examined the feasibility of nutritional support combined with exercise intervention for restoring muscle and physical functions in convalescent orthopedic patients.

Methods: We used a crossover design in which nutritional support combined with exercise intervention was administered daily during the early (1 month) and late (1 month) cycles with a 1-week washout period. The exercise intervention was performed twice daily for 2 months in the early and late groups. The exercise intervention consisted of one set of muscle strength, stretching, and physical activity exercises for 20 min each. Nutritional interventions were administered immediately after the exercise. A 3.4 g of branched-chain amino acid supplements (BCAAs) or 1.2 g of starch was ingested. We measured the skeletal muscle mass and isometric muscle strength of the limbs and performed balance tests. After the crossover, the BCAA and Placebo groups were compared.

Results: The ratio of improvement in the echo intensity of the rectus femoris (RF) was significantly higher in the BCAA group. A comparison of the order of nutritional intervention showed a significant effect on the RF echo intensity in both groups only when BCAAs were administered.

Conclusion: This study's results suggest that the proposed combined intervention improves muscle quality and mass in convalescent orthopedic patients.

KEYWORDS

amino acid supplementation, combined therapy, convalescent rehabilitation hospital, dietary analysis, echo intensity of muscle, muscle mass

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1 | INTRODUCTION

Convalescent rehabilitation hospitals specialize in promoting discharge to the home through an intensive rehabilitation intervention that improves patients' activities of daily living (ADL). Okamoto et al.[1] reported that intensive rehabilitation intervention led to the possible maintenance of functional independence measure (FIM) gain and discharge rate to home, even for patients with severe disorders. Among rehabilitation interventions, muscle-strengthening exercises have generally been performed as the first choice for improving ADL function. A recent systematic review[2] showed that muscle-strengthening exercises were effective even for older adults aged >90 years with decreased physical activity. However, most older adults and inpatients cannot tolerate high-load or high-volume exercises. Low-intensity load exercises can improve muscle strength[3]; however, their effect on muscle gain is less than that of high-intensity load exercises.[4]

Recently, the concepts of sarcopenia and frailty have become more common. Also, several clinical guidelines or consensus papers on sarcopenia[5–9] and frailty[9–11] in European or Asian populations have been published. A common view shared in these studies was that a combination of exercise and nutritional therapy was recommended for improving muscle strength and mass. The recommended type and intensity of exercise were resistance exercise and 50% of one repetition maximum,[10,12] respectively. For nutritional therapy, sufficient protein intake, such as a daily protein intake of 1–1.5 g per kg (body weight), was recommended,[8,11] and vitamin D intake was recommended for frailty only in Asian regions,[11] whereas there is insufficient evidence of the recommendation for sarcopenia.[8] Protein is the main source of essential amino acids, and branched-chain amino acids (BCAA) are involved in triggering muscle protein synthesis.[13] The combination of BCAA intake and exercise is known to have a superior effect than each administered alone.[13–15]

Sarcopenia occurs widely among orthopedic patients[16] and those with stroke.[17] Besides, >40% of Japanese patients with degenerative scoliosis and hip fracture have had concomitant sarcopenia.[18] These recommendations for sarcopenia and frailty have been applied to patients with hip osteoarthritis,[19] artificial joints,[20–22] and stroke[23,24] to improve muscle strength. BCAA intake has been reported to promote knee extensor strengthening and prevent the decline of skeletal muscle mass in orthopedic patients before and after surgery.[20–22,25]

Diagnostic criteria for sarcopenia and frailty include muscle strength and skeletal muscle mass assessed using dual-energy X-ray absorptiometry and bioelectrical impedance analysis according to the Asian Working Group for Sarcopenia 2019.[7] In addition, the need to assess fatty infiltration in the skeletal muscle and muscle mass as a qualitative assessment of the muscle has also been raised in recent years.[26] Fatty infiltration in the skeletal muscle has been reported to occur even in healthy individuals after a short period (3 days) of severe inactivity.[27] Fatty infiltration in the skeletal muscle may also occur in cases of orthopedic diseases in which the affected part requires a certain rest period.

However, there has been only one crossover study on the feasibility of combined therapies for frail older adults.[28] Therefore, it has been impossible to determine the feasibility of combined therapies from previous randomized controlled trials.[29–32] The present study investigated the effectiveness and feasibility of a combination of exercise and nutritional intervention in improving muscle mass, intramuscular fat, and physical function in orthopedic patients in a convalescent rehabilitation hospital.

2 | MATERIALS AND METHODS

2.1 | Participants

Eighty-nine individuals aged ≥20 years who were hospitalized in a convalescent rehabilitation ward after orthopedic surgery or symptom onset were included in this study. The inclusion criteria were: orthopedic surgery after a fracture or trauma, spinal surgery, artificial joint surgery, and vertebral compression fracture. The exclusion criteria were: conservative therapy after lower limb fracture, restrictions on weight-bearing to the limbs, dietary restrictions due to diabetes mellitus or renal failure, and exercise due to cardiovascular disorder, dementia, depression, or schizophrenic disorder.

This study was registered in the UMIN-CTR Clinical Trial Registry, a Japanese official clinical trial registration system (ID: UMIN000037903 URL Available: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000043195 [Accessed April 17, 2023]) on September 3, 2019. Participants were recruited at Showa University Fujigaoka Rehabilitation hospital between September 15, 2019, and January 21, 2021. Follow-up examinations were performed during the inpatient period and before discharge. Clinical trial information registered in UMIN-CTR was sent to the International Clinical Trials Registry Platform (WHO) for inclusion in an international database.

2.2 | Study design

This feasibility study used a randomized controlled crossover design. A flow of two 1-month periods of a combination of exercise and nutritional intervention (1-month BCAA cycle; 1-month placebo cycle) and a 1-week washout period of exercise intervention alone was used. The allocation list was created in advance by a coinvestigator (A. K.) using computer-generated random numbers. For recruitment, consecutive code numbers were allocated to each participant. Randomization was performed using an age-based randomization method (Stratify 1: 20–39, 2: 40–59, and 3: ≥60 years). The participants were divided into two groups according to the order of dosage: Group 1: the early group ($n = 46$) who received BCAA in the early cycle and a placebo in the later cycle; Group 2: the later group ($n = 43$) who received a placebo in the early cycle and BCAA in the later cycle. The other investigators were blinded to the randomization procedure (Figure 1). The allocation results were sent

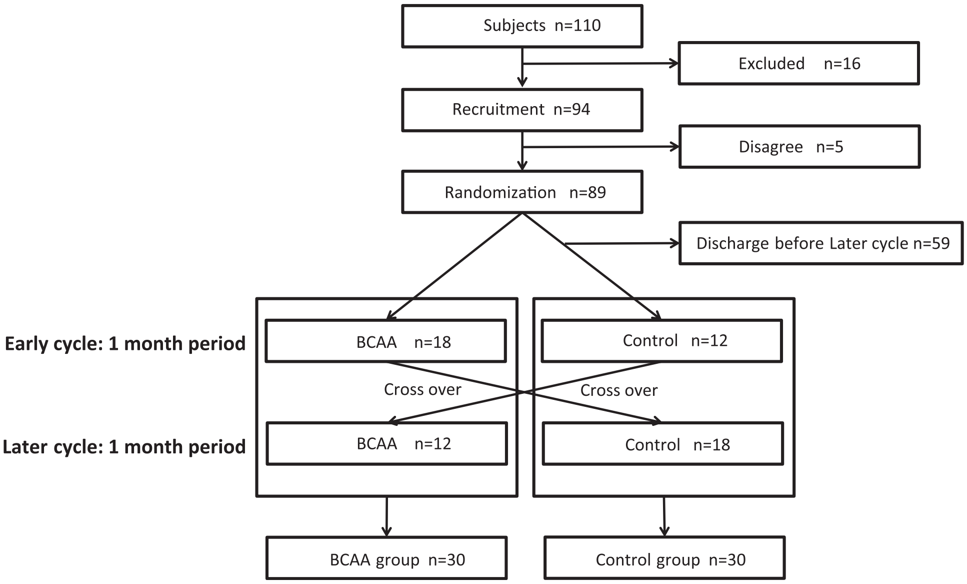

FIGURE 1 Flowchart of participants in the crossover trial of exercise therapy combined with branched-chain amino acid (BCAA) supplementation.

to the chief researcher (T. I.) by A. K. using the number-container method.

2.3 | Demographic data

The following demographic data were collected from the clinical records: sex, age, body mass index, diagnosis, days of hospitalization after surgery or at onset, and Charlson comorbidity index (CCI) values.

2.4 | Outcome measures

Measurements were performed before the intervention, 1 month after the early cycle, during the washout period, and 1 month after the late cycle. The researchers were not blinded to group allocation.

The primary outcomes were skeletal muscle mass and muscle strength of the limbs. The secondary outcomes were the FIM motor score, timed up and go test (TUGT), nutritional status (energy calculation [consumption and intake], albumin, and total protein in serum), and the number of combined therapy sessions.

2.4.1 | Skeletal muscle mass

The measurements were performed by coinvestigators (Y. M. and Y. N.) dedicated to the measurements and involved in no other contributions. Skeletal muscle mass was measured in all participants placed in the supine position using an ultrasonic reflectometer. The measurements of the skeletal muscle mass and echo intensity of the rectus femoris (RF) muscle were taken simultaneously at a point 10 cm proximal to the top of the patella, and the cross-sectional area was measured using the method described by Berger.[28] Echo intensity reflects skeletal muscle quality[29] and intramuscular fat.[30] Echo intensity was measured using an 8-bit gray scale with 256 shades (0–255 a.u.). Burton et al.[30] reported that RF adiposity obtained using ultrasonography might be a reliable tool for tracking changes in lower-limb intramuscular adiposity.

2.4.2 | Muscle strength measurement

A handheld dynamometer (HHD) was used to measure isometric muscle strength in the affected and healthy limbs (Mobie; SAKAI Medical Co., Ltd.). Knee extensor strength was measured in the sitting position, and the body weight ratio (kgF/kg) was calculated. The HHD was set at the front of the lower leg, 2.5 cm proximal to the lateral malleolus. The higher value was used for the analysis. The affected limb was defined as the one operated on after fracture or trauma, the one that received an artificial joint, or the side with weaker muscle strength in patients who underwent spine surgery or had a vertebral compression fracture.

A digital hand dynamometer (Grip-D; Takei Scientific Instruments Co. Ltd.) was used to assess grip strength. The measurement positions were standing, handling the dynamometer, and drooping the dominant upper limb. The measurement was performed twice at maximum effort, and the higher measurement was used for analysis.

2.4.3 | Dynamic balance test

The TUGT was performed twice for dynamic balance ability, and the lower value was used for the analysis.

2.4.4 | Energy calculation

Energy consumption was measured using a tri-axis accelerometer (Active style PRO HJA-750C; OMRON Corporation), worn on the pelvis for 5 days; the mid 3 days without the day to attach and collect the accelerometer were used for analysis.

Food intake data were collected from the clinical records. The nurse recorded the intake of staple food and a side dish separately after three meals and graded the intake using a numerical rating scale (0–10; 1 indicates 10% of food intake, and 10 indicates 100% of food intake). Daily energy intake was calculated using the required amount of energy set by the dietitian and the food intake ratio.

None of the participants had a restricted supplementary food intake besides three meals. The energy sufficiency ratio of the quotient of energy consumption and intake was used for the energy calculation.

2.4.5 | Harms

Adverse events were defined as symptoms or falls and trauma requiring some additional treatment during the study period. If an adverse event occurred, it was recorded in the patient file. As an assessment of the harm of BCAA intake, kidney functions were measured using urea nitrogen or creatine in serum, and estimated glomerular filtration rate (eGFR) in preintervention and postintervention (post-later cycle).

2.5 | Interventions

2.5.1 | Nutritional interventions

The methodology of nutritional intervention was based on that of Ikeda et al.[20] and Kim et al.[14] The supplements were provided daily to the participants after exercise, and they ingested 200 mL of water. In the BCAA cycle, participants received a BCAA supplement (Aminoaile; Ajinomoto Co., Inc.) that contained 3.0 g of amino acids, 17.6 kcal of energy: BCAA and essential AA (leucine [40%]: 1.2 g, isoleucine, valine, and lysine [60%]: 1.8 g). In the placebo cycle, participants received 1.2 g of polysaccharide (starch), 4.8 kcal of energy.

The presence or absence of placebo intake might be affected as a motivator for exercise adherence and physical activity. Therefore, placebo was used to account for psychological effects. Also, it was reported that a high number of tablets affected adherence to medication[32] (in this study, placebo required 22 tablets to be ingested for the same amount of energy), so the number of tablets was set at six, which had relatively little effect on adherence and energy intake.

2.5.2 | Exercise intervention

In the rehabilitation room, exercise interventions were performed in two sessions daily for 2 months in the early and later groups. The rehabilitation session consisted of three exercise sessions (1: 20 min of muscle strength training, 2: 20 min of stretching the limbs and trunk, and 3: 20 min of physical activity exercise, including gait and ADL motion).

2.6 | Statistical analysis

Based on a crossover trial by Ikeda,[15] the minimum sample size for a two-sided analysis using the unpaired *t*-test to examine the mean differences between groups ($p = 0.05$, power = 0.8, and effect size = 0.5) was calculated. The required sample size was 33. Formal statistical analyses were performed by a coinvestigator (A. K.) who was not involved in the recruitment, intervention, or data curation. After crossover, the early and later groups assigned a random dosage order were reorganized into the BCAA and Placebo groups (Figure 1) according to the allocation of supplements. The baseline for BCAA supplementation was set to the preintervention period for the early group and the post-early cycle for the later group. The baseline for the placebo was set to the post-early cycle for the early group and the preintervention period for the later group. A per-protocol analysis was performed before and after the crossover in the above allocations. Patients discharged before the later cycle were excluded from the statistical analysis because they did not crossover.

The unpaired *t*-test, Wilcoxon test, and χ^2 test were used to compare the early and later groups. The unpaired *t*-test was used for demographic data, CCI, hospitalization days after surgery or at onset, energy calculation (consumption and intake), nutritional status, number of combined therapy sessions, skeletal muscle mass, muscle strength of the limbs, balance ability, and FIM motor score. The χ^2 test was used for dichotomous data. A continuous data was expressed as the mean and the standard deviation number (mean ± standard deviation).

An unpaired *t*-test was used to compare the ratio of improvement in skeletal muscle mass, muscle strength of the limbs, balance ability, and FIM motor score between the BCAA and Placebo groups. Statistical software (JMP Pro version 16; SAS Institute Japan Ltd.) was used to analyze all data.

3 | RESULTS

A total of 110 patients participated in the present study, and no patients experienced adverse events associated with the exercise and nutritional intervention. Nineteen patients were excluded, of whom 14 matched the exclusion criteria, and 5 refused to participate. Sixty-one participants were discharged before the later cycle and did not crossover. Therefore, 30 participants were finally included in the analysis (Figure 1).

The mean age was 75.7 ± 17.8 and 76.1 ± 15.0 years for the early and later groups, respectively, with no significant difference observed between the groups ($p = 0.94$). The allocation results

TABLE 1 Baseline demographic data of the participants.

	Early dosage group (*n* = 18)	Late dosage group (*n* = 12)	*p* Value
Age (years)	75.7 ± 17.8	76.1 ± 15.0	0.94
Sex (male: female)	4:14	3:9	0.86
Body mass index (kg/m^2)	21.9 ± 3.4	24.1 ± 4.2	0.95
Comorbidity index (score)	4.6 ± 1.5	4.5 ± 1.4	0.83
Diagnosis: Spine surgery	6 persons	5 persons	
Artificial joint	6 persons	3 persons	0.80
Hip fracture	3 persons	1 person	
Vertebral compression fracture	2 persons	1 person	
Other	1 persons	2 persons	
Days of hospitalization after surgery or onset	21.9 ± 7.5	21.8 ± 6.7	0.95

Note: Mean ± standard deviation. There are no differences between groups.

based on the age-stratified randomization method were as follows: the early group included 1 person in Stratify 1 (age, 20–39 years) and 17 persons in Stratify 3 (≥60 years); the later group included 1 person in Stratify 1 and 11 persons in Stratify 3. Neither group had a participant in Stratify 2 (age, 40–59 years) in both groups. The age-stratified allocation groups were similar in both groups ($p = 0.76$).

After crossover, the early and later groups were reorganized into BCAA (30 persons) and placebo groups (30 persons) according to the allocation of supplements. Demographic data before the crossover were similar between the early and late groups (Tables 1 and 2). Baseline of nutritional status, energy intake, and consumption were also similar between the groups (Table 2).

For comparison of the groups based on the order of nutritional intervention, the echo intensity of RF muscle was significantly lower on the affected side in the early group after the early cycle (early group: 96.9 ± 21.0 a.u., later group: 116.0 ± 24.8 a.u., $p = 0.03$), whereas there was no significant difference between the groups after the later cycle (Table 3 and Figure 2). Skeletal muscle mass, muscle strength of the limbs, TUGT, and FIM scores did not differ significantly between the groups (Table 3).

After crossover, the ratio of improvement in the echo intensity of RF muscle on the affected side was significantly higher in the BCAA group (BCAA group: 101.4 ± 16.7%, Placebo group: 94.2 ± 18.0%, $p = 0.03$; Table 4). The ratios of improvement in skeletal muscle mass, limb muscle strength, and TUGT and FIM scores did not differ significantly between the groups (Table 4).

As an assessment of the harm of BCAA intake, kidney functions did not deteriorate in the overall pre- and postintervention comparison (urea nitrogen: pre- 15.6 ± 3.9 mg/dL, post- 15.4 ± 4.1 mg/dL, $p = 0.8$, creatine: pre- 0.6 ± 0.2 mg/dL, post- 0.7 ± 0.2 mg/dL, $p = 0.21$, eGFR (mL/min): pre- 77.6 ± 22.5 mL/min, post- 75.0 ± 21.4 mL/min, $p = 0.2$), nor in the comparison of the order of nutritional intervention (Table 2).

4 | DISCUSSION

Exercise combined with a nutritional intervention containing BCAA was administered to orthopedic patients admitted to a convalescent rehabilitation ward, and the feasibility of the combined therapy was examined with 1-month periods of exercise combined with BCAA supplementation for the early and later cycles. In the analysis of the order of dosage, the echo intensity of the RF of the affected limb was significantly lower in the early group, in which BCAA was administered in the early cycle, and also decreased in the later group, in which BCAA was administered in the later cycle. Neither group differed in the post-late cycle (Table 3). In addition, after crossover, the early and late groups were reorganized into BCAA and Placebo groups. The echo intensity of the RF of the affected limb was significantly improved in the BCAA group (Table 4). Figure 2 shows the change in the echo intensity of the RF on the affected side. In the present study, the echo intensity of the RF on the affected side decreased with a similar slope when BCAA was administered, whether in the early or later cycle. Because echo intensity reflects intramuscular fat,[28] a decrease in echo intensity may indicate a reduction in intramuscular fat. These results suggest the feasibility of combined therapy for the qualitative improvement of muscle tissue. Besides, the muscle cross-sectional area on the affected side did not increase in the early cycle but increased in the post-later cycle in both groups. The feasibility of using the skeletal muscle cross-sectional area could not be confirmed in the present study; however, if there was no change in the cross-sectional area and intramuscular fat decreased, it may be assumed that a substantial increase in muscle mass was obtained. These results suggested that exercise combined with BCAA supplementation for convalescent orthopedic patients could improved muscle quality and mass, consistent with previous studies by Ikeda et al.,[20] Ueyama et al.,[21,22] and Dreyer et al.[25]

TABLE 2 Comparison of the number of sessions, nutritional status, and energy status between the two groups.

	Early dosage group (*n* = 18)	Later dosage group (*n* = 12)	*p* Value
Number of sessions			
Exercise therapy: Early cycle (*n*)	55.1 ± 12.1	53.7 ± 14.8	0.78
Later cycle (*n*)	35.8 ± 14.9	44.7 ± 16.8	0.15
Supplementation: Early cycle (*n*)	28.8 ± 2.7	28.7 ± 3.1	0.92
Later cycle (*n*)	19.8 ± 7.0	23.7 ± 6.5	0.14
Nutritional status			
Albumin (g/dL): Preintervention	3.7 ± 0.5	3.8 ± 0.4	0.80
Post-early cycle	3.9 ± 0.4	3.9 ± 0.4	0.63
Post-later cycle	4.0 ± 0.4	4.0 ± 0.4	0.67
Total protein (g/dL): Preintervention	6.4 ± 0.7	6.8 ± 0.6	0.07
Post-early cycle	6.6 ± 0.4	6.8 ± 0.5	0.28
Post-later cycle	6.8 ± 0.4	6.8 ± 0.5	0.81
Kidney functions			
Urea nitrogen (mg/dL): Preintervention	15.3 ± 3.2	16.0 ± 4.9	0.63
Post-later cycle	15.7 ± 3.9	14.9 ± 4.5	0.59
Creatinine (mg/dL): Preintervention	0.6 ± 0.2	0.7 ± 0.3	0.57
Post-later cycle	0.7 ± 0.2	0.7 ± 0.2	0.68
Estimated glomerular filtration rate (mL/min)			
Preintervention	76.8 ± 18.2	78.9 ± 28.7	0.81
Post-later cycle	74.7 ± 19.1	75.6 ± 25.3	0.81
Energy status (kcal/day)			
Energy consumption (a): Preintervention	1482.0 ± 403.8	1523.2 ± 283.5	0.74
Pre-later cycle	1516.3 ± 387.9	1653.3 ± 368.1	0.34
Energy intake (b): Preintervention	1404.0 ± 327.3	1466.8 ± 378.5	0.64
Pre-later cycle	1489.5 ± 280.8	1551.5 ± 0.372.7	0.62
Energy balance (b–a): Preintervention	−77.0 ± 295.7	−132.0 ± 202.9	0.55
Pre-later cycle	−16.0 ± 355.9	−124.8 ± 261.2	0.34

Note: Mean ± standard deviation. There are no differences between groups.

The effects of combined therapy on muscle strength are widely known in patients with sarcopenia and frailty,[5–12] orthopedic diseases,[19–22] and stroke[23,24]; however, in the present study, no effect was observed on muscle strength in the limbs. This result was inconsistent with that of previous studies.[19–22] Tipton et al.[31] reported that many reports on sports injuries claimed positive results; however, sufficient evidence had not been obtained. Therefore, publication bias should be considered. The average age of the participants was 75.9 years, which was equivalent to that of late-stage older adults, and 60% of the participants had a spinal disorder and hip fracture. Hida et al. reported that the coexistence rate of sarcopenia with spinal disorders and hip fractures was extremely high at 46.6%–47.3%.[18] The Ministry of Health, Labor, and Welfare of Japan reported that approximately 70% of patients admitted to convalescent wards were >75 years of age.[33] The excluded patients discharged in the early cycle before the crossover might had an early recovery compared with the included participants and might had been younger. Therefore, it is necessary to compare the BCAA and placebo groups in the early cycle without selection bias, including the excluded patients, and to confirm whether the results are consistent with the current results.

This study had several limitations, including using a crossover design for convalescent patients, excluding patients discharged

TABLE 3 Comparison of muscle mass of rectus femoris, muscle strength, and balance ability between the two groups.

	Group	Preintervention	95% confidence interval	*p* Value	Post-early cycle	95% confidence interval	*p* Value	Post-later cycle	95% confidence interval	*p* Value
Muscle mass on affected side (cm^2)	Early dosage	1.73 ± 0.60	1.469–2.139	0.70	1.74 ± 0.71	1.393–2.096	0.77	2.05 ± 0.66	1.720–2.376	0.76
	Later dosage	1.81 ± 0.53	1.470–2.024		1.81 ± 0.57	1.448–2.174		2.11 ± 0.48	1.806–2.417	
Muscle mass on sound side (cm^2)	Early dosage	2.14 ± 0.81	1.738–2.547	0.85	2.26 ± 0.71	1.909–2.616	0.51	2.37 ± 0.79	1.972–2.761	0.41
	Later dosage	2.08 ± 0.77	1.593–2.583		2.42 ± 0.61	2.032–2.819		2.59 ± 0.61	2.193–2.964	
Echo intensity on affected side	Early dosage	115.9 ± 20.7	105.65–126.20	0.26	96.9 ± 21.0	83.51–110.24	**0.03***	106.2 ± 16.4	98.02–114.34	**0.38**
	Later dosage	106.8 ± 21.9	92.85–120.68		116.0 ± 24.8	103.65–128.36		99.9 ± 20.5	86.84–112.94	
Echo intensity on sound side	Early dosage	118.8 ± 23.7	107.01–130.62	0.37	120.6 ± 22.1	109.57–131.53	0.16	106.8 ± 17.7	98.05–115.66	0.48
	Later dosage	110.3 ± 26.3	93.58–127.04		104.6 ± 30.3	84.80–123.31		100.7 ± 26.5	83.82–117.49	
Knee extension on affected side (BW%)	Early dosage	21.2 ± 8.6	16.91–25.49	0.21	26.5 ± 9.7	21.68–31.34	0.21	29.5 ± 8.1	25.47–33.51	0.32
	Later dosage	16.7 ± 6.2	12.78–20.67		22.1 ± 5.0	18.87–25.29		26.5 ± 7.9	21.48–31.55	
Knee extension on sound side (BW%)	Early dosage	65.4 ± 25.9	41.44–85.27	0.86	80.6 ± 25.1	68.16–93.11	0.43	83.9 ± 24.6	71.74–96.19	0.99
	Later dosage	63.3 ± 34.5	52.54–78.29		72.7 ± 27.8	55.04–90.36		84.0 ± 34.4	62.17–105.89	
Grip strength (kgf)	Early dosage	19.4 ± 6.5	16.10–22.59	0.58	20.0 ± 6.2	16.94–23.06	0.75	20.6 ± 6.2	17.45–23.67	0.93
	Later dosage	18.3 ± 4.0	15.75–20.80		19.4 ± 4.3	16.66–22.12		20.4 ± 5.2	17.10–23.69	
Timed up and go test (s)	Early dosage	45.5 ± 32.5	29.37–61.71	0.42	20.6 ± 10.1	15.52–25.60	0.15	18.4 ± 17.5	9.705–27.14	0.38
	Later dosage	56.4 ± 37.4	32.64–80.16		33.3 ± 28.4	15.29–51.33		26.2 ± 26.7	9.199–43.11	
Functional independence measure (point)	Early dosage	70.8 ± 11.6	65.04–76.62	0.87	76.7 ± 11.9	70.77–82.56	0.92	81.7 ± 10.7	76.42–87.03	0.76
	Later dosage	70.1 ± 13.8	61.29–78.88		76.2 ± 15.9	66.00–86.33		80.5 ± 11.0	0.51–87.49	

Note: Mean ± standard deviation.

*$p < 0.05$.

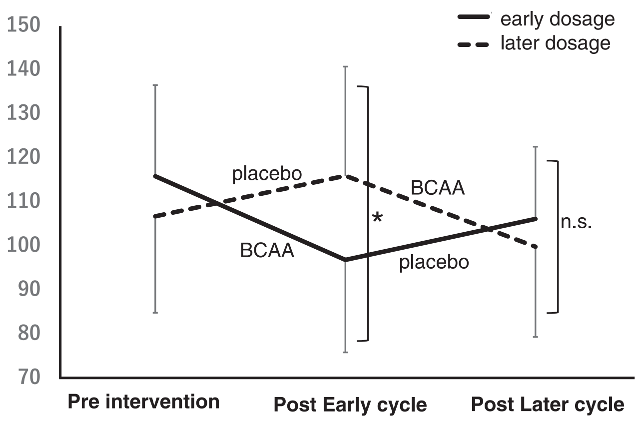

FIGURE 2 Echo intensity of rectus femoris muscle in affected side. BCAA, branched-chain amino acids.

before the later cycle, and lacking standardized dietary protein intake in the two groups.

Regarding the first limitation, a crossover design was often indicated for older persons or those with chronic diseases; however, it was also used for convalescent patients with stroke[34] and after orthopedic surgery.[35] The present study's participants were convalescent orthopedic patients; however, those who recovered early were excluded, and rehabilitation was performed at the same frequency in both groups. Based on these findings, we believe that the effect of the difference due to disease recovery was limited.

Second, excluding patients after randomization causes selection bias; therefore, it is common to neither exclude them nor use the last observation carried forward (LOCF) method. Because the purpose was to investigate the feasibility of this study, if the LOCF method had been used, the values of the post-early and later cycles would have been the same in many patients, and a crossover study would not have been established. Therefore, this study was conducted using a per-protocol analysis. All data for the early cycle, including the excluded patients' data, were subanalyzed and published separately. Therefore, there were no ethical issues associated with the lack of data on the excluded patients.

Third, the participants' age was skewed to >60 years, with only 2 of the 30 participants included in Stratify 1 (age, 20–39 years) and no participant included in Stratify 2 (age, 40–59 years). This study excluded the participants discharged before the later cycle, which might had included many participants aged <60 years. Therefore, whether this study's results apply to patients <60 years remains unclear.

Fourth, protein intake per body weight was not specified in the present study, and the dietitian used the Harris–Benedict formula to determine the prescribed energy amount and dietary content. However, because there was no difference between the early and late groups in terms of energy intake, consumption, and nutritional status during the study period, it can be assumed that the effects of dietary protein and energy intake were relatively small.

TABLE 4 Comparisons of the improvement rates of muscle mass of rectus femoris, muscle strength between the groups after crossover.

	BCAA (n = 30: 7 men and 23 women)	95% confidence interval	Placebo (n = 30: 7 men and 23 women)	95% confidence interval	p Value
Muscle mass on affected side	108.1 ± 30.4	96.71–119.41	111.5 ± 40.3	96.69–126.56	0.70
Muscle mass on sound side	113.2 ± 29.9	102.07–124.38	120.6 ± 53.2	106.68–140.44	0.51
Echo intensity on affected side	101.4 ± 16.7	95.14–107.60	94.2 ± 18.0	87.57–100.98	0.03*
Echo intensity on sound side	103.0 ± 16.9	96.72–109.37	97.5 ± 19.7	90.11–104.83	0.24
Knee extension on affected side	123.3 ± 26.6	113.31–133.20	125.5 ± 35.1	112.42–138.63	0.77
Knee extension on sound side	121.3 ± 25.3	111.82–130.74	114.5 ± 30.6	103.08–125.89	0.35
Grip strength	104.3 ± 13.8	99.12–109.43	104.2 ± 13.0	99.37–109.06	0.98
Timed up and go test	67.4 ± 23.5	58.71–76.23	76.3 ± 30.0	65.08–87.51	0.21
Functional independence measure	108.9 ± 16.7	102.69–115.16	107.6 ± 10.6	103.63–111.55	0.71

Note: Mean ± standard deviation.

Abbreviation: BCAA, branched-chain amino acids.

*p < 0.05.

5 | CONCLUSION

This study investigated the effectiveness and feasibility of BCAA combined with exercise intervention in improving muscle and physical function in convalescent orthopedic patients. A significant improvement in the echo intensity of the RF was achieved using the combined therapy. Therefore, achieving the desired effect appears feasible using the proposed combined therapy. In the future, a well-designed crossover study with a statistically sufficient number of cases is warranted.

AUTHOR CONTRIBUTIONS

Takashi Ikeda: Conceptualization; funding acquisition; methodology; project administration; writing—original draft. **Sadaoki Suzuki**: Data curation; project administration. **Kenji Aimoto and Yu Noguchi**: Data curation. **Arinori Kamono**: Formal analysis. **Yuki Matsunaga**: Conceptualization; methodology. **Tetsuya Jinno**: Conceptualization; writing—review and editing. **Koji Kanzaki**: Supervision. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

According to Japan's rules for personal information protection, primary research data are stored in hospital charts as individual patient files. Therefore, they cannot be accessed externally. Takashi Ikeda has full access to all data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

Informed consent was obtained from all participants before their participation in this study. The Showa University Fujigaoka Hospital Ethics Committee approved the study protocol (ID: F2019C09). This study was conducted in accordance with the Declaration of Helsinki.

TRANSPARENCY STATEMENT

The lead author Takashi Ikeda affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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