Original Article

Effect of exercise therapy combined with branched-chain amino acid supplementation on muscle strength in elderly women after total hip arthroplasty: a randomized controlled trial

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Background and Objectives: Many patients develop a prolonged decrease of muscle strength after total hip arthroplasty (THA) despite their reconstructed hip joint. Physical exercise combined with branched-chain amino acid (BCAA) supplementation has been reported to improve muscle strength in elderly persons with sarcopenia. However, the effect of BCAA supplementation in patients after THA is unknown. This study examined the effects of BCAA supplementation combined with exercise therapy on the improvement of physical function in elderly patients after THA. **Methods and Study Design:** The subjects were 31 elderly women who underwent THA. The participants were randomly assigned to two groups: BCAA (n=18) and control (n=13). The combined therapy was carried out for one month after THA. For the exercise intervention, a 3-set physical exercise program was conducted. For the nutritional intervention, the participants consumed 3.4 g of BCAA supplement or 1.2 g of starch immediately after the exercise intervention. **Results:** BCAA supplementation combined with muscle strengthening exercises had a significant effect on knee extension strength of the contralateral side and on upper arm cross-sectional area. The improvement ratio of knee extension strength before and after intervention on the operated side was also significantly higher in the BCAA group. **Conclusions:** BCAA supplementation is effective for patients to improve the strength of some muscles when combined with physical exercises, but hip abductor muscle strength of the operated leg did not improve. A future study is needed to determine the efficacy of this combined therapy for hip abductor muscle strength.

Key Words: total hip arthroplasty, muscle strength, branched-chain amino acid, elderly persons, convalescence

INTRODUCTION

Total hip arthroplasty (THA) is widely performed to decrease pain and improve physical function. However, previous studies have reported that, even after THA, many patients develop a prolonged decrease of hip muscle strength despite their reconstructed hip joint and improved mechanical efficiency.[1-3] In particular, Bertocci et al[4] showed that hip osteoarthritis (OA) patients who underwent THA had residual hip muscle atrophy 5 months after surgery. To prevent a prolonged decrease of hip muscle strength, positive intervention is important. However, for patients with OA who are scheduled for THA, it is often hard to implement high-load exercises because of joint deformity and pain. Furthermore, until 2 months after surgery, when the artificial joint becomes steady with bone tissue ingrowth into the implant,[5] it is difficult to implement high-load exercises, such as leg presses or squatting, that are damaging to the implanted joint.

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Based on statistics from a THA registry of Japanese patients in 2018,[6] at the time of THA, 71% of patients were over 60 years of age (39,098 between the age of 70 and 79 years and 33,525 between the age of 60 and 69 years). This means that Japanese THA patients are mostly elderly. In addition, sarcopenia in elderly persons, which has recently attracted attention and is defined by ageing, nutrition, and activities,[7] must be considered when dealing with elderly THA patients.

Muscle protein metabolism requires more branched-chain amino acids (BCAAs), particularly more in older than in younger persons.[8] In addition, the BCAA uptake response is reduced[9] and delayed[10] with aging. On the other hand, Atherton et al[11] reported that muscle protein synthesis peaked despite sustained elevation of serum amino acids. This phenomenon is called "muscle-full". Moreover, exercise combined with amino acid ingestion causes an increasing amino acid uptake response, and this increase may continue for up to 24 hours.[12]

Based on these previous findings, several studies have reported the effects of physical exercises combined with BCAA supplementation in elderly persons with sarcopenia.[13-16] In a systematic review regarding interventions for sarcopenia, Yoshimura et al[17] showed that the combination of exercise and BCAA intake significantly improved muscle strength and muscle mass compared with exercise or BCAA intake alone. These results proved that the combined therapy, rather than either one alone, is useful for the purpose of muscle strengthening. Weijzen et al[18] reported that protein intake fell below 0.6 g·kg-1·d-1 in elderly patients after THA and total knee arthroplasty (TKA). A recent clinical trial[19] showed that BCAA supplementation for 7 days preoperatively and 6 weeks postoperatively would lead to less decrease in the quadriceps muscle in the operated leg and the contralateral leg after TKA. However, a nutritional support regimen after joint replacement surgery has not been established.[20]

In persons with hip OA, combined therapy using BCAAs with low-load, high-volume tube exercise can significantly strengthen not the affected side, but the contralateral side hip muscle.[21] This study suggested that, in non-operated hip OA with joint deformity, decreased mechanical efficiency, and pain, it was difficult to strengthen hip muscles even with combined BCAA supplementation and exercise. Hypothetically, the combined therapy after hip reconstruction that improves mechanical efficiency and eliminates pain may be more effective in muscle strengthening.

Therefore, this study investigated the effects of combined treatment with muscle strengthening exercises and BCAA supplementation on improving muscle strength and muscle mass in patients after undergoing THA.

METHODS

Subjects

The eligible patients were 31 elderly women who were admitted to a ward for rehabilitation during convalescence after THA and revisions. Inclusion criteria were as follows: female, age 70 years and older, and no deglutition disorder. Exclusion criteria were as follows: rheumatoid arthritis; disorders of the nervous system and muscles; dementia; depression; schizophrenic disorder; and untreated cardiovascular disease. Recruitment was conducted at Showa University Fujigaka Rehabilitation Hospital from February 28, 2017 to February 28, 2018. The follow-up was conducted during the discharge period.

The Showa University Fujigaka Ethics Committee approved the study protocol (ID: 2016099). The intervention procedures were fully explained to all participants, and their written, informed consent was obtained. Fourteen patients were excluded: 10 met the exclusion criteria, and 4 refused to participate. The demographic data of the 31 participants (age: 75.4±5.8 years) are presented in Table 1.

Experimental design

A single-blinded, randomized experimental study was designed. A one-month period of supplementation was combined with physical exercises.

One co-investigator (AK) created the assignment list using computer-generated random numbers in advance. Participants were allocated a code number in order of recruitment. Randomization was performed using the assignment list and the code number after recruitment to

Table 1. Baseline demographic data of the participants†

	BCAA group (n=18)	Control group (n=13)
Age (years)	75.2±4.9	75.6±6.6
Body mass index (kg/m^2)	21.9±4.0	25.5±3.7*
Co-morbidity Index (score)	1.4±2.1	1.8±2.4
Diagnosis		
Osteoarthritis	13	13
Loosening of artificial joint	3	0
Other	2	0
Surgical procedure		
Postero-lateral (PL)	14	10
PL + Osteotomy	1	1
Antero-lateral	0	2
Revision	3	0
Postoperative days of admission (days)	23.3±4.3	20.4±4.6

†Values expressed as mean±standard deviation except for values under diagnosis and surgical procedure which are expressed as number of subjects.
*$p<0.05$.

the study. The subjects were randomly assigned to two groups: the BCAA group (n=18) and the control group (n=13). The chief researcher (IK) was informed of the allocation using the number container method by AK.

Interventions

BCAA supplementation

BCAA supplementation was conducted on the basis of Kim et al[13] and Ikeda et al.[21] A BCAA supplement was provided every day for participants in the BCAA group. Immediately after the exercise therapy session, participants ingested a 3.4 g amino acid supplement (Amino-aile, Ajinomoto Co., Inc., Tokyo, Japan). The supplement contained 3.0 g of amino acids: BCAAs and essential amino acids (1.2 g leucine, isoleucine, and valine and 1.8 g lysine; the percentage content of leucine was 40%). Starch (polysaccharide) was provided every day for participants in the control group. Immediately after the exercise therapy session, participants ingested 1.2 g of starch. BCAA supplements and starch were taken with 200 mL of water. The starch did not contain amino acids.

Exercise

The exercise intervention was performed in the rehabilitation hospital every day for 1 month in both groups. Each rehabilitation session consisted of a 3 set exercise menu (1 set of 20-min muscle strength exercises, 1 set of 20-min range of motion exercises, and 1 set of 20-min gait training) and activities of daily living (ADL) training. Muscle strength exercises included hip abduction exercise, clamshell exercise, and knee extension.

Outcome measures

Demographic data were collected from clinical records and included age, body mass index (BMI), co-morbidity index, diagnosis, surgical procedure, duration of hospital stay, the number of combined therapy sessions, nutritional status, and prescribed analgesic medicines. The anti-inflammatory activity of non-steroidal anti-inflammatory drugs (NSAIDs) has been reported to impair satellite cell activity, which is required for muscle protein synthesis.[22,23] Evaluations were conducted in the pre-intervention period and the post-intervention period. Investigators assessed muscle strength, skeletal muscle mass, and the functional independence measure (FIM) score.

Muscle strength

Hip abductor and knee extension muscle strength

Isometric muscle strength on the operated side and on the contralateral side was measured in all patients using a hand-held dynamometer (Mobie, SAKAI Medical Co., Ltd., Shinjuku, Tokyo, Japan). Hip abductor muscle strength was measured in the supine position. The hand-held dynamometer was placed lateral to the fibula, 2.5 cm proximal to the malleolus. The torque and body weight ratio (Nm/kg) were measured using the spina malleolar distance and body weight. Knee extension muscle strength was measured in the sitting position. The hand-held dynamometer was placed anterior to the fibula, 2.5 cm proximal to the malleolus. The body weight ratio (kgf/kg) was also measured.

Grip strength

The grip strength of all patients was measured using a Smedley type grip dynamometer (Grip-D, Takei Scientific Instruments Co., Ltd., Niigata, Japan). The grip strength of the dominant side was measured at maximum effort.

Upper arm muscle cross-sectional area

Upper arm muscle cross-sectional area (AMA) was measured as a representative value of skeletal muscle mass.[24] In the present study, bioelectrical impedance analysis was not used to measure skeletal muscle mass because a metallic artificial joint was implanted in the patients. AMA was calculated by the circumference of the upper arm (AC) and the triceps brachii muscle skinfold thickness (TSF), using the following formula: $(AC-TSF\times3.14/10)^2 / (4\times3.14)$.

Statistical analyses

Statistical analyses were conducted by a co-investigator (AK) who was independent of the recruitment, intervention, and data collection.

On the basis of the studies by Invernizzi et al[25] and Dreyer et al,[26] the sample size for the present study was set to 30 participants. The two groups were created by random assignment of supplementation: BCAA group (n=18) and control group (n=13).

An intention-to-treat analysis was conducted for the groups. The data of participants who dropped out of the intervention were replaced by the last observation carried forward method.

The unpaired t-test was used to determine the significance of differences between the groups in age, BMI, co-morbidity index, duration of hospital stay, number of intervention sessions, and nutrition status. Muscle strength, circumference of the upper arm, grip strength, and the FIM score were analyzed by two-way repeated-measures ANOVA (group × time). The interaction was evaluated by combined BCAA intake and exercise therapy. The improvement rates of muscle strength from baseline were compared between the BCAA group and the control group; the t-test was used to evaluate the significance of differences. All data were analyzed using JMP software (version 14, SAS Institute Japan Ltd., Minato, Tokyo, Japan).

RESULTS

Demographic data, except the BMI, intervention duration, and nutritional status were similar between the two groups (Tables 1, 2). No participants were unable to complete the study after randomization, and no participants had adverse events associated with BCAA supplementation.

There were significant differences in the main effect and interaction between the groups in knee extension strength on the contralateral side (pre- and post-combined therapy: p=0.028) and the circumference of the upper arm (pre- and post-combined therapy: p=0.012) (Table 3). There were no significant effects and interactions between the groups in hip abductor muscle strength, grip strength, and the FIM score.

The comparison of improvement rates for knee exten-

Table 2. Comparisons of the number of sessions, nutritional status, and analgesic medicines between the two groups†

	BCAA group (n=18)	Control group (n=13)
Duration of hospital stay (days)	23.8±9.6	25.2±10.6
Number of sessions		
Exercise therapy	40.6±17.4	42.5±18.5
Supplementation	40.6±17.4	42.5±18.5
Total hours of exercise therapy (hours)	37.8±17.3	40.7±17.6
Nutritional status		
Albumin (g/dL)		
Pre-intervention		
Post-intervention	3.6±0.4	3.7±0.4
Total protein (g/dL)	3.7±0.4	3.8±0.2
Pre-intervention	6.7±0.5	6.7±0.4
Post-intervention	7.0±0.5	6.8±0.4
Analgesic medicines		
Acetaminophen	1	1
NSAIDs	9	9
None	8	3

†Values expressed as mean±standard deviation except for values under analgesic medicines which are expressed as number of subjects.

Table 3. Group × time analysis of muscle strength, upper-limb muscle cross-sectional area, and the functional independence measure

	Control		BCAA		Interaction (Synergistic effect)
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	
Hip abduction (Nm/kg)					
Operated side	0.55±0.22	0.78±0.25	0.52±0.35	0.78±0.33	
Contra-lateral side	0.70±0.29	0.85±0.26	0.73±0.32	0.95±0.33	
Knee extension (kgf/kg)					
Operated side	0.26±0.06	0.31±0.08	0.24±0.10	0.31±0.08	
Contra-lateral side	0.31±0.09	0.33±0.09	0.37±0.13	0.43±0.13	*
Grip strength (kgf)	18.6±5.0	19.3±4.3	17.4±5.2	18.4±4.3	
Upper arm muscle(cm^2) Cross-sectional area	61.3±19.9	58.5±12.8	48.4±11.6	47.0±11.6	*
Functional Independence Measure (FIM score)	75.6±7.4	84.4±4.0	78.8±9.2	82.7±9.8	

†Values expressed as mean±standard deviation.
*p<0.05.

Table 4. Comparisons of the improvement rates from baseline between the two groups

	BCAA (n=18)	Control group (n=13)	p-value
Hip abduction strength:			
Operated side (%)	108.9±21.6	99.7±14.2	0.305
Contra-lateral side (%)	114.9±19.4	97.4±16.5	0.188
Knee extension strength:			
Operated side (%)	147.7±53.5	114.4±18.3	0.040*
Contra-lateral side (%)	118.9±19.1	110.0±10.4	0.137
Grip strength (%)	105.7±8.2	103.7±8.6	0.485

†Values expressed as mean±standard deviation.
*p<0.05.

sion strength showed that the operated side rate (BCAA group: 108.9%±21.6%; control group: 99.7%±14.2%) was significantly higher in the BCAA group (Table 4). Hip abduction strength did not differ significantly between the two groups (Table 4). The grip strength (BCAA group: 105.7%±8.2%; control group: 103.7%±8.6%) did not show a significant difference between the two groups (Table 4).

DISCUSSION

The present study showed that BCAA supplementation combined with muscle strengthening exercises showed significant effects on knee extension strength on the contralateral side and upper arm cross-sectional area. In addition, the improvement rate of knee extension strength on the operated side was significantly higher in the BCAA group than in the control group.

There was no significant interaction for hip muscle strength, and the improvement rate of hip muscle strength did not differ significantly between the groups. Considering the effects were observed in other than the hip joint, these results did not support our hypothesis and a similar previous study. Ikeda et al[21] reported that there was significant hip strength improvement not on the affected side, but on the healthy side in persons with hip OA. The present study suggests that it may be difficult to strengthen the operated hip muscle effectively even if BCAA supplementation is combined with exercise both before and after surgery.

Why did the combined therapy not improve hip muscle strength? Because the improvement rate of hip abductor strength was over 50% from baseline in both groups (BCAA group: 72.5%, control group: 53.5%), there was no prolonged decrease of hip muscle strength during hospitalization. The primary purpose of THA is reconstructing the joint lever arm and improving mechanical efficiency. Asayama et al[27] reported that the joint lever arm of the gluteus muscle is directly altered according to femoral offset. In addition, Ikeda et al[28] found that preoperative hip abductor strength was the strongest factor affecting hip abductor strength up to 6 months after surgery. Thus, we believe that the impact of BCAA on postoperative hip muscle strength compared with that of femoral offset or preoperative strength would be limited.

On the other hand, the combined therapy showed a significant effect on knee extension strength on the healthy side. Furthermore, the improvement rate of knee extension strength on the operated side was significantly higher than that of the control group. It differed from hip muscle strength, since the lever arm of the quadriceps muscle was not changed by surgery. The rectus femoris muscle was stretched due to limb lengthening because the hip center was reconstructed with proximal and lateral subluxation to anatomical geometry. The effect of BCAA might be prominently reflected on knee extension muscle strength because there are few mechanical changes related to the knee joint in THA.

In the present study, measurement of skeletal muscle mass was not performed by the bioelectrical impedance analysis method, but by AMA, because the participants had a metallic artificial joint implanted. The main effect and interaction were observed by AMA. Despite the similar nutritional status and NSAID utilization rate in the two groups, AMA showed a significant decrease in the control group. There was also a slight AMA decrease in the BCAA group. This result was similar to that of Dreyer et al.[19] The combined therapy would lead to less decrease in AMA.

It is important that reduction of AMA was affected by physical activity during the hospitalization period. Most participants had rehabilitation sessions for approximately 1.6 h per day and were inactive at other times. Compared with household work before surgery, the participants might have had a sedentary lifestyle during hospitalization. Previous studies reported a relationship between immobilization and skeletal muscle atrophy. Ferrando et al[29] reported a 3% decrease in thigh muscle volume after 7 days of bed rest. Reich et al[30] showed that unloading for only 48 hours led to muscle protein catabolism. Skeletal muscle mass might be decreased by the sedentary lifestyle in the control group. On the other hand, skeletal muscle mass reduction might be limited in the BCAA group because BCAAs facilitate muscle protein synthesis.

Although the improvement rate of hip muscle strength was not significant, the present results warrant further exploration in a future study to determine the efficacy of the combined therapy for hip muscle strength.

This study has several limitations, including: 1) there was no group that had only taken BCAA without exercise; 2) the participants were women only; 3) energy balance was not controlled during the study period; and 4) 58% of participants used NSAIDs regularly or on an as-needed basis.

First, it has not been possible to examine the effects on muscle strength and muscle mass when consuming BCAA alone, because it is ethically difficult to not perform rehabilitation in a convalescent ward. This is the same issue seen in the previous studies.[19,25] Regarding elderly sarcopenic women, Kim et al[13] reported that BCAAs alone did not increase muscle strength and muscle mass compared with a combination of BCAAs and exercise or exercise alone. Similar results may occur in elderly women after THA.

Second, the participants of the present study were only women. In a THA registry of Japanese patients in 2018,[6] 83 % of the patients were women. Especially in a convalescent ward, most of the elderly patients after THA were women. One cannot exclude the fact that the results of present study may not be applicable to elderly male patients after THA.

Third, in regard to energy balance, though estimated energy demand was calculated by the Harries-Benedict formula,[31] one cannot exclude the fact that dietary intake did not meet required energy demands. However, there was no malnutrition in both groups. Therefore, the effect of energy balance was relatively low.

Fourth, the utilization rate of NSAIDs, which might have affected muscle metabolism, was 58 %. However, both groups contained the same number of patients who ingested NSAIDs.

Conclusion

BCAA supplementation combined with muscle strengthening exercises showed a significant effect on knee extension strength of the contralateral side and on skeletal muscle mass. In addition, the improvement rate of knee extension strength on the operated side was significantly higher in the BCAA group than in the control group. Although the improvement rate of hip muscle strength was not significant, the results of the present study warrant further exploration in a future study to determine the efficacy of the combined therapy for hip muscle strength.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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