



Effect of exercise therapy combined with branched-chain amino acid supplementation on muscle strengthening in persons with osteoarthritis

Takashi Ikeda^{1,2,*}, Tetsuya Jinno², Tadashi Masuda³, Junya Aizawa⁴, Kazunari Ninomiya⁵, Koji Suzuki⁵ and Kazuo Hirakawa⁵

¹*School of Nursing and Rehabilitation Sciences, Showa University, Yokohama, Japan*

²*Department of Rehabilitation Medicine
Tokyo Medical and Dental University Graduate School, Tokyo, Japan*

³*Faculty of Symbiotic Systems Science, Fukushima University, Japan*

⁴*Clinical Center for Sports Medicine & Sports Dentistry
Tokyo Medical and Dental University, Tokyo, Japan*

⁵*Shonan Kamakura Joint Reconstruction Center, Kamakura, Japan*

*tk.ikeda@nr.showa-u.ac.jp

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Background: Improving lower limb muscle strength is important in preventing progression of osteoarthritis (OA) and its symptoms. Exercise with branched-chain amino acid (BCAA) supplementation has been reported to affect protein anabolism in young and elderly persons. However, few studies provided daily BCAAs for patients with OA.

Objective: This study examined the effects of combined BCAAs and exercise therapy on physical function improvement in women with hip OA scheduled for total hip arthroplasty.

Methods: The subjects were 43 women with OA (age: 64.2 ± 9.4). The participants were randomly divided into two groups: BCAA ($n = 21$) and control ($n = 22$). The combined therapy was carried out for one month. Exercise intervention involved hip abductor muscle exercise in both groups. For the nutritional intervention, 6 g of BCAAs or 1.2 g of starch were consumed within 10 min before starting the exercise.

*Corresponding author.

Results: There was a marginally significant difference in the main effect between the groups in 10-m timed gait time. The improvement rate in hip abductor muscle strength of the contralateral side was significantly greater in the BCAA group.

Conclusion: By combining BCAA intake and exercise therapy, a significant improvement in hip abductor muscle strength of the contralateral side was achieved in women with OA.

Keywords: Amino acid supplementation; combined therapy; exercise therapy; muscle strength; osteoarthritis.

Introduction

Hip osteoarthritis (OA) can cause worsening of mechanical dynamic efficiency due to shortening of the lever arm associated with joint deformity. Moreover, activity restriction due to joint pain and limited range of motion (ROM) and muscle weakness due to disuse may occur. Liu *et al.*¹ reported a significant decrease in cross-sectional area and length of the gluteus medius muscle in patients with hip dysplasia compared to the healthy side. Rosemann *et al.*² found that physical activity in OA patients was affected by limited lower limb function, pain and disease duration. Because decreased lower limb muscle strength further reduces physical activity and function associated with disuse, improving lower limb muscle strength is important in preventing OA progression and symptoms. Effective exercise therapy for OA includes pool exercises and muscle strengthening exercises,³ but exercise intensity and specific regimens have not been established.⁴

In recent years, the effects of amino acid ingestion have actively been investigated in nutritional science, and an effect on muscle protein anabolism has been demonstrated physiologically. Muscle protein metabolism requires more branched-chain amino acids (BCAAs), particularly more in older than in younger persons.⁵ In addition, the BCAA uptake response is reduced⁶ and delayed⁷ with aging.

In regard to muscle protein synthesis, Burd *et al.*⁸ reported that amino acid uptake into the vastus lateralis muscle stops after a certain amount, even though serum amino acid levels remain elevated. However, exercise combined with amino acid ingestion increases this uptake, and this increase may continue for up to 24 h in recreationally active men. In terms of muscle strengthening, low-load high-volume exercise stimulates muscle protein synthesis at the vastus lateralis muscle more than high-load low-volume exercise in young men.⁹ Combined treatment using BCAAs with low-load high-volume exercise, even twice weekly in frail elderly persons, can effectively

strengthen muscles (quadriceps and gluteus maximus).¹⁰ These studies^{8–10} suggest that low-load exercise can strengthen muscles, and when combined with BCAAs, it 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 in OA patients.

Methods

Subjects

The eligible patients were 55 women with secondary hip OA scheduled for primary unilateral total hip arthroplasty (THA) with a delay of 1.5 months. Exclusion criteria were as follows: patients with Charnley classes B and C; rheumatoid arthritis; osteonecrosis; untreated OA on the contralateral side hip; previous surgery on the affected hip; disorders of the nervous system and muscles; dementia; or a schizophrenic disorder. Recruitment was conducted at Shonan Kamakura Joint Reconstruction Center from February 1, 2015 to June 1, 2015. The follow-up was conducted 1 month after the pre-intervention period.

This trial was registered at UMIN-CTR clinical trial as UMIN000016333. The trial protocol of this paper can be found at <https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000016333&type=summary&language=E>

The Tokushukai Group Ethics Committee approved the study protocol (ID: TGE00454-115). The intervention procedures were fully explained to all participants, and their written, informed consent was obtained. Twelve patients were excluded; 6 met the exclusion criteria, and 6 declined to participate. The demographic data of the 43 participants (age: 64.2 ± 9.4 years) are presented in [Table 1](#).

Table 1. Demographic data of the patients.

| | | BCAA group ($n = 21$) | Control group ($n = 22$) |
|--------------------------------------|---------------|-------------------------|----------------------------|
| Age | | 63.6 \pm 8.9 | 64.8 \pm 9.9 |
| BMI | | 24.4 \pm 4.4 | 23.9 \pm 4.5 |
| Comorbidity index | | 1.3 \pm 1.9 | 1.1 \pm 1.8 |
| FAI | | 28.3 \pm 6.6 | 29.2 \pm 5.7 |
| JHEQ (score) | Pain score | 8.6 \pm 4.7 | 11.6 \pm 6.7 |
| | Mental score | 9.6 \pm 5.2 | 12.2 \pm 6.2 |
| Analgesic medicines (times of doses) | Tramadol | 5.5 \pm 17.7 | 2.7 \pm 12.2 |
| | Acetaminophen | 10.9 \pm 22.9 | 5.5 \pm 17.5 |
| | NSAIDs | 8.0 \pm 22.1 | 6.2 \pm 21.3 |

Experimental design

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

The Clinical Trial Center of Shonan Kamakura Joint Reconstruction Center 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 the study. The subjects were randomly divided into two groups: the BCAA group ($n = 21$) and the control group ($n = 22$). The chief-researcher (IK) was informed of the allocation using the number container method from the Clinical Trial Center.

Interventions

BCAA supplementation

BCAA supplementation was conducted on the basis of Kim *et al.*¹¹ and Ikeda *et al.*¹⁰ A BCAA supplement was provided every day for participants in the BCAA group. Within 10 min before the exercise, participants ingested a 6-g tablet amino acid supplement (6 tablets, amino-vital tablet, Ajinomoto Co., Inc., Tokyo, Japan). The supplement contained 500 mg of amino acids per 1 g: 260 mg of BCAA and 240 mg of conditionally essential amino acids (105 mg leucine, 85 mg isoleucine, 70 mg valine, 123 mg glutamate and 117 mg arginine; the percentage content of leucine was 21%). Starch was provided for participants in the control group every day. Within 10 min before starting exercise, participants ingested 1.2-g starch (6 tablets). BCAA supplements and starch were taken with 200-mL water. Amino acid supplementation contained 3 g of amino acids per 6 g.

Starch, a polysaccharide, did not contain amino acids.

A comparison study¹² of supplementation before and after exercise indicated that post-exercise supplementation had better effectiveness than pre-exercise supplementation. In the present study, however, supplementation was performed before exercise to gain a greater effect on muscle protein kinetics¹³ and to prevent muscle soreness during and after exercise,^{14,15} considering the low exercise tolerance of patients with OA.

Exercise

The exercise intervention was performed as self-exercise in both groups without any supervision at home every day for 1 month. Muscle strength exercises included hip abduction (HA) exercise and clamshell (CS) exercise and was performed using an exercise band (TheraBand Latex Free Resistance Bands: yellow color, Hygenic Co., Akron, OH, USA). An exercise band was placed around the femur 5 cm proximal to the lateral joint space of the knee. Exercise was conducted while the subjects lay in the supine position with their hips in the neutral position (HA: Fig. 2(a)) or the knee at 90° of flexion (CS: Fig. 2(b)). The exercise protocol was matched to that of the report of Watanabe *et al.*¹⁶: low-intensity resistance training with slow movement and the tonic force generation method (seated on the muscle training machine, 3 s eccentric, 3 s concentric, and 1 s isometric actions, with no rest between each repetition). Each exercise session consisted of 2 sets of 20 repetitions.

Outcome measures

Demographic data were collected from clinical records and included age, body mass index (BMI),

diagnosis, co-morbidity index, duration of intervention and prescribed analgesic medicine. Evaluations were conducted in the pre-intervention period and the post-intervention period. Investigators assessed muscle strength and the 10-m timed gait test before and after the intervention. The Frenchay Activities Index (FAI) and the Japanese Orthopedic Association Hip-Disease Evaluation Questionnaire (JHEQ) were evaluated before the intervention. The compliance rate with home exercise was measured after the intervention.

Muscle strength

(i) Hip abductor muscle strength

Isometric hip abductor strength on the affected side and the contralateral side was measured in all patients using a handheld dynamometer (Micro-FET2, Hoggan Health Industries, Salt Lake City, UT, USA) in the supine position. The handheld 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.

(ii) 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 strengths of the dominant side and the non-dominant side at maximum effort were measured, and the higher value was used for analysis.

10-m timed gait test

The 10-m timed gait test was performed using a 16-m straight gait lane that contained a 3-m approach lane and a 3-m supplement lane. Each test was done twice, and the lower value was used for analysis.

Physical activities during activities of daily living (ADLs)

Physical activities were measured by the FAI.^{17,18} The FAI evaluates the frequency and intensity of physical activities in the ADL setting. The FAI score (0–45 points) ranges from 0 points for a sedentary lifestyle to 45 points for a very active lifestyle. Patients completed a questionnaire form regarding regular activities in the ADL setting three months before the start of the present study.

Japanese Orthopedic Association Hip-Disease Evaluation Questionnaire

Hip joint function status measurements of all patients were performed using the JHEQ score of two subscales: the pain score and the mental score.¹⁹ The JHEQ score is a self-administered questionnaire that can be useful in patients who frequently engage in deep flexion of the hip joint due to lifestyle and culture.

Compliance rate with self-exercise and supplementation

Patients were told to do self-exercises and supplementation and to complete the self-report sheet every day for one month. They were also asked to collect the self-report sheets at the preoperative evaluation before THA (one month after the first evaluation). The compliance rates with exercises and supplementation were calculated based on the number of exercise sessions and supplementation.

Statistical analyses

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

On the basis of Pennings *et al.*,^{20,21} the minimum sample size for two-way repeated-measures analysis of variance (ANOVA) to examine differences between the groups ($\alpha = 0.05$, power = 0.8, effect size = 0.35) was calculated, and 44 participants were required. The two groups were created by random assignment of supplementation: BCAA group ($n = 21$) and control group ($n = 22$) (Fig. 1).

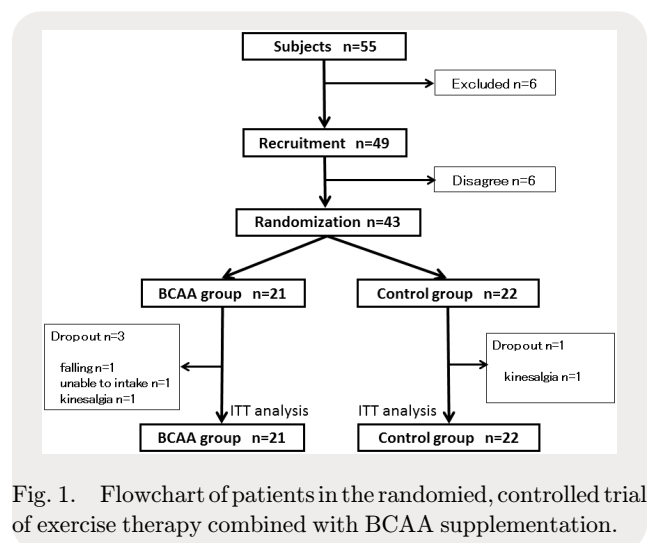


Fig. 1. Flowchart of patients in the randomized, controlled trial of exercise therapy combined with BCAA supplementation.

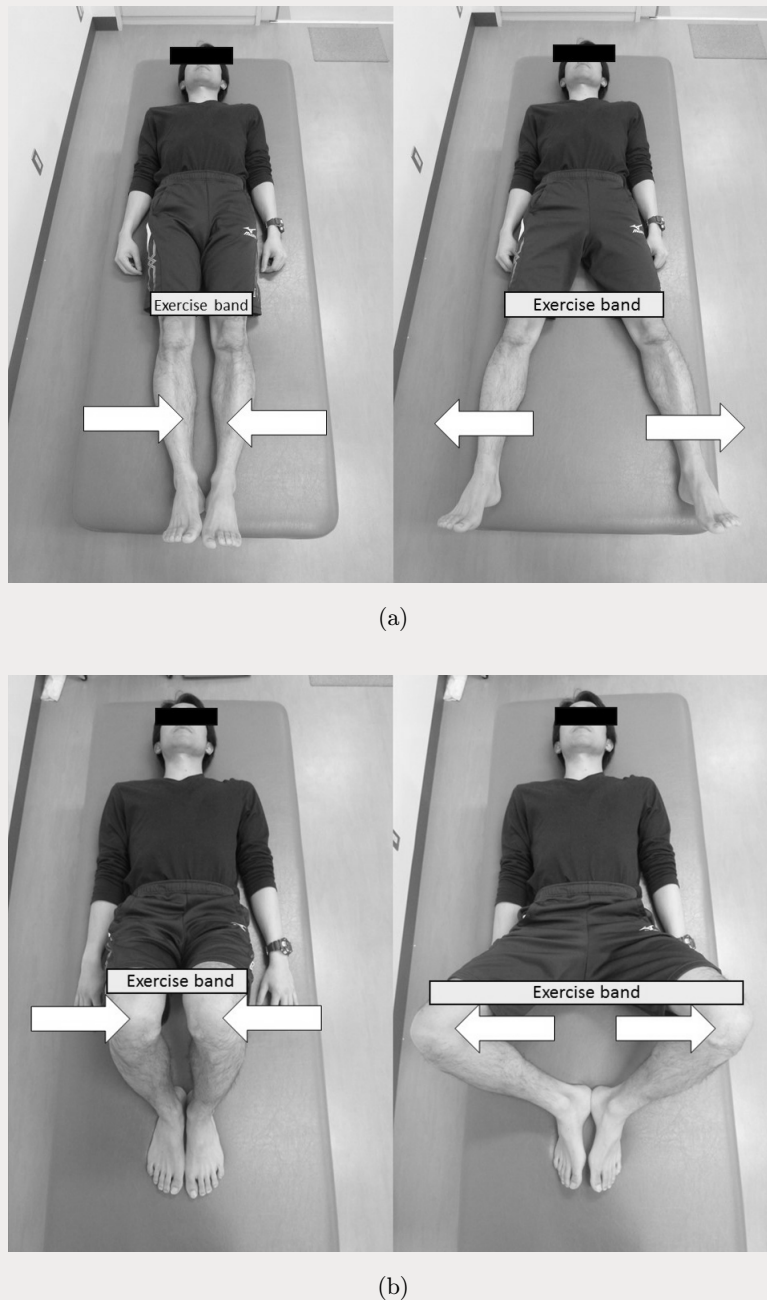


Fig. 2. (a) Hip abduction (HA) exercise and (b) Clamshell (CS) exercise.

Notes: An exercise band was placed to the femur, 5 cm proximal to the lateral joint space of the knee. Each exercise session consisted of 2 sets of 20 repetitions in the supine position.

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. The unpaired *t*-test was used for age, BMI, the duration of interventions, FAI and JHEQ score. Muscle

strength, the 10-m gait test and grip strength were analyzed with two-way repeated-measures ANOVA (group \times time). The interaction was evaluated by the combined BCAA intake and exercise therapy. The comparison of the BCAA group with the control group was conducted using the improvement rate of the muscle strength and prescribed analgesic medicines; the *U* test was used

Table 2. Group \times time analysis of physical function and compliance rate with interventions.

| | | BCAA group ($n = 21$) | Control group ($n = 22$) |
|---|-------------------|-------------------------|----------------------------|
| Hip abductor strength (affected side) | pre-intervention | 0.68 ± 0.18 | 0.69 ± 0.2 |
| | post-intervention | 0.7 ± 0.15 | 0.68 ± 0.2 |
| Hip abductor strength (contralateral side) | pre-intervention | 0.78 ± 0.15 | 0.81 ± 0.19 |
| | post-intervention | 0.87 ± 0.14 | 0.8 ± 0.22 |
| 10-m timed gait test | pre-intervention | 8.6 ± 2.2 | 8.3 ± 2.3 |
| | post-intervention | 7.7 ± 1.5 | $7.6 \pm 1.9^*$ |
| Grip strength | pre-intervention | 23.0 ± 4.9 | 23.3 ± 5.6 |
| | post-intervention | 24.7 ± 3.2 | 24.1 ± 4.9 |
| Intervention duration (days) | | 27.8 ± 3.5 | 27.3 ± 4.0 |
| Compliance rate (%) | Exercise | 85.0 ± 22.0 | 88.2 ± 13.1 |
| | Supplementation | 83.4 ± 27.7 | 92.0 ± 11.8 |

Note: $*p < 0.1$.

to evaluate the significance of differences. All data were analyzed using SPSS software (version 21, IBM, Chicago, IL, USA).

Results

Demographic data and intervention duration were similar between the two groups (Tables 1 and 2). The compliance rates for exercise and supplementation in each period were at least 80%, and they did not differ significantly between the two groups (Table 2). The percentage of patients prescribed non-steroidal anti-inflammatory drugs (NSAIDs) as analgesics was approximately 20% (BCAA group: 19.0%; control group: 18.2%). The times of doses of analgesic medicines were similar between the two groups (Table 1).

Four participants were unable to complete the study after randomization because of kinesiophobia ($n = 2$), stopped ingesting BCAAs due to the

flavor ($n = 1$), or falling ($n = 1$; Fig. 1). No participants had adverse events associated with BCAA supplementation.

There was a marginally significant difference in the main effect between the groups in 10-m timed gait time (pre- and post-combined therapy: $p = 0.057$) (Table 2). There were no significant effects and interactions between the groups in hip abductor muscle strength and grip strength.

A comparison of improvement rates for hip abductor muscle strength showed that the contralateral side rate (BCAA group: $14.2\% \pm 19.4\%$; control group: $-2.6\% \pm 16.5\%$) was significantly higher in the BCAA group (Table 3). The affected side rate (BCAA group: $8.9\% \pm 21.6\%$; control group: $-0.3\% \pm 14.2\%$) did not differ significantly between the two groups (Table 3). The 10-m timed gait time and grip strength did not show significant differences between the two groups (Table 3).

Table 3. Comparisons of the improvement rates of physical function between the groups.

| | BCAA group ($n = 21$) | Control group ($n = 22$) |
|--|-------------------------|----------------------------|
| Hip abductor muscle strength (%) (affected side) | 8.9 ± 21.6 | -0.3 ± 14.2 |
| Hip abductor muscle strength (%) (contralateral side) | 14.2 ± 19.4 | $-2.6 \pm 16.5^*$ |
| 10-m timed gait test (%) | -10.0 ± 13.6 | -6.6 ± 10.1 |
| Grip strength (%) | 8.0 ± 14.5 | 6.1 ± 9.4 |

Note: $*p < 0.01$.

The percentage of each parameter means the difference from baseline. Hip abductor muscle strength of the contralateral side differed significantly between the groups.

Discussion

The present study showed that BCAA supplementation combined with muscle strengthening exercises showed a marginally significant effect with 10-m timed gait time. In addition, the improvement rate of hip abductor muscle strength on the contralateral side was significantly higher in the BCAA group than in the control group.

Considering the fact that lower limb function affects physical activity of both of the affected side and the unaffected (healthy) side in OA patients,²² lower limb function and physical activity are mutually affected. Arai *et al.*²³ reported that muscle strength of the unaffected lower limb is important for gait independence after a femoral neck fracture. In OA, which is also a hip-joint disease, improved function of the unaffected lower limb contributes to increased physical activity and prevents a further decrease in lower limb function due to disuse.

On the other hand, there was no significant interaction for hip abductor muscle strength, and the muscle strength improvement rate on the affected side did not differ significantly between the groups. Considering the fact that the combined therapy showed a marginally significant effect in the 10-m timed gait time, even though there was no significant interaction between the groups in muscle strength, the improvement rate for hip abductor muscle strength on the contralateral side may also have affected 10-m timed gait time. What can be assumed is that joint deformity or pain with movement was involved. In regard to joint deformity, most participants with secondary OA scheduled for THA had shortening of the lever arm associated with joint deformity.

The JHEQ pain score did not differ between the groups when the intervention was started, and one patient in each group discontinued the intervention because of pain with movement (kinesalgia). The exercise intervention was performed without supervision, but this was complemented by self-report sheets to confirm that exercise was performed. The compliance rate for independent training was $\geq 80\%$ in both groups, so this served as a type of check function. However, one cannot exclude the effect of joint pain that may also have affected muscle strengthening in the present study.

Moreover, in the 10-m timed gait test, another related factor besides muscle strength is stride length. Stride length reflects the magnitude of

the arc of hip flexion and extension ROM on the affected and unaffected sides during walking. Exercise intervention in the present study included muscle strengthening exercises, but without specific intervention for joint ROM. Although hip abductor muscle strength did improve, this did not lead to improvement in the 10-m gait time.

Grip strength results did not show a significant main effect and, improvement rates from before to after intervention were not significantly different. Ikeda *et al.*¹⁰ reported that combined exercise therapy twice weekly with BCAA supplementation in frail elderly patients improved lower limb muscle strength, but had no effect on grip strength. A common feature in the study by Ikeda *et al.* and the present study was the absence of any direct exercise intervention for grip strength. Kim *et al.*¹¹ reported that BCAA supplementation alone did not enhance muscle strength, and even with combined therapy, specific exercise intervention for target muscles was necessary.

THA is widely performed in OA patients to relieve pain and improve function. However, even after hip geometry is restored, decreased hip abductor muscle strength is often prolonged.^{22,24,25} Disuse muscle atrophy may persist after surgery, especially in OA patients.²⁶ Rooks *et al.*²⁷ reported that preoperative rehabilitation was important. They found that six weeks of preoperative exercise therapy in OA patients undergoing THA improved lower limb function before surgery and greatly reduced postoperative rehabilitation admission rates. For smooth gait independence after THA, muscle strengthening exercises combined with BCAA supplementation may be useful from the standpoint of effectively improving hip abductor muscle strength on the unaffected side even before surgery.

This study has several limitations, including: (1) muscle strengthening exercises and BCAA supplementation were not supervised; (2) nutritional parameters based on hematological data were not evaluated; (3) dietary intake was not controlled during the study period; (4) some participants used NSAIDs regularly or on an as-needed basis and (5) the duration of combined treatment was limited to one month, so whether a longer period would have been more effective is unknown.

Because the nutritional and exercise interventions were not supervised, one cannot exclude the

fact, even though the compliance rates were high, that the intake and use of BCAA supplementation and the implementation and methods of muscle strengthening exercises may not have been followed as prescribed. In regard to dietary intake, if caloric intake does not meet required energy demands, malnutrition can lead to a high risk of malnutrition-related sarcopenia. However, the patients in this study had no underlying diseases associated with a nutritional disorder or dysphagia. Therefore, the risk of malnutrition was relatively low.

In regard to NSAIDs, the anti-inflammatory activity of NSAIDs is reported to impair satellite cell activity, which is required for muscle protein synthesis.^{28,29} Mikkelsen *et al.*³⁰ reported that local NSAID infusion significantly inhibited satellite cell activity up to eight days after eccentric muscle strengthening exercise, and that, in the non-infusion group, satellite cell activity increased up to about two times higher than the previous exercise. Therefore, one cannot exclude the fact that NSAID use, even though the utilization rate of NSAIDs was approximately 20%, may also have affected muscle strengthening in the present study. NSAID use, dietary intake control and intervention duration need to be considered in future studies.

Exercise therapy for OA, exercise intensity and specific regimens have not been established. Based on the current findings, the optimal amount of BCAA intake and exercise intensity for combined therapy for OA in the pre-operative period should be investigated. Future work should be devoted to a study of the best combination for improving muscle weakness.

Conclusion

BCAA supplementation combined with muscle strengthening exercises showed a marginally significant effect in 10-m timed gait time. There was no significant effect on hip muscle strength. In addition, the improvement rate of hip abductor muscle strength on the contralateral side was significantly higher in the BCAA group than in the control group.

Conflict of Interest

There were no financial relationships to disclose in the present study.

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The present study received no funding or support.

Author Contributions

Study design (TI, TJ and TM), data collection (KN and KS), subject recruitment (TI and KH), data analysis (JA), data interpretation (TI and TM), writing the manuscript (TI, TJ and TM), revising the manuscript (TI, TJ and TM) and project management (TI and KH) were contributed.

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