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2020 Chitranjan S. Ranawat Award: Perioperative essential amino acid supplementation suppresses rectus femoris muscle atrophy and accelerates early functional recovery following total knee arthroplasty

A PROSPECTIVE DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

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Aims

The aim of this study was to assess the effectiveness of perioperative essential amino acid (EAA) supplementation to prevent rectus femoris muscle atrophy and facilitate early recovery of function after total knee arthroplasty (TKA).

Methods

The study involved 60 patients who underwent unilateral TKA for primary knee osteoarthritis (OA). This was a double-blind, placebo-controlled, randomized control trial with patients randomly allocated to two groups, 30 patients each: the essential amino acid supplementation (9 g daily) and placebo (lactose powder, 9 g daily) groups. Supplementation and placebo were provided from one week before to two weeks after surgery. The area of the rectus femoris muscle were measured by ultrasound imaging one month before surgery and one, two, three, and four weeks postoperatively. The serum albumin level, a visual analogue knee pain score, and mobility were also measured at each time point. The time to recovery of activities of daily living (ADLs) was recorded. Postoperative nutrition and physiotherapy were identical in both groups.

Results

The mean relative change from baseline was as follows for the amino acid group: 116% in rectus femoris muscle area (71% to 206%); 95% in serum albumin (80% to 115%) and 39% in VAS pain (0% to 100%) at four weeks after surgery. These values in the placebo group were: 97% in muscle area (68 to 155); 89% in serum albumin (71% to 100%) and 56% in VAS pain four weeks after surgery (0% to 100%). All changes were statistically significant ($p < 0.05$). The mean time to recovery of ADLs was shorter in the amino acid group compared with the placebo group ($p = 0.005$).

Conclusion

Perioperative essential amino acid supplementation prevents rectus femoris muscle atrophy and accelerates early functional recovery after TKA.

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Introduction

Total knee arthroplasty (TKA) may be complicated by atrophy of lower limb muscles with decreased mobility, an increased risk of falling,[1,2] and of readmission to hospital.[3] Muscle atrophy has also been observed in the nonoperated lower limb following arthroplasty.[4] A decline in mobility has other consequences including a prolonged

length of hospital stay and an increase in the need for nursing care and cost.[5,6] It is thus important to prevent lower limb muscle atrophy after TKA. A recent cohort study reported that educating patients about a preoperative high-protein intake had favourable effects on the outcome of TKA in malnourished patients.[7] However, the main outcomes in this study were assessed in relation to the length of stay in hospital, readmission and costs. The anatomical and functional outcomes of TKA were not clarified. Therefore, a rigorous clinical study evaluating organic and functional outcomes is needed to determine the effectiveness of protein supplementation.

The area of the rectus femoris muscle (RFA) correlates with quadriceps strength and general mobility.[8,9] Thus the perioperative monitoring of the rectus femoris area is important. Essential amino acid supplementation has been reported contribute to the prevention of muscle atrophy in the elderly.[10] Muscle synthesis can be promoted by exercise augmented by an adequate protein intake.[11] Considering that surgery accelerates catabolism and proteolysis in muscle,[12] essential amino acid supplementation might help to suppress catabolism in the affected muscles.[13] Perioperative supplements might reduce muscle atrophy after TKA and improve early mobilization. We hypothesized that perioperative essential amino acid supplements would suppress the postoperative atrophy of the rectus femoris muscle and contribute to the early recovery of lower limb function after TKA. The aim of this study was to clarify the effectiveness of perioperative amino acid supplementation in the prevention of rectus femoris atrophy after TKA.

Methods

We used a two-arm, parallel trial, design, with a 1:1 allocation ratio to the essential amino acid and placebo group (Figure 1). Randomization was performed by concealed allocation (sequential number), with 30 patients allocated to each group.[14] The envelopes were opened by medical staff who were not involved in the study, with only the allocation number provided to the physician. Baseline measures were obtained one month before TKA. Primary and secondary outcomes, with the exception of radiological assessment, were measured at baseline, and at one, two, three, and four weeks postoperatively. Radiological assessments were performed at baseline and two weeks postoperatively.

We included patients who underwent unilateral TKA for the treatment of primary osteoarthritis (OA) of the knee. We excluded patients with rheumatoid arthritis, osteonecrosis of the knee, post-traumatic OA, severe hepatic or renal disease, or other condition which could affect the metabolism of nutrients such as cancer, diabetes mellitus, and obesity (defined by WHO as a BMI equal to or greater than 30). Patients in whom TKA of the contralateral knee was also planned and those who underwent a bilateral procedure were also excluded.

A dose of 3 g of essential amino acids or a placebo was administered to the patients three times daily after every meal, from one week before to two weeks after TKA. This included isoleucine (603 mg, 6.7%), leucine (684 mg, 7.6%), lysine (756 mg, 8.4%), methionine (603 mg, 6.7%), phenylalanine (405 mg, 4.5%), threonine (405 mg, 4.5%), tryptophan (207 mg, 2.3%), valine (603 mg, 6.7%), arginine (630 mg, 7%), histidine (315 mg, 3.5%), and starch (1,089 mg, 12.1%). This composition is packaged for commercial sale as ES-polytamin (EA Pharma Co., Ltd. Tokyo, Japan) and has been approved by the Japanese government (insurance approval number is 22100AMX01509). The dose was determined as appropriate based on information supplied by the manufacturer. The placebo involved the same amount (9 g daily) of lactose powder.

The primary outcome was the RFA. Secondary outcomes were the diameter of the quadriceps muscle, the serum albumin level, a visual analogue scale (VAS) for knee pain, mobility, the femorotibial angle (FTA),[15] and prosthetic alignment (α, β, γ, δ).[16]

The RFA was measured as shown in (Figure 2a), as previously described in another study assessing the relationship between RFA and quadriceps muscle strength in patients with chronic respiratory disease.[8] For this measurement, patients were placed supine with the knee relaxed in extension. The patients were asked not to perform any exercises on the day that the measurement was made. The probe was placed perpendicular to the long axis of the femur, with minimal pressure. Images were obtained using B-mode ultrasound, with an 8 MHz linear probe, with a 5.6 cm array (Xario SSA-660A; Toshiba Medical Systems, Tokyo, Japan). The RFA was calculated using a planimetric technique, based on measurement of the outline and diameter of the quadriceps on a static ultrasound image (Figure 2b). One technician, blinded to group allocation, measured all RFAs. The intraobserver reliability of these measurements was determined using intraclass correlation coefficients (ICCs), based on measurements of the unaffected limb in 20 patients, measured twice at an interval of > four weeks. The ICC was interpreted as follows: 0 to 0.40, poor; 0.41 to 0.60, moderate; 0.61 to 0.80, good; and 0.81 to 1.00, excellent.[17] The ICC was 0.85 (95% confidence interval (CI), 0.48 to 0.97) and deemed to be excellent, corresponding to previous reports.[8]

The diameter of the quadriceps was measured from ultrasound images obtained at the same location as the RFA. The diameter was defined as the vertical distance from the superficial fat-muscle interface to the underlying femur, as also previously reported in another study assessing effects of exercise for patients having respiratory disease.[18] This diameter included the rectus femoris and the vastus intermedius muscles. The serum albumin level was measured from blood samples at each time point.[19] Knee pain was evaluated using a ten-point VAS scale, measured using a ruler, by a nurse,[20] between ‘zero’ (no pain) and ‘ten’ (worst possible pain). The six metre walking time, quadriceps muscle strength, grip strength, range of motion of the knee, and level of mobility in activities of daily living (ADL) were assessed as a measure of functional ability. The six metre walking time was measured as the time taken to walk a distance of six metres at the patient’s “comfortable speed”.[21] Quadriceps muscle strength was quantified, in newtons, using a digital pull-type hand-held dynamometer (Mobie; Sakaiika, Tokyo, Japan).[22,23] For quantification, patients sat on the edge of a bed, with their feet not touching the floor with the band of the dynamometer attached to the ankle. They were asked to exert maximal knee extension. The level of ADL was classified as either ‘independent walk’, ‘walk with cane’, ‘walk with walker’, or ‘wheelchair’ (Supplementary Figure a). This level was recorded at each time of measurement, with recovery defined

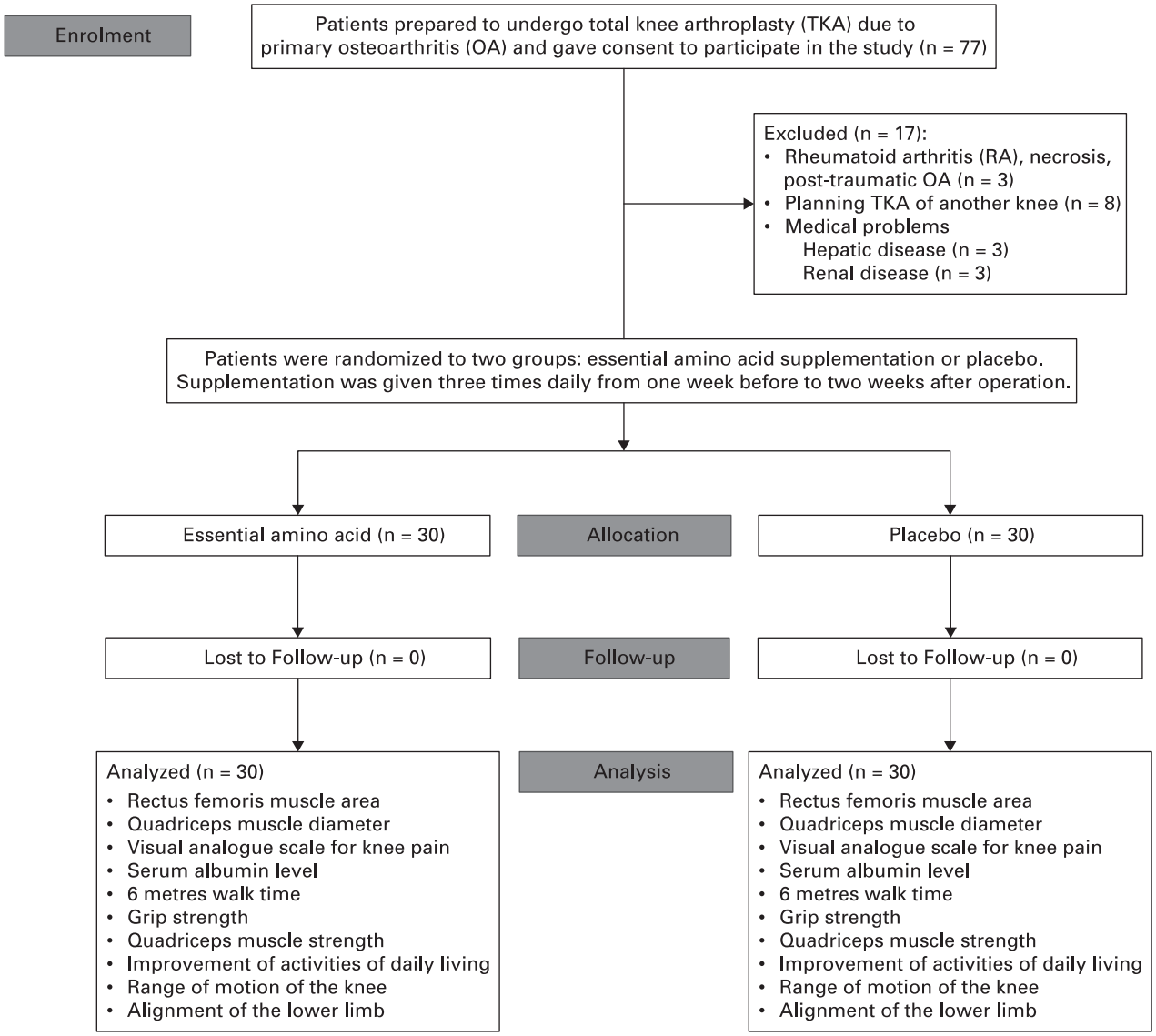


Fig. 1

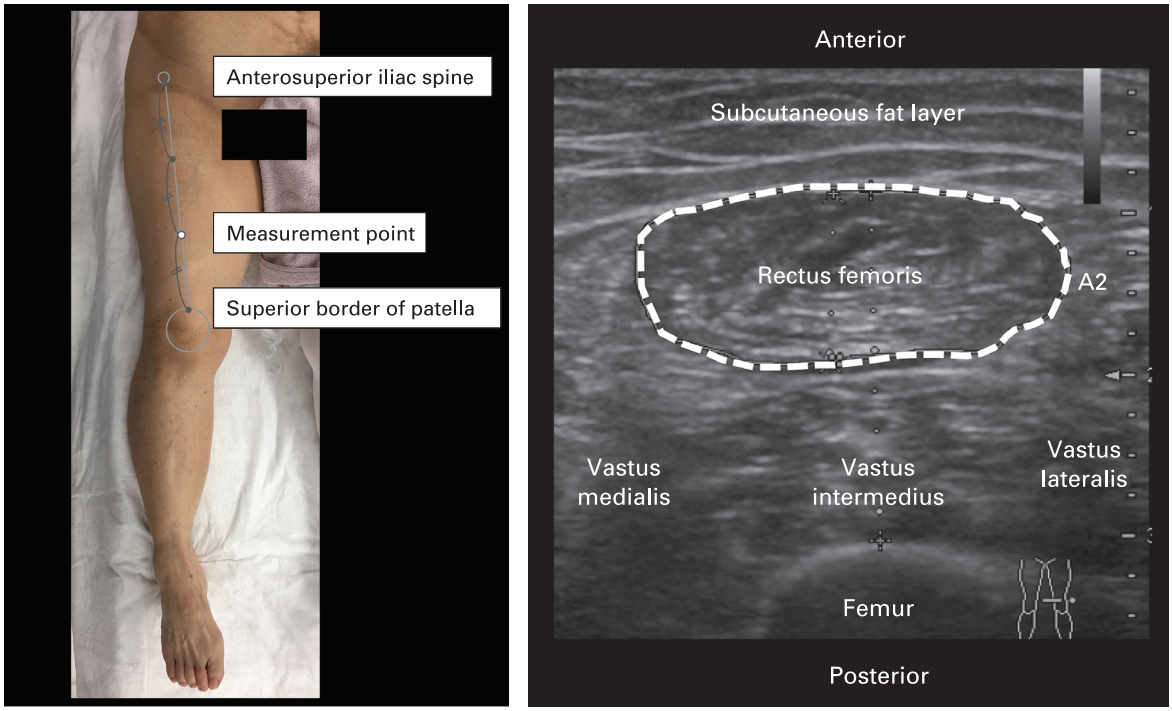
Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing the recruitment and design of the study. OA; osteoarthritis, RA; rheumatoid arthritis.

as a return to the preoperative ADL level. All measurements of function were obtained by physiotherapists who were blinded to the group allocation. The femorotibial angle and prosthetic alignment were measured from standing short film radiographs of the knee by a surgeon (HU) who was not involved in the treatment of the patients.[16] The values of the RFA, quadriceps muscle diameter, grip strength, and quadriceps muscle strength were provided as both an absolute value without adjustment and an absolute value adjusted for body weight.

All TKAs were performed by a single surgeon (NK), using the same technique and the same prosthesis (EVOLUTION; MicroPort Orthopedics Inc., Arlington, Tennessee, USA). A medial parapatellar approach was used and an intramedullary rod was used for alignment of the femoral component and an extramedullary rod for alignment of the tibial component.

All patients received the same nutritional and physiotherapeutic management. The appropriate intake of nutrition was planned by a nutritionist, based on each patient's physical constitution. The nutritional plan was well balanced, particularly with regard to the amount of protein consumed. All meals were recorded and snacks were not permitted during the period of hospitalization. The nutritional intake from meals during the hospital stay was recorded for both groups (Supplementary Table i). Postoperative physiotherapy was undertaken for two hours per day, starting on postoperative day one and continued throughout the period of hospitalization for all patients.

The flowchart of this study is shown in Figure 1. No patients were lost to follow-up. The demographic data are summarized in Table I. The length of stay in hospital was four weeks after surgery for all patients.



a b

Fig. 2

Ultrasound measurements of the rectus femoris muscle area (RFA). a) The scheme of time points for the measurements. The location of the measurement (white dot) was at two-thirds of the distance between the anterior-superior iliac spine to the superior border of the patella, with the patient in a supine position with the knee in extension. b) The white circle shows the axial rectus femoris muscle area (RFA) measured on a static image. The area was measured at the same location in all patients, and at each time point of measurement, before (baseline) and after surgery.

Table I. Patient demographics. Mean (range) or case (rate).

Parameters	EAA group (n = 30)	Placebo group (n = 30)	p-value
Age at the operation, years	75.9 (58 to 92)	75.8 (65 to 87)	0.957*
Sex, male:female	7:23	3:27	0.299†
Body weight, kg	59.4 (40 to 84)	55.8 (41 to 77)	0.242*
Height, cm	153 (143 to 168)	152 (140 to 168)	0.589*
Side, right:left	12:18	19:11	0.121†
Complications, n, %			
Hypertension	17 (57)	12 (40)	0.302†
Eye disease	8 (27)	10 (33)	0.779†
Osteoporosis	3 (10)	2 (7)	1.000†
Gynaecological disease	3 (10)	3 (10)	1.000†
Otorhinolaryngological diseases	3 (10)	3 (10)	1.000†
Operating time, mins	97 (74 to 117)	94 (81 to 118)	0.258*

*Independent-samples *t*-test.
†Fisher's exact test.
EAA, essential amino acid.

Statistical analysis. Primary and secondary outcome measures were compared between the two groups at baseline using independent-samples *t*-test and Fisher's exact test. Two-way repeated analysis of variance (ANOVA), with a post-hoc Bonferroni test, was used to compare absolute values and relative change from baseline, at each timepoint after surgery. The time to recovery of ADLs after surgery was compared between the groups using Kaplan-Meier analysis with log rank test, with the end point defined as the recovery of ADLs to baseline values. This analysis was used to assess the difference in the recovery of ADLs between the groups. The preservation of the RFA was defined by RFA values, relative to baseline, ≥ 100%. Multivariate logistic regression analysis was used to identify factors predictive of preservation of RFA. A p-value < 0.05 was considered statistically significant for all analyses.

A power analysis was performed on the basis of an expected difference of 15% in the primary outcome measure, generated from the preliminary data and an a priori study with a similar

Table II. Absolute values of each outcome measure at baseline and four weeks after the operation. Mean (range) or case (rate).

Parameters	EAA group (n = 30)	Placebo group (n = 30)	p-value
At baseline			
Rectus femoris muscle area, mm^2	256 (126 to 409)	301 (159 to 467)	0.073*
Quadriceps muscle diameter, mm	17.9 (10.2 to 29.7)	19.7 (11.0 to 29.5)	0.231*
Serum albumin level, g/dl	4.4 (3.3 to 5.0)	4.5 (3.7 to 5.1)	0.697*
VAS for knee pain, points	5 (0 to 9)	5 (2 to 8)	0.941*
6 m time walk, seconds	7.9 (4.5 to 20)	7.6 (3.9 to 12)	0.530*
Grip strength, kg	20 (10 to 29)	21 (10 to 39)	0.718*
Quadriceps muscle strength, N	140 (31 to 310)	130 (36 to 287)	0.573*
Knee extension, °	-5.9 (-15 to 0)	-5.0 (-20 to 0)	0.571*
Knee flexion, °	126 (110 to 140)	124 (100 to 135)	0.255*
Femorotibial angle, °	183 (174 to 191)	183 (174 to 195)	0.970*
ADL, n, %			
Gait without cane	22 (73)	23 (77)	1.000†
Gait with cane	7 (23)	5 (17)	0.748†
Gait with walker	1 (3.3)	2 (6.7)	1.000†
Wheelchair	0 (0)	0 (0)	1.000†
Four weeks after the operation			
Rectus femoris muscle area, mm^2	276 (141 to 418)	291 (108 to 479)	0.457*
Quadriceps muscle diameter, mm	21.3 (12.3 to 35.8)	21.1 (10.9 to 32.4)	0.861*
Serum albumin level, g/dl	4.2 (3.8 to 4.7)	4.0 (3.5 to 4.3)	0.009*
VAS for knee pain, points	1.8 (0 to 4)	2.5 (0 to 5)	0.038*
6 m walk, second	6.8 (4.0 to 12)	6.9 (4.5 to 11)	0.821*
Grip strength, kg	20 (10 to 31)	21 (11 to 36)	0.364*
Quadriceps muscle strength, N	90 (34 to 193)	95 (29 to 245)	0.687*
Knee extension, °	-2.5 (-10 to 0)	-1.3 (-15 to 0)	0.249†
Knee flexion, °	126 (110 to 135)	125 (90 to 140)	0.697†
Femorotibial angle, °	176 (174 to 176)	175 (174 to 176)	0.756†
Prosthetic alignment, °			
A	94.0 (91.0 to 96.9)	93.9 (92.1 to 96.3)	0.754†
B	91.1 (89.0 to 94.5)	90.8 (88.1 to 92.5)	0.172†
Γ	2.6 (-0.9 to 5.7)	1.9 (-1.0 to 4.9)	0.188†
Δ	2.6 (0 to 5.9)	2.8 (0 to 5.1)	0.691†
ADL, n, %			
Gait without cane	25 (83)	22 (73)	0.532†
Gait with cane	4 (13)	4 (13)	1.000†
Gait with walker	1 (3.3)	4 (13)	0.203†
Wheelchair	0 (0)	0 (0)	1.000†

*Independent-samples *t*-test
†Fisher's exact test
ADL, activities of daily living; EAA, essential amino acid; VAS, visual analogue scale.

cohort.[1] Assuming a two-tailed type I error rate of 0.05 and a power of 80%, a sample of 24 patients in each group would be adequate to detect this difference between the groups. Therefore, 30 patients per group was thought to be sufficient. Statistical analyses were performed using the R software package (version 3.1.1; R Core Team 2014, R foundation for statistical computing, Vienna, Austria).

Results

The absolute values of the outcomes measured at baseline and four weeks after surgery are shown in Table II, with absolute values measured at other times shown in Supplementary Table ii. The serum albumin level was significantly higher (p = 0.009, independent-samples *t*-test) and the VAS score was significantly lower (p = 0.038, independent-samples *t*-test) four weeks after surgery in the essential amino acid group. There were no statistically significant differences in the absolute values adjusted for body weight between the groups (Supplementary Table iii).

The relative change in the outcome measures at three and four weeks after surgery are shown in Table III, with the relative changes at other times shown in Supplementary Table iv. The relative changes in RFA, quadriceps muscle diameter, and serum albumin level at three and four weeks after surgery were significantly higher in the essential amino acid group (Figures 3 and 4). The relative change in VAS was significantly less in this group at four weeks after surgery (Figure 5), and he recovery of ADLs was significantly earlier in this group (p = 0.005, log rank test; Figure 6). No other significant differences were seen between the groups.

Essential amino acid supplementation was an independent factor for the preservation of RFA after TKA, with an odds ratio

Table III. Relative changes of each outcome at three and four weeks after the operation. Mean (range).

Parameter	EAA group (n = 30)	Placebo group (n = 30)	p-value*
Three weeks after the operation, %			
Rectus femoris muscle area	119 (79 to 179)	102 (63 to 186)	0.040†
Quadriceps muscle diameter	127 (78 to 192)	111 (72 to 179)	0.038†
Serum albumin level	91 (80 to 111)	87 (76 to 108)	0.034†
VAS for knee pain	59 (14 to 150)	71 (14 to 200)	0.214
6 m time walk	97 (43 to 143)	103 (66 to 154)	0.287
Grip strength	105 (68 to 147)	103 (71 to 134)	0.647
Quadriceps muscle strength	64 (19 to 255)	75 (16 to 188)	0.329
Four weeks after the operation, %			
Rectus femoris muscle area	116 (71 to 206)	97 (68 to 155)	0.026†
Quadriceps muscle diameter	123 (86 to 171)	109 (84 to 163)	0.029†
Serum albumin level	95 (80 to 115)	89 (71 to 100)	0.004†
VAS for knee pain	39 (0 to 100)	56 (0 to 100)	0.035†
6 m time walk	92 (38 to 148)	94 (62 to 120)	0.662
Grip strength	102 (64 to 174)	105 (79 to 163)	0.514
Quadriceps muscle strength	78 (22 to 257)	84 (15 to 248)	0.687

The relative changes were shown as percentage from the baseline. Mean and range of relative changes were provided.
*Independent-samples *t*-test
†p < 0.05.
EAA, essential amino acid; VAS; visual analogue scale.

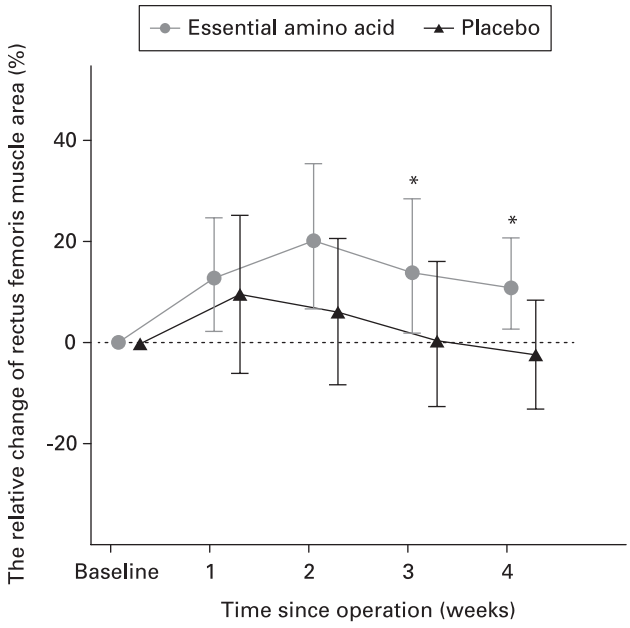


Fig. 3

The relative change in the rectus femoris muscle area (RFA; mean and SD) at each time point of measurement. The muscle atrophy was suppressed in the essential amino acid group compared with the placebo group, at three and four weeks after surgery. The asterisks denote p < 0.05.

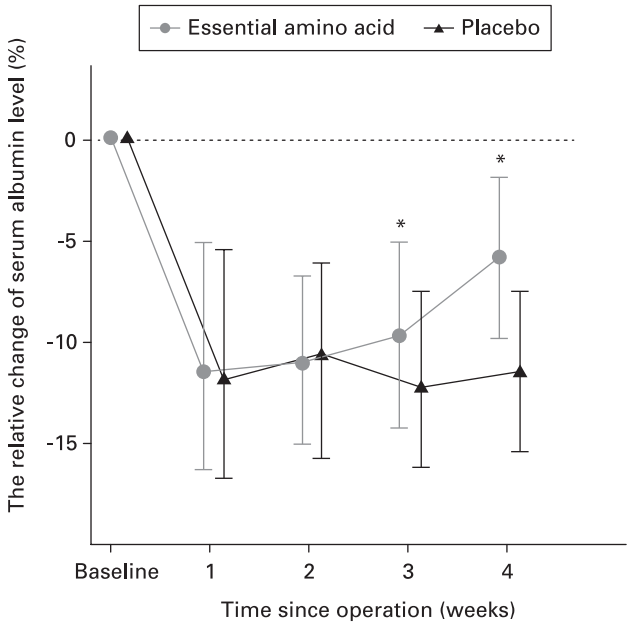


Fig. 4

The relative change in serum albumin level (mean and SD) at each time point of measurement. The serum albumin levels recovered in the essential amino acid group compared with the placebo group at three and four weeks after surgery.

(OR) of 3.96 (95% CI, 1.17 to 13.4; Table IV). No patient in either group required treatment other than the standard management provided, within 90 days after surgery.

Discussion

We found, in this randomized controlled trial (RCT), that perioperative essential amino acid supplementation suppressed postoperative rectus femoris muscle atrophy and improved early functional recovery after TKA, suggesting that it is associated with early postoperative clinical improvement. This supports results from a recent study showing the effectiveness of educational intervention for TKA.[7] However, this study did not assess the influence of protein intervention on the organic and functional outcomes.

Serum albumin levels decrease postoperatively due to the increase in catabolism associated with surgery.[19] The rapid recovery of this level which we found reflects the slowed

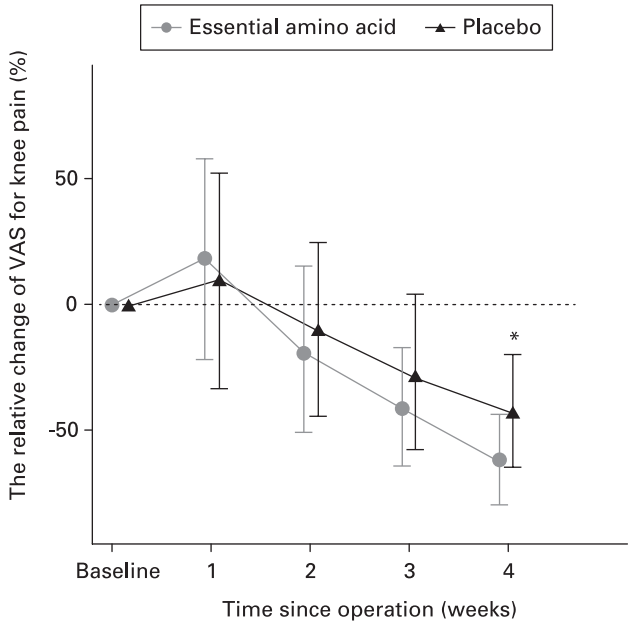


Fig. 5

The relative change in visual analogue scale (VAS; mean and SD) at each time point of measurement. It was lower in the essential amino acid than in the placebo group at four weeks after surgery.

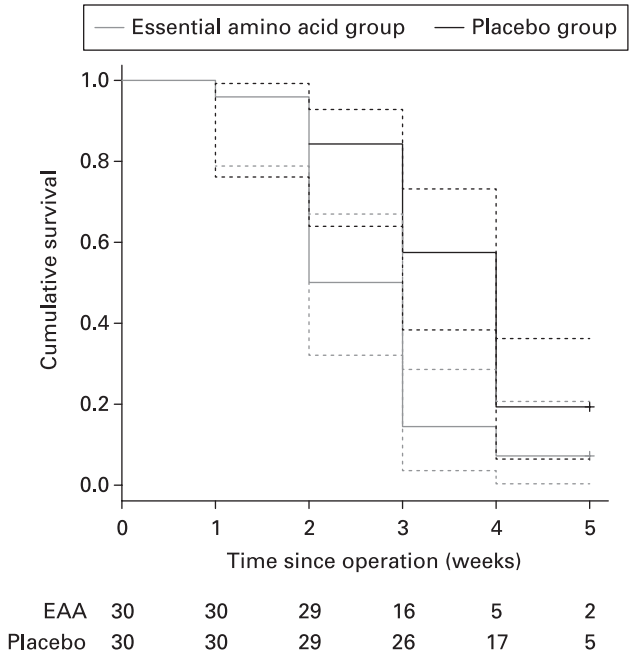


Fig. 6

The Kaplan-Meier curve of the time to recovery of activities of daily living (ADLs) to baseline levels after surgery. Patients in the essential amino acid (EAA) group had a significantly shorter time to recovery than those in the placebo group (p = 0.005). Statistical difference was evaluated by log rank test. The dashed lines represent the 95% confidence intervals. ADL; activities of daily living.

postoperative catabolism with essential amino acid supplementation, which is probably the reason for the preservation of the

Table IV. Factors associated with the preservation of rectus femoris muscle area.

Variables	Adjusted odd's ratio (95% CI)	p-value*
Age at operation	0.98 (0.89 to 1.07)	0.590
Height	0.99 (0.91 to 1.10)	0.981
Body weight	0.93 (0.87 to 1.01)	0.064
Gender		
Female	1 (reference)	N/A
Male	1.47 (0.25 to 8.79)	0.670
Supplementation		
Placebo	1 [reference]	N/A
Essential amino acid	3.96 (1.17 to 13.4)	0.027

Multiple logistic regression model (p = 0.01).
CI, confidence interval; N/A, not applicable.

volume of the rectus femoris muscle in this study. However, we did not analyze whether perioperative amino acid supplementation without postoperative exercise would also be effective. It has previously been reported that protein intake does not prevent loss of muscle volume during the immobilization of a limb.[24] Therefore, a combination of essential amino acid supplementation and exercise may be important to prevent muscle atrophy.

It has been reported that swelling of the knee after TKA peaks about two weeks postoperatively and then decreases gradually for 90 days.[25] The increase of RFA up to two weeks postoperatively in the present study may reflect postoperative swelling. The RFA after four weeks may not only reflect muscle volume but include some postoperative swelling. However, as the relative changes in RFA were significantly different between the groups, the most likely explanation is that amino acid supplementation decreases the reduction in muscle volume.

A previous study reported that knee pain improved with improved stability,[26] with stability of the knee correlating with local muscle strength.[27] Therefore, in this study, the maintenance of thigh muscle volume may have had a favourable effect on maintaining strength and thus stability. However, as there was no statistically significant difference in quadriceps strength between the groups, the VAS for pain might have been affected by other undetected factors. Further research is required to assess factors influencing the VAS for knee pain in detail.

Although muscle strength did not differ significantly between the groups in this study, the RFA was only preserved after surgery in the amino acid group. This might be because quadriceps strength was measured using a hand-held dynamometer. Although this quantitatively evaluates quadriceps strength reliably,[22,23] hand-held dynamometers show larger deviations than isokinetic dynamometers, which are the gold standard when measuring quadriceps strength.[23,28] For a sensitive assessment of muscle strength, studies having larger power or using isokinetic dynamometers are needed. Furthermore, we only evaluated isometric muscle strength in the sitting position. Measurements in different positions of the knee or with dynamic contraction may provide different results.[29] Moreover, we did not evaluate pain during the muscle strength test. This aspect may require further attention, although pain has been reported to affect muscle strength only weakly.[30]

Previous authors have reported many factors that are associated with improvements in ADLs in elderly patients after TKA, including pain, muscle strength, muscle volume, and

mental illness.[31,32] In the present study, the prevention of muscle atrophy and an improved VAS for pain potentially contributed to improvements in ADLs. However, other possible contributing factors were not evaluated.

The study had strengths. First, we used a double blind RCT design, with 100% follow-up. Secondly, nutritional intake and exercise after surgery were well controlled due to the four-week period of hospitalization after TKA, which is the standard postoperative length of hospital stay in our country. Thirdly, other clinical factors, such as the experience of the surgeon, surgical technique and type of implant were identical in the two groups, thus controlling for external factors.

The study also had weaknesses. First, although we identified the benefit of the 9 g daily of essential amino acid supplementation, the amount and duration of supplementation which is associated with maximal improvement in outcome needs to be identified. Secondly, our aim was to clarify the effectiveness of essential amino acid supplementation on early recovery after TKA and the long-term effects remain to be investigated. Thirdly, the medical staff monitored the administration of drugs during the hospital stay. However, if patients are discharged early after TKA the taking of drugs would not be monitored which would affect the outcomes. Fourthly, a sample size analysis was only performed for the primary outcome.

In conclusion, our findings support the use of perioperative essential amino acid supplementation to suppress postoperative atrophy of the rectus femoris muscle and to accelerate early functional recovery after TKA.

Take home message

- Perioperative essential amino acid supplementation prevents rectus femoris muscle atrophy and accelerates early functional recovery after TKA.

Supplementary material

Tables displaying additional results and a figure to aid understanding of the schema of activities of daily living (ADL) grades.

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