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SHORT COMMUNICATION

Supplemented amino acids may enhance the walking recovery of elderly subjects after hip fracture surgery

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Abstract
The purpose of this study was to investigate whether supplemented essential amino acids (EAAs) could enhance rehabilitation therapy (Rehab) for recovery of walking capacity in subjects after hip fracture surgery (HFS). Eighty-three elderly subjects with HFS (20 ± 11 days after acute trauma) were eligible for the study and randomized to receive Rehab only (Rehab; $n = 27$), Rehab + placebo (RP; $n = 28$) or Rehab + EAAs (RE 8 g/day; $n = 28$). The patients' walking capacity (m) was measured by 6-min walking distance (6MWD) at admission and at discharge (median 66 days after admission). All patient groups were treated with the same Rehab (2 sessions/day × 5 days/week). The results showed that the gain in 6MWD was higher in RE than in Rehab and RP ($p = 0.034$; $p = 0.024$). The study shows that EAA supplementation can enhance walking recovery rate in subjects with HFS.

Keywords Hip fracture · Amino acids · Walking test

Introduction

Hip fracture surgery (HFS) increases patient demand for extensive rehabilitation (Rehab) to be able to return to the community. Standard care, however, has a limited effect on HFS patient Rehab [1], explained in part by the difficulty in regaining post-traumatic walking ability or self-care [2]. A recent study reported that only 50.3% of patients recovered walking ability 6 months after trauma [3]. The absence of consensus on what type of Rehab therapy is effective after HFS [4] could be considered a major factor contributing to unsatisfactory Rehab outcome. As low walking ability reduces quality of life and survival [1], any strategy used in conjunction with Rehab and potentiating post-HFS walking recovery could be beneficial for both patient health status and the economic sustainability of the health-care system.

Here, we hypothesized that supplemented essential amino acids (EAAs) for rehabilitative patients after HFS could enhance the rate of walking recovery. Firstly, EAAs exert important bodily (especially muscle) anabolic activities, which could counteract/limit HFS hypermetabolic state promoted by inflammatory syndrome, which can last for up to 3 months after surgery [5]. Secondly, EAAs attenuate muscle loss and mobility impairment in older subjects, following total knee arthroplasty [6] and improve walking capacity in subjects with end-stage chronic diseases such as heart failure [7] and obstructive pulmonary disease [8].

Thus, the purposes of this study were, firstly, to document whether the Rehab protocol adopted in our institute could allow post-HFS patients to achieve the minimal clinically significant change of + 50 m in walking performance [9] and, secondly, whether EAA supplementation could enhance the rate of walking recovery and increase the number of patients achieving + 50 m gain.

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Methods

Ninety-six subjects with HFS, consecutively admitted to our Rehab Institute, 20 ± 11 days after acute trauma, were recruited for this study. Thirteen were excluded because of prefixed exclusion criteria such as chronic heart failure (5), pre-event muscle–skeletal disorders (2), chronic obstructive pulmonary disease (4) and depression (2). The remaining patients (83) underwent routine clinical examination, anthropometric and biohumoral measurements and nutritional intake analysis and were randomized into three groups: Rehab + EAAs (RE), Rehab + placebo (RP), Rehab only (Rehab). Each EAA packet (4 g) contained (g) leucine 1.25, lysine 0.65, isoleucine 0.625, valine 0.625, threonine 0.35, cysteine 0.15, histidine 0.15, phenylalanine 0.1, methionine 0.05, tyrosine 0.03, tryptophan 0.02. (Aminotrofic®, ErreKappa, Milan, Italy). The EAA packet was provided daily at 10 a.m. and at 4 p.m. until patient discharge. Placebo consisted of isocaloric maltodextrin (4 g) administered at the same times as the EAAs. The supplementations (EAAs, placebo) were provided the day after randomization. At 10 ± 6 days from admission, the patients underwent 6-Min Walking Distance test (6MWD) to measure walking capacity. In our laboratory, 6MWD for healthy old subjects (79 ± 4.5 years) was 251 ± 71 m (range 77–360 m) (unpublished data). 6MWD was repeated at patient discharge from the rehab institute (60 ± 8 days from admission).

By the week before discharge, the patients kept a 3-day food diary for nutritional analysis. The three patient groups were treated with Rehab therapy protocol adopted for HFS, consisting of two sessions per day (40–50 min for each session), 5 days a week, of passive-assisted active mobilization of the operated limb, muscle strength isotonic and isometric exercises, isotonic exercises and against resistance, and assisted gait training with the use of walking sticks.

All subjects gave their informed written consent. The study was approved by the scientific ethics committee of the institute (Direzione Generale/Atti/2008/FF/R002/13.2.2008).

Statistical analysis

Kruskal–Wallis test (K–W test) and χ^2 test were used to test differences in the baseline variables of the three groups when appropriate.

To investigate whether the rehabilitation therapies influenced the gain in walking test (calculated as difference between discharge measures and admission measures), Kruskal–Wallis test (K–W test) was performed, followed by Dunn's multiple comparison test as post hoc test. Differences between groups in the number of patients achieving + 50 m in walking performance were evaluated using χ^2 test.

In addition to evaluating the differences between treatment groups in serum albumin values, a linear mixed effect model was used. In this model, treatment groups, follow-up (admission and discharge) and their interaction were tested as fixed effects, while patient identities were analyzed as random effects. Unless otherwise stated, values reported are means ± SD. Statistical analyses were performed using R software version 3.4.1 [10].

Table 1 Base demographic, anthropometric characteristics and biohumoral variables of the three patient groups: Rehab + EAAs (RE), Rehab + placebo (RP), Rehab only (Rehab)

	Rehab, $n = 27$	RP, $n = 28$	RE, $n = 28$	p value
Age (years)	81.5 ± 5.9	82 ± 6.3	79.6 ± 8	0.37
Males/females (number)	8/19	10/18	12/16	0.61
Body mass index (kg/m^2)	26.1 ± 4.9	24.7 ± 3.8	25.9 ± 5.2	0.45
C-reactive protein (mg/l; nv < 5)	21.4 ± 26	18.4 ± 23.2	20 ± 25.95	0.89
Serum albumin (g/dl; nv 3.5–5)	3.43 ± 0.44	3.47 ± 0.4	3.44 ± 0.52	0.93
Plasma glucose (mg/dl; nv 70–105)	109 ± 5.8	105 ± 12.9	111 ± 14	0.18
Blood urea (mg/dl; nv 18–40)	46.8 ± 10.6	45.9 ± 13.4	41 ± 16.8	0.25
Serum creatinine (mg/dl; nv 0.5–0.9)	1.12 ± 0.4	0.98 ± 0.25	1.06 ± 0.31	0.27
Nutritional intakes				
Kcal/day	1303 ± 233.4	1384 ± 352	1327 ± 361	0.64
Protein (g/day)	53.7 ± 12.1	56.2 ± 14.1	54.5 ± 14.2	0.71
CHO (g/day)	149 ± 44.8	157.8 ± 43.3	156.2 ± 41.2	0.80
Lipid (g/day)	54.7 ± 14.2	58.6 ± 15.8	53.8 ± 16.4	0.53

Statistical analysis K–W test: no significant differences among the groups

Nv normal value

Results

At admission (Table 1), the three patient groups (Rehab, RP, RE) were similar for demographic, anthropometric and biohumural characteristics and nutritional intakes. An inflammatory state was present. At discharge, the RE group, compared to the other groups, had significantly improved circulating Alb ($+0.34 \pm 0.14$ vs $+0.08 \pm 0.08$ of RP and $+0.07 \pm 0.05$ of Rehab); $p < 0.05$. Inflammation persisted in all three groups.

Table 2 shows patient walking performance at 6MWD test, both at admission and discharge times. At baseline, the three groups showed lower than normal physical capacity. At discharge, each group had significantly improved walking capacity. During the Rehab period, the patients' body weight remained virtually unchanged, indicating that their daily calorie (25.9 ± 2.8 Kcal/kg) and protein intakes (0.902 ± 0.12 g/kg) were adequate for bodily requirements.

In each group, the average change in walking capacity was above the minimal clinically significant + 50 m. However, the improvement rate in RE was higher than in the other two groups, while RP showed no significant differences with Rehab (K–W test: $\chi^2 = 6.4$, p value = 0.04; pairwise comparison: RE vs RP: p value = 0.024; RE vs Rehab: p value = 0.034; RP vs Rehab: p value = 0.9).

The study found that EAA supplementation increased the number of patients (75%) achieving + 50 m in comparison to RP (46.4%) and Rehab (66.7%), even if this was not statistically significant ($\chi^2 = 5.16$, $df = 2$, p value = 0.075).

Discussion

We found that our Rehab protocol was effective in achieving minimal, but clinically significant changes in walking recovery. Supplementation with EAAs not only enhanced Rehab outcomes, but also increased the number of subjects reaching + 50 m gain.

Multiple mechanisms can explain the benefits derived from EAAs. Firstly, EAAs exert anabolic activity for wound repair. Indeed, wound healing in all its phases requires EAA availability [11] for de novo synthesis of an enormous amount of proteins and peptides. Interestingly, ß-hydroxy-ß-methylbutyrate (HMB), a leucine metabolite, is effective for muscle protein synthesis and prevention of protein degradation, and accelerating wound heading [12] Secondly, EAAs can increase muscle mass and strength of both operated and non-operated limbs [6], compromised by surgical metabolic stress, immobilization and unloading.

The essential branched chain amino acids (BCAAs), indeed are the main fuel in skeletal muscle tissue for aerobic energy production.

Moreover, EAAs can attenuate muscle soreness, an important factor interrupting physical therapy [13, 14]. That study patients on EAAs were in net anabolic status during Rehab phase was suggested by the increased visceral protein synthesis (albumin) despite persistent inflammation [15, 16].

Our results contrast with an investigation [6] carried out in subjects following total knee arthroplasty supplemented with 20 g EAAs × 2/day, who did not improve compared to the placebo group at 6MWD at 2 and 6 weeks after surgery. The discrepancy may be due to different therapy duration, which was higher in our investigation. Unfortunately, our research did not document whether the patients regained pre-fracture walking capacity levels, as this functional state was not known. However, it is worth noting that the EAA-associated walking capacity levels were within normal value ranges.

Future studies should try to overcome study limitations such as the long-term (6–12 months after surgery) effect of EAAs after withdrawal and how to benefit the non-responder population with EAA by changing the dose and/or mixture composition, which should also include vitamin D [13]. In addition, based on the results of this preliminary study,

Table 2 Patient walking performance at the 6MWD test, both at admission and discharge times

	Rehab, $n = 27$	RP, $n = 28$	RE, $n = 28$
Admission	65.3 ± 69.1 (0–315; median 120)	72.2 ± 69.9 (0–220; median 50)	46.4 ± 44.1 (0–180; median 40)
Discharge	130.7 ± 71.6 (15–350; median 120)	145.8 ± 98.7 (0–300; median 150)	164.6 ± 108.1 (20–425; median 150)
Gain (discharge–admission)	$+65.4 \pm 52.4$*§ (40–120; median + 60)	$+73.6 \pm 66.3$** (0–270; median + 47)	$+118.2 \pm 100.3$ (0–400; median + 89)

The gain (in m) is also reported

Statistical analysis K–W test

RE Rehab + EAAs, *RP* Rehab + placebo, *Rehab* Rehab only

§ $p = 0.9$ vs RP

* $p = 0.034$ vs RE

** $p = 0.024$ vs RE

we will optimize the experimental design by computing an appropriate power analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the scientific ethics committee of the institute (Direzione Generale/Atti/2008/FF/R002/13.2.2008).

Informed consent All subjects gave their informed written consent.

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