A commentary by Robert M. Harris, MD, is linked to the online version of this article.

Conditionally Essential Amino Acid Supplementation Reduces Postoperative Complications and Muscle Wasting After Fracture Fixation

A Randomized Controlled Trial

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Background: Postoperative complications and substantial loss of physical function are common after musculoskeletal trauma. We conducted a prospective randomized controlled trial to assess the impact of conditionally essential amino acid (CEAA) supplementation on complications and skeletal muscle mass in adults after operative fixation of acute fractures.

Methods: Adults who sustained pelvic and extremity fractures that were indicated for operative fixation at a level-I trauma center were enrolled. The subjects were stratified based on injury characteristics (open fractures and/or polytrauma, fragility fractures, isolated injuries) and randomized to standard nutrition (control group) or oral CEAA supplementation twice daily for 2 weeks. Body composition (fat-free mass [FFM]) was measured at baseline and at 6 and 12 weeks postoperatively. Complications were prospectively collected. An intention-to-treat analysis was performed. The relative risk (RR) of complications for the control group relative to the CEAA group was determined, and linear mixed-effects models were used to model the relationship between CEAA supplementation and changes in FFM.

Results: Four hundred subjects (control group: 200; CEAA group: 200) were enrolled. The CEAA group had significantly lower overall complications than the control group (30.5% vs. 43.8%; adjusted RR = 0.71; 95% confidence interval [CI] = 0.55 to 0.92; p = 0.008). The FFM decreased significantly at 6 weeks in the control subjects (–0.9 kg, p = 0.0205), whereas the FFM was maintained at 6 weeks in the CEAA subjects (−0.33 kg, p = 0.3606). This difference in FFM was not seen at subsequent time points.

Conclusions: Our results indicate that CEAA supplementation has a protective effect against common complications and early skeletal muscle wasting after operative fixation of extremity and pelvic fractures. Given the potential benefits of this inexpensive, low-risk intervention, multicenter prospective studies in focused trauma populations are warranted.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Despite continued advances in surgical management of extremity and pelvic fractures, complications and prolonged loss of function continue to adversely impact clinical outcomes[1-5]. In the musculoskeletal trauma population, malnutrition is common, and when diagnosed by a registered dietitian, it is associated with a 3-fold greater complication rate[6]. Malnutrition is a potentially modifiable risk factor for mortality, fracture nonunion, wound complications, and increased length of stay[6-9].

Baseline malnutrition is further compounded by inadequate calorie and protein intake following trauma and subsequent surgery[10,11]. An already poor diet is further suppressed by pain, medication side effects, and nausea, leading to worsening nutrition deficiencies and limiting healing potential. These deficiencies, in combination with the detrimental effects of prolonged immobilization, result in a catabolic state with decreased muscle protein synthesis and skeletal muscle wasting[12-15]. Conditionally

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/G920).

A **data-sharing statement** is provided with the online version of the article (http://links.lww.com/JBJS/G924).

essential amino acid (CEAA) supplementation has the potential to reduce the rate of complications and loss of muscle mass associated with malnutrition in the recovery phase after trauma[16-19].

To our knowledge, the impact of nutrition interventions on complications and loss of skeletal muscle mass after musculoskeletal trauma has not been thoroughly investigated. Well-designed prospective studies evaluating the impact of nutrition interventions are needed to inform evidence-based recommendations in the trauma population. The aim of this randomized controlled trial (RCT) was to evaluate the effect of CEAA supplementation on postoperative complications and skeletal muscle wasting following operative fracture fixation.

Materials and Methods

This prospective, single-blinded RCT was approved by our investigational review board and registered on ClinicalTrials.gov (03658278). We recruited adults (≥18 years old) who presented to a level-I trauma center for operative treatment of fractures of the pelvis and extremities with the following exclusion criteria: patients with inability to follow up (e.g., prisoners, those who were homeless, those with intellectual disabilities without adequate support), documented dementia, traumatic brain injury, prolonged intubation or impaired mental status lasting for >72 hours after the injury, head or neck trauma preventing oral intake, or a medical condition contraindicating intake of the nutrition supplementation (e.g., patients with phenylketonuria). There were no changes to the inclusion or exclusion criteria after commencement of the study.

Eligible subjects received standardized information about the trial verbally and in writing from a single trained research coordinator (J.D.), and they signed a consent form prior to enrollment. All subjects were enrolled within 72 hours of surgical fixation. Subjects were stratified by the research coordinator to 1 of the following 3 groups: (1) fragility fracture, (2) polytrauma and/or open fracture, and (3) isolated fracture. Stratified randomization was employed to decrease potential confounding among the experimental condition groups, as no comparisons across the stratified groups were intended. Subjects stratified to the fragility fracture group were ≥65 years of age and had sustained a low-energy injury, such as a ground-level fall, with an isolated fracture. The polytrauma and/or open fracture group had either an open fracture or multiple fractures indicated for operative fixation. The isolated fracture group included those who were <65 years of age with an isolated injury. Patients with isolated distal radius and/or hand fractures were not enrolled.

After injury stratification, subjects were allocated to 2 groups in a 1:1 ratio using block sizes of 4: (1) standard nutrition (control group) or (2) standard nutrition with CEAA supplementation. One investigator (N.R.H.) was exclusively responsible for the randomization, which was generated with the use of Excel 2016 (Microsoft). The primary investigator (M.C.W.) and the statistician responsible for data analysis (N.A.G.) were blinded to the randomization.

All subjects received standard perioperative nutrition during hospitalization. Subjects were not excluded from receiving dietetic consultation or protein-calorie supplementation when clinically indicated, although nutrition supplementation was not provided to trauma patients eligible for this study during the study period. Subjects randomized to the CEAA group were provided twice daily supplementation for 2 weeks with a commercially available supplement containing 7 g of arginine, 7 g of glutamine, and 1.5 g of the leucine metabolite beta-hydroxymethylbutyrate (Juven; Abbott Nutrition). The supplement was provided in a flavored or unflavored powder form that was mixed with water or juice. Supplement compliance was monitored by self-reporting, and subjects were instructed to bring any unconsumed product to their clinical follow-up as a secondary compliance measure.

Subject demographics, comorbidities, Orthopaedic Trauma Association (OTA) fracture classification[20], and Charlson Comorbidity Index (CCI)[21] were documented prospectively at enrollment. Malnutrition risk was assessed by the research coordinator using subjective global assessment (SGA)[22,23].

Outcomes

The primary outcome was the overall complication rate, which included unplanned reoperation, fracture nonunion, surgical site infections (SSIs), mortality, and medical complications. Medical complications included cardiovascular events, thromboembolism, pneumonia, and urinary tract infections, among others. Postoperative complications were prospectively recorded for 12 months after surgery during regularly scheduled clinical follow-up. If patients were discharged by the attending surgeon, research staff conducted an identical interview and data collection regarding complications via telephone. The electronic medical record was reviewed to identify any unreported hospitalizations or complications prior to data analysis. SSIs were classified according to the Clavien-Dindo classification[24]. Nonunion was defined as failure of radiographic union at a minimum follow-up of 6 months or the need for operative intervention for nonunion.

The secondary outcome, body composition (fat-free mass [FFM]), was assessed using A-mode ultrasound (BodyView ProFit software; IntelaMetrix) within 72 hours of surgery and again at 6 and 12 weeks postoperatively using methods previously validated in the trauma population[25]. Dominant-hand grip strength was recorded with a handheld dynamometer at baseline and at 2, 6, and 12 weeks after surgery[26]. If the dominant hand was injured, then the uninjured hand was used to measure strength at baseline and subsequent visits. All data were stored in Excel, except for body composition, which was stored in the BodyView ProFit software. Outcomes were collected at standard clinical follow-up times for fracture care at our institution: grip strength at 2 weeks, body composition and grip strength at 6 and 12 weeks, and postoperative complications at all visits (from 2 weeks to 12 months). All primary and secondary outcomes were prospectively collected by the research coordinator responsible for enrollment, who was not blinded to randomization.

Data Analysis

Sample size analysis was performed a priori: for the primary outcome of overall complications, assuming a rate of 20%, 197

TABLE I Comparison of Demographic Variables Between the Groups*

Variable	Control (N = 194)	CEAA Supplementation (N = 200)	P Value
Age (mean ± SD) *(yr)*	53.4 ± 17.7	51.9 ± 20.3	0.5359
Female sex *(no. [%])*	97 (50%)	86 (43%)	0.1637
BMI (mean ± SD) *(kg/m²)*	**30.5 ± 8.0**	**28.8 ± 7.4**	**0.0241**
Obese *(no. [%])*	84 (43.3%)	70 (35%)	0.0914
Body fat (mean ± SD) *(%)*	28.8 ± 8.0	27.6 ± 8.5	0.1674
Baseline FM (mean ± SD) *(kg)*	26.4 ± 11.8	24.3 ± 11.2	0.0890
Baseline FFM (mean ± SD) *(kg)*	62.7 ± 15.6	61.4 ± 14.7	0.6287
Diabetes *(no. [%])*	34 (18%)	26 (13%)	0.2003
Smoker† *(no. [%])*	53 (27%)	51 (26%)	0.6595
CCI > 2 *(no. [%])*	23 (12%)	21 (11%)	0.4394
SGA categories† *(no. [%])*			0.3680
A	173 (89.6%)	184 (92%)	
B	16 (8.3%)	10 (5%)	
C	4 (2.1%)	6 (3%)	
ISS (median [IQR])	9 (9-18)	9 (9-16)	0.4162
Open fractures *(no. [%])*			0.2323
None	166 (85.6%)	174 (87.0%)	
Minor	12 (6.2%)	17 (8.5%)	
Severe	16 (8.3%)	9 (4.5%)	
High-risk injury‡ *(no. [%])*	39 (20.1%)	37 (18.5%)	0.6868
Fracture location§ *(no. [%])*			0.1835
Upper extremity	37 (14.98%)	54 (20.15%)	
Lower extremity	190 (76.92%)	187 (69.78%)	
Pelvis	20 (8.10%)	27 (10.07%)	
Adherence (median [IQR]) *(%)*	NA	71.4 (21.4-100)	NA

*CEAA = conditionally essential amino acid, SD = standard deviation, BMI = body mass index, FM = fat mass, FFM = fat-free mass, CCI = Charlson Comorbidity Index, SGA = subjective global assessment, ISS = Injury Severity Score, IQR = interquartile range, and NA = not applicable. Statistical comparisons are between the control and intervention groups. Boldface indicates significance. The total number of fractures exceeds the total number of enrolled patients because subjects with multiple injured extremities were included. †One patient was excluded for missing recorded SGA and smoking status. ‡High-risk injury includes tibial pilon, tibial plateau, and/or pelvic ring fractures. §Reported as the total number of operated fractures in each group (control had a total of 247 fractures, and the CEAA supplementation group had a total of 268 fractures).

subjects per group would provide the ability to detect a 50% reduction in complications with 95% confidence and 80% power; therefore, we targeted enrollment of 400 subjects. An estimated complication rate of 20% was determined based on the results of a previously published retrospective study evaluating the impact of malnutrition assessment on medical and surgical complications[6]. For comparison of the secondary outcome (body composition change), with similar parameters, 71 patients were required to detect a 10% difference in postoperative skeletal muscle mass change; we again targeted enrollment of 400 subjects.

Baseline characteristics were compared between the groups using independent t tests (or the Wilcoxon rank sum test, if the characteristics were not normally distributed) for continuous measures and the chi-square test for categorical measures. Analyses were performed according to intention-to-treat. Log-binomial regression was used to determine the relative risk (RR) of complications in the CEAA group versus the control group, without and with adjustment for fracture group and follow-up duration. Secondary outcomes (FFM and grip strength) were modeled using linear mixed-effects models, and the results were expressed as least-square means and 95% confidence intervals (CIs). Analyses were performed using SAS statistical software (SAS Institute).

Source of Funding

This research was supported by a grant from the American Academy of Orthopaedic Surgeons Board of Specialty Societies Quality and Patient Safety Action Fund.

Results

A total of 879 patients who underwent acute operative fracture fixation were screened between March 15, 2018, and

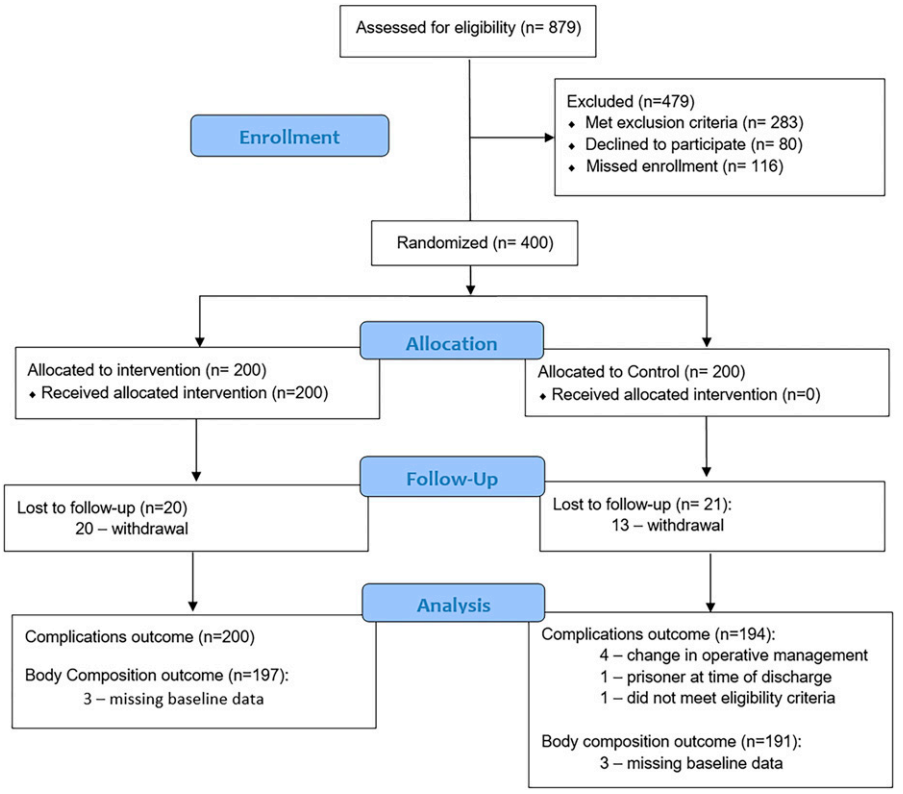

Fig. 1

Flow diagram showing enrollment, allocation, follow-up, and analysis.

November 13, 2019. There were 80 patients who declined to participate, 283 who met exclusion criteria, and 116 patients who were not approached within the enrollment timeline due to after-hours management (total n = 479). Enrollment concluded with 400 subjects (control group: 200; CEAA group: 200). Following randomization, 6 participants (all control subjects) later became ineligible due to nonoperative treatment (n = 4), did not meet eligibility criteria (n = 1), and incarceration (n = 1).

There were no significant differences between the groups for age, sex, baseline FFM, fat mass, percent of body fat, diabetes, smoking, CCI, Injury Severity Score (ISS), open fractures (including Gustilo-Anderson type-III injuries), high-risk injuries (tibial pilon fractures, tibial plateau fractures, or pelvic ring injuries), fracture location (upper extremity, lower extremity, or pelvis), or SGA (all $p > 0.05$) (Table I). The baseline body mass index (BMI) of the control group (30.5 ± 8 kg/m^2) was significantly higher than that of the CEAA group (28.8 ± 7.4 kg/m^2) ($p = 0.0241$). However, the proportions of overweight, obese, and underweight patients did not significantly differ between the groups ($p = 0.2953$).

TABLE II Incidence of Complications with and without Adjustment by Follow-up Duration and Fracture Group*

Effect	Control Group (N = 194) *(no. [%])*	CEAA Supplementation (N = 200) *(no. [%])*	Unadjusted		Adjusted	
			RR (95% CI)†	P Value	RR (95% CI)†	P Value
Overall complications	**85 (43.8%)**	**61 (30.5%)**	**0.70 (0.54-0.91)**	**0.0069**	**0.71 (0.55-0.92)**	**0.0083**
Medical complications	52 (26.8%)	37 (18.5%)	0.69 (0.48-1.00)	0.0510	0.71 (0.49-1.02)	0.0648
Nonunion‡	**24 (13.2%)**	**10 (5.1%)**	**0.39 (0.19-0.79)**	**0.0087**	**0.43 (0.22-0.88)**	**0.0200**
Mortality	**8 (4.1%)**	**1 (0.5%)**	**0.12 (0.02-0.96)**	**0.0457**	**0.13 (0.02-0.98)**	**0.0477**
SSI	32 (16.5%)	20 (10.0%)	0.61 (0.36-1.02)	0.0605	0.62 (0.38-1.03)	0.0633
Reoperation	27 (13.9%)	20 (10.0%)	0.72 (0.42-1.24)	0.2332	0.77 (0.46-1.29)	0.3135

*CEAA = conditionally essential amino acid, RR = relative risk, CI = confidence interval, and SSI = surgical site infection. Boldface indicates significance. †Control versus CEAA supplementation. ‡Sixteen participants removed from analysis of nonunion due to inadequate clinical and/or radiographic follow-up (12 from the control group and 4 from the CEAA supplementation group).

TABLE III Changes Observed in FFM (Body Composition) Over Time and Between Groups*

	Mean	Standard Error	95% CI	P Value
Control group				
Baseline value	62.71	1.13 (SD = 15.64)	60.49 to 64.93	0.6287†
Baseline to week 6	**−0.90**	**0.39**	**−1.66 to −0.14**	**0.0205**
Baseline to week 12	0.01	0.38	−0.74 to 0.76	0.9803
Week 6 to week 12	**0.91**	**0.42**	**0.09 to 1.73**	**0.0301**
Intervention group (CEAA supplementation)				
Baseline value	61.42	1.11 (SD = 14.68)	59.24 to 63.61	
Baseline to week 6	−0.33	0.36	−1.03 to 0.38	0.3606
Baseline to week 12	0.10	0.37	−0.64 to 0.83	0.7984
Week 6 to week 12	0.42	0.4	−0.35 to 1.2	0.2852
Compared change in control to change in CEAA groups				
Baseline to week 2	0.77	0.53	−0.27 to 1.81	0.1446
Baseline to week 6	−0.57	0.53	−1.61 to 0.46	0.2792
Baseline to week 12	−0.09	0.54	−1.14 to 0.97	0.8723
Week 6 to week 12	0.49	0.58	−0.65 to 1.62	0.3996

*FFM = fat-free mass, CEAA = conditionally essential amino acid, and SD = standard deviation. Boldface indicates significance. †Compared with the intervention group.

Follow-up

The enrollment and follow-up procedures are depicted in Figure 1. Of the eligible enrolled subjects, 142 of 194 patients (73%) in the control group and 145 of 200 CEAA patients (73%) completed full 12-month follow-up to assess complications (p = 0.876). Body composition (FFM) was recorded for 191 control and 197 CEAA subjects at baseline; 147 of 191 control subjects (77%) and 160 of 197 CEAA subjects (81%) were evaluated at 6 weeks, and 109 control subjects (57%) and 117 CEAA subjects (59%) were evaluated at 12 weeks (p = 0.595). Baseline body composition measures were lost on 3 subjects in each treatment group due to software

TABLE IV Changes Observed in Grip Strength Over Time and Between Groups*

	Mean	Standard Error	95% CI	P Value
Control group				
Baseline value	**32.91**	**1.01 (SD = 13.17)**	**30.92 to 34.90**	**0.0227†**
Baseline to week 2	**9.10**	**1.31**	**6.53 to 11.67**	**<0.0001**
Baseline to week 6	**2.86**	**0.61**	**1.66 to 4.06**	**<0.0001**
Baseline to week 12	**5.55**	**0.94**	**3.70 to 7.41**	**<0.0001**
Week 6 to week 12	**2.69**	**0.91**	**0.90 to 4.48**	**0.0033**
Intervention group (CEAA supplementation)				
Baseline value	**36.17**	**1.00 (SD = 13.70)**	**34.20 to 38.14**	
Baseline to week 2	**6.82**	**1.26**	**4.34 to 9.29**	**<0.0001**
Baseline to week 6	**2.67**	**0.58**	**1.52 to 3.81**	**<0.0001**
Baseline to week 12	**3.26**	**0.92**	**1.46 to 5.07**	**0.0004**
Week 6 to week 12	0.59	0.87	−1.12 to 2.31	0.4957
Compared change in control to change in CEAA groups				
Baseline to week 2	2.28	1.81	−1.29 to 5.85	0.2092
Baseline to week 6	0.19	0.84	−1.46 to 1.85	0.8183
Baseline to week 12	2.29	1.31	−0.30 to 4.88	0.0827
Week 6 to week 12	2.10	1.26	−0.38 to 4.58	0.0971

*CEAA = conditionally essential amino acid and SD = standard deviation. Boldface indicates significance. †Compared with the intervention group.

complications and therefore were excluded from body composition analysis. Hand grip strength was recorded for 177 control and 180 CEAA subjects at baseline; hand strength was recorded for 122 of 194 control subjects (63%) and 134 of 200 CEAA subjects (67%) at 2 weeks, 118 control subjects (61%) and 137 CEAA subjects (69%) at 6 weeks, and 116 control subjects (60%) and 124 CEAA subjects (62%) at 12 weeks (p = 1.0000). Analysis was performed on subjects who completed follow-up based on intention-to-treat; we did not adjust for compliance. There were no adverse events related to CEAA supplement consumption.

Primary Outcomes

In analysis adjusted for follow-up duration and injury stratification, subjects randomized to the CEAA group had significantly lower rates of overall complications than the control group (30.5% versus 43.8%; RR = 0.71; 95% CI = 0.55-0.92; p = 0.008) (Table II). The CEAA group had significantly lower rates of nonunion (5.1% versus 13.2%; RR = 0.43; 95% CI = 0.22-0.88; p = 0.020) and mortality (0.5% versus 4.1%; RR = 0.13; 95% CI = 0.02-0.98; p = 0.048). Significant differences were not seen in the rates of SSI (10.0% in the CEAA group versus 16.5% in the control group, RR = 0.62; 95% CI = 0.38 to 1.03; p = 0.063) or overall medical complications (18.5% in the CEAA group versus 26.8% in the control group; RR = 0.71; 95% CI = 0.49 to 1.02; p = 0.065), although both results were near the predetermined alpha value and the study was not powered to detect differences in these specific outcomes. There was no difference in the unplanned reoperation rate between the groups (10.0% in the CEAA group versus 13.9% in the control group; RR = 0.77; 95% CI = 0.46 to 1.29; p = 0.314). The Clavien-Dindo classification for SSI grades (n = 52) included 29 with grade II (20 in the control group and 9 in the CEAA group), 22 with grade III-b (12 in the control group and 10 in the CEAA group), and 1 with grade V (0 in the control group and 1 in the CEAA group).

Secondary Outcomes

FFM decreased significantly at 6 weeks in the control group (mean and standard deviation, –0.90 ± 0.39 kg; p = 0.0205) but recovered at 12 weeks (+0.01 ± 0.38 kg; p = 0.9803). In contrast, the CEAA group had no significant change in FFM at 6 weeks (−0.33 ± 0.36 kg; p = 0.3606) or 12 weeks (+0.10 ± 0.37 kg; p = 0.7984), although the difference in change was not significant between groups at any time point (Table III). Grip strength was significantly higher at each time point (2, 6, and 12 weeks) compared with baseline values in both groups (Table IV). There was no significant difference in grip strength between the groups at any time point.

Discussion

Despite operative treatment, musculoskeletal injuries have a substantial risk of complications and persistent functional limitations. Targeted nutrition supplementation with CEAA is an inexpensive, low-risk intervention with considerable potential to improve clinical outcomes and preserve functional muscle mass following musculoskeletal trauma. The results of this RCT regarding CEAA supplementation in an adult fracture population indicate that 2 weeks of twice-daily supplementation can reduce overall complications and prevent early loss of muscle mass. The observed difference in mortality was unexpected; this was not a primary outcome and should be interpreted cautiously as mortality was relatively rare and may have resulted from unidentified confounding factors. Although we did not observe significant differences in SSI or medical complication rates, the results of the statistical testing were near the predetermined alpha value in both cases despite the study not being powered to identify differences in these specific outcomes.

Previous investigations of nutrition supplementation have focused on the geriatric hip fracture population. Malnutrition is common in the geriatric population (18% to 45%)[27] and is associated with an increased risk of poor functional recovery and complications[28,29]. Nutrition support with protein supplementation in this population has been shown to improve postoperative mobility, decrease postoperative complications, and reduce in-hospital and 1-year mortality[30-36]. Despite evidence supporting the benefits of nutrition supplementation, there is a lack of consistency in defining the diagnosis of malnutrition, the optimum composition of nutrition supplementation, and the impact on clinically relevant outcomes.

There is a growing body of literature demonstrating the benefits of CEAA supplementation in elective orthopaedic surgery. A recent RCT found that CEAA supplementation in patients undergoing elective total knee replacement reduced loss of quadriceps and hamstring muscle area at 6 weeks postoperatively[17]. Additionally, CEAA supplementation increased the density of quadriceps progenitor cells[37]. The ability of CEAA supplementation to preserve muscle mass and function has been reproduced in other studies of total knee arthroplasty[19] and hip fracture[35,36]. Other investigations of CEAA supplementation have focused on maintaining lean muscle mass in chronic disease and the management of wounds[38,39]. These compelling results encouraged us to investigate CEAA supplementation in adults with operative fracture fixation.

We found that CEAA supplementation impacted relevant clinical outcomes, including overall complications, postoperative skeletal muscle loss, nonunion, and mortality. Differences in medical complications and SSIs approached significance. Future work should focus on high-risk populations to clarify the effect of CEAA supplementation on these specific outcomes. The benefit we observed in maintaining muscle mass was transient. The protective effect of CEAA supplementation at 6 weeks was no longer seen at 12 weeks after injury. These results suggest that supplementation prevents only early muscle loss, and >2 weeks of supplementation may be required for longer benefit.

Limitations

This was a single-center trial in a rural American Midwest level-I trauma center with a wide spectrum of injuries. Our trauma population is relatively homogeneous and predominantly

Caucasian. Future investigations should include centers in multiple regions to increase the diversity of the study population and the generalizability of the results. We enrolled all adults undergoing operative fixation of acute fractures, including patients with a wide age range with both low- and high-energy trauma (isolated distal radius and/or hand fractures were not enrolled). These broad inclusion criteria were selected to increase generalizability. To account for this variability, we stratified our randomization. Future investigations should focus on high-risk populations in whom targeted nutrition supplementation may show a greater effect.

Subjects were not blinded to randomization in this study. Only subjects in the intervention group received an oral supplement; subjects in the control group did not receive a placebo. Future studies of CEAA supplementation should consider providing alanine as a placebo[17]. We observed a significant difference in baseline BMI between the groups, although there were no significant differences in the percentages of overweight, obese, and underweight subjects or body composition. Future nutrition investigations should consider stratifying by body composition.

Compliance is challenging in investigations of nutrition interventions despite a patient's willingness to comply with nutrition supplementation when presented with the benefits[40]. We used education at the time of enrollment and reminders by daily automated text messages to optimize compliance. Future investigations should work to optimize education and automated reminders to improve compliance.

Additionally, the rate of completion of the body composition measurement at 12 weeks was low (57% for the control group and 59% for the intervention group). The completion of body composition measurement at 6 weeks was higher (77% for the control group versus 81% for the intervention group), and the loss of FFM in the control group reached significance at this time point. This should be noted when considering these results. A significant difference was observed in overall complication rates as well as mortality and nonunion rates between the groups. Mortality was not a primary outcome in this study, and the incidence was too low, with a wide confidence interval and a marginal p value, which made the determination that there was a significant difference between the groups not valid. Mortality occurred in 9 subjects at a median of 15 days (interquartile range [IQR], 10 to 183 days) after enrollment, and some subjects died outside the time frame when we would expect to see an influence from CEAA supplementation. The median age of these subjects was 72 years (IQR, 56 to 89 years), with 6 of 9 stratified to the fragility fracture group. This study reports the potential impact of the intervention on these outcomes but does not describe the specific mechanism of how CEAA supplementation impacts the outcomes.

The incidence of nonunion was high (8.6%). Criteria for nonunion were failure to achieve radiographic union at a minimum follow-up of 6 months or the need for operative intervention for nonunion prior to the 6-month follow-up. This high nonunion rate may reflect the severity of the injuries, comorbidities, and surgical treatment. Grip strength improved over time but a significant difference was not shown between the groups. Physical performance measures chosen for specific injury types should be used in future investigations.

Conclusions

We found that CEAA supplementation had a significant benefit in an adult population undergoing operative fixation of acute fractures. Supplementation resulted in reduced overall complications and in skeletal muscle loss at 6 weeks after injury. Our results suggest that this inexpensive, low-risk intervention has considerable potential to improve outcomes after fracture fixation. This study will serve as the foundation for multicenter RCTs that are designed to assess the impact of CEAA nutrition supplementation in reducing complications and loss of functional muscle mass in high-risk populations. ■

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