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Effect of branched chain amino acid enrichment of total parenteral nutrition on nitrogen sparing and clinical outcome of sepsis and trauma: a prospective randomized double blind trial

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Administration of extra branched chain amino acids (BCAA) has been associated with a nitrogen sparing effect in septic and traumatized patients. Whether nitrogen sparing is associated with decreased morbidity and mortality rates is unknown. We therefore undertook a prospective, randomized, double blind trial investigating the effects of BCAA enrichment of a total parenteral nutrition (TPN) regimen on nitrogen balance, 3-methylhistidine excretion, morbidity as evidenced by disturbances in organ function, severity of sepsis and mortality. One hundred and one patients entered the study; 52 received a standard TPN solution and 49 a BCAA-enriched solution. Both groups received 30 kcal kg^{-1} body-weight, 15 per cent fat calories and 0·17 g nitrogen kg^{-1} body-weight. In the BCAA-enriched group, patients received 0·56 g BCAA kg^{-1} body-weight (50·2 per cent BCAA). Standard group patients received 0·18 g BCAA kg^{-1} body-weight (15·6 per cent BCAA). Nitrogen balances and 3-methylhistidine excretion were not significantly different between groups. Although morbidity scores tended to decrease during the study, no difference was observed between groups. Mortality (early or late), sepsis or stress-related, did not differ significantly between groups. We were not able to confirm the reported beneficial effects of BCAA-enriched TPN solutions for use in septic and traumatized patients.

Keywords: Branched chain amino acids, total parenteral nutrition, sepsis, trauma

In an effort to reduce catabolism and loss of body mass during sepsis or after severe injury, a parenteral nutrition regimen has been advocated in which the amino acid component consists of 45–50 per cent of branched chain amino acids (BCAA), compared with 15–20 per cent in conventional regimens.

Transamination of BCAA occurs chiefly at extrahepatic sites because transaminase activity in the liver is low[1]. The resulting branched chain keto acids (BCKA) are released into the circulation only in very limited quantities. They are irreversibly degraded by BCKA dehydrogenase, a rate-limiting enzyme in the breakdown of BCAA chiefly located in liver, muscle, adipose tissue, kidney and brain. As a result, BCAA are degraded largely in muscle and adipose tissue. Because BCKA dehydrogenase activity in muscle is regulated by the energy charge and the energy charge has been reported to be low[2–4], BCAA degradation may be enhanced during severe sepsis and trauma. BCAA enrichment may also improve the precursor amino acid pattern for hepatic protein synthesis which is characterized during severe sepsis by decreased plasma BCAA levels and increased aromatic amino acid levels (AAA)[5]. *In vitro* studies demonstrate that BCAA, especially leucine, promote protein synthesis and BCKA inhibit protein degradation[6]. These reasons may provide a rationale for BCAA enrichment of total parenteral nutrition (TPN) solutions.

Several clinical studies have examined the effects of BCAA enrichment of TPN solutions in sepsis and trauma[7–13] but most were small without accurate patient descriptions. No studies have established a possible beneficial effect on morbidity and mortality rates in addition to the study for nitrogen sparing or effects on plasma proteins. We have therefore undertaken a prospective, randomized, double blind trial in septic and traumatized patients to confirm the nitrogen sparing effects of the BCAA enrichment and to establish the effects of such enrichment on outcome, measured through morbidity and mortality rates. The study was reviewed and approved by the Human Studies Committee of the University Hospital, Maastricht.

Patients and methods

Patients

Septic and metabolically stressed patients were eligible to enter the study. Sepsis was defined as the presence of a combination of the following criteria: spiking temperature, hyperventilation, tachycardia, elevated white blood cell count, decreased blood pressure, diminished urine output and positive blood cultures. A clinically manifest septic focus and signs of septic shock were considered obligatory. Patients were considered metabolically stressed if they had: suffered multiple trauma, undergone operation for ruptured abdominal aortic aneurysm, severe non-septic pancreatitis, major gastrointestinal surgery or non-septic enterocolitis. Because it may be argued that under conditions without significant metabolic stress the presumed need for additional BCAA is absent and that in extremely ill patients no reasonably stable study conditions may be reached, patients suffering stress ranging from 20 to 50 per cent according to the criteria of Kinney *et al.*[14] were considered moderately stressed and analysed as a separate group.

Study design

Patients were stratified for the presence of sepsis or stress and for age (under or over 65 years). They were randomized through the hospital

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Table 1 *Amino acid content per litre of the study solutions*

	BCAA (g)	Standard (g)
Essential amino acids		
L-leucine	6·10	1·80
L-phenylalanine	1·25	1·80
L-methionine	1·20	1·70
L-lysine hydrochloride	1·50	2·10
L-isoleucine	5·90	1·40
L-valine	5·30	1·30
L-histidine	0·90	1·30
L-threonine	0·80	1·20
L-tryptophan	0·40	0·50
Non-essential amino acids		
L-alanine	4·20	6·10
L-glycine	4·20	6·10
L-arginine	2·10	3·10
L-proline	0·80	1·20
L-tyrosine	0·08	0·12
Total amino acids	34·70	29·70
Total nitrogen	5·01	4·98

BCAA, branched chain amino acids

Table 2 *Stress factors in traumatized patients*

	Percentage
Elective surgery, postoperative	5
Soft tissue trauma	10–15
Peritonitis	10–20
Fracture, long bone	20–25
Multisystem trauma	20–50
Mild infection	0–20
Moderate infection	20–40
Severe infection	40–60

pharmacy to receive a BCAA-enriched or a standard solution. Both solutions were delivered to the ward labelled 'BCAA study solution' to ensure a double blind study design.

If renal failure progressed to a level necessitating protein restriction or dialysis, and if fluid restriction prohibited the use of the study solution, patients were withdrawn. The study was limited to 7 days. Each day, starting on day 0, 24 h urine was collected for nitrogen and 3-methylhistidine determination. Bistrian catabolic indices[15], Elebute and Stoner sepsis scores[16] and nitrogen balances were calculated daily. Mortality was recorded as early sepsis-related if death in overwhelming sepsis occurred within the 7-day study period, late sepsis-related if death occurred under septic conditions after the study period, or not sepsis-related.

Solutions

Both amino acid–dextrose mixtures contained equal amounts of amino acid nitrogen l^{-1}, derived in the standard solution from a balanced synthetic amino acid solution (Synthamin 14®, Baxter Healthcare Corporation, Deerfield, Illinois, USA), and derived in the BCAA-enriched solution from a more concentrated balanced synthetic amino acid solution (Synthamin 17®) and a 4 per cent BCAA solution containing equimolar amounts of valine, isoleucine and leucine. The standard solution contained 15·6 per cent BCAA and the BCAA solution contained 50·2 per cent BCAA of total nitrogen (*Table 1*). Each mixture contained 20 per cent glucose. Both nutritional support solutions were composed according to the standards of today's practice, providing sufficient minerals, trace elements, vitamins and free fatty acids. Caloric intake was calculated to meet basal energy expenditure (Harris–Benedict) augmented with 10 per cent specific dynamic action of food and a stress percentage as suggested by Kinney, ranging from 10 to 60 per cent[14] (*Table 2*), resulting in sufficient caloric intake to cover actual total energy expenditure[17]. Patients were not allowed any additional food. Blood and blood products were administered as required.

Morbidity parameters

Organ function was assessed using the scoring method as proposed by Stevens[18]. The scoring method was adapted to fit local treatment policies, e.g. the use of ventilatory support would not always reflect the presence of respiratory insufficiency and scoring respiratory function was therefore adapted as summarized in *Table 3*. Similar adjustments were made for scoring renal (creatinine clearance with each patient as his or her own control instead of plasma creatinine levels) and circulatory function (grouping of the Stevens scores to compensate for the use of dopamine to improve tissue perfusion, rather than to treat hypotension). In each organ system high scores represent organ function impairment, while low scores indicate a more normal function. Because of our interest in organ function *per se* rather than an overall morbidity score, our adaptation of the scoring system would not need further validation than performed by Stevens.

Organ function scores were assessed on days 0, 4 and 7.

Laboratory determinations

Urinary 3-methylhistidine content was analysed after hydrolysis on an LKB automated amino acid analyser (LKB Biochrom Ltd., Cambridge, UK). Urinary nitrogen excretion was analysed using the Kjeldahl method. Nitrogen balances were estimated by subtracting urinary nitrogen plus a correction factor for faecal and insensible losses from total nitrogen intake. Furthermore, a correction for accumulation or loss of urea was carried out, assuming the distribution volume for urea to be 60 per cent of body-weight. Nitrogen in plasma and albumin was considered protein available for metabolic processing and was therefore accounted for in nitrogen balances.

Statistical considerations

It was estimated that a 30 per cent reduction of a −20 g cumulative nitrogen balance in 1 week with a standard deviation of 10 g would be significant. To demonstrate such a result with $\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}1$, we calculated that approximately 45 patients per study arm were required[19].

Results were evaluated using one way analyses of variance. Organ function scoring was evaluated using χ^2 tests.

Table 3 *Organ function scores*

Respiratory function
0. No respiratory support.
1. Spontaneous breathing with oxygen enrichment up to 30 per cent.
2. Spontaneous breathing with oxygen enrichment over 30 per cent.
3. Mechanical ventilation with less than 35 per cent oxygen.
4. Mechanical ventilation with more than 35 per cent oxygen or positive end-expiratory respiration.

If the ratio of arterial partial oxygen pressure (kPa) over oxygen fraction of inspired air (per cent) was under 40 the support was considered insufficient and one point was added to the original score.

Circulatory function
0. No impaired circulatory function (stable blood pressure).
2. Moderate circulatory insufficiency (stable blood pressure with more than normal fluid support and/or dopamine/dobutamine administration).
4. Severe circulatory insufficiency (labile blood pressure, despite increasing fluid needs and/or increasing doses of dopamine/dobutamine).

Myocardial infarction was excluded from the scoring.

Renal function
Renal function was assessed using creatinine clearance and expressed as a percentage of predisease levels, that were derived from a nomogram that considers serum creatinine concentrations and weight, age and sex[24].
0. ⩾100 per cent.
1. 75–100 per cent.
2. 30–75 per cent.
3. <30 per cent
4. Dialysis needed.

Hyperbilirubinaemia
Primary hepatobiliary disease was excluded. Five categories were defined as follows:
0. 0–17 μmol l^{-1}
1. 17–34 μmol l^{-1}
2. 34–68 μmol l^{-1}
3. 68–136 μmol l^{-1}
4. >136 μmol l^{-1}

Table 4 *Study population*

	Total group ($n=101$)		Moderately stressed group ($n=73$)	
	BCAA ($n=49$) $\bar{x}$(s.e.m.)	Standard ($n=52$) $\bar{x}$(s.e.m.)	BCAA ($n=35$) $\bar{x}$(s.e.m.)	Standard ($n=38$) $\bar{x}$(s.e.m.)
Sex: female	21	25	14	19
male	28	27	21	19
Age (years)	56(2)	58(2)	59(2)	57(3)
BEE (kcal day^{-1})	1440(40)	1390(30)	1400(41)	1390(31)
Stress: 0–20%	5	4	–	–
20–50%	35	38	–	–
>50%	9	10	–	–
Elebute and Stoner sepsis score (day 0)	11·1(0·8)	10·9(0·9)	11·0(0·9)	10·0(0·8)
Bistrian score (day 0)	10·3(1·3)	9·8(1·0)	8·1(0·9)	9·8(0·9)

BCAA, branched chain amino acids; BEE, basal energy expenditure

Table 5 *Diagnoses*

	Total group ($n=101$)		Moderately stressed group ($n=73$)	
	BCAA	Standard	BCAA	Standard
Perforated viscera, anastomotic leakage, etc.	9	15	7	11
Pancreatitis	8	11	7	8
Enterocolitis (radiation, Crohn's disease, ulcerative colitis, ischaemia)	7	6	4	5
Intra-abdominal abscess	9	6	7	5
Multiple injuries	4	2	2	1
Ruptured aortic aneurysm	3	2	2	1
Other	9	10	6	7
Total	49	52	35	38

BCAA, branched chain amino acids

Results

Patients

One hundred and one patients were included in the study, with 61 of them requiring treatment in the intensive care unit. Forty-nine patients received the BCAA solution, and 52 the standard solution. Both groups were comparable for age and sex, calculated basal energy expenditure values on day 0, day 0 sepsis scores and catabolic indices (*Table 4*). Primary diagnoses were reasonably equally distributed (*Table 5*). Diagnoses listed under 'other' included tetanus, sepsis of unknown origin, respiratory insufficiency with pneumonia and prolonged paralytic ileus. The subgroup of moderately stressed patients (stress factor ranging between 20 and 50 per cent) was the largest in size and more homogeneous, because the more severely stressed group contained extremely ill patients, some of whom underwent one or more operations. Study groups within this moderately stressed population were also comparable with respect to all of the above criteria (*Tables 4* and *5*).

Solutions

Patients in both study groups received a similar nutritional support regimen, except for the BCAA content: 0·09 g BCAA nitrogen (0·56 g BCAA protein) *versus* 0·03 g BCAA nitrogen (0·18 g BCAA protein) kg^{-1} body-weight (*Table 6*).

Catabolic indices

Mean catabolic index scores in both groups decreased during the study without statistically significant differences between groups (*Figure 1*).

Sepsis scores

Mean sepsis scores remained in the same range in the branched chain group and tended to decrease in the standard group, but without a statistically significant difference between groups (*Figure 2*).

Morbidity scores

Results of organ function scoring are depicted in *Figure 3*. With the frequency of each score being expressed as a percentage of the total number of patients per study group, improvement of organ function was observed within each organ system, without difference between study groups. For statistical considerations changes of each organ function score were pooled per study group as increasing, stable or decreasing in the 0–4-day and 4–7-day periods and subsequently evaluated by a χ^2 test. No significant difference within any organ system was observed between groups.

Biochemical data

Figure 4 displays mean daily nitrogen balances corrected for urea accumulation per study group. The number of available

Table 6 *Total parenteral nutrition*

	Total group ($n=101$)		Moderately stressed group ($n=73$)	
	BCAA $\bar{x}$(s.d.)	Standard $\bar{x}$(s.d.)	BCAA $\bar{x}$(s.d.)	Standard $\bar{x}$(s.d.)
NPE (kcal g^{-1} N)	205(33)	214(28)	202(24)	214(28)
NPE (kcal kg^{-1})	33(11)	34(9)	34(12)	34(9)
Nitrogen (g kg^{-1})	0·17(0·05)	0·17(0·04)	0·17(0·04)	0·17(0·04)
BCAA (g N kg^{-1})	0·09	0·03	0·09	0·03
Fat (%)	13(9)	16(8)	13(9)	16(8)
BEE (%)	148(35)	157(4)	152(36)	155(3)

BCAA, branched chain amino acids; NPE, non-protein energy; N, nitrogen; BEE, basal energy expenditure

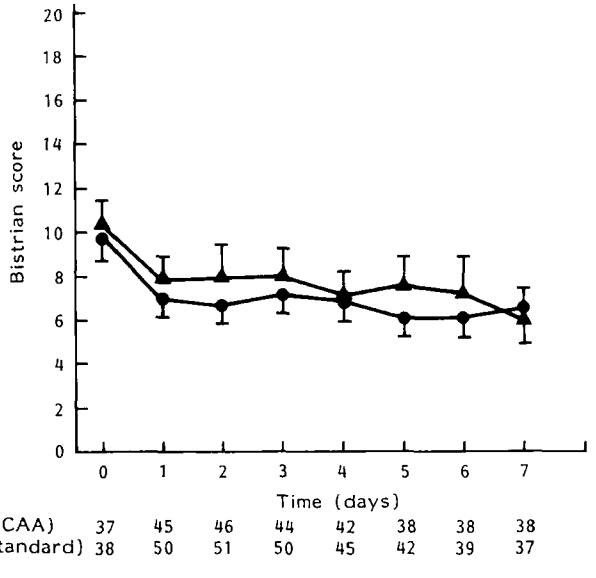

Figure 1 *Catabolic indices (mean(s.e.m.)) calculated according to Bistrian's method: ▲—▲, branched chain amino acids (BCAA); ●—●, control*

analyses is displayed, as in all other figures. Plasma protein-derived nitrogen intake was not different between study groups. Although in the total study population days 4 and 7 show a significantly ($P < 0{\cdot}05$, analysis of variance) less negative nitrogen balance in the BCAA group as compared with the standard group, cumulative 7-day nitrogen balances are not significantly different between groups (*Table 7*). Nitrogen balances in the moderately stressed patient group were consistently, albeit not significantly, less negative in the BCAA group (*Figure 5*). Cumulative nitrogen balances were less negative in the BCAA group but significance was not reached ($P = 0{\cdot}06$) (*Table 7*). Mean daily urinary 3-methylhistidine

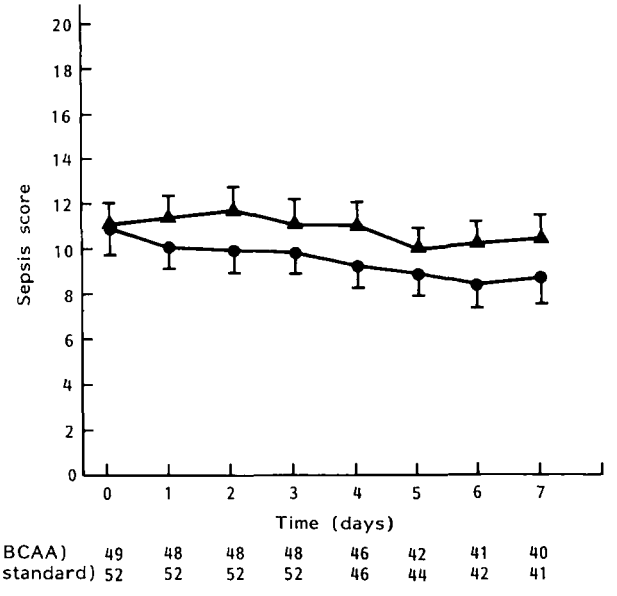

Figure 2 *Sepsis scores (mean(s.e.m.)) calculated as described by Elebute and Stoner: ▲—▲, branched chain amino acids (BCAA); ●—●, control*

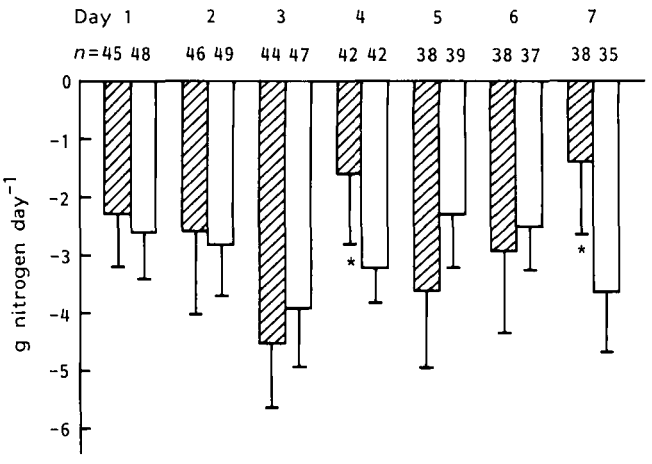

Figure 4 *Mean daily nitrogen balances in branched chain amino acids (BCAA) (▨) and control (□) groups. Nitrogen balances are corrected for urea accumulation or loss, excessive stool, stoma or fistula output, and administration of plasma proteins.* * $P < 0{\cdot}05$

Table 7 *Cumulative 7-day nitrogen balance*

	Total group		Moderately stressed group	
	n	$\bar{x}$(s.e.m.) (g)	*n*	$\bar{x}$(s.e.m.) (g)
BCAA	37	−19·1(7·3)	28	−8·5(5·2)*
Standard	34	−20·8(4·5)	26	−23·0(5·5)

BCAA, branched chain amino acids; * $P = 0{\cdot}06$ *versus* standard solution, moderately stressed group

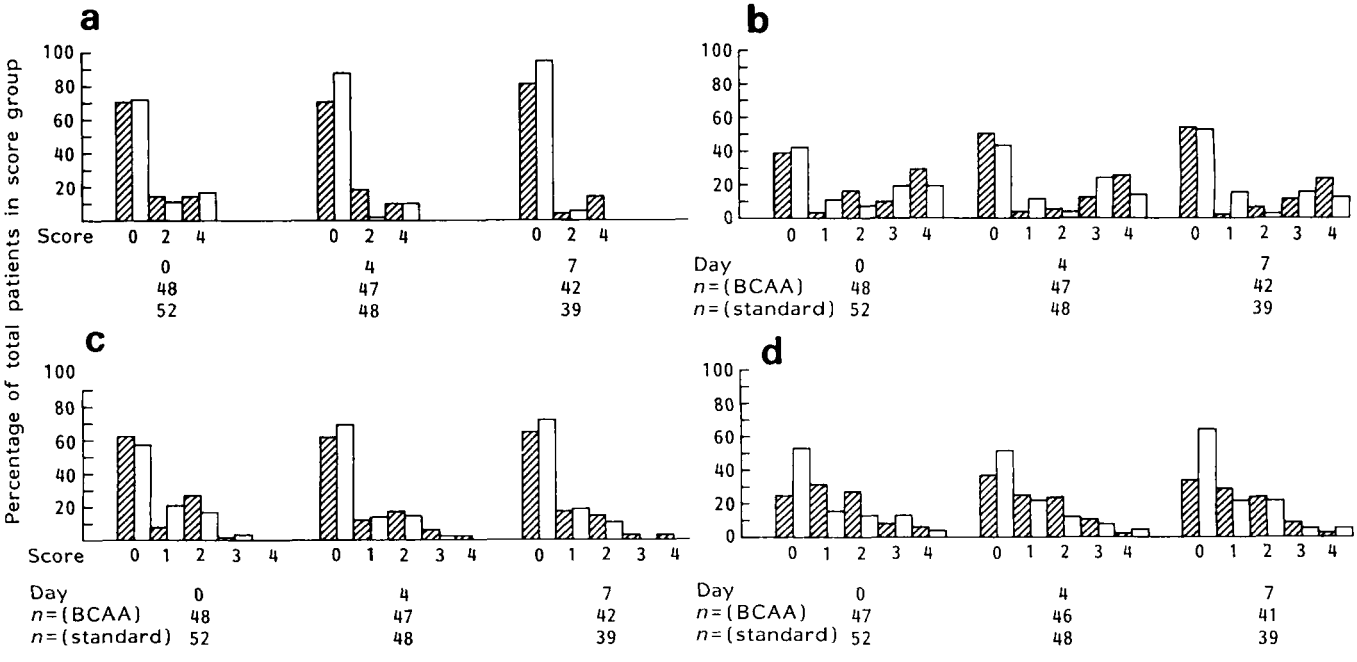

Figure 3 *Results of organ function scoring in branched chain amino acids (BCAA) (▨) and standard (□) groups:* **a** *circulatory function: the number of low scores increases across days. Although high scores seem to diminish more in the standard group, a convincing advantage for the standard solution is not seen;* **b** *respiratory function: the number of 0 scores increases across days in both groups while higher scores decrease. No obvious difference between study groups is noticeable;* **c** *renal function: frequency of scores distribution does not seem to change across days in either solution:* **d** *liver function: distribution of scores for hyperbilirubinaemia was not equal in the study groups on day 0, with patients in the standard group showing score 0 significantly more frequently. A tendency towards improved organ function is noticeable without obvious advantage for either solution*

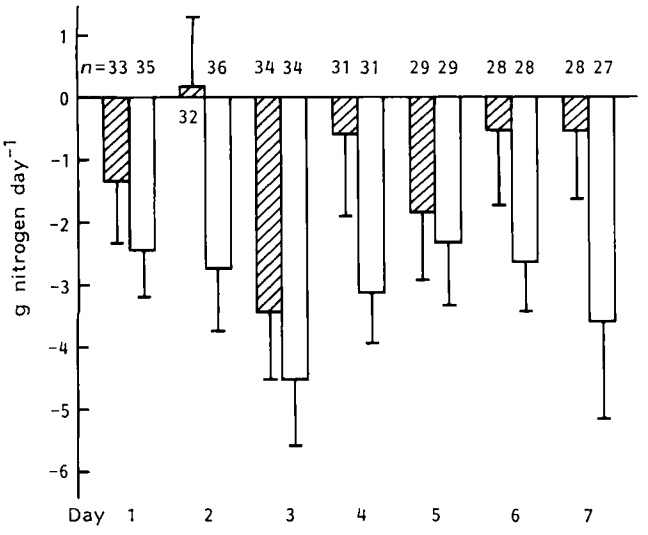

Figure 5 *Mean daily nitrogen balances in branched chain amino acids (BCAA) (▨) and control (□) groups in the moderately stressed patient population*

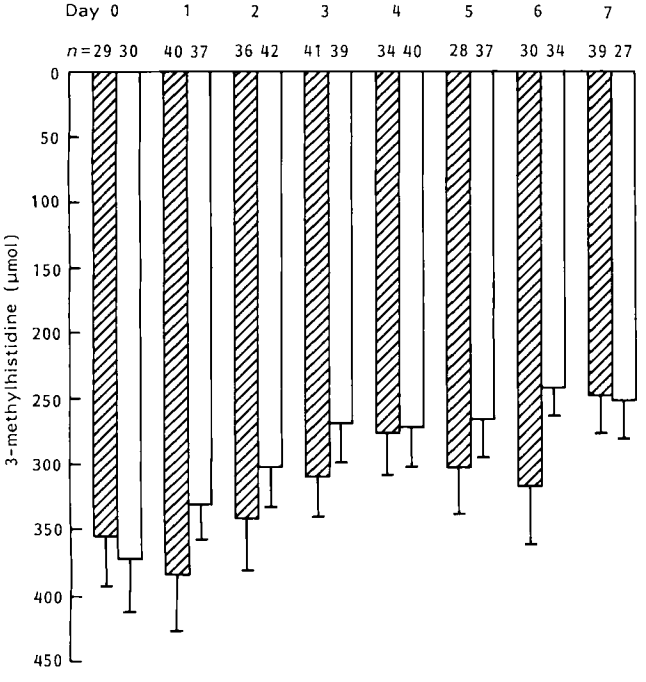

Figure 6 *Mean daily urinary 3-methylhistidine excretion in branched chain amino acids (BCAA) (▨) and control (□) groups*

excretion diminished significantly during the study period, but no significant differences between groups were noted (*Figure 6*).

Mortality

Overall mortality rate was not different between groups (*Table 8*), nor was late or early sepsis-related mortality rate or non-sepsis-related mortality rate. Mortality rate was not different between groups in the moderately stressed study population either.

Discussion

The observation that nitrogen losses during sepsis and trauma can be diminished but not reversed with nutritional regimens of conventional composition, stimulated the development of special amino acid compositions. Specifically enrichment with BCAA may correct decreased plasma BCAA levels reported during sepsis and trauma, and consequently improve the precursor pattern for protein synthesis[20,21]. BCAA may further furnish fuel and promote protein synthesis[6].

Only two prospective randomized trials have been published investigating the effect of BCAA enrichment of TPN solutions in sufficiently large study populations[11,12]. In one trial patients with pancreatitis and organ failure were excluded[11]. An improvement of nitrogen balance was found only on the fourth day of the 7-day study period. In the other trial, patients suffering a uniform trauma were studied in a multicentre study design[12]. Patients were dropped from the study once the development of organ failure became apparent. As in the previous study a modest though not statistically significant improvement of nitrogen balance was observed in one of the trial subgroups. In these studies the clinical state of the patients was not detailed before, during or after the study period, nor was this done in either of the other smaller studies[7–10,13].

We tried in this trial to demonstrate an improved nitrogen balance and clinical benefit in an unselected study population suffering from severe illness or sepsis. The assessment of clinical performance of each individual organ system must be the most accurate and independently obtainable measure to study clinical efficacy. To detect differences larger patient groups were necessary which were comparable in every respect. We therefore stratified for age, sepsis and stress and ensured that patients received an amount of calories equalling their estimated actual energy expenditure. All patients received fat, and no patient received more than 35 carbohydrate calories kg^{-1} $24\ h^{-1}$. Patients received on average 1·1 g AA kg^{-1} $24\ h^{-1}$ and 0·56 g BCAA kg^{-1} $24\ h^{-1}$ in the enriched group which is in the range where an eventual benefit on nitrogen balance should have manifested itself[22]. If patients were considered more severely stressed they received proportionally more calories and nitrogen, including BCAA. Both groups (controls and BCAA-enriched) proved to be comparable at day 0 with regard to disease, age, sex, sepsis scores, Bistrian score and organ function score. Only hyperbilirubinaemia was encountered more often in the BCAA-enriched group.

We are aware that the methods used to estimate nitrogen balances include crude approximations but few studies have made an attempt to correct for total body urea accumulation or the metabolic fate of exogenous protein[23].

The study failed to confirm a clear benefit of BCAA enrichment on nitrogen balance in the total patient population. When the subgroup that was considered moderately stressed on day 0 was selected ($n=73$), cumulative nitrogen balance improved in the BCAA-enriched group although this improvement failed to reach significance ($P=0·06$). In this group nitrogen balance was better on any single day (days 1–7) although on no occasion was significance reached.

BCAA enrichment may improve nitrogen balance in moderately stressed patients but differences in clinical outcome (mortality, organ function, catabolic indices and sepsis score) were not observed. The results of this trial may be explained by the fact that clinical outcome in septic or traumatized patients is much more dependent on the success of primary treatment (drainage of abscesses, debridement of necrotic tissue,

Table 8 *Mortality*

	Total group		Moderately stressed group	
	BCAA ($n=49$)	Standard ($n=52$)	BCAA ($n=35$)	Standard ($n=38$)
Early sepsis-related	4 (8·2)	2 (3·8)	2 (5·7)	2 (5·3)
Late sepsis-related	8 (16·3)	10 (19·2)	7 (20·0)	3 (7·9)
Not sepsis-related	5 (10·2)	4 (7·7)	5 (14·3)	3 (7·9)
Total	17 (34·7)	16 (30·7)	14 (40·0)	8 (21·1)

Values in parentheses are percentages. BCAA, branched chain amino acids

stabilization of fractures, etc.) than on supportive care. The acute effects of nutritional support, let alone the effects of a modification of nutritional support under such conditions, must be limited. We conclude that BCAA-enriched TPN solutions, commonly marketed as 'trauma solutions', possibly achieve a modest improvement in nitrogen balance in moderately stressed patients but do not induce a clear clinical benefit.

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