ORIGINAL ARTICLE

Branched-Chain Amino Acids May Improve Recovery From a Vegetative or Minimally Conscious State in Patients With Traumatic Brain Injury: A Pilot Study

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ABSTRACT. Aquilani R, Boselli M, Boschi F, Viglio S, Iadarola P, Dossena M, Pastoris O, Verri M. Branched-chain amino acids may improve recovery from a vegetative or minimally conscious state in patients with traumatic brain injury: a pilot study. Arch Phys Med Rehabil 2008;89:1642-7.

Objective: To investigate whether supplementation with branched-chain amino acids (BCAAs) may improve recovery of patients with a posttraumatic vegetative or minimally conscious state.

Design: Patients were randomly assigned to 15 days of intravenous BCAA supplementation (n=22; 19.6g/d) or an isonitrogenous placebo (n=19).

Setting: Tertiary care rehabilitation setting.

Participants: Patients (N=41; 29 men, 12 women; mean age, 49.5±21y) with a posttraumatic vegetative or minimally conscious state, 47±24 days after the index traumatic event.

Intervention: Supplementation with BCAAs.

Main Outcome Measure: Disability Rating Scale (DRS) as $\log_{10}$DRS.

Results: Fifteen days after admission to the rehabilitation department, the $\log_{10}$DRS score improved significantly only in patients who had received BCAAs ($\log_{10}$DRS score, 1.365±0.08 to 1.294±0.05; $P<.001$), while the $\log_{10}$DRS score in the placebo recipients remained virtually unchanged ($\log_{10}$DRS score, 1.373±0.03 to 1.37±0.03; P not significant). The difference in improvement of $\log_{10}$DRS score between the 2 groups was highly significant ($P<.000$). Moreover, 68.2% (n=15) of treated patients achieved a $\log_{10}$DRS point score of .477 or higher (3 as geometric mean) that allowed them to exit the vegetative or minimally conscious state.

Conclusions: Supplemented BCAAs may improve the recovery from a vegetative or minimally conscious state in patients with posttraumatic vegetative or minimally conscious state.

Key Words: Amino acids, branched-chain; Minimally conscious state; Rehabilitation.

TRAUMATIC BRAIN INJURY may reduce a patient to a vegetative or minimally conscious state[1] that, in Italy, accounts for 23% of the TBI population admitted to rehabilitation wards.[2]

It is reasonable to believe that some alterations in brain metabolism, which have been documented in acute TBI,[3,4] may persist during the rehabilitation phase of patients with TBI and contribute to maintaining brain dysfunction. Indeed, alterations in both brain glucose and oxygen metabolism occur acutely after TBI.

As regards glucose metabolism, abnormalities in both the anaerobic and aerobic metabolism of this substrate have been documented. Anaerobic glucose metabolism was found to be either increased or decreased. In fact, perihemorrhagic lesion hyperglycolysis (ie, an increased glucose metabolism relative to the rate of oxygen utilization) was found in 56% of patients with TBI within 1 week after cerebral injury.[4,5] In contrast, a selective reduction in the cerebral metabolic rate of glucose was found in the cortical gray matter of patients with moderate TBI.[6]

As regards brain oxygen utilization during acute TBI, subcortical white matter is characterized by a unique metabolic change consisting of depression of the $CMRO_2$ without a concomitant reduction in cerebral metabolic rate of glucose.[7] Actually, impairments in mitochondrial function after TBI could be responsible for the reduced $CMRO_2$.[3,8] A reduced $CMRO_2$ very probably means reduced aerobic glucose utilization.

We formulated 2 main hypotheses for testing in the present investigation. First, the common and final result deriving from alterations in brain cerebral metabolic rate of glucose and $CMRO_2$ is a reduction of the brain's capacity to produce high-energy compounds (creatine phosphate, ATP). In patients with TBI, an energy deficit could lead or contribute to derangements in brain ion homeostasis, protein synthesis, axonal transport, neurotransmitter release, and metabolism.[9] Thus, a possible continuation of the metabolic alterations mentioned above in rehabilitation patients with TBI may contribute to persistence of damage to cerebral regions, mainly the subcortical white matter, which represents the fundamental structural abnormality characterizing the vegetative or minimally conscious state.[10]

The second hypothesis was that the supplementation of nutritional substrates such as BCAAs (leucine, valine, isoleu-

List of Abbreviations

ATP	adenosine triphosphate
BCAA	branched-chain amino acid
$CMRO_2$	cerebral metabolic rate of oxygen
DRS	Disability Rating Scale
GABA	γ-aminobutyric acid
TBI	traumatic brain injury

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cine) could enhance the recovery of posttraumatic vegetative or minimally conscious state patients. The rationale for using BCAAs relies on a number of considerations. First, amino acids can act on both oxidative metabolism for energy production[11,12] and protein metabolism.[13,14] As far as oxidative metabolism is concerned, BCAAs might reactivate the brain aerobic pathway. In normative conditions, there is a very large neuronal consumption of amino acids in the Krebs cycle for the synthesis of neurotransmitters and the production of high-energy compounds (ATP, creatine phosphate). The amino acid utilization can be particularly important in the case of altered glucose utilization.[15]

Because these amino acids are essential, they can be used for improving protein synthesis[13,14] and, in particular, brain repairing. Moreover, BCAAs, particularly leucine, increase peripheral insulin production[16] and, therefore, brain insulin availability.[17] This hormone influences cognitive activity.[18] Last, BCAA supplementation has been documented to enhance cognitive recovery of rehabilitation patients not in a vegetative state.[19]

Therefore, in the present investigation, we sought to determine whether intravenous infusion of BCAAs may improve the recovery from a vegetative or minimally conscious state in rehabilitation patients with TBI.

METHODS

Forty-one patients (29 men, 12 women; mean age, 49.5±21y) with a posttraumatic vegetative or minimally conscious state, consecutively admitted to our rehabilitation department 47±24 days (range, 19–90d) after the index traumatic event, were investigated in this randomized, placebo-controlled study. The patients were enrolled immediately after their admission (first week).

The diagnosis of a vegetative or minimally conscious state was made using the DRS,[20,21] a neuropsychologic test that ranks various degrees of disability by a score from 0 (normative) to 30 (death). The classification of the vegetative or minimally conscious state (score of 22–29) comprises degrees of vegetative state (score of 22–24) and degrees of severe vegetative state (score of 25–29).

Patients were admitted to our department from intensive care units. All had diffuse brain damage caused by road traffic crashes (78%) or accidental falls (22%). Their neurologic scores within the first 24 hours averaged 5.5±1.3 on the Glasgow Coma Scale (data from referral information). On admission to our department, 60.9% of patients were receiving antibiotic therapy for urinary tract and/or respiratory infections. All were on artificial nutrition with polymeric formulas administered by nasogastric tube (n=27) or percutaneous endoscopic gastrostomy (n=14).

After completion of routine laboratory and biochemical investigations, patients were weighed[a] and then randomly assigned to the BCAA treatment group (BCAA posttraumatic vegetative or minimally conscious state, n=22) or placebo group (placebo posttraumatic vegetative/minimally conscious state, n=19). The physician who evaluated the DRS was different from the physician who prescribed the BCAAs and was blinded to the experimental design. Moreover, the physician who evaluated the results of the study was blinded to the allocation of treated patients and to the placebo group. However, in order to obtain their consent, caregivers were not fully blinded to the investigation because they were informed about the possibility of treating patients with BCAAs or placebo, but they had no contact with the physicians who evaluated the disability tests.

Supplementation of BCAAs consisted of 15 days of intravenous infusion (through an antecubital vein) of a 500-mL solution once a day, over a 5-hour period. The solution (4% mixture of amino acids [Isoram][b]) provided 19.6g of BCAAs (nitrogen, 3.13g; leucine, 7.5g; isoleucine, 3.01g; valine, 9.1g) and 1.6g of arginine (nitrogen, .26g). This formula provided 85kcal of extra calories. The placebo group received once a day a mixture of 22g proteins (nitrogen, 3.52g), 40mL sugar-free fruit juice, and 160mL water. This mixture contained 90kcal of energy and a nitrogen amount similar to that of BCAAs. It was administered through nasogastric tube or percutaneous endoscopic gastrostomy.

At the end of day 15, the BCAA infusion was stopped, and the day after, the DRS was re-evaluated in both groups. The DRS was also evaluated again at the patients' discharge from our institute (137.5±36.5d after admission).

The study was approved by the ethical, techno-scientific committee of our institute. Written, informed consent was obtained from the patients' caregivers. In particular, caregivers were carefully informed that BCAAs should not be considered as drugs, but rather as nutritional substrates with the potential of acting on brain structures.

Statistical Analysis

Baseline characteristics in the 2 groups were compared by Student unpaired *t* test or chi-square, when appropriate. To obtain a more normative distribution of values, DRS scores were transformed to $\log_{10}$DRS. We also considered the geometric mean of $\log_{10}$DRS when useful. Repeated-measure analysis of variance was applied to test differences over time in $\log_{10}$DRS between the treatment and placebo groups.

Data are given as means ± SDs. *P* values less than .05 were considered statistically significant.

RESULTS

Baseline characteristics of the 2 groups were not different (tables 1, 2). In particular, the 2 groups of patients admitted to rehabilitation at the same time postinjury showed similar DRS ($\log_{10}$DRS).

The study showed that patients with a posttraumatic vegetative or minimally conscious state on BCAA treatment, but not those on placebo, had an improvement in vegetative/minimally conscious state on the 15th day after starting the treatment. Indeed, the $\log_{10}$DRS in the BCAA posttraumatic vegetative or minimally conscious state group significantly improved ($\log_{10}$DRS score, 1.365±0.08 to 1.294±0.05; $P<.001$; as geometric mean, 23.17–19.68), whereas in the placebo posttraumatic vegetative or minimally conscious state group, it remained virtually unchanged ($\log_{10}$DRS score, 1.373±0.03 to 1.37±0.03; *P* not significant; as geometric mean, 23.6–23.4). The difference in the improvement of the $\log_{10}$DRS between the 2 groups was highly significant ($P<.000$). Moreover, within the placebo group, the maximum reduction in the $\log_{10}$DRS score was .08 points (as geometric mean of DRS, 1.2), which was achieved by 21% of the patients.

Within the treatment group, the data showed that 68.2% (n=15) of patients achieved a $\log_{10}$DRS point score of .477 or higher (3 as geometric mean) that allowed them to exit the vegetative or minimally conscious state. Seven patients (31.8%) failed to exit the vegetative or minimally conscious state, although their DRS score improved by $\log_{10}$DRS .08 (1.2 as geometric mean). In summary, 26 patients (19 placebo, 7 BCAA-treated; 63.4% of the entire population) failed to exit their vegetative or minimally conscious state.

Furthermore, from day 15 (the time of BCAA withdrawal) to discharge from our rehabilitation institute (137.5±36.5d after admission), brain function in patients with a posttraumatic

Table 1: Baseline Demographic, Anthropometric, Biochemical, Clinical, and Functional Characteristics of the Study Patients on Admission to the Rehabilitation Center

Characteristics	All Patients (N=41)	Placebo T-VMCS (n=19)	BCAA T-VMCS (n=22)	*P*
Demographic data				
Sex (male/female)	29/12	13/6	18/4	
Age (y)	51.5±20.8	48.4±24.6	55±17.5	NS
Anthropometric data				
Body weight (kg)	56.2±11.7	52.3±13.3	60±15.2	NS
Body mass index (kg/m^2; NV, 19–24kg/m^2)	19.5±3.2	18.8±2.8	20.6±3.5	NS
Days from injury		45±21 (19–79)	49.6±26 (21–90)	NS
Blood biochemical parameters				
Erythrocyte sedimentation rate (1st h; mm; NV, <15mm)	70±32	69.5±27	71±38	NS
Glucose (mg/dL; NV, 70–110mg/dL)	138±71	129±56	148±85	NS
Urea (mg/dL; NV, 19–40mg/dL)	33±17	31±15	35±19	NS
Hemoglobin (g/dL; NV, 12–16g/dL)	11.6±1.9	11.9±1.1	11.3±2.7	NS
Serum albumin (g/dL; NV, 3.5–5 g/dL)	3.2±0.5	3.3±0.6	3.1±0.4	NS
Main findings on CT scan				
Enlargement of ventricles	28	15	13	NS
Hydrocephalus drainage	5	2	3	NS
Malacic area	4	1	3	NS
Frontoparietal and diffuse hemorrhagic lesions	7	3	4	NS
Functional characteristics				
DRS				
$\log_{10}$DRS	1.369±0.028	1.373±0.03	1.365±0.08	NS
Geometric mean	23.4±1.5	23.6±1.9	23.3±1.2	NS

NOTE. Values are n, mean ± SD, or mean ± SD (range).
Abbreviations: CT, computed tomography; NS, nonsignificant; NV, normative value; T-VMCS, posttraumatic vegetative or minimally conscious state.

vegetative or minimally conscious state previously treated with BCAAs improved, such that the $\log_{10}$DRS score decreased by another .568±.66 ($P<.03$). Here again, no change in $\log_{10}$DRS score was noted in patients on placebo ($\log_{10}$DRS, 1.37±0.03 to 1.37±0.03; *P* not significant).

DISCUSSION

This study shows that short-term parenteral supplementation of BCAAs in rehabilitation patients in a posttraumatic vegetative or minimally conscious state may induce an effective recovery from the vegetative or minimally conscious state in more than two-thirds of treated patients.

Likely these results are attributable to the treatment with BCAAs given that 2 very strong prognostic predictors,[22,23] baseline DRS score and time between injury and baseline assessment, were similar for supplemented and placebo patients. Given the metabolic fate of amino acids within the brain, the results of this study would support our hypothesis that some metabolic alterations after acute TBI may persist in patients with a posttraumatic vegetative or minimally conscious state at the time of their admission to a rehabilitation unit.

Table 2: Nutritional Intake and Nitrogen Balance of the Study Patients on Admission to the Rehabilitation Center

Measures	All Patients (N=41)	Placebo T-VMCS (n=19)	BCAA T-VMCS (n=22)	*P*
Daily nutritional intake				
Energy (kcal/kg)	30.8±7.1	31±6.5	30.6±7.8	NS
Carbohydrates (g/kg)	3.7±0.8	3.5±0.7	3.9±1.05	NS
Proteins (g/kg)	1.2±0.28	1.1±0.25	1.3±0.31	NS
Lipids (g/kg)	1.16±0.27	1.09±0.25	1.24±0.29	NS
Nitrogen balance (g/24h)	1.37±4	1.1±2.5	1.6±5.5	NS

NOTE. Values are mean ± SD.
Abbreviations: NS, nonsignificant; T-VMCS, posttraumatic vegetative or minimally conscious state.

Potential Mechanisms of the Effect of BCAAs on the Recovery From a Vegetative State

At present, we can only speculate about the mechanisms underlying the positive effect of BCAAs in a posttraumatic vegetative or minimally conscious state. The supplementary BCAA very probably reached the brain because it is well documented that amino acids in the brain change in response to food ingestion.[24]

BCAAs may influence the recovery of cognition in a posttraumatic vegetative or minimally conscious state mainly by inducing increases in both brain energy production (ATP, creatine phosphate)[15,25,26] and insulin levels, with the latter effect secondary to peripheral overproduction of the hormone.[16] Increased brain energy availability (ATP) can restore ionic homeostasis,[27] reducing in this way membrane depolarization[28] and neuronal injury, particularly in ischemic regions.[29,30]

Restoration of ionic homeostasis may reduce the risk of cell swelling, a condition that can aggravate cerebral blood flow in ischemic territories. Indeed, moderate or severe ischemic brain damage has been found in 43% of patients who have remained in a vegetative state for more than 1 month after acute brain damage.[10]

Moreover, increased brain energy may preserve neuron viability by limiting or stopping cellular damage derived from free radical overproduction, which is widely implicated in the pathology of TBI[31-34] and leads to lipid peroxidation[35] and mitochondrial dysfunction.[8]

Another important potential effect from BCAA-induced increased ATP availability may be the improvement in chemical neurotransmission in a posttraumatic vegetative or minimally conscious state because the synthesis, axonal transport, and secretion of neurotransmitters all are ATP-consuming processes.[36] For instance, among the various neurotransmitters, acetylcholine and GABA, important neurotransmitters for learning and memory, may be formed directly in the BCAA-activated Krebs cycle.[6] An important action of GABA-ergic transmission is regulation of the functions of the prefrontal cortex, a region of the brain that is critically involved in the control of cognition and emotion,[37] because the neurotransmitter controls the timing of neuronal activity during cognitive operations.[38]

BCAA-induced increased ATP availability may also improve axonal damage because mismatches in energy supply are a major factor involved in progressive axonal injury.[39]

In synthesis, an increase in brain energy availability is of paramount importance for the anatomical and functional recovery of damaged brain structures because brain repair, sprouting, and circuitry remodelling[40] are all processes that require ATP-driven de novo protein synthesis.

The other mechanism by which BCAAs may favor recovery from a posttraumatic vegetative or minimally conscious state is insulin-mediated. Leucine can increase peripheral production and secretion of insulin,[16] which, after crossing the blood-brain barrier,[17] reaches many brain structures, particularly the choroid plexus, olfactory bulb, pyriform cortex, amygdaloid nucleus, hippocampus, hypothalamic nucleus, and cerebellar cortex.[41,42] Brain insulin, through its receptors, normally governs higher cognitive processes such as learning, memory, and attention.[43] In a posttraumatic vegetative or minimally conscious state, insulin may contribute to cognitive recovery through a multitude of mechanisms including electric conduction and brain metabolism.[18]

Electric conduction may be augmented by insulin modulation of both membrane potential[44-46] and synaptic function. At the synaptic level, the transmission may be improved at both presynaptic and postsynaptic sites.[42,47-52]

Insulin may contribute to cognitive recovery in a posttraumatic vegetative or minimally conscious state by directly acting on metabolic activity of cerebral structures important for cognition. Indeed, the hormone affects neuronal activity in hippocampal, pyramidal neurons, increasing hippocampal long-term potentiation as well as glucose utilization in the entorhinal and hippocampal neurons.[53-55] Increased glucose utilization in the hippocampus, an important system for many types of learning and memory,[6] suggests that energy utilization in this structure may be sensitive to insulin[56] and that normative cognitive functioning may be insulin-dependent[57] because glucose uptake can affect cholinergic activity during behavioral tasks.[58,59]

In summary, BCAAs may improve brain function in patients with a posttraumatic vegetative or minimally conscious state by limiting alterations in the energy metabolism of the brain, in electrical and chemical neurotransmission, and in metabolic activity of important structures involved in cognitive functions. Whatever the mechanisms involved, these amino acids, as previously found on sequelae of less TBI,[19] seem to be useful for both maintenance or survival of still viable brain structures and improvement of functional connections between cerebral areas. The continued BCAA-driven recovery of brain function, after withdrawal of the supplemental BCAA, probably indicates that the repair of brain is adequately directed and self-maintaining. These results seem to confirm the data by Whyte et al,[22] who reported that the rate of DRS change during the first 2 weeks of observation was predictive of DRS score 4 months after injury. The repair did not seem to occur over time in patients who did not receive BCAA supplementation.

Study Limitations

Because of its limitations, we would like to consider this investigation a pilot study that needs a larger clinical trial before considering BCAAs as a treatment for patients with a vegetative or minimally conscious state. If the results of the study will be confirmed by a larger clinical trial, BCAA supplementation may be advised as a means to reduce the risk of irreversible cerebral atrophy in patients with chronic TBI (6–18mo after the index event).[60]

A major limitation is the small sample size. We cannot exclude that, if a larger number of patients had been investigated, some improvement in DRS score might also have been observed in subjects not BCAA-supplemented.

Another limitation of the investigation is that we assessed a short-term outcome, and this did not allow us to understand whether the treatment hastens recovery or actually elevates it. Nevertheless, the ultimate intent of our study was to seek whether simple nutritional substrates, even though intravenously administered, could induce some improvements of disability in a specific population of patients for whom a valid pharmacologic treatment has not yet been identified.

Another major limitation of the study is that the patients' cerebral metabolism was not investigated by positron emission tomography and/or functional nuclear magnetic resonance. These imaging methods would have enabled detection of remaining global/local metabolic damage in rehabilitation prior to the infusions of BCAAs, and possible recovery of metabolic function in brain structures after the BCAA protocol. This issue deserves further investigation in a future, well planned study.

Another limitation of the study is that we did not analyze the results in relation to sex. Differences in cognition recovery between men and women cannot be excluded.

Cases of postanoxic vegetative state were not considered, which could be important given that the functional prognosis of this condition is far less favorable than that of a posttraumatic vegetative or minimally conscious state.[61]

Finally, another important aspect that should be addressed in the future is the time beyond 3 months after the index event at which a nutritional intervention could still be useful for recovery from a vegetative state.

CONCLUSIONS

The study shows that supplementation of BCAAs may aid recovery from a posttraumatic vegetative or minimally conscious state, thus reducing the risk of the vegetative state persisting over time.

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