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Meta-analyses

Branched-chain amino acid supplementation in adults with cirrhosis and porto-systemic encephalopathy: Systematic review☆

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SUMMARY

Background & aims: Branched-chain amino acid supplementation in porto-systemic encephalopathy remains controversial. Here, we examined the systematic review evidence for their effect on encephalopathy, hepatic decompensation, survival, infection, hospital stay and quality of life, and review data on adherence, side-effects and cost/economic evaluation.

Methods: Four electronic databases were searched from 1980 to June 2011, with an update search in two databases in July 2013. Hand-searching was performed of references lists from included trials and six conference proceedings from 2005 to 2010. We included randomised controlled trials of branched chain amino acids versus other nutritional supplements in adults with cirrhosis and porto-systemic encephalopathy. Data extraction and quality assessment were performed by two independent assessors. Meta-analysis was performed if data were sufficient.

Results: The search identified nine randomised controlled trials (436 patients in total) of branched-chain amino acid therapy for ≥2 weeks' duration. The overall quality of trials was poor. At meta-analysis, a significant improvement in the grade of encephalopathy was demonstrated in favour of branched-chain amino acids compared to other nutritional supplements (Risk Ratio 2.6, 95% Confidence Interval 1.7–3.9, $p < 0.001$, 2 trials, n 122) but no significant difference was found for either resolution or worsening of encephalopathy, gastrointestinal bleeding, survival or infection. Limited data suggested no difference in health-related quality of life, ascites or admission to hospital. Studies did not include cost data or economic evaluations. Side-effects appeared mild and gastrointestinal in nature.

Conclusions: Branched-chain amino acids might improve porto-systemic encephalopathy but more robust trials are needed to determine their role.

1. Introduction

The main causes of chronic liver disease worldwide are alcohol and chronic viral hepatitis,[1] with an increasing contribution from obesity-associated fatty liver disease.[2] Hospital admissions and mortality rates in the UK continue to rise by 8–10% per annum, with marked increases in younger populations.[3] Health-care costs for decompensated liver disease in the UK are around £3400 per hospital admission.[4] Prevalence rates of overt and minimal porto-systemic encephalopathy (PSE) in decompensated liver disease are as high as 30–45%[5] and 60–80%,[6] respectively, although accurate assessment is difficult as study populations are heterogenous and definitions of PSE are inconsistent. Survival rates following overt encephalopathy are estimated at 42% and 23% at one and three years, respectively.[7]

Protein-calorie malnutrition is found in 20% and 60–100% of patients with compensated and decompensated disease, respectively.[8,9]

Non-standard abbreviations: PSE, Porto-Systemic Encephalopathy; BCAAs, Branched Chain Amino Acids; AAAs, Aromatic Amino Acids; ESPEN, European Society for Parenteral and Enteral Nutrition; RR, Risk Ratio; CI, Confidence Interval; RCTs, Randomised Controlled Trials; CCRCT, Cochrane Register of Controlled Trials; AASLD, American Association for the Study of Liver Disease; AGA, American Gastroenterological Association; ASPEN, American Society of Parenteral and Enteral Nutrition; BAPEN, British Association for Parenteral and Enteral Nutrition; EASL, European Association for the Study of Liver Disease; MD, Mean Difference; EEG, Electro-encephalogram; LOLA, L-Ornithine L-Aspartate.

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Branched-chain amino acids (BCAAs) (i.e. isoleucine, leucine and valine) are three essential human amino acids which, since degraded peripherally and metabolised regardless of liver function, are important energy substrates in this setting. The imbalance between circulating BCAAs and aromatic amino acids (AAAs) in chronic liver disease is well recognised.[10] Supplementation with BCAAs is thought to promote ammonia detoxification in skeletal muscle, prevent false neurotransmitter generation, and reduce muscle catabolism.[11,12] A role has also been postulated in improving the disease-associated anorexia.[13] Studies have demonstrated areas of reduced cerebral perfusion in cirrhosis[14,15] and significant improvement following administration of BCAAs.[15] Some trials have suggested a role in improving nutritional parameters and quality of life,[16,17] preventing disease progression,[17,18] and reducing hospitalisation.[16] A previous systematic review demonstrated a significant improvement in encephalopathy over a five to fourteen day follow-up period in favour of BCAAs ($p < 0.001$), although the trials were heterogeneous and noted to have problems with methodology.[19] A Cochrane review, last assessed as up-to-date in 2002, demonstrated a significant improvement in encephalopathy in favour of BCAAs compared to other therapies (Risk Ratio RR 1.31, 95% Confidence Interval CI 1.04–1.66, $p = 0.022$) although this was not maintained at sensitivity analysis when only trials with adequate methodology were selected. Meta-analysis revealed no evidence of overall survival benefit (RR 1.05, 95% CI 0.97–1.13, $p = 0.21$).[20] Current ESPEN (European Society for Parenteral and Enteral Nutrition) guidelines recommend (i) BCAA supplementation in patients when encephalopathy develops despite enteral feeding[21] and (ii) parenteral supplementation with a "liver-adapted complete amino acid solution" containing an increased amount of BCAAs in patients with more severe encephalopathy (i.e. grade III–IV).[22]

We examined the systematic review evidence for BCAA supplementation versus other nutritional supplements in adult patients with cirrhosis and PSE, focusing primarily on their effect on encephalopathy.

2. Materials and methods

The review received no external funding or sponsorship.

A pre-specified protocol was devised by the authors to maximise use of available data which was predicted to be limited and of poor quality. All trials of participants ≥18 years of age with a diagnosis of cirrhosis and previous or current PSE were assessed. Trials with PSE secondary to fulminant liver failure and recent surgical or radiological porto-systemic shunting were excluded. Once the search was complete, only randomised controlled trials (RCTs) which satisfied the inclusion criteria above were included.

For our definition of cirrhosis we used a histological, clinical/laboratory and/or radiological diagnosis, and included any aetiology. In mixed trials the majority of participants had to have cirrhosis.

We accepted any definition of PSE in the trials, but all patients had to be affected. Branched-chain amino acid therapy had to be intended for at least two weeks' duration, either by oral, enteral or parenteral administration. The comparator was any other nutritional supplement.

Our main outcomes were clinically relevant relating to morbidity and mortality:

- PSE – resolution (including time to recovery), improvement, re-emergence/worsening, change in cognitive function (however defined)
- Survival
- Hepatic decompensation: (i.e. ascites – development and failure of resolution, gastrointestinal bleeding)

We also sought data on infection, adherence to therapy, adverse events, length of hospital stay, cost or economic data, and quality of life outcomes.

Trials were identified through a literature search of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CCRCT) (Table 1) and BIOSIS from 1980 to June 2011, adding patient population terms to intervention terms, which retrieved 1447 records for screening. An updated search was performed for both Medline and Embase, up to and including July 2013, which retrieved a further 166 records to screen. There were no language restrictions. A manual search of abstracts from AASLD (American Association for the Study of Liver Disease), AGA (American Gastroenterological Association), ASPEN (American Society of Parenteral and Enteral Nutrition), BAPEN (British Association for Parenteral and Enteral Nutrition), EASL (European Association for the Study of Liver Disease) and ESPEN from 2005 to 2010 was performed. Reference lists from included trials were hand-searched in addition to trials registers (Clinical Trials, WHO trials registry and Current Controlled Trials). Branched-chain amino acid manufacturers were contacted by e-mail. For included trials less than five years old, where data were not clear from the original report, authors were contacted directly for clarification of results.

The search was performed by one reviewer. 200 references from MEDLINE were searched independently by two reviewers and inter-rater agreement was very good (Cohen's kappa coefficient 0.92). All data were independently extracted by two of the three independent assessors. Disagreements were resolved by discussion.

Methodological quality of trials was assessed using the Cochrane Risk of Bias Tool.[23] Intention-to-treat data analysis was performed where possible. Review Manager 5, from the Cochrane Collaboration, was used for the analysis. Binary outcomes were expressed as a RR with their associated 95% CI. Continuous outcomes measured on the same scale were expressed as mean differences (MD) with their associated 95% CI. A conservative random effects model was used due to the anticipated variability between trials. Heterogeneity was assessed using I^2 and subsequently explored if I^2 >50%.[23] Data unsuitable for meta-analysis were summarised in narrative format.

Where at least three trials were available, sensitivity analysis was performed to assess the effect of the following on PSE outcomes: (i) sequence generation, (ii) allocation concealment, (iii) blinding and (iv) availability of abstract versus complete report.

Table 1
Search strategy for Medline, EMBASE and CCRCT.

Patient population	Intervention
exp Hepatic Encephalopathy/ or exp Liver Cirrhosis/ or (hepatic adj encephalopathy?).tw. or (porto?systemic adj encephalopathy?).tw. or cirrhosis.tw.	exp Amino Acids Branched-Chain/ or BCAA?tw. or valine.tw. or leucine.tw. or iso?leucine.tw. or aminoiso?butyric acid?tw. or branched-chain amino acid?tw. or generaid.tw. or generaid plus.tw. or hepatamine.tw.

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