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Review Article

Branched-Chain Amino Acids and Postoperative Quality of Life in Hepatectomied Patients

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Abstract

Patients with chronic liver disease often reach a state of protein-energy malnutrition, which may influence patient outcomes following surgery and subsequent quality-of-life (QOL). Recent assessments of QOL integrate a biochemical health model with a social science model that is based on the patient's subjective perception of functioning and wellbeing across a range of physical, mental and social aspects of life. Since most liver neoplasms occur in patients with chronic liver disease, hepatic resection could potentially reduce QOL in these patients by further compromising liver function.

Advances in surgical technology and perioperative management have led to hepatic surgical procedures, including liver resection and radiofrequency ablation, being the mainstay of curative treatment for not only hepatocellular carcinoma (HCC), but also metastatic liver tumors. However, hepatic surgery is still associated with postoperative morbidities due to the inevitable deterioration of liver function following a reduction in functioning liver mass. Based on the clinical assessment, dieticians should therefore educate patients and carers about sodium and fluid restriction, and appropriate food choices. In this context, branched-chain amino acid (BCAA) nutritional supplementation improves postoperative QOL over the long term after hepatic resection by restoring and maintaining nutritional status and whole-body kinetics. BCAA may also inhibit carcinogenesis in heavier patients with cirrhosis and play a key role in liver regeneration. Individualized intervention is thus recommended based on patient's nutritional status.

Keywords: Branched-chain amino acids, quality of life, surgery, liver, liver cirrhosis, chronic liver diseases.

Introduction

Traditional medical outcomes, which are important endpoints for clinicians, need to be integrated with patients' survival rate after adequate management for various diseases. However, it would be of note that it has been considered patients' opinions on health status, reflecting how they really feel, and how much their disease affects their way of living to be more important, because the treatment consensus over almost all disorders has been established to some extent.

Liver is the central organ for nutrient production and metabolism [1]. Patients with chronic liver disease often become severely malnourished, which can seriously damage their capacity for liver regeneration [2] and increase the risk of hepatocellular carcinoma (HCC). In particular, a state of protein energy malnutrition (PEM) [3,4] affects patient outcomes following management as shown by quality of life (QOL) estimations [5-7]. Recent assessments of QOL integrate a biochemical health model with a social science model that is based on the patient's subjective perception of their physical, mental and social functioning and well being [8].

Recent advances in surgical technology and perioperative management have made hepatic surgical procedures, such as liver resection and radiofrequency ablation, the mainstay of curative treatment for both primary and metastatic liver tumors [9-12]. However, since most liver neoplasms occur in patients with chronic liver disease, hepatic resection could potentially reduce QOL in these patients by further compromising liver function. Hence, it is important to consider QOL among the more traditional treatment outcomes of operative mortality and long-term survival rates. Some recent studies implicated an important role for nutritional support using branched-chain amino acids (BCAA) in the surgical management and postoperative QOL of patients undergoing hepatic resection for liver neoplasms [13,14]. BCAAs are a group of essential amino acids comprising valine, leucine, and isoleucine. Recently, it has been reported that BCAAs have been shown to affect gene expression, protein metabolism, apoptosis and regeneration of hepatocytes, and insulin resistance and BCAA supplementation improves not only nutritional status, but also prognosis and quality of life in patients with liver cirrhosis [15-19]. In this article, we revisit the basic concept of BCAA administration and review how BCAA supplementation affects long-term self-estimated QOL and health in these patients.

Quality of Life in Patients with Chronic Liver Diseases

Evaluation of QOL

A QOL assessment concept was developed in the mid-1990s by integrating biochemical and social science models of health assessment [20,21]. In patients with hepatobiliary disease, this could include the patients' feelings about their potential QOL following

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suggested surgical, medical or palliative interventions. Indeed, such perceptions could be more relevant to acceptance of treatment than predicted length of life, because patients are frequently more concerned about quality and disability than about longevity [22]. This is especially true with chronic diseases, where survival is not at risk for a long time, and the goal of interventions is to maintain symptom-free and community-living patients.

This conceptualization is based on the World Health Organization definition of health as 'a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity'. Opportunity, education, spiritual attitudes, social security, working satisfaction, social relationships and goods availability are elements of QOL that are independent of medicine. From the 1990s on, there has been a growing emphasis on assessing QOL in patients with cancer, and this assessment may be as important as the evaluation of long-term survival. The most widely used generic instruments to assess QOL for patients with cancer are the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ) – the EORTC QLQ-C30 - and the Functional Assessment of Cancer Therapy - General (FACT-G) [23,24]. More recently, a study about health-related QOL of chronic liver disease patients with and without hepatocellular carcinoma (HCC) reported that impaired QOL is not associated with the presence of cancer itself, but is dependent on the level of liver function, indicating the importance of preserving liver function [25]. In recent years, the Italian versions of the Medical Outcome Study Short Form–36 (SF-36) and the Nottingham Health Profile (NHP) questionnaires, two generic instruments assessing patients' well-being, have been validated and used to compare the impacts of chronic diseases in a general population and to determine health policies and resource allocation (Table 1) [26-28].

Poor health-related quality of life of patients with cirrhosis

Globally, cirrhosis/chronic liver disease of varying aetiologies, is responsible for major mortality and morbidity [29]. Liver cirrhosis is one of the commonest causes of hospitalisation, and a number of studies over the past decade have convincingly demonstrated that health-related QOL is significantly impaired in patients with cirrhosis compared to the general population [28,30-32]. Hyperammonaemia is a condition characterised by raised serum ammonia levels. Mild and transient hyperammonaemia can often be asymptomatic and is usually triggered by protein loads and catabolic states. In symptomatic cases, the clinical features may be variable and episodic. Many cases present with acute mental status changes characterised by confusion, personality changes, irritability, ataxia, visual disturbance, lethargy and somnolence, and may also report nausea, vomiting and hyperventilation. More severe cases can lead to encephalopathy characterised by stupor and coma [33]. The pathogenesis of hyperammonaemic encephalopathy remains unclear. Changes in mental status have been attributed to high levels of ammonia and the presence of other organic acids, with raised brain ammonia concentrations sometimes present even when the serum ammonia level is normal. Hyperammonaemia can also cause encephalopathy via the inhibition of glutamate uptake by astrocytes. The resulting astroglial processes surround the brain microvessels of the blood brain barrier and swell in the presence of advanced hepatic encephalopathy. However, despite these significant astroglial changes, the barrier function remains intact, suggesting that cytotoxic rather than vasogenic mechanisms predominate in the pathogenesis of hepatic encephalopathy [34]. As with delirium, elderly patients may present with several concomitant predisposing factors for developing hyperammonaemia and encephalopathy.

QOL in Patients Undergoing Liver Resection

Branched-Chain Amino Acids (BCAA) improved both PEM and QOL

Protein-energy malnutrition (PEM) is a common finding in chronic liver disease and affects about 50% of patients with liver cirrhosis [6]. Since malnutrition adversely affects clinical outcomes, guidelines of the European, American and Japanese Societies for Parenteral and Enteral Nutrition (ESPEN) advocated nutritional support for cirrhotic patients [35,36], recommending the following consensus nutrition standard: 35-40 kcal/kg/day in energy and 1.2-1.5 kcal/kg/day in proteins [35]. However, such standards are not always pertinent and should be altered depending on conditions such as race, intensity of daily activity, PEM, glucose intolerance, protein intolerance and obesity. Flexible handling of the ESPEN guideline is therefore necessary, and calorimetry might be the best way to assess the nutritional status of patients with liver cirrhosis. Possible

Table 1: SF-36 and NHP score

SF-36	Physical functioning (PF)	PF scale measures the extent to which physical activities are limited for reasons of health.
	Role physical (RP)	RP scale measures how physical health impacts work and daily activities.
	Bodily pain (BP)	BP scale measures limitations due to pain.
	General health (GH)	GH scale measures how a subject sees personal health and the potential for decline.
	Vitality (VT)	VT scale measures how tired/full of energy subject feels.
	Social functioning (SF)	SF scale measures how much physical or emotional problems interfere with normal social activities.
	Role emotional (RE)	RE scale measures the impact of emotional problems on work and daily activities.
	Mental health (MH)	MH scale measures the general state of feeling (e.g. depressed, happy, peaceful).
	Physical Component (Summary) Score (PCS): PCS summarizes the physical health component of SF-36: PF, RP, BP and GH.	
	Mental Component (Summary) Score (MCS): MCS summarizes the mental health component of SF-36: VT, SF, RE and MH.	
NHP	The Nottingham Health Profile is a multi-dimensional, 45-item questionnaire designed to measure subjective health status. Part 1 comprises six dimensions of health: physical mobility, pain, sleep, energy, social isolation and emotional reactions. Part 2 consists of seven aspects of daily life (i.e. paid employment, jobs around the house, social life, personal relationships, sex life, hobbies and interests, and holidays).	

SF-36, Short Form–36 questionnaires; NHP, the Nottingham Health Profile questionnaires treatments for PEM include BCAA supplementation and a late-evening snack (LES). BCAA effectively corrects protein malnutrition by increasing plasma albumin, and prolongs event-free survival in patients with advanced cirrhosis [8]. Since energy deficiency is related to worse survival rates, it is also important to address the early-morning energy starvation that is typical in cirrhosis and equivalent to a 3-day starvation period in healthy individuals. To this end, the ESPEN and ASPEN guidelines recommend a LES or divided meals to reduce the starvation period between dinner and breakfast. BCAA as a LES is an ideal supplement in patients with cirrhosis because it provides more energy and protein than the ordinary enteral formula or BCAA granules, significantly reduces fatigue, and improves energy metabolism, protein levels and nitrogen balance [37]. Furthermore, a Hong Kong study also showed that long-term dietary supplementation with BCAA twice daily significantly reduced complications such as ascites and peripheral edema, and improved survival in patients undergoing chemoembolization for HCC [38].

QOL after curative hepatectomy

Postoperative QOL

Since most liver neoplasms occur in patients with chronic liver disease, hepatic resection could potentially reduce QOL in these patients by further compromising liver function. QOL assessment has proven to be a valuable parameter for such patients and surgeons and may be helpful in determining the optimal treatment. As an outcome parameter, QOL is considered as important as disease-free and overall survival. In various benign and malignant liver diseases, surgical management is a common procedure with intent-to-cure treatment, as a result of recent advances in surgical technology and peri-operative management. Although major and minor liver resections are both safe procedures, little is known about postoperative QOL in these patients [39,40]. Recent studies indicated that QOL returns to baseline within 3-6 months after liver resection for malignancies in most cases [41-44].

BCAA-enriched nutritional support in surgical patients (Table 2)

In a prospective randomized clinical trial, the San-in Group of Liver Surgery [13] studied the effects of long-term oral administration of BCAA after curative resection of HCC. Between 2 and 3 weeks after surgery, 75 patients were randomized to receive oral BCAAs (Aminoleban EN) at 100 g per day for 1 year, and another 75 patients were assigned to a control group. Flapping tremor was less common, body weight was increased and performance status was better in the BCAA-treated group than in controls throughout the 1-year period. BCAA treatment also significantly increased red blood cell and serum albumin levels in patients with Child grade B and C disease. Substantially similar effects were observed in patients treated with major hepatic resection. The San-in Group summarized that long-term oral nutritional support with BCAAs after resection of HCC is beneficial in improving clinical features and laboratory data without increasing the rate of tumor recurrence, particularly in patients with advanced cirrhosis or after major hepatic resection.

In a prospective study, Meng et al [14]. Evaluated the effect of BCAA treatment in patients undergoing liver resection for HCC. A prospective randomized controlled clinical trial was conducted involving 44 patients. The BCAA group (21 patients) received Aminoleban EN in addition to a normal diet for 12 weeks and the control group (23 patients) received an isonitrogenous and isocaloric diet only. The BCAA group had a shorter hospital stay, and showed a significantly higher haemoglobin level, higher sodium level, higher albumin level and lower bilirubin level during the postoperative course. The authors concluded that Aminoleban EN is safe to administer and does not have significant adverse effects, while contributing to a shorter hospital stay and quicker improvement of liver function in the early postoperative period.

In a retrospective study involving 43 elective hepatectomized patients, Togo et al. [45] evaluated the usefulness of granular BCAA after hepatectomy for liver cancer complicated with liver cirrhosis. In the BCAA group (21 patients), postoperative ascites and edema tended to improve earlier than in the control group (22 patients), and nutritional status based on serum albumin and total protein levels recovered immediately after liver surgery in the BCAA group. Furthermore, the BCAA group showed a more rapid improvement in hyaluronic acid and type IV collagen 7S levels compared to controls.

In a large retrospective study involving 112 elective hepatectomized patients, Okabayashi et al. [46] evaluated the effects of BCAA-enriched nutrient support for patients undergoing liver resection for HCC. These patients were divided into two groups: 40 patients received perioperative supplementation of a BCAA-enriched nutrient mixture (BCAA group) and 72 patients had no supplement (control group). Laboratory data, postoperative complications, duration of hospitalisation and survival were compared between groups. The overall incidence of postoperative complications was lower in the BCAA group (17.5%) than in the control group (44.4%) ($P = 0.01$). Among the postoperative complications, surgical site infection and bile leakage was observed in 5% of patients in the BCAA group and in 15.3% and 12.5% of patients in the control group, respectively. Ascites appeared after the surgery in 7.5% of patients in the BCAA group and in 16.7% of control patients, while the duration of hospitalisation was significantly shorter in the BCAA group than in the control group ($P < 0.05$). The authors suggested that their perioperative BCAA supplementation protocol is clinically beneficial in reducing the morbidity associated with postoperative complications and in shortening the duration of hospitalisation of patients with chronic liver disease who undergo liver resection for HCC.

In a prospective study involving 24 elective hepatectomized patients, including some with a non-hepatitis liver, Ishikawa et al [47]. studied the benefits of perioperative oral nutrition (ON) with BCAA. The patients (20 with malignant liver tumors and 4 with benign liver tumors) were randomly assigned to receive perioperative ON with BCAA (11 patients, BCAA group) or a usual diet (13 patients, control group). The BCAA group received a BCAA supplement twice daily plus a usual diet for 14 days before operation and on days 1 to 7 after operation. Two of the 11 patients in the BCAA group developed postoperative complications, as compared with 3 of the 13 patients in the control group (18.2% vs. 23.1%, $P = 0.7686$). Among patients with non-hepatitis, serum erythropoietin (EPO) levels on POD 3, 5 and 7 were significantly higher in the BCAA group than in the control group ($P = 0.0174$, $P = 0.0141$ and $P = 0.0328$, respectively). The short-term ON support with BCAA was thus associated with higher serum EPO

Table 2: Effect of BCAA-enriched nutritional support in surgical patients with liver cancer.

Author [ref]	Study Design	Administration	Benefits of BCAA
San-in group [13]	Prospective 150 patients	Aminoleban EN	• Improved clinical features (body weight) • Improved laboratory data (red blood cell, serum albumin • level and Fischer molar ratios)
Meng [14]	Prospective 44 patients	Aminoleban EN	• Shorter postoperative hospital stay • Higher haemoglobin level, higher sodium level, higher albumin level and lower bilirubin during the postoperative course
Togo [45]	Retrospective 43 patients	LIVACT	• Rapid improvement in protein metabolism and inhibition of progression to liver cirrhosis
Okabayashi [43]	Retrospective 36 patients	Aminoleban EN	• Shortened hospitalisation after surgery • Restoration of peripheral lymphocyte count and serum total cholesterol level at 3 months after the operation
Okabayashi [46]	Retrospective 112 patients	Aminoleban EN	• Reduced morbidity associated with postoperative complications • Shortened duration of hospitalisation
Ishikawa [47]	Prospective 24 patients	Aminoleban EN	• Higher serum erythropoietin levels after liver surgery
Okabayashi [44]	Prospective 96 patients	Aminoleban EN	• Significant improvement in QOL after hepatectomy • Restored and maintained nutritional status
Ichikawa [48]	Prospective 56 patients	LIVACT	• Reduced early recurrence after hepatic resection in patients with HCC

levels in patients with non-hepatitis who underwent curative hepatic resection, and higher EPO levels might be beneficial in protecting liver cells from ischemic injury and preventing intraoperative hemorrhage associated with lower perioperative levels of alanine aminotransferase and aspartate aminotransferase in serum.

In a prospective randomized clinical study, Okabayashi et al [44]. assessed the impact of oral supplementation with BCAA-enriched nutrients on postoperative QOL in patients undergoing liver resection. To our knowledge, this was the first prospective clinical study evaluating an association between perioperative supplementation of BCAA and postoperative QOL. Patients were randomly assigned to receive BCAA supplementation (BCAA group, n = 48) or a conventional diet (control group, n = 48). Postoperative QOL and short-term outcomes were regularly and continuously evaluated in all patients using a short-form 36 (SF-36) health questionnaire and by measuring various clinical parameters. This study demonstrated a significant improvement in QOL after hepatectomy for liver neoplasm in the BCAA group based on the same patients' preoperative SF-36 scores ($P < 0.05$). Perioperative BCAA supplementation preserved liver function and general patient health in the short term compared to a normal diet. The authors on this study concluded that BCAA supplementation improves postoperative QOL after hepatic resection over the long term by restoring and maintaining nutritional status and whole-body kinetics.

In a prospective randomized clinical study, Ichikawa et al [48]. studied the effect of oral supplementation with BCAA on the development of liver tumorigenesis after hepatic resection in HCC patients. Fifty-six patients were randomly assigned to receive either BCAA supplementation orally for 2 weeks before and 6 months after hepatic resection (BCAA group, n = 26) or a conventional diet (control group, n = 30). Postoperative tumor recurrence was continuously evaluated in all patients by measuring various clinical parameters. Recurrence rate at 30 months after surgery was significantly better in the BCAA group than in controls. Interestingly, tumor markers, including AFP and PIVKA-II, significantly decreased at 36 months after liver resection in the BCAA group in comparison to the control group. These findings therefore indicated that oral supplementation of BCAA also reduces the incidence of early recurrence after hepatic resection in patients with HCC, and this treatment regimen offers potential benefits for clinical use in such patients, even in cases with a well-preserved preoperative liver function [49,50]. Preventing recurrence after curative treatment of HCC remains a major challenge for the management for liver cancer. As a recent topic in 2013, several studies have revealed that BCAA prevents hepatocarcinogenesis and prolongssurvival of cirrhotic patients [51-54]. In support of these findings, several recent studies suggested that long-term supplementation with BCAA can inhibit hepatocarcinogenesis, especially in overweight or obese patients [55,56]. BCAA is known to exert multiple pharmacological activities; however, mechanisms underlying this possible prevention of tumorigenesis in HCC remain unknown.

Future: Improving Postoperative QOL According to Liver Regeneration Following the Administration of BCAA

Liver regeneration is unique among organ systems [57,58]. In the adult liver, there are two major populations of cells that have been thought to explain liver regeneration and/or repair. The first consists of unipotential cells, specifically hepatocytes and bile duct epithelial cells that regenerate during normal tissue turnover. The second population consists of bipotential cells, intrahepatic liver stem cells and/or oval cells that can differentiate into hepatocytes and bile duct epithelial cells. Recent reports suggest that bone marrow (BM) stem cells may harbor unexpected developmental plasticity [59-61], although it remains unclear precisely how and to what extent BM cells contribute to liver regeneration, and whether it is by cell fusion, trans differentiation or both. Previous studies reported that under certain conditions BM cells are recruited into the liver and become not only Kupffer cells, endothelial cells, oval cells, stromal cells and cholangiocytes, but also functioning hepatocytes [59-61]. Further examination is required to address the possible association between BCAA and liver regeneration, especially the mechanisms by which BM-derived extra-hepatic stem cell develop after liver resection with perioperative BCAA supplementation.

Liver cirrhosis negatively impacts the patient's nutritional status, with derangements in energy expenditure and in protein, carbohydrate and fat metabolism. Common complications of cirrhosis such as ascites, hepatic encephalopathy and esophageal varices require appropriate nutritional intervention. However, for patients with hepatic encephalopathy, the evidence is controversial; while some studies indicate that protein restriction is beneficial, others found that this strategy does not have apparent benefits in acute encephalopathy. For patients unable to tolerate animal proteins, other protein sources should be considered, such as proteins from vegetables or BCAA-enriched formulations. In general, it is recommended that nutrition is individualized according to a patient's nutritional status and monitored to ensure well being and nutritional adequacy. Following the assessment, dieticians should educate patients and carers about sodium and fluid restriction and appropriate food choices. Nutrient-dense meals, snacks and oral supplements are recommended.

Conclusion

This review article was mention a focus on the effectiveness of BCAA nutrient therapy on postoperative QOL in the patients after hepatic resection. Supplementation of BCAA has been shown to improve the nutritional status and QOL in patients with cirrhosis. BCAA may also inhibit carcinogenesis in heavier patients with cirrhosis and play a key role in liver regeneration. Individualized intervention is recommended based on each patient's nutritional status.

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