

Systematic review of peri-operative nutritional support for patients undergoing hepatobiliary surgery

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Background: Malnutrition is prevalent among peri-operative patients undergoing hepatobiliary surgery and is an important prognostic factor. Both hepatobiliary disease and surgical trauma significantly affects body's metabolism and environment. Therefore, it is very important for patients with liver diseases undergoing hepatobiliary surgery to receive essential nutritional support during peri-operative period.

Methods: We summarized our clinical experience and reviewed of related literature to find the way for implementing the appropriate nutritional strategy.

Results: We found after comprehensively evaluating nutrition status, function of liver and gastrointestinal tract, nutritional strategy would be selected correctly. In severe malnutrition, initiation of enteral nutrition (EN) and/or parenteral nutrition (PN) with essential or special formulae is often recommended. Especially nasojejunal feeding is indicated that early application can improve nutritional status and liver function, reduce complications and prolong survival.

Conclusions: The reasonable peri-operative nutritional support therapy can improve the effect of surgical treatment and promote the patients' recovery.

Keywords: Hepatobiliary surgery; malnutrition; peri-operative nutritional support

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Introduction

There are approximately 30 million people enduring hepatobiliary disease in China, accounted for 45% of the total global (1-3), such as hepatitis, pancreatitis, cholecystitis, alcoholic liver disease, drug-induced liver disease, cirrhosis, hepatocellular carcinoma, pancreatic cancer and so on. And 5-20% of them will undergo high risk hepatobiliary surgery each year for both benign and malignant disorders (4).

The liver, cholecyst and pancreas are main organs of nutritional metabolism, including protein synthesis, glycogen storage, fat digestion and detoxification. These functions become damaged to a greater or lesser extent in patients with diseases, resulting in various metabolic disorders, and their disturbed nutritional condition is associated with disease progression. Most patients

present with significant weight loss due to anorexia and malabsorption, and are expected to have a period of inadequate oral intake up to 10 d after surgery (5,6). At least more than half of these patients occur malnutrition of different degree (7). Therefore, dietary counsel and nutritional intervention is essential support, particularly, when therapeutic procedures, providing nutrition for patients during peri-operative is vital but can be challenged.

Perioperative nutrition is a well recognised aspect of care in recent years and has been shown to reduce the incidence of complications and to reduce hospital stay (8). In the past decades, parenteral nutrition (PN) was recommended for patients with hepatobiliary diseases (9), but recently, significant progress has been achieved in the field of enteral nutrition (EN). Clinical research has shown that early delivery of nutrition via the gastrointestinal tract after severe

injury can reduce septic morbidity and mortality in critically injured patients (10,11). But these days evidence suggests that routine post-operative enteral nutritional support may lead to an increased incidence of gastric stasis (12). Now the effects of nutritional supplements given to initiate EN or PN are still debated. Further, the decision the optimal timing of delivery of feed and the nutritional supplementation should be given after surgery or should support cover the entire peri-operative period is still remain unclear. This review examines metabolic alterations of hepatobiliary diseases and effects on multiple peri-operative nutrition strategies, evaluates the indications, feeding access and assesses the clinical role of peri-operative nutrition in hepatobiliary surgical diseases.

Metabolic alterations of hepatobiliary disease

Liver is an important organ for uptake, metabolism, conjugation and excretion. An impairment of nutritional status is a frequent finding in patients with hepatobiliary disease (13,14).

Clinical features of patients with hepatobiliary disease

There is an increased severity of gastrointestinal symptoms associated with recent weight loss and impaired health-related quality of life and the severity of liver disease. Patients with hepatobiliary diseases experience abdominal pain, nausea and bloating and are found to have altered gut motility (15). All of which lead to the development of functional dyspepsia, malnutrition even cachexia.

Loss of appetite is currently attributed to the presence of cytokines such as tumor necrosis factor- α (TNF- α) and leptin (16), or alcohol-induced anorexia (17), which is the most common reason. Also, early satiety damages gastric accommodation, and impairs expansion capacity of the stomach due to the presence of clinically evident ascites quite often lead to a deficient nutrient intake (18). One other important factor is the presence of impaired digestion and nutrient absorption due to portal hypertension, suggesting that medication or controlling the pressure in the portal vein either by transjugular intrahepatic portocaval shunts (TIPS) could decrease the risk of 3- and 5-year mortality and of clinical decompensation after surgery for hepatocellular carcinoma (19). Cholestatic liver disease is another reason to impair hepatobiliary and intestinal homeostasis and digestion. The reduced in transluminal bile salt concentrations disturb the absorption of dietary lipids

and fat-soluble vitamins such as A, D, E and K (20).

Furthermore, patients who are candidates for hepatobiliary surgery often have associated comorbidities such as coexistent small intestinal disease (inflammatory bowel disease, celiac sprue); diabetes and protein-energy malnutrition because of poor dietary intake and the catabolic effects of bacterial overgrowth contribute to the impaired absorption and utilization of nutrients (21).

Unfortunately, iatrogenic low protein diets required in order to avoid hepatic encephalopathy also lead to poorer nutritional status. Other iatrogenic causes for caloric and protein loss include loss of regular meals for reasons of pending examinations and procedures during multiple hospitalizations (14).

Pathophysiological mechanisms of hepatobiliary disease

The metabolic alterations of hepatobiliary disease are characterized by hyperdynamic changes, hypermetabolism, and catabolism. The hyperdynamic changes raise energy expenditure through increasing cardiac output and activation of the sympathetic nervous system, decreasing systemic vascular resistance, and so on.

The hypermetabolic defined as resting energy expenditure (REE) >120% compared with the expected value. Studies reported 30% of patients with ascites, cirrhosis or hepatocellular carcinoma are considered hypermetabolic (13). The diminished synthetic capacity of the liver and the impaired absorption of nutrients are the main reasons that disrupt the metabolic balance in end-stage liver disease (ESLD). Elevated pro-inflammatory and anti-inflammatory cytokine levels point to a cytokine-driven hypermetabolism in cirrhosis.

Catabolism is another important metabolic alteration. Isotope techniques have been used to demonstrate that patients with hepatobiliary disease have a significantly higher urea production compared with controls, indicating both increased protein catabolism and diminished muscle protein synthesis. The resultant negative nitrogen balance is, therefore, a net effect of both of these changes. Catabolism and proteolysis of skeletal muscle protein raises concentrations of aromatic amino acids, decreases levels of branched-chain amino acids (BCAAs), and accelerates urea genesis. Abnormal metabolism of carbohydrate and fat also occur with hepatobiliary disease. This may result from cortisol and catecholamine increased, while glucose clearance and oxidation diminished. In hepatobiliary disease, glucose intolerance occurs in 40-90% of cases, and

insulin is required in as many as 80% of patients (22).

Function alterations after hepatobiliary surgery

Not only the disease cause metabolism change occurred, hepatobiliary surgery transiently aggravated the changes.

After liver resection, patients appear to have increased level of aminotransferase, caused by surgical trauma, damage of liver cell and liver ultrastructure, and release of inflammatory mediators, such as interleukin-1 (IL-1), IL-6, IL-8, TNF- α and platelet-activating factor (23). All these associated with metabolic changes.

Experimental studies have shown that the fasted state reduces the secretion of several gastrointestinal hormones (24), such as cholecystokinin, gastrin and peptide YY after pancreaticoduodenectomy (25). These hormones are instrumental in stimulating bile flow and gallbladder contraction, and for maintaining intestinal motility. For another, pancreaticoduodenectomy results in loss of gastric pacemaker activity due to removal of the interstitial cells of Cajal and this together with the physiologic consequences of partial pancreatic resection and biliary and pancreatic diversion lead to a high incidence of postoperative gastric stasis (12).

A decreased level can affect many systems and functions including respiratory failure, cardiac and neurological dysfunction, and insulin resistance. Hypo/hyperglycemia, hypocalcaemia and hypophosphataemia particularly after major resection should not be ignored and require correction.

Nutrition status assessment

Essential nutritional assessments should be performed before instituting nutritional and diet therapy. Nutritional management will adjust main according to liver and gastrointestinal tract function.

Anthropometric parameters include age, sex, height, bodyweight, changes in bodyweight, arm circumference (AC) and triceps, skinfold thickness (TSF), the condition of loss of subcutaneous fat and muscles, the presence of edema/ascites, hair condition. Body mass index (BMI: kg/m²) and arm muscle circumference (AMC) are calculated further. These data should be collected to evaluate nutritional status by subjective global assessment (SGA) (26) or nutritional risk screening 2002 (NRS2002) (27,28) or other nutritional assessment scales (29).

SGA is an effective method in the screening of

malnourished patients (30). On the basis of these features of the history and physical examination, clinicians identify a SGA rank which indicates the patient's nutritional status. These categories are: A is well nutrition, B is moderate or suspected malnutrition, and C is severe malnutrition. The NRS2002 was performed as described by ESPEN guidelines. Thus, patients are classified as: without risk, 0; at low risk, 1-2; at medium risk, 3-5; and at high risk, >5 of malnutrition. The previous prospective, randomized studies showed that for the patients suffering serious illness who had obvious nutritional risk (SGA at last rank B, NRS 2002 greater than three points), it is beneficial to the patients in postoperative recovery and clinical outcomes if they were provided perioperative nutrition support (31-33).

It is apparent that there is a significant fall in BMI with associated deterioration in anthropometric indices after surgery and that recovery has not taken place by 3-month after surgery (34).

Biochemical parameters should be collected exactly for assessment of liver function (35).

Liver function includes the uptake, metabolism, conjugation and excretion. Liver insufficiency and failure were defined as prolonged hyperbilirubinemia unrelated to biliary obstruction or leak, clinically apparent ascites, prolonged coagulopathy requiring frozen fresh plasma, and/or hepatic encephalopathy.

A transient early rise in serum hepatic transaminase levels, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are released from hepatocytes into the bloodstream in patients with liver disease and those who have undergone hepatectomy and thus, as a result of hepatocellular damage is common, usually peaking at 24-48 h with the extent of derangement being related to the extent of resection.

Bilirubin, a breakdown product of hemoglobin, is produced by the liver and reflects the uptake, conjugation and excretion function of liver. Serum bilirubin is useful in separating the causes of jaundice (36). Increase of conjugated bilirubin usually suggests injury of hepatocytes; unconjugated bilirubin is increased with little or no increase in conjugated bilirubin points out haemolysis. A sustained rise in bilirubin coupled with elevation in ALP should prompt a search for a cause of biliary obstruction. This is uncommon after a minor liver resection and is usually seen after a major resection in which a biliary reconstruction has been performed.

An isolated rise in ALP or an elevation of this enzyme in association with gamma-glutamyl transferase may indicate

normal hepatic regeneration rather than a pathological process, with levels of the enzyme peaking at around 14 d (37,38).

Changes in platelet count, prothrombin international normalized ratio (INR) and activated partial thromboplastin times (aPPT), which are markers of coagulation status, may be deranged and reflect the magnitude of resection (39).

Specifically, a post-operative rise in INR between days 1-5 as well as a decrease in platelet count and fibrinogen levels are common and thought to be due to a combination of decreased synthetic function of the remnant liver and a consumptive coagulopathy (40).

Many important proteins are synthesized exclusively by the liver, such as albumin and coagulation factors including V, VII, VIII, IX, X, XI and XII. Partial damage or resection of the liver reduces hepatic synthesis of these proteins. Therefore, the plasma concentrations of these proteins reflect liver synthetic function. Plasma albumin concentration, prothrombin time and INR are indicators of liver function. These tests are always used together with dynamic and quantitative tests.

Serum prealbumin which is more sensitive than albumin for evaluating protein synthesis in the liver due to its shorter half-life of 48 h and does not accumulate in the body to undergo redistribution. Therefore, it might be a better indicator to assess nutritional status than the widely used albumin serum level, and any fluctuations in nutritional status can be detected rapidly. Huang *et al.* found that patients with postoperative liver insufficiency were correlated with elder age and lower serum level of prealbumin, and prealbumin serum level <170 mg/dL remained predictive for liver insufficiency after hepatectomy (41).

Child-Pugh score's parameters, based on some of the above mentioned routine laboratory testing and reflecting different aspects of liver disease, are easy to measure (42). The Child-Pugh score can be used to assess global liver function, which is particularly useful in selecting patients with HCC and cirrhosis for resection or transplantation.

Although serological tests are used frequently in practice, they reflect the degree of total liver damage or function, not the remnant of liver function. Morphological detection methods, such as computed tomography (CT) volumetry, ultrasonic, nuclear imaging techniques can indirectly predict liver function, especially of remnant liver function (43).

Evaluation of other aspects of body

Evaluation of gastrointestinal function mainly accord

clinical symptoms. Serious diarrhea, distention, cramps, celiacgia all suggest poor of gastrointestinal function. There may be exist mucosal hyperemia and edema, gastrointestinal obstruction, peritonitis or operation complication.

Lately a novel finding has demonstrated corticotropin-releasing factor (CRF) peptide in human small intestine secretes increased following surgery and traumatic shock (44). Circulating CRF as a potential mediator of the gut dysfunction associated with critical injury is associated with poor gastric emptying and gut permeability though enhancing ion secretion and intestinal permeability, which prolong hospital stay.

Glucose tolerance, insulin resistance (22), capacity of kidney excrete (45), and so on, which are associated with nutritional status and choice of nutritional strategy also need be evaluated.

Nutrition therapy for hepatobiliary patients

Malnutrition adversely affects the prognosis of these hepatobiliary patients, and poor nutritional status in patients undergoing surgery is well known to increase postoperative morbidity by deteriorating various organ functions and the immune system of the patients (46). If patients are unable to maintain adequate intake via the mouth, artificial nutrition is used to improve nutritional status.

Peri-operative nutritional support composes with pre-operative and postoperative nutrition.

At present, the view about pre-operative nutritional therapy is that the treatment should be provide to hepatobiliary patients with serious malnutrition or who prepare to have major surgical treatment with mild to moderate malnutrition. The main purpose is to improve the nutritional status of the patients, to improve their operation tolerance, reduce or avoid postoperative complications and mortality.

Studies of pre-operative nutritional support have evaluated a wide range of protocols, considered there is a potential 'window of opportunity' for preoperative nutritional supplementation. Several trials have implicated lower incidence of septic complications and faster wound healing upon early enteral feeding (10,47,48).

Postoperative nutrition should be provide to the patients have accepted with preoperative nutritional therapy, or who have severe malnutrition and/or complications after surgery. Patients fasts more than 1 week also need postoperative nutrition support.

There is some evidence that early intervention in replenishing the nutrient deficit containing additional protein, fat, carbohydrates, and micronutrients in malnourished patients

with liver disease can prolong life expectancy, ameliorate quality of life, diminish complications by improvement of nutritional and biological variables (49,50). Other trials have shown opposite results (51,52). The immediate advantage of caloric intake could be a faster recovery with fewer complications, to be evaluated systematically.

Nutritional treatment strategy accepted by majority mediciners is that EN support should be actively applied, as long as the gastrointestinal anatomy and function allows. Otherwise PN should be applied until gastrointestinal function recovery (53). PN is lifesaving.

EN is defined as all oral intakes (i.e., registered oral intake, supplemented oral feeding) and any kind of feeding provided through the gastrointestinal tract (gastric, duodenal or jejunal) via a tube, catheter, or stom containing caloric content.

On current evidence surgeon preference is a reasonable way to decide EN (47). EN improves nutritional status and liver function, enhanced immunocompetence, decreased clinical infection rates, maintained gut structure and function, potentially attenuate catabolic stress responses in patients after surgery and prolongs survival (48) through following aspects: to maintain and improve the intestinal mucosal barrier function; to prevent gastrointestinal mucosa atrophy (54); to promote the secretion of gastrointestinal hormones and promoting the recovery of intestinal peristalsis; to decrease gut permeability and maintain mucosal immunity and gut associated lymphatic tissue (GALT) (55); to maintain the normal growth of natural gut microflora and inhibited microbial translocation from the gut to the blood stream (56); to accelerate the blood circulation of portal vein system; to provide more oxygen, nutrients and metabolic substrates to hepatocytes.

EN following hepatobiliary surgery can be delivered in different ways: nasojejunal tube, percutaneous gastrostomy/ jejunostomy tube and surgical jejunostomy with gastrostomy. Several comparative studies have dated on efficacy and complications of jejunostomy, nasojejunal (52,57,58). Each strategy was associated with specific complications (59). Overall nasojejunal feeding is safer than jejunostomy, and it is associated with only minor complications. Compared with percutaneous methods, nasojejunal feeding can significantly decrease the incidence of delayed gastric emptying and shorten the postoperative hospital stay.

EN can also stimulate hepatic circulation and ameliorate liver function. In the present study, a significant decrease in TB and DB in the EEN/PN group was observed compared with that in the total PN (TPN) group (58).

Following pancreatic resection, early postoperative jejunal nutrition was shown to be safe and positively affect outcomes including nutritional status and whole body protein kinetics. Furthermore, it was found to contribute to a significantly lower incidence of pancreatic fistula (60), resulting in a shorter duration of hospitalization compared to patients receiving late postoperative EN.

However, postoperative total enteral feeding is associated with complications such as diarrhea, abdominal distention, and abdominal cramps. These symptoms worsen with increasing caloric intake and can lead to discontinuance of enteral feeding.

PN is an intravenous administration of nutrients (for example, carbohydrates, proteins, fat, vitamins, minerals, and water) delivered into a large-diameter vein, usually the superior vena cava adjacent to the right atrium or a peripheral vein, usually of the hand or forearm.

Numerous studies have suggested that routine TPN had a poor performance of reducing infectious complications, delaying gastric emptying and shortening postoperative hospital stay compared with EN or combined method (49,61-63). If the patients enduring diffuse peritonitis, intestinal obstruction intractable vomiting, paralysis of intestine or intractable diarrhea, PN should be supply firstly until gastrointestinal function resume. PN offers the possibility of increasing or ensuring nutrient intake in patients in whom normal food intake is inadequate and EN is not feasible.

Nutrition formulas

Avoidance of alcohol and excess fat and ingestion of 4-6 meals/day containing carbohydrates and protein are the most common recommendations. In worse malnutrition, initiation of enteral feeding and/or PN use of formulae normally contain nutrients like protein, fat, carbohydrates, and fibre in different combinations. In severe status special formulae such as BCAA-enriched nutrient mixtures (64) are often recommended.

How to choose different EN formulations depends on the degree of hepatic dysfunction and ascites. Low-calorie (18-23 kcal/kg/d) supply is encouraged since postoperative patients with liver disease are intolerant of an excess of nutritional support (65,66), while previous high-calorie supply (30 kcal/kg/d) has been abandoned. If the patient still cannot eat after surgery 3-4 days or is at the alternative stage of EN during the postoperative rehabilitation or any abnormalities are seen in glucose tolerance, the caloric

supply should be adjusted to normal standard [25 kcal/kg (ideal bodyweight) per day]. If patients do not have hepatic encephalopathy, general elemental diet or non-elemental diet will be good choice (protein intake 1.0-1.5 g/kg/day; lipid energy intake ratio 20-25%). Special elemental diet (0.5-0.7 g/kg/d with high BCAA protein intake) is preferable for liver failure in patients with hepatic encephalopathy (67). The higher content of BCAA in compound amino acids for liver disease can correct the disproportionality of BCAA, reduce aromatic amino acid that pass blood brain barrier, further relieve hepatic encephalopathy and may also have an effect on immunity and infections. EN preparations of low-sodium (<5 g/d), high-calorie density are better for patients with more ascites and/or edema, respectively. Iron intake should be control in 27 mg/day if serum ferritin levels are above the upper limit of the reference interval. Zinc deficiency also often occurs in patients with cirrhosis and has been associated with the pathogenesis of hepatic encephalopathy. Zinc vitamins and dietary fiber supplementation should be adequate intake.

Nowadays, most experts believe that PN combined with EN should be considered when EN cannot satisfy the energy needs (<60% energy needs) for patients who has indications of nutritional support (9).

There is also some evidence that nutritional supplementation with immunonutrient formulas containing arginine, fish oil lipid emulsion with omega-3 fatty acids (68), dextrose, structured triglyceride might offer a benefit in terms of preserved liver function and better clinical outcome, including the promote wound healing, decreased infectious morbidities and hospital stay. Synchronously, glutamine-enriched early EN or PN proved to be a potent protectant against intestinal mucosal barrier injury after liver transplantation (69).

Efficacy access and complications

Peri-operative artificial feeding is associated with complications such as diarrhea, abdominal distention, abdominal cramps and hyperglycemia. These symptoms worsen with increasing caloric intake and can lead to discontinuance of feeding.

EN following pancreatic resection can be delivered in different ways. The clinical research by doctors of China compared the efficacy and complications of nasojejunal and jejunostomy on patients undergoing pancreaticoduodenectomy. The results of this study showed that the rate of intestinal obstruction and delayed gastric emptying was significantly lower in the nasojejunal group

than jejunostomy group. Catheter-related complications were more common in the jejunostomy group as compared with the nasojejunal group (35.3% vs. 20.6%). Nasojejunal group showed superiorities on shortening time of removal the feeding tube and postoperative hospital stay. Mohammad Abu-Hilal's study support similar results. The incidence of catheter-related complications was higher in percutaneous techniques: 24% in percutaneous transperitoneal jejunostomy and 34% in percutaneous transperitoneal gastrojejunostomy as compared to nasojejunal technique (12%). Jejunal feeding is well tolerated and, unlike gastric and duodenal feeding, does not stimulate pancreatic secretions. Whereas Gerritsen *et al.*'s research (52) suggested that none of the analysed feeding strategies was found superior with respect to time to resumption of normal oral intake, morbidity and mortality by comparison of the efficacy and complications of nasojejunal, jejunostomy and parenteral feeding after pancreaticoduodenectomy. Each strategy was associated with specific complications. Nasojejunal tubes dislodged in a third of patients, jejunostomy tubes caused few but potentially life-threatening bowel strangulation and total PN doubled the risk of infections.

On current evidence have proved nasojejunal feeding was associated with fewest and less serious complications, as replacement of a nasojejunal tube (although frequently required) is to be preferred over infections and bowel strangulation.

Conclusions

Peri-operative nutritional support is a significant strategy for patients undergoing hepatobiliary surgery to obtain better results. For perioperative individualized therapy in patients with liver diseases, the nutritional need of the patient, disease mechanism characteristics, function of liver and the tolerance of the gastrointestinal tract should be adopted. EN or EN combined/sequential PN is safer and less expensive than TPN, unless PN is the only choice. While in different EN strategies, nasojejunal feeding has the potential advantage of maintaining intestinal trophism more effectively and was associated with fewest and less serious complications.

Through the reasonable peri-operative nutritional support therapy, immune regulation, regulation of blood glucose, maintenance of tissue and organ function, and improve the effect of surgical treatment is our ultimate purpose and future effort direction.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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