

# Perioperative nutritional support and fluid therapy in patients with liver diseases

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**Abstract:** The prevalence of liver dysfunction and malnutrition is common among patients with obstructive jaundice or cirrhosis, the poor nutrition status in patients with indications for hepatic resection increases the risk of postoperative complications and/or mortality. Hepatic surgery significantly affects body's metabolism and environment. Therefore, it is very important for patients with liver diseases undergoing hepatic surgery to receive essential nutritional support and fluid therapy during perioperative period. There are several principles in nutritional support and fluid therapy that surgeons need to pay attention to, for example, time, nutritional approach, fluid volume, choice of fat emulsions and amino acids. Some issues, such as albumin and plasma application, choice of crystalloid and colloid, liver protective therapy, also need further attention.

**Keywords:** Hepatic resection; liver disease; nutritional support; fluid therapy

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Liver is the largest gland in human body, and it is also the center of nutrition metabolism that provides complex physiological function. The prevalence of liver dysfunction and malnutrition is reported to be 50-90% in patients with obstructive jaundice or moderate to severe cirrhosis (1). And liver dysfunction and nutritional deficiency are common among patients with indications for liver surgery. It has been suggested that the poor nutrition status before hepatic resection increase the risk of postoperative complications and/or mortality (2-6). Hepatic surgery significantly affects body's metabolism and environment. Meanwhile, a high catabolic state caused by stress response will result in postoperative malnutrition, recovery delay and inhibition of the immune function, which leads to an increased risk for morbidity and mortality (1,7-9).

Therefore, essential nutritional support and nutrition therapy for patients with liver diseases undergoing hepatic surgery is very important, as it may improve their clinical outcome (4,10). However, considering the nutrient metabolism abnormalities in the liver during perioperative period, the nutritional support and fluid therapy could become complex. How to implement rational fluid therapy

and nutritional support after liver surgery and effectively protect liver function should be attached sufficient importance.

According to the changes in nutrient status of the liver and metabolism function during perioperative period, there are several principles in nutritional support and fluid therapy we need to pay attention to.

## Time

In the first 3 days after surgery, the body is in a stress state associated with a catabolic state, negative nitrogen balance. In this stage, it should be paid attention to maintaining major organs function. The peak of stress state should be taken into full consideration in nutritional support in order to avoid high calorie intake (11).

## Enteral nutrition (EN) support

EN should be given high priority in patients receiving hepatic resection if conditions permit. The integrity of gastrointestinal function is not impaired in these patients,

which gives us the opportunity to provide postoperative EN support at an early stage. Evidence shows that there are many benefits for patients receiving EN support perioperatively, such as helping to maintain the structure and functional integrity of the intestinal mucosal cells, protecting the intestinal mucosal barrier, reducing bacterial translocation and intestinal infection, improving the recovery of gastrointestinal function, and maintaining the body's immune function. Reports have demonstrated the superiority of early EN in postoperative complication rates over parenteral nutrition (PN) (12-14). The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines also support that EN is favored to preserve gut integrity and immune markers and to simplify glycemic management (15).

Reports showed that for patients undergoing hepatic resection, perioperative nutrition support, either enteral or parenteral, can reduce septic complications. Furthermore, postoperative early EN, especially The branched-chain amino acids (BCAA) -enriched nutrition, may prevent postoperative infections (10,12,13,16). How to choose different EN formulations depends on the degree of hepatic dysfunction and ascites. If patients do not have hepatic encephalopathy, general elemental diet or non-elemental diet will be good. Special elemental diet is preferable for liver failure with high BCAA in patients with hepatic encephalopathy, and EN preparations of low-sodium, high-calorie density are better for patients with more ascites. Pre-digested peptide preparations would be used in following condition: insufficiency exocrine pancreas, pancreatic drainage or intestinal bile shortage. And the concentration (from 12% increase to 24%) and infusion rate (from 50 mL/h increase to 100 mL/h) of nutrient solution should be increased day by day. The nutrient solution should not be more than 2,000 mL/d in total. 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 (17).

### **Volume fluid of total parenteral nutrition (TPN)**

The daily dose is approximately 50 mL/kg/day for adult patients requiring TPN. TPN volume should be no more than 3,000 mL for a 70 kg adult patient. If vomit, diarrhea, excessive drainage and other special circumstances occur, the amount of liquid could be appropriately increased, while the liquid intake should be limited depending on the status of patients with chronic renal insufficiency or heart failure (17,18).

### **Caloric intake**

Low-calorie supply is encouraged since postoperative patients with liver disease are intolerant of an excess of nutritional support, while previous high-calorie supply (30 kcal/kg/d) has been abandoned. However, caloric standard of TPN for surgical patients is inconsistent in different professional fields and textbooks, ranging around 25-30 kcal/kg/d. Beth Israel Deaconess Medical Center (BIDMC) provides 21-23 kcal/kg/d for critically ill and postoperative patients to achieve good outcomes (19-21).

There is also a proactive downward trend for calories in China, but still no data on a wide range of surgical patients of moderate to severe degree. Researches, both domestic and abroad, show that excessive caloric intake for surgical patients would not reach the goal of nutritional support, but increase metabolic burden on patients, which causes hyperglycemic, liver damage and other metabolic disorders and complications. In fact, low caloric supplement in a short term after the surgery can avoid the metabolic burden and uncontrolled glucose regulation caused by excessive calorie supply exogenous, as well as decrease the incidence of related postoperative complications under traumatic stress and significant hormone antagonist stage, rather than change nutritional status. Peking Union Medical College Hospital explored the application of permissive inadequate intake firstly in China. The result confirmed that the permissive inadequate intake (18 kcal/kg/d) would not change the blood biochemistry and nutritional status of patients postoperatively in a short term (3-4 days), and it can avoid uncontrolled glucose regulation and benefit patients with successful rehabilitation. If the patient still cannot eat or is at the alternative stage of EN during the postoperative rehabilitation, the caloric supply should be adjusted to normal standard, 25 kcal/kg/d, to supply sufficient of calories to facilitate the rehabilitation of patients (22,23).

### **Fat emulsion choice**

Patients with cirrhosis and other liver dysfunction are often accompanied by metabolic disorders, concomitant hypoalbuminemia and malnutrition. In clinical applications, long chain triglyceride (LCT) and medium chain triglycerides (MCT) are physically mixed at a ratio of 1:1 to meet the needs of essential fatty acids for human body, which is also helpful to the improvement of liver function and hepatocyte regeneration. In recent years, structured triglyceride (STG) has been widely used for

its heat releasing stability and high safety. Compared with the conventional fat emulsion, STG fat emulsion is better in improving the nitrogen balance and more easily being removed by hepatocyte. Regarding the impact on monocyte-macrophage system, STG fat emulsion does not change the function of monocyte-macrophage system, and inhibits the human neutrophil migration (24-26).

In addition, the efficacy of the application of  $\omega$ -3 fatty acids in critically ill patients has caused great concern. Clinical practice has proved that  $\omega$ -3 fatty acids and other nutrients, such as immune glutamine, arginine, nucleosides and nucleotides, dietary fiber, and so on, can reduce the incidence of infection complications and promote wound healing. 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. Studies have proved that,  $\omega$ -3 fat emulsion can significantly improve liver function of patients after hepatic resection, by decreased IL-6 in peripheral blood and relief of HLA-DR -related inhibition. Another study suggests that  $\omega$ -3 fatty acids can increase the liver perfusion, provide more oxygen, nutrients and metabolic substrates to hepatocytes (27-29).

The latest fat emulsion contains fish oil-SMOF that is composed of vitamin E—added soy long-chain fatty acids, medium chain fatty acids, olive oil, fish oil and vitamin E. This newly developed fat emulsion is mixed according to the ratio recommended by the U.S. National Institutes of Health (NIH) in 1999 which reduces the content of  $\omega$ -6 fatty acids, increases the  $\omega$ -3 fatty acids and provides sufficient of MUFA. Currently, on the basis of double-blind trial, it is believed that immune function can be best regulated by this ratio. Furst *et al.* pointed out that compared with the classic fat emulsion, SMOF fat emulsion is well tolerated in surgical patients. Due to its anti-inflammatory ability, it can help to regulate immune system and significantly shorten hospitalization time, but its efficacy in the application after partial liver resection has yet to be clinically validated (30-33).

The component contents of different conventional fat emulsions in clinic are compared in *Table 1*.

### Amino acid choice

Currently, balanced amino acid preparation and specific amino acid preparation are widely used in clinic. The specific amino acid preparation includes compound amino acids for liver disease, kidney disease, trauma, children, and so on.

BCAAs—leucine, isoleucine, and valine—are essential amino acids. 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 (34-37). Supplemental BCAA is commonly applied in patients with liver cirrhosis (38,39), especially in compensated cirrhosis (40,41) or hepatocellular carcinoma (42-46). Some studies reported that perioperative administration of BCAA to patients undergoing hepatic resection can increase albumin synthesis and quickly improve liver function during the early postoperative period (36,47-49).

It should be remembered that the supplement of serum albumin and BCAA after hepatic surgery is important. We should not only supply amino acid preparation rich in BCAA but also in other comprehensive amino acids to prevent disorder of protein synthesis.

### Some issues on fluid theory during perioperative liver surgery

#### *Albumin in liver surgery*

In recent years, there are some new tendencies in applying of albumin among patients after abdominal surgery. Most evidence states that albumin is not directly involved in wound healing process of the body, and cannot improve the immune-related protein generation for immunity improvement either. After supplement, there will be 30% of albumin that will remain in the blood, indicating that it is mainly used for maintaining the colloid osmotic pressure and increasing capacity. The decrease of albumin after severe trauma and serious surgery can suggest the level of trauma degree in a certain extent (50,51).

Because albumin is almost entirely synthesized in the liver, liver resection surgery may lead to further dysfunction of albumin synthesis which reflects the trauma degree, especially in patients with impaired hepatic function. This decline may be related to temporarily blocked synthesis of albumin in the liver with obviously increased loss or decomposition. During tissue trauma, increased vascular permeability and albumin leakage lead to albumin redistribution. This is one of the most important reasons for the decline of serum albumin after surgery. According to a double blind, randomized controlled trial (SAFE study) that included 6,045 participants in Australia and New Zealand,

**Table 1** The comparison of conventional fat emulsions in clinic

Conventional fat emulsions	Representative preparation	Component content
LCT	Intralipid 20%	1,000 mL of Intralipid 20% contains: purified soybean oil 200 g, purified egg phospholipids, glycerol anhydrous, sodium hydroxide and water for injections, and the major component fatty acids are linoleic (44-62%), oleic (19-30%), palmitic (7-14%), linolenic (4-11%) and stearic (1.4-5.5%); pH: appr. 8; osmolality: 350 mosm/kg; energy content: 8.4 MJ (2,000 kcal)/1,000 mL
LCT/MCT	Lipofundin 20%	1,000 mL lipofundin 20% contains: soya oil 100.0 g, medium-chain triglycerides 100.0 g, glycerol 25.0 g, egg lecithin 12.0 g, $\alpha$ -tocopherol 0.2 g, sodium oleate and water for Injections; PH: 6.5-8.5; osmolality: 380 mosm/kg; energy content: 7.99 MJ (1,908 kcal)/1,000 mL
STG	Strucktokabiven	1,206 mL strucktokabiven contains: glucose 13%: glucose (as monohydrate) 85 g; amino acid solution with electrolytes: alanine 5.3 g, arginine 4.6 g, glycine 4.2 g, histidine 1.1 g, isoleucine 1.9 g, leucine 2.8 g, lysine (as acetate) 2.5 g, methionine 1.6 g, phenylalanine 1.9 g, proline 4.2 g, serine 2.5 g, taurine 0.38 g, threonine 1.7 g, tryptophan 0.76 g, tyrosine 0.15 g, valine 2.4 g; calcium chloride (as dihydrate) 0.21 g, sodium glycerophosphate (as hydrate) 1.6 g, magnesium sulphate (as heptahydrate) 0.46 g, potassium chloride 1.7 g, sodium acetate (as trihydrate) 1.3 g, zinc sulphate (as heptahydrate) 0.005 g; lipid emulsion: purified structured triglyceride 34 g; corresponding to: amino acids 38 g, nitrogen 6.2 g, carbohydrates (glucose anhydrous) 85 g, lipids 34 g; electrolytes: sodium 30 mmol, potassium 23 mmol, magnesium 3.8 mmol, calcium 1.9 mmol, phosphate (contribution from lipid emulsion and amino acid solution) 9.9 mmol, zinc 0.03 mmol, sulphate 3.8 mmol, chloride 27 mmol, acetate 79 mmol; pH: appr. 5.6; osmolality: approx. 950 mosmol/kg water; energy content: 3.48 MJ (830 Kcal)/1,206 mL
SMOF	SMOFlipid	1,000 mL SMOFlipid contains: soya-bean oil, refined 60.0 g, triglycerides, medium-chain 60.0 g, olive oil, refined 50.0 g, fish oil, rich in omega-3-acids 30.0 g; pH: appr. 8; osmolality: 380 mosm/kg; energy content: 8.4 MJ (2,000 kcal)/1,000 mL
Fish oil fat emulsion	Omegaven	100 mL omegaven contains: 10.0 g highly refined fish oil containing EPA 1.25-2.82 g; DMA 1.4-3.09 g; myristic acid 0.1-0.6 g; palmitic acid 0.25-1.0 g; palmitoleic acid 0.3-0.9 g; stearic acid 0.05-0.2 g; oleic acid 0.6-1.3 g; linoleic acid 0.1-0.7 g; linolenic acid =0.2 g; octadecatetraenoic acid 0.05-0.4 g; eicosaenoic acid 0.05-0.3 g; arachidonic acid 0.1-0.4 g; docosaenoic acid =0.15 g; docosapentaenoic acid 0.15-0.45 g; dl- $\alpha$ -tocopherol 0.015-0.0296 g; glycerol 2.5 g; purified egg phosphatide 1.2 g; pH: 7.5 to 8.7; osmolality: 308-376 mosm/kg; energy content: 0.47 MJ (112 kcal)/100 mL

LCT, long chain triglyceride; MCT, medium chain triglycerides; STG, structured triglyceride; EPA, eicosapentaenoic acid; DMA, docosahexaenoic acid.

the outcomes of resuscitation with albumin were not significantly better than saline in mortality, length of stay in the intensive care unit, length of hospital stay, duration of renal replacement therapy, or duration of mechanical ventilation (52).

However, more and more evidence suggests that preoperative hypoalbuminemia could become a single risk factor obviously related with the prognosis of severe patients (53-56). According to the authors' experience, limiting albumin supplement could be considered when

the preoperative serum albumin of liver function is normal in patients undergoing partial hepatectomy, instead of in patients with cirrhosis, liver function damage, a clear hypoalbuminemia, or undergoing multi-segmental hepatectomy. Perioperative supplemental albumin can supply the shortage of albumin caused by cirrhosis liver, correct hypoproteinemia, and reduce the probability of postoperative complications incidence. There is a clearly benefit of improving recovery in these postoperative patients.

### *Application of plasma*

Plasma therapy is an important treatment during perioperative period. However, the application of plasma is not standardized and even misapplied in many cases, including the correction of hypoproteinemia, plasma protein supplements, improvement of colloid osmotic pressure; nutrition supplement; supplement of blood volume; increasing immunity; and improvement of liver function. Unnecessary application of the plasma wastes the scarce blood resources and also makes patients potentially exposed to risks of transfusion, such as increasing the chance of transfusion-related infections, transfusion-related lung injury, and transfusion-associated graft-versus-host disease (57,58).

Based on systematic analysis and literature review, we believe that perioperative plasma applications are limited into two conditions: firstly, improve plastic osmotic pressure if needed and maintain blood volume, especially for the patients who bleed much in a short period; secondly, supply coagulation factors and improve coagulation function.

### *Choice of crystalloid and colloid*

The debate between crystalloid and colloid has existed for more than thirty years. Studies have showed that crystalloid mainly supply extracellular fluid and supplement the blood volume to ensure the volume of urine. High dose of crystalloid must be supplied if we want to maintain blood volume simply by crystalloid, but this therapeutic schedule often results in systemic edema, increased risk of pulmonary edema, cerebral edema and inadequate tissue perfusion. Meanwhile, electrolyte and acid-base disequilibrium such as hypernatremia, hyponatremia and alkalosis are often accompanied. The combined use of colloids, improvement of safety and effectiveness in volume therapy are the most basic problems in establishing clinical treatment scheme (52,59,60).

An evidence-based medical research in 1998 reported that application of albumin or plasma protein fraction may bring more probability of mortality than crystalloid or non-protein liquid. And a double blind, randomized controlled trial (SAFE study) showed similar mortality of resuscitation with albumin or saline (52). But a subsequent meta-analysis indicated that, compared with protein liquid, albumin can lower the morbidity and mortality rate (61). Latest studies showed that all artificial colloids (HES, gelatin, dextran) have renal side effects (62). With albumin as reference

colloid, the anaphylactic reactions of artificial colloids are HES 4.51%, dextran 2.32%, gelatin 12.4% (63).

Based on the research results of large-scale monitoring of drug safety, albumin is the safest colloid and the incidence of side effect and serious adverse events are at an acceptable level (64). Reasonable selection of proportion of crystalloid and colloid, and infusion order according to individual conditions is necessary.

### *Liver protective therapy*

Hepatic protectant is the drug that could repair the damage of hepatocytes. There are many causes of hepatocytes injure, such as hepatitis and obstructive jaundice. During the treatment of protecting liver, we should eliminate the etiological factor at first, and then the treatment could include anti-viral therapy, surgery or removing the obstruction through interventional methods. There are a variety of liver drugs with different functions. By understanding the mechanism, properties and the application of these hepatic protectants would help hepatobiliary surgeons properly utilize these drugs. Clinical application of hepatic protectant should follow the principle of easy, safe, effective and low cost. The liver is the major organ that is responsible for the metabolism and detoxification of the drug in the body. Overdose would increase the burden of the liver, and some hepatic protectant with hepatotoxicity may cause liver toxicity and further damage hepatocytes. Hence, hepatic protectants with less liver toxicity should be chosen in clinic. The classification and mechanism of conventional hepatic protectants are shown in *Table 2*.

### **Conclusions**

For perioperative therapy in patients with liver diseases, individualized nutritional support and fluid therapy plan should be adopted, on account of the need of the patient, disease mechanism characteristics, function of liver and the tolerance of the gastrointestinal tract. In order to restore EN and satisfy the needs of the patient for nutrition metabolism, we suggest use parenteral and EN sequential therapy for different perioperative stage and attach importance to the choice of fat emulsions containing medium chain fatty acids, olive oil and amino acids rich in BCAA. In the process of nutrition support and fluid therapy, reasonable selection of proportion and infusion order of crystalloid and colloid is necessary, and glucose level

Table 2 Conventional liver protectants in clinic		
Classification	Representative drug	Mechanism
Essential phospholipids	Polyene phosphatidylcholine	Possess the membranotropic properties, metabolic and hepatoprotective action; regulate lipid and carbohydrate metabolism; promote liver regeneration
Cholagogic hepatoprotective drug	S-adenosylmethionine	Act as a common cosubstrate involved in methyl group transfers, transmethylation, transsulfuration, and aminopropylation are the metabolic pathways that use SAM, which can help in preventing cholestasis in the liver
	Ursodesoxycholic acid	Help regulate cholesterol by reducing the rate at which the intestine absorbs cholesterol molecules while breaking up micelles containing cholesterol; reduce liver fat, relax of the sphincter of Oddi, and promote gallstone dissolving and bile excretion
Detoxification of drug	Reduced glutathione	Combine the body with peroxides and free radicals that exceeds the body's ability to neutralize and eliminate them; antagonism sulfhydryl damage caused by oxidant; protect thiol containing proteins and enzymes in cells. A primary function of glutathione is to alleviate oxidative stress
	Tiopronin	Provide sulfhedryl, detoxicate, antihistamines and eliminate the free radical to protect hepatocytes
	Green enzyme amine	Complex heavy metal, and the formation of stable water-soluble compounds can be excreted through the urine, it can be used in heavy metal poisoning and Wilson disease
Anti-inflammatory drug	Compound ammonium glycyrrhetate	Competitively combine with adrenal cortical hormone enzyme in liver, improve the adrenal cortex hormone level in the body; anti-inflammatory, act as cholagogue, protect liver cells, reduce transaminase; promote jaundice extinction and adjust the body's immunological function
Drop enzyme drug	Diphenyl dimethyl bicarboxylate	Induce activation of cytochrome P450 enzyme, strengthen the detoxification capability to carbon tetrachloride and carcinogens
Vitamins and coenzymes	Vitamin B compound and coenzyme A	Promote energy metabolism, maintain normal metabolism activity of the various enzymes
Biological agent	Hepatocyte growth factor	Promote the regeneration of liver tissue
Chinese herbal medicine		Unknown

should be controlled strictly. With the treatment of hepatic protectants, albumin and plasma should be applied strictly in accordance with the indications.

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