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Peri-Operative Care of Patients with Hepatocellular Carcinoma Undergoing Hepatectomy

Key Words
Hepatocellular carcinoma
Major hepatectomy
Cirrhosis
Peri-operative care

Abstract
Peri-operative care of patients with hepatocellular carcinoma is critical for the survival of cirrhotic patients undergoing major hepatectomy. Peri-operative nutritional support in the form of branched-chain amino-acid-enriched solution, medium chain triglyceride, inorganic phosphate and multivitamins may be beneficial in sustaining liver function after hepatectomy. Intra-operatively, anaesthetic agents which are potentially harmful to the liver should be avoided, and haemodynamic monitoring to ensure adequate volume replacement should be made to maintain hepatic blood flow. The surgeon has to prevent unnecessary liver injury and excessive bleeding, and to exercise the technique meticulously avoiding bile leakage, haematoma and excessive rotation of the liver which may result in twisting of inflow and outflow vascular pedicles. Postoperatively, prolonged monitoring of haemodynamics is essential; the use of mechanical ventilation enables adequate administration of intravenous analgesics without respiratory depression and provides appropriate oxygenation of the liver and prevents pleural effusion. In the immediate postoperative period, continuation of parenteral nutrition would be beneficial to maintain a higher level of short half-life carrier proteins, decrease the requirement of diuretics to control ascites, induce less weight loss and reduce septic morbidity. Early resumption of enteral feeding may positively affect hepatic function and regeneration, and should be instituted as soon as the bowel function returns.

Introduction

The success of a hepatectomy in patients with hepatocellular carcinoma (HCC) depends not only on the ability of the surgeon to perform a flawless operation but also on perfect peri-operative care. This is particularly crucial in patients with chronic liver diseases, which are present in about 80% of resectable HCCs in Asia. In the majority of cases, patients with chronic liver diseases chosen for hepatectomy do not have decompensated liver function,

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but resection of a part of functioning liver parenchyma together with the tumour and intra-operative injury to the liver remnant may tip the balance to the decompensated stage leading eventually to hepatic coma and death.

Pre-Operative Assessment

Similar to any major operation, screening of haematological, biochemical, renal, pulmonary and cardiac functions is essential. Liver function is assessed by Child's grading [1]. Only patients with Child's A liver function should be selected for major hepatectomy, since patients with Child's B liver function tolerate major hepatectomy poorly [2]. However, even in patients with Child's A liver function, hospital mortality for major hepatectomy was 17% [2]. A more refined measurement of liver function, the indocyanine green clearance test, was shown to be the only factor that can predict hospital mortality using multivariate analysis of all biochemical parameters [3]. By discriminant analysis of the data of our recent series, indocyanine green retention of 14% at 15 min is the cutoff line that could confidently separate patients with or without poor outcome following major hepatectomy. Another selection criterion is the volume of remnant liver measured by computed tomography. Using a combination of both parameters with the patient's age, safe limits for hepatectomy can be assessed pre-operatively [4].

Pre-Operative Preparation

Preparation of blood, platelet concentrates and fresh-frozen plasma is essential for intra- or postoperative use. The average blood loss for major hepatectomy is about 1–2 litres [5]. To avoid exogenous blood transfusion, autologous blood donation of 1–2 U 1–2 weeks before operation should be encouraged if the operation is not very urgent.

Although major hepatectomy could be performed in cirrhotic patients with exceptional low mortality rate [6] in general the mortality rate in reported series is very high (26–50%) [7–10]. This is because hepatectomy is a major operation that can induce severe catabolic response, increased proteolysis and depression of immunocompetence, and the cirrhotic patients are hypercatabolic [11, 12], malnourished and immunocomprised [13]. Since intensive nutritional support can reduce the net catabolic response to surgery [14], improve protein synthesis which is critical for maintaining muscular, respiratory, metabolic and immunological function and stimulate liver regeneration [15, 16], it is logical to implement peri-operative nutritional support to cirrhotic patients undergoing major hepatectomy. The formula we favour is as follows:

Line A
Branched-chain amino acid (BCAA) solution 1,000 ml Q 24 h

Line B
D50 500 ml Q 16 h
Lipid emulsion 20% (with 50% medium chain triglycerides, MCT) 250 ml Q 8 h

BCAA-enriched solution is employed because it is anticatabolic [17], and it promotes hepatic, muscle and plasma protein synthesis in patients with chronic liver disease [18, 19] and accelerates liver regeneration in animals [20]. It is also useful in providing energy to the liver and peripheral tissues [21], especially in the immediate post-operative period when the liver function is abnormal and the patient is not feeding orally.

Lipid emulsion is also chosen as an energy source because cirrhotic patients often have glucose intolerance and insulin resistance [22]. However, the usual preparation of lipid emulsion is composed of long-chain triglycerides which are not suitable for cirrhotic patients who have impaired synthesis of apoprotein CII [23], albumin, hepatic triglyceride lipase [24] and carnitine [25]. MCT, which have a reduced dependence on albumin and apoprotein CII for breakdown [26] and carnitine for intracellular metabolism [27] is more appropriate in this situation. Moreover, MCT is readily oxidized by all body tissues and little is deposited in the liver [27].

Multivitamins and trace minerals are added to the dextrose solution and lipid emulsion accordingly. A period of 7 days of pre-operative nutritional therapy may be adequate and can be given while the patients undergo pre-operative assessment; accordingly, operation is not unduly delayed and tumour growth is not stimulated. In patients who are not malnourished, the administration can be given in the evening and during the night so that the patients are fully ambulatory during the daytime and the lack of oral intake during pre-operative investigations can be compensated. The formula of nutritional therapy is then modified as follows:

Line A
BCAA-enriched solution 500 ml Q 12 h

Line B
D30 500 ml Q 6 h
Lipid emulsion 20% (with 50% MCT) 250 ml Q 6 h

The parenteral nutrition fluid should be given via Broviac catheter; thus catheter sepsis can be avoided and the catheter can be used in the postoperative period.

Bowel preparation is necessary especially for a large tumour in the right lobe. In case the hepatic flexure of the colon is invaded by the tumour, en bloc resection of the liver tumour with the colon can be carried out without fear of bacterial contamination. In addition, in case liver insufficiency develops after hepatectomy, the bacterial load will be low and the chance of hepatic encephalopathy reduced. It should be noted that the gut permeability of cirrhotic patients to bacteria, fungi and endotoxin is increased and therefore the chance of postoperative sepsis is increased [28]. Bowel preparation is conveniently achieved by giving Golytely the day before operation. Lactulose should be avoided as it may lead to gaseous distension of the bowel making the operation difficult [28].

Antibiotic cover is by broad-spectrum cephalosporin. Premedication in the form of sedative (benzodiazepam) or opioid (pethidine) can be given in patients with normal liver function. These drugs should be avoided in patients with impaired liver function since excessive sedation may occur even with a small dose.

Table 1. Anaesthetic implications of patients with cirrhosis

1	Abnormal pharmacokinetics: distribution, protein binding and elimination
2	Encephalopathy, increased susceptibility to CNS depressants
3	Coagulopathy
4	Portal hypertension: oesophageal varices and hypersplenism
5	Mechanical effect of ascites on respiration, gastric content regurgitation
6	Circulatory: peripheral vasodilatation, increased cardiac output, decreased catecholamine response
7	Metabolic: hypoglycaemia
8	Transmission of viral hepatitis

Intra-Operative Care

Special consideration should be given to patients with metabolic derangement (table 1). For hepatectomy, the inhalational anaesthetic nitrous oxide and volatile anaesthetics supplemented with systemic opioid, endotracheal intubation and mechanical ventilation together with administration of muscle relaxants are employed. Regional techniques are not favoured as peri-operative coagulopathy may occur. The volatile anaesthetic agent of choice is isoflurane or enflurane because hepatic perfusion and oxygenation is better preserved and these drugs are not associated with hepatotoxicity. Halothane should be avoided because it causes more depression of hepatic perfusion and oxygenation at equipotent dose, and it is associated with a rare but lethal complication of postoperative hepatitis [29]. The muscle relaxant of choice in hepatectomy is atracurium because its elimination is independent of liver and renal function. Muscle relaxant is given by using a syringe pump so that adequate and constant muscle relaxation can be provided throughout the surgical procedure.

Adequate monitoring of blood loss, haemodynamics, urine output and fluid balance is of crucial importance during hepatectomy. Continuous measurement of blood pressure and central venous pressure via arterial cannula and central venous line is mandatory. When massive haemorrhage is anticipated and in patients with impaired left ventricular function, insertion of a Swan-Ganz catheter to measure left-sided heart filling pressure is necessary because left atrial pressure may be 6–9 mm Hg lower than central venous pressure [28]. Patients with hepatic dysfunction are associated with peripheral vasodilatation and are less responsive to pressor action of catecholamines. In addition, there is increased shunting of blood to skin, muscle and splanchnic beds, and away from the heart and kidneys, which therefore receive a lower percentage of the elevated cardiac output [28]. Hence, adequate replacement of the circulatory volume is important to maintain vital organ perfusion. However, overperfusion may result in elevated central venous pressure and engorgement of hepatic veins leading to severe haemorrhage during parenchymal transection. Careful adjustment is therefore necessary.

Blood loss can be compensated by colloid and electrolyte solution, and immediate blood transfusion may not be necessary unless massive bleeding occurs or when the haemoglobin level is less than 8 g/dl. Unnecessary blood transfusion may increase the risk of postoperative sepsis [30] and tumour recurrence [31].

It is essential to maintain an adequate blood flow to the liver during the operation. The surgeon as well as the anaesthetist share the responsibility of maintaining normal liver perfusion. Careful dissection and haemostasis are necessary to avoid massive blood loss and hypoperfusion of the liver. Excessive manipulation of the inflow

vasculature may cause spasm of the hepatic artery and should be avoided. It should be noted that a cirrhotic liver receives 50% of its blood supply from the hepatic artery which can be reduced by up to 80% during general anaesthesia [32]. Dissection of the inflow vasculature should be limited to the ipsilateral branches only. In the presence of a large tumour, rotation of the right lobe of the liver to expose the right hepatic vein is sometimes associated with twisting of the vascular inflow and outflow pedicles and depressed hepatic function [33]. The anterior approach should be employed in such instances [33]. During parenchymal transection, intermittent or continuous clamping of the portal vein and the hepatic artery is often employed to reduce bleeding. Although the manoeuvre was shown to be well tolerated even in cirrhotic livers in several studies, the patient population included in the studies were not strictly comparable. For example, in the study by Kim et al. [34] the group of patients with continuous portal inflow clamping for over 1 h shown to have better postoperative outcome had actually much better pre-operative liver function than the group of patients without portal inflow clamping. It is doubtful if intermittent portal inflow clamping is ever necessary because after control of the ipsilateral branches of the portal vein and the hepatic artery bleeding occurs only from branches of the hepatic vein. Nowadays, it is possible to perform parenchymal transection by the ultrasonic dissector without portal inflow clamping and without major bleeding. The role of portal inflow clamping is still controversial because a prospective randomized study has not been available to address this issue. We consider that portal inflow clamping can be harmful to the cirrhotic liver and should be avoided if possible.

Prostaglandin E_1 has been employed to improve liver function following liver transplantation [35]. It has a protective effect against cold or warm ischaemia. In patients with hepatectomy, it was shown to improve the function of the liver and other organs in a small series [36]. The exact value has to be confirmed in a large scale study.

After tumour resection, haemostasis of the transection surface is essential. Continuation or recurrence of bleeding will result in hypoperfusion of the liver leading to cell death which can be detrimental in cirrhotic patients. Haematomas will also act as a nidus of abscess formation which is equally detrimental as persistent bleeding. Other potential sites of bleeding include the adrenal glands, small branches of hepatic veins draining from the posterior surface of the liver into the inferior vena cava and the diaphragm, especially from the cut edge when part of the diaphragm is excised with the tumour. Bleeding from these sites requires accurate suturing; haemostatic material, fibrin glue and argon beam coagulator are unreliable.

Bile leakage is another important cause of postoperative sepsis and mortality that can be avoided if adequate care is given during the operation. It can occur from the transection plane, from the divided end of the ipsilateral branch of the hepatic duct or from bile duct injury. Bile leakage from the transection plane is usually minor and can be easily controlled by fine stitches. Bile leakage from the divided end of the hepatic duct may be due to insecure stitches, but more often it is due to thinning of the bile duct wall secondary to overzealous dissection at the liver hilum including the ipsilateral duct. To avoid injury or insecure closure of the hepatic duct, dissection of the hepatic duct at the liver hilum should be avoided. It will be identified during parenchymal transection by ultrasonic dissector. Ligation is preferred to stitching. Bile duct injury occurs especially in hepatectomy of large tumours encroaching on the liver hilum and in extended left hepatectomy. Deep stitches at the liver hilum for haemostasis should be avoided as the bile duct may be included accidentally. To identify bile leakage, methylene blue is injected into the biliary tract via a cannula inserted into the cystic duct. The application of fibrin glue would be useful for sealing of bile leakage from the transection plane but is not useful for gross bile leakage from hepatic duct injury. If the integrity of the bile duct is suspicious an operative cholangiogram should be performed.

After right hepatectomy, the left liver lobe tends to rotate into the right subphrenic cavity. This occurs especially when the left triangular ligament has been divided. Rotation of the left lobe will result in twisting of the left and middle hepatic veins leading to congestion and impaired liver function [37]. Reconstruction of the falciform ligament will prevent rotation of the left lobe.

Following hepatectomy, the right subphrenic cavity will be occupied by the hepatic flexure of the colon, the pyloric antrum and the duodenum. Mobilization of the greater omentum has been advocated to occupy the space and to provide haemostatic effect and to seal the sites of bile leakage. In contrast, a prospective randomized trial [38] demonstrated that such endeavour has shown to be ineffective in reducing the incidence of postoperative complications. Nevertheless, in obese patients omentoplasty has the advantage of occupying the space left after hepatectomy and prevents the left lobe rotating into it. One danger of omentoplasty is that the small bowels are no longer covered by the greater omentum and they may be displaced into the right subphrenic space resulting in

intestinal obstruction. To prevent such complication, proper placement of the small bowel in the infracolic compartment must be ascertained at the time of closure. Placing the patient in an anti-Trendelenburg and right-sided upward position during wound closure may be helpful.

The practice of drain placement is controversial. It varies from many drains to no drain at all. A prospective randomized trial did not demonstrate any benefit of routine drain placement [39]. In practice, in patients with minor hepatectomy, a drain is probably unnecessary. In patients with major hepatectomy, insertion of many drains may not be effective in reducing clot collection if the haemostasis has not been perfect. On the other hand, even if the haemostasis is perfect after major hepatectomy in a cirrhotic patient, the drain fluid is usually blood stained in the first 2–3 days after the operation. It is therefore appropriate to insert one drain in the cirrhotic patient. The drain is preferably a closed suction type to avoid contamination of the subphrenic cavity.

Table 2. Postoperative analgesic regimen

Patients on mechanical ventilation: intravenous morphine infusion
Initial loading: 3–15 mg in divided doses
Continuous intravenous infusion commenced at 2–3 mg/h
Subsequent adjustment by nursing staff in the intensive care unit
Spontaneously breathing patient: PCA morphine
Initial loading: increments of 1-mg morphine boluses every 5 min till patient's VQS less than 3
PCA settings (Graseby model 3300 PCA pump):
(a) Morphine concentration: 1 mg/ml normal saline
(b) Background infusion: 0.2–1.0 mg/h
(c) PCA bolus: 1.0–1.5 mg
(d) Lock-out interval: 5–8 min
(e) One-hour maximum dose: 0.1 mg/kg

Postoperative Care

For patients having major hepatectomy, admission to the intensive care unit for continuation of close monitoring of haemodynamics, oxygen saturation, vital signs, fluid balance, electrolytes and blood glucose is essential. In the intensive care unit, mechanical ventilation in the first 1 or 2 postoperative days is preferred. The purpose is to ensure adequate ventilation and oxygenation. In the immediate postoperative period the patient's vital functions may not readily recover and adequate respiratory effort may be difficult to sustain in the presence of pain and residual effect of anaesthesia. Severe postoperative pain is definitely a major contributory cause to cardiopulmonary complications. Another advantage of mechanical ventilation is that the incidence of pleural effusion which, in turn, leads to atelectasis and pneumonia can probably be reduced [40].

In the presence of mechanical ventilation, the clinician can give adequate systemic opioid analgesics to the patient without worrying about respiratory depression. Effective pain management on a routine basis can be provided by an anaesthesiologist based acute pain service [41]. Continuous intravenous infusion of morphine is the most common analgesic given in our patients (table 2). Initial loading with 3–15 mg of morphine in divided boluses followed by intravenous infusion of 2–3 mg/h is administered by the attending anaesthesiologist. The infusion rate is subsequently adjusted by nurses under the supervision of the acute pain service. Continuous intravenous infusion of morphine is replaced by the patient-controlled analgesia (PCA) [42] after the patient is weaned off the ventilator. PCA adopts the concept of analgesic customization and the patient is involved in titrating his own analgesics. In a series of 90 patients undergoing hepatectomy in our institution from January 1992 to June 1994, the mean ± SD morphine consumption over 72 h was 0.032 ± 0.016 mg/kg/h. Using the zero-to-ten verbal quantitative scale (VQS) for pain assessment, the respective mean (± SEM) VQS at rest and during cough were 2.26 ± 0.23 and 4.53 ± 0.28 during the operative day. This decreased to 0.64 ± 0.15 and 2.3 ± 0.25, respectively, on the 3rd postoperative day. Most patients cooperated well with chest physiotherapy, and early ambulation was possible.

Fluid balance is the most important aspect in the postoperative care because fluid retention secondary to impaired liver function is likely. Excessive fluid accumulation may lead to liver congestion and impaired liver function. If parenteral nutrition is to continue after hepatectomy, the electrolyte solution should be limited to no more than 500 ml normal saline/day to maintain patency of the central venous line.

Parenteral nutritional support is justified in cirrhotic patients having major hepatectomy. Our preferred formula is similar to that of the preoperative period. The volume of parenteral nutrition fluid should be limited to about 1.75 litres per day. As cirrhotic patients may not tolerate glucose well, monitoring of blood and urine glu-

cose is necessary. Excessive glucose infusion above the requirement of resting energy expenditure may actually be harmful in that the endogenous fat utilization of hepatocytes is suppressed [43]. In the critical early postoperative period, there is evidence to suggest that adenosine triphosphate synthesis in the remnant liver is mainly dependent on oxidation of fatty acids rather than glucose-derived acetyl-CoA [43]. However, hydrolysis of lipid emulsion in the form of a mixture of long chain triglyceride and MCT (the only preparation available commercially) may be slow in patients with severely impaired liver function [44]. It is therefore important to reduce the calorie load in the postoperative phase and to adjust the dosage according to the clinical condition.

In a prospective randomized trial [45], peri-operative nutritional support was shown to produce a significantly higher level of serum transferrin, serum pre-albumin and serum retinol-binding protein in the postoperative period. The postoperative morbidity was also reduced. The degree of deterioration of liver function as measured by the indocyanine green clearance test and the amount of weight loss were also less with peri-operative nutritional support. Such benefits were seen predominantly in patients having major hepatectomy and cirrhosis.

Potassium phosphate is added to the parenteral nutrition fluid. This is because hypophosphataemia is frequently observed after major hepatectomy [46]. Supply of sufficient phosphate is necessary for the production of adenosine triphosphate in liver cells.

Serum albumin levels were shown to be decreased in the immediate postoperative period. The reduction may be related to impaired hepatic synthesis or simply a dilutional effect. Albumin (salt-poor) infusion at a dosage of 25 g twice daily will rapidly normalize serum levels within 3–4 days. The prothrombin time may be increased in the initial postoperative period and is not an indication for fresh-frozen plasma infusion when there is no evidence of bleeding.

Metabolic acidosis may also occur in the immediate postoperative period [47]. Together with hypoglycaemia and impaired sensorium, it indicates hepatic failure and consequently a poor prognosis. Isolated occurrence of metabolic acidosis may be observed in patients with borderline liver function or with hypothermia secondary to prolonged operation. With adequate support and infusion of sodium bicarbonate, metabolic acidosis is usually not persistent unless hepatic failure ensues.

The haemoglobin concentration decreases in the immediate postoperative period in most patients even in the absence of bleeding. This may be due to the degradation of stored red cells from blood transfusion but is more likely to a dilutional effect when fluid, accumulating in the intestitial space during the operation, returns to the circulation. Since patients can tolerate a haemoglobin concentration down to 8 g/dl, transfusion is rarely needed. Excessive transfusion is also harmful. In addition to the disadvantages mentioned previously, blood transfusion may lead to fluid overload. Degradation of stored red cells increases the bilirubin load to the cirrhotic liver so that hyperbilirubinaemia may be more prolonged than otherwise.

Hyperbilirubinaemia is transient, but progressive hyperbilirubinaemia is an ominous sign. Persistently high serum bilirubin can be due to liver failure, haematoma collection, intra-abdominal sepsis and bile leakage [48]. Investigation should include ultrasonography, computed tomography and endoscopic retrograde cholangiopancreatography. When a haematoma is demonstrated, relaparotomy is indicated before infection and liver failure occur. Demonstration of subphrenic fluid collection necessitates percutaneous drainage. The fluid may be bile leaking from the cut surface of the liver or more likely from the bile duct. Endoscopic stenting may facilitate spontaneous healing of the biliary fistula. When endoscopic retrograde cholangiogram cannot delineate biliary obstruction and computed tomography cannot indicate any collection, the cause of hyperbilirubinaemia can only be ascribed to liver failure.

Liver failure once established is resistant to all forms of supportive treatment. Bioartificial liver [49] would be potentially useful in this situation but the technique is not yet widely available. Liver transplantation remains the only option. In Asia, such an option is hampered by the lack of donors and the fact that the majority of patients are hepatitis B surface antigen positive.

Recovery of the patient and liver function is signalled by the disappearance of paralytic ileus and reappearing appetite. Parenteral nutrition, if given, can be withdrawn on postoperative days 5–7 and oral feeding started as soon as bowel function returns. Oral feeding with BCAA-enriched solution may be beneficial. Although data about the value of postoperative enteral feeding in the form of BCAA-enriched solution are not yet available, data in patients with decompensated liver cirrhosis showed that the liver function and Karnofsky performance scale improved significantly 2 weeks after its administration [50]. Early resumption of oral intake is also advantageous as stimulation of the gut may supply a hormone profile that is useful for hepatic function and regeneration [28].

Excessive output of ascitic fluid from the drain may be observed in patients with cirrhosis. Once the fluid is not blood stained, the drain should be removed. If the volume of drain output is excessive, albumin infusion and diuretics are given before and after removal of the drain. Early postoperative nutritional support is helpful in reducing the diuretic requirement [45].

Conclusion

Peri-operative care of patients undergoing hepatectomy is complex but can be streamlined by close co-operation between anaesthesiologists, surgeons and intensive care physicians. Since hepatectomy is the only hope of cure for patients suffering from HCC, this chance should not be jeopardized by lack of peri-operative care.

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