Review Article

Postoperative management after hepatic resection

Lindsay J. Wrighton, Karen R. O'Bosky, Jukes P. Namm, Maheswari Senthil

Department of Surgery, Loma Linda University, Loma Linda, California, USA

ABSTRACT Hepatic resection has become the mainstay of treatment for both primary and certain secondary malignancies. Outcomes after hepatic resection have significantly improved with advances in surgical and anesthetic techniques and perioperative care. Metabolic and functional changes after hepatic resection are unique and cause significant challenges in management. In-depth understanding of hepatic physiology is essential to properly address the postoperative issues. Strategies implemented in the postoperative period to improve outcomes include adequate nutritional support, proper glycemic control, and interventions to reduce postoperative infectious complications among several others. This review article focuses on the major postoperative issues after hepatic resection and presents the current management.

KEY WORDS Management; postoperative; hepatic resection; liver resection

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Introduction

Outcomes after hepatic resection have significantly improved over the last few decades (1-4). Although, no single factor is solely responsible, overall advances in surgical and anesthetic techniques, better understanding of hepatic physiology and improvement in perioperative management have all been contributory. Majority of postoperative management issues after liver resection are unique and require a thorough understanding of liver metabolism and the pathophysiology of liver disease. The purpose of this review is to elaborate on specific early postoperative management issues after liver resection, examine current evidence and present the management options.

Fluid and Electrolyte management

The immediate postoperative period after hepatic resection is characterized by fluid and electrolyte imbalances that are further accentuated by derangements of liver function. Maintenance of adequate fluid balance and normal renal function is critical. Cirrhotics are prone to fluid shifts, vasodilation and resultant hypotension. In this setting, colloids rather than crystalloids should be administered to restore intravascular volume. New onset postoperative ascites frequently occurs in cirrhotic patients. Management with sodium restriction and judicious use of diuretic therapy is recommended. Paracentesis may be necessary to prevent tense ascites.

Hyperlactemia and hypophosphatemia are common derangements in patients undergoing liver resection. Gluconeogenesis carried out by the liver normally consumes 40-60% of lactate. When the liver is damaged or stressed, it produces lactate rather than metabolizing it. Watanabe, *et al*., examined the relationship between lactate and base excess with clinical outcomes in 151 hepatic resection patients. The initial arterial plasma lactate concentration was significantly higher in non-survivors than in survivors, and correlated with bilirubin levels and was an excellent independent predictor of morbidity and mortality. Due to the additive effects of lactate-containing intravenous solution, non-lactate containing solutions are recommended for postoperative use (5).

Hypophosphatemia

Hypophosphatemia is encountered in nearly all patients after major hepatic resection. The pathogenesis of hypophosphatemia after hepatic resection is poorly

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Corresponding to: Maheswari Senthil, MD. Department of Surgery, Division of Surgical Oncology, Loma Linda University, Coleman Pavilion, Room # 21112, 11175 Campus Street, Loma Linda, California, USA. Tel: 909-558-8390; Fax: 909-558-0236. Email: msenthil@llu.edu.

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understood and is generally believed to be due to increased phosphate uptake by regenerating hepatocytes. However, recent work by several investigators has suggested that excessive urinary losses mediated by phosphaturic mediators termed phosphatonins might be responsible for post-hepatic resection hypophosphatemia (6,7). Whether this reflects an increased production of phosphaturic mediators by the injured liver versus decreased clearance of a circulating mediator by the remnant liver is unclear.

Hypophosphatemia results in impaired energy metabolism, leading to cellular dysfunction in many organ systems including respiratory failure, cardiac arrhythmias, hematologic dysfunction, insulin resistance, and neuromuscular dysfunction (8,9). Standard liver resection management includes adequate replacement of phosphate with supplementation of maintenance fluids with potassium phosphate and oral/parenteral replacement. Currently, management of hypophosphatemia relies on serum phosphate measurements, which may not be an accurate measure of actual intracellular phosphate levels due to intra-extracellular shifts. Acidosis can cause a shift of intracellular phosphate to extracellular space resulting in normalization of extracellular phosphate levels. Alternatively, measurements of serum 2,3- diphosphoglycerol (DPG) and nucleotide breakdown products in the urine have been reported to be more sensitive physiologic markers of hypophosphatemia-related cellular stress. Persistently low serum 2,3-DPG levels and high nucleotide breakdown products in the urine would potentially indicate inadequate intracellular phosphate replenishment (7). Further validation studies are needed to assess the clinical utility of these measures in the management of hypophosphatemia.

In summary, hypophosphatemia after hepatic resection can lead to deleterious consequences and should be properly addressed. Universally accepted method for investigation, optimal replacement and target serum levels are lacking. Future studies that further elucidate the pathophysiology of hypophosphatemia after hepatic resection might lead to better management.

Nutrition

The post-hepatic resection period is characterized by a catabolic state, often with glucose and electrolyte imbalances as the body attempts to supply the high demand of the regenerating liver (10). Nutritional support during this critical period is of paramount importance to ensure adequate hepatic regeneration and postoperative-recovery. A perioperative nutritional plan should be devised for each individual patient based on the nutritional status and hepatic function. Non-cirrhotic patients with adequate preoperative nutritional status may not require any special intervention and should be started on early oral/enteral diet. On the other hand, patients who are either malnourished, with or without compromised liver function (cirrhosis or steatosis) and who undergo major hepatic resection will benefit from perioperative nutritional support preferably through enteral route. The benefit of early enteral nutrition has now been firmly established in a wide variety of surgical patients. Richter, *et al*. (11) evaluated five randomized controlled studies that compared enteral versus parenteral nutrition in the post-hepatic resection patients (12-16). Based on the results, the authors concluded that enteral nutrition resulted in significantly lower rate of wound infections and catheter related complications than parenteral nutrition. While there was no difference in mortality, patients receiving enteral nutrition showed better post-operative immune competence as evidenced by decreased post-operative infectious complications. Hotta, *et al*. found that supplementation with TPN had no effect on the post-operative outcomes (17). Current evidence strongly supports the use of enteral route for nutritional support unless otherwise contraindicated.

In addition to early enteral nutrition, branched chain amino acids and other immune-enhancing agents have received recent attention and deserve special mention. Liver disease results in altered amino acid metabolism characterized by low circulating levels of branched chain amino acids (leucine, isoleucine and valine), elevated circulating levels of methionine and aromatic amino acids. Results from two large randomized controlled trials have shown that branched chain amino acids (BCAA) supplementation in patients with advanced cirrhosis was associated with improved nutritional status and decreased frequency of complications of cirrhosis (18,19). Okabayashi *et al*. evaluated the impact of oral supplementation of branched chain amino acids and carbohydrates on quality of life (QOL) measures in patients undergoing hepatic resection (20). In this study QOL measures was assessed by subjective perception of functioning and physical, mental, and social well-being and were evaluated before and after surgery, up to 12 months post-operatively. The BCAA group showed steadily improving QOL measures from pre-operative measurements - this trend continued 12 months post-operatively even after supplements had been discontinued, while the control group showed no change. The authors concluded that nutritional supplementation with BCAA restored nutritional status and "whole-body kinetics" in patients following hepatic resection, with subjective improvement in post-operative quality of life. In animal studies, BCAA supplementation has been shown to promote liver regeneration after major hepatic resection (21). Ishikawa *et al*. demonstrated that short-term supplementation with BCAA was associated with higher serum erythropoietin levels in non-hepatitis patients undergoing curative hepatic resection (22). It is hypothesized that higher erythropoietin levels might be beneficial in protecting liver cells from ischemic injury. Recent randomized study in patients undergoing radiotherapy for hepatocellular carcinoma reported that BCAA supplementation might be beneficial (23). Currently there is reasonable evidence to support the use of BCAA supplementation in patients undergoing liver resection particularly in patients with chronic liver disease.

Carefully devised nutritional plan based on patient's overall clinical condition and degree of malnutrition is essential. Adequate perioperative nutritional support and institution of early enteral nutrition are crucial. Specialized nutrients such as BCAA might be beneficial in select subset of patients.

Glycemic control

Hyperglycemia induced by surgical stress causes dysregulation of liver metabolism and immune function, resulting in adverse postoperative outcomes (24,25). Strict control of blood glucose by intensive insulin therapy in surgical patients admitted to intensive care unit has been shown to reduce morbidity and mortality (26). Insulin resistance after liver resection can make adequate blood glucose control challenging. Interventions to achieve tight blood glucose control without increasing the incidence of severe hypoglycemia are being evaluated by several investigators. Okabayashi *et al*. examined the use of continuous blood glucose monitoring with closed loop insulin administration system, a type of artificial pancreas (STG-22, Nikkiso, Tokyo, Japan) in patients undergoing hepatic resection. Although the closed looped insulin administration system was reported to be safe and effective, the mean blood glucose level remained above the target range of 90-110 mg/dl (27). Fisette *et al*. evaluated the use hyperinsulinemic-normoglycemic clamp technique with 24-h preoperative carbohydrate load (intervention) or standard glucose control through insulin sliding scale treatment (control) in patients undergoing hepatic resection. The hyperinsulinemic-normoglycemic clamp technique reduced post-operative liver dysfunction, infections, and complications when compared to insulin sliding scale (28). Many different strategies have been proposed to achieve tight glucose control in hepatic resection patients. Adoption of a particular glycemic control technique requires an institution wide, standardized, multi-team approach to achieve optimal results.

Coagulopathy

Derangements in conventional markers of coagulation such as PT/INR, PTT and platelet count are common post hepatectomy and correlates with the extent of resection. Multiple studies have noted a postoperative increase in INR between postoperative day one and five and a corresponding decrease in platelet count and fibrinogen (29-32). This is thought to be due to decreased synthetic function of the remnant liver as well as hemodilution and consumption of clotting factors. Postoperative coagulopathy peaks 2-5 days post surgery.

Prolongation of PT/INR is often self-limited and usually resolves without the need for transfusion of fresh frozen plasma (FFP) in non-cirrhotics. Prophylactic administration of fresh frozen plasma to avoid postoperative bleeding has been reported by several centers. Martin *et al*. from Memorial Sloan Kettering cancer center reported their experience with prophylactic FFP transfusions for prothrombin time >16 seconds in patients undergoing major liver resection for colorectal liver metastases. In this study of 260 patients, 83 patients (32%) received FFP. One patient (0.4%) needed reoperation for postoperative bleeding. There were no major transfusion related complications (33). Although the incidence of postoperative bleeding is extremely low in this study, it is unclear if this is due to the aggressive prophylactic use of FFP or better surgical technique. Other centers have reported prophylactic use of FFP for INR above 2.0. Currently, there is no consensus regarding the criteria for prophylactic FFP transfusion after hepatic resection. Cirrhotics are at increased risk of bleeding after resection. A combination of FFP transfusions, vitamin K, octreotide and human r FVIIa may be utilized to correct coagulopathy and prevent bleeding.

Pain management

Optimal postoperative pain control is necessary for early mobilization and improved respiratory function. Postoperative pain management begins with preoperative planning and formulating a pain management plan that is tailored to an individual patient's liver function, respiratory and coagulation status, comorbidities, and extent of resection. Opioids are the mainstay of postoperative pain control. The most common opioids used are morphine, hydromorphone, and fentanyl. Side effects of opioid administration include sedation, respiratory depression, nausea, vomiting, constipation, hypotension and exacerbation of hepatic encephalopathy. Cirrhotic patients have increased bioavailability of opioids and benzodiazepines due to decreased drug metabolism in the liver resulting in drug accumulation. The size of liver resection has been correlated to the impairment of opioid metabolism, larger volume resections result in greater impairment of opioid metabolism (34). Morphine is poorly excreted in the setting of renal failure. Hydromorphone and fentanyl elimination is less affected by renal impairment (35) and serve as better alternatives in cirrhotic patients with renal dysfunction. Although opioids are frequently used in patients undergoing hepatic resection, the importance of close monitoring for drug overdose and side effects cannot be overstressed.

Epidural anesthesia is an effective pain management option and adjunct to intravenous opioids for large abdominal operations. It helps to reduce the pulmonary complications, duration of ileus and provides better pain control than opioids alone (36,37). Risks associated with epidural catheter placement include epidural hematoma, epidural abscess, and spinal cord injury. These risks are increased post hepatectomy due to alterations in coagulation profile. Postoperative coagulopathy is at its peak 2-5 days post surgery. This time frame coincides with the recommended time of removal for epidural catheters and may necessitate transfusion of fresh frozen plasma and/or platelets (32,38-40). Due to these risks, the role of single dose epidural shots has been examined. Ko *et al*. reported that the combination of single intrathecal injection of morphine combined with postoperative patient controlled analgesia (PCA) resulted in improved pain control in the early postoperative period than PCA alone (41). Epidural catheter use in hepatic resection has also been associated with greater transfusion requirement (see Page and Kooby, this issue).

There are other drugs that may be useful as adjuncts to opioid administration. Intravenous acetaminophen has recently become available in the United States. The recommended maximal dose is 2g/day in patients with hepatic impairment (35). NSAID use is generally not recommended post hepatectomy, in cirrhotic patients, or in patients with renal insufficiency due to the risks of bleeding and hepatorenal syndrome (35,42). Other non-opioid analgesics such as nefopam is widely used in European countries but is not currently FDA (Food and Drug Administration) approved for routine use in United States.

The use of local anesthetic infusions via the On-Q Pain Buster system placed in the musculofascial layer of the subcostal wound combined with PCA decreased total morphine consumption and improved pain at rest and after spirometry when compared to PCA alone in patients who underwent open hepatic resection (43). An infusion of no more than 0.25% ropivacaine or duration of infusion of less than 2 days is recommended due to increased plasma levels post hepatectomy. There are also case reports of the use of paravertebral infusion of local anesthetic with PCA. However comparative studies are needed prior to routine use of this technique (44).

There are many options available for post hepatectomy pain control. A multimodal approach specifically chosen for an individual patient is recommended and may consist of intravenous opioids, non-opioid injectables, continuous or single dose epidural anesthesia, and local anesthetic infusions with the transition to oral opioids as tolerated.

Postoperative infection

Infection after hepatic resection is a major contributor of postoperative morbidity and mortality and might be predictive of long-term outcomes (45). Risk factors predictive of postoperative infectious complications are obesity, preoperative biliary drainage, extent of hepatic resection, operative blood loss, comorbid conditions and postoperative bile leak (46-49). Shorter operating times and meticulous surgical technique to decrease operative blood loss and postoperative bile leak may help reduce the incidence of both the infectious and non-infectious complication after liver resection. Standard measures to reduce the incidence of postoperative infectious complications such as early mobilization, proper care and removal of central venous catheters and aggressive pulmonary toilet should be routine in the postoperative period. Early recognition of postoperative infection, prompt institution of broad-spectrum antibiotics and aggressive source control is of utmost importance. A recent study by Garwood et al found that delay in antibiotic therapy was associated with increased infectious mortality (49).

Among the interventions investigated to reduce the postoperative infections, synbiotic treatment has recently emerged as a promising approach. The concept of gut-mediated SIRS and end organ injury after major traumatic insult is now well established. Studies in patients undergoing liver resection have shown that disruption of gut barrier function and intestinal microbial balance can result in systemic inflammation and lead to infectious complications (50,51). Strategies such as early enteral nutrition are aimed to protect the gut-barrier function and reduce infectious complication. Synbiotic treatment helps improve intestinal microbial balance and reduce postoperative infectious complications. Pro-biotics are viable bacteria that benefit the host by improving the intestinal microbial balance and are studied for their effects on gut flora and impact on the immune system. Prebiotics are a group of non-digestive food constituents that selectively alter the growth and activity of colonic flora. Combination of pro- and prebiotics is termed the synbiotic therapy. Usami *et al*. examined the role of perioperative synbiotic treatment in patients undergoing hepatic resection. In this study, patients were randomized to receive either oral synbiotics or no synbiotics during the perioperative period. Perioperative synbiotic treatment attenuated the decrease in intestinal integrity as evidenced by decreased serum diamine oxidase levels (DAO) and reduced the rate of infectious complications (0% vs. 17.2% in the control group) (52). Sugawara et al reported similar results from a study comparing perioperative synbiotics therapy with postoperative synbiotic therapy. Overall infectious complication rate was 12.1% in the perioperative synbiotic group vs. 30% in the control group (53). Administration of synbiotics is simple and safe and can be utilized in patients undergoing major hepatic resection.

Thromboprophylaxis

The prevalence of postoperative venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolus (PE), in general surgery patients is 15-40% and is associated with significant morbidity, mortality, and increased length of hospital stay (54). Early mobilization, intermittent pneumatic compression devices and pharmacologic agents are used to prevent VTE. While pharmacologic thromboprophylaxis is widely accepted for most general surgery procedures, the fear of bleeding after major hepatectomy has limited its use (55). On the contrary, it is now evident that partial hepatectomy patients are in fact hypercoagulable. This hypercoagulability is a result of many factors including tissue trauma, decreased synthesis of factors involved in the clotting cascade by the remnant liver, blood loss, hemodilution, increased acute phase response, malignant diagnosis, prior chemotherapy, increased age, long anesthetic times, and limited postoperative mobility (26,54,55).

The reduced volume of liver not only results in reduced synthesis of procoagulants but the levels of anticoagulants: protein C, S and antithrombin decrease by more than 50%. Von Willebrand factor and factor VIII levels are increased especially in larger resections likely due to surgical trauma. Prothombotic markers sP-Selectin and thrombin-antithrombin complexes are also significantly increased post hepatectomy. Decreased anticoagulant levels combined with increased von Willebrand factor and factor VIII produce a prothrombotic milieu that persists on postoperative day 5 when most INR values have normalized (30). Thromboelastogram monitoring also demonstrates a state of postoperative hypercoagulability after living donor hepatectomy (31). VTE may occur in the presence of elevated standard measures of anticoagulation such as INR and PTT (56,57). A higher incidence of VTE has been noted in patients not receiving thromboprophylaxis the night of surgery (29). In a retrospective review of 415 patients undergoing major hepatectomy administration of pharmacologic thromboprophylaxis lowered the rate of VTE but did not increase the rate of red blood cell transfusion post hepatectomy (55). Pharmacologic thromboprophylaxis should be administered starting the day of surgery unless high risk of bleeding exists.

Conclusion

Postoperative management after hepatic resection is challenging. Complex resections are being increasingly performed in high risk and older patient population. A well-devised, customized management approach based on patient's overall condition, liver function, and nutritional status is vital to reduce postoperative complications and to achieve optimal outcomes.

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