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Critical Care Issues After Major Hepatic Surgery

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1. Introduction

Major hepatic resections have become the routine aspect of managing certain liver conditions such as primary liver malignancies and certain secondaries. Five-year survival is negligible in un-treated patients compared with around 30% in those receiving hepatic resection [1]. Patients with liver disease who require surgery are at greater risk for surgical and anesthesia related complications than those with a healthy liver [2, 3, 4]. The magnitude of the risk depends upon the type of liver disease and its severity, the surgical procedure, and the type of anesthesia.

The first few days after major hepatic surgery are critical to successful outcome of the procedure. Metabolic and functional changes after hepatic resection are unique and cause significant challenges in management. A multidisciplinary approach is required along with effective communication among all caregivers. With attentive, anticipatory care, many potential problems can be averted and new problems can be detected early and treated appropriately. Contemporary critical care management after major hepatic surgery doesn't differ from standard intensive care which includes invasive hemodynamic monitoring, mechanical ventilation, vital parameter monitoring, strict antisepsis measures, metabolic control with due attention to the glycemic control and nutritional aspect which more or less always affected in the patients with cirrhosis.

The post-operative management after hepatic surgery is greatly influenced by hemodynamic monitoring intraoperatively. Patient's intra-operative course, blood loss, requirement of blood products during surgery largely defines the outcome in post-operative period along with patient's nutritional status, liver functions and associated comorbidities. Hence close co-operation with the anesthesiologist and surgeon is necessary.

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.

2. Hepatic resections and general considerations

Through the recent surgical advances, hepatic resection could be carried out under the condition of liver cirrhosis or obstructive jaundice, but there are many complications and associated mortality in these cases. Hepatic cirrhosis limits the ability of the liver to regenerate. Fortunately, it appears that most of the advanced cirrhotic livers can tolerate even major resections, and the presence of cirrhosis should not preclude potentially curative or life-prolonging surgery [5]. Careful patient selection based on preoperative Child-Pugh score and ICG test, resections can be limited leaving behind enough liver parenchyma to avoid postoperative liver dysfunction. But such patients are more vulnerable to perioperative insults secondary to ischemia and hypoperfusion, which is reflected in perioperative morbidity and mortality [6]. The Child-Pugh clinical scoring system has been used as a reliable, validated prognostic tool for patients with chronic liver disease undergoing general or porto-caval shunt surgery and has gained widespread use in hepato-biliary surgery. It has recently been suggested that patients with scores of B or C should not receive liver resection surgery [7].

The associated cirrhosis greatly increases the risk for partial hepatectomy. In normal liver, even up to 70% of resection of liver is well tolerated. With underlying liver cirrhosis, partial hepatectomy is only offered to patients who are Pugh-Child's A and the most favorable class B patients [8]. While in Child C patients even minor hepatic surgery or even locoregional therapy can cause hepatic dysfunction. Post-operative outcome and level of post-operative care largely influenced by the underlying cirrhosis and post cirrhotic complications present at the time of surgery. Hence, even enucleation of hepatocellular carcinoma in Child C patients is a major surgery and procedure related mortality is present in one-third of patients [9].

3. Post-operative care

Variables such as severity of underlying cirrhosis, degree of debility before surgery, associated co-morbid diseases and operative complexity appear to have a significant influence on the rapidity at which patients progress through their early postoperative recovery phase.

Attributed to regenerating capacity of the liver, most of the major liver resections are well tolerated and seldom patients have significant biochemical abnormalities. Patients with compensated liver cirrhosis and its complications are more prone for intraoperative blood loss causing deterioration of organ functions and loss of reserve capacity to withstand even minor stress causing life-threatening complications. The disturbances in cardio-respiratory function should be carefully monitored in high Dependency unit. The complications are more in elderly patients. The condition of older patients can change rapidly and therapy may need to be adjusted every few hours if optimum cardio-respiratory function is to be maintained.

- Planning of intensive monitoring for high risk patients with associated co-morbidities should be done during surgery and in postoperative wards
- Diagnose and treat complications quickly
- Institute invasive monitoring and elective ventilation when required
- Continue postoperative care to increase the rate of recovery.

3.1. Immediate post operative

Initial postoperative assessment begins in operating room. Most patients with pre-operative normal liver functions and child A patients recover without any systemic effects. Such patients may not need intensive care unit and can directly be transferred to inpatient wards after an appropriate period of extremely close observation in recovery unit. Many centers usually monitor the patients in ICU for 24 hours before being transferred to inpatient setting after major liver resections.

Most of the patients are awakened in operating room after surgery, and if extubation criteria are fulfilled, the patient is extubated [10, 11]. It is advised that not all patients are candidates of early extubation and each case should be judged on its own merits. But prolonged intubation and mechanical ventilation in postoperative period associated with more pulmonary complications that further prolongs patient's recovery and increases the mortality & morbidity [12]. In addition, Mandell et al. demonstrated that immediately extubated patients experienced a shorter stay in the ICU, resulting in a significant reduction in ICU services and associated costs for extubated patients [13].

After arrival in ICU, initial vital assessment should be done. Most centers follow more or less same protocol. Fluid management is strictly based on patient's present hemodynamic conditions and blood products are administered as per the present condition requires. Input and output fluid charts are maintained with due attention to hourly urine output which should be minimum 0.5 ml/kg/min. Any renal dysfunction in the form of oliguria should be treated immediately because optimum renal function is of paramount importance as a determinant of good outcome [14].

Routine blood investigations, coagulation profile and organ specific tests are ordered. Patients still on ventilatory support, baseline arterial blood gas estimation is done at the arrival. Serum lactate level is determined as it depicts the imbalance between tissue oxygen supply and consumption, thus an indirect measure of tissue perfusion and cardiac output [15]. Postoperative aminotransferase and alanine aminotransferase and total bilirubin levels are not routinely measured after trauma-related surgery. However, in postoperative liver resection and living donor hepatectomy, these values are to be followed to ensure recovery of liver function [16]. A transient early increase in serum hepatic transaminase and alkaline phosphatase levels as a result of hepatocellular damage is common, but a persisting elevation suggests ongoing hepatic ischemia.

Hypothermia in postoperative period is prevented and core body temperature is maintained above 37°C. Hypothermia can cause vaso-constriction and coagulopathy. Core temperature

should be monitored and normothermia maintained using warmed fluids and forced warm air blankets. The abdominal drains are examined for the color and content as postoperative hemorrhage is not uncommon after major liver resections and may require re-exploration. In liver transplant setting, due to underlying coagulopathy, ongoing hemorrhage must be detected at earliest. Gross blood stained drain fluid with acute fall in hemoglobin level should alarm surgeon and patient should be re-explored at earliest.

All patients receive broad spectrum antibiotics. The choice of antibiotics is usually center dependent. In our center, we usually administer single broad spectrum antibiotic, mostly third generation cephalosporin in stable patients with Child A score. But in high risk patients, defined by Child score & nutritional status, and patients who are on ventilator support postoperatively, we prefer to use combination broad spectrum antibiotics. In presence of fever, blood culture and antibiotics sensitivity defines the course of antibiotics administered.

3.2. Monitoring of vital parameters

Monitoring the vital parameters like pulse, blood pressure, respiratory rate, ECG, oxygen saturation and the urine output and immediate intervention are instituted to prevent postoperative complications. Vital organ functioning is monitored as follow:

1. Blood pressure, temperature, pulse, respiratory rate.
2. Electrolytes, glycemic control, liver and renal functions
3. Fluid balance and urine output
4. Drain and wound status and appropriate care
5. Medication for pain relief
6. Neurological and cardiac functions
7. Good nutritional intake and bowel movement

3.2.1. Cardiac Monitoring

Central venous line, arterial blood pressure monitoring, continuous record of pulse rate and heart rate are routine standards for monitoring the patients after major hepatic surgery. Arterial blood pressure monitoring accurately measures blood pressure even in presence of hypotension and hypovolemia. In addition, repeated blood sampling can be obtained for routine laboratory investigations and arterial blood gas monitoring. Patients are usually tachycardic postoperatively. But heart rate >100/min should be thoroughly checked for ongoing insults such as persistent hypovolemia, pain, ongoing hemorrhage (drain fluid & falling HB level are indicators) or cardiac arrhythmias. Sinus tachycardia is common after major surgery and should revert without any complications. If tachycardia increases, persistent infection, hypovolemia, pain or presence of cardiac arrhythmia are detected and treated promptly.

At least two large-bore intravenous cannulas are inserted. Although rapid infusion devices are seldom needed, they are available and primed in the ICU at all times. Pulmonary artery

catheterization is reserved for patients with known preoperative left-ventricular dysfunction. This allows continuous measurement of cardiac output and instantaneous calculation of systemic vascular resistance. Real-time ECG monitoring is carried out routinely on most critically ill patients. Changes in rate, rhythm, and character can be identified rapidly by physicians and nurses and acted on immediately.

Monitoring of central venous pressure (CVP) is an important aspect in patients after major liver resections. Measurement of CVP acts as guide for fluid management and hemodynamic manipulation. Liver resections usually carried out under low CVP, usually between 2-5 mm of Hg, to prevent blood loss. This especially an important strategy in patients with underlying liver cirrhosis with child score B & C. CVP is usually kept in same range after surgery and excess fluid administration is restricted. If patient is normotensive and urine output is adequate (>0.5 mL/kg/hr), any attempt to administer extra fluid to elevate CVP is avoided especially in first 48 hours. But after major liver resection, a hyperdynamic state with increased cardiac index and augmented splanchnic blood flow persists for at least 3 days postoperatively [17]. This increased blood supply to the residual liver parenchyma ensures rapid growth.

Signs and symptoms of the heart failure can easily be overlooked as they mimic those of cirrhosis and liver failure. Transthoracic echocardiography is a useful modality in such patients which can measure right ventricular systolic pressure and also shows the cardiac changes.

3.2.2. Pulmonary monitoring

Pulmonary functions are assessed by continuous pulse oximetry, intermittent arterial blood gas analysis, respiratory rate and if patient is on ventilator support, patients are observed via end-tidal carbon dioxide monitoring in addition to the standard ventilatory monitoring and alarm systems.

The course of extubated patients is fairly predictable and most of them recover without any complications. However, after major resections pulmonary complications such as pleural effusion, right sub-diaphragmatic collection causing right lung collapse and pulmonary edema are frequent. These complications range from 50% to over 80% according to literature [18, 19]. Atelectasis is most common amongst these. Atelectasis can be reduced by early mobilization, aggressive chest physiotherapy, adequate pain control and incentive spirometry. Extubated patients should be given chest physiotherapy and incentive spirometry exercises as early as 8 hours post operatively. This will help the expansion of lung and prevent accumulation of the secretions causing atelectasis. Nebulisation with saline with or without anti-cholinergics is given daily 2-3 times and continued till patients are ambulatory.

If the patient is admitted to the ICU while intubated after reversal of the paralytic agents, the ventilatory settings are adjusted according to the patient's respiratory status and arterial blood gases. Patients with good cough and gag reflex, respiratory rate <30 breaths per minute, tidal volume >5 ml/kg and arterial $PO_2 >70$ mmHg can be extubated. But in presence of pulmonary complications (described later), in very ill, malnourished patients weaning is not possible and may require prolonged ventilation. Metabolic abnormalities such as hypophosphatemia, hypomagnesemia, hypocalcemia and hypokalemia may lead

to respiratory muscle dysfunction and inability to wean from ventilator [20]. Such patients in whom prolonged mechanical ventilation is needed for more than 1 week, tracheostomy should be considered to clear airway secretions and reduce the resistance that accompanies the use of standard long endotracheal tubes.

Extubated patients with postoperative hypoxemia are benefited by continuous positive airway pressure (CPAP) that increases the lung expansion and improves fair gas exchange across alveolar capillary membrane. Appropriate analgesia is essential to prevent pulmonary complications, but oversedation needs to be carefully avoided. In absence of coagulopathy and other contraindications, epidural analgesia should be considered and it has been shown to reduce the pulmonary complications [21]. Deep vein thrombosis prophylaxis is strongly encouraged after major liver surgery to prevent any thromboembolic complications.

However, in absence of complications in relatively stable postoperative patients, recovery is smooth and extubation is possible within 12 hours.

3.2.3. Renal function monitoring

Maintenance of effective renal function is a critical factor after major hepatic surgery including liver transplantation [22]. 3% of patients experience permanent and 10% transient renal dysfunction following major liver surgery [23]. Hence every attempt must be made to prevent and control renal failure in perioperative period.

Renal autoregulation effectively ceases below renal perfusion pressures of 70 mmHg to 75 mmHg, below which flow becomes pressure dependent. In cirrhotic patients, the concomitant sympathetic activation results in a rightward shift of the autoregulation curve; thus these patients have even less tolerance of reductions in renal perfusion pressure [24]. Adequate fluid management is imperative for both adequate renal perfusion pressure and flow throughout the entire post-operative period to prevent renal impairment.

Hourly monitoring of urine output and laboratory values such as blood urea and serum creatinine are good measures of adequate renal functioning. Urine output is monitored with an indwelling catheter and urine output is maintained at more than 1-2 ml/kg. Any decrease in urinary output should be assessed for the intravascular volume and hypovolemia if any should be corrected.

In presence of normal blood pressure and satisfactory intravascular volume, diuretics are used to improve the urine output. 1 to 2 mg/kg furosemide is given intravenously as bolus followed by a furosemide infusion of 0.2-0.4 mg/kg/hr titrated to maintain adequate urine flow. Continuous infusion results in increased urine output without much alteration in volume status often seen with intermittent bolus therapy.

Intraoperative hemodynamic instability and clamping of major vessels during major liver resections are the main causes of postoperative renal failure. Intraoperative blood loss can lead to renal perfusion problems leading to acute tubular necrosis (ATN) especially in cirrhotic patients with marginal renal functions from the outset. Drug induced nephrotoxicity is another cause of post-operative renal insufficiency.

Renal insufficiency, probably the most ominous perioperative complication in patients with liver disease, is usually a predictor of markedly reduced survival and a sign that hepatorenal syndrome may have developed.

3.2.4. Neurological assessment

Postoperative drowsiness and confusion are commonly caused by neuraxial or systemic opioid administration, which responds to simple changes in administration. However, these patients should be carefully assessed for more serious pathology. Most of the patients show normal neurological recovery. The patients who are extubated immediately after surgery, neurological recovery is complete and not associated with any morbidity. The intubated patients who require mechanical ventilation are usually sedated and neurological assessment in such patients is difficult and usually misleading.

Assessment of the patient's neurological status is done by Glasgow coma scale (GCS) scoring system that records the conscious state of the patient. Patients with GCS score 12 or more are fully conscious and if with endotracheal tube, can be extubated if other pulmonary criteria for extubation are met. Mechanically ventilated patients with sedation and under effect of paralyzing drugs are difficult to assess neurologically and assessment should be performed after wearing off effects of these drugs.

In patients undergoing liver transplantation, the marginal metabolism of anesthetic agents can cause delayed emergence from surgery, as well as residual hepatic encephalopathy [9]. Many patients usually resolve without any neurological aftereffects after major hepatic resections, but prolonged ICU stay due to postoperative complications can result in neurological dysfunction that range from anxiety, depression and sleep deprivation to frank hallucinations and delusional states. ICU psychosis is not uncommon. Patients developing postoperative hepatic dysfunction may develop hepatic encephalopathy which reflects a spectrum of neuropsychiatric abnormalities seen in patients with altered liver functions after exclusion of other known central nervous system disorders [25]. Drugs such as narcotics and sedatives should be avoided in patients with postoperative impairment of liver functions and used cautiously with underlying liver cirrhosis as they may cause prolonged depression of consciousness and precipitate hepatic encephalopathy [4]. Encephalopathy must be considered in a patient with deteriorating liver function and unexplained neurological symptoms. Measurement of blood ammonia may be useful if the diagnosis is unclear. Encephalopathy is treated with cardio-respiratory optimization, further lactulose and may require invasive ventilation.

3.3. Fluid and electrolyte management

Optimizing perioperative fluid management is essential in reducing the risk of postoperative complications and mortality as the cirrhotic patients tend to have limited physiologic reserve. Adequate fluid administration may reduce the stress response to surgical trauma and support recovery [26].

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. 50% of patients will also develop significant but self-limiting ascites during the first 48 h, which can cause hypovolemia. Management with sodium restriction and judicious use of diuretic therapy is recommended. Paracentesis may be necessary to prevent tense ascites [27].

At present, no widely accepted recommendations are available for the optimal peri-operative fluid regimen to be used in major non-thoracic surgery. The exact balance of fluid transfusion will be determined by the size of resection, plasma electrolytes and glucose measurements, and volaemic status of the patient. In liver transplantation, fluid overload has been shown to be a predictor of poor graft function and increased postoperative morbidity [28]. In liver resection it has been shown repeatedly that keeping the CVP low results in reduced blood loss and blood transfusion requirements [29-33].

Crystalloids mainly, 0.9% saline and lactated ringer, usually are used postoperatively as replacement and maintenance fluid. Colloids act as plasma expander and can be added as maintenance fluid, but should not be used as resuscitation fluid in case of shock.

Electrolyte abnormalities are common after major hepatic resections, especially beyond Child A patients. Hyponatremia is often seen in patients with cirrhosis and ascites. However, asymptomatic patients treated with normal saline and serum sodium is monitored. Sodium deficit is corrected gradually. In symptomatic patients, a goal increase of sodium with 1.5-2 mEq/L/hr for 3-4 hours until symptoms resolve appears to be safe. But it should not exceed 10 mEq/L in first 24 hours [34]. Rapid correction in any patients is avoided as it may result in central pontine myelinosis.

Hyperlactemia and hypophosphatemia are common derangements in patients undergoing liver resection. Due to the additive effects of lactate-containing intravenous solution, non-lactate containing solutions are recommended for postoperative use [35]. Hypophosphatemia is encountered in nearly all patients after major hepatic resection is believed to be due to increased phosphate uptake by regenerating hepatocytes. It may cause impaired energy metabolism in many organs and may lead to respiratory failure, cardiac arrhythmias, hematologic dysfunction, insulin resistance, and neuromuscular dysfunction [36, 37]. Standard liver resection management includes adequate replacement of phosphate with supplementation of maintenance fluids with potassium phosphate and oral/parenteral replacement.

Correction of potassium is an ongoing process after major liver resections. Patients with high urine output may have hypokalemia which should be corrected. In most cases supplementation is administered by the intravenous route, but it can also be given orally via nasogastric tube. Patients who have received multiple transfusions tend to have hyperkalemia. Before potassium correction underlying metabolic acidosis must be treated first. Severe hyperkalemia in patients with renal dysfunction or failure requires urgent treatment with pharmacological agents or early dialysis. In presence electrocardiographic changes, intrave-

nous calcium to stabilize the cardiac membrane, intravenous insulin and glucose can be given to decrease serum potassium levels. However associated hypomagnesemia should be corrected as it is commonly seen in association with hypokalemia and hypercalcemia.

3.4. Glycemic control

Strict control of blood glucose in surgical patients admitted to intensive care unit has been shown to reduce morbidity and mortality [38]. Hyperglycemia may be induced by surgical stress causing dysregulation of liver metabolism and immune function, resulting in adverse postoperative outcomes [39]. Insulin therapy is particularly important and blood glucose levels are monitored serially to keep glucose levels in target range of 90-120 mg/dl. But development of insulin resistance after the liver resection makes adequate blood glucose control challenging. Some centers use insulin-sliding scale to keep blood glucose in target range, in which blood glucose levels are monitored at regular intervals and doses of insulin changed accordingly while some centers use continuous insulin infusion to control glucose levels. The doses of insulin are to be modified depending on the blood sugar levels.

Okabayashi et al. [40] examined the safety and effectiveness of closed loop insulin administration system, a type of artificial pancreas (STG-22, Nikkiso, Tokyo, Japan) in patients undergoing hepatic resection, but the mean sugar level was above the target levels 90-120 mg/dl. Hypoglycemia after insulin therapy is not uncommon. Hypoglycaemia may as well occur in postoperative due to result of impaired hepatic mobilization of glucose is in high-risk patients or large resections and may necessitate glucose infusion. Dextrose solutions are used to restore normal sugar level. If patients can take orally, or no contraindications for enteral feeding, oral or nasogastric feeding is always preferred.

3.5. Nutrition

Malnutrition is common in patients with liver disease and it may increase risk of postoperative complications after major liver surgeries [41].

The post-hepatic resection period the high demand of the regenerating liver is characterized by a catabolic state and often has glucose and electrolyte imbalances. Nutritional support during this critical period is of paramount importance to ensure adequate hepatic regeneration and postoperative-recovery. Non-cirrhotic patients with adequate preoperative nutritional status may not require any special intervention and should be started on early oral/enteral diet.

But patients who have poor nutritional intake, with or without compromised liver functions (cirrhosis or steatosis), after major liver resections the short-term outcome in such patients may be improved with the use of supplemental enteral nutrition. This may as well improve the child class of patients and reduce the mortality in patients with cirrhosis and malnutrition. If oral feeding can be tolerated, enteral feeding is always preferred over parenteral as it also maintains the intestinal integrity.

Richter, et al. [42] evaluated five randomized controlled studies that compared enteral versus parenteral nutrition in the post-hepatic resection patients [43-45] and concluded that the

postoperative complications were significantly low in patients with enteral feeding. In addition, supplementation of branched chain amino acids has got immunomodulating role. Liver disease alters the metabolism of amino acids resulting in low levels of branched chain amino acids such as leucine, isoleucine and valine. Branched chain amino acids (BCAA) supplementation in patients with advanced cirrhosis is associated with improved nutritional status and decreased frequency of complications of cirrhosis. Okabayashi et al. showed improved quality of life in patients supplemented with BCAA after they underwent major hepatic resections [46]. Ishikawa et al. demonstrated increased levels of erythropoietin after short term supplementation with BCAA in non-hepatitis patients undergoing curative resection [47]. Erythropoietin has got protective effects on liver cells from ischemic injury.

Thus, adequate perioperative nutritional support and institution of early enteral nutrition are crucial. Protein restriction is advised only in presence of neurological complications like encephalopathy.

3.6. Correction of coagulopathy

Derangements in conventional markers of coagulation such as prothrombin time/ international ratio (PT/INR), partial thromboplastin time (PTT) and platelet count are common post hepatectomy and correlates with the extent of resection. Postoperative coagulopathy peaks 2-5 days post surgery. Decreased synthetic functions of the liver remnant and consumption of coagulation factors postoperatively can cause increase in INR postoperatively between 1 to 5 days with corresponding decrease in platelets and fibrinogen [48, 49].

Prolongation of PT/INR is often self-limited and usually resolves without the need for transfusion of fresh frozen plasma (FFP) in non-cirrhotics. In patients with cirrhosis, decreased hepatic protein synthesis contributes to a prolonged prothrombin time and partial thromboplastin time, both of which are prolonged usually in direct proportion to the impairment of hepatic reserve. Administration of fresh frozen plasma provides all necessary clotting factors and can correct underlying coagulopathy.

Patients having preoperative obstructive jaundice should receive vitamin K injection both before and after surgery. Sometimes determination of the precise cause of coagulopathy may be difficult in some patients with advanced liver disease, both vitamin K and fresh frozen plasma given together in such patients. In case of postoperative drop in hemoglobin and hematocrit, fresh whole blood transfusion is ideal replacement. A platelet count of 50,000/ μ l is acceptable. Administration of platelets in the absence of bleeding often results in platelet antibodies, even if type-specific platelets are used. Thrombocytopenia should be treated with platelet transfusion only if platelet count is less than 10,000/ μ l or between 10,000-30,000/ μ l in presence of active bleeding.

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.

4. Pain management

Postoperative pain following liver surgery is significant, and adequate analgesia remains a challenge for the caregivers. It helps in early mobilization, improves respiratory functions, permits smooth extubation and decreases systemic blood pressure [50]. Opioids are mainstay of postoperative pain management, morphine and fentanyl being most commonly used analgesics. However, opioids can certainly cause sedation, respiratory depression and exacerbation of hepatic encephalopathy. Due to decreased metabolism of opioids in cirrhotic patients, the bioavailability of these drugs is increased. Size of liver resection has been correlated with impaired opioid metabolism, larger volume resections result in greater impairment of opioid metabolism [51]. Hence, patients should be closely monitored for any signs of respiratory depression. In presence of renal dysfunction, fentanyl is better choice as it is less affected by renal impairment [52].

Epidural analgesia has emerged as an important pain management option in major surgeries and with adjunct to intravenous analgesics provides better pain control & less sedation. But many patients presenting for hepatic surgery have a coagulopathy or thrombocytopenia that makes them ineligible for an epidural or intrathecal therapy. The prolonged prothrombin time potentially predisposes these patients to spinal hematoma and cord compression. In our institute we use epidural analgesia only in patients with normal coagulation profile and good hepatic functions. Intrathecal morphine in doses of 0.5 mg to 0.7 mg can be used as an alternative in patients without coagulopathy. This significantly reduces systemic morphine requirements postoperatively.

Patient controlled analgesia (PCA) is newly emerged concept of self administration of analgesics in controlled doses by patient himself with a pump. This is preferred mode of administering opioids for moderate to severe pain. Randomized controlled trials have shown the effectiveness of PCA over conventional parenteral analgesia in providing better pain control and increased patient satisfaction [53].

The use of NSAIDs is not recommended post hepatectomy in cirrhotic patients and in renal insufficiency due to risk of hemorrhage and hepatorenal syndrome. However, intravenous acetaminophen can be used in doses not exceeding more than 2 g/day in patients with liver impairment [54].

5. Postoperative complications

Approximately 20% of otherwise healthy patients may experience postoperative complications after elective liver resections [6]. Postoperative complications included surgical complications (bleeding from the surgical site and bile leak), hepatic dysfunction, cardiovascular, respiratory, and renal system dysfunction, and infection. Preoperative American Society of Anesthesiologists (ASA) classification [55], presence of steatosis, extent of resection, simultaneous extrahepatic resection, and perioperative blood transfusion [56] have been found to be independent predictors for the development of postoperative complications.

5.1. Infections

Infection after hepatic resection is a major contributor of postoperative morbidity and mortality and might be predictive of long-term outcomes [57]. Obesity, preoperative biliary drainage, extent of hepatic resection, operative blood loss, comorbid conditions and postoperative bile leak are the risk factors predictive of postoperative infectious complications [58, 59]. Standard measures to reduce the incidence of postoperative infectious complications such as early mobilization, strict antiseptic measures during patient care, changing or removing the urinary catheters within 10 days, removal of central venous catheters earliest possible and aggressive chest physiotherapy should be routine in the postoperative period.

Most frequent complications are pulmonary infection and intra-abdominal infections with abscess formation. Both of these complications are well responsive to the antibiotics. Intra-abdominal collections either biloma or frank abscesses should be drained under radiologic guidance. Septic shock is rare and associated mortality is high if develops. Early recognition of postoperative infection, prompt institution of broad-spectrum antibiotics and aggressive source control is of utmost importance.

Early enteral feeding has protective role in maintaining gut mucosal barrier function. Disruption of this barrier results in translocation of intestinal organisms that is the source of postoperative infections especially in malnourished patients. Strategies such as early enteral nutrition are aimed to protect the gut-barrier function and reduce infectious complication.

5.2. Post operative hemorrhage

Less frequent complications include post-operative hemorrhage that is associated with increased mortality. Underlying coagulopathy is the main reason. Patients with cirrhosis, steatosis, and after chemotherapy are at especially increased risk of coagulopathy and bleeding. Postoperative coagulopathy is at its peak 2-5 days post surgery may act as another contributory factor. Immediate re-exploration and hemostasis is the treatment. This may necessitate the blood transfusion.

5.3. Pulmonary complications

Pulmonary complications are not uncommon after major hepatic resections. Pulmonary complications are a major cause of morbidity and mortality during the postoperative period [60]. Common pulmonary complications occurring in the postoperative period include pulmonary atelectasis, pleural effusion, pulmonary edema and pneumonia.

5.3.1. Atelectasis

Atelectasis is one of the most common postoperative pulmonary complications, particularly following abdominal and thoraco-abdominal procedures [(61). Postoperative atelectasis is usually caused by decreased compliance of lung tissue, impaired regional ventilation, retained airway secretions, and/or postoperative pain that interferes with spontaneous deep breathing and coughing [62]. After major hepatic resections right sub-diaphragmatic collec-

tions and postoperative pain are the major causes. Continuous positive airway pressure (CPAP) is beneficial to patients who develop hypoxemia and/or increased respiratory effort due to postoperative atelectasis in the setting of few secretions. Patients with abundant respiratory secretions receive frequent chest physiotherapy such as postural drainage & percussion and oral suctioning. Flexible bronchoscopy should be performed for the patients who are unresponsive to chest physiotherapy and oral suctioning.

Any accumulation in right sub-diaphragmatic space should be drained under radiologic guidance. Atelectasis can be reduced by early mobilization, incentive spirometry, aggressive chest physiotherapy and adequate postoperative analgesia.

5.3.2. Pneumonia

Pneumonia is uncommon complication but may prove life threatening. It usually tends to occur within first five postoperative days [63]. It presents with fever, leukocytosis, increased secretions, and pulmonary infiltrates on chest radiographs. Patients develop hypoxemia and eventually respiratory distress. Postoperative pneumonia should be suspected in presence of fever, leukocytosis and development of new pulmonary infiltrates on chest radiographs. Empiric antibiotic treatment must be started and tailored as per the microbiological analysis of sputum samples.

5.3.3. Pleural effusion

Pleural effusion occurs mostly on right side and related to surgical manipulation or hepatic hydrothorax. Minimal pleural effusion is common during the immediate postoperative period and disappears within few days. However, larger collections and persistent pleural effusion affecting respiratory functions must be drained.

Subphrenic abscess is a complication of surgery that may induce pleural effusions; however, the effusions associated with a subphrenic abscess are distinct from the usual postoperative pleural effusion in that they usually become apparent about 10 days after surgery and are typically associated with signs and symptoms of systemic infection [64]. Subphrenic abscess must be drained and appropriate antibiotic treatment should be started.

5.3.4. Pulmonary edema

Extravascular lung-water accumulation, indicating mild to moderate pulmonary edema following liver resection, has been reported; however, this does not appear to affect oxygenation significantly in the postoperative period [65]. Early onset may be related to transfusion-related acute lung injury or overzealous fluid administration. It is due to increased permeability across alveolar capillary membrane [66]. Other causes include sepsis and acute respiratory distress syndrome. Treatment of pulmonary edema includes fluid restriction, diuretics and continuous positive airway pressure. Most cases resolve spontaneously in a relatively short period of time with no long-term sequelae [67]

5.3.5. *Hepatic dysfunction*

Postoperative hepatic failure remains a significant challenge. Liver dysfunction is common after liver surgery and anesthesia. It can range from mild enzyme elevations to fulminant hepatic failure. The abnormalities of liver functions noted postoperatively are mostly due to surgery itself or anaesthetic agents used. Although increased serum bilirubin is common postoperatively especially in cirrhotic patients (upto 20%), jaundice is infrequent (<1%) and its presence should prompt a thorough evaluation of the cause.

Although low residual liver volume was found to be associated with postoperative liver failure, the regenerative ability of the liver is remarkable, and the residual, otherwise healthy liver is expected to double in size within the first week following the resection. Increase in hepatic parenchymal mass does not necessarily result in full restoration of functional ability. Pre-existing cirrhosis or positive virus carrier status limits liver regeneration, and these patients are more susceptible to developing postoperative hepatic failure. Liver regenerating is also reduced in diabetic patients predisposing them for the liver failure after major resections [68].

But liver dysfunction can also occur in absence of any pre-existing liver disease. The hepatocellular dysfunction may occur due to drugs including anaesthetic agents, ischemia, shock, iatrogenic injury or viral hepatitis. Known causes of cholestatic dysfunction include sepsis, prolonged blood transfusions, drugs, biliary tract injury, choledocholithiasis and total parenteral nutrition [4]. Even if abnormalities are not noted on computed tomography or ultrasonography, choangiographic studies are warranted in presence of strong suspicion of biliary obstruction.

Most cases of benign postoperative jaundice (without any obvious cause) eventually resolve spontaneously with supportive treatment only. Usually all cases of hepatic dysfunction are managed in ICU and liver functions are monitored serially along with the coagulation parameters. Hepatic failure is a life threatening complications. Presence of hepatic encephalopathy increases mortality. Increased ammonia due to underlying hepatic failure is a key element in the pathogenesis of encephalopathy. Coagulation parameters are often deranged with underlying liver failure and should be corrected with blood transfusion and fresh frozen plasma transfusion. If patient doesn't respond to the supportive medical management, liver transplantation must be considered. However, hepatic failure is rare complication after major resection and presence of underlying liver dysfunction should prompt specialized management of underlying cause to prevent progression of liver failure.

5.3.6. *Other complications*

In-hospital mortality following liver resection has been associated with perioperative myocardial infarction, sepsis with multiple organ failure and pulmonary embolism. After major abdominal surgeries, the risk of deep venous thrombosis and pulmonary embolism is 15-40% that increases the mortality, morbidity and length of hospital stay significantly [69].

Early mobilization, intermittent pneumatic compression devices and pharmacologic agents have important role in prevention of venous thromboembolism (VTE). While pharmacologic thromboprophylaxis is widely accepted for most general surgery procedures, the fear of

bleeding after major hepatectomy has limited its use. But venous thromboembolism can still occur even in presence of deranged coagulation parameters (prolonged INR & aPTT [70]. A higher incidence of VTE has been noted in patients not receiving thromboprophylaxis and should be administered starting the day of surgery unless high risk of bleeding exists.

6. Summary

The expansion of major liver surgery as a treatment option for various liver tumours has presented new challenges to surgeons and physicians in terms of the assessment and management of postoperative complications, particularly those involving hepatic insufficiency and susceptibility to infection. Understanding of hepatic pathophysiology is important for optimal perioperative care. Multiple factors contribute to increased mortality in patients with underlying liver disease. But due to advances in surgery, anesthesia and improved critical care management, there is progressive improvement in survival even in complex situations. Patient selection with evaluation of the risk factors in various liver conditions is needed. Reduction in mortality in patients with liver disease undergoing resection depends on close attention to coagulation, intravascular volume, renal function, electrolyte levels, cardiovascular status and nutrition. patient selection, appropriate monitoring, and multidisciplinary postoperative management are the key elements in improved survival among patients undergoing liver resections.

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