Immediate postoperative management and complications on the intensive care unit

ABSTRACT

The postoperative management of patients immediately after liver transplantation requires knowledge of this complex surgery and the physiology that accompanies liver failure. A multidisciplinary approach to the care of these patients is essential in order to reduce postoperative complications and preserve function in the transplanted organ. By their nature, patients undergoing liver transplantation have complicated medical problems before surgery which must be borne in mind when managing them after surgery.

Haemorrhage, haemodynamic instability, acute renal failure, hepatic artery thrombosis and primary graft non-function are some of the complications that clinicians must be prepared for in the first days after transplantation. Pre-empting complications and acting rapidly to overt them is likely to have a considerable positive impact in these patients.

INTRODUCTION

Approximately 700 adult orthotopic liver transplants in the UK are performed each year across seven specialist centres (Martin et al, 2015). Patients with liver disease have multisystem effects of their illness, which affect the postoperative course. The complexity of the operation, the recipient's physiology, the quality of the graft and the specific complications that can arise make care of the liver transplant patient uniquely challenging.

This article discusses the outcome of liver transplantation and immediate postoperative management by organ system. The most common technical and non-technical complications are presented, including diagnosis and subsequent management of these complications.

Clinical outcomes data

National audit data for adult elective first orthotopic liver transplant in the UK across all centres show 90-day patient survival is 96%, and 92.4% of surviving patients had a functioning graft. Three-year patient survival decreases to 85.5%, and 5-year survival is 79.3%. For adult superurgent first liver transplant (in patients with fulminant hepatic failure), 90-day patient survival nationally is 91.5% with 90-day graft function of 88.7%. Three year patient survival is 81.6% in this cohort, and 5-year survival is 81.2% (Martin et al, 2015).

Immediate postoperative management

Immediate postoperative management of the orthotopic liver transplant recipient requires close liaison with all the specialties involved in the transplantation process: surgeons, anaesthetists, hepatologists, radiologists, intensivists and specialist nurses. In general, the postoperative care is similar to that for major abdominal surgery, with additional focus on the management of the transplanted liver itself, on immunosuppression and on early detection of graft dysfunction or other complications. The usual model for postoperative management of the liver transplant recipient is to transfer the patient to an intensive care unit sedated,

intubated and mechanically ventilated, although there is now a trend for early extubation in theatre or soon after arrival on the intensive care unit if appropriate (Biancofiore et al, 2001).

From a cardiovascular perspective, maintenance of an adequate blood pressure is necessary to ensure optimal organ perfusion. Most patients have a high cardiac output with low systemic vascular resistance (particularly those with advanced cirrhosis), and require a vasopressor infusion (such as noradrenaline) to maintain a mean arterial pressure >65mmHg. Haemoglobin concentration is targeted at 80–100 g/litre and haematocrit at 0.26–0.32; it is important to avoid a high haematocrit to reduce the risk of thrombotic complications such as hepatic artery thrombosis (Buckels et al, 1989). Close monitoring of potassium and glucose levels is essential; patients often require supplementation of potassium in the first 36 hours after surgery. Analgesia is provided initially with a background opiate infusion, and as the majority of opioid metabolism is liver-dependent, these patients have reduced requirements compared to those undergoing major abdominal surgery (Aniskevich and Pai, 2015). Around a quarter of patients will have postoperative renal impairment, and renal replacement therapy will be required in those with a deteriorating renal function and low urine output despite adequate intravascular fluid resuscitation and renal perfusion.

During this immediate postoperative phase, particular attention is paid to the function of the new liver and patency of its blood supply. Assessment of the latter by ultrasound Doppler of liver blood vessels is recommended for all patients in the first 24 hours. Liver function tests, lactate concentration and blood coagulation are monitored closely during this time (6-hourly to begin with) – many centres use dynamic clot function tests, such as thromboelastography, to assist with this assessment. Immunosuppression is often commenced intraoperatively with methylprednisolone given during the anhepatic phase, and then prescribed postoperatively by the hepatology team. The precise immunosuppression regimen will be determined according to individual patient characteristics. Bacterial infection is common post-orthotopic liver transplant, most often with Gram-negative bacteria, and adequate antimicrobial cover with vigilance for developing infection is essential. All patients should receive gastric ulcer prophylaxis, and enteral feeding is started if the patient remains sedated and unable to eat and drink, unless there are specific surgical contraindications.

In these first postoperative days, therapies and monitoring (such as pulmonary artery catheter measurements and vasopressor support) are steadily de-escalated as dictated by the patient's needs, with the aim of achieving ward level care within 24–48 hours if there are no immediate complications.

Complications

Postoperative complications are common post-orthotopic liver transplant, with over half of all patients developing at least one significant complication. Patients with complications have a longer length of stay in the intensive care unit and a longer hospital length of stay. This affects longer term outcome: graft failure and mortality at 90 days is higher in those who have had complications. High complication rates may be the result of increasing use of marginal quality organs, increasing number of donors after circulatory death, or the increasing burden of recipient comorbidities of patients on the liver transplant waiting list.

Respiratory system

Respiratory complications have been reported in up to 87% of patients post-orthotopic liver transplant (De Gasperi et al, 2014). These include infectious (early or late lower respiratory tract infections) and non-infectious (atelectasis, pleural effusion) complications. Chest physiotherapy, deep breathing exercises and early mobilization are all important after orthotopic liver transplant to prevent basal atelectasis and development of respiratory infections.

More specific to this patient population is transfusion related lung injury in those who received blood or blood products during surgery. Other comorbidities include pulmonary hypertension (in approximately 8.5% of liver transplant patients), or hepatopulmonary syndrome (present in 10–30% of cirrhotic patients, where pulmonary vascular vasodilatation leads to pulmonary shunt), both of which can cause significant problems in orthotopic liver transplant. During reperfusion of the new liver, there is an acute rise in pulmonary artery pressure as a result of a rise in preload and cardiac output. In patients with pulmonary hypertension, the decrease in afterload is not appropriately balanced (Acosta et al, 2005), potentially leading to right ventricular dysfunction and a worse outcome.

Complications can be caused by ineffective ventilation or oxygenation. Ineffective ventilation may be secondary to upper abdominal wall incisions, ascites, or paralysis of the right hemi-diaphragm as a result of damage to the phrenic nerve during surgery or following retraction. Ineffective oxygenation may result from atelectasis, prolonged intubation, pleural effusions, massive blood transfusion, acute respiratory distress syndrome, or a combination of these.

There is a trend towards early extubation of these patients where possible (Biancofiore et al, 2001), which reduces length of time on a ventilator, reduces sedation and vasopressor use, and allows patients to start mobilizing earlier. Early extubation may not be achievable, however, and is less likely with increasing severity of liver disease, age, and complexity and duration of surgery.

Cardiovascular system

In end-stage liver disease, systemic and splanchnic arteriolar vasodilatation occurs as a response to progressive liver fibrosis and metabolic impairment, leading to a hyperdynamic, low resistance circulation (Møller and Bendtsen, 2015). Up to 50% of patients with cirrhosis will have features of cardiomyopathy associated with their cirrhosis and unrelated to alcohol consumption. This recently recognized clinical condition is often latent at rest, but evident at periods of stress. These patients display a blunted inotropic and chronotropic response to stress, such as during the reperfusion phase of orthotopic liver transplant (Rahman and Mallett, 2015). Owing to their altered circulation, patients may have high vasopressor requirements. During the perioperative phase of liver transplantation, care is taken to avoid pulmonary oedema, right heart overload and excess hepatic venous pressure. Hypotension can result from a systemic inflammatory response, hypovolaemia secondary to fluid shift or bleeding (as a result of coagulopathy, or bleeding from surgical sites).

Of note, Marik et al (2005) showed that 92% of patients who had undergone recent orthotopic liver transplant with a steroid-sparing immunosuppressive regimen had adrenal insufficiency, which may present with hypotension, while the prevalence of subclinical adrenal insufficiency in patients with acute hepatic dysfunction is 62%.

Hypertension can be a longer term complication following orthotopic liver transplant, present for a few days or weeks, or persisting for several months postoperatively. The exact cause is not clear – proposed aetiological factors include increased systemic vascular

resistance resulting from catecholamine release during the stress response, manipulation of the right adrenal gland during surgery, hypothermia, hypervolaemia, renal insufficiency, and administration of calcineurin inhibitors.

Neurological system

Neurological complications after orthotopic liver transplant affect up to a third of patients (Campagna et al, 2010). Agitation is the most common complication post-orthotopic liver transplant, and complications may be a result of a combination of factors, such as a poorly functioning graft, immunosuppressant toxicity, metabolic and electrolyte abnormalities, infections, and hypertension or hypotension. These complications can be divided into metabolic-toxic complications (e.g. confusion, hallucinations, coma, pontine myelinolysis, posterior reversible encephalopathy syndrome) and non-metabolic complications (e.g. cerebral ischaemia, intracranial haemorrhage, subarachnoid bleeding, CNS infection). In a single centre prospective study (Bernhardt et al, 2015), patients in the metabolic-toxic group had a longer hospital length of stay and those in the non-metabolic group had an increased mortality rate compared to patients with no neurological complications. Diagnosis and treatment of neurological complications will differ depending on the cause, but a high index of suspicion is required given the prevalence of complications. As a late complication, many authors, including Bronster et al (2000), describe immunosuppressant toxicity, particularly calcineurin inhibitor toxicity, potentially causing microvascular injury and endothelial dysfunction, to be a diagnosis of exclusion.

Gastrointestinal system

Post-orthotopic liver transplant biliary complications occur in up to 5–25% of cases and have an associated increase in mortality. Biliary complications include anastomotic leaks, biliary strictures, non-anastomotic strictures and biliary obstruction. Anastomotic leaks result from breakdown of the surgical connection, insufficient bile duct arterialisation, or rarely from the resection surface of a split liver or living donor liver. Biliary strictures are most commonly caused by inadequate anastomoses, while non-anastomotic strictures are thought to be secondary to ischaemic events – hepatic artery thrombosis is a risk factor. Outflow obstruction can be caused by dysfunction of the sphincter of Oddi, as a result of inflammation or bile stones or casts. Cholangiography remains the gold standard investigation for biliary complications (Memeo et al, 2015).

Renal function

Acute kidney injury post-orthotopic liver transplant is common, with one large single centre study reporting an incidence of 52% at 72 hours post-orthotopic liver transplant (as defined by the Kidney Disease Improving Global Outcomes – KDIGO – criteria, namely a rise in serum creatinine level of >50% baseline preoperative value, or increase of 26.5 μmol/litre within 48 hours from baseline, without urine output). Risk factors for acute kidney injury were identified as female sex, weight >100 kg, high Child–Pugh score, diabetes mellitus, and transfusion of blood or blood products. Patients who develop acute kidney injury have a reduced graft survival and increased mortality (Hilmi et al, 2015). About 10% of patients who develop acute kidney injury post-orthotopic liver transplant progress to end-stage renal failure (Razonable et al, 2011). The focus should be on prevention of acute kidney injury and early renal replacement therapy post-orthotopic liver transplant where required. Intraoperatively the risks can be reduced by avoiding hypotension and reducing requirements

for blood products by inducing isovolaemic haemodilution. Surgical techniques that reduce manipulation of the inferior vena cava and optimize renal blood flow reduce postoperative acute kidney injury. Avoiding hyperglycaemia and nephrotoxic drugs (e.g. aminoglycosides), and delaying the introduction of calcineurin inhibitors until 72 hours post-orthotopic liver transplant have all been suggested to reduce the risk of developing acute kidney injury.

The initiation of renal replacement therapy remains a clinical decision, with fluid overload and electrolyte derangement the most common factors prompting the commencement of renal replacement therapy. The majority of patients will regain long-term renal function following the immediate postoperative period.

Coagulation

In patients with end-stage liver disease, abnormal haematology results are common, e.g. thrombocytopaenia, coagulation factor deficiency, and fibrinolysis. Thrombocytopaenia is thought to result from a combination of bone marrow suppression, splenic sequestration and, where applicable, antiviral therapy. Coagulation factor deficiency results from the compromised capacity of the liver to synthesize proteins. Increased levels of tissue plasminogen activator in plasma and a decrease in the naturally-occurring inhibitors of plasmin result in hyperfibrinolysis in patients with end-stage liver disease.

There is a newly emerging concept that blood coagulation in these patients is rebalanced as a result of a parallel reduction of procoagulant and anticoagulant factors. Patients with end-stage liver disease can have low levels of platelets but often have high levels of von Willebrand factor, such that platelet adhesion to the subendothelium in vascular injury is likely to be preserved (Tripodi and Mannucci, 2011). Prolongation of routine coagulation tests (prothrombin ratio, international normalized ratio and activated partial thromboplastin time) are all associated with liver disease, but are poorly predictive of bleeding in these patients. These assays are insensitive to the effect of natural anticoagulants, and measure time to the first clot, whereas newer tests such as thrombin generation assays give a clearer picture of overall coagulability (Habib et al, 2014).

When assessing post-orthotopic liver transplant patients, consideration needs to be given to their bleeding and blood product use intraoperatively, and the trend of dynamic clot testing, e.g. thromboelastography. Post-orthotopic liver transplant, the risk of thrombosis (arterial, e.g. hepatic artery thrombosis, or venous, e.g. deep vein thrombosis) is high and could result in graft failure and need for urgent retransplantation. Therefore a moderate degree of bleeding is tolerated, where correction of prothrombin time and platelet count is avoided. Usual targets are to maintain haemoglobin at 8–10 g/dl and platelet count >20x109/litre. In addition, good postoperative care includes avoidance of hypothermia and targeted full anticoagulation in patients at high risk of hepatic artery thrombosis. Low or intermediate risk patients usually start a standard prophylactic anticoagulation protocol within 6 hours of orthotopic liver transplant provided there is no ongoing bleeding. High risk patients may be started on intravenous unfractionated heparin or regular treatment dose low molecular weight heparin. The rate of deep vein thrombosis and pulmonary embolism post-orthotopic liver transplant is similar to that of other major surgeries (Emuakhagbon et al, 2016).

Infection

Infectious complications are a leading cause of critical illness, morbidity and mortality after orthotopic liver transplant, with more than 50% of patients developing an infection during the first year after orthotopic liver transplant. Risk factors include prolonged surgery and hospitalization, gastrointestinal tract translocation, multiple catheter and drain insertions, and immunosuppression. This risk is reduced by standard perioperative antibacterial prophylaxis – third generation cephalosporins (e.g. cefotaxime) are preferred, although no single agent is widely recommended (Razonable et al, 2011). Early infections tend to be bacterial, although in this early period herpes simplex virus re-activation may lead to fulminant hepatic dysfunction and organ failure. Later opportunistic viral infections include cytomegalovirus, and fungal infections frequently involve Candida spp. in orthotopic liver transplant recipients (Razonable et al, 2011).

Detection of graft failure

Early graft failure is heralded by metabolic, cardiovascular and renal derangements. The reasons for failure of the graft include primary graft non-function, acute cellular rejection and ischaemia reperfusion injury. Primary graft nonfunction clinically presents as fulminant hepatic failure and coagulopathy, and may be evident before the patient has left the operating theatre or shortly after admission to intensive care. Primary graft non-function is uncommon (2–14% of orthotopic liver transplants) and requires urgent retransplantation. Risk factors include advanced age (of recipient and donor), prolonged graft ischaemia time, haemodynamic instability intraoperatively, and severe reperfusion damage. Different scoring systems for primary non-function exist in North America, Asia and Europe. For example, in the UK, the NHS Blood and Transplant Advisory Committee have set the criteria for early graft dysfunction (on days 0–7 after liver transplantation) with at least two of the following: aspartate transaminase >10 000 IU/litre, international normalized ratio >3.0, arterial lactate >3 mmol/litre, absence of bile production (Al-Freah et al, 2017).

There is some evidence that ischaemic pre- and postconditioning of the graft during surgery improves graft histology, but improvements to clinical outcomes with these techniques have not been shown (Ricca et al, 2015).

Complications of transplant

Technical

Hepatic artery thrombosis is a serious technical complication, occurring in 3% of orthotopic liver transplants, and is the most common technical complication to require retransplantation. Hepatic artery thrombosis acutely presents as fulminant hepatic ischaemic necrosis or can have a more insidious onset, usually within the first week following orthotopic liver transplant. Diagnosis is by a duplex ultrasound scan in the first instance, followed by triple-phase computed tomography or angiography. Urgent surgical exploration and assessment for re-anastomosis is the treatment of choice. Owing to the potentially devastating outcome from hepatic artery thrombosis, all patients have an ultrasound Doppler of liver vessels within 24 hours of orthotopic liver transplant. Risk factors for hepatic artery thrombosis include small vessels, ischaemic injury, multiple anastomoses or reconstruction, and a pro-thrombotic state.

Portal venous thrombosis is much rarer (<1% of orthotopic liver transplants). This presents with symptoms including raised transaminase levels, ascites, gastrointestinal

bleeding, intestinal congestion and bacterial translocation leading to systemic inflammatory response syndrome. Treatment options include thrombectomy, porto-systemic shunt insertion and retransplantation. Hepatic venous thrombosis is a very rare complication post-orthotopic liver transplant.

Non-technical

Non-technical complications of transplantation include primary graft non-function (discussed previously), and immunological complications. Characteristics of the donor associated with liver graft failure have been incorporated into a donor risk index (Feng et al, 2006) aimed at reducing these complications. Early immunological complications include hyperacute rejection and acute cellular rejection. The former, hyperacute rejection, is an antibody-mediated process caused by circulating antibodies formed at the time of transplantation. ABO incompatible grafts account for around 60% of cases. Management options such as antibody removal therapy (plasma exchange, B-cell depleting therapy), intravenous immunoglobulin administration, or surgery (splenectomy, retransplantation) can be considered. Acute cellular rejection occurs in 25–50% recipients within first 6 months post-orthotopic liver transplant, caused by sub-therapeutic immunosuppression. Management includes maintenance of optimum immunosuppression and steroids. Use of T-cell depletion therapies has been described.

Conclusions

The postoperative care of the liver transplant recipient requires an understanding of the operation and the potential impact of a patient's comorbidities. Initial care should focus on a structured system-based approach with vigilance for postoperative complications, in particular respiratory and renal impairment, as these are the most likely to occur. Assessment and preservation of the blood supply to the new graft and the function of that graft is a priority in the first hours after transplant. Awareness of
the technical and non-technical complications of liver transplant is important to ensure that when these occur, they are identified early on. As intraoperative point of care testing improves and becomes more widespread, and trends to early extubation and mobilization take hold, future orthotopic liver transplant recipients with fewer comorbidities and an uncomplicated operative course may be recovered in a postoperative critical care area rather than the intensive care unit.

Conflict of interest: none.

KEY POINTS

■Orthotopic liver transplantation is a complex procedure where close postoperative monitoring and management is essential to reduce complications and thereby improve outcomes.

■Immediate postoperative management involves the principles of good general intensive care, including preparing for extubation, chest physiotherapy, maintenance of adequate perfusion pressure, monitoring and management of electrolytes and glycaemic control, fluid balance, stress ulcer prophylaxis and antimicrobial prophylaxis.

■Optimal organ support can be achieved by taking a structured systems-based approach, where each aspect is optimized for perfusion and support of the new liver.

■Specific attention is paid to limitation of postoperative complications which include hepatic or portal vein thrombosis, primary graft non-function and complications involving immunomodulation.

■Early detection of graft failure is paramount to survival of patients. Identification involves monitoring of liver enzymes and liver function, in the form of measurement and detection of worsening coagulopathy and acidaemia, and clearance of lactate.

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