Anesthesia for Liver Transplantation

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Anesthesiologists are essential personnel in a successful liver transplant program, yet the contributions of anesthesiologists to liver transplantation are not easily found by searching the literature. There is a reason for the obscurity of these contributions: In general, anesthesiologists have not generated literature in proportion to their real contribution to the field. Every liver transplant program requires anesthesiologists, yet few liver transplant anesthesiologists conduct the kinds of studies that that have been needed for years, if not decades, to improve the care of liver transplant patients. The community of liver transplant anesthesiologists has been fairly effective in exposing our experiences, mostly at meetings. Conversely, the necessary cooperation between programs to conduct sufficiently-powered clinical research has simply not happened on the scale necessary for real progress. In November 2006, PubMed search using key words "anesthesia," "liver transplant" and "clinical study" retrieved 48 references from 1989 to the present, the vast majority from non-U.S. centers. By comparison, the same key words with "neurosurgery" substituted for "liver transplant" brought 2057 references. Though this is not necessarily a fair comparison, the numbers highlight the problem: We need an infusion of new methods for optimizing the perioperative care of liver transplant patients. For this reason, this review will focus on areas of ongoing controversy in management of liver transplant recipients, areas in which anesthesiologists have opportunities to make important contributions.

PREOPERATIVE PREPARATION

Muscle, Fat, and Bone

An important organ that is given insufficient attention in patients with liver disease is skeletal muscle. Loss of muscle mass in patients with liver disease can be extreme. Combined with encephalopathy and general sense of feeling ill, the patients are often sedentary, further exacerbating loss of muscle and bone. One study suggested that general measures of fitness were reduced by about half in pretransplant patients (1), but this study likely underestimates the degree of frailty seen in our patients today. Liver transplantation can result in considerably improved muscle mass and performance especially if combined with physical rehabilitation (1) but results vary widely (2).

The loss of muscle mass is generally attributed to increased muscle catabolism, and muscle wasting is generally associated with poor prognosis in patients with liver disease (3). Muscle loss is due to impaired protein substrate utilization in muscle, resistance to anabolic hormones, low insulin-like growth factor-1, increased cytokines such as tumor necrosis factor-α (TNF-α), complicated by poor nutrition, and physical inactivity (4). Animal models show that increased proteasome activity contributes to liver disease-associated catabolic muscle loss (5). We recently screened liver transplant candidates for blood levels of the TGF-β-family member, myostatin, probably the most potent negative regulator of muscle mass (6). We found that myostatin levels were significantly elevated in patients with liver disease compared with that in normal controls (manuscript in preparation), suggesting that this hormone may play a role in loss of muscle with liver disease. It will be of considerable interest to follow the development of myostatin inhibitor drugs (7). These drugs could potentially help improve the profound frailty seen in many patients awaiting liver transplant, especially because patients are often refused transplantation because of extreme deconditioning and muscle loss. Physical rehabilitation of patients while they await liver transplantation is underused, often limited by insurance issues.

The natural history of liver disease is classically associated with loss of body fat stores. However, modern sedentary lifestyles combined with overeating and poor nutrition have made fatty liver a common cause of liver disease in the U.S., with 2%–3% of the population meeting criteria for nonalcoholic steatohepatitis (8). Fat in the liver also complicates and worsens other liver diseases including hepatitis C (9). A recent study also suggests that *de novo* fatty liver after transplantation is not uncommon, and in this case, drug therapy with angiotensin converting enzyme inhibitors was retrospectively associated with prevention of this complication (10). This study opens the door to possible uses of ACE-I in other kinds of fatty liver, though patients with liver disease will have trouble tolerating its hypotensive effects. Currently, treatment options for fatty liver are limited. Before fatty liver becomes end-stage, patients who lose weight can also lose liver fat, inflammation, and fibrosis (11). These findings reinforce the importance of weight control after transplantation to preserve graft function. They also raise the uncomfortable question of obesity as a contraindication to liver transplantation.

Obesity is associated with wound complications after transplantation, similar to other abdominal procedures. Collectively studies linking obesity to increased posttransplant graft and patient mortality suggest decreased survival in obese recipients (12), but results vary in smaller studies from single centers. Some centers report decreased survival after liver transplantation in obese patients (13), whereas others cannot link obesity to decreased survival (14,15) despite increased length of stays in intensive care and increased morbidity (16,17). A study from a decade ago suggested that renal function is relatively impaired in obese versus non-obese liver transplant recipients (15), and this finding may still be relevant: The cumulative risk of renal failure after liver transplantation (over a 10-yr horizon) is more than 0.24 (18) and obesity has been identified as a risk factor for postliver transplant renal dysfunction (19). The transplant community clearly deals with obesity on a center by center basis. Some centers require but do not necessarily enforce weight reduction to a target body mass index (BMI) of 35 or 40 kg/m^2 before patients can be placed on the transplant waiting list. It does seem to be time for a retrospective study pooling national data on BMI and survival after liver transplantation, to make rational policy, since the obesity epidemic has progressively worsened over the last decade (http://www.cdc.gov).

Osteopenia and frank osteoporosis are distressingly common in both men and women undergoing liver transplantation, especially those with cholestatic disease. The precise cause of bone loss with cholestatic disease is not known, but most patients have some improvement in bone mass in the long-term after transplantation (20). Nonetheless, the fragility of spinal bone in particular deserves special care when moving patients, and supporting them when they are first mobilized after transplantation.

Hepatopulmonary Syndrome and Portpulmonary Hypertension

These are the yin and yang of lung disease in liver transplant recipient. Virtually all patients with severe liver disease have decreased diffusion capacity for carbon monoxide (DL_{CO}), reflecting hormonal changes in the pulmonary vasculature that increase the distance between alveoli and red cells in a dilated microcirculation (21). Only a minority of patients progress from subclinical DL_{CO} abnormalities to full-blown HPS, which can be defined as hypoxemia due to pulmonary vascular dilation in the setting of liver disease. Most patients coming to liver transplantation with hypoxemia have some element of ventilation/perfusion (V/Q) mismatch, on top of some true anatomical shunting. Because HPS is associated with decreased mortality after transplantation (22), many centers try to obtain exception points to get these patients to transplantation early. A very easy and inexpensive way to identify these patients early is to incorporate noninvasive oxygen saturation measurements in the routine pretransplant clinic visits. In our clinic, when low saturations are measured, we also ask the nurses to obtain oxygen saturations with the patients breathing 100% oxygen by face mask. Patients with inadequate responses to oxygen are quickly referred to a full evaluation by a pulmonologist or anesthesiologist to obtain oxygen saturations in supine and upright positions, and after walking, to determine the severity of HPS. This aggressiveness in making the diagnosis is based on the assumption that patients with HPS transplanted earlier, before fixed anatomic changes in the vasculature, are more likely to have reversal of the disease process after transplantation.

Anesthesiologists also can make a considerable contribution to posttransplant health by insisting on smoking cessation before transplantation, especially in patients with any evidence of obstructive lung disease. Given the negative impact of cardiovascular disease on liver transplantation, added to decreased diffusion capacity inherent in liver disease, advocacy for smoking cessation is a no-brainer. Furthermore, recent evidence suggests that smoking may contribute to the progression of fibrosis in liver disease (23).

PPH is portal hypertension in the setting of liver disease, and has been most extensively studied at the Mayo Clinic. Screening for PPH is usually done echocardiographically (24). Severe PPH can present on echo as an enlarged or dilated right ventricle, but most patients with PPH are picked up as a result of echocardiographic estimates of systolic pulmonary artery systolic pressures. This estimate is made by capturing the maximum velocity of regurgitant flow across the tricuspid valve, and incorporating this velocity into the Bernoulli equation for the pressure gradient between right ventricle and right atrium ($\triangle P = 4V^4$) (25). Usually a pulmonary artery systolic pressure of $\geq$50 mm Hg based on this calculation is considered to indicate a high risk of PPH. But good visualization of the tricuspid valve is not always possible, and the original description of this calculation (25) was also improved by clinical estimation of the jugular venous pressure, not done much these days. Consequently, it is not surprising that echocardiography and direct measurements of pulmonary artery pressures taken at catheterization do not correlate well with echo estimates in about a third of patients, and so right heart catheterization is still the gold standard for diagnosis of PPH (26). The Mayo group also recently reported that PPH and the Model for End-stage Liver Disease (MELD) do not correlate (26). Right heart dysfunction that does not reverse after treatment of PPH is considered a contraindication to liver transplantation (27) because of the stress on the right heart during surgery, especially at reperfusion. We recently transplanted a patient with PPH and RV dysfunction at the time of transplant, who survived (despite equalization of pulmonary and systemic pressures transiently at reperfusion) and has improved (though not normalized) right

heart function over the year since transplantation. Despite this patient's survival, the case points to the wisdom of waiting for normal RV function before proceeding to transplantation.

There is general agreement that patients with mean pulmonary systolic pressures <35 mm Hg are not at greatly increased risk of mortality in the perioperative period after transplantation, and so this number has become the target for preoperative treatment of PPH. The mainstay of treatment is IV epoprostenol (28), which usually means patients have a peripherally inserted central catheter (PICC) at home for therapy. Liver transplant patients have benefited by progress in treating primary pulmonary hypertension. For example, the 5 cGMP-specific phosphodiesterase inhibitor sildenafil (29) or Revatio® have been used in PPH, and can be administered in the nasogastric tube during transplantation. More recently, the mixed endothelin-A/B receptor antagonist bosentan (30) was borrowed from the primary pulmonary hypertension literature, and has been used successfully to lower pulmonary pressures in the setting of liver transplantation. Though a selective endothelin-A antagonist, atrasentan, has been developed (31), and theoretically, it makes more sense to selectively block endothelin-A for PPH, no reports of its use for PPH can be found. Perhaps its long half-life (26 h) versus the 5.4 h half-life of bosentan (32) is an issue. (An aside: Successful manipulation of endothelin signaling for experimental models of *portal* hypertension has not yet been translated.) Finally imatinib was recently reported to improve primary pulmonary hypertension (34), and we have used it with success in one post-transplant patient with severe pulmonary hypertension (manuscript in preparation).

In the operating room, inhaled nitric oxide can improve pulmonary hypertension (35), but many patients do not respond. Patients on epoprostenol are maintained on the drug during surgery. But patients with fairly well-controlled pulmonary hypertension can prove difficult to manage intraoperatively, and PPH can also appear *de novo* after liver transplantation. Donor organ quality is likely an important factor in right heart dysfunction at reperfusion, and mandates especially good communication between surgeons and anesthesiologists as donor organs become available for patients with PPH.

Coronary Artery Disease

Even patients without CAD are subject to cardiomyopathy due to severe demands on the heart with liver failure. Classically cirrhotic cardiomyopathy is characterized by decreased systolic and diastolic contractile responses to stress, and contributes to postoperative cardiac complications in patients without a history of cardiac disease (36). Many patients with liver disease have prolonged QT intervals, which can worsen with liver disease progression (37). Since chronic liver disease often takes decades to progress sufficiently to warrant transplantation, referrals for patients in their 60s and 70s are common, as is CAD in this age group. A recent study from Northwestern found that 26% of patients referred for liver transplantation there had moderate to severe CAD, confirmed by cardiac catheterization (38). Most centers use dobutamine stress echocardiography (DSE) to screen for coronary disease in liver transplant candidates. The Mayo group recently looked at perioperative troponin levels as a marker of myocardial injury during liver transplantation, and found that DSE had poor predictive power for intraoperative myocardial injury (39). DSE simply underestimates the stress of a liver transplant, and now that β-blockers are again being used by hepatologists to treat portal hypertension, many patients are not adequately stressed during the procedure. In addition to intraoperative complications, cardiac complications after liver transplantation are common (40). Anesthesiologists are often left to make the final decision about the suitability of patients with some CAD for liver transplantation; it is very common for us to see patients who clearly have some CAD but no critical lesions on catheterization. How will these patients fare after transplantation especially when given calcineurin inhibitors? This question represents yet another area where a massive retrospective review of data may help us make more rational decisions about patient candidacy.

Cardiologists at our center and elsewhere are pushing the use of single-photon emission computed tomographic (SPECT) instead of DSE (41) to diagnose ischemic cardiac disease, but we still need echocardiography for other reasons during liver transplant evaluation. For example, we need evaluation of valvular function, left ventricular outflow tract (LVOT) obstruction (42), the estimate of pulmonary artery pressure, and evaluation for patent foramen ovale or other septal defects (bubble study). The issues of aortic stenosis, LVOT and shunts are particularly important to diagnose pre-operatively since cardiologists can offer percutaneous approaches to treating these complications prior to transplantation to reduce intraoperative complications (42,43).

INTRAOPERATIVE CONTROVERSIES

Fluid Management and the Kidneys

Virtually all patients coming to liver transplantation have some degree of renal dysfunction, and many patients have extremely compromised kidneys at the time of transplantation. One reason for institution of the MELD was to capture patients with hepatorenal syndrome at a time when liver transplant had the potential to reverse renal dysfunction, before fixed anatomic changes in the renal vasculature. Hepatorenal syndrome has a grave prognosis without liver transplantation. Virtually all anesthetics reduce renal perfusion either directly or indirectly. Consequently a common scenario is that an oliguric liver transplant

patient becomes anuric after induction of anesthesia (often before filling pressures are monitored).

For decades, a mainstay of managing hepatorenal syndrome has been to assure that central venous pressure (CVP) is generous, to avoid pre-renal damage to already compromised kidneys. That approach has been recently challenged in the setting of liver transplantation, and some centers promote maintenance of low CVP as a measure to decrease blood loss (44), a carry-over practice for managing patients undergoing liver resection (45). This is a practice that simply does not work in our setting, where renal compromise is the primary anesthetic consideration. Why is there a difference between centers in this regard? In general, the successes with low CVP management are from places where the intraoperative transfusion requirements are low (<2 U red cells on average), and the patients seem less compromised in terms of renal dysfunction than those seen at our center. Patients undergoing liver resection (where the low CVP practice originated) generally do not have hepatorenal syndrome, and we have found that the unusual patient with hepatocellular carcinoma who comes to transplantation with good liver function can be managed successfully with low filling pressures. However, the average patient in our center will suffer further renal compromise unless CVP is maintained >5 mm Hg. A retrospective review of patients at two centers suggests that our experience is like that of other U.S. centers: Low CVP management was associated with decreased renal function in patients undergoing liver transplantation (46).

Anticipating incision, we also use albumin replacement before the start of surgery in patients with ascites, as is recommended for large volume paracentesis (47). If we are not giving fresh frozen plasma (FFP) before incision, albumin is given before the "total paracentesis" of incision (6–10 g/L of ascites). It seems counterintuitive to administer large amounts of albumin to patients who have PA diastolic pressures of 20 mm Hg, as is common in a supine ascitic patient, but these numbers are falsely elevated by ascites and will fall precipitously with incision and drainage. Later, fluid management is also largely dictated by surgical technique. In our center only one surgeon uses the piggyback technique to preserve caval flow (48) which is associated with significantly less hemodynamic compromise than the surgical techniques that require complete cross-clamping of the vena cava. In our experience and that of others, fluid and transfusion requirements are considerably less with the piggyback technique (49), and pressors are almost never required during the anhepatic period. With complete cross-clamping of the vena cava, pressors are required more often, which can further compromise renal perfusion. There is little to guide anesthesiologists who must use pressors during liver transplantation, but several European studies suggest that norepinephrine is a reasonable choice in patients with hepatorenal syndrome since its use is associated with reductions in renin and aldosterone (50). Probably the single most useful pharmacologic agent for hepatorenal syndrome (independent of liver transplantation) is terlipressin (51), which is not routinely available in the U.S. However, terlipressin is metabolized into vasopressin, and many anesthesiologists use vasopressin during liver transplantation to support blood pressure, and in theory, to support renal function. Despite this common practice, the efficacy (or dose) of vasopressin in perioperative protection of renal function has not been reported for liver transplant patients (but is currently under study).

Pharmacologic Management of Coagulopathy

Pharmacologic management of coagulopathy varies widely among transplant anesthesiologists, as do transfusion practices and monitoring for coagulation disturbances (52,53). It is clear that every effort should be made to limit bleeding, since massive transfusion is associated with poor outcome after liver transplantation. Our practice is to monitor platelet count, prothrombin time International Normalized Ratio (INR), fibrinogen, d-dimers, and some monitor of whole blood clotting (bedside Lee-White clotting time). Thrombelastography was made popular by the Pittsburgh group decades ago for monitoring coagulopathy and whole blood clotting, but is used by a minority of centers today (53). Some measure of whole blood clotting is important, though, since hypercoagulability in liver transplant patients is common even with severe coagulopathy.

The problem is that the reasons for hypercoagulability in liver transplant patients are myriad, and we have no easy way to measure the necessary parameters that allow a rational approach to treating both hypercoagulability and coagulopathy. Patients with autoimmune liver disease may have antiphospholipid antibodies, a small percentage of patients will present with Factor V Leiden mutations, patients with subclinical spontaneous bacterial peritonitis may have a disseminated intravascular coagulation picture, but most of the hypercoagulability in our patients has no good explanation. Furthermore, antifibrinolytic therapy may predispose liver transplant patients to complications of hypercoagulability, particularly massive pulmonary embolism, though no prospective studies support this conclusion, and the complication can occur without antifibrinolytics (54). So, how do we proceed rationally? Certainly this area deserves considerable study with the tools of molecular biology. In the meantime, caution with the use of antifibrinolytics is deserved. Our approach is to assume that a normal whole blood clotting test in the setting of a prolonged INR means the patient is hypercoagulable, and avoid antifibrinolytics in this case. If whole blood clotting is delayed, we use ε-aminocaproic acid (EACA) to improve coagulation, in addition to transfusion therapy. (FFP is infused to keep INR <2, and cryoprecipitate to

keep fibrinogen levels above 150 mg/dL.) We use EACA because of bad experiences using aprotinin (55), and because it has a short half-life compared to the similar drug, tranexamic acid. Most importantly, we use EACA because it is not a potent drug (56), it works at a defined site of action, and therefore, in theory is unlikely to cause a dramatic increase in hypercoagulability. In addition, we monitor whole blood clotting after administering EACA and after increasing the rate of infusion of the drug. Until virtuous studies comparing pharmacologic approaches to coagulopathy are performed, our community will continue to argue about optimal management of coagulopathy during transplantation. In the meantime, anesthesiologists should be aware that massive pulmonary embolism during liver transplantation does not necessarily have to be fatal. Patients sustaining this complication during transplantation have been rescued with extracorporeal membrane oxygenation (57) or with infusion of tissue plasminogen activator (58).

In summary, patients coming to liver transplantation have failure of multiple organ systems, exacerbated by extreme surgical stress. The input of anesthesiologists into preoperative management of patients is essential to limit intraoperative complications. Though anesthesiologists have been essential to the improved outcome in liver transplantation over the last two decades, there has been little optimization of therapy in the operating room for many important issues including renal protection, coagulation and transfusion management. These areas represent enormous research opportunities.

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