Chapter 35
Transplantation

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A 14-year-old female with a diagnosis of Budd–Chiari syndrome presents for liver transplantation. She has developed decreasing mental status, hyponatremia, and a reduction in urine output.

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Preoperative Evaluation

Questions

1. How would liver failure affect pulmonary function? What evaluation of pulmonary function would be helpful for this case? Would bronchodilator therapy be indicated preoperatively?

2. What cardiovascular abnormalities would you expect in this patient?

3. Is this patient exhibiting hepatic encephalopathy? Does she have raised ICP? What treatments should be given for each of these problems?

Preoperative Evaluation

Answers

1. Children with liver disease severe enough to be candidates for transplantation nearly always have abnormal pulmonary function [1–3]. Restrictive lung disease is caused by ascites in these children. In addition to the peritoneal space, there may be abnormal transudation of fluid in the pleural space. Pleural effusions will also compromise pulmonary function. Abdominal distention also decreases the functional residual capacity (FRC). These children are often malnourished, and the muscles of respiration, the diaphragm, and intercostal muscles are weakened, leading to a further decrease in the FRC. In addition to restrictive pulmonary pathophysiology, these children have other reasons for hypoxemia. The hepatopulmonary syndrome of hypoxemia and intrapulmonary shunts in these patients contributes to pulmonary morbidity. Intrapulmonary shunting of blood and impaired hypoxic pulmonary vasoconstriction lead to lower hemoglobin saturation. Pulmonary hypertension with increased pulmonary vascular resistance (PVR) can affect right ventricular performance. A small subset of patients with severe liver disease will manifest pulmonary hypertension.

2. Children with end-stage liver disease (ESLD) presenting for transplantation have significant derangements of cardiovascular function [4, 5]. These children have an increased cardiac output, increased ejection fraction, and lowered systemic vascular resistance (SVR). Peripheral vasodilatation and arteriovenous shunts account for the lower SVR. The circulating plasma volume is increased. The etiology of the hyperdynamic state of the circulatory system is unclear. Although children with liver failure generally have preserved cardiac function, those with severely advanced disease can exhibit impaired left ventricular performance. S_vO_2 is often elevated, probably due to the A–V shunts and to decreased oxygen delivery to the tissues. The RBCs in these patients are depleted of 2, 3-DPG and deliver less oxygen to the periphery. These children nearly always have a low albumin as part of ESLD. The Child–Pugh classification system includes serum albumin (along with bilirubin, prothrombin time (PT), and degree of encephalopathy) as one of the factors in determining the severity of liver insufficiency.

3. Patients with severe liver disease often have CNS changes. The cause for hepatic encephalopathy is not known, but the severity of the CNS dysfunction does parallel the severity of the liver disease. Possible causes for hepatic encephalopathy are the elevated levels of ammonia and other products of metabolism that accumulate as the liver fails, or the appearance of false neurotransmitters derived from amino acids that had not undergone degradation. The encephalopathy usually improves when appropriate therapy for the liver failure is started. Acute worsening of hepatic encephalopathy is usually an indication that the underlying liver disease has also worsened. In situations where more is demanded of the

4. What is the relationship between ESLD and impaired renal function? Is the hepatorenal syndrome present?

5. Is this patient at risk for gastrointestinal hemorrhage? Would the presence of a portosystemic shunt affect the pre-op evaluation?

6. What disorders of the hematologic system would be expected in their patient?

liver such as GI hemorrhage or increased protein intake, hepatic encephalopathy will worsen. Infections or dehydration will also worsen hepatic encephalopathy. Treatment of hepatic encephalopathy includes restriction of protein intake, enteral lactulose, and neomycin and maintenance of as normal a metabolic state as possible [6–9]. If the patient is in fulminant hepatic failure, raised ICP is likely to be present. The exact etiology of the cerebral edema is not known, but vasogenic and cytotoxic mechanisms are thought to contribute. As the cerebral edema worsens, the ICP increases and the patient becomes more and more encephalopathic. Treatment is supportive and includes the usual measures used in the treatment of raised ICP [10]. These include intubation, sedation, and ventilation to modest hypocarbia, mild hypothermia, and treatment of blood pressure to maintain adequate cerebral perfusion pressure (CPP = MAP – ICP or CVP). Placement of an intracranial pressure monitor is necessary to have an accurate measurement of ICP.

4. Patients with ESLD often also have impaired renal function, secondary to lowered GFR resulting either from dehydration or from having developed the hepatorenal syndrome. Urine sodium concentration is generally low (<10 mEq/L) in both conditions, but in patients with prerenal azotemia, urine output increases, and serum BUN and Cr levels decrease following expansion of the intravascular volume. Patients with hepatorenal syndrome have oliguria and increased BUN levels that are generally not responsive to volume administration. Affected individuals also have ascites, and overly aggressive treatment of the ascites with diuretics may play a role in the development of the syndrome. Often dialysis is needed to reverse the pathophysiologic alterations of the hepatorenal syndrome until liver transplantation, which reverses the syndrome, can be accomplished [11, 12].

5. Portal hypertension is often part of liver failure [13]. Bleeding from esophageal and gastric varices are major consequences of portal hypertension. A moderately severe episode of GI hemorrhage may tip a patient in tenuous condition into fulminant hepatic failure. Even if the bleeding is controlled, as the blood in the GI tract is metabolized and absorbed, the encephalopathy will worsen, and the episode of hypotension associated with the bleeding episode will worsen the renal ischemia, with the possible development of hepatorenal syndrome. Breakdown of liver glycogen is an important mechanism in the maintenance of normoglycemia. In liver failure, there is diminished breakdown of liver glycogen, making these patients susceptible to episodes of hypoglycemia.

6. Coagulation abnormalities are quite likely in patients with severe liver insufficiency or failure. In addition, these patients usually are anemic and thrombocytopenic. Fibrinogen, prothrombin, plasminogen, and many other coagulation factors synthesized by the liver are greatly diminished in patients with liver dysfunction/failure. Many patients with liver failure produce an abnormal fibrinogen molecule. In addition, bile salts are needed for absorption of fat-soluble vitamins

7. How should she be evaluated for metabolic abnormalities?

Intraoperative Course

Questions

1. What are the effects of liver disease on pharmacokinetics and dynamics of medications?

2. What preparations should be made with the blood bank and laboratory support for this case? How will rapid transfusion be accomplished?

that includes vitamin K, a cofactor in the production of many coagulation factors. Many interventions by anesthesiologists, such as NG tube placement, intubation, and cannulation of vessels, have the potential to cause bleeding so that correction of coagulation abnormalities often is undertaken prior to the induction of anesthesia. Treatment of the coagulopathy seen in patients with liver failure may require replacement of factors and vitamin K. If platelet dysfunction is evident, DDAVP may be needed.

7. Patients with liver failure have derangements of many serum electrolytes. Common abnormalities are hypoglycemia and hyponatremia. Elevated BUN and Cr as a result of renal dysfunction are present, and elevated levels of ammonia are thought to be responsible for the encephalopathy [12].

Intraoperative Course

Answers

1. There is a complex set of effects on the action and distribution of medications in patients with liver failure. These patients have a decreased serum albumin, which would lead to an enhanced effect of IV medications given at the usual dose on a mg/kg basis. These patients also have impaired hepatic metabolic function as well as impaired renal function. As a result of these abnormalities, the serum levels of medications will remain high for longer periods of time and will be less bound to protein. In addition, these patients may have depressed cardiovascular and pulmonary function prior to the induction of anesthesia.

2. Preparation of the OR should be for a long case in which massive blood loss is expected, temperature maintenance will be problematic, invasive hemodynamic monitoring will be needed, and many metabolic derangements will occur [14]. The OR table should be particularly well padded since these cases may last for many hours. Devices for rapid transfusion should be, at the very least, available or fully prepared. In the past, in larger patients, venovenous bypass was used, with the expectation that bowel edema and bleeding would be decreased compared with cases in which the vena cava was simply clamped. This practice is generally no longer used, however, simplifying the intraoperative management of liver transplant patients. The blood bank should be given as much notice as possible in order that the proper amounts and types of blood products are available. As a general guideline, ten units of PRBCs, ten units of FFP, and six to ten units of pooled platelets should be immediately available, with the expectation that more may be needed. Of course, these amounts should be adjusted upward or downward based upon the size and condition of the patient. Throughout the case, many ABGs, sets of electrolytes, coagulation profiles, CBCs, etc. will be sent. It may be necessary to have additional laboratory personnel to run these frequent and multiple tests.

3. Describe special consideration for monitoring and vascular access for this patient and procedure.

4. How will induction be performed? Does this patient have a full stomach? How does ascites affect the induction plan?

5. Describe the conduct of maintenance during the procedure.

3. In addition to routine monitors, temperature should be measured in more than one location. Rectal or bladder probes can be used in addition to esophageal probes. Several large IVs are needed, preferably in the upper extremities. During the anhepatic phase of the procedure, when the inferior vena cava (IVC) is clamped, lower extremity venous return will be limited to collateral veins or the venovenous bypass if it is used. Similar considerations apply to the arterial catheter. In some cases, the aorta will be clamped during the arterial anastomosis. Some centers use two arterial catheters. The direct arterial pressure tracing is unavailable during the frequent sampling, and if, because of frequent use, one arterial line fails, the second line will be available. A large, sheath-type central line is used in these cases for monitoring of central venous pressure, administration of vasoactive medications, and also administration of fluids and/or blood products. In general, pediatric patients need not be monitored with a pulmonary artery catheter. On occasions when peripheral IV access is difficult, two central lines may be used.

4. The patient should be comfortably positioned on the padded OR table prior to induction. In the induction of general anesthesia in unintubated patients, full stomach precautions should be observed. Since these patients often have pulmonary dysfunction including a diminished FRC caused by ascites and abdominal distention and hepatopulmonary syndrome, thorough preoxygenation is essential prior to induction. Regardless of the specific IV hypnotic chosen, the dose should be adjusted based on the altered pharmacodynamics previously discussed. There is no specific contraindication to the use of succinylcholine. Often a combination of a hypnotic in a lowered dose and small doses of a benzodiazepine and opioid is used with the goal of rendering the patient unconscious without significant hypotension or heart rate alterations. As in most patients, the use of succinylcholine is associated with an increase in serum potassium of 0.5–0.7 mEq/L. If the patients have significant hyperkalemia prior to induction, the increase in potassium concentration may lead to cardiac arrhythmias. On the other hand, if the patient is compromised with a very small FRC, it is likely that significant hypoxemia will occur in the time required to achieve good intubating conditions using a nondepolarizing relaxant.

5. Although no particular technique has been proven to be advantageous or deleterious to children undergoing liver transplantation, it does seem prudent to avoid high doses of inhaled agents. High doses of inhaled agents have been shown to decrease splanchnic blood flow, possibly placing the graft at risk. A combination of an infusion of relaxant and an opioid with low-dose isoflurane or sevoflurane with additional benzodiazepines will likely achieve the goals of maintenance of an anesthetized state in the patient with minimal decrease in cardiac function. Since the procedure will last at least several hours and the child will generally remain intubated for the first postoperative night, concerns about the prolonged effect of IV medication affecting emergence are not important considerations.

6. What problems are expected during the preanhepatic phase?

7. What is important for the anesthesiologist during the anhepatic phase?

8. What problems are likely to occur during reperfusion?

6. The preanhepatic phase is the time of greatest blood loss. The surgeons are working to dissect free the failed liver. There may well be adhesions from previous procedures. Of course, during this time, the patient may be hemodynamically unstable and almost certainly has a coagulopathy. With significant bleeding and the massive transfusion required to maintain hemodynamic and metabolic stability, hyperkalemia, hypocalcemia, hypothermia, and hemolysis may all occur [15]. The use of washed PRBCs or newer PRBCs will decrease the amount of potassium in each unit. Ionized calcium and serum magnesium must be checked frequently during times of rapid transfusion since the citrate in the PRBC units chelates both divalent ions. Even with the administration of warmed blood products and fluids, the child's temperature may decrease during the preanhepatic phase. The abdomen is open and evaporative losses of fluid are significant. During this part of the procedure, ABGs, coagulation profiles, and electrolyte determinations should be done as often as every 30 min depending upon the amount of bleeding, transfusion requirements, and the degree of stability or instability of vital signs. In addition to blood loss, hypotension during the dissection phase may be due to either hypocalcemia or torsion of the liver during dissection with sudden decreased venous return.

7. The anhepatic stage of the procedure begins when the old liver is removed from the circulation, not with physical removal of the liver. When the infra- and suprahepatic cavae, portal vein, and hepatic artery are clamped, the child is anhepatic. Vigorous bleeding may still continue at the beginning of the anhepatic phase. In most pediatric liver transplants, femoral-axillary bypass is not used. Children tolerate clamping the vena cava during placement of the graft. While the old liver is out and the new liver not yet in the circulation, the child may demonstrate significant hemodynamic changes. There may be decreases in systemic blood pressure, central venous pressure, and cardiac output. As the child cools, oxygen consumption decreases with a concomitant decrease in carbon dioxide production. Also, during the anhepatic phase, any contribution the failing liver was making to glucose homeostasis is eliminated. The anesthesiologist should follow serum glucose frequently during the anhepatic phase and be prepared to treat hypoglycemia.

8. Once the vascular connections are complete, circulation is allowed into the new liver. The postreperfusion syndrome will occur in a significant number of patients once this happens. This syndrome includes hypotension and bradycardia, possibly even cardiac arrest. One preventable cause is inadequate flushing of the preservative solution from the graft. This solution is hyperkalemic, acidotic, and quite cold. If the graft is not thoroughly flushed, the patient will have profound hemodynamic instability once the preservative enters the circulation. The postperfusion syndrome can occur even if the graft is completely flushed of the preservative solution, however. Treatment is resuscitation with IV fluids and vasoactive agents. In some cases, only one or two doses of epinephrine are needed to maintain hemodynamic stability, but in others infusion of inotropes is

9. What problems are expected during the neo-hepatic/biliary reconstruction phase?

Additional Questions

Questions

1. A 6-year-old s/p cardiac transplant requires inotropic support due to acute rejection.

   What would your choices be to enhance cardiac output? Are anticholinergics effective? What are the relative effects of denervation on the adrenergic and cholinergic competency of the transplanted heart? Would milrinone be effective in enhancing contractility?

needed for several hours after the graft has been open to the circulation. In addition to the postperfusion syndrome, all patients have a rapid increase in end-tidal and arterial carbon dioxide once the IVC is unclamped.

9. As the new liver is connected to the recipient's hepatic veins and artery, coagulation problems begin to diminish. Hepatic artery thrombosis is more of a problem in pediatric liver transplantation, largely due to the smaller size of the vessel. Although no specific management of coagulation in the posttransplantation period has been shown to decrease the incidence of hepatic artery thrombosis, many anesthesiologists do not aggressively pursue complete normalization of PT/PTT as the liver is connected to the circulation unless significant, diffuse bleeding is ongoing. Correction of coagulation abnormalities generally begins as the new liver is connected to the circulation. However, if the patient has hypothermia or hypocalcemia, coagulation will be affected. These patients are sent to the ICU postoperatively with plans for mechanical ventilation [16]. Even in cases where the blood loss was not great, for example, less than half a blood volume, it is prudent to delay extubation, to later in the post-op period in the PICU or POD #1. The large incision will limit the child's ability to breathe. In addition, after such an extensive procedure, it may take some time to achieve hemodynamic stability.

Additional Questions

Answers

1. Cardiac transplant recipients present several challenges to the anesthesiologist [17, 18]. Denervated hearts do not respond normally to input mediated via the autonomic nervous system. Drugs which act through stimulation of the autonomic nervous system may have little or no effect on a denervated heart. The usual bradycardic response to hypertension, mediated through the vagus nerve, occurs rarely if at all in these patients. In general, these patients do not tolerate decreased preload well.

   Pharmacologic enhancement of cardiac output is best accomplished with direct-acting agents such as epinephrine, isoproterenol, or dopamine. A drug such as ephedrine which has both direct and indirect effects in patients with innervated hearts will have only the direct effects on denervated hearts. Catecholamines such as dobutamine, dopamine, epinephrine, and norepinephrine will, via a direct effect on the myocardium, increase cardiac output. Atropine or pancuronium, two agents pediatric anesthesiologists rely upon to increase heart rate, will not be effective in cardiac transplant recipients. The alpha agonist phenylephrine, on the other hand, will increase vascular tone, but the baroreceptor response of lowered heart rate will not occur in the denervated heart. The phosphodiesterase inhibitors such as amrinone have direct effects on myocardial cells; increasing cAMP levels with resulting increased contractility. The sys-

2. An adolescent s/p heart transplant for viral cardiomyopathy 6 years ago presents to the emergency room with hypotension, J-point depression on ECG, but without angina. Please explain.

3. An adult living-related kidney is being transplanted into a 4-year-old recipient. What problems should you anticipate with unclamping? What is the most common cause of renal failure leading to kidney transplantation in children? What age is the greatest risk period for difficulty with perioperative medical management? Does anemia resolve after renal transplantation? What long-term effects should you anticipate with immunosuppression after renal transplantation, and how will it affect your subsequent anesthetic management of patients?

temic effects on preload will also occur, but baroreceptor responses to decreased preload will be absent or partially and inconsistently present in patients with denervated hearts.

2. Unexplained hypotension in a cardiac transplant recipient may very well be due to myocardial ischemia. These patients often have coronary artery disease after transplant. Rejection remains a major problem limiting survival in heart transplant recipients. The coronary arteries are affected with atherosclerosis when rejection occurs. Coronary artery vasculopathy accounts for approximately 30 % of deaths after 1 year in transplant recipients. Angina may not occur in children with coronary artery disease since their hearts are denervated. Evaluation of cardiac transplant recipients for coronary atherosclerosis (vasculopathy) has been done in the cardiac cath lab using angiography. Dobutamine stress echocardiography has been used safely in children as a screen for coronary vasculopathy. Anesthetic management of children with coronary vasculopathy undergoing surgical procedures should be similar to techniques used for adults with coronary artery disease, with particular attention paid to the balance between oxygen supply and demand. The ECG may show ST segment changes with ischemia. Depending upon the procedure, consideration should be given to placement of a CVP or TEE. Children who have had cardiac transplantation who then return to the OR for procedures present several other problems to the anesthesiologist in addition to those outlined above relating to coronary artery disease. The denervated heart will not respond to autonomic input. Medications that affect cardiac rate or contractility via indirect mechanisms will not have those effects on the denervated heart. Direct-acting drugs such as epinephrine, norepinephrine, dopamine, and isoproterenol will affect cardiac performance. Baroreceptor responses to blood pressure changes are absent. Heart rate changes in response to decreased intravascular volume occur inconsistently. In addition, slowing of the heart rate, mediated by the vagus nerve, will not occur in these patients.

3. In cases where the kidney to be transplanted is from a person substantially larger than the recipient, significant hemodynamic consequences are likely, particularly when the graft is perfused. Hypotension may result not only from the release of graft preservative solution but also from depletion of intravascular volume as the new, large graft is perfused. Prior to opening the vascular clamps, the anesthesiologist should have given a generous amount of IV fluids, enough to elevate the CVP. Graft survival is dependent on adequate perfusion. The anesthesiologist must administer additional fluid as needed and/or use inotropes such as dopamine to maintain systemic blood pressure [19]. Although there are many causes of renal failure, obstructive uropathy, renal dysplasia/hypoplasia, and primary glomerular disease are the most common causes of ESRD in pediatrics. Younger transplant recipients present greater challenges with regard to perioperative anesthetic management as well as surgical technique [20]. Although renal trans-

4. Is flumazenil effective for hepatic encephalopathy? What is lactulose, and why is it used? What is the importance of a low-protein diet in liver failure?

plantation offers the best chance for normal growth and development in children with ESRD, nearly all such patients are maintained with either peritoneal or hemodialysis for varying lengths of time prior to renal transplantation.

The anemia seen in patients with ESRD has many causes such as decreased erythropoietin production, inadequate intake of iron and folate, low-grade hemolysis, and episodes of bleeding. In many patients, the hemoglobin will remain at approximately 6–9 mg/dL. With the administration of erythropoietin, the hemoglobin can be maintained at 10–11 g/dL. Following renal transplantation, most recipients are as anemic as they were preop. Many of the medications used to prevent rejection have deleterious effects on bone marrow production of red cells. For example, calcineurin inhibitors such as cyclosporine or tacrolimus (FK506) and antimetabolites such as azathioprine have bone marrow toxicity as a side effect. As the medications are adjusted to decrease all side effects, patients' hemoglobin increases, but it is not unusual for renal transplant recipients to be treated with erythropoietin (Epo) to increase the red cell mass.

Immunosuppression treatment for recipients of renal allografts includes steroids, cyclosporine, and tacrolimus. Cyclosporine is an 11 amino acid peptide that inhibits T cell function by a variety of mechanisms, one of which is inhibition of interleukin (IL)-2 formation and action. Without IL-2, T cell activation is significantly diminished. Cyclosporine is metabolized by the cytochrome P450 system, and its metabolism is affected by coadministration of a variety of other medications. This drug has significant side effects. Neurotoxicity, manifested as tremors, paresthesias, headache, confusion, etc., hepatotoxicity, and hypertension and renal toxicity may limit the use of cyclosporine. Tacrolimus (FK506), a macrolide antibiotic similar to streptomycin, has similar immunologic effects as cyclosporine, inhibiting Il-2 and IL-2 receptor expression. Although prednisone has many deleterious side effects, it remains a part of the immunosuppression strategy used after renal transplantation. Side effects of importance include hypertension, growth failure, GI bleeding, pancreatitis, and osteoporosis. Posttransplantation lymphoproliferative disease (PTLD) is a very serious complication of immunosuppression [21]. This complication occurs in 1–3 % of renal transplant recipients and can be seen at almost any time after the transplant. PTLD may result from B cell activation after a viral illness. The proliferation is seen in the GI tract and lymph nodes. The tonsils may be significantly enlarged as part of the presentation. Affected children may present for tonsillectomy/biopsy to confirm the diagnosis.

4. There are several possible explanations for the development of hepatic encephalopathy in the setting of liver failure. Ammonia, false neurotransmitters, and GABA are all often elevated significantly in patients with liver failure and hepatic encephalopathy. Although ammonia levels are often elevated in patients with liver failure accompanied by encephalopathy, it is not unusual for an individual patient to exhibit encephalopathy prior to having elevated serum ammonia. GABA (gamma aminobutyric acid) is an inhibitory neurotransmitter thought to play a role in hepatic encephalopathy. It is produced by intestinal bacteria as is

ammonia. Both are elevated in patients with liver failure. This molecule binds to CNS benzodiazepine receptors. Evidence in favor of this hypothesis is the fact that administration of flumazenil, a benzodiazepine antagonist, has partially reversed hepatic encephalopathy [7]. False neurotransmitters are also considered a possible cause of hepatic encephalopathy. Specifically, in liver failure the concentration of aromatic amino acids increases. These aromatic amino acids cross the blood–brain barrier and participate in the production of neurotransmitters [9]. Management of liver failure includes limiting protein intake as well as therapies to decrease serum ammonia levels [8]. Lactulose converts ammonia in the intestinal lumen into nonabsorbable ammonium. Minimizing the intake of protein also helps limit the production of ammonia. In addition, if there is less protein breakdown, fewer aromatic amino acids will be produced.

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