A practical approach to anaesthesia for paediatric liver transplantation

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Abstract
Anaesthesia for paediatric liver transplantation requires meticulous attention to detail, an understanding of the disease process leading up to the need for transplantation, and an awareness of the haematological, biochemical, and multi-organ consequences of this operation. In the past 20 years, significant advances in surgical techniques, organ procurement and preservation, immunosuppression, anaesthetic management and monitoring, and postoperative care in the intensive care unit have contributed to improved outcomes of both the graft and the patient. In more recent years, the use of reduced size and living related organs has increased the donor pool for infants and children.
Paediatric liver transplantation in South Africa, up until the present time, has been centered at the Red Cross Children's Hospital in Cape Town, and survival rates here are comparable with international figures. This paper highlights the preoperative problems which face the anaesthetist, emphasises the importance of good planning and preparation for the intraoperative procedure, simplifies the surgical technique of the operation, and stresses the value of a multidisciplinary approach to the child requiring liver transplantation.

Introduction

The first liver transplant in children was performed by Starzl in Pittsburg, Philadelphia, in 1967. Cyclosporine and steroid therapy were introduced in 1980, after which survival has significantly improved. The first paediatric liver transplant in South Africa was performed at the Red Cross Children's Hospital in December 1987. Despite limited resources, this transplant program has performed 79 transplants in 76 patients with excellent patient and graft survival figures.[1]

The actual liver transplantation in children is the culmination of a long pre-transplant program. Most paediatric liver transplants are the consequence of liver failure due to biliary atresia, inborn errors of metabolism of liver origin such as alpha1-antitrypsin deficiency, autoimmune disorders, or cirrhosis. Less commonly, an acute event such as mushroom poisoning or an adverse drug reaction may precipitate fulminant liver failure. This latter group of children and their families have very little time to prepare for this life-changing event, compared with those who have had an agonising wait for an appropriate donor. A shortage of donors due to infections with hepatitis B virus and the human immunodeficiency virus contributes to the waiting list mortality and infrequent transplantation.[1]

Anaesthesia for paediatric liver transplantation is a challenging event, and although many anaesthetists will not be involved in the actual operation, a working knowledge of this procedure is important. Many of the survivors may present for surgery unrelated to their transplantation.[2]

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Preoperative assessment

Important factors to consider include

1. The general health of the child. Document the age, weight, and height.
2. Bruising, signs of encephalopathy, and stigmata of liver disease may be present.
3. The cause of the liver failure: is this acute hepatic failure or end-stage liver disease? This will impact on the presence or absence of the consequences of chronic liver failure – varices, and portal hypertension, as well as on the general nutritional status of the child i.e. healthy as opposed to chronically ill. The liver disease should be regarded as fulminant, sub-acute, or chronic.
4. Liver disease may occur as part of well-recognised syndromes such as Alagille's syndrome, and the child may have other features, especially cardiac, in keeping with that particular syndrome. These need to be identified and documented.
5. Causes of renal dysfunction may be multi-factorial. Polycystic liver disease is associated with polycystic kidneys, and primary oxaluria may present initially with renal calculi. Hepato-renal syndrome, pre-renal azotaemia, and acute tubular necrosis may each be a factor.
6. Hepato-pulmonary or porto-pulmonary disease may result

in a child who is oxygen-dependent. It is advisable that these children have a cardiac echo prior to surgery to assess heart function and the degree of pulmonary hypertension. A cardiac catheterisation may also be necessary. Pre-existing right to left shunts in the pulmonary vascular bed increase the risk of intraoperative systemic air emboli at the time of venous anastomosis.[3]
Preoperative hypoxaemia may be due to intrapulmonary arteriovenous shunting, ventilation-perfusion mismatch, restrictive lung disease from ascites and raised intra-abdominal pressure, and a decreased pulmonary diffusing capacity. The oxygen dissociation curve is shifted to the right.[3]

7. A hyperdynamic circulation is usually present, with an increased heart rate, cardiac output, and stroke volume, but a decreased systemic peripheral vascular resistance, and low blood pressure.
8. Arteriovenous shunts may be present, which result in increased venous saturations and a decreased arterio-venous difference in oxygen content. These patients are prone to supraventricular tachycardias, cardiomyopathies, valvular lesions (Alagilles), and occasionally biventricular failure.[3,4,5] They are often anaemic preoperatively, especially if they have associated renal disease and/or bleeding varices.
9. Presence of varices: gastric, oesophageal, abdominal wall, or rectal. The date of the most recent sclerotherapy should be documented, as well as the date and type of the antibiotics most recently given.
10. Previous surgery. Has the child had previous abdominal surgery such as a Kasai portoenterostomy for biliary atresia or shunts for control of varices. If so, when was the surgery performed? This will impact on the complexity of the surgery, the amount of bleeding encountered in the pre-anhepatic phase, and the length of time before the diseased liver is removed.
11. Document any allergies, as well as the details of previous anaesthetics the child has had. The size of the endotracheal tube last used may be useful in the planning for the anaesthetic.
12. Most of these children have had an appropriate time for starvation before surgery starts, so are usually nil by mouth.
13. Confirm that blood bank and the haematology and biochemistry laboratories have been informed about the operation.
14. Plan for postoperative care; alert the Intensive Care Unit that the child will return to them after surgery.

Investigations

- Blood results required include a full blood count for haemoglobin, platelets, and white cell count, INR, clotting profile with fibrinogen and PTT. An arterial blood gas is not usually necessary and is a painful procedure, so only request this if it forms a useful baseline for management. Electrolytes are important, especially if there is concomitant renal disease, and calcium, phosphate and magnesium levels should be available. These patients may be alkalotic with low sodium, potassium, calcium, magnesium, and glucose measurements, and may be hyperphosphataemic. Acidosis usually reflects poor perfusion, liver necrosis, or renal tubular acidosis.
- Liver function tests results, especially albumin, should be documented. Low albumin may result in poor drug binding, ascites, and a low colloid oncotic pressure.
- Renal function: urea and creatinine levels are necessary.
- Baseline cytomegalovirus and Epstein Barr virus status is required.
- Blood cultures are performed in these children prior to transplantation.
- A chest X ray (CXR) is necessary to identify fluid overload, infection, and to exclude tuberculosis.
- Echo cardiography will be required for the patient who has hepato-pulmonary syndrome and/or pulmonary hypertension.

Preoperative medication

These drugs are usually administered under the instruction of the liver transplant medical team as per program for each individual child. In general this would include:

1. Tacrolimus 0.2mg/kg per os (po), or Cyclosporine 5mg/kg po. The choice of drugs will depend on the current regimen.
2. Mycostatin 2-5 mls per os stat (depending on the child's age).
3. Glycerine suppositories: 1 per rectum stat.
4. Depending on the coagulation status, a preoperative fresh frozen plasma infusion may be necessary.

Premedication

Anxiolysis is generally all that these children require, and oral midazolam 0.25-0.5 mg/kg half an hour preoperatively is satisfactory. If the child has hepato-pulmonary syndrome with significant shunts and is cyanosed, supplemental oxygen via face mask or nasal cannulae preoperatively is advised.

Preparation of theatre

1. Intravascular access. Invasive monitoring is essential. All lines should be placed in the upper limbs or neck. Peripheral venous access should involve one or two good lines. Where significant blood loss is anticipated in a bigger child (>15kg), a short sheath in the antecubital vein should be considered. Arterial cannulation of the radial artery with a 22g cannula is optimal, and in a child of <10kg, a 24g cannula may be preferable. In some units, two arterial lines are placed so that, at reperfusion, blood gas sampling can take place without interrupting the arterial trace and the monitoring of the blood pressure at this critical time.
Central venous cannulation is best via the internal jugular veins, and a 5 and 5.5 Fr 8 or 13 cm triple lumen on each side of the neck provide enough venous access for all the infusions necessary during the procedure. Antibiotic or antiseptic impregnated catheters are optimal as they can be left in for longer in the postoperative period. An example of one such catheter is the Arrow guard.
If at all possible, groin lines should be avoided.
Due to their immunosuppression, these patients are prone to serious infections in the postoperative period. Full sterile precautions are necessary for the placement of all drips, invasive monitors, and lines.
2. Drugs. Induction may be inhalational or intravenous. Sevoflurane induction followed by Isoflurane for

maintenance is preferred. If an intravenous line has already been placed, induction of anaesthesia can be performed with any agent used in paediatric anaesthesia. Many anaesthetists will perform a rapid sequence induction. The use of ketamine for induction followed by a constant infusion provides haemodynamic stability and vasoconstriction which decreases bleeding. The dose for induction is 2mg/kg followed by an infusion of 2-4 mg/kg/hr. Glycopyrrolate is given intravenously at a dose of 0.01mg/kg/dose to dry up the secretions caused by ketamine.

Nitrous oxide should be avoided

A dopamine infusion should be prepared to optimise cardiac output and maintain good renal perfusion.

Aprotinin (Trasylol) is used with a loading dose of 30,000 units/kg over an hour, followed by an infusion of 7,500 units/kg/hour until the anhepatic phase of the operation. It is discontinued at this stage so that there is no compromise, by an increase in the clotting, of hepatic arterial or portal vein blood flow to the new liver.

Calcium chloride should be used in preference to calcium gluconate during the anhepatic phase and during reperfusion of the new liver.

All other drugs, such as those needed for emergency management and muscle relaxation, should be prepared as for any paediatric anaesthetic. Avoid any hepatotoxic agents.

3. Analgesia. Options include one or a rational combination of the following:
- Ketamine infusion
- Fentanyl: boluses or an infusion
- Remifentanil: beware of bradycardia, especially in the child where a slow heart rate, due to the hyperbilirubinaemia, is present preoperatively. This is commonly seen in biliary atresia patients.
- Morphine
- Regional anaesthesia options are usually limited by the haematological status of the child, both in the pre- and postoperative periods. The decision to use caudals or epidurals needs to be individualised for each patient. Caudal morphine as a single dose of 0.03-0.05 mg/kg/dose has been used successfully, with or without local anaesthetic, for perioperative analgesia.
4. Blood loss. Inform blood bank timeously that the surgery will take place. Adequate blood products should be available. The equivalent of a child's estimated blood volume (80ml/kg) may be transfused during the operation. Some centres have fresh whole blood available, and this is preferred. If the clotting profile is very deranged, fresh frozen plasma (FFP) and/or cryoprecipitate may be necessary in the preoperative period and early during the surgical procedure. All blood products should be leucocyte depleted and filtered, but it is not necessary to irradiate the blood. The availability of hetastarch products, stabilised human serum, and albumin should be checked.
5. A nasogastric tube for decompressing the stomach is essential. A urinary catheter with a urimeter (a measuring bag which has millilitre markings), allows accurate monitoring of kidney function.
6. Unusual requirements
   - Eggbox sponge prevents pressure injuries during this long procedure. It should extend the entire length of the child or infant, and should include the area at the back of the head.
   - A convection forced air warmer with the appropriate blanket is very useful in maintaining normothermia.
   - Once all the lines are in place, all limbs should be wrapped in velband and then covered in plastic to avoid getting wet. This further optimises thermoregulation.
   - Plastic aprons with an adhesive edge are placed low on the sides of the abdomen to assist efforts in keeping the child dry and warm
   - Waterproof elastoplast at the skin edges of these plastic aprons adds to ensuring a dry patient.
7. To save time later:
- Fill in the forms for clotting profile blood tests.
- Ensure that the correct coagulation tubes are available in theatre.
- Pre-heparinise syringes for doing frequent arterial blood gases at reperfusion, if the commercially available ones are not available.

What the anaesthetist needs to know about the new liver

1. When the liver was harvested i.e. what the ischaemic time will be?
2. Is the new liver compatible with the recipient and checked for any diseases?
3. Is the donor an adult or a child? This will indicate the size of the new liver and whether or not the liver will need to be cut down to a size that will fit the recipient. This will impact on the need for side-bench surgery to operate on the liver, as well as on blood loss at the time of reperfusion.
4. The new liver should be washed out (with stabilised human serum, Ringers, or albumin) at least three times just before reperfusion so as to reduce the effects of reperfusion.
5. If the liver was cut down, how was the free edge "sealed"? This may impact on blood loss following re-vascularization.

Antibiotics at induction

The choice below may change if the patient has previously been on these agents.

Ampicillin: 25 mg/kg ivi (enterococcal cover)
Cefotaxime: 25 mg/kg ivi (broard spectrum)
Metronidazole: 7.5 mg/kg ivi (anaerobe cover)

Unless there are other reasons for its administration, Metronidazole may only be necessary at the time of biliary anastomosis.

Hepatic transplant surgery for the anaesthetist

Pre-anhepatic phase

An upper abdominal transverse incision is made, with a midline extension up to the xiphisternum. No irreversible surgery is performed until the new liver is in theatre, and compatability checked and documented. The time until the diseased liver is removed depends on the extent of previous surgery and the development of adhesions. Bleeding at this time may be significant. The use of a harmonic scalpel (ultracision) significantly decreases the amount of bleeding.

Children with chronic liver disease usually tolerate clamping of the inferior vena cava well, but those patients with no collaterals may have a significant drop in blood pressure at this

time. Trial clamping of the inferior vena cava (IVC) for 30 seconds is advised.

Veno-venous bypass is used less frequently today, and is even more uncommon in children under 10kgs, but may be useful if it is necessary to decompress the lower half of the body. This is usually done from the femoral to axillary vein.

Anhepatic phase

This starts with the interruption of hepatic flow and ends with the revascularization of the new liver. The order of interruption of blood flow is:

1. IVC clamp: the suprahepatic then the infrahepatic IVC
2. Portal vein
3. Hepatic artery

The diseased liver is removed and the new liver fitted into the abdomen. The child's body temperature will fall and progressive acidaemia will follow.

Vascular anastomoses occur in the following order:

1. Suprahepatic IVC
2. Infrahepatic IVC (partial)
3. Portal vein. Once this vein is anastamosed, the portal vein clamp is temporarily released to allow the blood to fill the new liver from retrograde flow from the portal vein. This blood flushes to the infrahepatic IVC and into the surgical field.
4. Infrahepatic IVC (completed)[3]

In many cases, the liver will be piggy-backed onto the IVC with a single anastomosis rather than separate suprahepatic and then infrahepatic connections (i.e. steps 1 and 2). This overcomes the differences in size with cut-down livers, and avoids venous outflow obstruction.[2]

Vascular clamps are removed in this order:

Portal vein, suprahepatic IVC, then infrahepatic IVC. Perfusion of the new liver is from the IVC and portal veins, and venous return to the heart is re-established.[3]

Neohepatic phase is the time from reperfusion to the end of surgery.

The method of reconstruction of the hepatic artery depends on the recipient and donor anatomy. The simplest method is an end-to-end anastomosis, but there are other options. During this time, it may sometimes be necessary to temporarily clamp the aorta, partially or totally.

Once adequate haemostasis is achieved, biliary reconstruction is performed. If it has not already been done as part of the Kasai operation in patients with biliary atresia, this usually involves the formation of a Roux limb of the jejunum to which the bile duct is attached (choledochojejunostomy).

A summary of important facts at the different stages of surgery

• *Before the diseased liver is out*

Bleeding is usually a problem. This is especially evident if numerous laparotomies for biliary atresia have been performed. Monitor the clotting profile. It may be necessary to give blood and blood products to attend to haematological derangements.

Maintain good urine output of 1-2 ml/kg/hour. Mannitol at _ g/kg may be necessary. (1ml/kg of 25% mannitol provides this dose), and/or a bolus of furosemide (Lasix) of 1-2 mg/kg/dose.

Constant vigilance of the cardiovascular parameters is necessary. The inferior vena cava may be kinked, and/or the heart compressed by vigorous retraction and rotation of the liver. The potential for tears of the major vessels is a very real threat.

Hypoglycaemia: it is preferable to run a 5% dextrose infusion until the new liver is in place, but monitor the glucose and treat accordingly

Start fluid loading to maintain good blood pressure and optimal preload. Colloids, especially stabilised human serum (SHS), are a good alternative to blood products, but treat any coagulopathy appropriately.

Electrolytes must be optimised. If the K+ is low, do not treat it at this stage, unless there are clinical reasons to do so, as it will rise on reperfusion. Treat a low Ca++. Have magnesium sulphate ready in case of malignant arrhythmias with reperfusion.

A trial clamping of the inferior vena cava is advised to assess the ability of the heart to maintain an adequate output and blood pressure in the face of the diminished venous return. If it fails to do this, a further bolus of intravenous fluids may be required, and, if that is insufficient, veno-venous bypass may be necessary. This is not usually a problem in the chronic liver disease patients who have developed collaterals, but may be a considerable challenge in patients with fulminant liver failure.

• *Anhepatic phase*

Hypoglycaemia: monitor and treat.

Hypocalcaemia: give calcium chloride (CaCl) at this stage, not calcium gluconate. Calcium is important for the reperfusion phase to mop up the potassium.

Prepare for the reperfusion of the new liver: CaCl, fluids, sufficient blood and blood products in theatre. Platelets are not often a problem, but, with massive transfusion, may become so. The coagulation status should be checked and the appropriate blood products available in theatre.

Check that all drugs to be given with reperfusion are ready, correct, and labelled.

Just before reperfusion administer:

Azathioprine (Imuran): 0.5-1 mg/kg ivi
Medrol 10 mg/kg ivi
Antibiotics: a second dose of those given at induction may be necessary if more than 6 hours has elapsed since the first dosage.

• *Neohepatic stage: Re-perfusion of new liver*

At reperfusion, severe hypotension, bradycardia, bizarre arrhythmias, supraventricular tachycardia, complete heart block, ventricular arrhythmias, and asystole may occur. Air emboli are uncommon but are possible, and result in acute right ventricular failure.

Bleeding may be particularly problematic if the new liver has a raw surface from a cut-down procedure.

Arrhythmias occur if the calcium is not adequate and if the new liver was not washed out sufficiently.

Hypotension from bleeding and the effects of reperfusion is treated with fluids and normalisation of electrolytes. If in doubt, give calcium.

Hyperkalaemia may cause significant arrhythmias but this

responds well to calcium.

Hypocalcaemia is easily treated and ideally pre-empted.

Monitor frequently at first, and then as often as necessary to optimise serum biochemistry.

Acidosis caused by the release of acidaemic blood when the inferior vena cava clamp was removed, may continue for a while until the artery has been anastamosed, at which time full perfusion of the new liver has been completed. If the acidosis persists, it may require treatment at a later stage. Having a baseline lactate prior to the anhepatic phase, is useful.

Check the ventilation and $ETCO_2$ as the new larger liver may impair diaphragmatic function. Air embolism may occur during the hepatectomy as well as with re-vascularization. Monitoring and documenting end-tidal CO2 is vital.

• *Neohepatic phase: Post re-perfusion*

Maintain volume, give blood and blood products.

Correct the acid base status (usually acidotic, hyperkalaemic, hypocalcaemic)

Beware of over-transfusion, especially when there are big lines but not massive blood loss. The liver should be full with a sharp edge, but not tense.

Aim for a haemoglobin of 10-12 g%, as any higher increases the risk of clotting of the newly anastamosed hepatic artery and portal vein.

Prepare the antibiotics for the Roux enY:

Ampicillin: 25 mg/kg
Cefotaxime: 25 mg/kg
Metronidazole: 7.5 mg/kg

This is often a time when the anaesthetists are tired and expecting the operation to finish, but there is still 2-3 hours of operating time from the time of re-perfusion. Vigilance is mandatory, as all the problems mentioned previously may continue.

Therefore:

Monitor coagulation.

Monitor renal function.

Maintain normothermia. Hypothermia is likely to develop due to prolonged surgery, the ice-cold new liver, frequent intra-abdominal washes, wet drapes, and a large body surface area exposed.

Documentation

The anaesthetic record must be completed meticulously. It is a medico-legal document.

Results from investigations during the operation should be recorded separately from the anaesthetic chart.

A hand-over summary for the ICU is invaluable.

A print-out from the anaesthetic machine is optimal but not always possible.

Plans for the postoperative period

Postoperative ventilation is the norm. There is a massive incision with significant blood loss during prolonged surgery. The diaphragm is splinted by the new liver, and this will compromise ventilation. The abdomen is usually distended, and bowel paresis following surgery and the adjacent dissection aggravates the problem.

Analgesia should be pre-empted for continuation in the ICU. A morphine infusion is preferred by this author.

Blood products should be available to continue improving the haematological status. An infusion of fresh frozen plasma is often necessary in the immediate postoperative period.

Inotropes are usually continued into the postoperative period.

Contact the ICU with a view to the time of arrival of the patient, and any special requirements which may be necessary.

Transplant drugs in the postoperative period are administered according to the transplant team protocol. These may include Tacrolimus, Cyclosporine (Neoral), Methylprednisolone (Medrol), Azathioprine (Imuran), Ampicillin, Cefotaxime, Metronidazole, Ganciclovir, Polygam, Morphine, and Dopamine.

Maintenance fluids are run at 40% of usual in order to allow volume for blood products. For the first 24-48 hours postoperatively, fresh frozen plasma is infused at 10ml/hr in all patients.[2]

When these patients present for surgery unrelated to their transplant, the emphasis of anaesthetic management should be on the grafted organ and its function, the risks of infection in the perioperative period, and the function of other organs.[6]

Conclusion

The emphasis of anaesthetic management should be on the fact that blood loss may be massive and rapid; coagulation factors are required; hypothermia must be prevented; the impact of reperfusion may be considerable; and electrolyte, glucose, and acid-base status must be controlled.

As these are long operations, anaesthetists should come well prepared, with food and drinks for a long haul. Have frequent short breaks. The transplant team will often spend most of the operating time in theatre and are extremely helpful to the anaesthetists. The anaesthetist involved in surgery for transplantation may make the difference between a good and a poor outcome for both the child and the transplanted organ.

References

1. *Spearman CWN, McCulloch M, Millar AJW, Burger H, Numanoglu, Goddard E, Cooke L, Cywes S, Rode H, Kahn D. Liver transplantation for Children: Red Cross Children's Hospital Experience. Transplantation Proceedings 37, 1134-1137 2005.*
2. *Millar AJW, Spearman W, McCulloch M, Goddard E, Raad J, Rode H, Kahn D, Cywes S. Liver transplantation for children – the Red Cross Children's Hospital experience. Paediatric Transplantation 2004:8; 136-144.*
3. *Robertson K, Borland LM. Anesthesia for organ transplantation. Chapter 26 Smith's Anesthesia for Infants and Children. 5th edition 1990 ISBN 0-8016-3568-3*
4. *Bellamy M. Liver transplantation and liver resection. Chapter 28. 646-650.Oxford Handbook of Anaesthesia. 2003 Oxford University Press. ISBN 0 19 263273 6.*
5. *Hammer GH, Krane EJ. Anaesthesia for liver transplantation in children. Paed. Anaes 2001 11: 3-18.*
6. *Kostopanagiotou G, Smyrniotis V, Arkadopoulos N, Contis J, Briassoulis G, Kostopanagiotou E. Anaesthetic and perioperative management of paediatric organ recipients in non-transplant surgery. Paed Anaes 2003 13: 754-763.*
7. *Tejani AH, Harmon WE, Fine RN. Paediatric Solid Organ Transplantation. Section 4; 239-311. 1st edition 2000. Munksgaard, Copenhagen. ISBN 87-16-12273-9.*