Case Report

Anaesthetic considerations for liver transplantation in propionic acidemia

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ABSTRACT

Propionic acidemia (PA) is an autosomal recessive disorder of metabolism due to deficiency of the enzyme propionyl-CoA carboxylase (PCC) that converts propionyl-CoA to methylmalonyl-CoA with the help of the cofactor biotin inside the mitochondria. The resultant accumulation of propionyl-CoA causes severe hyperammonaemia and life-threatening metabolic acidosis. Based on the positive outcomes, liver transplantation is now recommended for individuals with recurrent episodes of hyperammonaemia or acidosis that is not adequately controlled with appropriate medical therapies. We report anaesthetic management of two children with PA for liver transplantation at our institution. It is essential for the anaesthesiologist, caring for these individuals to be familiar with the manifestations of the disease, the triggers for decompensation and management of an acute episode.

Key words: Hyperammonaemic crisis, inborn metabolic errors, liver transplantation, organic acidemia, propionic acidemia and anaesthesia

INTRODUCTION

Propionic acidemia (PA) is an autosomal recessive disorder of amino acid metabolism that results due to the deficiency of the enzyme propionyl-CoA carboxylase (PCC) that is predominantly expressed in the liver. This disorder usually presents at birth or within a few weeks after birth. It results in failure to thrive due to recurrent life-threatening metabolic acidosis with hyperammonaemia and multisystem disorders. Incidence of PA is reported as 1 in 1,00,000 in the US, 1 in 2000 to 1 in 5000 in Saudi Arabia while in Japan it is reported as 1 in 465,000 live births.[1] Based on the positive outcomes, liver transplantation is now recommended for individuals with recurrent episodes of hyperammonaemia or acidosis that are not adequately controlled with appropriate medical therapies.[2-5]

Anaesthetic management of these patients is very challenging and involves a thorough understanding of the disease process, the medical therapy, the triggers for metabolic crises and the prevention and management of the metabolic crises.

CASE REPORT

We report the anaesthetic management of two children with PA, who underwent living donor liver transplantation in our institution. The clinical features of the children at the time of presentation are listed in Table 1. Liver transplantation was indicated because of recurrent decompensation with metabolic crises, developmental delay and failure to thrive. Protein restriction, intermittent metronidazole and carnitine therapy (100 mg/kg/day) were continued until the day of surgery. On the day before surgery, the first child had hyperammonaemia and lactic acidosis with ammonia levels of 110 μM/l and lactate of 5.4 mmol/l.

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The child received carbaglu (N-carbamylglutamate) regimen following which the ammonia levels returned to normal and acidosis improved. The second child had an episode of diarrhoeal illness, a week before surgery, but did not suffer any decompensation. His pre-operative ammonia level was 49 μmol/l.

Both the children underwent auxiliary partial orthotopic liver transplantation (APOLT); extended left hepatectomy and caudate lobectomy with left lateral segment implantation.

Pre-operative fasting was limited to 6 h and both the children were started on dextrose infusion at the onset of fasting. Anaesthesia was induced with thiopentone and vecuronium and maintained with isoflurane in air-oxygen mixture. Fentanyl and vecuronium infusions were used. In addition to standard monitors, a central venous cannula was placed in the internal jugular vein and two arterial cannulae were placed, one in the radial artery and the other in the femoral artery. Warming blankets and fluid warmers were used to maintain the temperature during surgery. Dextrose infusion was started at a basal rate of 6 mg/kg/min. Insulin infusion was used to optimise fluctuating glucose levels. There were no episodes of hypoglycaemia in both the children. Continuous carnitine infusion was used throughout the surgery at the rate of 4.2 mg/kg/h in the first child and the second child received carnitine at a dose of 25 mg/kg 6th hourly. Arterial ammonia level was monitored throughout the surgery along with the blood gases. Intravenous sodium bicarbonate (8.4%) was used to correct metabolic acidosis. Both children required potassium supplementation guided by the laboratory values. Haemodialysis equipment was kept on standby for both the patients. Intraoperative details are given in Table 2.

The peak ammonia level in the first child was 90 μmol/l before reperfusion that settled down in the next few hours. In the second child, the ammonia levels were consistently below 30 μmol/l. The maximum base deficit was − 6.3 mmol/l in the first child and − 6.8 mmol/l in the second child.

The first child was extubated 10 h after surgery and the rest of the post-operative stay was uneventful. Total hospital stay was 14 days. The second child was extubated 9 h after surgery with good liver graft and renal function and normal ammonia levels. On post-operative day 2, the child was noted to have

Table 1: Presenting features

Features	Child 1	Child 2
Age (years)	4	3
Sex	Male	Male
Ethnic origin	Middle east	Indian
Diagnosis at (days after birth)	3	48
Body weight (kg)	15	11
Developmental delay	Yes	yes
Hypotonia	Yes	Yes
Pancytopenia	Yes	No
Cardiac status		
ECG and 2D ECHO	Normal	Normal
Seizures	No	One episode with ammonia of 580 μmol/l
Pancreatitis and ophthalmic abnormalities	No	No
Liver function tests	Normal	Normal
Renal function tests	Normal	Normal
Protein restricted diet	Yes	Yes
Carnitine, biotin and intermittent metronidazole therapy	Yes	Yes

ECG – Electrocardiogram; 2D – Two-dimensional; ECHO: Echocardiogram

Table 2: Intraoperative details

Features	Child 1	Child 2
GRWR	1.69	2.0
Duration of surgery (min)	530	740
Cold ischemia time (min)	50	63
Intravenous colloids (ml)	1100	1750
Intravenous crystalloids (ml)	800	1500
Packed cells (ml)	400	400
Pooled cryoprecipitate (ml)	100	50
Vasopressor requirement	Noradrenaline 0.01 μg/kg/min for a brief period before reperfusion	none
Urine output	Good	Good
Sodium bicarbonate 8.4% (ml)	40	43
Peak lactate (mmol/l)	3.8	3.8
Lactate at end of operation (mmol/l)	2.4	2.5

GRWR – Graft-recipient body weight ratio

hepatic artery thrombosis for which he was re-explored and the anastomosis was redone. Anaesthetic management was the same and ammonia and pH values were always in the acceptable range. The child developed pneumonia postoperatively requiring prolonged periods of ventilation. He was discharged home on day 98.

DISCUSSION

It is essential for the anaesthesiologist, caring for these individuals to be familiar with the whole pathophysiology of the disease process. Inappropriate anaesthesia care can lead to significant morbidity and poor outcomes in the peri-operative period. Appropriate control of metabolic decompensation

during the operative stress is essential for good outcomes.

Although a rare condition, the pathophysiology of PA is reasonably well-understood. The enzyme PCC converts propionyl-CoA to methylmalonyl-CoA with the help of the cofactor biotin inside the mitochondria.[6] The precursors of propionyl-CoA are the amino acids- isoleucine, methionine, threonine and valine, odd chain fatty acids, cholesterol, catabolism of the nucleotides thymine and uracil and from bacterial production of propionate from pyruvate in the gut. Coude *et al*.[7] have shown that hyperammonaemia in PA is caused by the inhibition of N-acetyl glutamate synthetase by the accumulation of propionyl-CoA, leading to diminished generation of acetyl glutamate and, in turn, diminished activation of the hepatic urea cycle. Hyperammonaemia is a relatively common manifestation of patients with PA during metabolic decompensation and could be life-threatening. Normal serum levels of ammonia ranges from 12 to 41 μmol/l. The rationale of specific medications in these children in the pre-operative period is as follows:[8]

Carnitine conjugates with propionic acid, helps its transfer out of mitochondria and promotes its excretion in the urine. Carnitine therapy given at a dose of 100 mg/kg for every 6 h, therefore, helps to scavenge the propionic acid in these individuals. Cyclical metronidazole therapy helps to reduce the propionate load from the gut flora. Carglumic acid is N-carbamylglutamate (carbaglu), a synthetic analogue of N-acetyl glutamate. It augments ureagenesis and reduces ammonia. It has been reported to be of benefit in several disorders presenting with hyperammonaemia. The enzyme PCC is predominantly located in the liver but expressed throughout the body. Therefore, replacing the liver only partially corrects the metabolic disorder.[9] After transplantation, children continue to show milder forms of metabolic decompensation, which were not life-threatening but show improvement in the neurological status and stabilisation of cardiac function.[2,3,5] APOLT, though technically demanding, is an effective strategy in acute liver failure and metabolic liver disease.[10,11] The rationale of APOLT in these patients is to provide a segment of the liver with normal enzyme activity to correct the underlying metabolic abnormality. Removal of the whole liver as in standard OLT is not deemed necessary. The advantage of the APOLT over OLT is that should the donor graft fail, it can be removed without endangering the life of the recipient and also the remnant liver acts as a back-up, preventing the cumulative effect of hepatic decompensation with an existing metabolic abnormality.[2] On long-term follow-up, APOLT recipients were shown to achieve acceptable growth and psychomotor development without any further metabolic decompensation.[2] Multiple systems are affected in children with PA. Central nervous system manifestations include developmental delay, seizures, extrapyramidal symptoms, hypotonia, coma and optic nerve atrophy. Cardiovascular manifestations could be in the form of cardiomyopathy and electrophysiological abnormalities. Other systems may be affected and patients may have acute pancreatitis, gastroesophageal reflux disease, bone marrow suppression, insulin resistance, exfoliative rash, etc.[9] The pathophysiology of all these complications has been attributed to possible mitochondrial dysfunction in these patients and they also have impaired responses to oxidative stresses.[12]

Patients with PA do not tolerate increased catabolism in the event of any stress in the form of febrile episodes, infections, prolonged fasting, vomiting/dehydration, surgery and trauma.[13] They can develop life-threatening metabolic decompensation in the form of hyperammonaemia and metabolic acidosis, which requires prompt therapy to minimise the complications.

In the peri-operative period, an acidotic crisis can be initiated by inadequate caloric intake, hypoxia, dehydration, hypotension or the use of an inappropriate anaesthetic.[14] All drugs which get metabolised to the precursors of propionic acid such as odd chain organic acids, odd chain alcohols, acrylic acid or odd chain fatty acids can increase the load of propionyl-CoA. Muscle relaxants metabolised by ester hydrolysis such as succinylcholine, atracurium, cisatracurium and mivacurium should not be used because their metabolic end products include odd chain organic molecules.[15] Propofol should be avoided because the soya bean oil contains high amounts of polyunsaturated fats which can be metabolised to propionic acid.[16] The various strategies used to prevent metabolic crisis are detailed in Table 3.

Acute decompensation can still occur in the peri-operative period despite all the precautions. Ammonia is very toxic to the brain and the damage might become irreversible when the levels reach between 200 and 500 μM/l.[17] The extent of neurological injury depends on the duration of

Table 3: Primary goals of anaesthetic management

Avoid prolonged periods of fasting. Dextrose infusion at the onset of fasting
Adequate glucose load to prevent breakdown of stored protein and odd chain fatty acids
Dextrose at the rate of 6-8 mg/kg/min ; Insulin infusion at a rate of 0.01U/kg/hr. Do not decrease basal dextrose or insulin infusion rate. Insulin drip will drive calories into the cell and reverse catabolism
Intravenous fluids at a rate of 1.5 times maintenance
Avoid lactic acid-containing fluids
Potassium supplementation
Metronidazole and carnitine to be continued during surgery
Avoiding anaesthetic drugs which can serve as a substrate for propionate
Ensure haemodynamic stability and good tissue perfusion to prevent anaerobic metabolism
Adequate depth of anaesthesia to reduce stress response
Maintenance of near normal acid base balance. Sodium bicarbonate or tris-hydroxy methyl aminomethane (THAM) infusions as required
Gastroesophageal reflux disease (GERD) and hypotonic airways – Increased risk of aspiration. Care during induction and extubation.

Table 4: Management of hyperammonaemic crisis

Sedation, ventilation, vasopressors as required
Continue reversal of catabolism
Haemodialysis/Haemofiltration/ECMO in patients with ammonia >300 μmol/L, extreme acidosis/electrolyte imbalance, coma, dilated pupils, poor neurological findings, deterioration, failure to improve or increased respiratory rate
Ammonia, electrolyte and blood gases at frequent intervals
Continuous neurological monitoring
Carnitine boluses 100 mg/kg/dose 3-4 times daily

hyperammonaemia. It is, therefore, important to bring down the levels promptly. Recommendations have been proposed for the acute management of patients with PA in a consensus conference in Washington in 2011.[18] The salient points of the recommendations that apply to the perioperative setting are given in Table 4.

It is essential to monitor arterial blood gases and arterial ammonia levels at frequent intervals to anticipate crises. Facilities for haemodialysis should be available in the theatre and in the ICU. There were no episodes of acute decompensation in both our patients during surgery or in the post-operative period.

CONCLUSION

A good understanding of the pathophysiology of PA is essential for anaesthesiologists, caring for these children in the peri-liver transplant period. Strict attention to detail with continuous monitoring, avoidance of triggers for acute decompensation, and aggressive and early management of decompensation episodes is essential.

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Conflicts of interest

There are no conflicts of interest.

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