Perioperative care of an infant with pyruvate dehydrogenase deficiency

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Abstract

The authors present the anaesthetic management of two infants with pyruvate dehydrogenase complex deficiency (PDCD), a rare genetic disorder of carbohydrate metabolism leading to lactic acidosis and neurological impairment. In the first case, a seven-month-old infant, undergoing closed reduction of a dislocated hip, received general anaesthesia with a volatile agent. In the second case, spinal anaesthesia was administered to a six-month-old infant undergoing Achilles tendon lengthening. There were no adverse outcomes in both cases. Key components of perioperative care included minimising perioperative stress, and avoiding exacerbation of the lactic acidosis. Previous reports regarding the perioperative care of such patients are reviewed, and recommendations for anaesthetic care discussed.

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Introduction

Pyruvate dehydrogenase complex deficiency (PDCD) is an x-linked inherited disorder of pyruvate metabolism. The pyruvate dehydrogenase complex (PDC) catalyses the oxidation of pyruvate to acetyl Co-A. This then enters the tricarboxylic acid cycle for adenosine triphosphate (ATP) production. The PDC consists of five components, and although the E_1 subunit is usually implicated, a defect of any of the components will lead to a build-up of pyruvate and lactate. There is a variable spectrum of time of presentation, severity of lactic academia, and the degree of neurological impairment, based on the quantity of residual enzyme activity. PDCD is one of the most commonly identified causes of primary lactic acidosis in the paediatric population. The most severe form of PDCD manifests during the neonatal period, with lethal lactic acidosis and brain malformations, including agenesis of the corpus callosum. In infants, psychomotor retardation and cystic lesions of the central nervous system accompany a more subacute, or chronic, lactic acidosis. Additionally, PDCD can also present in older children as ataxia exacerbated by a high carbohydrate diet. Facial dysmorphism may be present in all ages. Laboratory studies reveal an elevated pyruvate and lactate in plasma and urine. The definitive diagnosis requires the demonstration of diminished activity of pyruvate dehydrogenase in muscle or other tissue. Prognosis is usually poor, and limited treatment options include a ketogenic diet, thiamine therapy, and administration of dichloroacetate, an activator of the pyruvate dehydrogenase complex.[1]

Given the end-organ effects of the disorder, surgical interventions are frequently required in such patients. We report on the perioperative care of two infants with PDCD who required anaesthetic care during orthopaedic procedures. Previous reports of the anaesthetic care of such patients are reviewed, and the perioperative implications of the disorder discussed.

Case reports

Institutional review board approval is not required for case reports at Nationwide Children's Hospital.

Patient 1

A seven-month-old, 8.6kg infant with a diagnosis of PDCD, presented for manipulation and closed reduction of a dislocated hip under general anaesthesia. The infant had been born at term via a scheduled Caesarean section

for breech presentation. During the neonatal period, the diagnosis of PDCD was made due to the presence of hypotonia, seizures, hypoglycaemia and lactic acidosis. Treatment included frequent feedings with a ketogenic diet. Medications included phenobarbital, thiamine, biotin, and carnitine. An echocardiogram performed within the last two weeks revealed normal ventricular function. His past surgical history included two uneventful anaesthetics for ventriculoperitoneal (VP) shunt placement and revision; the last one at three months of age. The patient was held *nil per os* for clear liquids two hours and transported to the operating room, where routine American Society of Anesthesiologist's (ASA) monitors were placed. Anaesthetic induction included the inhalational of sevoflurane in a 50% oxygen-nitrous oxide mixture. This was followed by the placement of a peripheral intravenous cannula, and the administration of normal saline. Glycopyrrolate (0.05 mg) was administered, and tracheal intubation with a 4.0 uncuffed endotracheal tube (ETT) facilitated by the administration of succinylcholine (1 mg/kg). Following anaesthetic induction and tracheal intubation, laboratory evaluation revealed hematocrit 31.7%, serum potassium 3.8 mEq/l, and lactate 1.4 mmol/l (normal less than 2 mmol/l). Maintenance anaesthesia consisted of sevoflurane (exhaled concentration 1-2%) and fentanyl (1.5 µg/kg). On completion of the surgical procedure, which lasted 100 minutes, the infant's trachea was extubated, and he was transported to the post-anaesthesia care unit. He resumed his usual diet and medication regimen later that day. He was discharged home the following day.

Patient 2

A six-month-old, 7.2kg infant with a diagnosis of PDCD presented for Achilles tendon lengthening. He was born at term via a scheduled Caesarean section for breech presentation. During the neonatal period, a diagnosis of PDCD was made, due to the presence of hypotonia and lactic acidosis. Treatment included frequent feedings with a ketogenic diet. Preopearative examination revealed facial dysmorphism with micrognathia, and a Mallampati grade III view of the airway. Medications included thiamine, biotin, and carnitine. An echocardiogram performed during his preoperative visit revealed normal ventricular function. He had no previous surgical procedures. The patient was held *nil per os* for clear liquids for two hours. A topical anaesthetic cream was placed over a potential intravenous access site. He was transported to the operating room, where routine ASA monitors were placed. After breathing 70% nitrous oxide in 30% oxygen, a peripheral intravenous cannula was placed, and a normal saline infusion started, to provide maintenance fluids. Glycopyrrolate (0.05 mg) was administered, followed by 1 mg/kg of ketamine and 1 µg/kg of dexmedetomidine. A dexmedetomidine infusion was started at 1 µg/kg/hour to provide sedation during performance of the lumbar puncture for the administration of spinal anaesthesia, and during the surgical procedure. The patient was turned into the right lateral decubitus position, and a 1.5-inch, 22-gauge spinal needle with a stylet, was inserted into the L_{3-4} interspace. After the free flow of cerebrospinal fluid was obtained, isobaric bupivacaine (0.5 mg/kg), with an epinephrine wash, and clonidine (1 µg/kg) was injected. Successful spinal anaesthesia was achieved with a T_{6-8} sensory level. On completion of the surgical procedure, which lasted 85 minutes, the patient was transported to the post-anaesthesia care unit. He resumed his usual diet and medication regimen later that day. He was discharged home the following day.

Discussion

PDCD, a rare defect of carbohydrate metabolism, results in mild to life-threatening lactic acidosis, and a spectrum of neurological impairments. Multiple aspects of surgery and general anaesthesia may impact the disease process, including surgical stress, perioperative fasting, airway manipulation, respiratory and cardiovascular changes, as well as anaesthetic medications. The potential deleterious physiological impact of the perioperative period can be demonstrated by an animal study which reported decreased activity of the PDC at four, and 24 hours, following surgical trauma.[2] Given these effects, anaesthetic management should be tailored to effectively blunt the surgical stress response, and minimise the risk of exacerbating the lactic acidosis of PDCD.

Available literature on the anaesthetic management of patients with PDCD is limited to four case reports, outlining the care of patients during five anaesthetics (Table I).[3-6] Two patients had the more severe infant form of the disease, one of whom underwent two surgeries, while two were older, with the milder form of PDCD. All of these patients had been administered a general anaesthesic as the primary anaesthetic technique, although caudal blockade was used for postoperative analgaesia in one patient.[6] In all cases, blood gas analysis was performed at the start, and conclusion, of surgery. There was no clinically significant change in three of the five anaesthetics, and the authors reported an uneventful post operative course.

Dierdorf and McNiece's report, the earliest to appear in the literature in 1983, detailed an infant who developed metabolic acidosis after two separate surgeries.[3] Preoperatively, the patient was acutely ill, having presented with coma and respiratory failure. At the time of surgery, treatment included a continuous bicarbonate infusion and mechanical

Table I: Summary of previous reports of anaesthetic management of patients with pyruvate dehydrogenase complex deficiency

Author	Patient details	Surgical procedure	Anaesthetic management	Outcome
Dierdorf and McNiece[3]	10-month-old infant	Laparotomy, liver biopsy, gastrostomy tube placement, Nissen fundoplication	Induction of anaesthesia: thiopental, fentanyl, pancuronium. Maintenance anaesthesia: N_2O(60%)-O_2, fentanyl. Intravenous fluids: 5% dextrose.	Patient developed a worsening metabolic acidosis, with an increased lactate and base deficit. Values returned to baseline within 24 postoperative hours. Patient expired on day 30 of hospitalisation.
		Tracheostomy for failed weaning from mechanical ventilation	Induction and maintenance of anaesthesia: N_2O-O_2-isoflurane.	
Gilmore and Mayhew[4]	8-year-old child	Achilles tendon lengthening.	Premedication: midazolam 10 mg by mouth. Induction of anaesthesia: sevoflurane in 70% N_2O-30% O_2. Maintenance anaesthesia: Desflurane in 50% N_2O-50% O_2 and fentanyl. Intravenous fluids: normal saline	Uneventful
Milojevic and Simic[5]	5-year-old child	Achilles tendon lengthening.	Premedication: midazolam and atropine. Induction of anaesthesia: propofol and vecuronium. Maintenance anaesthesia: N_2O/O_2, fentanyl and vecuronium Intravenous fluids: normal saline	Uneventful perioperative course, except for difficult intubation due facial dysmorphism.
Acharya and Dearlove[6]	11-month-old child	Hypospadias repair	Induction of anaesthesia: sevoflurane. Regional anaesthesia: caudal epidural with bupivacaine and clonidine. Maintenance anaesthesia: sevoflurane in N_2O-O_2. Intravenous fluids: 10% dextrose	Uneventful

ventilation. A laparotomy, and later, a tracheostomy, were performed, using intravenous and inhalation techniques, respectively. In both cases, a similar rise in lactate and base deficit with a decrease of the pH was observed. Values returned to baseline within 24 hours. The authors hypothesised that intraoperative hyperventilation, resulting in hypocarbia, was the cause of the metabolic acidosis and elevated lactate. They also suggested that as thiopental and halothane may impair gluconeogenesis, leading to lactate accumulation, these agents should be avoided. However, Gilmore and Mayhew point out that this is merely a theoretical concern, with no clinical evidence to support this contention.[4] Given this information, it does not appear that volatile agents should be avoided. However, as metabolic compensation may occur quickly for respiratory alkalosis, we would suggest the maintenance of normocarbia, with close attention to end-tidal CO_2 values during anaesthetic care.

In our first case report, successful anaesthesia was provided using an inhalation agent (sevoflurane) for induction and maintenance. With the exception of one, all other reports from the literature also used a volatile agent. More recently, Milojevic and Simsic described using intravenous induction with propofol, followed by maintenance anaesthesia, with nitrous oxide and fentanyl.[5] Propofol has been shown to inhibit gluconeogenesis and mitochondrial function, thereby suggesting a theoretical contraindication to its use.[6] However, these issues are unlikely to be of clinical significance when propofol is used for induction, although more prolonged infusions should be avoided until more information is available to demonstrate its safety. Of note, Milojevic and Simic' report also listed difficulties with endotracheal intubation, secondary to the facial dysmorphism associated with PDCD.

Although the previous reports have demonstrated the safe use of non-depolarising neuromuscular blocking agents, given the associated hypotonia which may be present in patients with PDCD, short-acting agents may be preferred. Additionally, endotracheal intubation may be accomplished without such agents, using an inhalational agent supplemented with propofol. Our report is the first to describe the use of succinylcholine. Although we noted no adverse sequelae from its use, the potential for hyperkalaemia in patients with central and peripheral nervous system disorders resulting in hypotonia or spasticity, should be considered.

In our second case, in an effort to avoid general anaesthesia in a patient with a potentially difficult airway, we chose to provide sedation with dexmedetomidine and ketamine, followed by spinal anaesthesia. The latter is the first

report on the use of a regional anaesthetic technique, instead of general anaesthesia in a patient with PDCD, although Archarya and Dearlove used a caudal epidural block in combination with general anaesthesia.[6] Neuraxial anaesthetic techniques, used either alone, or in conjunction with, general anaesthesia, have been shown to decrease the surgical stress response. Therefore, regional anaesthesia could be recommended as useful in patients with PDCD.[7,8] Also, avoidance of opioids reduces the risk of postoperative respiratory depression which may be likely, due to the hypotonia and altered central control of respiration, that is a feature of PDCD. Regardless of the anaesthetic technique, we recommend postoperative monitoring, particularly for respiratory depression.

For intravenous fluid therapy, we recommend normal saline with avoidance of glucose- or lactate-containing solutions. Although dextrose-containing solutions were used in two of the previous cases, metabolic acidosis occurred in one of them. As these patients are dependent on fat for the maintenance of normal blood glucose, there is a risk of hypoglycaemia. In prolonged cases, preoperative fasting should be minimised and blood glucose monitored, and intermittent measurement of acid-base status and lactate concentrations may be indicated. Although not reported specifically in patients with PDCD, dilated cardiomyopathy may occur in mitochondrial disorders of oxidative phosphorylation. Therefore, we would recommend preoperative echocardiography, as performed in both our patients, to exclude cardiac dysfunction, as that could contribute to a lactic acidosis. For patients with PDCD, additional perioperative considerations include minimising other causes of perioperative stress that may also exacerbate the underlying metabolic defect. Effective premedication, psychological comfort measures, an adequate depth of anaesthesia, and effective postoperative analgaesia are recommended.

In summary, we report our experience with both inhalation anaesthesia and neuraxial techniques for two infants with known PDCD, undergoing elective lower limb surgery. Anaesthetic care should focus on minimising perioperative stress, and avoiding factors that could exacerbate lactic acidosis. There has been some disagreement on choice of anaesthetic agents based on possible interference with carbohydrate metabolism. Further research is needed to delineate the most appropriate anaesthetic regimen.[9] Regional anaesthesia, used either alone, or in conjunction, with general anaesthesia, offers the benefits of effective control of the surgical stress response and provision of postoperative analgaesia, while limiting opioid needs. Additional issues relate to the associated central nervous system involvement, including hypotonia and abnormalities in the central control of ventilation.

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