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Perioperative Management of a Child with Von Gierke Disease

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Abstract

Von Gierke disease (Glycogen storage disease type 1a) is an autosomal recessive disorder caused by a deficiency of the enzyme glucose 6-phosphatase. Glucose 6-phosphatase is the enzyme responsible for the hydrolysis of glucose-6-phosphate to orthophosphate and free glucose. The metabolic consequences of this deficiency include hypoglycemia, lactic acidosis, hyperlipidemia, and elevated serum triglycerides. Anemia and prolonged bleeding times are also not uncommon. Due to the complex nature of the associated metabolic abnormalities, patients with glycogen storage disease type 1a (GSD 1a) who present for surgery require coordinated care between several specialists to ensure a successful perioperative course. We present the coordinated perioperative care of a 15-year-old patient with GSD 1a who presented for retroperitoneoscopic resection of an adrenal mass. The management of fasting hypoglycemia and significant perioperative lactic acidosis are also discussed.

Keywords

Von Gierke disease; lactic acidosis; perioperative management

Background

Von Gierke disease (Glycogen storage disease type 1a) is an autosomal recessive disorder with a reported incidence of approximately 1 in 100000 newborns [1]. The disorder is caused by a deficiency of glucose 6-phosphatase, which is the enzyme responsible for the hydrolysis of glucose-6-phosphate to orthophosphate and free glucose [2]. The metabolic consequence of this deficiency is the excessive accumulation of glycogen in the liver, kidney and intestinal mucosa, with limited available free glucose. Patients are therefore prone to significant hypoglycemic episodes [2]. Secondary biochemical abnormalities include lactic acidosis, hyperlipidemia, and elevated serum triglycerides [3]. While neutropenia may be present in a small subset of patients with GSD 1a, anemia and prolonged bleeding times are common [4-7].

As a result of the above physiologic abnormalities, patients with GSD 1a present specific perioperative challenges which includethe management of glucose and lactate imbalances, the avoidance of potentially catastrophic hypoglycemia and lactic acidosis, and the management of prolonged bleeding after surgery [3,8,9]. Coordinated care with the involvement of several specialists is therefore essential to ensure the safe perioperative course of patients with GSD 1a.

We describe the successful coordinated perioperative management of a 15-year-old young male with GSD 1a, who presented for the retroperitoneoscopic resection of a suspicious adrenal mass. Perioperative care was coordinated by specialists including a pediatric geneticist, an endocrinologist, pediatric oncologist, anesthesiologist, and surgeon. Preoperative fasting guidelines, anesthetic management and the treatment of lactic acidosis are also discussed.

Case Presentation

A 15-year-old, 54.5 kg young male with a history of GSD 1a presented for the retroperitoneoscopic resection of a suspicious adrenal mass which was found on routine screening magnetic resonance imaging (MRI). Past medical history was significant for several hospital admissions for hypoglycemia. Home medications included glycosade 120 gm at bedtime and a corn starch diet for glucose management. The patient had no allergies and family history was significant for GSD in other siblings. Vital signs were age appropriate, and physical examination was significant for an enlarged liver. Laboratory studies on admission were significant for a blood glucose level of 167 mg/dl and a lactic acid level of 8.7 mmol/L (normal, 0.7-2.1). Other laboratory values including the complete blood count, coagulation studies, and catecholamine levels were all within normal limits. Preoperative preparation included a consultation with the patient's pediatric geneticist and endocrinologist. Their recommendations are outlined in tab le 1.

The patient was admitted to the hospital the day before surgery and perioperative management was initiated as outlined in table 1. Fasting was initiated after midnight, upon which intravenous fluids (D10 with 0.45% saline) was initiated at a glucose infusion rate of 2.3 mg/kg/min (78 ml/hr). Blood glucose and lactate levels were checked at hourly intervals with the goal of maintaining glucose levels between 70 and 100 mg/dl, and lactate levels below 3 mmol/L. Over the fasting period, the glucose infusion rate (GIR) had to be adjusted to maintain normoglycemia. The lactate levels, however, decreased to values lower than those on admission. On the morning of surgery, blood glucose and lactate levelswere 167 mg/dl and 3.1 mmol/L respectively (figure 1).

Intravenous midazolam (2 mg) was administered prior to transport to the OR. Induction of anesthesia was accomplished with propofol, fentanyl, and rocuronium. The patient was intubated without difficulty and a continuous infusion of propofol (150-200 mcg/kg/min) and dexmedetomidine (0.5 mcg/kg/hr) were initiated for maintenance of anesthesia. Due to the uncertain pathology of the adrenal mass, a left radial arterial line was placed for blood draws and hemodynamic monitoring. A maintenance glucose infusion of D10 with 0.45% saline was initiated at 78 ml/hrand Plasmalyte® was used for supplemental fluid boluses. The first arterial blood gas sample (obtained 1 hour after induction) revealed a lactate level of 10.5 mmol/l and a glucose level of 119 mg/dl. Although a subsequent glucose level was within normal range, the lactate level remained elevated despite two 500 ml fluid boluses of plasmalyte (figure 1). The patient remained hemodynamically stable throughout the 2-hour surgical procedure and was extubated and taken to the recovery room (PACU) in stable condition.Postoperative laboratory values obtained in the PACU were significant for continued lactic acidosis (> 11mmol/L) and mild hyperglycemia (figure 1). The patient's endocrinologist and medical geneticist were immediately consulted. Recommendations were to administer a 1-liter bolus of normal saline and initiate the patient's cornstarch diet regimen (table 1) as soon as oral feeding could be tolerated. Other recommendations were to wean the intravenous fluid (D10 with 0.45% NS) rate by 5 ml/hr as the patient increased intake of

his preoperative cornstarch diet. The postoperative course was managed by the patient's endocrinologist and oncologist. As a result of the aforementioned management strategy, serum lactate levels steadily decreased to preoperative levels over the ensuing several hours, and the patient was discharged home in stable condition approximately 24 hours after surgery. Histopathological examination of the resected adrenal gland revealed a heterogenous population of cells not consistent with a pheochromocytoma, and was considered benign.

Discussion

Patients with GSD 1a present several anesthetic and perioperative challenges. Due to the potential for severe hypoglycemia, special attention has to be paid to glucose management during the perioperative period. Hypoglycemia results in the increased production of lactate due to activation of the glycolytic and gluconeogenesis pathways, and may result in severe lactic acidosis [10]. Despite careful management, episodes of metabolically induced coma have been reported in patients with GSD 1 [3]; however, good glucose control will prevent lactic acidosis most of the time. In infants, blood glucose concentrations have been shown to fall to less than 40 mg/dl within 2 to 3 hours of a feed. Longer intervals between feeds have led to severe hypoglycemia and lactic acidosis [11]. Nier et al. described the case of a 30-year-old patient with undiagnosed GSD 1 who suffered a cardiac arrest, and subsequent perioperative death as a result of hypoglycemia and metabolic acidosis [8]. Therefore, the perioperative fasting period requires particular attention.

Current practice guidelines from the American College of Medical Genetics and Genomics recommend admission to the hospital the day before the surgery, so that a continuous intravenous infusion of 10% dextrose in 0.45% saline that simulates the age-appropriate liver glucose output can be provided. The authors recommend adjustment of the intravenous fluid rate to keep the blood glucose higher than 70 mg/dl. Frequent monitoring of blood glucose and lactate levels is also recommended [2]. In accordance with the described guidelines, our patient was admitted the day before surgery and placed under the care of an endocrinologist. The patient continued his regular diet until midnight, after which an infusion of D10 with 0.45% saline was initiated at a glucose infusion rate (GIR) of 2.3 mg/kg/min. The recommended GIR is based on isotope studies performed by Bier et al., who calculated that the endogenous production of glucose in healthy controls was 7.1 mg/kg/min for children under the age of six, 5.4 mg/kg/min for older children and 2.3 mg/kg/min for adults [12]. Hourly monitoring of blood glucose and lactate levels was performed and adjustments made accordingly (table 1). Frequent monitoring of glucose levels and providing a glucose infusion during the fasting period aided in the prevention of hypoglycemia and lactic acidosis.

Surgical stress during the intraoperative period may result in profound lactic acidosis. To prevent worsening acidosis, it is recommended that the preoperative dextrose containing infusion be maintained throughout the intraoperative period [13]. In our patient, a severe lactic acidosis was experienced despite normal blood glucose levels, and maintenance of the glucose infusion at the recommended rate. Our experience was similar to that described by Oshita et al. in 2 patients with GSD 1a undergoing partial hepatectomy. The authors described how the lactic acidosis worsened during the Pringle maneuver, and concluded that the worsening acidosis was due to a deficiency of glucose and oxygen supply to the liver. In our case, the procedure was performed laparoscopically with carbon dioxide insufflation. A study by

Ibraheim et al. demonstrated that high pressure pneumoperitoneum (12-14 mmHg) was associated with significantly higher lactate levels when compared to low pressure pneumoperitoneum (6-8 mmHg) [14]. Similar to our case, lactate levels increased 30 minutes after the establishment of pneumoperitoneum and remained significantly increased ($P<0.001$) until the end of surgery and one hour thereafter ($P<0.001$). The increase in blood lactate levels was attributed to tissue ischemia produced by high intraabdominal pressure [15]. We are therefore inclined to consider that carbon dioxide insufflation may have contributed to the lactic acidosis experienced in our case. A lower insufflation pressure may have reduced the degree of acidosis.

Other authors have described how normal lactate levels have been attained by increasing the glucose infusion rate. It is thought that extra administration of glucose stimulates glucose uptake into the cells, where it is metabolized via the tricarboxylic acid cycle to produce ATP under aerobic conditions, thus preventing an excess of lactate [16]. Glucose-6-phosphatase is the last enzyme activity before glucose is released from the liver. In absence of normal Glucose-6 phosphatase activity, Glucose-6 phosphate may take the pathway of less resistance and go through the glycolitic pathway. In the setting of a poorly oxygenated liver this may result in higher lactate liver production. It is also possible that despite good glucose control, lactic acid levels rose due to the effect of stress activated counter-regulatory hormones on gluconeogenesis, increasing the peripheral lactate delivery to the liver. In our case, normalization of lactate levels was only attained in the postoperative period after the administration of a liter bolus of 0.9% saline, and returning early the patient to his preoperative, more physiologic, Glycosade and Cornstarch diet regimen. Cornstarch and Glycosade act as an intestinal reservoir of glucose which is slowly absorbed into the circulation offering a continuous source of glucose [11]. Glycosade is a synthetic globular cornstarch that has a longer half-life compared to corn starch, and that is typically used at night time to offer longer fasting periods.

Based on prior metabolic monitoring, the optimum schedule and amounts of Glycosade and cornstarch feedings had been determined by the patient's geneticist and is described in table 1. The appropriate doses and timing of Cornstarch and Glycosade are age-dependent, and are titrated based on adequate glucose (>70 mg/dl) and lactate (< 2 mmol/L) concentrations. Due to continuous glucose administration, patients with GSD 1a have elevated baseline insulin levels, and may suffer rebound hypoglycemia if the supply of glucose is rapidly decreased [17].Intravenous Dextrose containing fluids were discontinued slowly after cornstarch, Glycosade and oral feedings were resumed, and blood glucose and lactate levels were monitored at hourly intervals during the full transition to oral feedings. Early introduction of Cornstarch, Glycosade and oral feedings, in order to prevent hypoglycemia and lactic acidosis, should be contemplated in the postoperative management of these patients.

Although the safe use of Lactated Ringers solution in patients with GSD 1a has been described, current guidelines recommend against the use of Lactated Ringers due to the risk of worsening lactic acidosis and metabolic decompensation [2,18]. Other authors have safely used Acetated Ringers solution instead of Lactated Ringers [19]. In an effort to minimize hyperglycemia and hyperchloremic acidosis, we elected to use a Plasmayte® infusion for fluid boluses. It is however notable that whereas intraoperative boluses of Plasmalyte® failed to improve the degree of lactic acidosis, a postoperative bolus of 0.9% saline resulted in a gradual reduction of lactic acid levels. It is difficult to claim the superiority of 0.9%

saline under these circumstances since the surgical procedure had been completed, and the patient's preoperative diet was resumed shortly after the saline bolus.

There is currently limited data on the safety of anesthetic agents in patients with GSD 1a. Bevan et al. safely utilized halothane, succinylcholine, promethazine, meperidine and atropine in a 9-year-old patient who presented for femoral osteotomy [18]. More recently, Kawai et al. described the use of sevoflurane, succinylcholine, vecuronium and nitrous oxide in a 45-year-old patient presenting for emergency appendectomy [20]. Other authors have described the safe use of epidural and spinal anesthesia [19,21]. In their report describing a case of acute pancreatitis after anesthesia with propofol in a 4 year old with GSD 1a, Bustamante et al. raised a valid concern regarding propofol use in this patient population [22]. The authors were concerned that the hypertriglyceridemia associated with GSD 1a may increase the risk of propofol induced pancreatitis. Our patient had no reported history of hyperlipidemia, therefore propofol (150-200 mcg/kg/min) and dexmedetomidine (0.5 mcg/kg/hr) infusions were used for maintenance anesthesia. The patient tolerated the infusions without any metabolic or hemodynamic consequences. Other authors have reported the safe use of a considerably lower dose of propofol (33 mcg/kg/min) in patients with GSD 1a [21]. It may however be beneficial to assess the lipid profile of patients with GSD 1a before administering a propofol infusion [22].

Due to the uncertain histopathology of the adrenal mass at the time of surgery, we did maintain a high index of suspicion that the adrenal mass may be a pheochromocytoma. We therefore utilized invasive blood pressure monitoring (left radial arterial line) and had vasoactive drugs (epinephrine and nicardipine) on hand. However, there were no blood pressure fluctuations during the procedure and the final pathology revealed a benign adrenal mass.

Although we did not experience any problems with postoperative bleeding, patients with GSD 1a have been shown to demonstrate defects in platelet aggregation and prolonged bleeding times [5,23]. Other patients with GSD 1 have features of von Willebrand disease [24]. Recurrent and severe epistaxis has also been reported [3,24]. The results of a bleeding time and other coagulation factors may have to be considered before the insertion of nasogastric tubes or the performance of regional anesthesia. Although the exact mechanism for the bleeding diathesis is unclear, glucose infusions have been shown to ameliorate the bleeding [5,23]. Other authors have successfully utilized infusions of DDAVP to correct prolonged bleeding times [7].

Characteristic features of patients with GSD 1a include short stature, a cushingoid appearance, hepatomegaly, and delayed motor development [2]. Although the described features were not present in our patient, their presence may pose difficulties during airway management. Hepatomegaly may predispose patients to an increased intraabdominal pressure and reduced functional residual capacity.

Conclusion

In summary, coordinated care between specialists familiar with GSD 1a is beneficial to ensuring the safe perioperative course of patients who require surgery. Close monitoring of serum glucose and lactate levels is essential in preventing hypoglycemia and minimizing lactic acidosis. Early resumption of the preoperative dietary regimen may aid in reversing any metabolic abnormalities encountered during the operative period.

Table

Table 1: Recommendations for Perioperative Management

1. Admit the day before surgery for the management of blood glucose and lactate levels.
2. Provide a continuous source of carbohydrates.
3. When fasting, provide D10 with 0.45% saline at a glucose infusion rate of 2.3 mg/kg/min.
4. If hypoglycemia occurs (FSBS<70mg/dl):
    I. While on fluids and fasting: Give bolus and increase the fluid rate to attain a glucose goal of 70-100 mg/dl.
    II. While off of IVF:
        a. If glucose 50-60mg/dl and patient is asymptomatic, please provide a snack containing no more than 5gm of sugar and recheck finger stick blood sugar in 15 minutes.
        b. If glucose is less than 50 mg/dl or symptomatic: Give 3 fast acting glucose tablets (5-10 gm), give 10 grams of cornstarch and recheck blood sugar every 15 minutes until blood sugar > or equal to 80 mg/dl. (They need 5-10 grams of simple sugars followed by 10 grams of complex sugars; otherwise, they have rebound hypoglycemia).
        c. If after first 15 minutes glucose levels don't improve please start D10w+1/2 NS at a glucose infusion rate of 2.3 mg/kg/min. (98 ml/hour).
5. Once oral feedings can be restarted, resume cornstarch according to the following schedule:
    I. 6 AM: 52 gr of cornstarch
    II. 10 AM: 52 gr of cornstarch
    III. 2 PM: 52 gr of cornstarch
    IV. 10 PM: 26 gr of cornstarch
    V. 12 AM: 120 gr of Glycosade
6. Once corn starch and diet are tolerated, wean intravenous fluids very slowly over an 18 hour period.

Figure

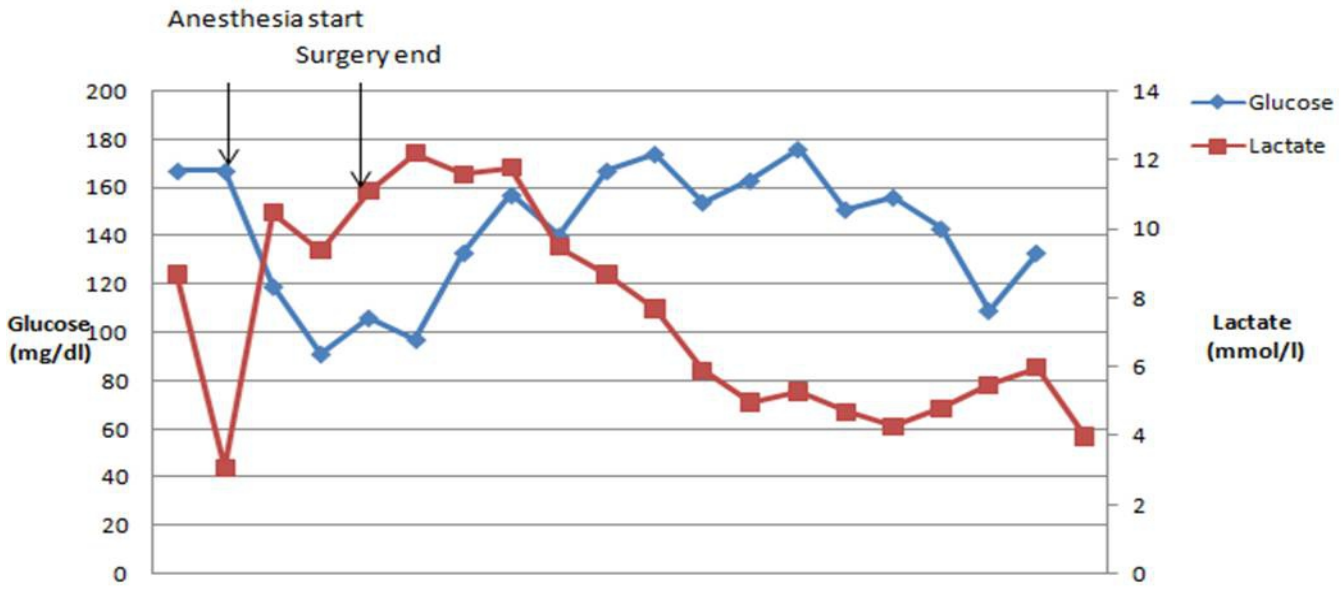

Figure 1: Perioperative glucose and lactate levels

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