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Anesthetic management in a patient with glucose-6-phosphate-dehydrogenase deficiency undergoing adenoidectomy and tonsillectomy: a case report

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited X-linked disorder that can result in abnormalities in the pentose phosphate pathway (PPP). G6PD deficiency is known to be the most common enzymatic deficiency affecting red blood cells (RBCs) and causing hemolysis [1]. Is estimated that 400 million people have been diagnosed with this disease worldwide, mostly males because of its X-linked recessive pattern. G6PD catalyzes the first step of the PPP that converts glucose-6-phosphate to 6-phosphogluconate and reduces nicotinamide adenine dinucleotide phosphate, thus enabling reduced glutathione and reducing oxidative stress. In this enzyme deficiency, there is an increased risk of oxidative stress, so minimization of possible oxidative stressors must be ensured. Fava beans, infections, metabolic conditions such as diabetic acidosis, surgical stress, and intake of certain drugs may precipitate hemolytic anemia (HA) in these patients. Another aspect of this condition is especially increased resistance to *Plasmodium falciparum* (malaria agent). There is no evidence of a global consensus regarding the use of anesthetic agents in G6PD deficiency [2]. Since PPP is the only mechanism protecting RBCs from oxidative stress, these cells are at an increased risk of hemolysis. Symptoms such as jaundice, pallor, colored urine, fatigue, anemia, and splenomegaly may be seen, especially in children. Usually, the hemolytic crisis may be seen up to 3 days postoperatively. Drugs such as propofol, remifentanil and dexmedetomidine may be safely used in these patients because of their reduction of oxidative stress. Volatile anesthetics and nitrous oxide have not been found to increase oxidative stress. Additionally, these patients have an increased risk of methemoglobinemia, so local anesthetics other than mepivacaine should be avoided; if methemoglobinemia were to occur as a side effect, it could not be treated with methylene blue, as its use is contraindicated in G6PD deficient patients. The list of medications that must not be used in these patients is shown in Table 1. In this case report, we present the successful anesthetic management of a child patient undergoing adenoidectomy and tonsillectomy.

TABLE 1. List of unsafe medications

Medications not recommended in class I–III
Acetanilide
Ciprofloxacin
Doxorubicin
Chloramphenicol
Isoniazid
Vitamin K
Methylene blue
Trinitrotoluene
Toluidine blue
Nitrofurantoin
Primaquine
Acetanilide
Dapsone
Furazolidone
Nalidixic acid
Nitrofurantoin
Sulfacetamide

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A 3-year-old girl (height 90 cm, weight 13 kg, BMI 16) with known G6PD deficiency was scheduled for an adenoidectomy and tonsillectomy procedure under general anesthesia at our medical center (Figure 1). Written consent was obtained from the patient's parents for the publication of this case report. She was diagnosed with pulmonary stenosis (PS) at the age of 2 and a balloon valvuloplasty was applied. Then she developed residual valvular and supravalvular PS so pediatric cardiology was consulted to optimize the anaesthesia. Both departments decided there were no indications for antibiotic endocarditis prophylaxis. In physical examination, there was a systolic ejection murmur at the left border of the sternum in intercostal space 2–3. The electrocardiographic (ECG) and echocardiographic findings were within the normal range. The patient was diagnosed with G6PD deficiency at the age of one upon developing jaundice and HA after eating honey. She had elevated total and direct bilirubin and elevated lactate dehydrogenase levels at that time. The patient was using no medications related to the disease. She has no signs of jaundice and no splenomegaly. Light hepatomegaly was detected but her bilirubin levels and liver enzymes levels were normal. G6PD was measured at 4.19 U g^{-1} hemoglobin (Hb), below the normal level. Her laboratory findings showed Hb 11.7 g dl^{-1}, and hematocrit (Hct) 35%. Because we did not suspect any active hemolysis, we did not require any further examinations preoperatively.

The patient was premedicated with 2 mg of oral midazolam to reduce emotional stress, as it can be a precipitating factor for hemolytic crises in these patients. She was then transferred to the operating room, where induction of anesthesia with sevoflurane was performed. After verbal response and lashes reflex were lost, a 20G intravenous (IV) cannula was established and the patient was monitored with ECG, pulse oximetry, non-invasive blood pressure and end-tidal carbon dioxide measurement, a nasopharyngeal temperature probe, and a bispectral index (BIS) sensor. Her vital signs were normal at the beginning of the operation. The patient was anesthetized IV with propofol (30 mg), fentanyl (6.5 µg), rocuronium (10 mg), and prednisolone (10 mg). Anaesthesia was then maintained with an infusion of dexmedetomidine 0.1–0.2 µg kg^{-1} h^{-1} and a mixture of 2% sevoflurane, oxygen 50% and 50% air. The BIS value stayed in the range of 40–65, with normothermia and stable hemodynamics during the operation. Venous blood gas was taken at the beginning and the end of the operation, showing normal values for Hb, Htc, lactate, methemoglobin, and metabolic or respiratory state. As an analgesic 10 mg per kg of IV paracetamol was infused, the surgical team also applied local lidocaine as an analgesic. The muscular blockade was reversed with atropine (0.25 mg) and neostigmine (1 mg) and was extubated with no complications. She was discharged from the hospital two days later and developed no signs of HA or other complications 1 month after the operation.

FIGURE 1. BIS usage for monitoring of the anesthesia depth

G6PD plays an important role as the first enzyme of the PPP and is the only source for generation of nicotinamide adenine dinucleotide phosphate (NADPH), which reduces glutathione and also prevents oxidative stress. When this enzyme is deficient, RBCs are vulnerable to oxidative stress and can undergo Coombs-positive HA. The diagnosis of the disease is usually made after the patient experiences jaundice and hemolysis. There can be symptoms such as pallor, fatigue, jaundice, and darkened urine. The laboratory findings may show increased levels of unconjugated bilirubin and lactate dehydrogenase and reduced Hb and Hct levels [1]. Elevated levels of urobilinogen and hemosiderin may also be detected in the urine tests. Schistocytes, reticulocytes and Heinz bodies may be seen in peripheral smears. A genetic test and G6PD enzyme level measurement may help diagnose the disease. The World Health Organization has divided these patients into 5 classes, as shown in Table 2. After diagnosis, these patients are recommended to avoid precipitating factors

TABLE 2. Classes of glucose-6-phosphate dehydrogenase enzyme variants

Class	Level of deficiency	Enzyme activity	Symptoms
I	Very severe	–	Chronic non-spherocytic hemolytic anemia
II	Severe	≤ 10%	No chronic anemia, oriental variants of acute hemolytic anemia
III	Moderate	10–60%	The common African form
IV	Mild to none	60–150%	Normal enzyme activity
V	None	≥ 150%	Increased enzyme activity

such as fava beans, stress, and the medicaments shown in Table 1.

From an anesthesiologist's point of view, the anesthetic management of these patients includes optimization of laboratory tests and minimization of precipitating factors. Our patient had a history of continuous previous adenoid and tonsillitis infections and the infection itself is an important factor that may cause HA. An antibiotic and nasal spray were prescribed 1 week before the operation. She had an adequate level of Hb and Htc, but 2 units of RBCs were prepared in case of an emergency. Preoperative emotional stress was reduced by oral benzodiazepines and induction was done with inhaled sevoflurane, even though Cho *et al*. [2] state that there is a controversy related to midazolam and sevoflurane usage in G6PD deficiency as *in vitro* studies have shown that it may have an inhibitory effect on G6PD [2, 3]. Cicvarić *et al*. [4] suggest that benzodiazepines, ketamine, propofol, fentanyl, paracetamol, and inhalation agents are safe for use in G6PD deficiency. Our experience in this case also suggests that both these drugs may be considered safe for these patients. Analgesia was provided with 10 mg kg^{-1} paracetamol (IV), even though use of paracetamol is also controversial, with the importance of overdose avoidance [5]. Prednisolone was used not only for its anti-inflammatory effect but also because it has an important role in the prevention and reduction of airway edema, as we were aiming for a deep anesthesia extubation with no airway obstruction that could cause any stress or respiratory acidosis. We did not use IV lidocaine because local anesthetics can cause methemoglobinemia, and methylene blue used for its treatment cannot be applied to these patients because it is normally reduced by NADPH-dependent enzymes to leucomethylene blue and then to the ferrous form, but in these patients, methylene blues remains unreduced, causing oxidative damage [6].

Takahiro *et al*. [7] used propofol and remifentanil infusion for maintenance of anesthesia in the case of a child undergoing dental anesthesia, stating that propofol has antioxidant activity and remifentanil inhibits the production of oxygen radicals. In our case, we used dexmedetomidine infusion, which also has an antioxidant, anti-inflammatory, and sedative effect with a reduced risk of hemolysis after surgery in patients with G6PD deficiency [7]. Kunisawa *et al*. [3] also state that dexmedetomidine plays an important role in oral surgery because it can inhibit salivary secretions. Additionally, a Foley catheter was not placed in our case, because the operation was expected to last no more than one hour and to minimize risk of infection (which could lead to a hemolytic crisis).

Patients with G6PD deficiency are at increased risk of HA and the avoidance of precipitating factors requires a detailed preoperative evaluation and a well-planned anesthetic strategy.

Normothermia, normoglycemia, hemodynamic stability and normalized metabolic state together with the avoidance of contraindicated drugs are the key to successful anesthetic management in these patients. We wanted to share this case report with our colleagues worldwide as the incidence of the disorder is increasing and so is the need for better understanding of anesthetic management in these patients.

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