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Case Report

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Caudal analgesia application with bupivacaine in a pediatric patient with glucose-6-phosphate dehydrogenase enzyme deficiency: case report*

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ABSTRACT

Glucose-6-phosphate dehydrogenase enzyme has a cells protecting feature from oxidative damage. Glucose-6-phosphate Dehydrogenase Enzyme Deficiency is a hereditary disease that causes hemolysis in cases of deficiency due to mutation in the X chromosome, due to oxidative stresses such as some drugs, chemicals or infection. The preoperative Hb of a 4-year-old patient who was to undergo circumcision surgery was determined as 8.9 g/dl. Since increased bleeding was not expected during this procedure, no attempt was made to increase the hemoglobin value. After the induction of general anesthesia with sevoflurane 8%, 1 ml/kg of 0.25% bupivacaine was administered caudally to the patient. The hemodynamic findings remained within normal limits during the surgical procedure. In the follow-up, it was determined that the pain score was low and that no additional analgesic drugs were required. Afterwards, no additional hematological abnormalities were detected and the patient was discharged two days later. We believe that during surgery, when routine monitoring measures are taken and conditions that may cause stress to the patient such as hypotension, hypoxemia, and dehydration are avoided, the patient's anesthesia and postoperative pain can be controlled with a general anesthetic gas such as sevoflurane and a local anesthetic such as bupivacaine, with attention to toxic doses.

Keywords: Bupivacaine, caudal analgesia, glucose-6-phosphate dehydrogenase deficiency, postoperative analgesia, sevorane

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INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common enzymopathies resulting from mutations in the G6PD gene linked to the X chromosome.[1]caused by inherited mutations of the X-linked gene G6PD. G6PD deficiency makes red cells highly vulnerable to oxidative damage, and therefore susceptible to hemolysis. Over 200 G6PD mutations are known: approximately one-half are polymorphic and therefore common in various populations. Some 500 million persons with any of these mutations are mostly asymptomatic throughout their lifetime; however, any of them may develop acute and sometimes very severe hemolytic anemia when triggered by ingestion of fava beans, by any of a number of drugs (for example, primaquine, rasburicase G6PD deficiency is typically inherited as an X-linked recessive trait, and is more common in males than females.[2] G6PD deficiency makes red blood cells highly vulnerable to oxidative damage, leading to sensitivity to hemolysis.[1]caused by inherited mutations of the X-linked gene G6PD. G6PD deficiency makes red cells highly vulnerable to oxidative damage, and therefore susceptible to hemolysis. Over 200 G6PD mutations are known: approximately one-half are polymorphic and therefore common in various populations. Some 500 million persons with any of these mutations are mostly asymptomatic throughout their lifetime; however, any of them may develop acute and sometimes very severe hemolytic anemia when triggered by ingestion of fava beans, by any of a number of drugs (for example, primaquine, rasburicase). Many agents used in anesthesia can cause hemolysis in patients with G6PD deficiency.[3] In this case, we planned to present the anesthesia management of a pediatric patient with G6PD deficiency who underwent orchidopexy and circumcision surgery.

CASE

Orchiopexy and circumcision surgery was planned by the pediatric surgery clinicians for a 4-year-old male patient weighing 16 kilograms. Parents of the child expressed that

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G6PD enzyme deficiency was diagnosed by the pediatric hematology clinicians at the age of 2 due to prolonged jaundice and the patient did not develop hemolytic crisis before or after this diagnosis. No pathological findings were detected in the patient's preoperative physical examination. Preoperative hemogram and biochemical values of the patient were observed as follows; hemoglobin (Hb): 8.9 g/dl, hematocrit (Hct): 28%, mean corpuscular volume (MCV): 55.3 fL, erythrocyte: $5.06x10^6$/µL, platelet (Plt): $411x10^3$/µL, blood urea nitrogen (BUN): 20.76 mg/dl, serum creatinine (sCrea): 0.40 mg/dl, alanine aminotransferase (ALT): 10.2 IU/L, aspartate aminotransferase (AST): 26.9 IU/L, INR: 1,12.

After a 6-hour preoperative fasting period, the patient was taken to the operating room 25 minutes after premedication with 0.5 mg/kg (8 mg) oral midazolam. After routine ASA monitoring and induction of general anesthesia with sevoflurane, intravenous line was inserted with a 24 G intracath. Fluid replacement was obtained with this intravenous line. After intravenous administration of 1 µg/kg fentanyl and 2.5 mg/kg propofol, a laryngeal mask (LMA) was successfully placed on the first attempt. LMA's appropriate placement was confirmed by auscultation of both lungs which were sufficiently and equally ventilated. After sterile staining and draping, the caudal space was located. In the right lateral decubitus position, After confirmation of the caudal needle's correct placement, 1 ml/kg 0.25% bupivacaine was injected in the epidural space for analgesia. The patient was placed in the supine position again and surgery was started. Anesthesia was maintained with a mixture of 50% O_2 + 50% dried air and 2% sevoflurane. No muscle relaxant was used during induction and maintenance. During the operation, which lasted approximately 80 (eighty) minutes, no complications such as hypotension, hyperthermia, hematuria, which could be signs of hemolytic crisis, were observed and the patient did not require additional opioids. At the end of the operation, the laryngeal mask was removed without any problems when spontaneous breathing became adequate and regular. In the recovery unit, the patient, who did not have any hemodynamic or respiratory problems, was transferred to the pediatric surgery ward.

Twenty four hours after the operation, Hb: 8.6 g/dL, Hct: 27.2%, MCV: 55.3 Fl, erythrocyte: 4.95, ALT: 8.5 IU/L, AST: 21.2 IU/L, direct bilirubin: 0.243 mg/dl, total bilirubin: 0.835 mg/dl, BUN: 10.7 mg/dL, sCrea: 0.46 mg/dl values were observed. The patient, who did not have any problems during the follow-up in the ward, was discharged 2 days later.

DISCUSSION

G6PD deficiency is a very common disease in which a severe erythrocyte enzyme defect results in acute hemolysis after exposure to an oxidative stressor caused by a mutation linked to the X chromosome.[1]caused by inherited mutations of the X-linked gene G6PD. G6PD deficiency makes red cells highly vulnerable to oxidative damage, and therefore susceptible to hemolysis. Over 200 G6PD mutations are known: approximately one-half are polymorphic and therefore common in various populations. Some 500 million persons with any of these mutations are mostly asymptomatic throughout their lifetime; however, any of them may develop acute and sometimes very severe hemolytic anemia when triggered by ingestion of fava beans, by any of a number of drugs (for example, primaquine, rasburicase).

The G6PD enzyme found in erythrocytes catalyzes the first step in the pentose monophosphate pathway of carbohydrate metabolism to protect the cell from oxidative damage. G6PD is involved in the production of nicotinamide adenine dinucleotide phosphate (NADPH), which is necessary to maintain normal intracellular glutathione levels. Glutathione is responsible for the destruction of oxidant substances formed in erythrocytes due to various external factors such as drugs, infections, and metabolic problems.[4]

The reason for hemolysis in G6PD deficiency is that erythrocytes cannot maintain glutathione in a reduced state when exposed to an oxidizing agent. The line of defense against oxidative stress is directly proportional to the current enzyme activation in the patient. While G6PD deficiency normally has little or no clinical effect, G6PD activity increases in oxidative stress situations and increases the cell's reducing capacity. Acute hemolysis may develop in people with G6PD deficiency because red blood cells cannot be protected from oxidant stress. While no clinical findings are observed in people with G6PD deficiency under normal conditions, acute hemolysis may occur in situations that cause oxidative stress, such as infection, metabolic problems and some medications.[5]diagnosis, and medication-use implications of glucose-6-phosphate dehydrogenase (G6PD).

Avoidance of the situations that may lead to oxidative stress in G6PD deficiency is the basis of treatment. Therefore, pain that may cause acute stress in these patients must be well controlled perioperatively.[6]

Hemolysis is common in the first 3 days after surgery. The severity and duration of hemolysis vary among patients. The agent causing hemolysis should be removed from the body as quickly as possible. Acute hemolysis may be self-limiting or may cause symptoms such as headache, cyanosis, tachycardia, dyspnea, substernal or lumbar pain, fatigue, hemoglobinuria, jaundice, and scleral icterus. Hemoglobinuria may be the first finding in the intraoperative period. If hemolysis is mild, supportive treatment may be required, and in severe cases, severe hemolytic anemia may develop, rarely requiring erythrocyte replacement. Blood transfusion is generally recommended when Hb falls below 7 g/dl or if hemoglobinuria persists when Hb is between 7-9 g/dl.[7]with its severe sequelae of bilirubin neurotoxicity and the potential of death, is the most devastating manifestation of G6PD deficiency. In a recent review of Favism, Luzzatto and Arese state that the pathophysiology of jaundice in G6PD-deficient neonates is different from that of favism, as there is little evidence of hemolysis in these infants. Objectives: To explore the role of hemolysis in neonatal hyperbilirubinemia associated with G6PD deficiency. Methods: Previously published works including studies of endogenous production of carbon monoxide (CO). Therefore, daily hemogram and urine should be monitored in patients receiving general anesthesia during the postoperative period.

Many agents used in anesthesia have been associated with acute hemolysis in individuals with G6PD deficiency. It has been suggested that anesthetic agents such as midazolam,

diazepam, ketamine, halothane, sevoflurane, and prilocaine have an effect on G6PD enzyme activity, and that especially sevoflurane, isoflurane, diazepam, and midazolam have an inhibitory effect, but it has been reported that further research is needed on the subject.[8]with an estimated 400 million people worldwide carrying a mutation in the G6PD gene that causes deficiency of the enzyme. Although drug-induced haemolysis is considered the most common adverse clinical consequence of G6PD deficiency, significant confusion exists regarding which drugs can cause haemolytic anaemia in patients with G6PD deficiency. In the absence of consensus among physicians, patients are subject to conflicting advice, causing uncertainty and distress. In the current review we aimed, by thorough search of the medical literature, to collect evidence on which to base decisions either to prohibit or allow the use of various medications in patients with G6PD deficiency. A literature search was conducted during May 2009 for studies and case reports on medication use and G6PD deficiency using the following sources: MEDLINE (May 2009 It has also been emphasized that when the use of these inhibitory agents is necessary, their side effects can be minimized by careful dose adjustment. Valiaveedan et al.[6] stated that all general anesthetic agents are generally safe and supported this in their study. In the literature, malignant hyperthermia has been reported in only one patient during the use of halothane due to the use of general anesthetic agents. In another case reported by Goi et al.[9], 3,5 ml of mepivacaine was used to a 3 year old boy necessitating dental therapy under general anesthesia. For this patient, also sevoflurane and rocuronium was used in the induction, and propofol and remifentanyl infusions were used during general anesthesia maintenance. Local anesthetic drugs such as prilocaine and lidocaine should be avoided in individuals with G6PD deficiency due to the risk of methemoglobinemia. Bupivacaine has been reported as a safe agent in G6PD deficiency.[9]

Takahashi et al.[10] reported anesthesia management of a 22 kg 5 year old boy in need of upper labial frenulum excision. They reported use of midazolam and dexmedetomidin infusion for sedation for 15 minutes duration of procedure and 1 ml of 2% lidocain for local anesthesia of the excision site. They reported no undesired side effect such as hemolytic crisis up to a week postoperatively.

In the postoperative period, reducing pain is important because it prevents oxidative stress and prevents hemolysis. Accordingly, agents containing antioxidant vitamins and minerals should be used in the preoperative period and pain should be reduced in the postoperative period. Adequate doses of paracetamol are generally recommended for postoperative pain in children, but there are some concerns about the safety of this drug in patients with G6PD deficiency and therefore it should be carefully evaluated for these patients. For this reason, paracetamol was not used in our patient. Regional anesthesia can be applied in children, but it is usually combined with general anesthesia or used for postoperative pain control.[11] We also applied the caudal analgesia technique in our patient for intraoperative analgesia and postoperative pain control. Successful postoperative analgesia was achieved in our patient whose Visual Analog Scale (VAS) value did not exceed 2 for 30 hours after surgery and who did not require additional analgesics.

In Gómez et al.'s[12] reported case, a 45 year old man with G6PD deficiency having laparoscopic low anterior rectal resection, general anesthesia management were performed with total intravenous anesthesia with propofol (2,5-3 mg/kg/h), rocuronium (50 mg), fentanyl 350 mcg in total, and 8 ml bupivacaine (0,125% in concentration) was used. And they reported no unfavorable effect.

There is ongoing debate about which medications are safe for people with G6PD. Our patient was restless and anxious preoperatively, so oral midazolam was administered before surgery. Sevoflurane was used for induction and maintenance, but it did not cause hemolysis and did not compromise the patient's stability. In order to reduce surgical stress and pain, our patient was provided with adequate pain management with the caudal analgesia technique. The lack of need for muscle relaxants with laryngeal mask application prevented the use of additional medications. No intraoperative or postoperative problems were experienced. We believe that the short duration of the operation and careful adjustment of the inhalation agent dosage contributed to this.

CONCLUSION

As a result, in patients diagnosed with G6PD deficiency who will undergo general anesthesia, the stress caused by surgery and anesthesia should be reduced, agents that may cause hemolytic crisis should be avoided, and a safe perioperative anesthesia plan should be made.

There are concerns about triggering hemolytic crisis with agents such as sevoflurane, isoflurane and midazolam in the performance of general anesthesia in patients with G6PD deficiency. Premedication with midazolam, induction of general anesthesia with sevoflurane + propofol, maintenance of general anesthesia with sevorlurane and caudal analgesia with bupivacaine, may be used with caution of local anesthetic toxic doses.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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