37Case Report

Anesthetic Management In A Patient With Crigler-Najjar Syndrome Undergoing A Dental Procedure: A Case Report

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ABSTRACT

Anesthetic management in a patient with Crigler-Najjar Syndrome undergoing a dental procedure: A Case Report.

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Crigler Najjar Syndrome (CNS) is an ultra-rare autosomal recessive inherited disorder caused by a mutation in the uridine glucronyl 5'-diphosphate-glucronyl transferase (UGT) gene. Children with this disease may have elevated non-hemolytic unconjugated bilirubin levels and as a consequence symptoms like jaundice, hypotony, lethargy, anorexia, ataxia and kernicterus may occur. The CNS is challenging for anesthesiologists because most anesthetic agents may affect the liver and may increase serum-free bilirubin levels. In this case report, we present the case of an 8 years old female patient, diagnosed with type II CNS, who underwent a dental procedure, while she was scheduled for an upcoming surgery for orthotopic liver transplantation (OLT).

Abbreviations: CNS - Crigler Najjar Syndrome, UGT - uridine diphosphate glucronyl transferase, OLT - orthotopic liver transplantation, BMI - body mass index, BIS - bispectral index, TOF - train of four, ABG - arterial blood gases.

Keywords: Anesthetic management, Crigler Najjar Syndrome, dental procedure, hyperbilirubinemia.

INTRODUCTION

Crigler Najjar Syndrome (CNS) is an ultra-rare autosomal recessive inherited disorder caused by a mutation in the uridine glucronyl 5'-diphosphate - glucronyl transferase (UGT) gene. It has an incidence of 0.6-1 in 1 million[1]. According to the partial or total lack of UGT activity, it is divided into two types. In CNS type I there is a complete lack of UGT activity, serum bilirubin > 20 mg/dL and irreversible symptoms like hepatic encephalopathy, also

known as kernicterus, may occur. On the other hand, in CNS type II, also known as Arias Syndrome, there is a partial lack of the enzyme with lower serum bilirubin concentrations (3.5-20 mg/dL). CNS type II patients may have no neurological impairment until adulthood. If elevated non-hemolytic unconjugated serum bilirubin levels are presented, those can accumulate in lipophilic tissues, like in cerebrum's basal ganglia and symptoms like hypotony, lethargy, anorexia, gait, impaired fine motor skills, ataxia, and kernicterus may occur[2]. Treatment of the disease may temporarily be provided with phototherapy (10-12 hours/day), phenobarbital (3-5mg/kg/day), bilirubin binding agents like calcium phosphate or orlistat, ursodeoxycholic acid (19-25mg/kg), heme-oxygen inhibitors, or plasmapheresis. The only ultimate treatment is liver transplantation. The CNS is challenging for anesthesiologists because most anesthetic agents may affect the liver and may increase serum-free bilirubin levels.

In this case report, we present the case of an 8 years old female patient diagnosed with CNS type II who underwent a dental procedure, while she was scheduled for an upcoming surgery for orthotopic liver transplantation (OLT).

CASE PRESENTATION

An 8-years-old female patient (Weight 37 kg, height 125 cm, BMI 23.7) was referred to our hospital for surgical treatment. The patient was born at the 39th week of pregnancy by normal delivery and weighed 2550 grams. On the second day after birth, jaundice appeared. Owing to the death of a child in the family and her high serum bilirubin values, that were found to be 14 mg/dL, a genetic test was performed by the pediatric metabolism department. The results showed a homozygote mutation of p. A497Pfs*4 (1488de1G) and the diagnosis of CNS type II was confirmed. During admission the patient was treated with phenobarbital (185 mg/day) and ursodeoxycholic acid (250mg/day). It is noted that phenobarbital increases the level of the enzyme by inducing its gene transcription while ursodeoxycholic acid functions as a choleretic[2].

On physical examination, the patient was alert and cooperative. She had macroscopic jaundice with the icteric sclera, lesions on the skin because of itching, and a widened abdominal circumference. An abdominal magnetic resonance showed hepatomegaly with a heterogenous appearance without the presence of ascites. She had normal echocardiography features. Her total bilirubin was 19 mg/dL, alanine transferase 123 U/L, aspartate transferase 70 U/L, prothrombin time 11.9 seconds, and Epstein-Barr virus Intra globulin M positive. The patient was evaluated with Child-Pugh Class C, Mallampati Score I, and American Society of Anesthesiologists III. The patient was a candidate for OLT but due to bad oral

health she was firstly scheduled for a dental restoration.

A written informed consent was obtained from the patient's parents for the publication of this case report.

On the operating room standard monitoring was applied, including a heart rate, respiratory rate, pulse oximeter, electrocardiogram, noninvasive blood pressure, capnography, temperature probe and additionally Bispectral Index (BIS) and Train of Four (TOF) were placed. After preoxygenation by 80 % O_2 for 3 min, general anesthesia was induced with 2 % sevoflurane, fentanyl 1 μg/kg, and rocuronium 0.6 mg/kg. Her mask ventilation was not difficult, her upper and lower dentition and her neck extension and flexion were normal, but she had a short neck and short thyromental distance. She was intubated with a size 5.5 cuffed endotracheal tube without any problem. Maintenance of general anesthesia was provided with a mixture of 2 % sevoflurane and a mixture of 50% oxygen and 40 % nitrous oxide. Fluids were administrated intravenously (i.v.), to provide hydration and to prevent hypoglycemia, containing given 500 mL of 5% Dextrose. A glucometer measured blood glucose every 30 minutes to prevent hypoglycemia. Her glycemic level remained within the normal range during the operation. A circulating-water mattress and a forced-air warming device were used to prevent hypothermia. During surgery, the patient remained at 100% oxygen saturation, with end-tidal carbon dioxide ($EtCO_2$) ranging from 35 to 40 mmHg, with a body temperature of 36.5◦C, adequate TOF 85%, BIS between 40-65, and normal arterial blood gases (ABG).

The duration of surgery was 60 minutes. Neuromuscular blockade was reversed with 50 mg of sugammadex and the patient was extubated without any complications. She was discharged from the operative room to the postoperative care unit and then from the hospital one day later without complications.

DISCUSSION

The anesthetic goal in the management of CNS patients is the prevention of hyperbilirubinemia and the usage of an anesthetic method that causes less damage to the liver. Dental restoration in children with bad oral health, who are candidates for OLT, is vital because are at high risk of oral infections, after the immunosuppressive treatment they receive after OLT [3]. Surgery may be a source of trauma and stress and may cause an elevation of bilirubin levels. Drugs such as sulfonamides, ceftriaxone, salicylates, furosemide, and ampicillin increase free serum bilirubin concentrations by displacing it from albumin[4]. Dehydration, hypercarbia, acidosis, and long-term fasting also increase the level of serum bilirubin concentrations. $EtCO_2$ must be kept within normal ranges (35-45 mmHg), ABG must be obtained to prevent acidosis and the preoperative fasting

period must not be prolongated by more than 6 hours. Dextrose-containing fluid must be infused and hypothermia must be prevented.

In 1992, Prager M.et al used for anesthesia induction, in these patients, halothane, nitrous oxide and atracurium, and for anesthesia maintenance isoflurane and morphine. In our patient, we used sevoflurane and nitrous oxide for induction and maintenance of anesthesia, rocuronium for neuromuscular blockage, and fentanyl for analgesia. Atracurium undergoes Hoffman elimination and ester hydrolysis and may have a minimal effect on hyperbilirubinemia[5]. We avoid the use of propofol because it induces displacement of bilirubin from albumin and may lead to hyperbilirubinemia[4]. Barbiturates, volatile anesthetics, and neuromuscular agents usage are safe in patients with CNS. Opioid usage is also safe because they are metabolized by other glucuronyl transferase systems than that defined in CNS. We also avoid the use of ceftriaxone in order to reduce the risk of postoperative infection because it is known that could bind albumin and cause hyperbilirubinemia. We administrated 5mg/kg i.v Gentamicin instead.

Bıçak M. et al stated that regional anesthesia is the safest type of anesthesia that can be used for CNS type II patients in their laparoscopic cholecystectomy case report[6]. Local anesthetics can bind albumin and can displace other molecules, but their affinity to albumin is 5-10000 times lower than their affinity to α-1-acid glycoprotein so they can be safely used. Unfortunately, our patient's operation was not suitable for regional anesthesia but we tried to minimize the pharmacological factors, that could elevate bilirubin levels.

CONCLUSION

In conclusion, detailed preoperative planning should be done to minimize the metabolic stress caused by the process of anesthesia and surgery in CNS patients. We must keep in mind that hyperbilirubinemia and hypoglycemia may develop. Pediatric patients with CNS should have their procedures done by trained multidisciplinary teams, including anesthesiologists, surgeons, pediatricians and metabolic professionals in special centers. The importance of a perioperative comprehensive, detailed assessment and treatment for these patients is very crucial.

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DH: helped with performing the literature review, writing the report, and editing the report, DK: helped with collecting the case data, editing the report, and obtaining consent, NÇ: was the attending anesthesiologist on the case and helped with performing the literature review, writing the report, editing the report,

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