Archives of Anesthesiology and Critical Care (Autumn 2022); 8(4): 336-338.

Available online at http://aacc.tums.ac.ir

Case Report

Inherited Unconjugated Hyperbilirubinemias and Radical Cancer Surgery: Perioperative Concerns for Bilateral Modified Radical Mastectomy

Amit Kumar, Uma Hariharan, Vijay K Nagpal, Devang Bharti*

Department of Anaesthesiology, Atal Bihari Vajpayee Institute of Medical Sciences & Dr. Ram Manohar Lohia Hospital, New Delhi, India.

ARTICLE INFO

Article history:
Received 01 December 2021
Revised 21 December 2021
Accepted 06 January 2022

Keywords:
Hyperbilirubinemia;
Gilbert syndrome;
Crigler Najjar syndrome;
Glucoronosyltransferase;
Anesthesia

ABSTRACT

Inherited defects of Uridine 5'-diphospho-glucuronosyltransferase (UDPGT) can cause congenital unconjugated hyperbilirubinemia. The perioperative anesthetic management of such patients poses several challenges. Here we report a case of bilateral carcinoma breast with congenital unconjugated hyperbilirubinemia posted for bilateral modified radical mastectomy. The patient was administered general anesthesia with no perioperative deterioration of liver function.

Hereditary disorders of bilirubin conjugation cause unconjugated hyperbilirubinemia. These disorders result from mutations that cause a decrease or loss of Uridine 5'-diphospho-glucuronosyltransferase (UDPGT) activity. UDPGT is an enzyme responsible for conjugation of bilirubin with glucuronic acid, thereby facilitating the excretion of bilirubin by making it more water soluble. Inherited defects of this enzyme can alter the metabolism and excretion of anesthetic drugs. Such congenital hyperbilirubinemias can pose challenges during the perioperative period in patients undergoing radical cancer surgeries. Here we report a case of bilateral carcinoma breast with congenital unconjugated hyperbilirubinemia posted for bilateral modified radical mastectomy.

Case Report

A 31-year-old, 60 kg female patient presented with bilateral breast lumps, diagnosed as invasive ductal carcinoma. She had undergone four cycles of adriamycin with cyclophosphamide followed by three cycles of paclitaxel based neoadjuvant chemotherapy and was referred for surgical management to our tertiary care center. She gave history of unrelieved and unevaluated yellowish discoloration of eyes, skin and urine since childhood. Her younger sister also had similar complaints. Patient had good effort tolerance with no other comorbidities and was not on any medication. Blood investigations were unremarkable except for indirect hyperbilirubinemia (total bilirubin: 30.5 mg dL^{-1}, direct bilirubin: 0.6 mg dL^{-1}, indirect bilirubin: 29.9 mg dL^{-1}). Chest x-ray, coagulation profile, electrocardiogram, echocardiogram and ultrasonography abdomen were normal. Markers for infective hepatitis and autoimmune hemolytic anemia were negative. Wilson's disease was ruled out with normal serum ceruloplasmin, serum copper and lactate dehydrogenase (LDH). A provisional diagnosis of Gilbert syndrome or Crigler-Najjar syndrome was made.

In the operating room, monitoring devices, including electrocardiography (ECG), pulse oximetry and invasive blood pressure (IBP), were attached. Under all aseptic precautions, a thoracic epidural catheter was placed in T_{4-5} interspace. The patient was premedicated with

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: dr.devangbharti@gmail.com

midazolam 1 mg IV, glycopyrrolate 0.2 mg IV and fentanyl 100 mcg IV. After adequate preoxygenation anesthesia was induced with propofol 120 mg IV and muscle relaxation was achieved using atracurium 30 mg IV. Airway was secured with 7.5 mm cuffed endotracheal tube. Anesthesia was maintained using 50% oxygen in air mixture and isoflurane, titrated to target a MAC of 0.8-1.0. For analgesia, 0.125% Bupivacaine with Fentanyl 2 mcg mL^{-1} solution was infused at the rate of 5 mL h^{-1} through thoracic epidural catheter. The patient remained hemodynamically stable throughout the procedure. Total intraoperative blood loss was 450 mL and total urine output was 200 mL. At the end of surgery, residual neuromuscular blockage was reversed and the trachea was extubated as per standard protocol. The patient was observed in the recovery room and then shifted to intensive care unit for further monitoring and care. The postoperative stay of the patient was uneventful with liver functions remaining comparable to preoperative period. The patient was discharged on postoperative day 5 and was advised follow up with onco-surgeon and medical gastroenterologist.

Discussion

Gilbert syndrome and Crigler Najjar syndrome are two hereditary disorders presenting with unconjugated hyperbilirubinemia. These reflect different degrees of deficiency in conjugating bilirubin characterized by decreased activity of UDPGT. Both these syndromes are predominantly autosomal recessive, although Gilbert occasionally shows autosomal dominant inheritance [1].

Patients with Gilbert's syndrome present with non-specific symptoms like abdominal pain, malaise, fatigue and mild jaundice. At least one third of them are asymptomatic. Menstruation, prolonged fasting, fatigue, alcohol intake and infection may aggravate the jaundice. Blood investigations, with the exception of raised indirect bilirubin, are usually within normal limits, making it a diagnosis of exclusion [2].

Crigler Najjar type – I is characterized by complete absence of UDPGT. These patients usually present with very high indirect bilirubin [3] (20 – 45 mg dl-1). Phototherapy is the mainstay of treatment while severe cases may require plasmapheresis and plasma exchange therapy [4]. Definitive therapy is liver transplant, which must be performed before profound neurological damage occurs.

Crigler Najjar type – II involves partial deficiency of UDPGT which results in around 90% reduction in enzyme activity [3]. Total bilirubin is in the range of 6 - 25 mg/dl. Treatment is usually in the form of UDPGT enzyme induction with the help of drugs like phenobarbital, rifampicin, phenytoin, omeprazole, clotrimazole, hydrocortisone, etc., to increase bilirubin conjugation.

Our patient was posted for time sensitive oncological surgery with minimal time for evaluation. Accordingly, the goals were to minimize the duration of fasting; decrease perioperative stress; avoid hepatotoxic drugs and medications predominantly metabolized in the liver; and to minimize polypharmacy. These were done in order to avoid hypoglycemia, dehydration, avoiding hypotension to prevent any decrease in hepatic blood flow, and to avoid any direct insult to the hepatocytes. These measures were undertaken to avoid any deterioration of liver function which was evident by no postoperative increase in bilirubin levels in our patient. The patient was administered general anesthesia with titrated dose of propofol to avoid hypotension. Intraoperative analgesia was given in the form of thoracic epidural infusion of bupivacaine with fentanyl. Fentanyl is metabolized in liver by CYP3A4 and its action is terminated by redistribution. Remifentanil may be a better choice due to its degradation with plasma and tissue esterases [5] but was not used due to its unavailability at our center. Paracetamol, which is metabolized by UDPGT, should be avoided [6]. Among inhalational agents, desflurane (0.02%) and isoflurane (<0.2%) are least metabolized in the liver [7-8]. The decrease in total hepatic blood flow is maximum with halothane and minimum with isoflurane [7] and hence, isoflurane was used in our case. Neuromuscular blockade may be achieved with atracurium, cis-atracurium or mivacurium as these are degraded through Hofmann elimination. Duration of action of steroid based neuromuscular agents may get prolonged and thus, they should be avoided in severe liver disease [9]. Regional anesthesia remains safe and appropriate provided there is no derangement of coagulation function. It also prevents polypharmacy. In our patient, general anesthesia with epidural analgesia was given with drugs having extrahepatic metabolism and excretion. The patient was kept first in the operation theatre list so as to minimize the duration of fasting. In this case, the entire perioperative course was uneventful.

Conclusion

Hereditary disorders of bilirubin conjugation like Gilbert syndrome and Crigler - Najjar syndromes pose clinical challenges to the anesthesiologist. Understanding the pathophysiology and aggravating factors of the disease, avoiding prolonged fasting, maintaining good hydration, employing short acting drugs with extrahepatic metabolism, and use of regional analgesia techniques wherever possible help in effective and safe perioperative management of the patient.

References

[1] Kasper DL, Longo DL, Jameson JL, Hauser SL,

Fauci AS, Loscalzo J, et al, eds. Harrisons Principles of Internal Medicine. 20th ed. New York: McGraw Hill; 2018.

[2] Thomsen HF, Hardt F, Juhl E. Diagnosis of Gilbert's syndrome. Reliability of the caloric restriction and phenobarbital stimulation tests. Scand J Gastroenterol. 1981; 16:699–703.

[3] Namasivayam, Ponnambala S. A case of Inherited Unconjugated Hyperbilirubinemia for an incidental surgery: Anesthetic management and Review. IOSR J Dent and Med Sci. 2013; 11:17-20.

[4] Pett S, Mowat AP. Crigler-Najjar syndrome types I and II. Clinical experience--King's College Hospital 1972-1978. Phenobarbitone, phototherapy and liver transplantation. Mol Aspects Med. 1987; 9(5):473-82.

[5] Radu P, Atsmon J. Gilbert's syndrome-clinical and pharmacological implications. Isr Med Assoc J. 2001; 3:593–8.

[6] Esteban A, Pérez-Mateo M. Heterogeneity of paracetamol metabolism in Gilbert's syndrome. Eur J Drug Metab Pharmacokinet. 1999; 24:9–13.

[7] Nag DS, Sinha N, Samaddar DP, Mahanty PR. General anesthesia in a patient with Gilbert's syndrome. J Anaesthesiol Clin Pharmacol. 2011; 27(2):253-5.

[8] Ehmer U, Kalthoff S, Fakundiny B, Pabst B, Freiberg N, Naumann R, et al. Gilbert syndrome redefined: a complex genetic haplotype influences the regulation of glucuronidation. Hepatology. 2012; 55(6):1912-21.

[9] Vaja R, Mc Nicol L, Sisley I. Anaesthesia for patients with liver disease. Contin Educ Anaesth Crit Care Pain. 2010; 10:16–19.