Perioperative management of a patient with hemophilia A and Crigler-Najjar Syndrome

Sir,

Hemophilia A results from an X-linked recessive defect of factor VIII coagulant protein, characterized by hemorrhage into joints and soft tissues.[1] Risk of delayed bleeding associated with hemophilia makes perioperative management of the patient undergoing laparoscopic surgery, more challenging.

Crigler-Najjar syndrome is a rare inherited deficiency of bilirubin uridine diphosphate-glucuronyl transferase (UDPGT), characterized by lifelong unconjugated hyperbilirubinemia. It exists in two forms: Type I is of severe variety associated with complete enzyme deficiency, whereas in type II there is partial deficiency. Hyperbilirubinemia may get exacerbated by drugs and metabolic perturbations in the perioperative period.[2] We are reporting anesthetic management of a patient with both hemophilia A and Crigler-Najjar type II syndrome.

A 32-year-old male, weighing 87 kg, presented with history of intermittent vomiting and abdominal pain in the right hypochondrium for the past 6 months. Ultrasonography of abdomen showed multiple calculi in the gall bladder. A laparoscopic cholecystectomy was planned. The patient had severe bleeding after tooth extraction which needed transfusion

of fresh frozen plasma. He was diagnosed as Hemophilia A with deficient factor VIII. One year later, he was diagnosed to have Crigler-Najjar syndrome type II responding to phenobarbitone. His father was a known case of Crigler-Najjar syndrome. There was no other abnormality on general and systemic examination. He had low factor VIII concentration, which was 13% of normal (<0.5 μg/ml); prothrmobin time (PT): 14 s (control 13 s); partial thromboplastin time (PTT): 45 s (control 30 s); and thrombin time (TT): 16 s (control 16 s). His hemoglobin was 16.1 g%, platelet count 104,000/mm^3, and total serum bilirubin 1.5 mg/dl (conjugated 0.5 mg/dl and unconjugated 1.0 mg/dl). Rest of the liver and renal function tests were within normal limits.

A perioperative plan was to maintain 100% factor VIII concentration on the day of surgery and first 2 postoperative days; 75% on day 3, 4, and 5; and then 50% for next 5 days. Preoperative PT, PTT, and TT were within normal limits. Phenobarbitone 60 mg was given night before the operation. On the morning of surgery; 3,750 unit of factor VIII concentrate was transfused to maintain 100% of factor VIII.

Monitoring included electrocardiogram (ECG), saturation of peripheral oxygen (SpO_2), noninvasive blood pressure (NIBP), and end-tidal carbon dioxide ($EtCO_2$). The baseline heart rate was 88/min, blood pressure (BP) 130/88 mmHg, and SpO_2 100%. Anesthesia was induced with IV fentanyl 120 μg and thiopentone 300 mg. Trachea was intubated with 8.5 mm cuffed endotracheal tube after administration of atracurium 30 mg. A pneumoperitoneum was created and intra-abdominal pressure was maintained below 15 mmHg. Anesthesia was maintained with O_2, air, isoflurane, and atracurium. Morphine 6 mg was given for analgesia. $EtCO_2$ was maintained at 35-40 mmHg. Laparoscopic cholecystectomy was uneventful with minimal blood loss. Trachea was extubated after reversal with neostigmine and glycopyrolate. Patient was shifted to high dependency unit (HDU) for postoperative management. Factor VIII concentrate was given for 10 days in the postoperative period to maintain the required concentration. Liver function tests and factor VIII were measured. The patient was discharged after 10 days.

Hemophilia A is an X-linked recessive hereditary disorder characterized by a deficiency or defective factor VIII coagulant (factor VIII C or antihemophilic factor). This disease is commonly seen in males with an incidence of 1:5,000.[3] Perioperative care of patients with hemophilia revolutionized after administration of recombinant factor VIII. Factor VIII activity levels of 1 U/ml correspond to 100% of the factor found in 1 ml of normal plasma. Normal plasma activity levels usually range between 0.5 and 1.5 U/ml (50-150%).[4] Hemophilia is categorized as mild (5-50%), moderate (1-4%), or severe (<1%) depending on factor VIII activity.[5] This patient had mild disease with 13% of factor VIII.

Most serious problem in hemophilia is the bleeding from larger vessels than smaller one, as there is defect in intrinsic pathway of coagulation system. There is always a risk of delayed bleeding after an early period of apparent hemostasis, which needs much attention in laparoscopic surgery.[6] So the goal of treatment is to achieve 100% levels of factor VIII during surgery. It can be achieved by recombinant factor VIII. The next choice is cryoprecipitate containing 80 units per bag.[6]

A single unit of factor VIII clotting activity per kilogram of bodyweight will increase plasma factor VIII levels approximately by 2%. So to achieve 100% activity in this patient with 13%, 3,750 units factor VIII are required. The half-life of factor VIII is 8-12 h, therefore it can be administered either as a continuous infusion or twice daily. A continuous infusion provides constant therapeutic levels with less total use of recombinant factor VIII.[7] In this patient, factor VIII concentrate was given as bolus injection twice daily. Even if he had mild hemophilia, 100% factor VIII activity was maintained as there was previous history of bleeding following tooth extraction. Even minor oozing or bleeding during laparoscopic cholecystectomy will hinder laparoscopic vision of the surgeon and may cause difficulty in conduct of operation. The continuation of this oozing in postoperative period may cause further problems. Therefore, factor VIII replacement was continued till the tenth postoperative day. But, there is risk of hepatitis A and HIV transmission with commercially produced factor. Cryoprecipitate can also be used as it contains 80 units of factor VIII activity per bag. However, excessive cryoprecipitate transfusion may lead to hyperfibrinogenemia increasing the risk of bleeding. Another option is transfusion of fresh frozen plasma which contains all plasma proteins including factor VIII.[6]

During minor operations, factor VIII administration should be done to achieve normal factor VIII activity for 2-6 days, however for major operations it is necessary to maintain a normal factor VIII activity for at least 10-14 days.[7]

As this patient had Crigler-Najjar syndrome along with hemophilia A, consideration has to be given to hepatic physiology and interaction of different anesthetic drugs. The mainstay of treatment for these patients is oral administration of drugs known to induce the UDPGT enzyme, thereby increasing bilirubin conjugation. The drugs that induce enzyme activity include phenobarbital, phenytoin, dexamethasone,

hydrocortisone, para-amino salicylic acid, omeprazole, clotrimazole, and rifampin.[8]

Hyperbilirubinemia can be avoided, by avoiding drugs and physiologic states that displace bilirubin from albumin. Brodersen *et al*., found that sulfonamides, ceftriaxozone, ampicillin, salicylates, and frusemide; they all displace bilirubin from albumin.[9] Same can also be done by dehydration, hypercarbia, and acidosis; thus resulting in hyperbilirubinemia.[8] In this case, $EtCO_2$ was monitored and normocarbia maintained.

The anesthetic goal in these patients with Crigler-Najjar syndrome is the prevention of increased serum-free bilirubin. The ability of drugs used in anesthesia to displace bilirubin from albumin has not been well studied. Benzodiazepines can be used as premedication as they bind to albumin, but does not displace bilirubin. Sodium thiopental is highly protein bound, but its ability to displace bilirubin has not been researched. Displacement of bilirubin from albumin induced by fatty acid components of propofol results in increased free bilirubin. However, barbiturates have been used by Robards *et al*.[8] Morphine can be used safely in these patients as it is 20-40% protein bound and is metabolized by a different glucuronyl transferase enzyme system than that is deficient in Crigler-Najjar syndrome.[2] Opioids with high potency like fentanyl and sufentanil are preferred as these will displace far fewer bilirubun molecules from albumin than those with low potency. Muscle relaxants atracurium and cis-atracurium undergo Hoffman elimination in the plasma, as well as ester hydrolysis and may have minimal effects on plasma bilirubin levels.[8] Inhaled anesthetics do not have a direct effect on the protein binding of bilirubin, but mild postoperative increases in serum bilirubin have been reported in surgical patients receiving sevoflurane and isoflurane.[10] But administration of sevoflurane or desflurane to volunteers who did not undergo surgery induced no abnormalities in liver function tests. So surgical factors were implicated for the alterations in liver function tests.[8]

In this patient, raised PTT was attributed to hemophilia rather than Crigler-Najjar syndrome II as these are good responder to barbiturate therapy than type I. So the PTT got corrected after factor VIII replacement. However, intramuscular injections were avoided and care taken during intubation to avoid submucosal hemorrhage. Nasal intubation should be avoided. Pressure points should be well padded to avoid intramuscular hematoma and hemarthosis.[6] For postoperative analgesia, patient-controlled analgesia (PCA) can be safely used rather than nonsteroidal anti-inflammatory drugs (NSAIDS) which increases the risk of gastrointestinal bleeding.

In view of above conditions, we maintained factor VIII levels in the perioperative period to prevent bleeding. Also, drugs that would alter the hepatic metabolism were avoided. Patients with hemophilia and Crigler-Najjar syndrome presented an anesthetic challenge and need good preoperative assessment and preparation, along with meticulous monitoring. A coordinated team effort of an anesthesiologist, surgeons, hematologist, and gastroenterologist is essential for a successful perioperative outcome.

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