Unconjugated Hyperbilirubinemia after Open Heart Surgery.

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Abstract

The occurrence of hyperbilirubinaemia after heart surgery using cardiopulmonary bypass or post-operative heart failure is fairly common. Mechanism of hyperbilirubinemiais still not completely clarified, and there are so few specific therapies available for acute hepatobiliary injury. Post-operative mortality well correlates with increasing total bilirubin values, particularly for bilirubin-associate acute kidney tubular necrosis. The difficulty to reduce mortality is partially a consequence of not completely understood physiopathology. It is obvious that long-lasting CPB plays an important role, in association with hemodilution, hypotension, ischemia-reperfusion, and increasing hematic level of endogenous catecholamine with reduction of hepatic blood flow. Case report. A 68 years old man with severe mitral valve regurgitation and pulmonary hypertension and low EF 30%. Mitral valve replacement and tricuspid anuloplastic was performed. Due to low cardiac output syndrome severe hyperbilirubiemeia was seen (24 mg/dl. and unconjugated fraction 16mg/dl) days after. Phenobarbital (luminal) was started 15 mg/kg daily. Two days later the level decreased until 8 mg/dl with normalization of conjugation/unconjugation ratio.Postoperative hyperbilirubinemia is a multifactorial process caused by both impaired liver function of bilirubin transport. In case of elevated level of unconjugated fraction, we suggest to use Luminal as alternative for decreasing unconjugated fraction.

Keywords: Unconjugated Hyperbilirubinaemia; Cardiopulmonary bypass; Luminal

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Full Text

Introduction

It has long been recognized that early hyperbilirubinemia or transient jaundice could occur after extracorporeal circulation surgery. Overall incidence of postoperative hyperbilirubinemia ranges from about 8.6% to even as high as 40%. [1-3] Postoperative hyperbilirubinemia has been cited as a cause of mortality in several studies. Gastrointestinal complications following cardiac surgery are associated with high morbidity and mortality rates, prolonged hospital stay, and increased cost of hospitalization.[4,5] To perform open heart surgery it is required the use of cardiopulmonary bypass (CPB) pomp. During CPB due hemodilution, hypothermia, activation of coagulation cascade and inflammatory cytokine, all organs including liver suffering from hypoperfusion and hypoxemia. [6] The liver is a strong organ that resists for many years against biochemical toxins and for hours against hypoxia. However, despite these excellent and significant abilities, cardiac surgery imposes degrees of liver failure on 2.3% of patients. As liver failure happens, the mortality rate significantly increases too. Despite numerous studies of hyperbilirubinemia, elevated unconjugated fraction is rare and the treatment is uncommon.

Case report

A patient 68 years old man was admitted in our hospital, complaining fever, shorten of breath, incapacity of walking few meters, which has been progressive in the last month. He fatigues easily and has lost "all my energy to do anything." He also complains of anorexia, and rapid weight gain. He generally sleeps with two or three pillows. During examination massive edema in legs was seen and liver was palpable under costal arc. He had and aorto-coronary bypass ten years ago. In ECG chronic atrial fibrillation with elevated heart rate 100 120 min, in echocardiography: severe dilatation of left ventricle with systolic function 25- 30%, severe mitral and tricuspindal regurgitation biatrial enlargement. PsAP 70 mmHg. Hypethyreosis after long treatment with amiodarone, now in treatment with unimazol. At the end diagnosis was: ischemic cardiomyopathy, severe reduction of EF, chronic atria fibrilation, severe mitral and tricuspid regurgitation, pulmonary hypertension, diabetes mellitus type 2, hypertireosis, chronic renal failure, right lobar pneumonia. Coronary angiography was performed and all grafts were patent. Few days of inotropes, antibiotics, and diuretics and the patient was discharged from hospital in good condition after the proposal for valve surgery. After one month the patient was recovered again with the acute decompensating of

chronic heart failure and fever (WBC and PCR were high). The calculated Euroscore 2 the risk of hospital mortality was high 73.69%. With the consent of the patient and its relatives the patient underwent redo surgery. After standart induction of anesthesia using fentanyl, rocuronium and propofoli, supporting hemodynamic with noradrenalini before CBP median sternotomy with was performed. After institution of CPB and aortic cross clamp and blood potassium cardioplegia, surgery was performed. Consisted in mitral valve replacement with biological valve SJM epic nr 33 and tricuspidal anuloplastic with Edwards ring NC3 nr 32. Cross clamp time 82 min and CPB time 133 min.Weaning from CPB was difficult, with the support of inotropic drugs, adrenaline, dopamine and noradrenaline, and intraaortic ballon (IABP). 2 units of red blood cells (RBS) were transfused. During operation metabolic acidosis with high level of lactatemia were present. Hemofiltration was performed during CPB using 15 L of replacement fluids. Only 100 ml of urinary output was totally in whole operation. First day in ICU, the patient situation was instable, hemodynamic support with high doses of inotropes, IABP, metabolic acidosis again with high level of lactatemia,(8 mmol/L, BE-8 mmol/L). Diuresis was maintained stimulating with 1 g furosemide per day. Two more RBC were transfused again in ICU. In the second and third day the situation was improved, no more metabolic acidosis and inotropic drugs were reduced. The patient was maintained sedated with propopol, ceftriaxone and levofloxacine was used as antibiotictherapy. Bilirubin level started to increase during days (total bilirubin was 4.3 mg before operation) also temperature remained high. After ten days, hemofiltration in CVVHDF was started for elevated level of urea and for decreasing and to control high temperature already installed. Elevated value of PCR decreased, CVVHDF was stopped,the patient was weaned from ventilator support initially in good situation. Meantime bilirubin level still increased until 24, 6 mg/dl, and unconjugated fraction was 16.3 mg/dl. Coombs test was negative. No change in hemoglobin level. Mental status became worse. He was confused, mioklonik contraction in right hemipart of the body was next symptom. Patient was intubated and was connected again with ventilator in continuous mandatory ventilation. Instead of propofol, luminal was used, not only for sedation, but also as stimulator of glucoronic conjugation system. Initially dose was 15 mg/kg daily. Percutaneous tracheostomy was performed for better control of airway system. After luminal administration, bilirubin level gradually decreased, until 8 mg/ dl and ratio conjugated vs unconjugated increase. The dose of luminal was reduced in 4 mg/dl, in the

way to evaluate, mental status. After good improvement of laboratory data (total bilirubin 8 mg/dl, AST 35, ALT 115, creatinemia 1,12, urea 94 mg/dl.) the patient went again in sepsis and after, in septic shock and died one month after operation.

Discussion

Bilirubin is the normal by-product of the breakdown of hemoglobin. Bilirubin circulates in the blood bound to albumin and is taken up by hepatocytes in the liver. Within hepatocytes, bilirubin is conjugated with glucuronic acid, a process catalysed by uridine diphosphoglucuronate-glucuronyltransferase (UDP-GT). Conjugated (direct) bilirubin is secreted into bile. This process is normally highly efficient so plasma unconjugated (indirect) bilirubin concentrations remain low. Hyperbilirubinemia can be caused by conditions leading to predominantly unconjugated hyperbilirubinemia and those characterized by predominantly conjugated hyperbilirubinemia. Diseases that increase the rate of bilirubin formation (eg, hemolysis, dyserythropoiesis), reduce hepatic uptake of bilirubin (eg, medications [gemfibrozil, irinotecan and the protease inhibitors, atazanavir, and indinavir]; portosystemic shunts), or reduce the rate of bilirubin conjugation (eg, Gilbert syndrome) result in increased levels of indirect bilirubin.[7] Hyperbilirubemia and transient hepatic disfunction is not uncommon during hear surgery when cardiopulmonary bypass is used. [8-12] In the analysis of contemporary cohort of cardiac surgery [13] patients showed an overall incidence of post-operative hyperbilirubinemia of 10.1%, which is relatively low in comparison with recent literature, where incidence was reported between 3% and 35%, albeit it mostly exceeds 20%. Nature of the hyperbilirubinemia. On the first postoperative day, the total and unconjugated bilirubin concentrations increased in both the patients with postoperative hyperbilirubinemia and those with nonpostoperative hyperbilirubinemia compared with preoperative levels ($p < 0.001$). For patients with postoperative hyperbilirubinemia, 70% of the increased total bilirubin was from an increase of unconjugated bilirubin (UCB). Serum haptoglobin concentrations decreased significantly on the first postoperative day in both groups of patients ($p< 0.0001$). In patients with postoperative hyperbilirubinemia, 60.3% reached peak total bilirubin concentration on the first postoperative day, 30.1% on the second day, and 9.4% on the seventh day. Proportions of UCB from total bilirubin at the peak level were 0.73 ± 0.01,0.62 ± 0.03, and $0.53 \pm 0.Q3$ for the patients who reached their peak total

bilirubin level at the first, second, and seventh postoperative days ($p < 0.05$), respectively. The time at which the peak bilirubin level was reached did not differ between the patients with and without preoperative hyperbilirubinemia.[14] Preoperative right atrium pressure, numbers of valves replaced, and blood transfusion requirement were identified as the important predictors for the postoperative hyperbilirubinemia. Combination of these four perioperative risk factors could predict development of postoperative hyperbilirubinemia in 81.2% of all patients. Patients with severe preoperative cardiac failure may have higher right atrial pressure and preoperative hyperbilirubinemia, both reflecting the degree of liver congestion. The capacity of both bilirubin disposal and bile transport may be impaired[15 16], which also can lead to a higher preoperative of total bilirubin level. Collins et al had suggested that severe heart failure predisposes the patients to the development of clinical jaundice after CPB.[17] In our patient there are a lot of factor contributing in severe postoperative hyperbilubinemia, as mentioned above. Obstructive factors of biliary track are excluded because there is no any obstruction in bile and cystic duct in ultrasonography. So, the problem was in the synthesis and metabolism of bilirubin. The difference is that the unconjugated fraction remained high when there are no signs of hemolysis (no change in hemoglobin level, Coombs test negative). The bilirubin level was normal years ago, so there is no hereditary hyperbilirubinemia. The capacity of glucoroconjugation was reduced during whole the period of hepatic stasis. UCB is normal in neonatal period and if high level is not treated cause kernikterius. There are two ways of treatment of UCB; phototherapy and pharmacological therapy. Pharmacological therapy consists in three strategies: decrease production of UCB, increasing hepatic clereance, treatment that interrupt, UCB s enterohepatic circulation.

Pnenobarbital (Luminal) is an antiepileptic drug, is a CAR agonist that enhances the three steps in hepatic UCB clereance; uptake and storage in the liver, hepatic conjugation and hepatic excretion of bilirubin. [18] Phenobarbital has been used to treat neonatal jaundice since 1960, and there are few evidences that is used also in adult patient with Gilbert and Crigler Najjar syndrome.[19, 20] Kernicterius is expected complication of UCB, but bilirubin encephalopathy is so rare in adults despite the fact that adult patient dying with jaundice are common in routine autopsy. Perhaps the explanation is either that blood bilirubin in such cases does not reach a sufficiently high level or that only conjugated bilirubin is elevated.[21] There is no evidence, or case report that suggest phenobarbital for treatment of UCB in

patient after open heart surgery with CPB.

Conclusion: Postoperative hyperbilirubinemia is a multifactorial process caused by both impaired liver function of bilirubin transport and increased production of bilirubin because of hemolysis. The development of postoperative hyperbilirubinemia is associated with a higher mortality rate, longer duration of artificial ventilation, and longer ICU stay. In case of elevated level of unconjugated fraction, we suggest to use Luminal as inductor of hepatic enzyme. We are waiting for other study to confirm or not our suggestion.

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