Hyperbilirubinemia is a common problem in neonatal period, occurring in 60-70% of term and 80% of preterm infants in the first week of life. The elevation of free unconjugated bilirubin can enter the central nervous system which is noxious to neuron and increase the risk of acute bilirubin encephalopathy (ABE). Risk factors of encephalopathy bilirubin or kernicterus with hemolytic disease such as ABO or Rhesus haemolytic disease, G6PD deficiency. The incidence of ABE is about 0.9/100 000. Clinically bilirubin encephalopathy can be divided into 2 phase, acute and chronic phase. The initial of acute phase is noted by lethargy, hypotonia, decreased movement and poor suck, the symptoms will get worsen if the baby doesn’t get adequate therapy. The main of management ABE is exchange transfusion and continues phototherapy to reduce bilirubin level and prevent further hemolysis. We report a case of exchange transfusion in initial phase of acute encephalopathy bilirubin in a 7-day old neonate with ABO incompatibility, whom had icterus since the first day of life. Other complaints are poor feeding, lethargy and hoarsness of cry since one day before admitted to hospital. He was born from mother with 0 blood type and positive rhesus. The patient had B blood type with positive rhesus, coomb test was positive and the total bilirubin was 41.49 mg/dL, direct bilirubin was 2.8 mg/dl and indirect bilirubin was 38.69 mg/dL. The patient was treated with exchange transfusion, intensive phototherapy.

Keywords: Exchange transfusion, encephalopathy bilirubin, ABO incompatibility.


ABSTRACT

Hyperbilirubinemia is a common problem in neonatal period, occurring in 60-70% of term and 80% of preterm infants in the first week of life. The elevation of free unconjugated bilirubin can enter the central nervous system which is noxious to neuron and increase the risk of acute bilirubin encephalopathy (ABE). Risk factors of encephalopathy bilirubin or kernicterus with hemolytic disease such as ABO or Rhesus haemolytic disease, G6PD deficiency. The incidence of ABE is about 0.9/100 000. Clinically bilirubin encephalopathy can be divided into 2 phase, acute and chronic phase. The initial of acute phase is noted by lethargy, hypotonia, decreased movement and poor suck, the symptoms will get worsen if the baby doesn’t get adequate therapy. The main of management ABE is exchange transfusion and continues phototherapy to reduce bilirubin level and prevent further hemolysis. We report a case of exchange transfusion in initial phase of acute encephalopathy bilirubin in a 7-day old neonate with ABO incompatibility, whom had icterus since the first day of life. Other complaints are poor feeding, lethargy and hoarsness of cry since one day before admitted to hospital. He was born from mother with 0 blood type and positive rhesus. The patient had B blood type with positive rhesus, coomb test was positive and the total bilirubin was 41.49 mg/dL, direct bilirubin was 2.8 mg/dl and indirect bilirubin was 38.69 mg/dL. The patient was treated with exchange transfusion, intensive phototherapy.

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ABSTRAK

Hiperbilirubinemia adalah masalah umum pada neonatus, kejadian hiperbilirubinemia mungkin pertama kehidupan berkisar 60-70% pada bayi cukup bulan dan 80% pada bayi kurang bulan. Peningkatan bilirubin bebas tidak terkonjugasi dapat masuk ke susunan saraf pusat yang dapat berbahaya serta dapat meningkatkan risiko terjadinya acute bilirubin encephalopathy (ABE). Faktor risiko bilirubin ensefalopati atau kern iterus pada penyakit hemolitik seperti inkompatibilitas ABO, inkompatibilitas rhesus atau kekurangan enzim G6PD. Insiden ABE berkisar 0,9 per 100.000 jiwa. Bilirubin ensefalopati secara klinis dibagi 2 fase yaitu fase akut dan fase kronis. Pada awal fase akut dengan gejala letargi, hipotonia, gerakan menurun dan reaksi fisik menurun, gejala akan semakin memberat jika tidak mendapatkan terapi yang adekuat. Tujuan tatalaksana ABE adalah transfusi tukar dan dilanjutkan fototerapi untuk menurunkan kadar bilirubin dan mencegah hemolisis berlanjut.Kami melaporkan kasus transfusi tukar pada awal fase akut bilirubin ensefalopati pada neonatus usia 7 hari dengan inkompatibilitas ABO, pasien dikeluarkan kuning sejak hari pertama kehidupan. Keluhan yang lain adalah minum yang kurang, letargi dan tangis lemah pada satu hari sebelum masuk rumah sakit. Pasien lahir dari ibu dengan golongan darah O dan resus positif, sedangkan pasien memiliki golongan darah B dengan resus positif. Hasil comb test adalah positif, hasil bilirubin total 41,49 mg/dL, bilirubin direk 2,8 mg/dL dan bilirubin indirek 38,69 mg/dL. Pasien ditatalaksana dengan transfusi tukar dan fototerapi intensif.

Kata kunci: Transfusi tukar, bilirubin ensefalopati, inkompatibilitas ABO

INTRODUCTION

Neonatal hyperbilirubinemia is one of the most common problem in newborns. Approximately 60-70% of term infants and 80% of preterm infants develop jaundice in first week of life and resolves spontaneously after 1 to 2 weeks. However, not all cases are normal physiological jaundice. There are some diseases that could induce pathologic hyperbilirubinemia which is manifest on the first day of life. The most common cause of pathologic jaundice in the neonatal period is usually due to hemolysis from ABO incompatibility. Rhesus (Rh) incompatibility, glucose-6 phosphate dehydrogenase (G6PD) deficiency, polycythemia, cephalhematoma, sepsis, hypothyroidism, infections, metabolic disorders, congenital malformations, prematurity, and breast-feeding jaundice are the other causes. Risk of ABO incompatibility is present in 12–15% of all pregnancies but symptomatic ABO hemolytic disease occurs in <1% of all newborn infants. Severe hyperbilirubinemia if untreated can cause neurologic sequel such as acute bilirubin encephalopathy. In these cases, the serum bilirubin level may be so high and accompanied by lethargy, hypotonia, decreased movement and poor suck, that will affects the brain and causes neurologic sequel of acute bilirubin encephalopathy. The incidence of developing acute hyperbilirubinemia is about 1/100 000 meanwhile the incidence of developing acute bilirubin encephalopathy is about 0.9/100 000. Acute bilirubin encephalopathy is one of the complication involving neural system and causes long term morbidities consisting of developmental delay, sensorineural hearing impairments, mental retardation and other significant brain damages. Acute bilirubin encephalopathy is an evolving encephalopathy that can progress in three clinical phases over several day. That is initial phase, intermediate phase and advanced phase. Initial phase is noted by lethargy, hypotonia, decreased movement and poor suck. Intermediate phase has cardinal sign of moderate stupor, irritability, and increased tone. Advanced phase is characterized by deep stupor or coma, increased tone, inability to feed, and shrill cry, seizure may occur. Management of hyperbilirubinemia must be adequate enough to prevent kernicterus and other complications. Treatment of hyperbilirubinemia is usually started with phototherapy but the treatment of acute encephalopathy bilirubin is exchange transfusion (ET) which is main therapy to decline bilirubin level and prevent further hemolysis. The faster and the more aggressive the treatment, the more reversible and the better outcomes.

The procedure of ET is relatively safe when performed by experienced practitioners; nevertheless, it carries a risk of both morbidity (2.8-5.2%) and mortality (0.1-0.5% in term neonates). Complications of ET may be increased by the amount of blood exchanged. Most of these complications were asymptomatic and transient, such as severe thrombocytopenia, apnea, hypocalcemia, seizures, bradycardia, catheter malfunction, hypekalemia, and necrotizing enterocolitis, which occur within seven days after the exchange.

CASE ILLUSTRATION

A 7-day old neonate, was referred by midwife to pediatric emergency care unit of Sanglah Hospital on June 29th 2016 with diagnosis of neonatal jaundice and low intake. Based on the anamnesis, the chief complaint was jaundice since the first day of life, on face then the whole body afterwards. The babys mother tried to solve it by tanning her baby every morning, but the symptoms getting worse. Baby was complained had poor feeding a day before admitted to hospital. Baby was said sleep all time, didn't want to suck since 5 days old which get worsen until baby reject feeding at all in the morning before admitted to hospital. Baby was able to breastfeed 10-12 times per day, with duration 20 minutes each time in optimal condition. His mother complained the baby had shrill cry, with sleep preference and limited movement. There was no seizure, respiratory distress, pale, vomit, apnoe period, nor bluish appearance. Baby had fever since two days before admitted to hospital. Gradual fever with maximal temperature was 38°C. Defecation and micturation were normal. The frequency of micturition 5-6 times a day, yellow colored. Defecate 3-4 times a day, with dark green color on the first 2 day, and soft consistency. Now the baby’s stool is yellow colored, soft consistency, without mucous nor blood. Clay colored was denied. This baby was born spontaneously in hospital on June 22th. The gestational age was 35 weeks, birth weight of 2300 grams, length 45 cm, head circumference 32 cm, and apgar score 7-8. No episode of apnea, cyanosis or seizure was found. Urination and defecation were normal. Mother with premature rupture of amniotic membrane more than 12 hour and age below 37 weeks as minor risk factor of infection to the baby. He is the second child, his sister had jaundice history since 3 days old and had phototherapy for 2 days then was discharged without knowing the etiology of it. His mother diagnosis...
was G2P1001, GA 35 weeks. His mother’s blood type O with positive rhesus, father’s blood type B with positive rhesus, and sister’s blood type B with positive rhesus.

From physical examination, patient activity, tonus, reflex, and cry were weak, with poor feeding and fever since 5 days old, heart rate of 156 bpm, respiratory rate 50 tpm, axillary temperature 38.9°C, and SpO2 96% in room air. Eyes: scleral icterus (+/+)) and normal pupil reflex (+/+). Mouth: showed yellowish mucosa, thorax: heart and lung was normal, abdomen: hepar just palpable and lien was normal; extremity: weak reflex and tonus, skin: looked yellowish in whole blood (Kramer 5).

Data from laboratory test performed in Sanglah Hospital (June 29th 2015) showed: WBC 25.56x103/ul, Neutrophyl 65.8%, Hgb 11.28 g/dL, Hct 30.54%, platelet 536x103/mm3, IT Ratio 0.06, C-reactive protein (CRP) 0.51 mg/L, reticulocyte 15.17%. Liver function test: total bilirubin 41.49 mg/dL, bilirubin direct 2.8 mg/dL, bilirubin indirect 38.69 mg/dL, SGOT 125.2 U/L, SGPT 13.7 U/L, GGT 284 U/L, total protein 5.4 g/dL, albumin 4.8 g/dL, blood sugar was 94 mg/dL. Electrolyte: sodium 140 mmol/L, potassium 4.35 mmol/L, calcium 9.24 mg/dL, klorida 103 mmol/L. Blood smear: normocytic hypochromic, anisopoikilocytosis, microcytes, ovalocytes, leucopenia, and normal thrombocytes. Indirect coomb test was positive and the patient had B blood type with positive rhesus. Peripheral blood smear: anemia normochromic micrositic anisopoikilocytosis, relative neutrophilia.

Based on anamnesis, physical examination, and laboratory results, this patient was diagnosed with acute encephalopathy bilirubin initial phase because of ABO incompatibility differential diagnosis deficiency G6PD with suspicion of late onset sepsis. Patient was treated in NICU, with fluid requirement of 150 mL/kgBW/day. Transfusion of PRC 3×25 ml. Antibiotics were continued until result of blood culture is available.

On July 9th 2016, Patient was stable and had good feeding tolerance, no more yellowish appearance. The lab results were: WBC 19.28x103/uL, Neutrophyl 51.04%, Hgb 12.79 g/dL, Hct 37.04%, platelet 259.6×103/mm3, IT ratio 0.01, CRP 3.24 mg/L, total bilirubin 6.83 mg/dL, direct bilirubin 0.52 mg/dL, and indirect bilirubin 6.31 mg/dL. Electrolytes and LFT were normal. G6PD were normal (13.7 U/g Hb). Blood culture was normal. Patient was reassessed with preterm baby with acute encephalopathy bilirubin initial phase because of ABO incompatibility. Antibiotics were stopped. Patient was discharged with good clinical condition and feeding tolerance.

DISCUSSION

Hyperbilirubinemia is one of the most common problems in newborns, the rate of bilirubin production exceeds the elimination rate which end to increment of total serum bilirubin (TSB). The accumulation of bilirubin on the skin, sclera and mucose known as jaundice. The severity of jaundice is devied from Kramer 1 to 5. Pathologic hyperbilirubinemia is jaundice with bilirubin concentration > 12 mg/dL in term infant or 10-14 mg/dL in preterm infants or a jaundice which appears within first 24 hours or beyond the first week of life or a jaundice which caused by an abnormal process. In this case, the patient is a preterm infant (35 weeks), had jaundice since 12 hours after birth from head and spread to entire body. Initial laboratory results showed: total bilirubin 41.49 mg/dL, direct bilirubin 2.8 mg/dL, and indirect bilirubin 38.69 mg/dL.
in the first day. This result showed that patient had a pathologic jaundice with Kramer 5.

Encephalopathy bilirubin is complication of hyperbilirubinemia caused by unconjugated hyperbilirubinemia that develops either as a result of hemolytic disease or because of inability of the liver to conjugated bilirubin due to defect of glucuronyl transferase enzyme or when this enzyme is not fully functional. Acute bilirubin encephalopathy incidence is very low. Bilirubin in brain especially in globus palidus, subthalamic nuclei, metabolic sector of hippocampus, oculomotor nuclei, ventral cochlear nuclei and purkinje cells of the cereberal cortex, can become severe cognitive deficits and mortality rate can be as high as 10%. Acute bilirubin encephalopathy is a preventable neurologic sequele of untreated severe hyperbilirubinemia. Encephalopathy can progress in three clinical phase over several days. The major clinical features involve disturbance in level of consciousness, tone, movement and brainstem function especially related to feeding and cry. The severity of abnormalities appears to correlate with both the severity and duration of hyperbilirubinemia. That is initial phase, intermediate phase and advanced phase. Initial phase is noted by lethargy, hypotonia, decreased movement and poor suck. Intermediate phase has cardinal sign of moderate stupor, irritability, and increased tone. Advanced phase is characterized by deep stupor or coma, increased tone, inability to feed, and shrill cry, seizure may occur. In this case, patient looked yellowish on his entire body with high bilirubin level poor feeding, weak movement and cry. Seizure was denied. Those indicate that bilirubin had passed through central nervous system in early phase or initial phase bilirubin encephalopathy.

The cause of severe hyperbilirubinemia which will end to acute encephalopathy bilirubin is neonatal hemolytic diseases varies from mild to severe, depend on the signs and symptoms of the patient. Most studies reported that severe cases of hyperbilirubinemia were related to ABO incompatibility, followed by Rh incompatibility. Isoimmune hemolytic anemia may result hyperbilirubinemia, when ABO incompatibility occurs between the mother and the newborn. This disorder is most common with blood type A or B infants born to type O mothers. The hemolytic process begins in uterine which resulting active placental transport of maternal isoantibody. Maternal isoaglutinins destroy fetal erythrocytes rapidly after the baby was born because some of the baby’s RBCs may be coated with the maternal antibodies, leading to destruction of RBCs by the baby’s immune system. Symptomatic clinical findings in ABO incompatibility disease, usually does not present until birth, with peripheral blood smear show compensated mild hemolytic anemia with reticulo cytosis, microspherocytosis, early-onset unconjugated hyperbilirubinemia usually appearing within the first 24 hours of life. Elevation of reticuloocyte level reflect the degree of compensation and support the diagnosis of an ongoing hemolytic process. A strong positive in indirect Coombs test indicates that fetal RBCs are coated with antibodies which is diagnosis for ABO incompatibility. In this case, patient appeared jaundice on 12 hours old. Patient was born from mother with blood type O and positive rhesus, while patient had blood type B with rhesus positive. The indirect coomb test showed positive result. Blood smear showed anemia normokromik microsith, relative neutrophilia, toxic granule, vacuole and increament of reticuloocyte count. From those, it was concluded that the etiology of hemolysis in this case was due to ABO incompatibility.

The aim main of management acute bilirubin encephalopathy is to decline rapidly the level bilirubin serum to prevent sequeance caused by bilirubin accumulation in brain which is noxious to central nervous system. Exchange transfusion is most commonly done in neonates with hyperbilirubinemia of any origins when the serum bilirubin level reaches the upper limit with signs of central nervous system toxicity. The common technique used for bilirubin removal and reduction is the double-volume ET, which taking 50–70 minutes in time. There are four types of exchange transfusions: single-volume exchange blood transfusion, double-volume exchange blood transfusion, Isovolumetric double-volume exchange blood transfusion, partial-volume exchange (<2 volumes) transfusion. In this case, we decided to perform double-volume exchange transfusion followed by intensive phototherapy, then there was decrease of indirect bilirubin concentration 6 hours after exchange transfusion and intensive phototherapy. Patient showed some clinical improvement after the exchange transfusion performed. There was a significant decreases of bilirubin where the total bilirubin decreased from 41.49 mg/dL to 19.76 mg/dL. The indirect bilirubin value falls from 38.69 mg/dL until birth, with peripheral blood smear show compensated mild hemolytic anemia with reticulo cytosis, microspherocytosis, early-onset unconjugated hyperbilirubinemia usually appearing within the first 24 hours of life. Elevation of reticuloocyte level reflect the degree of compensation and support the diagnosis of an ongoing hemolytic process. A strong positive in indirect Coombs test indicates that fetal RBCs are coated with antibodies which is diagnosis for ABO incompatibility. In this case, patient appeared jaundice on 12 hours old. Patient was born from mother with blood type O and positive rhesus, while patient had blood type B with rhesus positive. The indirect coomb test showed positive result. Blood smear showed anemia normokromik microsith, relative neutrophilia, toxic granule, vacuole and increament of reticuloocyte count. From those, it was concluded that the etiology of hemolysis in this case was due to ABO incompatibility.

ET is primary modality therapy for severe hyperbilirubinemia but complication may happen due to the procedure. Complication occurred in 57 (38.5%) neonates and the most common complications were thrombocytopenia in 26 (17.6%) and hypocalcemia in 17 (11.5%) neonates. In this case, patient had jaundice since the first day of life and become progressively increased accompanied by
LAPSUS

A male 7-day old neonate, was referred by private of midwife with chief complaint of jaundice since 12 hours old. The baby with yellowish appearance from face then spread to whole body accompanied by poor feeding, lethargic, weak cry, drowsiness. His mother had blood type O with positive rhesus while patient had blood type B with rhesus positive. From physical examination, the baby looked jaundice in whole body (Kramer 5). The laboratory results showed total bilirubin 41.49 mg/dL, direct bilirubin 2.8 mg/dL, indirect bilirubin was 38.69 mg/dL, G6PD hormone was normal. Indirect Coomb test was positive. Patient was diagnosed with acute encephalopathy bilirubin initial phase because of ABO incompatibility. He was treated with exchange transfusion as intial treatment and continued with intensive phototherapy. There was a significant decrease of bilirubin where the total bilirubin decreased from 41.49 mg/dL to 19.76 mg/dL. The indirect bilirubin value falls from 38.69 mg/dL to 19.02 mg/dL after exchange transfusion. Although the baby had been discharged in good condition, he needs to be follow up for hearing impairment and development disorders.

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neurologic disorder. His laboratory result showed high level of total bilirubin and indirect bilirubin so we did exchange transfusion. There was no sign of thrombocytopenia or hypocalcemia which is frequent complication of exchange transfusion.

Bilirubin is neurotoxic, but the inter-individual variations in venerability are not fully understood. However, it is likely that part of this variations may be due to different plasma concentrations of total serum bilirubin, caused inter alia by variations in albumin concentration, avidity of bilirubin-albumin binding, presence of substances competing for the same binding site and sepsis. In the absence of clinical risk factors, no residual neurologic or hearing impairment occurred unless TSB exceeded 31 mg/dl and/or B/A < 8.6 mg/g. Intervention values of TSB and B/A set at high sensitivity to detect different stages of neurotoxicity had nearly the same specificity. In this case, the first level of total bilirubin 41.49 mg/dL with bilirubin-albumin ratio 8.7 mg/g, this patient had risk factor to become neurologic residual or hearing impairment later. A follow up and good intervention was important. Outcome of severe neonatal hyperbilirubinemia in preterm newborn presented more often with sensorineural hearing loss (SNHL). Indirect bilirubin level was higher in children with SNHL (22.2 versus 18.7 mg/dL, P = 0.02). An increased risk of neurologic sequel was observed in children with SNHL. In this case, exchange transfusion was done to the patient and the baby discharged home in good condition. A follow up for hearing impairment and development was scheduled to monitor longterm outcome.

SUMMARY

A male 7-day old neonate, was referred by private of midwife with chief complaint of jaundice since 12 hours old. The baby with yellowish appearance from face then spread to whole body accompanied by poor feeding, lethargic, weak cry, drowsiness. His mother had blood type O with positive rhesus while patient had blood type B with rhesus positive. From physical examination, the baby looked jaundice in whole body (Kramer 5). The laboratory results showed total bilirubin 41.49 mg/dL, direct bilirubin 2.8 mg/dL, indirect bilirubin was 38.69 mg/dL, G6PD hormone was normal. Indirect Coomb test was positive. Patient was diagnosed with acute encephalopathy bilirubin initial phase because of ABO incompatibility. He was treated with exchange transfusion as intial treatment and continued with intensive phototherapy. There was a significant decrease of bilirubin where the total bilirubin decreased from 41.49 mg/dL to 19.76 mg/dL. The indirect bilirubin value falls from 38.69 mg/dL to 19.02 mg/dL after exchange transfusion. Although the baby had been discharged in good condition, he needs to be follow up for hearing impairment and development disorders.

