Correlation between Hemolysis and Jaundice in Glucose 6-Phosphate Dehydrogenase Deficient Neonates

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Abstract- Glucose 6-phosphate dehydrogenase (G6PD) deficiency is an enzyme deficiency of the red blood cells and the most important disease of hexose monophosphate pathway. The role of hemolysis in the pathophysiology of neonatal jaundice due to G6PD deficiency is in contencious. Our aim is to study the role of hemolysis in neonatal jaundice associated with G6PD deficiency. This prospective descriptive study has been done on 244 neonates who were admitted with the symptoms and signs of icter to the Ali-Asghar Children Hospital, affiliated to Iran University of Medical Sciences, Tehran, Iran, during April 2006 to April 2007. Two groups of the babies, G6PD-defcient with neonatal jaundice and G6PD-normal with neonatal jaundice, were compared based on the parameters related to hemolysis such as hemoglobin, reticulocyte count and bilirubin level. The criteria of hemolysis in our study were reticulocyte count more than >5% and hemoglobin less than <14 mg/dl. Our data have shown that 14 (5.7%) of 244 neonates with the chief complain of icter suffered G6PD-deficiency with high male to female ratio (3.6 to 1). The mean hemoglobin levels and reticulocyte counts (16.72 vs. 16.97 and %2.48 vs. %2.79 respectively) did not differ significantly between both groups (P>0.05). The present study indicate, G6PD- deficiency as a major cause of neonatal jaundice and hemolysis is not a main determinant of neonatal jaundice in G6PD-deficient babies and most of them have non hemolytic jaundice.

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Introduction

Glucose-6 phosphate dehydrogenase (G6PD) deficiency isthe most important disease of hexose monophosphate pathway (1). It is an X-linked-recessive disease, where the deficiency of the enzyme causes a spectrum of clinical manifestations. The vast majority of affected individuals are asymptomatic; however, G6PD deficiency neonates are at risk of severe acute hemolytic anemia following exposure to oxidant stresses (1-3). The incidences of G6PD-deficient in icteric newborns in numerous studies are from 40% to 3.5% (5-8). The relationship between G6PD deficiency and hyperbilirubinemia in the newborn period is well recognized, and one of the important manifestations is jaundice without hemolysis (1, 3).

Severe neonatal hyperbilirubinemia resulting in kernicterus is the most serious complication of this enzyme deficiency in the newborn period. It causes permanent neurological damage and death (3,4). Pathogenesis of hyperbilirubinemia in G6PD-deficiency neonates include: hemolysis, decreased conjugating capacity in infants with total serum bilirubin > 15 mg/dl, and association with variant UGT-promoter for Gilbert syndrome (1, 2).

It has long been thought that the jaundice in G6PD-deficient neonate is due to hemolysis. However, in most studies there is no overt evidence of hemolysis such as anemia and reticulocytosis (1).

In some studies blood carboxyhemoglobin (COHb) and end-tidal carbon monoxide (ETCO) are elevated in G6PD-deficient infants, while, Kaplan et al found no difference in COHb levels between hyperbilirubinemic (TSB > 15mg/dl) and non-hyperbilirubinemic G6PD–deficient infants (1,9). It is interesting, however, that multiple factors may be needed to produce a significant increase in total serum bilirubin levels in G6PD- deficient infants (1).

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The aim of this study is to determine the role of hemolysis in the pathophysiology of jaundice in G6PD-deficient neonates in the hospitalized babies referring to the Ali-asghar Children Hospital with chief complaint of icter.

Patients and Methods

This prospective descriptive study has been done on 244 neonates who were admitted with the symtomps (signs) of icter to the Ali-Asghar Children Hospital, affiliated to Iran University of Medical Sciences, Tehran, Iran, during April 2006 to April 2007.

To avoid bias, we have just included the hospitalized neonates due to pathologic jaundice (at least with a total bilirubin >15 mg/dl). The neonates who had direct hyperbilirubinemia (direct to total bilirubin more than 20%), ABO & Rh incompatibility, evidence of sepsis and coombs positive hemolytic anemia, were excluded from the study.

Physical examination was performed. Data collected prospectively included: age, sex, birth weight, total & direct bilirubin, hemoglobin, Retic count, blood group & Rh (mother and newborn), and D.coombs.test. G6PD activity was measured qualitatively in the patients with a fluorescent G6PD spot test method manufactured by Kimia co. Phototherapy was started for all babies.

Two groups of babies were compared based on the parameters related to hemolysis (hemoglobin, retic count, bilirubine level). The first group was defined as G6PD-defcient with neonatal jaundice and the second group as G6PD-normal with neonatal jaundice. The criteria of hemolysis in our study were reticulocyte count more than > 5% and hemoglobin less than < 14 mg/dl. This method is similar with definition of hemolysis by.and (1, 15) and Eghbalian study at Ecbatan Hospital in Hamedan (9).

Statistical analysis was carried out using SPSS statistical package. For comparing the groups, the Student t-test was performed. P-value less than 0.05 was considered statistically significant.

Results

Overall 244 newborns with chief complaint of icter (bilirubin >15mg/dl) were admitted to our neonatal icteric ward in the Ali-asghar Childern Hospital (Tehran, Iran) during the study period. Several cases were excluded from study (78 out of 244) because of ABO (38), Rh incompatibility (14), evidence of sepsis (10), UTI (4), direct hyperbilirubineia (3). The number of babies in the first group (G6PD-deficient with neonatal jaundice) was 14 out of 166 neonates (71.4% male, 28.5% female).

We found that 152 icteric babies out of 166 babies with normal G6PD as the second group (G6PD-normal with neonatal jaundice). The overall prevalence of G6PD deficiency was 5.8% (14/244). One case in the group of G6PD deficiency had Hb = 13.3 and retic = 3%. Four cases in the group of G6PD–normal had hemoglobin concentration less than 14,while, did not have high reticulocyte count . There was no any exchange transfusion in those cases. Table 1 shows the comparision of the parameters related to hemolysis (mean Hb, mean reticulocyte count and mean bilirubin) in both groups.

Discussion

One of the most common of all clinically significant enzyme defects is G6PD-deficiency. Its prevalence in neonates with indirect hyperbilrubinemia varies in different parts of the world (2, 3). In the present study, hemolysis in G6PD-deficient accompanied with jaundice may have been very mild and the results do not confirm the full criteria of hemolysis. In addition, almost all of icteric newborns with G6PD-deficiency were without any sign of hemolysis. We have found the G6PD-deficient rate of 5.7% (14/244) that is similar with Iranpour *et al.* study in Al-Zahra Hospital, Isfahan (7.5%) of cases G6PD deficiency was diagnosed (5).

Table 1. The mean of hemoglobin concentration, total bilirubin & retic count in normal and Glucose-6 -phosphate dehydrogenase deficiency groups

G6PD Enzyme	Hb Mean ± SD	Bilirubin Mean ± SD	Retic C. Mean ± SD
G6PD-deficiency neonate	16.72±1.98	19.97±1.95	2.48±1.19
G6PD-normal neonate	16.97±1.60	18.68±3.23	2.79±2
P = 0.9	*P* =0.7	*P* =0.8	

The mean hemoglobin and retic count were very similar between two groups. In addition, there was no significant correlation found between the parameters related to hemolysis in the G6PD deficiency and the presence of neonatal jaundice (Table 1). Our findings are consistent with the reports of foreign countries (e.g. 6, 7) and also with the study from Ecbatan Hospital in Hamedan (8). A study from Nigeria shows that 40% of icteric newborn had G6PD deficiency, and in most of them there was no concomitant hemolysis (7). The other study from India shows that the incidence of G6PD-deficiency in all icteric newborns was 12.2% and there was no hemolysis (9). While, a study from Saudi- Arabia shows that incidence of G6PD deficiency in icteric newborn without signs of hemolysis was 18.4% (10). Also, they had 7% blood exchange transfusion in group of G6PD-deficiency, while, blood exchange transfusion was excluded from our study. The difference between the later and the others viewpoint in the exchange transfusion may be up to the neonatologist approach about the exchange transfusion criteria and management of neonatal hyperbilirubinemia. The findings of Hospital University Sains Malaysia are consistent with our study in relation to the poor correlation between hemolysis and jaundice in G6PD deficiency newborns (10). It seems that there is no significant correlation between hemolysis and jaundice in G6PD deficiency. Furthermore, Seidman *et al*. measured the End-tidal carbon monoxide (ET-CO) in icteric newborns with G6PD -deficiency and shown that the hemolysis is not a sufficient explanation for jaundice in G6PD- deficiency infants (11,12).

Therefore, it emerges that the findings of the present study do not support the hypothesis that hemolysis, although may be present, but may not be the determining factor for development of jaundice in G6PD deficiency neonates. Pathogenesis of hyperbilirubinemia in G6PD deficient neonates is thought to be due to other factors it may be secondary to reduced hepatic conjugation and excretion of bilirubin, or may be there is a correlation between neonatal jaundice in G6PD-deficient babies and Gilbert Syndrome (1, 13). Other studies support this hypothesis. Kaplan showed that there was a significant increase in hyperbilirubinemia in G6PD- deficient infants who also had the variant UGT- promoter of Gilbert Syndrome (14). A more plausible explanation of the jaundice in G6PD-deficient neonates is G6PD deficiency play as one risk factor for neonatal jaundice. It may be nor very common or well known factors and have to be present at the same time to cause significant jaundice. In conclusion, the present study indicate that G6PD deficiency is a major cause of neonatal jaundice without hemolysis and suggests that hemolysis might not be the sole determinant in the pathophysiology of neonatal jaundice and recommend further research into other potential risk factors (as the variant UGT – promoter of Gilbert syndrome) in the population of Iran.

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