

Cohort Study on Hemolysis Associated with G6PD Deficiency in Jaundice NeonatesSeyed Hesamedin Nabavizadeh¹, Mehrdad Rezaie², Parisa Sabzali³, Abdolhamid Barati³, Mohammad Zoladl¹¹ Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran² (Corresponding author) Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran and Department of Neonate Medicine, Shiraz University of Medical Sciences, Shiraz, Iran³ Students Research Committee, Yasuj University of Medical Sciences, Yasuj, Iranmd_rezaie@yahoo.co.uk

Abstract: Glucose 6 phosphate dehydrogenase (G6PD) deficiency as an X-linked disorder is the most common human enzyme deficiency in the world. A Meta analysis regard G6PD deficiency showed its prevalence in Iran was between 2.1 to 7.6 percent. With regard to the fact that Iran is located in area with high prevalence of G6PD deficiency, and with respect to information that some other studies consider the role of hemolysis less important in the incidence of jaundice, therefore this cohort study was aimed to determine the relationship between hemolysis and G6PD enzyme deficiency by compare related data between 107 neonates suffering from jaundice having G6PD deficiency as experiment group, and the control group consisted of 127 neonates having normal G6PD enzyme activity. Result showed that the mean of bilirubin in the experiment group was 18.1 gram per deciliter, and 16.4 grams per deciliter in the control group (p=0.018). It can be concluded that there was no evidence of higher hemolysis among neonates suffering from jaundice having G6PD enzyme deficiency compared to neonates suffering from jaundice having normal G6PD enzyme activity. It also can be concluded that hemolysis is not an important factor in the incidence of jaundice in children having G6PD enzyme deficiency.

[Nabavizadeh S H, Rezaie M, Sabzali P, Barati A, Zoladl M. **Cohort Study on Hemolysis Associated with G6PD Deficiency in Jaundice Neonates.** *Life Sci J* 2012;9(3):702-705] (ISSN:1097-8135).

<http://www.lifesciencesite.com>. 98

Keywords: Hemolysis; neonate; Hyperbilirubinemia; G6PD deficiency

1. Introduction

Glucose 6-phosphate dehydrogenase is an enzyme found in normal red blood cells. Its primary metabolic role in normal concentration is to protect red cells against oxidative damage (George and Akani, 2011). This enzyme is a crucial enzyme in the regenerative mechanism of the aerobic cells too. Although patients with the enzyme deficiency in all tissues have G6PD deficiency activity, but it seems that except in red blood cells, it has no major dysfunction symptoms in other body tissues in a way that they are not marked due to the dysfunction of this enzyme (Behrman, Kliegman, and Jenson, 2008).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency as an X-linked disorder which affecting mostly African, Mediterranean and far-eastern populations is the most common human enzyme deficiency in the world; it affects an estimated 400 million people (Iranpour, Hashemipour, Talaei, Soroshnia, and Amini, 2008). This enzyme deficiency is widely observed in tropical and subtropical regions consist of Africa, South Europe, The Middle East, South Asia, and Oceania (Cappellini and Fiorelli, 2008).

Although according to WHO, Iran is in a moderately high incidence area for G6PD deficiency (Mohammadzadeh, Jafarzadeh, ShahFarhat, Keramati, Badiie, Esmaily, and Amiri, 2009) and

there is a 10-14.9% prevalence of G6PD deficiency in this country (Nabavizadeh and Anushiravani, 2007) but a meta analysis regard G6PD deficiency showed its prevalence in Iran was between 2.1 to 7.6 percent (Nkhoma, Poole, Vannappagari, Hall, and Beutler, 2009).

The difference in incidence is related to the different areas of residence and the groups themselves which are under study. The majority of people having G6PD enzyme deficiency are unmarked throughout their lives, but these people are at risk of producing neonate jaundice and increasing the risk of acute hemolysis due to contacting oxidants (Cappellini and Fiorelli, 2008).

The clinical manifestations of G6PD deficiency vary from no symptoms to acute haemolytic anaemia or severe chronic haemolytic anemia (Rahimi, Raygani, Siabani, Mozafari, Nagel, and Muniz, 2008).

Neonatal jaundice caused by G6PD enzyme deficiency is rarely observed on first day after birth. It is usually observed on day two or three. In most cases, neonates do not suffer from severe anemia; however, the presence of factors such as prematurity, infection, and environmental oxidants, neonatal jaundice due to G6PD enzyme deficiency may be severe, which may lead to brain damage or even death. Although jaundice due to G6PD enzyme

deficiency after neonatal stages may be due to Hemolysis, and as a result, the increase of bilirubin, but according to various studies, this is not true among neonates, and the incidence of jaundice at this stage is related to other factors such as liver dysfunction (Cloherty, Eichenwald, and Stark, 2008). With regard to the fact that Iran is located in an area with high prevalence of G6PD enzyme deficiency, and also with respect to the information that some other studies consider the role of hemolysis less important in the incidence of jaundice, therefore this study was aimed to determine the relationship between hemolysis and G6PD enzyme deficiency among neonates suffering from jaundice admitted at the Imam Sajjad Hospital of Yasuj, Iran.

2. Material and Methods

The samples of this cohort study were selected among neonates suffering from jaundice who admitted at the Imam Sajjad Hospital of Yasuj, Iran. The sample size estimated approximately 105 per each group by the formula with Z 0.95(1.96), G6PD deficiency ratio of seven percent, and $d=0.05$, and also considering the possibility of a 10 percent sample loss.

In research process, 107 neonates suffering from jaundice having G6PD enzyme deficiency were selected as experiment group, and the control group consisted of 127 neonates having normal G6PD enzyme activity; so 234 admitted neonates suffering from jaundice in the Neonatal Unit of Imam Sajjad Hospital of Yasuj were studied.

Data regarding age, place of parent's residence, laboratory findings were gathered from both groups by a questionnaire designed for this purpose. The collected data were analyzed by the SPSS software using inferential and descriptive statistics.

3. Results

In the present cohort study conducted on neonates suffering from jaundice neonates who admitted at the Imam Sajjad Hospital from 2008-first quarter of 2009, a total number of 234 neonates were studied in two groups. These two groups consisted of an experiment group of 107 neonates (%45.7) which had G6PD enzyme deficiency and a control group, 127 neonates (%54.3), having a normal range of G6PD enzyme activity.

The mean age of the neonates was 4.6 ± 4.2 days, which the mean age of hospitalization of the experiment and control groups was 4.7 and 4.5 days respectively showing no significant difference.

The average of overall hospitalization period for both experiment and control groups were 4.2 and 4.4 days respectively. Despite the existence of some

differences, no significant statistical differences were observed.

The mean of hemoglobin of the infants at the time referring to the hospital were 15.1 gram per deciliter in the experiment group, and 15 gram per deciliter in the control group. These amounts of hemoglobin showed no significant statistical difference.

The average amount of bilirubin in the experiment group was 18.1 gram per deciliter, and 16.4 grams per deciliter in the control group ($p=0.018$). The higher rate in the experiment group led to a significant statistical difference (Table 1).

Table 1. Bilirubin amount (milligram per deciliter) in admitted jaundice neonates based on status of deficiency of glucose 6 phosphate dehydrogenize

Group	Case	Control	Total
Bilirubin			
Mean	18.1	16.4	17.2
SD	5.2	5.2	5.2
	P= 0.018		SIG

In the meantime, the highest amount of Bilirubin in both the experiment and control group was 30 and 39 respectively.

Considering the average amount of reticulocyte, it was 2.1 and 1.7 for the experiment and control group respectively. Although $p=0.086$, and also considering the high amount of reticulocyte in the experiment group, no significant difference was observed.

Considering hemoglobinuria, from the 212 answers from the questionnaires, hemoglobin was found in the urine of 19 neonates (%9), its details showed in table 2. The calculated relative risk associated with the occurrence of hemoglobinuria in infants with G6PD enzyme deficiency was 1.24.

Table 2. hemoglobinuria in admitted jaundice neonates

Hemoglobinuria	Number	Percent
Group		
Case	11	10.3
Control	8	6.45
Total	19	8.2
SIG	P=0.47	

All the neonates in both groups had negative compose. Regarding mothers' blood group, 49 (%46.2) were O, 37 (%34.9) were A, 14 (%13.2) were B, and 6 (%5.7) were AB. Moreover, 97 (%91.5) were +Rh, and (%8.5) were -Rh.

From the 124 correct answers of the control group, the amount of blood groups of O, A, B, and AB were 60, 33, 29, and 2 respectively. 116 neonates were +Rh, and 8 were -Rh.

The amount of P regarding the mothers' blood group was %66. The number of blood group O, A, B, and AB of the neonates were 49, 31, 21, and 5 respectively. These amounts for the control group were 46, 38, 35, and 3 respectively. 104 neonates of the experiment group were +Rh and 2 were -Rh, but for the control group was 117 and 5 respectively, which showed no significant difference regarding blood groups and the Rh in both groups.

4. Discussions

In the present study, no statistical significance was observed between the amount of Reticulocyte, hemoglobin, and Humoglobinary between case and control group ($p > 0.05$). So, it can be concluded that there was no evidence of higher hemolysis among neonates suffering from jaundice having G6PD enzyme deficiency compared to neonates suffering from jaundice having normal G6PD enzyme activity. It also can be concluded that hemolysis is not an important factor in the incidence of jaundice in children having G6PD enzyme deficiency.

A study regard evaluation of Glucose 6 phosphate dehydrogenase deficiency without hemolysis in icteric newborns showed that despite reporting hemolysis among a number of patients having G6PD enzyme deficiency, in the majority of the cases with enzyme deficiency (%58.3), no sign of hemolysis was observed (Eghbalian and Monsef, 2007). This is in accordance with the results of the present study. It should be noted that the number of hemolysis among neonates with G6PD enzyme deficiency in the Eghbalian study is higher than other studies, which may be due to the small fraction of neonates with G6PD enzyme deficiency in his study.

In a study conducted in Nigeria, 40 percent of neonates suffering from jaundice had G6PD enzyme deficiency, which most cases had no sign of hemolysis (Ahmad, Yulubu, and Hendricks, 1999). Also, In study in India, it was observed that 12 percent of the neonates suffering from jaundice had G6PD enzyme deficiency, and among these, despite that 48.7 percent suffered from severe jaundice, no case of hemolysis was observed (Madam, Sundaram, and Bhargava, 2001).

In another study conducted at Saudi Arabia, 18.4 percent of the neonates suffering from jaundice had G6PD enzyme deficiency, but no case of hemolysis was observed (Yaish, Niazi, al Shaalan, Khan, and Ahmed, 1991).

In all the studies mentioned above, and also a study conducted in Malaysia (Jalloh, Van Rostenberghe, Yusoff, Ghazali, NikIsmail, Matsuo, Wahab, and Nishio, 2005), and a study conducted in Mazandaran province, Iran (Ahmadi and Ghazizadeh, 2008) with various severities reported, no sign of interference of hemolysis as a main factor of Hyperbilirubinemia was observed among neonates having G6PD enzyme deficiency, which is consistent with the results of the present study.

A report from Birmingham reveals a fatal incidence of severe hemolysis in a neonate suffering from jaundice having G6PD enzyme deficiency (Aaron, 2007). Also another study describes a case of hemolysis and Hyperbilirubinemia among a triplet having G6PD enzyme deficiency (Shah and Yeo, 2007). These cases were exceptional individual cases which cannot undermine the results of the present and previous studies.

It is worth to note that with respect to the results of the present study which has a considerable sample size (a similar sample size of the Saudi Arabia study), it can be said that the interference of hemolysis on neonates suffering from jaundice having G6PD enzyme deficiency is negligible and even be ignored.

In general, based on the present study, there is a significant difference in the severity of jaundice (amount of bilirubin in the blood) between both the experiment and the control group, in such a way that the severity of jaundice in children having G6PD enzyme deficiency is approximately two units more than neonates having normal G6PD enzyme activity. This result is in accordance with almost all of the studies mentioned above.

In this study no meaningful difference regarding the age of admitted neonates and the period of hospitalization were observed. This could explain the short hospitalization duration of the neonates suffering from jaundice having G6PD enzyme deficiency who rapidly admitted to the hospital.

Acknowledgements:

We hereby appreciate the Deputy of Research and Technology of Yasuj University of Medical Sciences for approves this project and paying its costs and also respectful staffs of neonatal ward and medical laboratory of Imam Sajjad Hospital of Yasuj who participated in the present research.

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6/25/2012