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Prevalence of Glucose-6-Phosphate Dehydrogenase and Thyroid Hormones Deficiency in Neonatal Jaundice

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Abstract

G6PD deficiency is the most common inherited metabolic disorder and clinically significant red cell enzyme defect in man. Severe neonatal jaundice proved to be the most common clinical manifestation and a globally important most dangerous consequence of G6PD deficiency. Prolonged jaundice is sometimes associated with congenital hypothyroidism. So the early characterization of G6PD activity and thyroid hormone levels provides an etiological diagnosis for neonatal jaundice as well as the opportunity to give the newborn's family information concerning hemolytic crisis prevention and an early management in case of hypothyroidism.

Aim: This study was conducted in an attempt to evaluate the prevalence of G6PD deficiency and hypothyroidism in relation to neonatal physiological hyperbilirubinemia.

Subjects and Methods: The study included 50 neonates aged between 6 hr – 5 days, forty infants had jaundice and the other ten (control), were healthy neonates, matching the same age. All infants of the study were subjected to C-RP test, routine hematological evaluation, and serum total bilirubin levels, quantitative red blood cells G6PD assay and thyroid hormone levels.

Results: All the fifty cases of both jaundiced and healthy neonates were negative for C-RP test indicating that the 40 cases had physiological jaundice .The study revealed that G6PD enzyme was lower than normal level in 2 cases (5%). TSH level was found to be higher than normal in 13 jaundiced neonates out of 40 (33%). Seven jaundiced neonates (18%) had T_4 hormone lower than normal while all the 40 jaundiced cases had normal T_3 level. Correlation of the total bilirubin was significant with TSH and T_3 at 0.05 levels, while there was no significance with both T_4 and G6PD.

Conclusion: statistically there was no correlation between bilirubin and both G6PD enzyme and thyroid hormones, but the incidence of hypothyroidism in this study was high (18%) and the incidence of G6PD deficiency was (5%). This indicates a role of G6PD deficiency and hypothyroidism in developing neonatal jaundice among neonates. So, early neonatal screening program is recommended for early management.

Key words: Neonatal jaundice, G6PD deficiency, Thyroid hormones.

Introduction

Early-onset hyperbilirubinaemia is a high-risk condition because it often presents with an acute and rapid rise in bilirubin values. Although the outcome for most is benign, infants with extremely high serum bilirubin can develop acute bilirubin encephalopathy in the absence of urgent intervention [(1)] depending on the permeability of the blood brain barrier to bilirubin or albumin [(2)]. Neonatal hyperbilirubinemia, (defined as a serum total bilirubin level exceeding 5 mg/dl) is a frequent problem [(3)]. Neonatal jaundice affects 60% of full-term infants and 80% of preterm infants in the first three days of life. Although transient, the condition accounts for up to 75% of hospital readmissions in the first week after birth [(4)] and it is a common reason for neonates to present in the emergency department [(5)].

Hyperbilirubinemia is caused both by increased production of bilirubin as the heme in red blood cells is broken down and by decreased bilirubin excretion due to inadequate hepatic conjugation and increased enterohepatic reabsorption [(6)].

Although physiological jaundice is more frequent as compared to pathological jaundice, it is very important to differentiate between the two, as pathological jaundice may lead to kernicterus and subsequently brain damage. Treatment is dependent upon the amount of serum bilirubin and various other laboratory investigations. Thus laboratory workup is very

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important for diagnosis and prevention of neonatal hyperbilirubinemia in newborn [7].

Causes of pathological jaundice are heamolysis, breast feeding, infections, hypothyroidism and extrahepatic biliary atresia and needs investigation and medical intervention [8].

Glucose-6-phosphate dehydrogenase is an x-linked recessive disease, where the deficiency of the enzyme causes a spectrum of clinical manifestations ranging from neonatal jaundice to chronic non-spherocytic anemia, to infection and drug-induced hemolysis [9].

Hypothyroidism is the disease state caused by insufficient production of thyroid hormones by the thyroid gland. Thyroid hormones are essential for normal organ growth, development and function. The major secretory product of the thyroid is a prohormone (T_4), which is activated in peripheral tissues by outer ring deiodination to T_3 [10]. Prolonged jaundice is sometimes associated with congenital hypothyroidism which appears to be associated with the delayed maturation of hepatic uridine diphosphate glucoronyl transferase enzyme activity [11].

Aim of the work

The aim of this work was to make an early detection of G6PD deficiency and hypothyroidism in neonates suffering from postnatal physiological jaundice in order to start early management.

Material and Methods

Fifty Egyptian neonates (6 hrs - 5 days) were chosen for this study after agreement of their families. Forty jaundiced infants were selected from the **Neonatal Care Unit of Tabarak Hospital**. They were treated only with phototherapy and there was no need for blood transfusion. Other ten healthy infants matching the same age were taken as control. All of the neonates were full-term, with good weight for the gestational age and no malformations.

Blood samples were collected from jaundiced and healthy neonates and each sample was divided into two parts: One part was used to separate serum to estimate C-Reactive protein (C-RP)[12], total bilirubin [13] and thyroid hormones; TSH [14] , T_4 and T_3 [15]. The other part was added to an anticoagulant (heparin) to be used within 3 hours to estimate G6PD enzyme activity [16] and complete blood picture (WBCs, RBCs, platelets ,reticulocytes, and total counts; hematocrit [17] and hemoglobin concentrations [18]. Calculation of MCH, MCV and MCHC was carried out.

Statistical Analysis:

SPSS for windows version 17.0 and Excel computer programs were used for statistical analysis. Descriptive, t test, correlation and percentage analysis were made. Pearson Correlation was significant at p 0.05 and high significant at p 0.01 levels.

Results

All the fifty cases of both jaundiced and healthy neonates were negative in the C-Reactive protein.

Figure (1) shows the mean (14.39 mg/dl) concentration of serum total bilirubin in jaundiced neonates group in comparison to the mean (2.28 mg/dl) value in healthy neonates. Table (1) shows the normal, low and high numbers and calculated percentage values (%) for each of serum total bilirubin, G6PD, TSH, T_4 and T_3 in the hyperbilirubinemic neonates group.

Table (2) shows that the correlation of total bilirubin with TSH and T_3 was significant at 0.05 level, while there was no significant difference with both T_4 and G6PD.

The mean level of G6PD enzyme activity was 14.93 U/gHb while in healthy neonates group it was 11.06 U/gHb as presented in figure (2). Table (1) also showed that 20 cases of the jaundiced neonates group, (50%) had normal G6PD activity, 18 cases (45%) had enzyme activity higher than normal and only 2 cases (5%) had G6PD deficiency. As shown in table (3) the two G6PD deficient infants enzyme activity was 1.6 and 4.0 U/gHb. The total WBCs count of the two cases was lower than normal level. On the other hand, hemoglobin (19.5 g/dl and 20.4 g/dl), hematocrite (80% and 60%) and reticulocytes (4% and 3%) were high compared to normal values. TSH, T_4, T_3, platelets, RBCs, MCH, MCV and MCHC were within the normal values as presented in table (3). Correlation of G6PD was significant with both TSH and T_4 at (0.01) level, but not significant with T_3 (Table 2).

Data presented in figure (3) showed the mean level of TSH in hyperbilirubinemic and healthy neonates groups (10.47 U/Iu ml) and (3.19 U/Iu ml respectively). In the jaundiced neonates group, TSH of 13 cases (33%) was higher than normal level, while 27 cases (67%) had normal hormone level as presented in table (1).

Correlation of TSH with both T_4 and T_3 was highly significant at 0.01 levels (Table 2).

The mean concentration of T_4 was 9.19 ng/dl in hyperbilirubinemic neonates group compared to 11.13 ng/dl in the healthy neonates as presented in figure (4). In the jaundiced neonates group, 30 cases (75%) had normal hormone level, 7 cases (18%) were lower than normal level and 3 cases (7%) were higher than normal level as presented in table (1).Of the seven cases with low T_4, six had high TSH level while the 7th case was within normal value. All parameters of the seven cases are shown in table (4). Correlation of T_4 with T_3 was not significant as shown in table (2).

Furthermore figure (5) shows pronounced elevation in T_3 level (151.14 ng/dl) of hyperbilirubinemic group compared to the healthy neonates mean value (94.2 ng/dl). All the 40 jaundiced neonates had normal T_3 level as presented in table (1).

As demonstrated in figure (6), total WBCs count mean value in hyperbilirubinemic group was 86.3×10^2 cells/mm^3 while in healthy neonates it was 86.80×10^2 cells/mm^3 and the mean count of RBCs in jaundiced neonates was 505×10^4cells/mm^3 while it was 494×10^4 cells/mm^3 in control group (figure 7). Meanwhile, platelets count mean value was decreased (255.50×10^3cells/mm^3) in hyperbilirubinemic group compared to healthy neonates group (Figure 7). Reticulocytes mean value in jaundiced neonates was much higher (7.45%) than that in healthy neonates group (1.1%) and it is presented in fig. (8) which also shows results of hematocrit mean that was slightly elevated (50.08%) in jaundiced neonates in comparison with that of control (48.0%). Moreover, hemoglobin mean concentration level in jaundiced neonates was 16.39gm/dl while it was 15.74gm/dl in healthy neonates (Fig.9). The mean calculated values of MCH, MCV and MCHC in hyperbilirubinemic group as well as that in control group are shown in figure (10).

Discussion

Neonatal hyperbilirubinaemia is a common finding during the first postnatal week. Physiological jaundice occurs in first week of life in 60% of term and 80% of premature neonates. On the other hand, non physiologic or pathologic jaundice occurs in 5-10% of newborns which require intervention [(19)].

It is well recognized that in G6PD deficiency, early destruction of RBCs under oxidative stress causes release of hemoglobin, which is subsequently metabolized to form bilirubin that leads to the development of hyperbilirubinemia of neonates [(20, 21)]. Hypothyroidism is the most common disorder arising from hormone deficiency [(22)]. Thyroxin (T_4) which is the main product of the thyroid and circulates in plasma is converted to T_3. T_4, in many respects, is considered as a prohormone for the more potent T_3 [(23)].

In the present study: All the investigated parameters in healthy neonates were within the normal range. Reticulocytes in jaundiced neonates was higher than the normal values and this could explain the high mean value of G6PD enzyme because in normal blood, reticulocytes have about five times more activity than the oldest erythrocyte subpopulation [(24-26)].

In the present study: G6PD percentage showed that only 5% (2 infants out of the forty hyperbilirubinemic neonates) were deficient in G6PD enzyme activity. Also the two cases were with normal levels of thyroid hormones and normal RBCs count. Incidence of G6PD deficiency in this study was in accordance with the finding of a study made on 2501 newborns and the overall incidence of G6PD deficiency was 3.2% [(27)]. Another study revealed that from 272 neonates 12 babies (4.4%) were found to have G6PD deficiency [(28)].

The current study revealed that, statistically, there was no correlation between bilirubin and G6PD enzyme. However, many studies showed significant correlation between G6PD deficiency and neonatal jaundice. Also those studies revealed that the severity of hyperbilirubinemia depends on degree of G6PD deficiency and that its prevalence in severe hyperbilirubinemia is more than moderate hyperbilirubinemia [(29, 30)].

Other studies agreed with the present study in that there is no statistical correlation between G6PD and jaundice and that jaundice is associated with normal and G6PD deficient status [(31)]. Also, another study suggested that hemolysis is only partly responsible of jaundice and that decreased bilirubin conjugation and elimination play a major role in the pathogenesis of neonatal jaundice [(32)].

In the current study, G6PD was directly proportional with TSH and inversely proportional with T_4. Earlier studies have shown that thyroid hormones do influence the levels of G6PD in the erythrocytes [(33, 34)]. In addition, many studies found that the levels and activity of the enzyme decreased in hyperthyroid and increased in hypothyroid patients [(35- 37)].

Of the 40 neonates, 7 cases (18%) had T_4 values lower than normal. Of the seven neonates with low T_4 six were with high TSH which indicated that they have hypothyroidism and the 7th neonate was with normal TSH and should make free T_4 hormone to ensure that he had hypothyroidism. The 7 neonates were with normal G6PD value but two of them had low RBCs count. Primary congenital hypothyroidism has a birth prevalence of 1:2750 [(38)] to 1:4000 newborns [(39)] but in jaundiced neonates ratio raises to 10% [(40)].

In this study, bilirubin showed no statistical significant correlation with T_4, but it was directly proportional to T_3. TSH result was similar to that of a study carried by [(41)] who recorded that total bilirubin values decreased as TSH increases. Bilirubin is increased in serum of critically-ill patients and was suggested as one of the factors causing the low T_3 plasma concentrations in these patients, by the inhibition of T_4 transport into the liver [(42)]. The decrease of thyroid hormones in case of hyperbilirubunemia is due to alterations of thyroid hormone metabolism in cases of unconjugated hyperbilirubinemia. These effects might involve inhibition of thyroid hormone uptake by their target cells [(43)]. On the other hand, other studies revealed that neither bilirubin nor biliverdin affected uptake of T_3 or T_4 [(44)].

The present study demonstrated that TSH was inversely proportional with both T_3 and T_4 that represented the classic negative feedback mechanism of the thyroid axis [(45, 46)].

The goal of newborn screening is the pre-symptomatic detection of infants with congenital conditions so that treatment may be commenced as early as possible to prevent, or ameliorate, the long-term consequences of the condition [(47)].

An Egyptian study made by **El-Menshay et al.[(48)]** concluded that the incidence of G6PD deficiency in jaundiced infants was high and signifies the role of G6PD deficiency in developing neonatal jaundice among Egyptian infants. So early screening programs should be instituted in countries where the deficiency is prevalent. Also **Abdel Fattah et al.[(49)]** concluded that G6PD deficiency is an important cause for neonatal jaundice in Egyptians and neonatal screening for its deficiency is recommended.

Newborn screening for congenital hypothyroidism followed by the early initiation of thyroid hormone treatment to normalize thyroxin (T_4) concentrations has been shown to prevent intellectual disability i.e., mental retardation[(50)]. Hypothyroidism after the age of three years, when most of the thyroid hormone-dependent brain development is complete, results in slow growth and delayed skeletal maturation[(51)].

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Table (1): Normal, low and high number and calculated percentage (%) for G6PD activity, TSH, T_4 and T_3 levels in hyperbilirubinemic neonates group.

No. & Percent. / Parameters	Normal	Low	High
Total Bilirubin	----	----	40(100%)
G6PD	20(50%)	2(5%)	18(45%)
TSH	27(67%)	----	13(33%)
T4	30(75%)	7(18%)	3(7%)
T3	40(100%)	----	----

Table (2): Correlation between bilirubin content, G6PD activity, TSH, T_4 and T_3 levels in hyperbilirubinemic neonates group.

Parameters		**Bilirubin**	**G6PD**	**TSH**	**T4**
G6PD	Pearson Correlation	0.054	----	----	----
	Sig. (2-tailed)	0.741	----	----	----
TSH	Pearson Correlation	-0.323-*	0.438**	----	----
	Sig. (2-tailed)	0.042	0.005	----	----
T4	Pearson Correlation	0.075	-0.439-**	-0.581-**	----
	Sig. (2-tailed)	0.644	0.005	0.000	----
T3	Pearson Correlation	0.362*	-0.252-	-0.643-**	0.188
	Sig. (2-tailed)	0.022	0.117	0.000	0.245

* Correlation is significant at the (0.05) level.
**Correlation is highly significant at the (0.01) level.

Table (3): Parameter results of the two cases with G6PD deficiency in the hyperbilirubinemic group.

Cases / Parameters	Case 1	Case 2	Healthy Neonates
Age (days)	2.00	3.50	3.00
G6PD U/g Hb	1.60	4.00	11.06
TSH U Iu/ml	5.90	5.20	3.19
T_4 ng/dl	7.70	10.20	11.13
T_3 ng/dl	180.00	185.0	94.2
WBCs($\times 10^2$)cells/mm^3	52.00	82.00	86.80
RBCs($\times 10^4$) cells/mm^3	598.0	618.0	494.0
Platelets($\times 10^3$)cells/mm^3	200.0	200.0	320.7
Reticulocytes (%)	4.00	3.00	1.1
Hematocrit (%)	80.00	60.00	48.00
Hemoglobin g/dl	19.50	20.40	15.74
MCH	32.00	33.00	32.62
MCV	100.00	97.00	86.8
MCHC	32.00	34.00	34.3

Table (4): Parameter results of the seven cases with T_4 deficiency in the hyperbilirubinemic group.

Parameters / Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Healthy Neonates
Age (days)	1.00	1.00	6 hrs	2.00	3.00	1.50	2.00	3.00
G6PD U/g Hb	10.40	19.80	25.00	22.00	25.00	12.20	18.00	11.06
TSH U Iu/ml	50.00	24.80	40.30	16.10	49.80	32.10	2.60	3.19
T_4 ng/dl	5.10	6.60	5.900	5.40	4.90	6.50	6.40	11.13
T_3 ng/dl	62.00	102.0	91.00	118.0	82.00	118.0	139.0	94.2
WBCs($\times 10^2$)cells/m^3	118.0	106.0	126.0	82.00	64.00	142.0	107.0	86.80
RBCs($\times 10^4$)cells/mm^3	484.0	312.0	374.0	562.0	448.0	392.0	658.0	494.0
Platelets($\times 10^3$)cells/mm^3	260.0	280.0	200.0	200.0	220.0	200.0	220.0	320.7
Reticulocytes (%)	9.00	12.00	14.00	5.00	8.00	7.00	11.00	1.1
Hematocrit (%)	48.00	33.00	40.00	55.00	44.00	38.00	70.00	48.0
Hemoglobin g/dl	15.50	11.40	13.10	18.80	14.90	12.30	22.80	15.74
MCH	32.00	36.00	35.00	33.00	33.00	31.00	34.00	32.62
MCV	99.00	106.0	107.0	97.00	98.00	97.00	106.0	86.8
MCHC	32.00	34.00	33.00	34.00	34.00	32.00	32.00	34.3

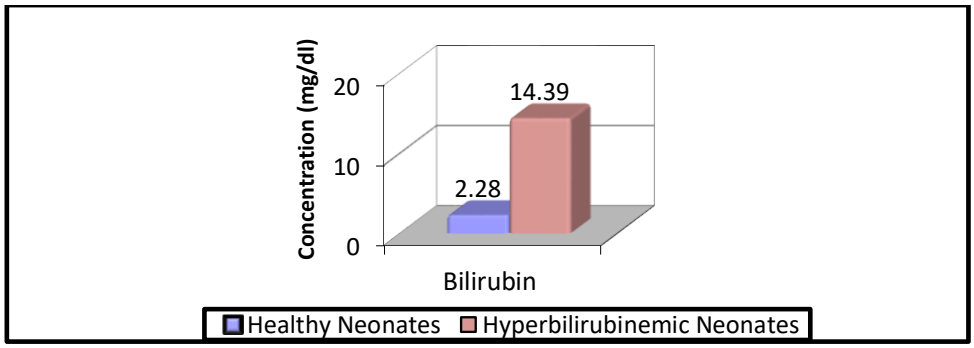

Figure (1): Diagrammatic representation of the mean value of serum total bilirubin (mg/dl) in healthy and hyperbilirubinemic neonates groups.

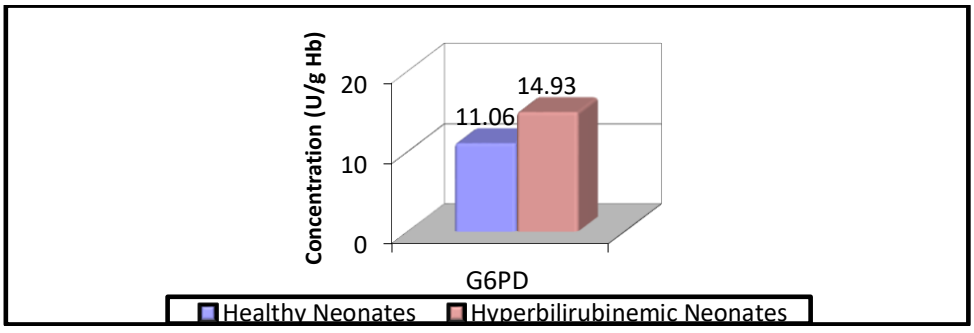

Figure (2): Diagrammatic representation of the mean value (U/ gHb) of G6PD enzyme activity in healthy and hyperbilirubinemic neonates groups.

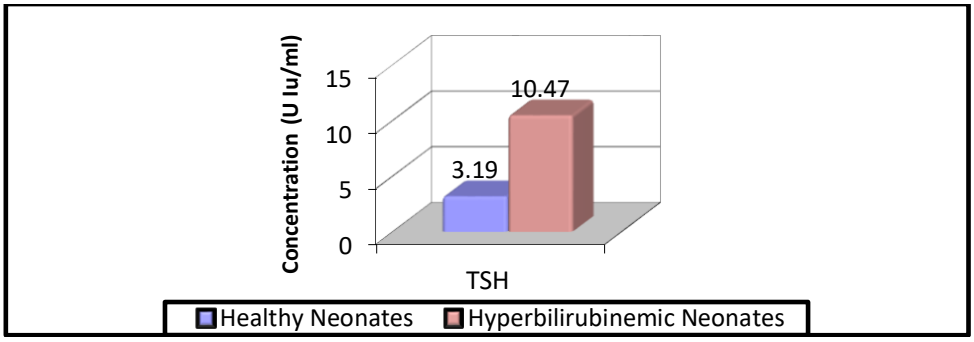

Figure (3): Diagrammatic representation of the mean value of TSH hormone concentration (Ulu/ml) in healthy and hyperbilirubinemic neonates groups.

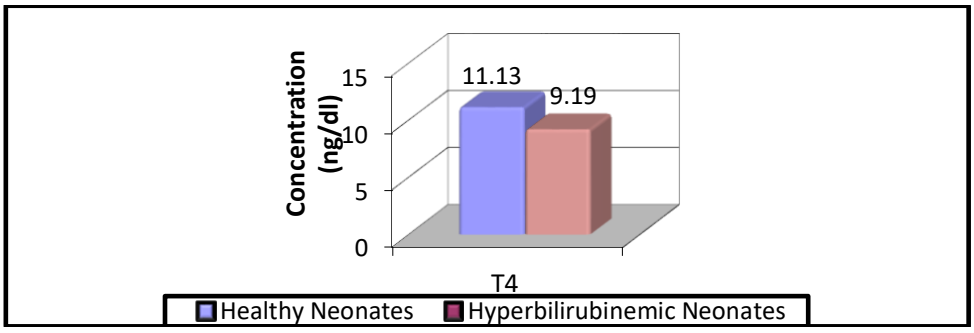

Figure (4): Diagrammatic representation of the mean value of T_4 hormone concentration (ng /dl) in healthy and hyperbilirubinemic neonates groups.

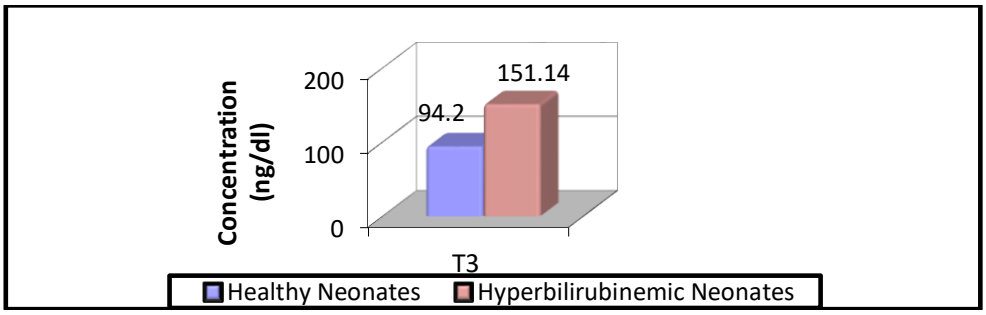

Figure (5): Diagrammatic representation of the mean value of T_3 hormone concentration (ng/dl) in healthy and hyperbilirubinemic neonates groups.

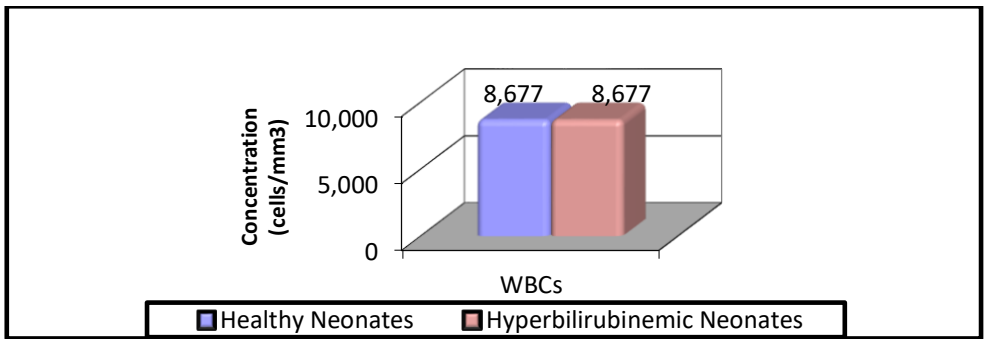

Figure (6): Diagrammatic representation of the mean value of WBCs total count (cells/mm^3) in healthy and hyperbilirubinemic neonates groups.

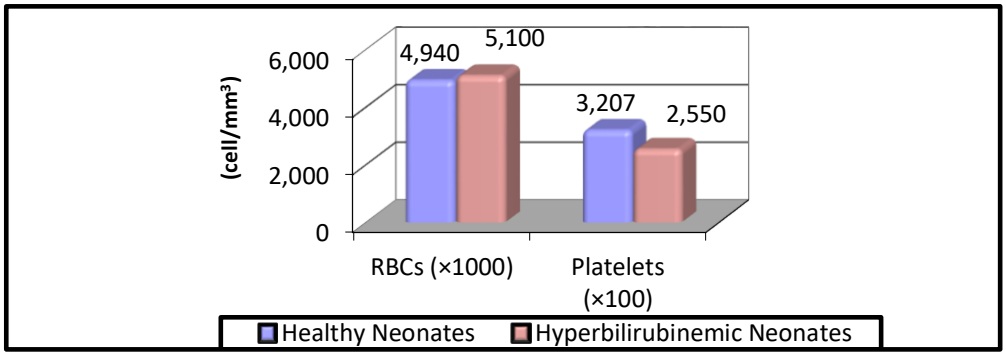

Figure (7): Diagrammatic representation of the mean value of RBCs and platelets counts (cells/mm^3) in healthy and hyperbilirubinemic neonates groups.

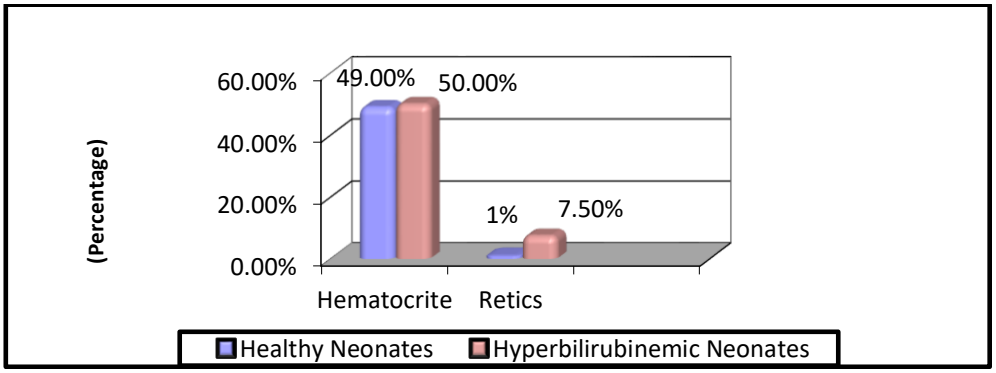

Figure (8): Diagrammatic representation of the mean values % of hematocrit and reticulocytes (retics) in healthy and hyperbilirubinemic neonates groups.

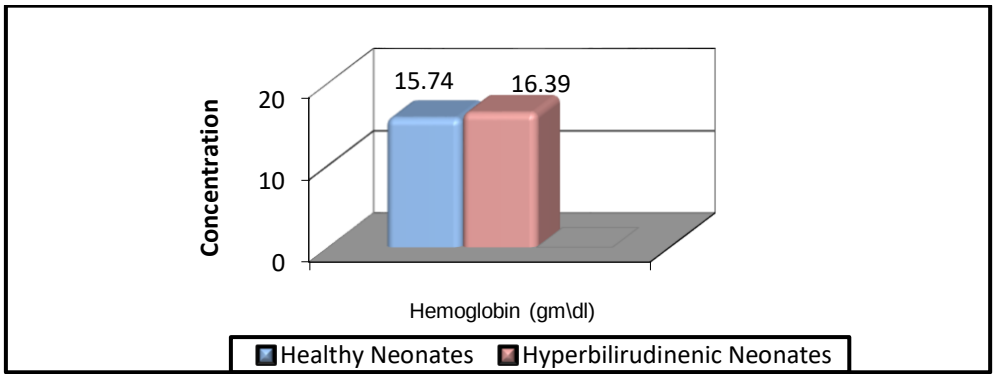

Figure (9): Diagrammatic representation of the mean value of hemoglobin concentration (gm/dl) healthy and hyperbilirubinemic neonates groups.

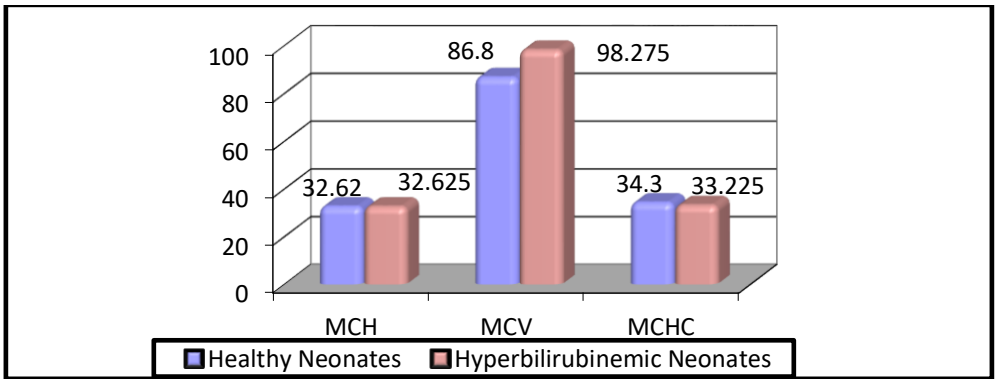

Figure (10): Diagrammatic representation of the mean value of MCH, MCV and MCHC in healthy and hyperbilirubinemic neonates groups.