Diagnosis and Assessment of Severity of Neonatal Hyperbilirubinæmia in Babylon Governorate, Incorporating Serum Albumin Level As A Sensitive Predictor of Outcome

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الخلاصة:

يعد اليرقان الولادي من المشاكل الصحية الشائعة في حديثي الولادة في العراق و الشرقيين بشكل عام . ان التشخيص و العلاج السليمين يعتبران من أهم العوامل لمنع حدوث تلف في الدماغ بسبب التركيزات العالية من البيليروبين (اليرقان) . ويعتبر يرقان حديثي الولادة أيضا هو السبب الأكثر شيوعا لدخول المستشفى في الاطفال حديثي الولادة. ومن المتفق عليه على نطاق واسع أن أسباب اليرقان الولادي هو تغييرات في مجموعة من العوامل الفسيولوجية بما في ذلك التحطيم السريع للفائض من خلايا الدم الحمراء، و اضطراب وظيفة الكبد و الولادةالمبكرة.

وقد تم تصميم هذه الدراسة بهدف الكشف عن أهمية تحديد مستوى الزلال في الدم باعتباره مؤشرا من وظائف الكبد في حديثي الولادة مع اليرقان. أدرج أربع وستون مريضا في هذه الدراسة خلال فترة أربعة أشهر. تم احتساب النسبة بين البيليروبين و بين مستويات الزلال (نسبة A/B). أظهرت هذه الدراسة ان (نسبة A/B) أقل من 2 لا تحمل اية خطورة لنقل الدم التبادلي كطريقة للعلاج في جميع المرضى الذين تتراوح أعمارهم بين 2-5 أيام أربعة ، و أيضا في جميع المرضى الأربعة الذين أعمارهم تراوحت بين 5-12 أيام . بينما أظهرت (نسبة A/B) أكثر من 4 احتمالية عالية لنقل الدم التبادلي (18 من أصل 23 في المرضى بعمر 5-12 يوما). و أعتبرت المنطقة الحرجة الواقعة بين (2-4) بحاجة إلى مزيد من المتابعة و معطيات سريرية اضافية، فقط 5 من أصل 21 وعولجوا عن طريق نقل الدم التبادلي للمرضى بعمر 5-12 يوم ، في حين عولج مريض واحد فقط من أصل 8 بعمر 2-5 يوم بنقل الدم التبادلي. ومن الواضح أن (نسبة A/B) تعد مؤشرا جيدا لشدة اليرقان الولادي و من العوامل المحددة لطريقة العلاج.

Abstract:

Neonatal jaundice is a common health problem in Iraqi neonates and oriental populations in general. Proper diagnosis and management is crucial to prevent brain damage by high concentrations of bilirubin (kernicterus). Neonatal jaundice is also regarded as the most common cause of hospitalization of neonates. It is widely agreed that the causes of neonatal jaundice is alteration of a panel of physiological factors including rapid postnatal destruction of excess red blood cells, derangement of liver clearance function and prematurity.

This study was designed to reveal the importance of determining serum albumin level as a predictor of liver function in neonates with jaundice. Sixty-four patients were included in this study during a period of four months. A ratio between bilirubin and albumin levels (B/A ratio) was depicted. A B/A ratio of < 2 showed no risk of exchange transfusion as a treatment modality in all four patients aged 5-12 days, noting that there are no neonates aging 2-5 days with a B/A ratio of < 2, reflecting the accelerated course in this age group. A ratio > 4 carried a high risk of exchange transfusion (18 out of 23 in those aging 5-12 days). The grey zone of B/A ratio lying between 2-4 needed further follow up and more clinical determinants to be treated properly, only 5 out 21 were treated by exchange transfusion aging 5-12 days, while only 1 out of 8 aging 2-5 days was subjected to exchange transfusion. It is clear that the B/A ratio is a good indicator of the severity of neonatal jaundice, predicting the modality of treatment options.

Key words: Neonatal hyperbilirubinæmia, exchange transfusion.

Introduction:

Neonatal jaundice is a yellow discoloration of the skin and eyes caused by hyperbilirubinemia in neonates. It is one of the commonest problems that can occur in neonates. It occurs in more than 60% of late preterm and term neonates, peaking at 3-5 days of life [(1)].

There are various conditions, both physiological and pathological leading to hyperbilirubinemia in newborn. Neonatal hyperbilirubinemia, defined as a total serum bilirubin level above 5 mg per dl (86 µmol per L). Neonatal jaundice is thought to be physiological, and the most acceptable explanation is that the liver is not mature enough to handle the excess bilirubin generated after reduction of the packed cell volume and hæmoglobin immediately after birth. Most cases of jaundice behave in a benign fashion, but because of the potential toxicity of bilirubin on nerve cells, newborn infants must be monitored to identify those who might develop severe hyperbilirubinemia[(2)].

In neonatal period, jaundice represents the most common reason for doing blood tests and hospitalization in neonates. In some neonates serum bilirubin levels may become excessively high, and in rare instances this may lead to brain damage (kernicterus)[(3)]. In such cases it is important to start treatment quickly. However, Early prediction will help in early discharge and prevent hospitalization of babies and mothers. Treatment of hyperbilirubinæmia has been based on total serum bilirubin (TSB) concentration. Phototherapy and exchange transfusion are therapeutic interventions to reduce the TSB levels in the blood, which is thought to prevent kernicterus.

In general, pathological mechanisms giving rise to jaundice fall into three groups: hemolytic , hepatocellular, cholestatic or obstructive[(4)]. The activity of several enzymes are used to estimate the status of liver function including the integrity of hepatocellular organelles and ability of the organ to synthesize or metabolically convert various compounds and the ability to secrete bile[(5)]. Serum alkaline phosphatase (ALP) is an intracellular enzyme found in red blood cells[(6)], liver bile ducts and bone[(7)], for this reason ALP is routinely used as an integral part for measuring liver function tests. It could be used for early diagnosis and prediction of hyperbilirubinæmia in newborns. The liver also is the major source of most serum proteins such as albumin. Albumin is a useful indicator of hepatic function. Liver is the only site of synthesis of albumin and it helps in transport of unconjugated bilirubin[(8)].

Objectives:

1. Evaluation of some relevant biochemical markers in jaundiced Iraqi neonates.
2. Correlating serum biochemical markers other than total serum bilirubin with the type of therapy required within the first two weeks of age.

Materials and Methods

Sixty four jaundiced newborns (male and female) were included in this study during a period of four months in the Babylon Maternity and Children Hospital/Al-Hillah. These babies were grouped according to age from 2-5 days and 5-12 days of life, some of them were submitted to follow up since their birth. Another group 30 healthy newborns (17 male and 15 female) were also studies as a control group. Three ml of venous blood were taken both from jaundiced and healthy neonates to estimate the TSB, hematological parameters (PCV, Hb), ALP, total serum albumin (TSA) and bilirubin/albumin (B/A) ratio. Total serum bilirubin of control and jaundiced neonates were determined according to a modified method described by Doumas and Wu [(9)]. A cyanomethemoglobin method was used to estimate the hemoglobin contents of the blood [(10)].

The microhematocrit method was used to determine the PCV [11]. Alkaline phosphatase enzyme activity was measured by King and Kid commercial kit method. Serum albumin was determined using bromocresol green commercial kit method. Statistical analysis between controls and jaundiced neonates was performed by using SPSS (Statistical Package for the Social Science Inc., Chicago, USA) version 17software as M±SD, frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables was done by Student T test for independent samples and ANOVA test. The differences were considered significant when the probability (P value) was less than 0.05.

Results:

During the study period, 64 neonates with neonatal jaundice (36 male and 28 female) and 30 healthy neonates served as a control with (17 male and 13 female) were included in this study as shown in table (1).

Table(1): The number of all groups (males and females) with their distribution.

Sex	***Newborns with neonatal jaundice No. (%)***	***Control group No. (%)***
Males	36 (56.25)	17 (56.67)
Females	28 (43.75)	13 (43.33)
Total	64 (100)	30 (100)
M/F ratio	1.3:1	1.3:1

The results in table (1) showed that 36 babies (56.25%) with neonatal jaundice were males and 28 babies (43.75%) were females while male to female ratio was 1.3:1.

Table (2): The clinical and laboratory characteristics of the study population expressed as mean ±SD.

Parameters	***Neonatal jaundice in age 2-5 days***	***Control group in age 2-5 days***	***Neonatal jaundice in age 5-12 days***	***Control group in age 5-12 days***
TSB(mg/dl)	14.16±1.6*	3.81±0.93	14.1±3.86*	4.23±1.12
PCV(%)	50.1±6.1*	57.2±6.02	49.6±6.7*	54.9±9.89
Hb(g/dl)	15.9±2.6*	18.7±2	16±2.06*	17.2±3.1
ALP(IU/L)	189.2±19.62*	150±32	182.8±41.9*	152.69±21.12
TSA(g/dl)	3.425±1.307*	4.9±1.37	3.347±1.599*	5.08±1.5
B/A ratio (mg/g)	4.14±1.81*	0.78±0.03	4.21±0.56*	0.83±0.04

*The mean difference is significant at $P < 0.05$ level.

As shown in table (2), there was a significant decrease in hematological parameters and TSA of jaundiced neonates, compared with control group revealing a significant P value (<0.05). There was a significant increase in TSB and ALP of neonatal jaundice when compared with control group ($P < 0.05$).

Table (3): The distribution of neonates aged 2-5 days, according to their B/A ratio and the type of therapy received.

B/A ratio	*< 2.0*	*2.0-4.0*	*> 4.0*
Number of jaundiced neonates	0	7	9
Phototherapy N (%)	0 (0%)	6 (85.71%)	5 (55.56%)
Exchange transfusion N (%)	0 (0%)	1 (14.28%)	4 (44.44%)

Table (3) shows the random distribution of patients with neonatal jaundice aged 2-5 days and segregated according to the type of therapy used, either phototherapy or exchange transfusion in comparison with their B/A ratio.

Table (4): The distribution of neonates aged 5-12 days, according to their B/A ratio and the type of therapy received.

B/A ratio	*< 2.0*	*2.0-4.0*	*> 4.0*
Number of jaundiced neonates	4	21	23
Phototherapy N (%)	4 (100%)	16 (76.2%)	5 (21.74%)
Exchange transfusion N (%)	0 (0%)	5 (23.8%)	18 (78.26%)

In table (4), a similar comparison was made between jaundiced neonates aged 5-12 days who required either phototherapy or exchange transfusion. This table also shows that there is a significant correlation between the B/A ratio and the type of therapy chosen; with increasing B/A ratio there is an increased need for exchange transfusion. Only four neonates at this age group out of 48 expressed a B/A ratio of < 2, and all were successfully subjected to traditional phototherapy, while 18 out of 23 patients (78.26%) with a B/A ratio of > 4 required exchange transfusion.

Both last two tables show that there is a grey zone represented by a B/A ratio between 2-4 for both age groups. Within the first five days of live, phototherapy was adequate for those babies expressing B/A ratio between 2-4 in 7 out of 8 (87.5%). On the other hand, the corresponding group of babies aged 5-12 days required phototherapy in 16 out of 21 (76.2%).

Discussion:

Neonatal jaundice is regarded a common problem, especially in Orientals. The prevalence of neonatal jaundice is 50% to 60% in term and 80% in preterm neonates[12]. Proper therapeutic measures should be critically determined to prevent kernicterus. The current study included 64 cases of neonatal jaundice, with an age range divided into two groups; 2-5 days and 5-12 days. Among them 56.25% were male while 43.75% females and male to female ratio was 1.3:1. Our results were similar to those expressed by Shah et al and Rasul et al [13,14]. In our study, neonatal jaundice was more common in male babies than in female babies, these results were compatible with those shown by Mantani et al and Sharma et al [15,16], but they were incompatible with study presented by Sadiq[12] from Kirkuk, probably reflecting demographical and racial differences.

The treatment strategy of neonatal jaundice depends on assessing

the risk factors of development of neonatal jaundice. Various methods and biochemical analyses have been proposed to determine this risk. This study showed that hematological parameters (PCV and Hb) decreased more than the control group in both ages and the differences were statistically significant ($p<0.05$).

In the present study, there was significant increase in ALP and TSB in both ages when compared with control group at $p<0.05$. Our study showed similar results revealed by Nalbantoğlu A et al[6], but disagreed with the results reported by Ahmad et al[17]. ALP is an intracellular enzyme found in RBCs and is secreted into plasma upon the destruction of these cells (hemolysis). Hemolysis is one of the risk factor to develop hyperbilirubinemia in neonates. ALP is also found in the liver and this increase which may be due to defects in the liver function as a result of viral infections, destruction of hepatic cells, liver dysfunction biliray obstruction or any other defects which cause secretion of these enzymes into the circulation [18,19].

Our findings showed that TSA is significantly decreased in neonates with age 5-12 days and 2-5 days as compared with controls at $P<0.05$. This may be due from low production of albumin that will lower its transport and binding capacity. This is especially important in preterm infants, in whom albumin binds to potentially toxic products such as bilirubin and antibiotics. Hepatic excretory capacity is low both because of low concentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid. There is shortage of reports on serum albumin as a predictor of hyperbilirubinemia. Early prediction will help in early discharge and prevent unnecessary hospitalization of jaundiced neonates.

Total Serum Bilirubin level (TSB) has been the golden standard indicator for treatment in jaundiced neonates for many years. This study was designed to assess the bilirubin/albumin (B/A) ratio as an indicator for treatment in the jaundiced neonates in comparison with TSB and also to evaluate the bilirubin albumin (B/A) ratio in comparison with total serum bilirubin (TSB) for predicting the risk factor to develop sever neonatal jaundice and prevent unnecessary invasive therapy such as exchange transfusion. B/A ratio is lower than in neonates with age 2-5 days compared with neonates with age 5-12 days. The results in this study showed that B/A ratio were significantly higher in both ages when compared with control groups at $P<0.05$. These findings were presented also by mousa et al [21]and Sato et al [22] but less significant results were presented by Ardakani et al [20] and Amin et al [23].

Conclusions:

1. Severity and treatment of physiological neonatal jaundice is greatly influenced by parameters other than total serum bilirubin alone.
2. Serum albumin is an important determinant of severity and progression of neonatal hyperbilirubinæmia. It could be an independent factor in determining the need for exchange transfusion in conjunction with bilirubin level (B/A ratio).

Recommendations:

Other studies may be designed to include other biochemical and clinical parameters, which could result in more specific results and determinants along with the B/A ratio, such as body weight, intrauterine age (prematurity) and other biochemical liver markers.

References:

1. El-Beshbishi SN, Shattuck KE, Mohammad AA, et al. Hyperbilirubinemia and transcutaneous

bilirubinometry. Clin Chem 2009;55(7):1280-7.
2. Vinod K. Bhutani A, B M. et al. Management of Jaundice and Prevention of Severe Neonatal Hyperbilirubinemia in Infants > 35 Weeks Gestation Neonatology 2008;94:63–67.
3. Marie Andersen Erlandsen, Thor Willy Ruud Hansen. Treatment of neonatal jaundice - more than phototherapy and exchange transfusions. Eastern Journal of Medicine 15 (2010) 175-185.
4. Al-Aga, M.H.: Clinical explanation for laboratory investigations. Ibn-Nafees House. Surye.Page, (2000)790-791.
5. Mayne, P.D.: Clinical chemistry in diagnosis and treatment. 6thedition. Arnold. London. (1994)p.280.
6. Nalbantoğlu A, Ovali F, Nalbantoğlu B. Alkaline phosphatase as an early marker of hemolysis in newborns. Pediatrics International (2011) 53, 936–938.
7. B.R.Thapa and Anuj Walia. Liver Function Tests and their Interpretation. Indian Journal of Pediatrics, Volume 74—July, 2007. 663- 669.
8. Doumas, B.T. and Wu, T.W. The measurement of bilirubin fractions in serum. Crit. Rev. Clin. Lab. (1991), 5-6, 415-445.
9. Markarem ,A .. Clinical Chemistry: Principles and techniques , 2nd .ed . ,Herny ,D.C. Cannon .J.W. and Winkelmen Editor .Hargeston. (1974)p 1128-1135.
10. Lewis, S. M.; Bain, B. J. & Bates, I.. Dacei & Lewis practical hematology. 10th ed., Churchil Livingstone Elsevier. Germany. nephropathy. Diabetologia (2006)52:691–697.
11. 12.Doumas BT, Peters T, Jr. Serum and urine albumin: A progress report on their measurement and clinical significance. Clin Chem Acta. 1997; 258: 3-20.
12. Ziad M. Sadiq. Neonatal jaundice In Kirkuk pediatric hospital: epidemiological study and outcome. Tikrit Medical Journal 2008; 14(2):115-119.
13. Amar Shah, Dr. C. K Shah, Dr. Venu Shah. Study of hæmatological parameters among neonates admitted with neonatal jaundice. Journal of Evolution of Medical and Dental Sciences/Volume1/ Issue3/July-Sept 2012 Page203- 208.
14. Choudhury Habibur Rasul, Md Abul Hasan, Farhana Yasmin. Outcome of Neonatal Hyperbilirubinemia in a Tertiary Care Hospital in Bangladesh Malaysian J Med Sci. Apr-Jun 2010; 17(2): 40-44.
15. Mantani M, Patel A, Renge R, Kulkarni H. Prognostic value of direct bilirubin in Neonatal Hyperbilirubinemia. Indian J Pediatr 2007; 79: 819-22.
16. Sharma P, Chhangani NP, Meena KR, Jora R, Sharma N, Gupta BD. Brainstem Evoked Response Audiometry (BAER) in neonates with hyperbilirubinemia. Indian J Pediatr 2006; 73: 413-16.
17. Aydin Siddiq Ahmad1 , Wahbi Abdul-Kadir Sulayman2 & Fatin Abdul-Wahid Majeed2 Changes in Activities of Alkaline Phosphatase and Transaminases in Jaundice. Tikrit Journal of Pure Science Vol. 13 No.(3) 2008 p 1-3.
18. Fischbach, F. (2004): An manual of laboratory and diagnostic tests. 7th edition. Lippincott.Williams and wilkins. pp88.
19. Khan, M., Coovadia, W.M., Karas, J.A. et al :Clinical significance of hepatic – dysfunction with jaundice in typhoid fever. Digest.Dis.Scien. (1999) I44:590-23.
20. Shahin Behjati Ardakani MD; Vahid Ghobadi Dana MD; Vahid Ziaee. Bilirubin/Albumin Ratio for Predicting Acute Bilirubin-induced Neurologic Dysfunction. Iranian Journal of Pediatrics, Volume 21 (Number 1), March 2011, Pages: 28-32.
21. Ahmadpour Kacho Mousa, Zahedpasha Yadollah, et al, Assessment of bilirubin to albumin ratio as a criterion for exchange transfusion in severe neonatal hyperbilirubinæmia. Medical Journal of Mashhad University of Medical Sciences. Fall 2011; 54(3):137-142.
22. Sato, Y., Morioka, I., Miwa, A., et al. Is bilirubin/albumin ratio correlated with unbound bilirubin concentration? Pediatrics International, 2012, 54: 81–85.
23. Amin SB, Ahlfors C, Orlando MS, et al. Bilirubin and serial auditory brainstem responses in premature infants. Pediatrics 2001;107(4):664-70.