Unconjugated Neonatal Hyperbilirubinemia: Evaluation and Treatment

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Abstract

Background: neonatal jaundice is a common problem with a lot of mistakes that happen during its management, requiring the doctors and medical staff to follow a certain guidelines for dealing with this disease to obtain the best results.

Objective: (1) to study some of the causes of neonatal unconjugated hyperbilirubinemia.
2) To discuss the causes and proper line of therapy.
(3) To discuss the complications associated with the management of this problem.

Methods: The study included 100 neonates aged 0-14 days with hyperbilirubinemia who were admitted to the Central Teaching Hospital for Children in Baghdad during the period from 1st of February – 1st of June2008. Term infants with TSB ≥ 22mg/dl were treated by exchange transfusion and phototherapy (Group A, 38 patients). Those with TSB level from 13-22mg/dl were treated by phototherapy only (Group B, 62 patients). These decisions were taken mostly according to the TSB level, gestational age and body weight.

Results: Twenty five percent of cases had hemolytic cause (Rh-isoimmunization, 13%; ABO-incompatibility, 10%; G6PD-deficiency, 2%). Other causes include: pretermaturty, 33%; sepsis, 8%; congenital CMV infection, 1%; and there were 33 (33%) infants had no evidence of hemolysis or other serious problems. There were 2 deaths in our study after exchange transfusion due to septicemia. The mortality rate after exchange transfusion in the study was 4.4% (from total number of exchange transfusion processes).

Conclusions: There appears to be lack of a protocol for the management of cases of neonatal unconjugated hyperbilirubinemia. The cause of hyperbilirubinemia is usually overlooked.

Key words: Neonate, hyperbilirubinemia, Jaundice.

Introduction:

Neonatal jaundice remains an important neonatal disease and pediatricians are confronted daily with the problems of the neonatal jaundice .Hyperbilirubinemia is very common and usually benign in the term newborn infant and the late preterm infant at 35 to 36 completed weeks' gestation. Critical hyperbilirubinemia is uncommon but has the potential for causing long-term neurological impairment. [1, 2].

Early discharge of the healthy newborn infant, particularly those in whom breastfeeding may not be fully established, may be associated with delayed diagnosis of significant hyperbilirubinemia. [3, 4, 5]

Jaundice is observed during the 1st week of life in approximately 60% of term infants and 80% of preterm infants. [6]

Risk factors for development of severe hyperbilirubinemia: [7,8,9]

1. Visible jaundice at younger than 24hr.
2. Prematurity (<37 weeks).
3. Previous sibling with severe hyperbilirubinemia.
4. Visible bruising.
5. Cephalohematoma.
6. Male sex.
7. Dehydration.
8. Exclusive breast feeding.
9. Infection.
10. East Asian and Mediterranean
11. Hemolytic disease (Rh and ABO incompatibility).

Kernicterus (*Bilirubin Encephalopathy*)

Kernicterus from Greek means yellow nucleus. [9] The word actually means "nuclear jaundice", which refers to the staining of dead neurons in the basal ganglia, hippocampal cortex, cerebellum, and subthalamic nuclei that fulfills the pathological definition of kernicterus. [10,11,12].

It is a neurological syndrome resulting from deposition of unconjugated (indirect reacting) bilirubin in the basal ganglia and brainstem nuclei. [13]The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the blood-brain barrier, and neuronal susceptibility to injury.[14]

Treatment:

Decisions about therapeutic intervention are tempered by clinical judgment based on the infant's history, course and physical examination and are balanced by comparing the potential benefits with the risk. Treatment should follow special guidelines and criteria for the use of phototherapy or exchange transfusion or both according to body weight, gestational age, level of bilirubin and cause of the jaundice. [15,16,17].

Patients & Methods:

The study involved 100 neonates with unconjugated hyperbilirubinemia, whose ages ranged from 0-14 days admitted to Central Teaching Hospital For Children, over 4 months period, from 1st of February 2008 to 1st of

June 2008. These infants were seen initially in the emergency department of the hospital, either due to referral from a physician for neonatal jaundice or jaundice noticed by the family. After thorough history and physical examination, a heel-prick was done and a sample of capillary blood was taken by capillary tube. Packed red cell volume was measured by special ruler and TSB was measured by a bilirubin analyzer (Bilirubinmeter, Bil Read, Optima; serial no. 9423; prod. June 1995). Then according to the TSB level of the infant, the line of treatment was decided either phototherapy or exchange transfusion. Term infants with TSB ≥ 22mg/dl were treated by exchange transfusion and phototherapy. Those with levels ranging from 13-21mg/dl were treated by phototherapy only, except for some premature infants in whom exchange transfusion is done at levels lower than 22 mg/dl. For sick and or premature infants, lower levels of TSB were regarded as threshold for management (phototherapy and exchange transfusion). The blood used for laboratory investigations was taken from the first 20 ml drawn from the patient (in case of exchange transfusion) and distributed in to 5 tubes (for Complete blood count and reticulocyte count, G6PD enzyme assay, blood culture, direct Coombs test, and biochemical measures). The tubes were sending to the laboratory immediately or stored in a refrigerator till the next morning (if the exchange transfusion is done at night. The same investigations (as above) were done to these infants who were admitted for phototherapy only. The patients were divided into 2 groups:

Group A: includes infants who were treated by exchange transfusion and phototherapy.

Group B: includes infants treated by phototherapy only.

After exchange transfusion infants were followed up clinically and by laboratory tests which include Complete blood count, serum electrolytes, serum calcium, and blood sugar and blood culture when indicated. P value < 0.05 was considered to be significant using chi-square test.

Results:

Males were more than females (57 males and 43 females with a male: female ratio of 1.32: 1) in the two groups (A and B). (**Table 1)**.

The ages on admission in both groups are considered to be high (101.6 hr for group A and 136.1hr for group B). The mean gestational age (wk) was 36.12 in group A and 37.92 in group B. The mean body weight in grams for group A patients was 2635 g and for group B was 2956 g. **(Table 2)**.

Two patients died, both had sepsis and died after exchange transfusion (within 24 hours) despite receiving antibiotics with ampicillin and cefotaxime. The main cause of jaundice in group A was hemolysis (36.8%) followed by prematurity (31.5%), while the main cause in group B was idiopathic (40.32%) followed by prematurity (33.87%). **(Table 3**).

Table 1: Distribution of the Patients According to SEX

	Group A (n =38)	**Group B (n =62)**	**Total (n =100)**
Male	20	37	57(57%)
Female	18	25	43(43%)
M:F ratio	1.11 : 1	1.48:1	1.32 : 1
Total	38(38%)	62(62%)	100(100%)

P=0.450 (Not significant)

Table 2: Ages, Gestational Ages, and Body Weight of Studied Infants

Characteristic	**Group A**	**Group B**
Age on admission (hr) (Mean±SD)	101.6±42	136.1±52
Gestational age (wk) (Mean±SD)	36.12±2.5	37.92±2.3
Body weight on admission (g) (Mean±SD)	2635±648	2956±742

Table 3: Distribution of Cases According to Causes of Hyperbilirubinemia.

Diagnosis	**Group A (n =38)**	**Group B (n =62)**	**P value**
Rh-isoimmunization#	9(23.6%)	4(6.45%)	0.041*
ABO-incompatibility#	4(10.5%)	6(9.7%)	0.615
G6PD-deficiency#	1(2.6%)	1(1.6%)	0.724
Sepsis (culture +ve)	3(7.8%)	5(8.06%)	0.976
Preterm	12(31.5%)	21(33.87%)	0.813
Healthy term infant without hemolysis	8(21.4%)	25(40.32%)	0.057
Congenital infection CMV IgM, IgG +ve	1(2.6%)	0(0%)	-
# Hemolytic cause	14(36.8%)	11(17%)	0.032*

*p< 0.05 is significant

There was one case of congenital CMV infection presented to the hospital with jaundice, lethargy, hepatosplenomegaly, detected by finding of positive IgM antibody in the infant's blood. He was treated by single exchange transfusion.

There were 10 cases of ABO-incompatibility, 4 of them required exchange transfusion (1 of them needed 2 exchange transfusions), and 6 infants treated by phototherapy only. There were 2 patients with G6PD enzyme deficiency, both of them are males, one of them required single exchange transfusion and the other treated by phototherapy only.

Neonatal septicemia with positive blood culture was found in 8 infants.

Duration of phototherapy after exchange transfusion had ranged from 1 to 6 days with a mean of 66.46 hr. Those who were treated by phototherapy alone were kept under phototherapy for a mean of 78.32 hours, with interruption for feeding and changing.

Discussion:

The male: female ratio was 1.32: 1 in the two groups (A and B). This is understood as male gender is considered as a risk factor for neonatal jaundice. In a study done by Dr. Tarik Al-Shujairy in 2001, male to female ratio was 1.43: 1. [18] In a study done by Jennifer A. et al at 2005, total of 840 infants were included in their study, bilirubin was significantly higher in males than in female with P value < 0.001.It may be related to the higher rate of prematurity in the males, G6PD deficiency (which is prevalent in male), or other factors. [19]

The ages on admission in both groups are considered to be high (101.6 hr for group A and 136.1hr for group B). This might be due to the believes in some of our families that jaundice is a normal phenomenon in the 1st week of life. However the ages in group A were lower than in group B which may be explained partly by the higher incidence of hemolytic causes of jaundice in the first days of life. The mean gestational age (wk) in our study 36.12 in group A and 37.92 in group B. Those in group A appears to have younger gestational age which is probably related to the higher risk of jaundice in premature infants.

In this study, hemolytic cause for jaundice was found in 25 patients (25%); 14 patients (36.8%) in group A and 11 patients (17%) in group B with a P value of 0.032 which indicate a significant risk for those who have hemolytic anemia to be exposed for exchange transfusion. Singhal et al (India), studied 454 newborns with pathological jaundice, and found a hemolytic cause in 62.5% of newborns. [20] Kalkan et al (Sarajevu) studied 185 jaundiced newborns and he found a hemolytic cause in 41% of patients. [21] Michael S. et al studied 258 neonates and found that the hemolytic causes represent 34% of the causes. [22].

These differences in the studies may be due to the small sample taken, different ethnic groups, geographic factors or other factors. In the current study there were 2(2%) patients with G6PD enzyme deficiency. In Micheal S. et al study, G6PD enzyme deficiency represents 7% of the cases. In this study sepsis present in 8 cases (8%). While in Michael S. et al study, there were 6 cases of sepsis (2.3%) which is probably due to the better hygiene and medical care in the delivery rooms and the nurseries.

In this study there were 33 premature neonates (33%), mean gestational age was 33.91wk, mean weight on admission was 1988 g, and the mean TSB was 16.8mg/dl. While in Michael S. et al study, there were 45 premature neonates (17%) and their mean gestational age was 34.2wk, mean body weight was 2187 g, which reflect the better antenatal care of the pregnant women, better nutrition, and health status.

Mortality due to the exchange transfusion in this study was 4.4% which is higher than internationally accepted figures. In Michael S. et al study, the mortality rate was 0.1% which is less than the mortality rate in this study, probably related to the better antiseptic measures (both in the nurseries and during the procedure of the exchange transfusion), better follow up with more dependable results of blood investigation (including blood culture), and probably earlier presentation of the infant to the hospital.

Conclusion:-

1-The cause of hyperbilirubinemia is usually overlooked.
2-No strong guidelines for the prevention of the Rh-isoimmunization because of shortage of the Anti-D immunoglobulin, neglect from the family e.g. midwife delivery.
3-Mortality rate from exchange transfusion is higher than internationally accepted figures.

Recommendations.

1-Standard protocol for treatment of neonatal hyperbilirubinemia should be established in our children's hospitals taking in to account the new guidelines in the management of unconjugated hyperbilirubinemia .
2-Exchange transfusion must be done under optimal conditions of sterility, environmental regulation, and monitoring of electrolytes, calcium, blood glucose, body temperature, and vital signs.
3-Phototherapy units must be assessed and maintained frequently for optimum function
4-Control programs for Rh-isoimmunization should be improved in our country

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