Unconjugated Neonatal Hyperbilirubinemia: Evaluation and Treatment

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Abstract

Background: Neonatal jaundice is a common problem with a lot of faults that may happen during its management.

Objective: To study the epidemiological features of the unconjugated hyperbilirubinemia(UHB)in Diyala Governorate and discuss the proper lines of therapy, as well as to discuss the daily practice adopted in our hospital, and its complications.

Patients and Methods: A cross-sectional study included 100 neonates (term and preterm babies) with unconjugated hyperbilirubinemia aged 0-7 days who were admitted to the Al-Batool Teaching Hospital in Baqubah, Iraq, from 1st February 2018 to the 1st November 2018. Term infants with total serum bilirubin (TSB) ≥ 22mg/dL were treated with exchange transfusion and phototherapy (Group A, 44 neonates). Those with total serum bilirubin levels from 13-<22mg/dL were treated with phototherapy only (Group B, 56 neonates). These decisions were made according to the TSB level and risk factors.

Results: Forty-eight percent of neonates had hemolytic causes (Rh-isoimmunization 13%; ABO-incompatibility 10%; G6PD-deficiency 25%). Other include: sepsis 8%; prematurity 33%; congenital CMV infection 1%; and there were 10% had no evidence of hemolysis or other serious problems. The mortality rate was 3.8% of those who had an exchange transfusion.

Conclusion: The decision of kind of treatment is dependent on the underlying etiology of unconjugated hyperbilirubinemia.

Keywords: Unconjugated hyperbilirubinemia, Neonates, complications

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Introduction

Hyperbilirubinemia (defined as a TB >95th percentile on the hour-specific Bhutani nomogram [1,2]. Hyperbilirubinemia with a TB >25 to 30 mg/dL is associated with an augmented risk for bilirubin-induced neurologic dysfunction (BIND) [3,4]. In developed countries, the incidence of "extreme" hyperbilirubinemia was 0.03 percent of live births [5]. Initial tests that should be obtained are Blood group and Rh

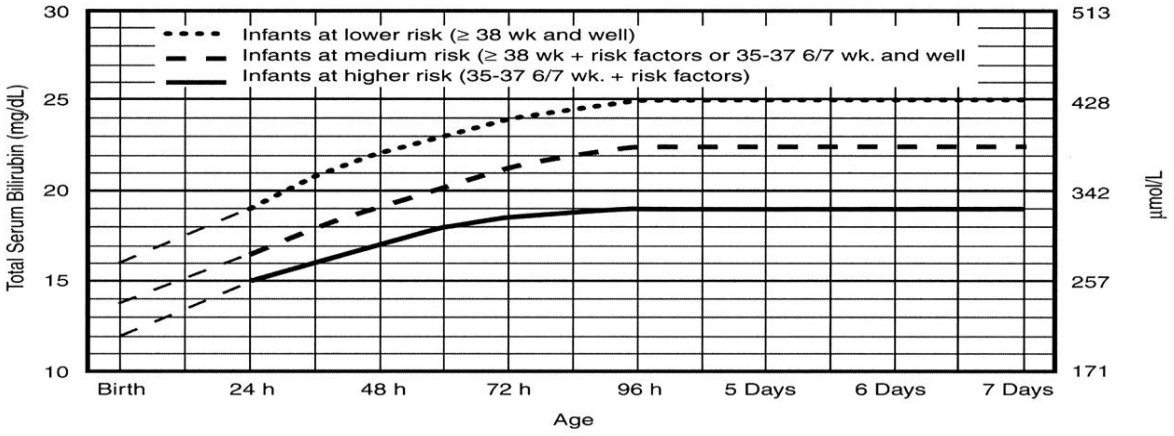
and direct Coombs test CBC and smear. Reticulocyte countGlucose-6-phosphate dehydrogenase (G6PD) measurement, if clinically appropriate[6,7].No data showing that phototherapy improves neurodevelopmental outcomes, but it reduces the likelihood that hyperbilirubinemia reaches a level associated with the risk of kernicterus [[8,9]. Exchange transfusion usually reduces total serum bilirubin (TSB) by about 50% [10,11]. Studies reported mortality rates around 0.3 % associated with the procedure [12,13] and a significant complication rate of 1 % [14]. When infants managed suitably, the outcome is excellent with minimal or no additional risk for adverse neurodevelopmental sequelae [15,16]. There were no reported cases of kernicterus after the implementation of treatment guidelines for hyperbilirubinemia [17].In developed countries, the results revealed no difference in development at 1-5 years of age from controls matched by gender, age, gestational age, and the municipality of residency[16,18]. The prevalence of kernicterus in premature infants is uncertain. There were reports of around a 4% rate of kernicterus based upon characteristic postmortem neuropathological findings preterm infants who died after 48 hours of life [8,18]. The aim of this study is to evaluate the epidemiological features of the UHB in Albatool Teaching Hospital and discuss the proper lines of therapy, and its complications.

Patients and Methods

A cross-sectional study involved 100 neonates with unconjugated hyperbilirubinemia, whose ages ranged from 0-7 days admitted to AlBatool teaching hospital for Gynecology and Obstetrics. and Pediatrics, Baqubah city, Diyala Province, Iraq, from 1st of February 2018 to 1st of November 2018. 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 proper clinical assessment, the gestational ages were estimated according to maternal history of last menstrual period, U/S reports, and clinical assessment of the infants by using "Pellard scoring system" for assessment of gestational ages in the 1st 48 hr. of life [12].

A heel- prick was done and a sample of capillary blood was taken by a capillary tube. Hematocrit was measured by a special ruler and TSB was measured by a bilirubin analyzer (*Bilirubinmeter, Bil Read, Optima; serial no. 9423; prod. June 1995*). As well as blood group and Rh. were done 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 was done at levels lower than 22 mg/dL. For sick and /or premature infants, lower levels of TSB were regarded as a threshold for management (phototherapy and exchange transfusion). In infants who were admitted for exchange transfusion, the umbilical vein was catheterized, and used for exchange transfusion. The process of exchange transfusion is done by the resident

doctors. blood used for laboratory investigations was taken from the first 20 ml drawn from the patient (in case of exchange transfusion) and distributed into 5 tubes (for CBC and reticulocyte count, G6PD enzyme assay, blood culture, direct Coombs test, and biochemical measures). The tubes were sent to the laboratory immediately or stored in a refrigerator till the next morning (if the exchange transfusion is done at night). All the infants who required exchange transfusion were put on a broad-spectrum antibiotic cover of a combination of the available antibiotics (ampicillin, gentamicin, or cefotaxime, ampicillin-cloxacillin combination) for a minimum of 5 days according to the infant's condition. The same investigations (as above) were done to these infants who were admitted for phototherapy only. Infants who were admitted principally for phototherapy and those who required exchange transfusion were put under phototherapy lamps till the TSB fall below the levels shown in Figure(1) and Table(1)



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Figure (1): Guidelines for phototherapy in hospitalized infants of 35 or more weeks´ gestation [14]

Table (1): Suggested Maximal Indirect Serum Bilirubin Concentrations (mg/dL) in Preterm Infants for exchange transfusion [14]

BIRTH WEIGHT (g)	UNCOMPLICATED	COMPLICATED*
<1,000	12–13	10–12
1,000–1,250	12–14	10–12
1,251–1,499	14–16	12–14
1,500–1,999	16–20	15–17
2,000–2,500	20–22	18–20

*Complications include perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus. Phototherapy is usually started at 50–70% of the maximal indirect level

Their eyes were covered and the rest of the body was exposed. They were kept under observation for about 24 hr. after the lamps were switched off for the possibility of rebound hyperbilirubinemia. Should TSB have remained relatively low, the infants were discharged home. 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 exchanging transfusion infants were followed up clinically and by investigations which include CBC, serum electrolytes, serum calcium, and blood sugar and with blood culture when indicated. Rh-isoimmunization was diagnosed when the mother is Rh –ve and the infant is Rh +ve with a positive direct Coombs test (21). We suggested ABO incompatibility when the maternal blood group is O and the infant's blood group is either A or B with weakly or moderately positive Coombs test, with spherocytosis and reticulocytosis.

Statistical analysis

The data were processed and analyzed using the Statistical Package for Social Sciences version 21 (SPSS Inc., Chicago, IL, USA. The results were expressed using percentages and frequencies. A P-value <0.05 was considered a significant Chi-square test.

Results

The number of neonates in both groups and their gender distribution are shown in table2 where males preponderance was noted in both groups of the study.

Table (2): Number of neonates and gender distribution

	Group A(n =44) %	Group B (n =56) %	Total(n =100) %
Male	3030 %	37 37 %	6767%
Female	1414 %	19 19 %	3333%
M:F ratio	1.11 : 1	1.48:1	2.03 : 1
Total	4444%	5656%	100100%

* P=0.450 (Not significant)

Table (3) showed the clinical characteristics of the babies in both groups on admission.

Table (3): Clinical characteristics of neonates in both studied groups

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

Table (4) showed the different causes of hyperbilirubinemia in the neonates of both groups and their frequency, where hemolytic causes and prematurity predominant

Table (4): Causes of hyperbilirubinemia in both studied groups

Diagnosis	Group A (n-44)	Group B (n =56)	P value
Rh-isoimmunization	9(20.4%)	4(7.14%)	0.041*
ABO-incompatibility	4(9.09%)	6(10.71%)	0.615
G6PD-deficiency	12(27.27%)	13(23.21%)	0.724
Sepsis (culture +ve)	3(6.81%)	5(8.92%)	0.976
Preterm	12(27.27%)	21(37.5%)	0.813
Healthy term neonate with no evidence of hemolysis	3(6.81%)	7(12.5%)	0.057
Congenital infection (CMV IgM, IgG antibody positive)	1(2.27%)	0(0%)	-
Hemolytic cause	25(56.81%)	23(41.00%)	0.032*

*p< 0.05 is significant

Table (5) showed the clinical and laboratory data of neonates with Rh-isoimmunization in both groups where missed anti-D and previously affected baby is predominant

Table (5): Clinical associations of 13 neonates with Rh-isoimmunization

Clinical association	Group A (n = 9) %	Group B (n = 4) %	P value
Strongly positive direct Coombs test(≥ ++)	4 (44.4%)	0 (0%)	-
Previously affected sibling	6 (66.6%)	2 (50%)	.157
Not exposed to Rh antigen	0 (0%)	0 (0%)	-
Mother has missed at least one dose of Anti-D	9 (9%)	1 (25%)	.011
Onset of jaundice (1^{st})24hr	4 (44.4%)	0 (0%)	-
Pallor	3 (33.3%)	1 (25%)	.317
PCV(mean±SD)	32.64±6.1%	40.33±3.7%	-
Reticulocytes(mean±SD)	15.31±4.2%	8.48±1.7%	-

Table (6) showed the number of exchange transfusion required in the 44 neonates in the study. There were 51process of exchange transfusion. 6 15.7% of the Group A) required two exchange transfusions, and one neonate (2.6% of the Group A) required three exchange transfusions.

Table (6): The number of exchange transfusion required in the 44 neonates

CAUSE	One exchange Transfusion	Two exchange Transfusions	Three exchange transfusions	P value
Rh-isoimmunization	9	3	1	.018
ABO-incompatibility	4	1	0	-
G6PD	12	0	0	-
Sepsis	3	0	0	-
Preterm	12	2	0	-
Healthy term infants	3	0	0	-
Congenital CMV infection	1	0	0	-
Total	44	6(15.7%)	1(2.6%)	.000

Neonatal septicemia with positive blood culture was found in 8 infants of both groups. Their clinical features are shown in Table (7). The two deaths were both males and death occurred after exchange transfusion. The cause of death was sepsis.

Table (7): Features of 8neonates with positive blood culture in both groups

Feature	Group A (n = 3)	Group B(n = 5)
Male: Female ratio	2:1	4:1
Gestational age(mean±SD)	35.25±2.5wk	37.3±1.4wk
Blood culture: a. *Escherichia Coli* b.Group *B streptococcus* *c.Klebsiella*	Male Female 2(66.6%) 0(0%) 0(0%) 1(33.4%) 0(0%) --------	Male Female 1(20%) ------ 2(40%) 1(20%) 1(20%) -----
Death	2(66.6%)	0(0%)

Prematurity was found to be the cause of hyperbilirubinemia in 33 infants, their clinical and laboratory characteristics were shown in Table (8). The duration of phototherapy after exchange transfusion had ranged from 1 to 6 days with a mean of 66.46 hr. Those who were treated with phototherapy alone were kept under phototherapy for a mean of 78.32 hours, with an interruption for feeding and changing diapers.

Table (8): Clinical characteristics of 33 premature infants in both groups

Clinical and lab. findings	Group A(n = 12)	Group B(n = 21)	Total(n=33)
Male: Female ratio	1:1	1.33:1	1.20:1
Gestational age(mean±SD)	33.58±3.21wk	34.72±2.74wk	33.11wk
Body weight on admission (mean±SD)	1755±452 gm	2117±365 gm	1988gm
Total Serum bilirubin (mean±SD)	19.8±2.8mg/dL	14.4±3.8mg/dL	16.8mg/dL

Table (9) showed the complications encountered during the treatment course, where transient bradycardia following exchange transfusion while fever and loose stools complicating phototherapy

Table (9): Complications of the 44 exchange transfusions and phototherapy

Complications of exchange transfusion	Out of total no. of exchange transfusion No. %	P-value
Transient bradycardia	25 (49.01%)	.000
Cyanosis	3 (5.8%)	
Apnea and bradycardia	3 (5.8%)	
Hyperkalemia	1(1.9%)	
Hypocalcaemia	2 (3.8%)	
Hypoglycemia	3(5.8%)	
Others Death (within 24 hours), Thrombocytopenia, Neutropenia	 2 (3.8%) 3 (5.8%) 2 (3.8%)	
Complications of phototherapy		P-value
Loose stool	25(25%)	.000
Erythematous rash	14(14%)	
Fever	33(33%)	
Hypothermia	5(5%)	

Discussion

Hyperbilirubinemia was noticed in males more than females (67 males, with a male: female ratio 2.03: 1) in both groups (A and B). This may be a male gender is considered as a risk factor for neonatal jaundice, [17,18] although no significant statistical difference was found. Alistair, showed that bilirubin was significantly higher in males than females. It may be related to the higher rate of prematurity in the males and G6PD deficiency (which is prevalent in males), or other factors [18]. The age at admission in both groups, are older than 4 days (101.6 hr. for group A and 136.1hr for group B). This might be due to the belief of families that jaundice is a normal phenomenon in the 1st week of life, or parents try to consult a local health care centers initially instead of consulting pediatric hospitals, which results in a delay of presentation, as well as the use of non-medical and traditional methods to deal with jaundice like water and glucose and others (herbal medicine). 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 day of life. The mean gestational age was 36.12/52 in group A and 37.92/52 in group B. Those in group A appear to have a lower gestational age, which is probably related to the higher risk of jaundice in premature infants. The mean body weight for group A neonates was 2.635 gm and for group B was 2.956 gm. It is clear that the gestational ages and body weights of group A patients were less than that in group B, which may explain their greater rate of exchange transfusion. Prematurity is a well-known risk factor for neonatal hyperbilirubinemia due to the more immaturity of the liver enzymes. [13, 16]. However, Al-Shujairy showed that the neonates who are treated by exchange transfusion were aged 127hr (mean), mean gestational age was 37.4/52, and the mean body weight was 2734 gm. This might be due to the chance effect, decreased health services, maternal distress both physical and psychological, which affect the birth weight and the gestational ages of the newborns. Hemolytic cause for jaundice was found in 48neonates (48%); 25 (52.0%) in group A and 23 (47.9%) in group B with a P-value 0.032 which indicates a significant risk for hemolytic anemia to be exposed for exchange transfusion. Singhal and Kalkan found a hemolytic cause in 62.5% and 41% respectively [15,16] of studied neonates, while Michael found that the hemolytic causes represent 34% of the causes[17]. These differences might be due to the small sample taken, different ethnic groups, geographic factors, or other factors.

Rh-isoimmunization was found in 13%, ABO-incompatibility in 10%and G6PD-deficiency in 25%. Nine neonates with Rh isoimmunization were treated by exchange transfusion and 4 by phototherapy only with a P-value of 0.041 which indicates a significant risk for jaundiced neonates who have Rh isoimmunization to be treated by exchange transfusion. Michael found Rh isoimmunization represents 3% of the causes of severe neonatal hyperbilirubinemia. This difference may be related to the variations in the distribution of the Rh antigen, better prophylactic measures against Rh-

isoimmunization diseases than in our locality. We found ABO- incompatibility in 10 infants, 4 of them were in group A and 6 in group B with a P-value of 0.615. The ABO-incompatibility is less severe than Rh-isoimmunization, thus fewer neonates had severe jaundice that required exchange transfusion [17,18]. Michael found ABO incompatibility represents 19% of the causes of neonatal hyperbilirubinemia, possibly because it may represent the most common hemolytic cause of neonatal hyperbilirubinemia in the area of the study. We found 25(25%) neonates had G6PD enzyme deficiency, while Micheal found 7% of the cases, and Al-Shujairy it represents 9% of his cases. Sepsis present in 8 studied neonates (8%), while Michael detected 6 cases of sepsis (2.3%) which is probably due to better hygiene and medical care in the delivery rooms and their nurseries. In septicemia, male gender and prematurity are considered important risk factors [13,17]. Two neonates died; both had sepsis and died after exchange transfusion (within 24 hours) despite receiving combined antibiotics. Premature neonates represent (33%) with a mean gestational age of 33.91/52 and the mean birth weight on admission was 1.988 gm, and the mean TSB was 16.8mg/dL. Michael detected 45 premature neonates 17% and their mean gestational age was 34.2/52, with a mean body weight of 2.187 gm, which reflects better antenatal care of the pregnant women, better nutrition, and health status. One patient was diagnosed with congenital CMV infection by clinical findings and positive CMV IgM, and received exchange transfusion once. Ten neonates (10%) were full-term and healthy with no abnormal findings apart from jaundice and no evidence of hemolysis. No cause was found from the investigations. Many series in different parts of the world have some percentage of their neonates with no clear cause for hyperbilirubinemia. Exchange transfusion, abroad, is uncommonly used nowadays because of the use of intensive phototherapy and because sensitization is being prevented [12,17]. In this study six neonates required two exchange transfusions, three of them had Rh-isoimmunization, one had ABO-incompatibility, and two infants were premature. However, one neonate with severe Rh isoimmunization required three exchange transfusions. The frequency of complications of the exchange transfusion in comparison to Al-Shujairy was nearly the same in both studies. Mortality following exchange transfusion was 3.8% which is higher than internationally accepted figures.

Conclusions

The cause of hyperbilirubinemia mayn't be taken into account especially at the start of treatment. Severe Rh-isoimmunization is still present in our locality. The mortality rate from exchange transfusion is higher than internationally accepted figures. The exchange transfusion is carried out more frequently than in other countries and done under nonstandard conditions which increases the risk of the associated complications.

Recommendations

The following recommendations may be drawn from this study:

1.Decisions for the treatment of the severely jaundiced neonates should not be made until

full history, a physical examination is done, and the recommended laboratory investigations are performed.

2. Standard guidelines for the treatment of neonatal hyperbilirubinemia should be followed in the management of unconjugated hyperbilirubinemia.

3.Exchange transfusion must be done under optimal conditions of sterility, environmental regulation, and monitoring of electrolytes, calcium, blood glucose, body temperature, and vital signs.

4.Control programs for Rh-isoimmunization should be improved in our country.

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