AETIOLOGICAL PROFILE AND OUTCOME OF JAUNDICED NEONATES ADMITTED TO BAB ALSHARYIA UNIVERSITY HOSPITAL

By

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ABSTRACT

Background: *Hyperbilirubinemia is the most common condition requiring evaluation and treatment in newborns. It must be treated early to avoid development of kernicterus. Management of unconjugated hyperbilirubinemia is clearly tied to the etiology. Early identification of known causes of non-physiologic hyperbilirubinemia should prompt appropriate laboratory investigations, and timely intervention.*

Objectives: *to make a survey to all jaundiced baby admitted to NICU to determine the different causes of neonatal hyperbilirubinemia, the different modalities of treatment and the risk factors for developing complications.*

Patients & Methods: *This study was an analytic observational study included all neonates presented by neonatal hyperbilirubinemia admitted to the NICU of Bab Alsharyia University Hospital over one year period from January 2019 to January 2020, the study included 260 neonates (142 males, and 118 females) with mean gestational age was 37.25 ± 0.91 weeks.*

Results: *neonatal jaundice in admitted cases was 54.6% in males and 45.4% in females. 19.2% of the cases were vaginally delivered and 80.8% were delivered by caesarean section. The mean gestational age was 37.25 ± 0.91 weeks. The mean birth weight was 2.79 ± 0.68 kg. The mean age of onset of neonatal jaundice was 4.01 ± 3.64 day of life. The mean total bilirubin level at presentation was 17.13 ± 3.74 mg/dL. The mean maximum total bilirubin level was 25.76 ± 7.13 mg/dL. ABO incompatibility as a cause found in (32.7%) of cases, with more neonates having blood group A (45.3%) than those having blood group B (33.1%), Rh incompatibility in (4.6)% of cases , combined ABO and Rh incompatibility in (6.2%) of cases, breast milk in (38.1%), breast feeding (18.1%), biliary atresia (0.4%) of cases.*

Conclusion: *Neonatal hyperbilirubinemia still the most common cause of admission in NICU.Many etiological factors are associated with neonatal hyperbilirubinemia, mostly ABO incombatibility and breast milk jaundice .Early intensive phototherapy may restrict the need for blood exchange and its hazards.*

Key words: *Neonatal jaundice, risk factors, NICU*

INTRODUCTION

Hyperbilirubinemia is the most common condition requiring evaluation and treatment in newborns. It must be treated early to avoid development of kernicterus. Phototherapy is the standard of care for the treatment of hyperbilirubinemia in infants. The use of exchange blood transfusion as a modality of treatment in neonatal jaundice has remarkably decreased due to emergence of intensive phototherapy as a mode of therapy. Intensive phototherapy has an important benefit in an infant with a bilirubin level high enough to increase the risk for neurological damage **(Hansen, 2017)**.

The exact definition of physiologic range and management of indirect hyperbilirubinemia is complex and based on many factors, including gestational age (GA),postnatal age, birth weight, disease status, degree of hydration and nutritional status and ethnicity **(Gomella,2013)**.

Management of unconjugated hyperbilirubinemia is clearly tied to the etiology. Early identification of known causes of non-physiologic hyperbilirubinemia should prompt close observation for development of jaundice, appropriate laboratory investigation, and timely intervention. Any medication or clinical factor that may interfere with bilirubin metabolism, bilirubin binding to albumin, or the integrity of the blood–brain barrier should be discontinued or corrected. If levels of bilirubin are so high that the infant is at risk for kernicterus, bilirubin may be removed mechanically by exchange transfusion, or its excretion increased by alternative pathways using phototherapy **(Stark and Bhutani, 2017)**.

Aims of the Work

The aim of this study was to make a survey to all jaundiced baby admitted to NICU to determine the different causes of neonatal hyperbilirubinemia, the different modalities of treatment and the risk factors for developing complications.

PATIENTS AND METHODS

This was analytic observational study included all neonates presented by neonatal hyperbilirubinemia admitted to the NICU of Bab Alsharyia University Hospital over one year period from January 2019 to January 2020, the study included 260 neonats (142 males, and 118 females) with mean gestational age (37.25± 0.91)weeks.

Inclusion criteria:

Full term and preterm newborns with jaundice needing treatment by phototherapy or exchange transfusion.

Exclusion criteria:

- Any baby admitted for any cause rather than neonatal jaundice, e.g respiratory distress, sepsis, seizures.
- Neonates with life threatening congenital anomalies.
- Neonates presenting with signs or symptoms suggestive of central nervous system abnormality due to HIE or inborn error of metabolism.

Ethical consideration:

- Approval of research ethics committee of Al-Azhar University was obtained before conducting the study.
- Informed written consent was obtained from parents.
- The steps of the study and the aims, was discussed with the parents.
- The authors declared no potential conflict of interest with respect to the research & publication of this article.
- All the data of the patient & results of the study are confidential & the patient has the right to keep it.
- The authors received no financial support for the research & publications of the article

Each patient included in this study was subjected to:

I. Thorough history talking:

Including date of birth, sex, gestational age, mode of delivery, history of premature rupture of membranes, history of maternal illness and/or drugs, history of previous siblings with neonatal jaundice, symptoms suggestive of kernicterus in the form of poor suckling, lethargy, hypotonia, hypertonia, arched back and seizures, time of onset of jaundice and any risk for ABO incompatibility.

II. Careful clinical examination:

Including assessment of anthropometric parameters, neonatal reflexes, pallor and neurological examination with special emphasis on signs of kernicterus, in addition to chest, cardiac and abdominal examination.

III. Laboratory investigations:

a) Routine investigations: Total serum bilirubin (on admission and maximum level), complete blood count, reticulocytic count, C-reactive protein (CRP), maternal and infant

blood group ABO and Rh typing and Coombs' test to suspected cases of hemolytic jaundice.

b) Investigations done to selected patients: Liver function tests in the form of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum albumin, and blood culture for patients suspected to have sepsis.

Samples: two samples were obtained into two tubes, one tube with EDTA for CBC , retics and Coombs' test. retics counted manually and CBC analysed by Ruby Cell-Dyn, American. The other tube without EDTA for bilirubin and chemistry analysed by Cobas 311C, German.

c) Selected investigations: if needed e.g. G6PD enzyme assay- pyruvate kinase enzyme assay - test for spherocytosis {flow cytometric EMA (eosin-5-maleimide)}.

IV. Therapy:

In the form of intensive phototherapy alone, or IVIG given with intensive phototherapy, or exchange transfusion according to the guidelines of American academy of pediatrics 2014.

V. Outcome:

Regard as improvement, development of complications or neurological sequelae e.g. poor feeding, tone abnormality or seizures.

Statistical analysis of results:

Statistical Package for Social Science (SPSS v20) was used after transforming the data from Excel 2013 sheet. Categorical variables were presented by number and percent. They were compared using Chi-square test or Fischer's exact test when appropriate. Continuous variables were presented by mean and standard deviation or median and range. They were compared by student's t-test if parametric data and using Mann Whitney U test if non parametric data. In all tests, P value was considered significant if less than 0.05.

RESULTS

Table (1): Distribution of the studied cases according to demographic data (n = 260)

Descriptive data	No.	%
Sex :		
Male	142	54.6
Female	118	45.4
Age (days):		
<10	244	93.8
≥10	16	6.2
Min. – Max.	1.0 – 60.0	
Mean ± SD.	5.59 ± 5.79	
Mode of delivery:		
CS	210	80.8
VD	50	19.2
Multiple gestation:		
No	254	97.7
Yes	6	2.3
Gestational age (weeks):		
Min. – Max.	34.0 – 39.0	
Mean ± SD.	37.25 ± 0.91	

CS= caesarian section, SD= standard deviation, VD= vaginal delivery

Table (1) shows that majority of cases (93.8%) were below 10 days old. Most of cases (80.8%) were delivered by caeserian section.

Table (2): Distribution of the studied cases according to pattern of feeding (n = 260)

Pattern of feeding	No.	%
Breast fed	236	90.8
Formula fed	20	7.7
Breast + Formula	4	1.5

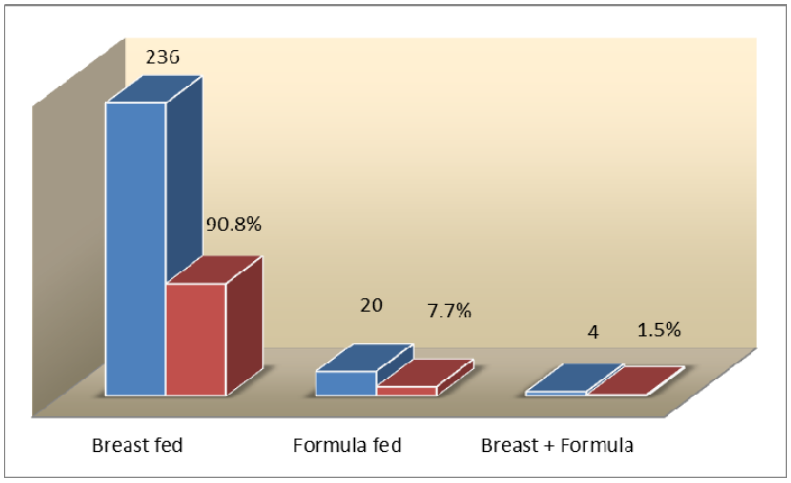

Figure (1): Distribution of the studied cases according to pattern of feeding.

Table (2) and Figure (1) show that 236 (90.8%) cases were breast fed babies, while 20 (7.7%) cases were formula fed babies, 4 (1.5%) cases were both breast and formula fed babies.

Table (3): Distribution of the studied cases according to maternal and infant blood groups (n = 260)

Blood groups	No.	%
Maternal blood groups		
A+	56	21.5
A-	6	2.3
B+	38	14.6
B-	4	1.5
O+	112	43.1
O-	20	7.7
AB+	22	8.5
AB-	2	0.8
Infant blood groups		
A+	114	43.8
A-	4	1.5
B+	84	32.3
B-	2	0.8
O+	40	15.4
O-	2	0.8
AB+	12	4.6
AB-	2	0.8

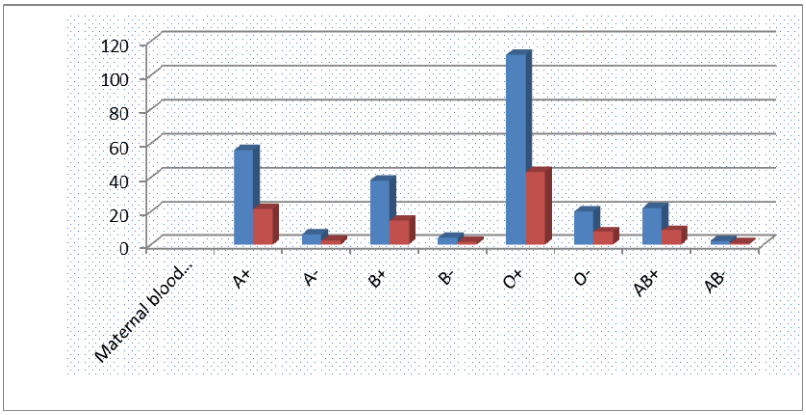

Figure (2): Distribution of the studied cases according to maternal blood groups.

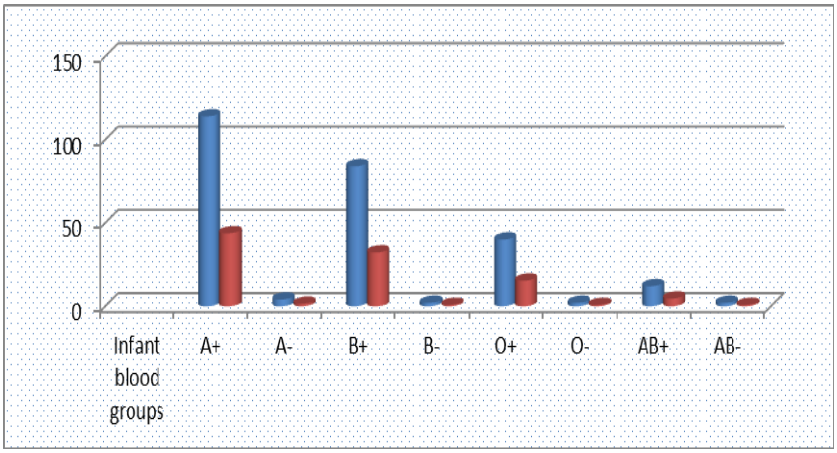

Figure (3): Distribution of the studied cases according infant blood groups.

Table (3) Figures (2&3) show blood group and Rh typing of the mothers and babies. For mothers, the majority of cases were O +ve (112) mothers (43.1%) and A +ve mothers were 56 (21.5%). For babies, 114 infants (43.8%) were A +ve, 84 infants (23.3%) were B +ve, 2 infants (0.8%) were B –ve, reflecting the main etiology of neonatal jaundice was ABO incompatibility.

Table (4): Distribution of the studied cases according to total and direct bilirubin level (n = 260)

Type of bilirubin	Min. – Max.	Mean ± SD.	Median (IQR)
Total bilirubin(mg/dl)	5.0 – 26.70	17.13 ± 3.74	17.70(15.2 – 19.5)
Direct bilirubin(mg/dl)	0.06 – 15.0	1.06 ± 1.34	0.90(0.7 – 1.2)

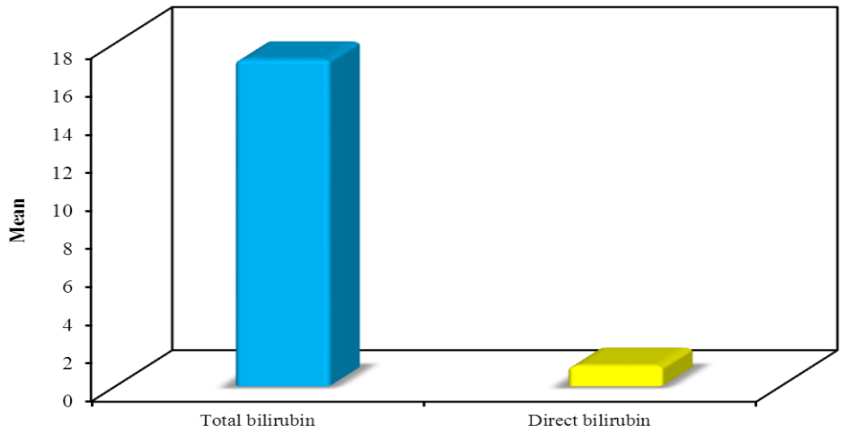

Figure (4): Distribution of the studied cases according to total and direct bilirubin level.

Table (4) and figure (4) show data about level of bilirubin at time of admission; the mean level of total serum bilirubin at admission was 17.13 ± 3.74.

Table (5): Distribution of the studied cases according to type of management (n = 260)

Management	**No.**	**%**
Intensive photo only	215	82.7
IVIG + intensive photo	32	12.3
Exchange transfusion + intensive photo	12	4.6
Duration of treatment (hours)		
Range	72 – 168	
Mean ± SD.	104.64 ± 67.44	

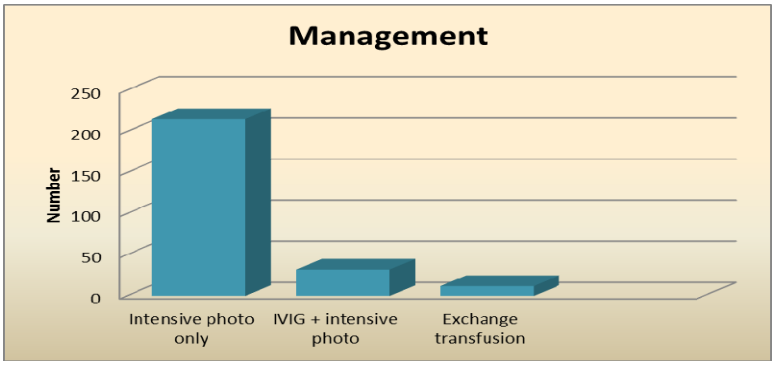

Figure (5): Distribution of the studied cases according to type of management.

Table and figure (5)show data about different modalities of management, 215 cases (82.7%) treated by intensive photo only, 32 cases (12.3%) treated by IVIG plus intensive photo. 12 cases (4.6%) treated by exchange transfusion plus intensive photo.

Table (6): Distribution of the studied cases according to final diagnosis (n= 260)

Final diagnosis (etiology)	No.	%
Breast milk J	99	38.1
ABO Incompatibility	85	32.7
Breast feeding J	47	18.1
ABO & RH Incompatibility	16	6.2
RH Incompatibility	12	4.6
Biliary atresia	1	0.4

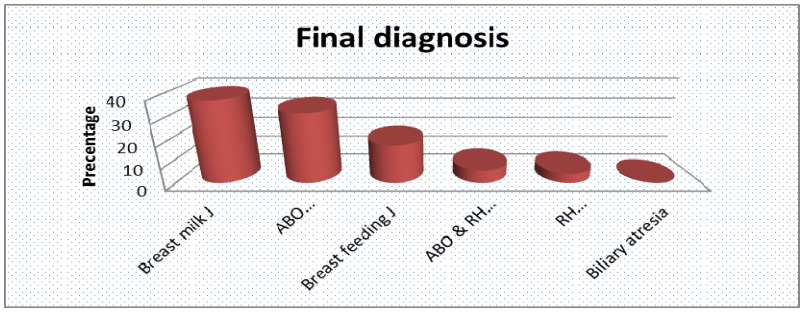

Figure (7): Distribution of the studied cases according to final diagnosis

Table (7) and figure (7)show data about final diagnosis; 99 cases (38.1%) due to breast milk jaundice, 47 cases (18.1%) due to breast feeding jaundice, 85 cases (32.7%) due to ABO incompatibility, 12 cases (4.6%) due to RH incompatibility, 16 cases (6.2%) due to ABO & RH Incompatibility, 1 case (0.4%) due to biliary atresia.

Table (7): Distribution of the studied cases according to outcome on discharge from NICU (n = 260)

Outcome (on discharge)	No.	%
Normal	259	99.6
Convulsions	0	0.0
Kernicterus	0	0.0
Death	1	0.4

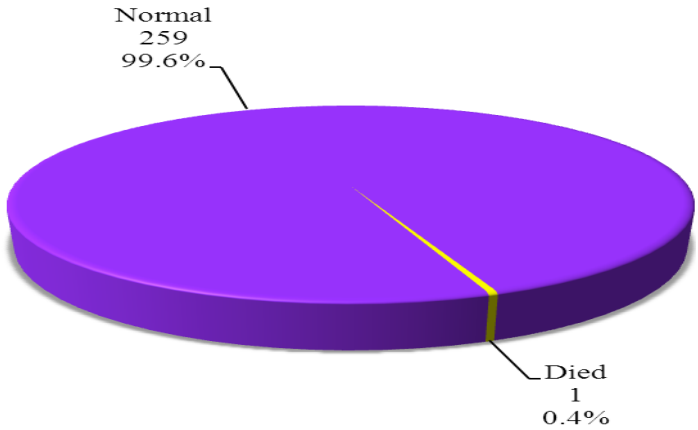

Figure (6): Distribution of the studied cases according to outcome on discharge from NICU.

Table (6) shows data about outcome on discharge from NICU, 1 case (0.4%) died due to biliary atresia, 259 cases (99.6%) discharged without complication.

DISCUSSION

The present study was an analytic observational one, carried out prospectively at NICU of Bab Alsharyia University Hospital on all neonates admitted with neonatal jaundice in attempt to evaluate cases of neonatal jaundice as regards magnitude of the problem, causes, management, prognosis and outcome.

Regarding the demographic and characteristic data of the studied cases (table 1) the mean

gestational age was 37.25 ± 0.91 weeks, with most of them (83.1%) were in the full term period (37 to 41 weeks). In a study conducted by **Davutoglu et al** in **2010**, the mean gestational age was 37.0 ± 2.1 weeks, and 12 neonates (15.2%) were below 38 weeks of gestation. **Iskander et al** conducted a study in **2012** on neonates aged 6 days or more, the mean gestational age was 38.2 ± 1.4 weeks.

Regarding sex distribution in this study, there was male predominance, with (54.6%) males and (45.4%) females. The percentage was very near to the study done in **2012** by **Henny-Harry and Trotman**, who reported (61%) males and (39%) females.

Gamaleldin et al conducted a study in **2011** on 249 newborns admitted with a TSB level of 25 mg/dL or more there were (54.2%) males and (45.8%) females.

In another study done by **Heydarian and Majdi** in **2010** on 118 neonates weighting 2 kg and more, who had exchange transfusion in pediatrics ward, there were (63.6%) males and (36.4%) females.

Regarding mode of delivery in this study, more cases were delivered by caesarean section. (80.8%) cases, and (19.2%) cases were delivered vaginally. In the study conducted by **Iskander et al** in **2012**, (72.3%) cases were vaginally delivered and (27.7%) cases were delivered by caesarean section.

Vaginally delivered babies are likely to be discharged early from hospital. This may cause delayed diagnosis of jaundice and increased risk of kernicterus **(Iskander et al, 2012)**.

In the present study, the mean birth weight was 2.79 ± 0.68 kilograms, and in the study conducted by **Davutoglu et al** in **2010**, the mean birth weight was 2.82 ± 0.68 kg. In the study done by **Henny-Harry and Trotman** in **2012**, the mean birth weight was 2.7 ± 0.8 kg.

The mean total bilirubin level at admission was 17.13 ± 3.74 mg/dL. In the study conducted by **Iskander et al** in **2012**, the mean total bilirubin at admission was 25.76 ± 4.39 mg/dL.

Another study was conducted by **Abdel Latif et al** in **2012** Two hundred and twelve neonates presented with TSB ≥ 20 mg/dL and admitted for intensive phototherapy. The mean TSB on admission for all the cases was 26.8 ± 6.2 mg/dL.

In the current study, the mean age of onset of jaundice was 4.01

± 3.64 days, this was in agreement with the study conducted by **Iskander et al** in **2012**, who reported that the mean age of onset of jaundice was 4.1 ± 3.4 days. Similar to this result, in the study conducted by **Davutoglu et al** in **2010**, also foud that the mean age of onset of jaundice was at the age of 4.9 ± 2.2 days. The mean age of maximum serum bilirubin level was 6.18 ± 3.76 days, and in the study done in **2012** by **Henny-Harry and Trotman**, they reported the mean age of maximum serum bilirubin level was 4.7 ± 2.1 days.

Regarding maternal blood group in our study (table3); the majority of mothers had blood group O +ve, 112 cases (43.1%). There were 20 cases (7.7%) O –ve mothers. The percentage of maternal blood group O was also the highest in the study of University Hospital of the West Indies done by **Henny-Harry and Trotman** in **2012**, which was 66%. There were 12% Rhesus negative mothers.

The majority of studied neonates in our study had the blood group A +ve (43.8%), B +ve (32.3%), O +ve (15.4%), AB +ve (4.6%). The study of **Henny-Harry and Trotman** in **2012** showed that there were (38%) infants with blood group O and (59%) with blood groups A or B.

In the current study, the cause of indirect hyperbilirubinemia (table 6) was ABO incompatibility in (32.7%) of cases, with more neonates with blood group A (45.3%) than those with group B (33.1%), Rh incompatibility in (4.6%) of cases, combined ABO and Rh incompatibility in (6.2%) of cases, breast milk jaundice (38.1%) of cases, breast feeding jaundice (18.1%) of cases, biliary atresia 1 case (0.4%).

On the contrary, in the study conducted by **Davutoglu et al** in **2010**, the causes of indirect hyperbilirubinemia were ABO incompatibility (38%), Rh incompatibility (12.6%), combined ABO and Rh incompatibility (2.5%), G6PD deficiency (11.4%), polycythemia (3.8%), hypothyroidism (2.5%), prematurity (6.3%) and unknown (13.9%).

In the study done by **Heydarian and Majdi** in **2010**, the causes of indirect hyperbilirubinemia were ABO incompatibility (38.1%), Rh incompatibility (16.1%), sepsis (8.5%), G6PD deficiency (3.4%), polycythemia (3.8%), urinary tract infection (5.1%), others (cephalhematoma, Crigler-Najjar) (3.4%) and unknown (25.4%).

Nearly similar to the results of our study, in the study conducted by **Iskander et al** in **2012**, the causes of indirect hyperbilirubinemia were ABO incompatibility (25.4%), Rh incompatibility (8.5%) with most mothers had blood group A -ve (3.6%) then O -ve and B -ve (each was 1.7%), sepsis (9.2%), dehydration (13.8%), polycythemia (4.6%), bruising (7.7%), other hemolytic disorders (5.4%), breast milk (1.5%) and undetermined (40%).

Regarding the modalities of management (Table5); most of patients 215 (82.7%) cases treated by intensive phototherapy (Bilisphere) only, 12 (4.6%) cases treated by exchange blood transfusion plus intensive phototherapy, 32 (12.3%) cases treated by intravenous immunoglobulin plus intensive phototherapy.

The low incidence of exchange transfusion is due to the early use of maximum intensive phototherapy (Bilisphere) in the NICU of Bab Alsharyia University Hospital for the high levels of serum indirect bilirubin.

Bilisphere caused marked reduction in the serum bilirubin level in a short period and decreased the period of hospital stay (average hospital stay of cases used Bilishere was 3.81 days, Therefore, it decreased the need for exchange transfusion and helped the rapid discharge of the jaundiced neonates.

The percentage of exchange transfusion in our study was as low as in the study conducted by **Owa and Ogunlesi** in **2009**, only 5.3% of the neonates treated by exchange transfusion. The percentage in the study done by **Henny-Harry and Trotman** in **2012**, reported that (5%) neonates required exchange transfusion.

In the study done by **Abd-Ellatif et al** in **2012**, the mean duration of intensive phototherapy use was 14 hours.

The outcome of cases of neonatal jaundice in the present study (table 7) showed that 259 patients (99.6%) discharged without complicaions and 1 patient (0.4%) died due to biliary atresia, the mean duration of hospital stay was 104.64 ± 67.44 hours.

In the study done by **Naderi et al** in **2009** on 40 neonates admitted for phototherapy, the mean length of hospital stay was 34.6 ± 16.5 hours for the group used double phototherapy and 41.5 ± 17.7 hours for the group used triple phototherapy.

In the current study, the number of cases who had ABO incompatibility or ABO & Rh incompatibility with a significant hemolysis which at the level of exchange transfusion and managed by intravenous immunoglobulins and intensive photo decreased the need for exchange transfusion in most cases.

In our study, the number of days of Bilisphere use affects significantly the morbidity among cases. This is due to the large number of cases have used Bilisphere in relation to the total number of cases of neonatal jaundice, and effectiveness of intenaive photo (Bilisphere) in rapid decreasing of bilirubin level and limiting the need for exchange transfusion.

CONCLUSION

- Neonatal hyperbilirubinemia still the most common cause of admission in NICU.
- Many etiological factors are associated with neonatal hyperbilirubinemia, mostly ABO incombatibility and breast milk jaundice.
- Early detection of neonatal hyperbilirubinemia associated with good prognosis.
- Early intensive phototherapy may restrict the need for blood exchange and it`s hazards.

RECOMMENDATIONS

- Screening of all newborns before discharge from maternity hospital to check the bilirubin level on the specific nomogram and to detect neonates at risk of severe hyperbilirubinemia, especially those whom mothers have blood group O or Rh-negative blood.
- Parental education about jaundice and proper timely follow up is essential.
- Continuous medical education for physicians for early detection of neonatal jaundice and providing appropriate treatment according to international or regional guidelines. This should help reduce risk of severe neonatal jaundice and kernicterus.
- Long-term follow up of cases with severe hyperbilirubinemia and cases of kernicterus is required to detect the long-term sequelae such as hearing defects, cognitive dysfunction, gaze impairment or dental hypoplasia.

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دراسة العوامل المسببة للصفراء والآثار المترتبة عليها للأطفال حديثي الولادة المحجوزين في مستشفى باب الشعرية الجامعي

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تعد الصفراء في الأطفال حديثي الولادة من أكثر الأعراض شيوعا والأكثر سببا في حجز الأطفال حديثي الولادة في الحضانة.

بأنها إصفرار في لون الجلد بسبب زيادة نسبة البيلروبين في الدم، وهناك نوعان من البيلروبين في الدم؛ نوع مباشر ونوع غير مباشر، وينتج النوع الغير مباشر بسبب زيادة نسبة البيلروبين الغير مرتبط في الدم، وهو النوع الأخطر لأنه يعبر خلايا المخ والذي بدوره في حالة الزيادة الشديدة قد يؤدي إلى تلف خلايا المخ وحدوث مشاكل عصبية للأطفال مما يستدعي المتابعة الدقيقة والمستمرة للأطفال حديثي الولادة فور ظهور الصفراء بالجلد.

كان الهدف من هذه الدراسة الوقوف على حجم المشكلة من حيث الأسباب وطرق العلاج المستخدمة والنتائج من حيث الشفاء الكامل أو حدوث مضاعفات طبية.

تعد هذه الدراسة دراسة تحليلية للأطفال حديثي الولادة الذين تم حجزهم في مستشفى باب الشعرية الجامعي على مدار عام كامل في الفترة من يناير 2018 وحتى يناير 2019، وقد تمت هذه الدراسة على 260 طفل و تم أخذ تاريخ مرضي كامل لكل منهم وعمل فحص شامل للجسم وعمل تحاليل طبية شاملة ومتابعة للطفل لحين خروجه من الحضانة.

وقد أظهرت النتائج أن نسبة الصفراء في الذكور 54.6%، ونسبتها في الإناث 45.4%، ومعدل الولادة القيصرية للأطفال 80.2%، ومعدل الولادة الطبيعية 19.8%، ومتوسط ظهور الصفراء في اليوم الرابع من عمر الطفل ومتوسط نسبة البيلروبين في الدم وقت حجز الأطفال في الحضانة 17 مجم/ديسيلتر.

كما أظهرت النتائج أن أكثر سبب لحدوث الصفراء هو لبن الأم بنسبة تصل إلى 38.1%، يليه عدم توافق فصيلة الدم بين الأم والطفل بنسبة 32.7%، ثم قلة الرضاعة للطفل من الثدي في أول 3 أيام من العمر بنسبة 18.1%، ثم عدم توافق عامل ريسس بنسبة 4.6%.

وقد خضع الأطفال في هذة الدراسة لطرق العلاج المختلفة وقد كان لإستخدام العلاج الضوئي المكثف الأثر الفعال في تقليل نسبة البيلروبين في الدم بشكل كبير وتقليل اللجوء إلى تغيير دم الطفل كطريقة للعلاج وبالتالي تقليل نسبة حدوث مضاعفات للطفل عند تغيير الدم، كما أدى إلى تقليل

عـــدد أيـــام حجـــز الأطفـــال فـــي المستشـــفى وخـــروج الأطفـــال بصـــحة جيدة ودون حدوث مضاعفات بنسة 99.6%.

وقـــد أوصـــت هـــذة الدراســـة بضـــرورة المتابعـــة المســـتمرة والدقيقـــة للأطفـــال حـــديثي الـــولادة فـــي الأيـــام الأولـــى مـــن العمـــر وبـــالأخص عنـــد ظهـــور إصـــفرار بالجلـــد لتجنـــب زيـــادة نســـبة البيلـــروبين بالـــدم وبالتـــالي حـــدوث مضـــاعفات طبيـــة، كمـــا أوصـــت بضـــرورة إســـتخدام الجهـــاز الضـــوئي المكثـــف كوســـيلة عـــلاج فعالـــة فـــي تقليـــل نســـبة البيلـــروبين فـــي الـــدم وتقليـــل اللجـــوء إلـــى عمليـــة إســـتبدال دم الطفـــل كوســـيلة أخـــرى للعـــلاج ومـــا يترتـــب عليهـــا مـــن مضاعفات طبية خطيرة.