Brief Communication

Outcome of Neonatal Hyperbilirubinemia in a Tertiary Care Hospital in Bangladesh

Choudhury Habibur Rasul, Md Abul Hasan, Farhana Yasmin

Department of Paediatrics, Khulna Medical College Hospital, Khulna-9000, Bangladesh

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Abstract

Background: **Kernicterus occurs in infants around the world. This study examined the outcomes of various treatments for neonatal hyperbilirubinemia (NH) used in the Khulna Medical College Hospital in Bangladesh.**

Methods: **All of the jaundiced newborns in the neonatal ward between 2005 and 2008 were included in the study. Total serum bilirubin and fractional levels were measured in all cases, regardless of the degree of jaundice. NH was classified as mild, moderate or severe depending on the bilirubin level; mild NH was treated with a sunbath, moderate NH was treated with phototherapy, and severe NH was treated with exchange transfusion.**

Results: **Of 1981 neonates, 426 (22%) were diagnosed with NH. Physiological jaundice (26.7%) was most common, followed by the jaundice of prematurity (20.9%). Haemolytic jaundice was primarily caused by ABO incompatibility (11.3%) and Rh incompatibility (5.4%). Exchange transfusion (ET) was performed in 22 patients; four (18.2%) died as a result of hazards that could have been avoided with skilled monitoring. Twelve (2.8%) individuals with jaundice died. Kernicterus developed in nine (2.1%) children, four of whom survived with neurological sequelae.**

Conclusion: **ABO incompatibility is twice as common as Rh incompatibility. The majority of kernicterus patients died in the acute phase.**

Keywords: *exchange transfusion, kernicterus, neonatal hyperbilirubinemia, medical sciences*

Introduction

Neonatal hyperbilirubinemia (NH) is a common problem that occurs in about 60% of newborns during the first week of life (1). Bilirubin is a known antioxidant at low concentrations but a potent neurotoxin at high concentrations (2). The transition from progressive hyperbilirubinemia to acute bilirubin encephalopathy is often rapid and unpredictable because of a very narrow margin of safety. Studies in the early 1990s suggested that kernicterus from NH was rare in developed countries, and researchers argued that too many children were being treated unnecessarily (3,4). After new guidelines that recommended the treatment of NH at higher levels than before were published, the incidence of kernicterus increased in several countries (5,6).

Many changes have occurred in the management of NH. The hour-specific nomogram, introduced by Bhutani et al. and supported by the American Academy of Paediatrics (AAP), was found to be an effective means of predicting NH (7,8). Many studies have questioned the accuracy of visual assessments used in developing countries (9) but non-invasive bilirubin estimation by transcutaneous bilirubinometry is not available everywhere. At the same time, as the incidence of severe jaundice due to Rh incompatibility has declined, ABO incompatibility has become the most common cause of haemolytic jaundice in newborns (10). These changes in global and national contexts have prompted this work. The objective of this study was to evaluate the effect of different treatment modalities on jaundice outcomes in a tertiary care hospital in Bangladesh.

Material and Methods

This prospective cross-sectional study examined patients admitted to the Khulna Medical College Hospital (KMCH) between July 2005 and June 2008. All of the newborns with visible jaundice in the neonatal ward were included in this study. These neonates were either admitted with jaundice or developed it after they were hospitalised for other reasons. Patients with jaundice who were over the age of two weeks were excluded from the study. A careful general examination was carried out to explore possible aetiologies. All of the patients with clinical jaundice, regardless of the severity,

were assessed for total serum bilirubin as well as for direct and indirect fractions. The serum collected from venous blood samples was tested in an automated analyser with the colorimetric method. Additional tests, including a full blood count, peripheral blood film, blood group, Coombs test, blood culture, serum electrolytes and neuroimaging, were completed in all cases of severe NH; these tests were used to determine the causes or effects of NH. Neuroimaging was used only in survivors with neurological sequelae. Lab tests for G-6-PD, pyruvate kinase and gluronyl transferase could not be completed because of a lack of facilities. Twenty-four hours after birth, mild NH was defined as a total bilirubin level of up to 10 mg/dL (171 μmol/L) in preterm infants and up to 12 mg/dL (205 μmol/L) in full-term infants. Bilurubin levels above 18 mg/dL (308 μmol/L) in preterm infants and above 20 mg/dL (342 μmol/L) in full-term infants were used to identify severe hyperbilirubinemia. Bilirubin levels between these values indicated moderate NH (10). Kernicterus was diagnosed in severely jaundiced infants on clinical grounds; poor sucking, stupor and hypotonia were symptoms in the early phase, while hypertonia, retrocollis and opisthotonus were symptoms in the late phase (11).

The Paediatric Association of Bangladesh has advocated for the simplified management of NH outside of neonatal intensive care units (12). This study used the recommended therapies according to total serum bilirubin. Mild NH cases were treated conservatively with breast-feeding and sunbaths. Infants were exposed to the sun for a brief period (1–2 hours) in the early morning and afternoon; a filter of tinted glass was used to avoid the possible hazards of radiation. Infants with moderate NH were treated with phototherapy applied in a standard cycle (45 minutes of therapy and 15 minutes of rest). Exchange Transfusion (ET) and phototherapy were used to treat severe NH. Total serum bilirubin was measured each morning. The risk factors for kernicterus, such as prematurity, birth asphyxia, acidosis, hypothermia and hypoglycemia, were monitored to determine whether the treatment needed to be intensified. The clinical course and treatment outcome were noted twice daily. The data at the end of study were analyzed with SPSS-11.5 (SPSS Inc., Chicago). Ethical approval was obtained from the Ethical Review Committee of the KMCH.

Results

During the three-year study period, 1981 patients were admitted to the neonatal ward; 426 (22%) of these infants had jaundice. Of these jaundiced infants, 179 (42%) had a low birth weight (<2.5 kg) and 158 (37%) were preterm (<37 weeks). The male-to-female ratio was 1.3:1. The mean age at the appearance of jaundice was 4.5 ± 2.3 days. Physiological jaundice was most common and was diagnosed in 114 (26.7%) cases. These individuals had mild jaundice persisting from days three to seven after birth. Prematurity (20.9%) and sepsis (17.6%) were also major causes of jaundice.. No correlation was found between prematurity and sepsis. Premature infants observed in the study period were between 30 and 36 weeks gestational age. Escherichia coli and Klebsiella were the most common organisms isolated in cultures from septic infants. ABO incompatibility was responsible for jaundice in 48 cases (11.3%) and Rh incompatibility was responsibly for only 23 (5.4%) cases of jaundice.

One hundred and thirty-seven (32.2%) infants were treated conservatively; most (48) of these infants had physiological jaundice (Table 1). Phototherapy was the most common treatment and was used in 267 (62.6%) cases. ET was used in 22 (5.2%) cases; most (68.2%) of these patients suffered from Rh incompatibility. Four hundred and one (94.1%) infants improved satisfactorily, including all those with physiological jaundice and cephalhaematoma. Twelve (2.8%) patients died in the hospital, five of whom developed kernicterus before death (Table 2). Three of the fatal cases were admitted to the hospital in a very late stage with neurological symptoms. ET resulted in the death of four (18.2%) patients: in sepsis (1 case), of ABO incompatibility (1 case) and of Rh incompatibility (2 cases). The rest of the fatalities were attributed to co-morbidities (4) or an unknown cause (1). A shortage of fresh blood and electrolyte imbalance were the principal obstacles and dangers during the ET procedure. Four (0.9%) survivors had neurological sequelae; MRIs of their brains revealed evidence of neuronal atrophy of the basal ganglia, particularly in the globus pallidus and, in two cases, the cerebellum.

Among the 28 infants with severe NH, six did not receive ET due to either their frail state (2) or delayed admission (4). Table 3 compares the characteristics of infants with severe NH who developed kernicterus with those of infants who did not develop kernicterus. Although the proportions of premature infants and those with low birth weight were higher in the group

Table 1: Modalities of treatment for various conditions

Cause	Modalities			Total, (%)
	Sunbath	Phototherapy	Exchange Transfusion + Phototherapy	
Physiological	48	66	0	114 (26.8)
Prematurity	27	62	0	89 (20.9)
Sepsis	24	49	2	75 (17.6)
ABO incompatibility	13	30	5	48 (11.3)
Rh incompatibility	0	8	15	23 (5.4)
Cephalhaematoma	3	7	0	10 (2.3)
Others	22	45	0	67 (15.7)
Total (%)	137 (32.3)	267 (62.6)	22 (5.2)	426 (100)

Table 2: Outcome of neonatal hyperbilirubinemia

Cause	Outcome					Total
	Improved	Expired	Expired with Kernicterus	Kernicterus	Absconded	
Physiological	114	0	0	0	0	114
Prematurity	84	1	1	0	3	89
Sepsis	69	2[a]	1	1	2	75
ABO incompatibility	46	1[a]	0	1	0	48
Rh incompatibility	17	2[a]	2[a]	2	0	23
Cephalhaematoma	10	0	0	0	0	10
Others	61	1	1	0	4	67
Total (%)	401 (94.1)	7 (1.6)	5 (1.2)	4 (0.9)	9 (2.1)	426 (100)

Total deaths: 12 (2.8%); Total Kernicterus cases: 9 (2.1%)
[a]Single death from Exchange Transfusion; Total deaths from Exchange Transfusion: 4 (18.2%)

developing kernicterus; this difference was not statistically significant. Aetiology, gender and feeding patterns were similar in the two groups.

Discussion

This study found that approximately one in five (22%) infants admitted to the neonatal ward had jaundice. Among these jaundiced infants, 37% were preterm. Khatun et al. reported a similar observation in the neonatal unit of a university hospital, where 35% of newborns had jaundice and 31% of jaundiced infants were preterm (12). ABO incompatibility (11.3%) was more than twice as common as Rh incompatibility (5.4%); this finding is similar to those reported a study (10). The incidence of Rh isoimmunization has decreased as a result of the introduction of Rh (D) immunoglobulin to Rh-negative mothers. However, Hoque studied haemolytic disease in newborns and found that 39% of cases were the result of ABO incompatibility and 34% cases were the result of Rh incompatibility (13).

One-third (32.2%) of our patients improved with conservative treatment alone. Phototherapy was applied in most (62.6%) cases with good success. A small portion (5.2%) of patients underwent ET. Our findings are consistent with those of other medical centres, where 61% of patients required only phototherapy (12). Fifteen years ago, Rh incompatibility was the

Table 3: Risk factors for kernicterus in severe neonatal hyperbilirubinemia (n=28)

Factors	Kernicterus-9 (% within group)	No kernicterus-19 (% within group)	P-value[a]
Aetiology			
Prematurity	1 (11)	1 (5)	0.426
Sepsis	2 (22)	2 (11)	
ABO incompatibility	1 (11)	5 (26)	
Rh incompatibility	4 (44)	11 (58)	
Unknown	1 (11)	0 (0)	
Gender			
Male	5 (56)	11 (58)	0.907
Female	4 (44)	8 (42)	
Birth weight			
1 - 1.5 kg	2 (22)	2 (11)	0.301
1.5 - <2.5 kg	5 (56)	7 (37)	
≥ 2.5 kg	2 (22)	10 (52)	
Gestational age			
30–32 weeks	2 (22)	1 (5)	0.292
33–<37 weeks	4 (44)	7 (37)	
≥ 37 weeks	3 (33)	11 (58)	
Feeding			
Formula	1 (11)	2 (11)	0.996
Mixed	2 (22)	4 (21)	
Exclusive Breast milk	6 (67)	13 (68)	

[a]Association between risk factors and kernicterus were calculated using Chi-Square test

most common (40%) cause of ET, followed by ABO incompatibility (35%) (12). Although the incidence of Rh incompatibility has decreased, ET was used most frequently (68%) in cases of Rh incompatibility.

Twelve (2.8%) patients in this study died in the hospital and four (0.9%) neonates were discharged with neurological sequelae. Two studies found that mortality from NH decreased from 36% to 5% over ten years as a result of the wide-spread use of phototherapy, improved ET techniques and increased awareness among health workers of the importance of early management (10,12). ET itself may cause severe complications like acidosis, hypoglycemia, air embolism, arrhythmia and death (14). The mortality from ET in this study (18.2%) is consistent with the ranges (from 8% to 20%) found in other studies (13,15). The clinical features of kernicterus vary, and overt neurological signs have a grave prognosis: 75% of the affected infants die and 80% of survivors bear several neurological complications (14). The majority (55.6%) of infants developing kernicterus in this study died as well.

It is quite alarming to note that nine patients developed kernicterus and five of them died in the hospital. G-6-PD deficiency is common in Bangladesh and is an important contributor to kernicterus; this deficiency may have been an unmeasured factor that led to the high incidence of severe hyperbilirubinemia and kernicterus. Most of the fatalities resulted from delayed admission. The proportion of infants dying from ET was also high in comparison to those in developed countries (7,14). While sterile procedures and thermal stabilisation were maintained during the procedure, the availability of fresh blood and electrolyte monitoring could not be properly ensured; this may have increased the rate of fatality.

ET is the definitive therapy for the prevention of kernicterus in patients with severe NH. However, 22% of children in this study could not receive ET because of the advanced stage of

the disease. The development of kernicterus may be attributed to several potential risk factors (14,15). In this analysis, no significant association was found with aetiology, gender, birth weight, gestational age, and feeding patterns. While infants with a normal birth weight were the least susceptible to severe NH, premature infants (30–32 weeks gestation) were most vulnerable; this finding highlights the need for early and vigorous intervention in these cases.

The primary limitations of this study include the use of absolute bilirubin values in the grading of jaundice, the lack of extensive investigations to determine the cause of jaundice and the lack of follow-up for kernicterus cases. However, this study shows that NH should be regarded as a potentially dangerous problem. Early and appropriate treatment is essential to prevent disastrous neurological sequelae.

In conclusion, kernicterus due to severe hyperbilirubinemia causes permanent neurological damage. In certain parts of the world, kernicterus is still a major cause of mortality and long-term morbidity.

Authors' contributions

Conception and design; drafting, critical revision and final approval of the article: CHR
Provision of study materials or patients: MAH
Data analysis and intepretation, final
Final approval of the article: CHR, MAH, FY
Data collection and assembly, statistical expertise: FY

Correspondence

Dr Choudhury Habibur Rasul
FCPS (BD), MMEd (UK), FRCP (Edin)
Department of Paediatrics
Khulna Medical College & Hospital
Khulna-9000, Bangladesh
Tel: +88-041-813679
Fax: +88-041-760350
E mail: chrasul@btcl.net.bd

References

1. Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. *N Eng J Med*. 2008;**358**: 920–928.
2. Smitherman H, Stark AR, Bhutani VK. Early recognition of neonatal hyperbilirubinemia and its emergency management. *Semin Fetal Neonatal Med*. 2006;**11**:214–224.
3. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Eng J Med*. 2001;**44**;581–590.
4. Newman TB, Klebanoff MA, Neonatal hyperbilirubinemia and longterm outcome-another look at the perinatal collaborative perinatal project. *Pediatrics*. 1993;**92**:651–657.
5. Riskin A, Tamir A, Kugelman A, Hemo M, Badur D. Is visual assessment of jaundice reliable as a screening tool to detect significant hyperbilirubinemia? *J Pediatr*. 2008;**152**:782–787.
6. Chowdhury AR, Hussey MH, Shortland DB. Critical overview of management of neonatal jaundice in the UK. *Public Health*. 2007;**121**:137–143.
7. Bhutani VK, Johnson L. The jaundiced newborn in the emergency department: Prevention of kernicterus. *Clin Ped Emer Med*. 2008;**9**:149–159.
8. American Academy of Pediatrics Subcommittee on hyperbilirubinemia. Management of hyperbilirubinemia in the newborn 35 or more weeks of gestation. *Pediatrics*. 2004;**114(1)**:297–316.
9. Moyer VA, Ahn C, Sneed S, Accuracy of clinical judgment in neonatal jaundice. *Arch Pediatr Adolesc Med*. 2005;**154**:391–394.
10. Ahmed S, Parvin M, Khan AH, Islam MN. Jaundice in the newborn in Bangladesh— a comparison of data 10 years apart. *Bang J Child Health*. 1994;**18**:46–50.
11. Shapiro SM. Definition of clinical spectrum of kernicterus and bilirubin induced neurologic dysfunction. *J Perinatol*. 2005;**25**:54–59.
12. Khatoon S, Islam MN. Neonatal Jaundice—Clinical profile of 140 cases. *Bang J Child Health*. 1993;**17**:158–163.
13. Hoque MM, Hossain MM, Hassan MQ, Uddin ASMN, Begum JA, Chowdhury MAK. Neonatal hyperbilirubinemia requiring exchange transfusion–management and outcome. *Bang J Child Health*. 2004;**28**:55–59.
14. Stoll BJ, Kleigman RM. Kernicterus. In: Behrman RE, Kleigman RM, Jenson HB (editors). *Nelson Textbook of Pediatrics-17th edition*. Saunders: Philadelphia;2004. p.596–598.
15. Merchant RH, Abhyankar SH. Exchange transfusion in newborn- an analysis of 100 cases. *Ind Pediatr*. 1985;**22**:344–353.