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Research Article

Prevalence of Critical Bilirubin Results among Neonatal Patients in Windhoek, Namibia

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Abstract

Neonatal jaundice is a frequently encountered paediatric problem in Africa that is associated with sickness and death. The research was undertaken to determine the prevalence of critical jaundice values in neonates in Windhoek, Namibia. Although several risk factors and aetiologies may be attributed to neonatal jaundice, the research focused on establishing the number of neonates with critical bilirubin levels in Windhoek, Namibia. Secondary data of bilirubin tests performed on neonates was obtained from the Namibia Institute of Pathology's (NIP's) archived patient records for the years 2013 and 2014. Only neonates that were less than 31 days old were included in the study. Data was analysed using the Statistical Package for Social Sciences (SPSS) version 22. The prevalence of critical jaundice values was estimated to be 12.4%. Neonates >3 to ≤6 days of age were noted to be the most affected. It was notable that 9.6% of neonates that were 3 to 6 days old had a potential for developing kernicterus. Males had a higher prevalence of critical values (13.4%) as compared to females (11.5%) and were at greater risk of kernicterus. The critical values and kernicterus cases increased with age. Neonates between 3 to 6 days were most affected as they had bilirubin values depicting risk to kernicterus. The cause of the male preponderance in elevated bilirubin levels is not known. Further studies thus need to be conducted to establish the causes of critical jaundice.

Introduction

Every year approximately 10.8 million children under the age of five years die worldwide and 38% of these mortalities are said to occur in the first month of life [1]. Correspondingly, recent global estimates suggested that approximately 3.6 million deaths occur in the neonatal period [1]. The global burden of neonatal hyperbilirubinemia impacts mostly the world's poorest countries (low-income countries), especially in South Asia and sub-Saharan Africa [2]. Latin America, sub-Saharan Africa and South Asia account for 4%, 32% and 39% of cases of extreme hyperbilirubinemia (total bilirubin exceeding 428 μmol/L) respectively, that is for a combined prevalence of 10/100 000 live births [2].

In Africa, neonatal jaundice is a common pediatric problem particularly in West Africa that is associated with sickness and death [3,4]. A study conducted in Southeast Nigeria found that neonatal jaundice accounted for 35% of hospital admissions and 9.7% of newborns developed kernicterus [5]. The differences in the prevalence of neonatal jaundice may be related to the difference in bilirubin metabolism in the early neonatal period [4]. A study conducted in 2013 to determine the global estimates of extreme hyper bilirubinemia found that sub-Saharan Africa accounts for 35% of the kernicterus cases [2]. In Namibia little is known on the risk of neonatal jaundice and the extent of its contribution to neonatal disease and death.

The mechanisms leading to jaundice include excessive bilirubin production, decreased hepatic uptake or impaired conjugation of bilirubin by the liver, intra-hepatic cholestasis and extra hepatic obstruction [4,6]. These factors are said to account for most cases of pathologic jaundice [6]. Unconjugated hyperbilirubinemia is said to pose a risk for the development of kernicterus, particularly in premature, low-birth weight infants [7]. The major risk factors identified for extreme hyperbilirubinemia are haemolysis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, sepsis, and a range of familial and genetic disorders [2].

Severe neonatal jaundice is not only the major cause for the hospital readmissions of neonates but also represents a significant cause of neonatal morbidity and mortality [1]. Neonatal hyperbilirubinemia resulting in clinical jaundice is believed to be a common problem among neonates predominantly in the first weeks of life, affecting 60% of full-term and 80% of preterm neonates in the first three days of life [8,9]. There are two types of jaundice, namely physiologic jaundice and pathologic jaundice. Terms relating to jaundice include congenital hyperbilirubinemia, pathophysiologic neonatal jaundice, icterus and/or icterus neonatorum. Symptoms of jaundice include dermal icterus progressing from the face to the trunk, to extremities and finally to the palms

of the hand and soles of the feet. The aim of the study was therefore, to determine the prevalence of critical bilirubin values from samples analysed at NIP in Windhoek, Namibia.

Materials and Methods

Research design

The research was a retrospective cross-sectional study which examined bilirubin values in neonates for the period January 2013 to December 2014.

Study population and setting

The study population comprised of neonates that were born at the Katutura State Hospital and Windhoek Central Hospital in Windhoek, Namibia who had bilirubin measurements done. Archived bilirubin results of these neonates were retrieved from NIP's Windhoek Central Reference Laboratory (WCRL) and selected using non-probability purposive sampling. The expected sample size which was statistically acceptable was 385. However, 1870 (n=1870) results were reviewed in the study and used to estimate the prevalence of critical jaundice values in neonates.

Inclusion and exclusion criteria

Archived results of neonates born at Katutura State Hospital and Windhoek Central Hospital who had bilirubin tests done were included in the study. Neonatal bilirubin results that were reported as not done were excluded from the study. Such tests were not performed due to the specimens being icteric, haemolysed, insufficient, delayed in transit or old. Patient records with no specified date of birth, collection date or incomplete results were also excluded from the study. The study population included neonate's ≤31 days of age. Neonates >31 days of age were excluded from the study. Only the initial patient records were considered and repeat measurements of bilirubin were excluded.

Specimen analysis

This was a retrospective study but sample processing for the results used was performed as follows: Samples were centrifuged at 3000 revolutions per minute (rpm) for 10 minutes. Total serum bilirubin was measured using the Architect instrument (Abbott) and reagent kits manufactured by Abbott Laboratories (Illinois, USA). The testing procedure was based on the Diazonium salt methodology. The assay was used for the quantitative analysis of total bilirubin in human serum or plasma of neonates. The principle of the procedure was based on total bilirubin coupling with a diazo reagent in the presence of a surfactant to form azobilirubin. The increase in absorbance at 548 nm was directly proportional to the total bilirubin concentration. Interferences included lipaemia, haemolysis, light or sunlight. The samples were protected from light as bilirubin is photolabile (Abbott Laboratories, 2010).

Data analysis

The data was entered into Microsoft Excel spread sheets. For this study all neonates were assumed to be full-term newborns as the patient reports did not indicate the gestational age or comment on whether they were premature or full-term newborns. The data was coded in a Microsoft Excel spread sheet according to age, gender and results.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 22 was used for statistical analysis. This entailed cross tabulating variables such as age, gender and results. The association between variables were explored with Chi-square tests. Chi-square tests were used to establish if the results were statistically significant. Strength of association was estimated by 95% Confidence Interval (CI). Significant factors were defined as those which had a *P* value less than 0.05 ($P<0.05$).

Ethical considerations

Permission to conduct the study was granted by the Ministry of Health and Social Services (MoHSS), NIP and Namibia University of Science and Technology (NUST) research committees. Patient data was treated with strict confidentiality and patient identification was not used.

Results

The study population consisted of 1870 ($n=1870$) neonates born in the Katutura state hospital and Windhoek Central hospital wards in Windhoek. The neonate's were ≤31 days of age. The data collected was for a two year period that is for the years January 2013 and December 2014.

Out of the 1870 cases analyzed for 2013 and 2014, 872 (46.6%) were female, 897 (48.0%) were male and 101 (5.4%) of the cases had an unknown gender. The mean total bilirubin result over the 2 years was 173.5µmol/L and the standard deviation 82.7. The prevalence of critical jaundice values in samples of neonates analyzed at NIP was estimated to be 12.4%.

Discussion

The findings of this study indicate that the majority of the bilirubin requests (normal, high and critical) were done in the >2 to ≤6 days age group which has 915 requests (48.9%) as shown in Table 1. This makes up almost half of the sample population. Similarly, a study done in Egypt [9] suggested that neonatal jaundice affects 60% of full-term and 80% of preterm infants in the first three days of life.

The prevalence of critical jaundice values at NIP for the period January 2013 to December 2014 was estimated to be 12.4%. Out of the 1870 records sampled, 12.4% of the neonates had high threshold bilirubin values. The high threshold for neonatal bilirubin defined for this study was 256.5µmmol/L (15 mg/dL). The critical values included kernicterus cases, which were defined as critical values more than 291 µmol/L with a potential ofcausing brain damage in neonates. The aetiological factors for such high values were not established in this study. Similar studies that were done to determine the prevalence or

Table 1: Distribution of neonates according to age.

Age (Days)	Frequency	Percentage
>0 to ≤1	290	15.5%
>1 to ≤2	446	23.9%
>2 to ≤6	915	48.9%
>6 to ≤31	219	11.7%
Total	1870	

The table shows that most of the neonates (48.9%) were >2 to ≤ 6 days old.

Table 2: Prevalence of critical bilirubin values according to age.

Age (Days)	Total count of neonates	Count with critical values	Percentage of critical values
>0 to ≤1	290	16	5.5%
>1 to ≤2	446	36	8.1%
>2 to ≤6	915	152	16.6%
>6 to ≤31	219	27	12.3%
Total	1870	231	

Out of the total sample population of 1870 (*n*=1870), a total of 231 (42.5%) neonates had critical values for 2013 and 2014. The group most affected was the one between >2 to ≤6 days (16.6%).

incidence of severe neonatal hyperbilirubinemia, found the prevalence to be 15% in the South of Iran [10], and 36% in Canada [11] which was higher than the prevalence obtained in this current study. The differences in prevalence can be attributed to the fact that the study done in Canada covered a larger age group, that is infants less than 60 days and had a different study design which is a prospective study over a three year period [11]. In comparison, the prevalence found in the South of Iran was closer to the prevalence obtained in this study, possibly due to the fact that the age group selected (≤28 days) closely resembles the age group selected for this study (≤31 days).

In the current study, it was established that a total of 231 (42.5%) neonates had critical jaundice values over the two year period as shown in Table 2. In 2013, it was found that there were 145 cases of critical values (15.2%) which were higher than the 86 cases of critical values (9.4%) reported in 2014 as shown in Table 3. The decline may be indicative of an improvement in treatment or prenatal screening methods for neonatal jaundice. This is in agreement with [2], indicating that with emerging affordable technologies the worldwide prevention and management of newborn jaundice can practically reach infants even in low-income settings. Literature shows that the concern with severe hyperbilirubinemia is the consequence of bilirubin toxicity that may result leading to bilirubin encephalopathy [12]. The most reported cases of kernicterus in the world originate from the United States (27%), Singapore (19%), Turkey (16%) and Greece (8%) [13]. A study done in Nigeria in 2011 found that 9.7% of neonates developed kernicterus [5]. The current study had a lower proportion (7.4%) of neonates that were potentially at a risk for developing kernicterus.

Based on the neonates ages, it was found that 165 (56.9%) of the neonates that were ≤1 day old had high bilirubin results, that is their values exceeded the upper limit of the reference range which is 0-103 µmol/L. It was noted that the prevalence declined in the subsequent age groups. Neonates that were >6 to ≤31 days old which is the oldest age group had 60 (27.4%) high results as seen in Table 4. The >3 to ≤6 days age group was identified to have the highest prevalence of critical values, which was 16.6% (152) while 12.3% (27) of neonates that were >6 to ≤31 days old had critical values. Age groups that

Table 3: Distribution of critical jaundice values by year.

Year	Total count of neonates	Count with critical values	Percentage
2013	954	145	15.2%
2014	916	86	9.4%
Total	1870	231	

The year 2013 had more critical jaundice values (15.2%) than 2014 (9.4%).

Table 4: Distribution of cases according to age in 2013 and 2014.

Age in days	Patient result comment				
	Normal	High	Critical value	Kernicterus	**Total**
>0 to ≤1	109 (37.6%)	165 (56.9%)	6 (2.1%)	10 (3.4%)	290 (100.0%)
>1 to ≤2	278 (62.3%)	132 (29.6%)	10 (2.2%)	26 (5.8%)	446 (100.0%)
>2 to ≤6	589 (64.4%)	174 (19.0%)	64 (7.0%)	88 (9.6%)	915 (100.0%)
>6 to ≤31	132 (60.3%)	60 (27.4%)	12 (5.5%)	15 (6.8%)	219 (100.0%)
Total	1108(59.3%)	531 (28.4%)	92 (4.9%)	139 (7.4%)	1870(100.0%)

The >2 to ≤6 days age group had the highest prevalence of critical values (kernicterus cases included) which is 16.6% (152), followed by the >7 to ≤31 age group with a prevalence of 12.3% (27). It was notable that the critical value and kernicterus proportions increased with age that is from 0 to 31 days reaching their peak in the >2 to ≤6 days age group.

were least affected were the >1 to ≤2 days that had 36 (8%) neonates with critical values and the ≤1 day old age group that had 16 (5.5%) neonates with critical values. Conversely, a study done in Romania found that neonatal jaundice was highest in the 7 to 28 days age group followed by the 3 to 7 days age group [14]. A significant association was found to exist between the patient age in days and the results (P<0.05). This shows that age has an influence on the bilirubin level.

A study done in Italy explained that in the early days of life, all newborns are expected to have unconjugated serum bilirubin levels higher than in subsequent ages, which is defined as physiological hyperbilirubinemia [15]. With physiological jaundice the intensity of the jaundice decreases spontaneously within 1 or 2 weeks [7]. For this study, the decrease of high values in the subsequent age groups may be an indication that a normal physiological process was taking place and that the jaundice was resolving. However, neonates would require monitoring to establish the type of jaundice present. The exclusion criteria for this study involved deleting repeated bilirubin measurements which would be needed for monitoring. Although this current study did not focus on establishing the aetiological factors, physiological jaundice could be caused by erythrocytes with a reduced lifespan and high turnover [6], deficiency of the conjugating enzyme glucuronyl transferase [16] and breastfeeding which are identified as a risk factor for hyperbilirubinemia [17].

Any Total Serum Bilirubin (TSB) exceeding 17 mg/dL (291µmol/L) is to be considered pathologic [18]. For this study, neonates that had critical values exceeding 291µmol/L were identified as neonates at a risk of developing kernicterus. It was notable that 88 (9.6%) neonates that were >3 to ≤6 days old had a potential for

Table 5: Distribution of cases according to gender in 2013 and 2014.

Gender	Patient result comment				Total
	Normal	High	Critical value	Kernicterus	
Females	505 (57.9%)	267 (30.6%)	42 (4.8%)	58 (6.7%)	872 (100%)
Males	535 (59.6%)	241 (26.9%)	47 (5.2%)	74 (8.2%)	597 (100%)
Unknown	68 (67.3%)	23 (26.9%)	3 (3.0%)	7 (6.9%)	101 (100%)
Total	1108(59.3%)	531 (28.4%)	92 (4.9%)	139 (7.4%)	1870(100%)

The table shows that males had a higher prevalence of critical values (kernicterus cases included) 13.4% (121 cases) in comparison to females that had a prevalence of 11.5% (100 cases).

kernicterus, 15 (6.8%) neonates that were >6 to ≤31 days old had a potential for kernicterus, 26 neonates (5.8%) that were 1 to ≤2 days old had a potential for kernicterus and lastly 10 (3.4%) neonates in the ≤1 day age group were at a possible risk of developing kernicterus. This simply identifies neonates at a risk and does not mean that such complications manifested. The critical values obtained for this study may be associated with a more serious type of jaundice (pathologic) that is clinically significant and persists over 8-10 days in full-term neonates and over 21 days in premature newborns. The gestational age thus needs to be established and monitoring needs to take place to come up with a diagnosis.

With respect to age, a few studies that were carried out in Nigeria [1,4-5] describe prematurity as a risk factor for the development hyperbilirubinemia. These studies however did not define the neonates' ages in relation to bilirubin values as was done in the current study. It can be noted from the results that the bilirubin values are different or fluctuate in the different age groups. Age has a notable effect on reference intervals, although the degree of change could differ in various reports and may depend on the analytical method that is used [7], in this case the one provided by Abbott Laboratories (2010). A study done in Turkey suggests that the occurrence of neonatal jaundice as well as contributory factors vary according to ethnicity and geographical location [19]. This could explain why the prevalence of neonatal jaundice differs in different studies that were done in the world.

The results in Table 5 showed that, out of the 1870 cases studied males had a higher prevalence of critical values 13.4% (121) as compared to females that had a prevalence of 11.5% (100). The cause of the male preponderance is not known. Based on the Chi-square test performed, the association between the results and the patient gender was found not to be statistically significant (P= 0.292). It was notable that out of the critical values studied 8.2% (74) of the males were at a possible risk of developing brain damage while 6.7% (58) of the females were at risk of developing kernicterus.

A similar study that was done in the South of Iran found that severe hyperbilirubinemia was more prevalent in males [10]. This is in agreement with the findings of ourcurrent study. A study done in Nigeria, found that more males (21%) were jaundiced in comparison to females (12%) [4]. A few studies that were done identified the male gender as a risk factor for the development of severe hyperbilirubinemia [3,10,20,21]. Another study that was carried out, determined that there is no proposed mechanism that explains the male susceptibility to increased bilirubin concentrations [22]. The disadvantage in males may be a reflection of maturational and genetically determined pathophysiological characteristics particularly in low birth weight infants [22].

Conclusion

The prevalence of critical neonatal bilirubin values at NIP was estimated to be 12.4% for the years 2013 and 2014 which is low compared to the rest of the world. The >3 to ≤6 days age group was the most affected as it was identified to have the highest prevalence of critical values (16.6%). The same age group had the highest fraction of kernicterus cases (9.6%) followed by the >6 to ≤31 days age group with a fraction of 6.8%. Male newborns were identified to have a higher prevalence of critical values 13.4% as compared to females that had a prevalence of 11.5%. Although literature shows that males are more disadvantaged, research needs to be conducted to establish if there is a relationship between the male gender and elevated bilirubin levels. Moreover, there was a 5.8% decline in the prevalence rate of critical jaundice values from 2013 to 2014. This is a good indication as it may reflect on the management of neonatal jaundice in the associated hospitals. Further comprehensive studies are needed that will focus more on establishing the causes of critical jaundice values in neonates, particularly in the 3 to 6 days age group that was mostly affected.

Refernces

1. Olusanya BO, Akande AA, Emokpae A, Olowe SA. Infants with severe neonatal jaundice in Lagos, Nigeria: incidence, correlates and hearing screening outcomes. Tropical Medicine and International Health. 2009; 14: 301-310.
2. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbeson F, et al. Neonatal hyperbilirubinemia and rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatric Research. 2013; 74: 86-100.
3. Ogunfowora OB, Adefuye PO, Fetuga MB. What do expectant mothers know about jaundice? International electronic journal of health education. 2006; 9: 134-140.
4. Chime HE, Egende JA, Arute JE. Prevalence of neonatal jaundice on central hospital, Warri, Delta State, Nigeria. International journal of health research. 2012; 4: 123-126.
5. Onyearugha CN, Onyire BN, Ugboma Haa. Neonatal jaundice: prevalence and associated factors as seen in federal medical centre Abakaliki, Southeast Nigeria. Journal of Clinical medicine and Research. 2011; 3: 40-45.
6. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. New England Journal of Medicine. 2001; 344: 581-590.
7. Burtis CA, Ashwood ER, Bruns DE. Tietz fundamentals of clinical chemistry. Philadelphia: Saunders Elsevier. 2008.
8. Tikman SS, Warraich JH, Abbasai F, Rizvi A, Darmstadt GL, Zaidi AKM. Incidence of neonatal hyperbilirubinaemia: a population based prospective study in Pakistan. Tropical Medicine and Internation Health. 2010; 15: 502-507.
9. Abosdera MM, Almasry AE. Prevalence of glucose 6 phosphate dehydrogenase among hyperbilirubinemic neonates in Sohag Governate, Egypt. Life Science Journal. 2014; 11: 227-232.
10. Najib KS, Saki F, Hemmati F, Inaloo S. Incidence, risk factors and causes of severe neonatal hyperbilirubinemia in the south of Iran (Fars Province). Iranian Red Crescent Medical Journal. 2013; 15: 260-263.
11. Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ. 2006; 175: 587-590.
12. Vandborg PK, Hansen BM, Greisen G, Jepsen M, Ebbesen F. Follow-up of neonates with total bilirubin levels≥25 mg/dl: A Danish population based study. 2012; 130: 61-66.
13. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S. Subcommittee on Hyperbilirubinemia. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics. 2004; 114: 130-153.
14. Lacob D, Boia M, Iacob R, Manea A. Neonatal jaundice-etiology and incidence. Jurnalul Pediatrului. 2011; 14: 55-56.
15. Soldi A, Tonetto P, Varalda A, Bertino E. Neonatal jaundice and human milk. The Journal of Maternal-Fetal and Neonatal Medicine. 2011; 24: 85-87.
16. Bishop ML, Fody EP, Schoeff LE. Clinical chemistry: Principals, techniques and correlations (7th ed.). Philadelphia: Wolters Kluwer. 2013.
17. Chen YJ, Chen WC, Chen CM. Risk factors for hyperbilirubinemia in breastfed term neonates. European journal of paediatrics. 2012; 171: 167-171.

18. Nahar Z, Shahidullah MD, Mannan A, Dey SK, Mitra U, Selimuzzaman SM. The value of umbilical cord blood bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy newborn. Bangladesh J Child Health. 2009; 33: 50-54.

19. Lpek IO, Bozaykut A. Clinically significant neonatal hyperbilirubinemia: an analysis of 646 cases in Istanbul. Journal of Tropical Pediatrics. 2008; 54: 211-213.

20. Porter ML, Dennis BL. Hyperbilirubinemia in the term newborn. American Family Physician. 2002; 65: 599-606.

21. American Academy of Pediatrics. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Official journal of the American Academy of Pediatrics. 2004; 144: 297-316.

22. Tioseco JA, Aly H, Milner J, Patel K, El-Mohandes AAE. Does gender affect neonatal hyperbilirubinemia in low-birth-weight infants? Pediatric Critical Care Medicine. 2005; 6: 171-174.