

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE
DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH.

**PREVALENCE OF BILIRUBIN INDUCED NEUROLOGICAL DYSFUNCTION AMONG
JAUNDICED NEONATES ADMITTED TO KENYATTA NATIONAL HOSPITAL.**

BY

DR DAHABA MAALIM ALI: MBCHB

RESIDENT: PAEDIATRICS AND CHILD HEALTH

REG NO: H58/64022/2013

**A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT
FOR THE DEGREE OF MASTERS OF MEDICINE IN PAEDIATRIC AND CHILD HEALTH
UNIVERSITY OF NAIROBI.**

2016 ACADEMIC YEAR.

DECLARATION

I declare that this dissertation is my original work and has not been presented for the award of a degree in any other university.

DR. DAHABA MAALIM ALI: MBCHB

Resident of Pediatrics and Child Health

University of Nairobi.

Reg: No: H58/64022/2013

Signed: _____ Date: _____

SUPERVISORS APPROVAL

This dissertation has been submitted for examination with our approval as the university supervisors.

PROF: DALTON WAMALWA

MBChB, MMed (paeds), MPH

Associate Professor Department of Paediatrics and Child Health.

Signed: _____ Date: _____

PROF: RUTH NDUATI

MBchB, MMed (Paeds), MPH

Professor Department of Paediatrics and Child Health.

Signed: _____ Date: _____

PROF: RACHEAL MUSOKE

MBchB, MMed (paeds), Diploma in Neonatology (UK), FABM.

Signed: _____ Date: _____

DEDICATION

I dedicate this work to my lovely husband for his enormous support and my children Jawahir, Abdulbasid, and abdulwadud.

ACKNOWLEDGEMENT

I wish to express my sincere appreciation to the University of Nairobi department of paediatrics and child health; to my supervisors for their guidance and support throughout the study period; Kenyatta National Hospital staff for their continued support and the patients and their caregivers who voluntarily participated in the study.

I also thank my colleagues' and friends who assisted me in one way or another.

CONTENTS

DECLARATION.....	ii
DEDICATION	iii
ACKNOWLEDGEMENT.....	iv
CONTENTS.....	v
LIST OF TABLES AND FIGURES	vii
ABBREVIATIONS AND ACRONYMS.....	viii
DEFINITION OF TERMS.....	ix
ABSTRACT.....	x
INTRODUCTION AND LITERATURE REVIEW	1
1.1 INTRODUCTION.....	1
1.2 LITERATURE REVIEW	2
1.2.1. PATHOPHYSIOLOGY OF BILIRUBIN INDUCED INJURY.....	2
1.2.2 BILIRUBIN INDUCED NEUROLOGICAL DYSFUNCTION.....	4
STATEMENT OF THE PROBLEM AND JUSTIFICATION.....	10
2.1. JUSTIFICATION AND UTILITY OF THE STUDY.....	10
2.2 AIMS AND OBJECTIVES OF THE STUDY	10
2.2.1 PRIMARY OBJECTIVE.....	10
2.2.2 SECONDARY OBJECTIVE	10
RESEARCH METHODOLOGY	11
3.1 STUDY AREA.....	11
3.2 STUDY DESIGN	11
3.3 SAMPLE SIZE AND PROCEDURE.....	11
3.3.1 STUDY PERIOD.....	11
3.3.2 SAMPLE SIZE DETERMINATION AND CALCULATION	11
3.3.3 INCLUSION CRITERIA.....	12
3.3.4 EXCLUSION CRITERIA.....	12
3.4 STUDY POPULATION.....	12

3.5 METHODS	13
3.5. 1 SAMPLING PROCEDURE.....	13
3.5.2 STUDY PROCEDURES	13
3.6 DATA COLLECTION, MANAGEMENT AND ANALYSIS	14
3.7 ETHICAL CONSIDERATION	14
3.7.1 CONFIDENTIALITY	14
3.7.2 ETHICAL APPROVAL.....	15
3.8 RESULTS	15
DISCUSSION	18
3.9 LIMITATIONS OF THE STUDY	20
CONCLUSSION.....	21
RECOMMENDATIONS	21
REFERENCES.....	22
APPENDICES	25
APPENDIX 1: INFORMED CONSENT.....	25
APPENDIX 11: STUDY QUESTIONNAIRE.....	29

LIST OF TABLES AND FIGURES

FIGURE 1.CELL TYPES AND METABOLIC PROCESSES AFFECTED BY BILIRUBIN IN THE CNS.....	3
FIGURE 2 SHOWS THE SAME PREVALENCE GRAPHICALLY.	18
TABLE 1: BIND SCORING CRITERIA.....	5
TABLE 2: BIND SCORE AS A PREDICTOR OF BILIRUBIN ENCEPHALOPHATHY ²⁴	8
TABLE 3: SUMMARISES BURDEN OF ABE FROM DIFFERENT SITES.....	9
STATEMENT OF THE PROBLEM AND JUSTIFICATION.....	10
TABLE 4 DEMOGRAPHIC INFORMATION OF THE NEONATES.....	15
TABLE 5 REASONS FOR SEEKING CARE.....	16
TABLE 6 Below shows levels of bilirubin for the Neonates.....	16
TABLE 7 BELOW SUMMARIZES THE PREVALENCE OF BIND AT 12HOURS, 72 HOURSAND AT SEVEN DAYS.	17

ABBREVIATIONS AND ACRONYMS.

BIND	Bilirubin Induced Neurological Dysfunction.
ABE	Acute Bilirubin Encephalopathy.
BE	Bilirubin Encephalopathy.
NNJ	Neonatal Jaundice.
KNH	Kenyatta National Hospital.
TSB	Total Serum Bilirubin.
USA	United States of America
UON	University Of Nairobi.
CSF	Cerebrospinal Fluid
UCB	Unconjugated Bilirubin
SD	Standard Deviation

DEFINITION OF TERMS.

Jaundice: Yellowish discolorations of the skin and the mucus membrane.

Acute Bilirubin Encephalopathy: ABE is a term used to describe the variable spectrum, from subtle to advanced manifestations of bilirubin toxicity that is usually reversible.

Chronic Bilirubin Encephalopathy (kernicterus): is a term used to describe persistent and permanent brain damage secondary to bilirubin toxicity.

Opisthotonos: the position of the body in which the head, neck, and spine are arched backwards.

Apgar score: A method of rapidly assessing the general state of the baby immediately after birth, usually measured at 1, 5, and 10 minutes.

Ballard score: A method of rapidly assessing gestational age of babies at birth using physical examination.

ABSTRACT

Background: Hyperbilirubinemia is a common and often benign problem in neonates. In the first week of life around 60% of term neonates and 80% of preterm neonates develop jaundice. Untreated severe unconjugated hyperbilirubinemia is potentially neurotoxic while conjugated hyperbilirubinemia signifies serious hepatic or systemic illness. Neonatal jaundice is a major cause of mortality and morbidity characterized by acute bilirubin encephalopathy, kernicterus and subsequently chorio-athetoid cerebral palsy.

Study justification:-The local prevalence of bilirubin induced neurological dysfunction is not known and the BIND criteria have not been adopted as standard for newborn assessment. This study is set to estimate the magnitude of the problem as it is easily preventable using simple measures.

Objectives: primary objective: To determine the prevalence of bilirubin induced neurological dysfunction (BIND) in jaundiced neonates admitted to Kenyatta National Hospital.

Secondary objectives: To describe the short term outcomes of neonates with BIND. The specific outcomes are mortality and the status of neurologic function within seven days of admission.

Study design: Primary objective: A cross sectional study.

Secondary objective: Short longitudinal survey.

Study period: From April to June 2016.

Settings: The general paediatric wards and newborn unit of Kenyatta National Hospital.

Subject: All newborns presenting with jaundice who met the inclusion criteria.

Methods: All term neonates aged one to fourteen days of life presenting with jaundice, whose guardian/parents gave written informed consent were assessed. A pretested questionnaire was administered to collect data on prenatal and birth history to assess gestational age and to rule out other co morbid conditions like asphyxia. This was then followed by screening for the presence of jaundice using physical examination. Thereafter neurological examination was carried out within or at 12 hours post admission to determine the initial bilirubin induced neurological dysfunction score. Repeat neurological examinations were performed at 72 hours post admission and at seven days using the clinical BIND scoring system to assess the short term outcomes. The BIND scoring system was administered to detect changes in mental states, muscle tone and cry pattern of neonates affected with

acute bilirubin encephalopathy. Each category was assigned a total score of 0 to 3, yielding a total score ranging from 0 to 9.

RESULTS

Eighty eight neonates were enrolled into the study, of these 59 were females and 29 were males. The mean birth weight was 3070 grams SD 0.41 and mean weight at admission was 3600 grams SD 0.78. The mean gestational age at birth was 39 weeks SD 1.35 and all neonates were admitted at a mean age of 5days SD 2.41. Using the BIND scoring criteria, the prevalence of bilirubin induced neurological was as follows according to the severity, fifty eight 65.9% had subtle acute bilirubin encephalopathy, twenty seven 30.7% had moderate acute bilirubin encephalopathy and two 2.3% had severe acute bilirubin encephalopathy at twelve hours post admission.

After a repeat neurological examinations within 72 hours of admission to determine the short term outcome, the prevalence of BIND was as follows twenty nine 33.3% had subtle ABE, six 6.9% had moderate ABE and one 1.1% had severe ABE. The mortality was one 1.1% and twelve 13.8% had neurological deficit at seven days post admission.

CONCLUSION

The prevalence of bilirubin induced neurological dysfunction was initially very high with almost all the neonates (except one) manifesting signs and symptoms of bilirubin toxicity. A high promotion of these neonates had subtle acute bilirubin encephalopathy 65.9% within 12 hours of admission which were reversed almost 90% at the end of the study period. Mortality was low at one 1.1% and 12 neonates 13.8% had neurological deficit at seven days post admission.

RECOMMENDATIONS

1. The incorporation of the BIND scoring criteria in the neonatal checklist at the time of admission would help in classifying the severity of BIND and early interventions for those presenting with severe manifestations of BIND.
2. Since a significant number of neonates had persistent signs and symptoms of BIND, 13.8% at seven days post admission, a follow up clinic would be helpful to monitor their progress.

INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION.

Hyperbilirubinemia is a common and often benign problem in neonates. In the first week of life, around 60% of term neonates and 80% of preterm develop neonatal jaundice. Untreated severe unconjugated hyperbilirubinemia is potentially neurotoxic while conjugated hyperbilirubinemia signifies serious hepatic or systemic illness. Bilirubin induced neurological dysfunction (BIND) refers to clinical signs and symptoms associated with bilirubin toxicity which can either be acute or chronic. Kernicterus which is the severe form of bilirubin induced neurological dysfunction continues to be reported worldwide.¹ In North America and Europe, the estimated incidence of kernicterus ranges from 0.4 to 2.7 cases per 100,000 live births among term and late preterm². In a recent review of the global burden of neonatal jaundice, Sub-Saharan Africa and South Asia were reported to be the leading contributors to an estimated 1.1 million neonates with severe hyperbilirubinemia total bilirubin level (TB) >20 mg/dL (342 μ mol/L) worldwide³. In some developing nations, the incidence of severe hyperbilirubinemia is approximately 100 times as high as it is in the developed world.⁴ In such areas, approximately 3% of neonates admitted to a hospital have signs and symptoms of acute bilirubin encephalopathy.⁵

Classic signs and symptoms of acute bilirubin encephalopathy (ABE) in the severely hyperbilirubinemic term neonates have been described by van Praagh,⁶ Jones,⁷ Volpe,⁸ and Perlstein.⁹ These include tone abnormalities such as hypotonia, hypertonia, retrocollis and opisthotonos, in association with varying degrees of drowsiness, lethargy, decreased feeding and irritability when described in terms of the infant's mental status, muscle tone and cry pattern.

Kernicterus leads to devastating disability including athetoid cerebral palsy, speech and hearing impairment. These features represent the severe manifestations of BIND. This condition not only ranks amongst the highest cost per new case (according to the Center for Disease Control's Financial Burden of Disability study in 1992), but also results in profound and uncompromising grief for the family. And for children with kernicterus, grief and frustration are enormous since they are not able to keep up with other children.

The progression of acute bilirubin encephalopathy can be documented and provides a schema for grading its severity.^{10, 11, 12, 13} A higher BIND score would be indicative of worsening signs and symptoms of acute neurotoxicity. The earliest signs and symptoms of ABE are non specific therefore

may be easily missed unless elicited by direct questioning of care givers and close clinical observation. Moderate signs of ABE have been considered as a definitive signs of kernicterus and include beginning arching of the neck and trunk on stimulation, alternating with increasing lethargy, decreased feeding, unexplained irritability and usually accompanied by a shrill cry.

During the early phases, prompt and effective treatment could prevent chronic kernicterus sequelae. Advanced signs are progressive and marked by cessation of feeding, bicycling movements, inconsolable crying, irritability, inability to feed, fever, seizures and coma. These late findings are ominous predictors of the probability of severe kernicterus complications, even with intensive treatment.

1.2 LITERATURE REVIEW

The first description of kernicterus of the brain in newborns with jaundice was provided by Hervieux in 1847.^{14,15} The relation between the clinical encephalopathy associated with elevated total serum bilirubin (TSB) concentration and the gross pathologic changes seen as yellow staining of specific areas of the central nervous system was observed and described as early as 1875¹⁶.

The terms bilirubin encephalopathy and kernicterus represent clinical and pathologic abnormalities respectively resulting from bilirubin toxicity in the central nervous system; to avoid confusion and encourage greater consistency in the literature, the American Academy of Pediatrics (APP) recommended that the term acute bilirubin encephalopathy be used to describe the acute manifestations of bilirubin toxicity seen in the first week after birth and the term kernicterus be reserved for chronic and permanent clinical sequel of bilirubin toxicity.¹⁷

1.2.1. PATHOPHYSIOLOGY OF BILIRUBIN INDUCED INJURY.

The unconjugated bilirubin anion is the cause of bilirubin neurotoxicity. The anion binds to phospholipids (gangliosides) of neuronal plasma membrane causing injury. Intracellular bilirubin anion binds to the membrane phospholipids of sub cellular organelles causing: impaired energy metabolism, altered excitatory amino acid homeostasis and excitotoxic neuronal injury and cell death.¹⁸ The blood–brain barrier has been considered to play an important role in the protection of the brain from bilirubin toxicity; however, its disruption produces diffuse yellow staining, not the specific pattern of kernicterus.¹⁹ It has been recently suggested that the blood–brain barrier, through ATP-dependent export by transporter molecules, acts as a pump to remove free bilirubin from the brain and to maintain the concentration gradient of unconjugated bilirubin from plasma to cerebro spinal fluid (CSF).⁽²⁰⁾

Bilirubin damages brain tissue cells via necrosis and apoptosis, either alone or in combination, in a neuro-anatomical distribution dependent on the amount, duration, and the developmental timing of the exposure of sensitive brain tissue to free bilirubin. Bilirubin may also kill cells by causing neuronal hyper excitability perhaps via excitatory amino-acid neurotoxicity, or it may have other membrane or neurotransmitter effects. Finally, it may act by interfering with mitochondrial respiration and energy production. Kernicterus causes selective yellow staining in the basal ganglia, especially the globus pallidus and sub thalamic nucleus. Brainstem nuclei, especially the auditory (cochlear nucleus, inferior colliculus, superior olivary complex), oculomotor and vestibular nuclei are especially vulnerable.

Other susceptible areas are the cerebellum, especially the Purkinje cells, and the hippocampus. The basal ganglia lesions are clinically correlated with the movement disorders of dystonia and athetosis. Abnormalities of the auditory brainstem nuclei are associated with deafness, hearing loss, and a recently described entity known as auditory neuropathy (AN), also known as auditory dys-synchrony (AD). Abnormalities of the brainstem oculomotor nuclei are associated with strabismus and gaze palsies, especially paresis of up gaze.²¹

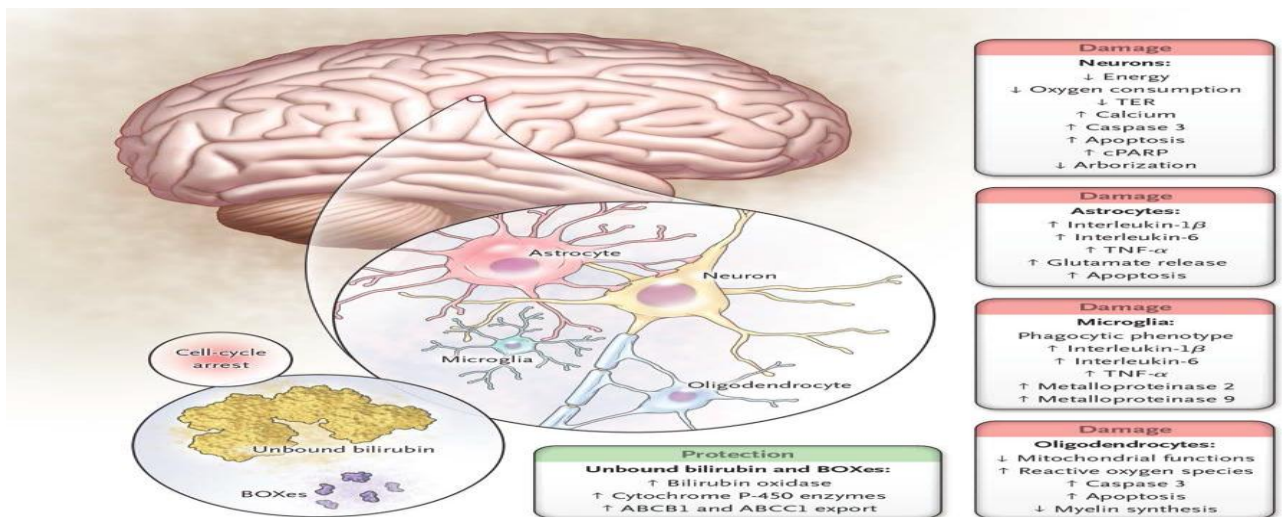


FIGURE 1.CELL TYPES AND METABOLIC PROCESSES AFFECTED BY BILIRUBIN IN THE CNS.

The main effects of bilirubin on neurons are decreased oxygen consumption and increased release of calcium and caspase 3, resulting in apoptosis. There is also decreased dendritic and axonal arborization, suggesting impairment of the intercellular exchange. A similar pattern is observed in oligodendrocytes, with increased apoptosis, impairment of the redox state (oxidative stress), and reduced synthesis of myelin. Microglia react to toxic injury associated with bilirubin by increased release of proinflammatory cytokines and metalloproteinase activity as cells manifest the phagocytic phenotype. A similar proinflammatory pattern is observed in astrocytes, with enhanced release of glutamate and resultant apoptosis. At the same time, cells may reduce the intracellular concentration of bilirubin either by extruding the pigment through the ABC transporters or by increasing the formation of the less toxic bilirubin oxidation products (BOXes) through bilirubin oxidase, cytochrome P-450 enzymes (1a1 and 1a2, in particular), or both. These responses are protective, whereas all others result in cell damage; this suggests that once the intracellular concentration of bilirubin exceeds a toxic threshold (still to be defined), the polymorphic meta-bolic cascade leading to neurotoxicity ensues. The term cPARP denotes cleaved poly (adenosine diphosphate–ribose) polymerase, TNF- α tumor necrosis factor α , and TER transcellular resistance.

Adapted from New England Journal MED NEJM 369:-21 .ORG November 21 2013.

1.2.2 BILIRUBIN INDUCED NEUROLOGICAL DYSFUNCTION.

The pilot kernicterus registry group in the U.S.A (1992-2004)²² in an effort to provide a National reporting system proposed a BIND scoring system to grade the severity and progression of bilirubin induced neurological dysfunction among term and late term neonates. (Table 1.1)

TABLE 1: BIND SCORING CRITERIA.

CLINICAL SIGNS	BIND SCORE	ACUTE BILIRUBIN ENCEPHALOPHATHY
MENTAL STATUS		
Normal.	0	None
Sleepy, could be awoken	1	Subtle ABE
Lethargy and poor suck.	2	Moderate ABE
Semicoma, apnea and seizures.	3	Severe ABE
MUSCLE TONE		
Normal	0	None
Mild to moderate hypotonic	1	Subtle ABE
Hypertonia arching of the back	2	Moderate ABE
Retrocolis,, ophisthotonus	3	Severe ABE
CRY PATTERNS		
Normal	0	None
High pitched cry	1	Subtle ABE
Shrill difficult to console	2	Moderate ABE
Weak or absent cry	3	Severe ABE

INTERPRETATIONS

A BIND score of 7-9 represent advanced signs of ABE and urgent interventions needed to avoid further damage

Score of 4-6 represent moderate signs of ABE and are easily reversible with prompt interventions.

Score of 1-3: consistent with subtle signs of ABE and are highly reversible.

The Pilot Registry group²² followed up a hundred and twenty five (125) patients with acute bilirubin encephalopathy who voluntarily reported to the registry to assess the root cause of their condition. Multiple providers at several sites managed this cohort of neonates for their newborn jaundice and progressive hyperbilirubinemia. Clinical signs and symptoms of ABE, verbalized by care givers,

were often inadequately elicited or recorded and often not recognized as an emergency. Clinical signs and symptoms of ABE were reported in 7 of 125 neonates with a subsequent diagnosis of kernicterus who were not re-evaluated or treated for hyperbilirubinemia, although jaundice was noted at outpatient visits. The remaining neonates, one hundred and eighteen had total serum bilirubin (TSB) levels >20 mg per 100 ml ($342 \mu\text{mol l}^{-1}$; range: 20.7 to 59.9 mg per 100 ml). There was no specific total serum bilirubin threshold which coincided with the onset of ABE and mortality was around 4% (5 of 125) in neonates readmitted at age less than one week. Progression of jaundice to hazardous levels and onset of neurological signs and symptoms were often not identified as neonatal care and medical supervision transitioned during the first week of life. Using the BIND scoring criteria, nine neonates with clinical signs and symptoms of ABE with a BIND scores less than four were identified. These neonates were labeled to have subtle or non-specific ABE. Severe sequelae were noted in 4 of 9 neonates. In contrast, among 91 of 116 neonates with advanced signs of ABE (BIND scores >6), nine neonates subsequently had no ($n=3$), mild ($n=1$) and moderate ($n=5$) post-icteric complications. The major underlying root cause for kernicterus was systems failure of services by multiple providers at multiple sites and inability to identify neonates who are at risk and manage severe hyperbilirubinemia in a timely manner.

In a study done in Nigeria to validate the use of modified BIND score in resource limited setting (modified meaning additional sign of paralysis of upward gaze to the above BIND scoring system) three hundred and thirty three (333) term neonates with jaundice were followed up for a period of twelve months. Both specialist pediatricians and junior residents were trained in the use of modified BIND scoring system and their results compared at the end of the study.

Specialist paediatricians deemed fifty three patients (15.9%) of the three hundred and thirty three neonates to have Acute Bilirubin Encephalopathy. Total BIND - M scores were evaluated for clinical utility in diagnosing ABE. A total score greater than or equal to three was highly predictive of a clinical diagnosis of Acute Bilirubin Encephalopathy, with sensitivity of 90.7%, specificity of 97.7%, positive predictive value of 88.9%, and negative predictive value of 98.2%. Fifty (94.3%) of the fifty three neonates with ABE had scores of “2” (“moderate”) or “3” (“severe”) on at least one subscale (mental status, muscle tone, cry or eye findings). The most consistently detected sign was change in muscle tone where residents scored forty eight of the fifty three (90.6%) neonates with Acute Bilirubin Encephalopathy in the “moderate-to-severe” range; and the specialist paediatricians similarly scored 84.9% of these neonates. The less consistent finding for ABE was alteration in mental status ; residents

found that “moderate-to-severe” change in mental status for forty two out of the fifty three (79.2%) neonates with ABE versus forty four (83%) noted by the specialist paediatricians. Change in cry pattern was similarly found by residents and specialist paediatricians (44 and 43 of 53, respectively).

Specialist paediatricians recognized paralysis of upward gaze in twenty six (49%) of the fifty three neonates with encephalopathy, versus only nineteen (35.8%) that were detected by residents. Almost all neonates with eye findings had a diagnosis of Acute Bilirubin Encephalopathy, however when eye finding points were removed from the modified BIND score, all neonates with ABE still had a score of three and above. The final results have shown that the physical diagnosis of ABE can be facilitated by a modified BIND-M score. The BIND M score showed excellent agreement between residents and specialist paediatricians, and appeared to be accurate in predicting neonates with ABE. Thus, BIND-M may be an important and yet simple tool to provide a uniform measure of the degree of ABE in clinically jaundiced neonates in resource limited areas.²³

Gamaleldin et al described the importance of TSB level and other risk factors for neurotoxicity in predicting ABE in two hundred and forty nine (249) infants with total bilirubin levels of 25mg/dl (427umol/l) seen in Cairo university hospital over a period of twelve months. TSB values at admission ranged from 25mg (42 umol/l) to 76.4 mg/dl (1306.4 umol/l) and the threshold TSB level that identified ninety percent 90% of infants with bilirubin encephalopathy was 25mg/dl (434.3umol/l) when neurotoxicity risk factors were present. In contrast neurotoxicity was first seen at a total serum bilirubin level of 35.5mg/d l(607 umol/l) in one hundred and eleven infants without risk factors. Although the correlation between total serum bilirubin level and encephalopathy was poor, patients with hyperbilirubinemia resulting from Rhesus incompatibility developed BIND at an odds ratio of 48.6 and those with sepsis at an odds ratio of 20.6 as compared to other etiologies. At admission, forty four neonates (18%) had moderate to severe signs of ABE (score 4 –9), 55 neonates had subtle signs of neurotoxicity (score 1–3), and 150 neonates (60%) had no signs of ABE. Thirty-five neonates (14%) had signs of BE at discharge (9 [3.6%]) or at the time of death 26 [10.4%]) and all deaths were associated with signs of kernicterus²⁴.

TABLE 2: BIND SCORE AS A PREDICTOR OF BILIRUBIN ENCEPHALOPHATHY²⁴

BIND score at admission	Number	Resolved cases	Survived with BE	Death with BE	Total bilirubin, Median(range)
Zero (normal)	150	NA	0	0	28.3(25.0-59.0)
1-3 (subtle ABE))	55	36 (65%)	2 (4%)	1(2%)	33.0(25.1-57.0)
4-6(Moderate ABE)	25	11 (44%)	5 (20%)	9 (36%)	32.0(25.0-76.4)
7-9(Severe ABE)	19	1 (5%)	2 (11%)	16 (84%)	36.5(25.0-51.0)
Total	249	49 (20%)	9 (4%)	26 (10%)	30.0(25.0-76.4)

Bao et al conducted a retrospective study over a seven year period in Eastern China where they followed up one hundred and sixteen (116) term and near term infants with ABE. Among the one hundred and sixteen patients enrolled in this study, fourteen (12.1%), eighty three (71.6%) and nineteen (16.4%) neonates were classified as having subtle signs, moderate signs and severe signs of ABE respectively at admission according to the BIND scoring criteria. The group with moderate signs of ABE had a higher peak bilirubin level than the group with subtle signs of ABE while the group with severe signs of ABE had a higher peak bilirubin level than the group with moderate signs of ABE ($p<0.05$). In the subtle ABE group, no neonate died, only one (7.1%) neonate was discharged with hypertonia; the remaining (92.9%) were discharged without any signs of bilirubin encephalopathy. The group with moderate acute bilirubin encephalopathy, seven (8.4%) neonates died including four neonates directly related to acute bilirubin encephalopathy and three to other complications. Thirty one (37.3%) neonates had persistent signs of acute bilirubin encephalopathy such as hypertonia and hypotonia on discharge; the remaining neonates (49.4%) were discharged without any evidence of bilirubin encephalopathy.

The brain damage incurred by the toxicity of bilirubin is not always reversible. Nearly half of the neonates with moderate signs of ABE and almost all those with severe signs of ABE had persistent signs of bilirubin encephalopathy at the time of discharge or death. Eighty two percent of the group with moderate signs of ABE followed up had abnormal neuro-developmental outcomes at three months of age and some might maintain the state for their whole life²⁵. It is too late for intervention in infant presenting with intermediate or advanced signs of ABE. Effective and prompt intervention during the

early phase can prevent chronic kernicterus sequelae²⁶, thus pediatricians should be familiar with the warning signs of ABE and ensure to intervene timely and effectively.

In another study done in Iran to evaluate the prevalence of Bilirubin induced neurological dysfunction in term neonates with jaundice requiring exchange transfusion, one hundred and thirty three newborn were followed up over two years. The prevalence of BIND from this study was 48%, sixty four patients demonstrated signs and symptoms of acute bilirubin encephalopathy at the time of admission. Unsuccessful breast feeding was found to be a statistically significant risk factor for Bilirubin induced neurological dysfunction (p= 0.001)²⁷.

TABLE 3: SUMMARISES BURDEN OF ABE FROM DIFFERENT SITES.

TITLE&AUTHORS	DESIGN	SAMPLE SIZE	BURDEN OF ABE
Modified BIND is useful in evaluating the severity of jaundice in resource poor settings: Paula G, Joshua A, Bolajoko O, and Frank D. Nigeria 2015.	Cross sectional study	N=133	16%.
Risk factors for neurotoxicity in newborn with severe hyperbilirubinemia. Iskandar I, Aborraya Sampson PD and Gamaleldin R et al .Cairo 2011.	Cross sectional study	N=249	40%.
ABE in term neonates requiring exchange transfusion. Seyedeh Khatami, P Ouya.Iran,2012	Cross sectional study	N=133	48%.

STATEMENT OF THE PROBLEM AND JUSTIFICATION.

2.1. JUSTIFICATION AND UTILITY OF THE STUDY.

Neonatal jaundice is a major cause of neonatal mortality and morbidity characterized by ABE, kernicterus and subsequently chorio-athetoid cerebral palsy.²⁸In a study done in Kenya (Kilifi), severe neonatal jaundice accounts for 22% of admissions to hospital with an in-patient case fatality rate of 26%.²⁹ Neonatal jaundice is not easily appreciated by care providers at home until it's too late for appropriate interventions resulting in brain injury. Signs and features of ABE especially in the early stages may be missed even by trained medical professionals thus delaying interventions for neonates with reversible brain injury. The local prevalence of BIND is not known. This study sought to estimate the magnitude of the problem as it is easily preventable using simple measures. Such information would support the work of child health advocates to make solutions to reduce or eliminate this preventable morbidity which has long-term tragic consequences for the neonates, their families and their communities. The study provides an opportunity for introducing the BIND scoring criteria which has been shown in other set ups to be a sensitive and reference level for the diagnosis of ABE in jaundiced infants.

2.2 AIMS AND OBJECTIVES OF THE STUDY

2.2.1 PRIMARY OBJECTIVE

To determine the prevalence of bilirubin induced neurological dysfunction (BIND) among jaundiced neonates admitted to Kenyatta National Hospital using the BIND scoring criteria.

2.2.2 SECONDARY OBJECTIVE

To describe the short term outcomes of neonates with BIND. The specific outcomes are mortality and status of neurological function within seven days of admission.

RESEARCH METHODOLOGY

3.1 STUDY AREA.

This study was carried out at a paediatrics general wards and the Newborn unit of the Kenyatta National Hospital. KNH is Kenya's National referral hospital and is located in the Upper Hill area of Nairobi, the country's capital city. It serves referrals from all over the country mainly those of low socio economic status of approximately around one thousand patients per month. The hospital is staffed by specialist pediatricians, resident doctors, medical and clinical officers and well trained nurses among others. Monthly around fifty patients with jaundice are admitted to the general pediatric wards and the newborn unit, but the prevalence of bilirubin induced brain injury is not known yet.

3.2 STUDY DESIGN

The study design for the primary objective was a cross sectional study.

And for the Secondary objective was a short longitudinal survey.

3.3 SAMPLE SIZE AND PROCEDURE.

3.3.1 STUDY PERIOD

The study period was between April and June 2016.

3.3.2 SAMPLE SIZE DETERMINATION AND CALCULATION

The sample size was calculated using Fishers formula (Wanga and Lameshow, 1991)³⁰ given below.

$$n_1 = \frac{Z^2 \times p \times q}{d^2}$$

$$n_1 = \frac{1.96^2 \times 0.16 \times 0.84}{0.05^2} = 205$$

$$n = \frac{n_1}{1 + \frac{n_1 - 1}{N}} \quad \text{Adjusting for finite population}$$

Where, n_1 =sample size

p=estimated prevalence of bilirubin induced neurological dysfunction ((BIND).Estimated to be 16 %¹⁹

z=confidence level at 95 %(corresponding to a standard Z value of 1.96)

q=1-p.

d= margin of error (0.05)

N=is estimated population size around 150

n= sample size.

So the actual sample size after adjusting is **87**.

3.3.3 INCLUSION CRITERIA

All term newborns aged one to fourteen days of life with jaundice admitted to the general paediatric wards and the Newborn unit of Kenyatta National Hospital and whose parents gave written informed consent. One day old neonates were selected because severe neonatal jaundice do occur in utero necessitating treatment at delivery. Neonates with prolonged neonatal jaundice past 14 days of life mainly present with direct reacting hyperbilirubinemia which in this study were excluded because it does not lead to central nervous system toxicity.

3.3.4 EXCLUSION CRITERIA

1. Newborns with birth asphyxia defined as Apgar score of less than eight at five minutes.
2. Newborns with obvious central nervous system malformation like hydrocephalous.
3. Those with predominantly direct reacting bilirubin defined as twenty percent of the total bilirubin level as it does not lead to central nervous system toxicity.
4. Neonates with clinical features of meningitis persistent convulsions, bulging fontanel and neck retraction.

3.4 STUDY POPULATION.

The study populations were term babies aged one to fourteen days of life with jaundice who presented to the general paediatric wards and the Newborn unit of Kenyatta National Hospital during the study period.

3.5 METHODS

The Principal investigator with the help of a research assistant explained to the caregiver the study objectives, procedures, risks and benefit so as to obtain a written informed consent. Prenatal and birth history was then taken from the caregiver to identify gestation and to rule out any co-morbid conditions like birth asphyxia. The gestation was determined by dates from the last menstrual period or obstetric scan if available for the newborns who were two days and older while the Ballard scoring system was administered for those less than two days old. The mother and the child booklet was also reviewed to assess for any complications during pregnancy such as bleeding, hypertension and decreased fetal movements that can affect central nervous system development in utero. The Apgar score at birth was also extracted from the mother and the child booklet. In case the booklet was not available, the study depended on the prenatal and birth history taken from the mother.

Once the history was obtained, the Principal investigator and the research assistant performed physical examination to screen for the presence of jaundice and to rule out any obvious central nervous system malformations like neural tube defects. Thereafter laboratory results for the patients were reviewed twelve hours post admission to assess the level and type of hyperbilirubinemia. Those with predominantly direct reacting hyperbilirubinemia (defined as twenty percent of total serum bilirubin level) were excluded from the study. Neurological examination was performed at 12 hours post admission to determine the prevalence of bilirubin induced neurological dysfunction a few hours after initiating treatment as the signs and symptoms of bilirubin toxicity were easily identified. A repeat neurological examination was performed at 72 hours and at seven days post admission to assess the short term outcomes. The bilirubin levels were done in Kenyatta National Hospital biochemistry laboratory with Biolis 501 superior machine that was standardized.

3.5.1 SAMPLING PROCEDURE

Consecutive sampling was performed from eight am to eight am using a pretested questionnaire for all patients who met the inclusion criteria.

3.5.2 STUDY PROCEDURES

1. Babies who met the inclusion criteria and whose parents gave a written informed consent were recruited into the study and a questionnaire filled for each patient.

2. Neurological examination was done within twelve hours of admission by the Principal investigator to determine the prevalence of bilirubin induced neurological dysfunction.
3. A repeat neurological examination was again performed seventy two hours post admission to detect any change in the BIND score.
4. The patients were then followed up to the seventh post admission day and/or at discharge to assess the short term outcomes whether clinical improvement, death or deteriorations based on the initial assessment at admission

3.6 DATA COLLECTION, MANAGEMENT AND ANALYSIS

The research assistant, a qualified clinical officer was trained for five days on the study objectives, procedures and how to perform physical examination prior to the data collection. Data was collected using a pretested questionnaire, confirmed for completeness, coded and then entered into the computer using MS Access. The entered data was compared with the hardcopy forms to ensure accuracy and completeness. Exploratory data analysis was then performed to identify any inconsistencies and make appropriate corrections. All discrete variables were summarized using counts and percentages while continuous variables were summarized using measures of central tendency and dispersion (mean median and quantities).

The prevalence of BIND was estimated by calculating the proportion of neonates with neurological dysfunction secondary to hyperbilirubinemia among neonates identified to have jaundice within twelve hours of admission using the BIND scoring criteria. A similar approach was used to summarize the short term outcomes among neonates identified to have BIND at seventy two hours and at seven days post admission. Results were presented using tables, charts and narratives.

3.7 ETHICAL CONSIDERATION

3.7.1 CONFIDENTIALITY

The researcher maintained maximum confidentiality for all information and data presented by the respondents. All information obtained from the patients were considered confidential and treated as such. The instruments used for the research were void of the patient's names to ensure confidentiality. Documents containing patients' confidential information were neither photocopied nor were names of

the patients recorded. The information on the questionnaire was accessible only to the investigators and the statistician. The consent form was translated into Swahili for ease of understanding.

3.7.2 ETHICAL APPROVAL.

The dissertation was submitted to the University of Nairobi (UON), KNH ethics and research committee for approval. Informed written consent from the primary care giver/guardian was provided for enrolment into the study. The purpose of the study was well explained to the parents and made clear to them that there were no potential risks involved in participation. All neonates with jaundice were managed under direction of the unit protocol for the management of jaundice.

3.8 RESULTS

During the three months study period, a total of 88 neonates who met the inclusion criteria were enrolled into the study. The demographic characteristics of the neonates are shown in table 4 below. Fifty nine infants (67%) were females and twenty nine (33%) were males. The mean birth weight was 3070 grams SD 0.41 and the mean weight at admission was 3600 grams SD 0.78. The mean gestational age at birth was 39 weeks (SD1.35) and all babies were admitted at a mean age of 5days (SD 2.41).

TABLE 4 DEMOGRAPHIC INFORMATION OF THE NEONATES.

	N	Mean	Std. Deviation	95% CI for mean
Age in days	85	5.51	2.41	4.99 - 6.03
Birth weight	52	3.07	0.41	2.95 - 3.18
Current weight	85	3.60	0.78	3.43 - 3.77
Gestation at birth	87	39.79	1.35	39.51 - 40.08
APGAR at 1 min	88	8.69	0.46	8.59 - 8.79
APGAR at 5 min	88	9.56	0.64	9.42 - 9.69
APGAR at 10 min	88	9.66	0.54	9.54 - 9.77
Duration of yellowing	84	3.12	1.38	2.82 – 3.42

These infants mainly presented to the facility with complaints of jaundice and a large percentage had associated symptoms like fever, poor feeding, diarrhea and vomiting as shown in the table 5 below. Although 93% of the babies presented with jaundice, most of the other signs and symptoms were overlapping. There are others whose main complaints were fever but on examination were found to be jaundiced and they were recruited into the study.

TABLE 5 REASONS FOR SEEKING CARE

	n	%
Fever	69	78.4
Poor feeding	63	71.6
Yellow eyes	82	93.2
Diarrhea and vomiting	2	2.3

TABLE 6 BELOW SHOWS LEVELS OF BILIRUBIN FOR THE NEONATES.

	N	Mean	Median	Minimum	Maximum	Standard Deviation
Total bilirubin	88	317	285	38	715	133
Direct bilirubin	88	26	17	2	230	32

The mean total bilirubin level was 317umol/l with a maximum bilirubin level of 715umol/l. Most neonates with bilirubin above 500 umol/l were managed with exchange transfusions.

PREVALENCE OF BILIRUBIN INDUCED NEUROLOGICAL DYSFUNCTION.

Using the BIND scoring criteria the overall prevalence of BIND was high within 12 hours of admission. The break down was as follows:-

- Fifty eight (65.9%) had subtle acute bilirubin encephalopathy.
- Twenty seven (30.7%) had moderate acute bilirubin encephalopathy.
- Two (2.3%) had severe acute bilirubin encephalopathy.

- One baby was found to be normal with score of zero at the time of admission.

OUTCOME

Within seventy two hours of admission a repeat neurological examination was performed to assess the short term outcomes: -

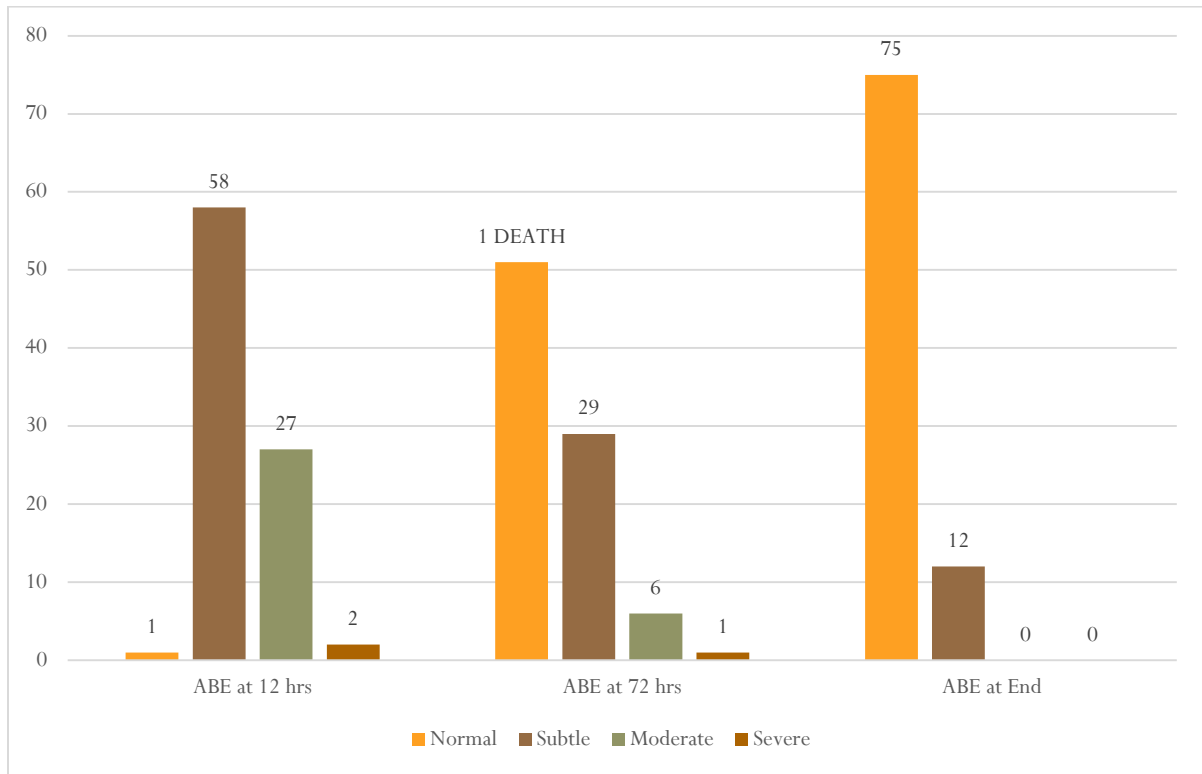
- Twenty nine (33.3%) had subtle acute bilirubin encephalopathy.
- Six (6.9%) had moderate acute bilirubin encephalopathy.
- One (1.1%) had severe acute bilirubin encephalopathy.
- Mortality was (1.1 %.)
- Normal was fifty one (58.6 %.)

At seven days post admission 13.8% of neonates had subtle acute bilirubin encephalopathy while 75(86.2%) of the children had no evidence of bilirubin toxicity.

TABLE 7 BELOW SUMMARIZES THE PREVALENCE OF BIND AT 12HOURS, 72 HOURS AND AT SEVEN DAYS.

TIME		Normal Score=0	Subtle Score=1-3	Moderate Score=4-6	Severe Score=7-9
ABE at 12 hrs	N	1	58	27	2
	%	1.1%	65.9%	30.7%	2.3%
ABE at 72 hrs	N	51	29	6	1
	%	58.6%	33.3%	6.9%	1.1%
ABE at 7 days	N	75	12	0	0
	%	86.2%	13.8%	0.0%	0.0%

FIGURE 2 SHOWS THE SAME PREVALENCE GRAPHICALLY.



DISCUSSION

Acute bilirubin encephalopathy (ABE) is rarely found in the developed world due to the effective preventive measures that are in place including pre –discharge risk assessment, strict observance of treatment guidelines and effective treatment modalities like intensive phototherapy. In developing countries like Kenya it is still not an uncommon occurrence.

Bilirubin induced neurological dysfunction is a spectrum of diseases characterized by acute bilirubin encephalopathy and chronic bilirubin encephalopathy with permanent neurological sequelae. This study mainly investigated the acute manifestations of bilirubin toxicity (ABE) among children admitted with neonatal jaundice and their short term outcomes. It depended on the clinical BIND scoring criteria that was developed in the USA and validated.

The main key findings were: 58(65.9%) had subtle ABE, 27 (30.7%) had moderate ABE, 2(2.3%) had severe ABE and 1(1.1%) were normal at the time of the initial contact. These figures were high when compared to the study done in Egypt Cairo University Hospital where they found subtle ABE 55(22%), moderate ABE 25 (10%), severe ABE 19 (7.6%) and 150 (62%) normal among 249 children

admitted with jaundice over a twelve month study period. The overall prevalence of BIND in the Egyptian study was 40%.

This difference may be attributed to study methodology as well as geographical differences. The Egyptian study was a cross sectional study over a 12 month period and included both term and preterm infants over 34 weeks gestation with a cut off bilirubin level of 25mg/dl(427umol/l) while our study included only term babies irrespective of bilirubin levels. Also 65.9% of children had subtle signs at admission which could be caused by other diseases like neonatal sepsis or meningitis. Neonatal sepsis and rhesus incompatibility were shown in several studies to increase the risk of acute bilirubin encephalopathy OR 20.6 and 48.6 respectively. This study also found similar results as a large percentage 71% of neonates presented with fever.

The other important factor for the high prevalence of BIND is the fact that Kenyatta National Hospital is a referral hospital and most of these neonates were referred from peripheral facilities for exchange transfusions due to high bilirubin levels mean of 318umol/l at admission and features of bilirubin induced neurological dysfunction. It actually shows pool from all over the county and not only neonates born in Kenyatta National Hospital.

Within 72 hours of admission most signs and symptoms of ABE had reversed where 29 neonates had (33.3 %) had subtle signs of ABE, 6 (6.9%) had moderate signs of ABE, 1(1.1 %) had severe signs of ABE and 51 (58.6 %) were found to be normal. Mortality was 1 (1.1 %) among those with severe ABE as compared with the Egyptian study where mortality was 10%. These patients were followed up to seven days post admission to assess for any neurological deficit, 12 (13.8%) of them had persistent neurological signs mainly hypertonia and hypotonia at the time of assessment which was fairly the same with the Egyptian study 35(14%) patient.

Also it was observed that there was a slight increase in female to male ratio of 2:1 in this study as compared to the Egyptian study where they found female to male ratio to be equal. Johnson et al found that sixty seven percent of cases of acute ABE were males with a mean birth weight of 3281 grams and mean gestational age of 38 weeks. This differs with our study where the majority of neonates were female (67%) with a mean birth weight of 3070 gram. In a retrospective study done in China over a seven year period, majority of patients demonstrated features of moderate acute bilirubin encephalopathy (71.6%) with only 12% of the neonates demonstrating subtle acute bilirubin encephalopathy in contrast to our study where majority had subtle signs of acute bilirubin encephalopathy (65.9%).

In a study done in Nigeria to validate the modified BIND score, the overall prevalence of acute bilirubin encephalopathy was found to be 16% as compared to our study where each category was found to be very high. This was mainly due to difference in methodology. In Nigerian study no time limit was reported for the neurological examination using the BIND score as compared to our study where the neurological examination was performed 12 hours post admission. This probably had contributed to the big difference because as was shown in our study an early intervention really helps in the reversal of signs and symptoms of ABE.

3.9 LIMITATIONS OF THE STUDY

- Most signs and symptoms of acute bilirubin encephalopathy could also be caused by many conditions like neonatal sepsis or neonatal meningitis thus difficult to differentiate if the patient is suffering from both.

CONCLUSION

The prevalence of bilirubin induced neurological dysfunction was initially very high with almost all the neonates (except one) manifesting signs and symptoms of bilirubin toxicity. A high proportion of these neonates had subtle acute bilirubin encephalopathy 65.9% within 12 hours of admission which were reversed almost 90% at the end of the study period. Mortality was low at one 1.1% and 12 neonates 13.8% had neurological deficit at seven days post admission.

RECOMMENDATIONS

1. The incorporation of the BIND scoring criteria in the neonatal checklist at the time of admission would help in classifying the severity of BIND and early interventions for those presenting with severe manifestations of BIND.
2. Since a significant number of neonates had persistent signs and symptoms of BIND, 13.8% at seven days post admission, a follow up clinic would be helpful to monitor their progress.

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APPENDICES

APPENDIX 1: INFORMED CONSENT.

Patient study identification number-----Date-----

Prevalence of Bilirubin Induced Neurological Dysfunction among jaundiced neonates admitted to KNH.

I am Dr. DAHABA MAALIM ALI, a postgraduate student at the University of Nairobi, department of paediatric and child health, would like to conduct the above study as part of the requirement for the degree of master of medicine in pediatric and child health.

The study aims to evaluate the prevalence of bilirubin induced neurological dysfunction (BIND) among neonates admitted to the general paediatric wards and the Newborn unit with jaundice at the Kenyatta National Hospital. Jaundice is a common condition in neonates but in most cases it is a benign problem. Untreated severe jaundice is potentially neurotoxic. I would like to invite you to participate in this study by providing me with some information regarding your child's illness.

Approval for this Study has been given by the Kenyatta National Hospital/University of Nairobi Ethics Committee {KNH/UON-ERC}.

I will be available to answer any questions that will help you understand the nature of the study. If you wish to seek any clarification, kindly contact me on **0721229847** or **email address dahabac@hotmail.com**.

PROCEDURE.

A questionnaire will be provided to you and it should take approximately 10-15 minutes to complete. The research assistant and I will be available to guide you through the questionnaire and to answer any questions, if you agree to participate in the study; you will be requested to fill in a questionnaire with the assistance of the researcher or the research assistant. The nature of the questions that will be asked is in regard to jaundice and prenatal history. Physical and neurological examination will be performed on your child to assess for the presence of jaundice and central nervous system involvement. Laboratory results (bilirubin level) and the mother and the child booklet will be reviewed to assess for eligibility. Questionnaires in which this information will be filled will have no personal identifiers to protect your confidentiality.

RISKS/ DISCOMFORT.

There is no risk associated in participating in this study and no invasive procedures that will be carried out in this study that may cause harm to your child. Refusal to participate will not change any treatment that your child will receive while at the facility.

BENEFITS.

There will be no direct benefit in participating in the study, Participation in the study is voluntary, but in case you have any questions the interviewer will readily assist you. If you choose not to participate, you will not be denied any service. You will be free to withdraw from the study at any time and at the same time you will get your health services provided completely.

CONFIDENTIALITY.

Strict confidentiality will be maintained at all times. There shall be no mention of names or identifiers in the report or publications which may arise from the study. Each participant in the study will be identified by use of codes in order to link them with their results and the data collected will only be accessible to the investigators.

PERSONS TO CONTACT.

If you have any questions regarding the study, you may contact Dr.DAHABA MAALIM ALI on mobile number 0721229847 email address dahabac@hotmail.com or Prof. Ruth Nduati at telephone number 0722235323.

If you have any question on your rights as a research participant you can contact the Kenyatta National Hospital Ethics & Research Committee by calling 2726300 Ext 44355.

Your participation in the study will be highly appreciated.

CONSENT FORM

I -----having received information on the study, benefits, risks hereby AGREE/DISAGREE (cross out as appropriate) to participate in the study with my child. I understand that participation is voluntary and i am free to withdraw at any time.

Parent/ guardian's signature-----date-----.

I -----declare that i have adequately explained to the parent/guardian the study procedure, risks, benefits, and given the mother time to ask questions and seek clarification regarding the study. I have answered all the questions to the best of my ability.

Investigator's signature-----date-----.

FOMU YA IDHINI

NAMBARI YA MGONJWA-----TAREHE-----.

Mimi ni Daktari DAHABA MAALIM ALI, mwanafunzi wa chuo kikuu cha Nairobi, Department of paediatric and Child Health na ninafanya utafiti kama mahitaji ya shahada ya Master of Medicine in Paediatrics. Utafiti huu inachunguza matokeo ya madhara inayotokea na kubadilika rangi ya macho na ya mwili kwa watoto wadogo na jinsi itakavyo weza kurekebishwa. Utafiti huu utafanywa katika hospitali kuu ya Kenyatta katika ward ya watotona newborn unit. Nakukaribisha uweze kushiriki katika utafitii huu Kwa kutupatia ujumbe kuhusu wewe na motto wako kulinganana vile alivyokuwa na ugonjwa huu.Ugonjwa huu ni hatari ikiwa haijatiwiwa kwa sababu itaenea kwa ubongo na kuleta matatizo.

Idhini ya kufanya utafiti umepewa Na Kenyatta National Hospital/University of Nairobi Ethics Committee {KNH/UON-ERC}. Nitakuwa wakati wowote ili niweze kujibu maswali yote amabyo itakuwezesha kufahamu utafiti huu.Ukiwa na swali lolote wasiliana na mimi kwa nambari ya simu0721229847 **email address dahabac@hotmail.com.**

Procedure

Tutapeana karatasi ya kujibu maswali. Itachukuwa Kama dakika 10-15 kujaza maswali. Wanaofanya utafiti watakuwa ili wakusaidie kujaza karatasi ya kujibu maswali. Ukikubali

kujumuishwa katika utafitihuu, utahitajika kujaza karatasi na utasaidiwa na wanaofanya utafiti. Tutaangalia kitabu cha mama na watoto na majibu ya damu ilituweze kujua kama utashiriki kwa utafitihuu.

1. Madhara.

Utafiti huu hauna madhara yeyote kwa mtoto. Hatadungwa dawa yeyote au kutolewa kitu chochote kwa mwili kwa sababu ya utafiti. Iwapo utakataa kushiriki, hili halitabadilisha matibabu ya mtoto wakati anapokaa kwa hospitali.

2 Manufaa.

Utapokea mawaida kuhusu uchungaji wa mtoto na jinsi ya kutambua ugonjwa huu kwa mtoto. Matokea ya utafiti yatakuwa ya manufaa kwa washikadau na wafanyikazi katika Kitengo cha afya haswa kwa kuimarisha matibabu ya watoto wengine.

3 Ya siri.

Wewe kama mhusika, utajulikana kwa nambari tu na sio kwa jina lako au lile la mtoto. Majibu ya utafiti yatabaki kuwa siri na hayataruhusiwa kuonekana na mtu mwingine bila ruhusa yako. Matokeo ya utafiti kwa jumla yatapewa washikadau ambao wanahusika na mipango na matibabu ya watoto wachanga lakini hayatuzungumzia mtoto wako kibinafsi. Kama uko na swali lolote, wasiliana na mtafiti mkuu; Daktari DAHABA MAALIM ALI, nambari ya simu 0721229847.

Kama uko na swali kuhusu haki yako kama mshiriki, unaweza kuwasiliana na Kamiti ya haki na utafiti katika hospitali kuu ya Kenyatta nambari ya simu 2726300 Ugani 44355.

Mimi -----nimeelewa maana na jinsi utafiti huu, na nimepeana idhini baada ya kuelezwa kuhusu madhara na manufaa yake. NIMEKUBALI/NIMEKATAA (futa moja ya haya mawili)kushiriki katika utafiti huu na ninafahamu kuwa ni wa kujitolea na nina uhuru wa kujiondoa.

Sahihi -----Tarehe -----

Mimi -----natangaza kuwa nimepeana habari ya utafiti huu kwa mzazi wa mtoto haswa kuhusu madhara na manufaa na nimekubali kuulizwa maswali na nimeyajibu kwa uwezo wangu wote.

Sahihi ya mtafiti-----Tarehe-----.

APPENDIX 11: STUDY QUESTIONNAIRE

QUESTIONNAIRE.

Prevalence of Bilirubin Induced Neurological Dysfunction among jaundiced neonates admitted to KNH.

Patient study identification number-----Date -----.

Section A: Demographic Information of the Child

1. Date of birthAge in days-----.
2. What is the birth weight?-----and current weight?-----head circumference-----
3. Sex of Child.
a) Male b) Female
4. What is your area of residence? -----.
5. Was the child born term? Yes/No.(tick as appropriate)
6. If yes, at what gestational age? -----in weeks.
7. When is your last menstrual period? -----.
8. Pregnancy: primigravida Yes/No. Rhesus factor 1=positive 2=negative (tick as appropriate)
9. Maternal blood group:- A Yes/No (tick as appropriate)
-B Yes/No (tick as appropriate)
-AB Yes/No (tick as appropriate)
-O Yes/No (tick as appropriate)
10. Complications during pregnancy:- Hypertension Yes/No (tick as appropriate)
-Gestational diabetes Yes/No.
-Bleeding Yes/No
-Decreased fetal movements Yes/No
11. Did the child cry immediately after birth? Yes/No.
12. What is the duration of labour pains-----in hours?
13. Any congenital abnormalities noticed after delivery? -----.
14. What is the Apgar score at birth? At 1 minutes-----at 5 minutes-----at 10 minutes-----.

SECTION B: ASSESMENT OF JAUNDICE.

15. What is the problem that made you bring your child to the hospital?
-fever Yes/No

- Poor feeding Yes/No
- Yellowness of the eyes Yes/No
- Diarrhea and vomiting Yes/No
- Any other specify-----.

16. If yellowness of the eyes, for how long? -----in days.

SECTION C: GENERAL EXAMINATION.

17. Any presence of jaundice? Yes/no.

18. If yes, at what level?-just on the sclera-----at the abdomen-----at the feet-----.

19. Any congenital abnormality noted during physical examination yes/no.

20. Any neurological deficit at discharge-----

21. Date of discharge or death-----.

22. Duration of hospital stay-----.

23. Level of hyperbilirubinemia? Total bilirubin level-----.direct bilirubin-----;

SECTION D: NEUROLOGICAL EXAMINATION USING CLINICAL BIND SCORING CRITERIA

Clinical signs	BIND score within 12 hours of admission,	BIND score after 72 hours of admission	BIND score at discharge or death.
Mental status			
Normal			
Sleepy but easily aroused.			
Lethargy, poor suck.			
Semi coma, apnea Seizure.			
Muscle tone			
Normal			
Hypotonia			
Hypertonia arching of the back.			
Retrocolis, ophisthotonus			
Cry patterns			
Normal			
High pitched			
Shrill difficult to console.			
Absent or weak cry.			

TOTAL SCORE: -----.