EVALUATING THE INGRAM ICTEROMETER AS A SCREENING TOOL FOR SIGNIFICANT NEONATAL HYPERBILIRUBINEMIA AT THE KENYATTA NATIONAL HOSPITAL.

BY

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DECLARATION

I declare that this dissertation in part fulfillment of MMed (Paediatrics and Child Health) is my original work and has not been presented to any other university or forum.

Signed---------- Date 25th November 2009

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DEDICATION

This dissertation is dedicated to all the neonates whose precious lives we seek to improve.

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First and foremost, I wish to thank my three supervisors for their patience, commitment and valuable criticism which made it possible for this dissertation to be completed. I really appreciate their time and availability when I needed them.

I wish to acknowledge all the staff in the Paediatric Emergency Unit, the Newborn unit and the Paediatric wards for their patience and cooperation during the study period.

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LIST OF ABBREVIATIONS

BIND: Bilirubin -induced neurologic dysfunction

CI : Confidence interval

GA: Gestational Age

HPLC: High pressure liquid chromatography

ICC: Intraclass correlation coefficient

KNH : Kenyatta National Hospital

Lab : Laboratory

-LR : Negative likelihood ratio

+LR : Positive likelihood ratio

NPV : Negative Predictive value

NNJ : Neonatal Jaundice

NBU: Newborn Unit

PFC : Paediatric Filter clinic

PPV: Positive Predictive Value

ROC : Receiver operator characteristic curve

r : Regression coefficient

Sen: Sensitivity

Spec : Specificity

SD: Standard deviation

TSB : Total Serum Bilirubin

TcB : Transcutaneous Bilirubin

vs: versus

g: grams

≥: More than or equal to

>: More than

<: Less than

≤ : Less than or equal to

ABSTRACT

Background: Neonatal Jaundice (NNJ) occurs in 30-60% term newborns and is significant (>221 μmol/l) in 3.5-12% of these neonates. Kernicterus is the worst complication of NNJ and is associated with at least 70% morbidity and 10% mortality. In Kenya (Kilifi), severe NNJ accounts for about 22% admissions with an in-patient case fatality rate of 26%. At present all jaundiced newborns are screened by a serum bilirubin test. There is no noninvasive, sensitive, screening device in place to enable early detection of those neonates who may require intervention, hence the need to evaluate the icterometer. The icterometer, in studies conducted in Turkey, India and the USA, has shown a linear correlation with total serum bilirubin (TSB), with high sensitivity and specificity for detecting significant neonatal jaundice.

Objectives: The main objective of this study was to determine the sensitivity and specificity of the Ingram icterometer for predicting the serum bilirubin levels in jaundiced term newborns, and the secondary objective was to determine the sensitivity and specificity of clinical assessment on the sole of the foot.

Study design: Cross-sectional study.

Study setting: Kenyatta National Hospital (KNH), paediatric filter clinic (PFC), new born unit (NBU), and the paediatric wards.

Study population: Jaundiced term newborns: ≥37 weeks gestation or ≥2500 g birth weight.

Sampling: Consecutive sampling of subjects who met the study inclusion criteria.

Sample size: 143 jaundiced neonates.

Procedures: Transcutaneous bilirubin (TcB) measurements were done with the icterometer on neonates for whom the primary clinician had requested serum bilirubin. Only those neonates who had not had phototherapy or exchange transfusion were included. Two icterometer readings were done and the higher reading was taken. Serum bilirubin was determined in routine biochemistry laboratory (lab) at KNH. A follow up was done to document how many of the tested neonates had phototherapy and/or exchange transfusion, and what the eventual outcome was. Clinical assessment was done by blanching the sole of the foot and documenting presence or absence of jaundice.

Results: A total of 143 jaundiced term neonates were recruited into the study. The mean gestational age was 39.3 weeks and the mean birth weight was 3100 g with the commonest comorbidity being neonatal sepsis. The sensitivity and specificity of the icterometer at index 3 and at a serum bilirubin cut-off of 221 mcmol/l, was 99% and 55.3% respectively. At serum bilirubin cut-off of 257 mcmol/l, the sensitivity and specificity of clinical assessment at the sole of the foot was 67% and 74.5% respectively. Poor outcome was associated with higher mean serum bilirubin levels.

Conclusion: The icterometer at a cut-off index of 3 offers excellent sensitivity but only moderate specificity. The clinical assessment at the sole of the foot offers moderate sensitivity and specificity.

Recommendations: The icterometer performs well to detect possibly serious jaundice and is recommended for routine screening in term jaundiced neonates. Although it lacks specificity, its performance compares favourably with clinical assessment which it might usefully replace.

1. LITERATURE REVIEW

1.1. INTRODUCTION

Clinically severe hyperbilirubinaemia in infants ≥35 weeks gestation is defined as a TSB >95th percentile for hours-of-age on the Bhutani nomogram (as shown in appendix II). Such hyperbilirubinaemia with a TSB >25 to 30 mg/dL (428 to 513 µmol/L) is associated with an increased risk for bilirubin-induced neurologic dysfunction (BIND) [1] and therefore warrants aggressive intervention (as shown in appendix III).

Significant hyperbilirubinaemia is defined as serum bilirubin concentration > 221 µmol/l (> 12.9 mg/dl) or > 40th percentile on the Bhutani nomogram as it marks the transition from the low risk zone to the low-intermediate risk zone[1] (see bilirubin nomogram in appendix II). Above this threshold, bilirubin level >221µmol/l, definitive testing to establish the bilirubin concentration accurately is recommended and therefore previous studies have explored the ability of the icterometer to identify children with significant hyperbilirubunaemia to prevent missing cases of clinically severe hyperbilirubinemia. [2-6]

Serum bilirubin measurement remains the routine screening method for neonatal jaundice. Unfortunately, it is invasive, painful and costly. To overcome these problems, non-invasive methods of bilirubin estimation have been developed. These transcutaneous bilirubinometry (TcB) devices have been shown in various studies to give results that have a linear correlation with total serum bilirubin (TSB).[9]

When the bilirubin concentration in serum increases, bilirubin is deposited in the skin and subcutaneous tissues producing the yellow coloration of the skin or icterus (jaundice).[1,73] There is a well established relationship between the total serum bilirubin (TSB) concentration and the intensity of jaundice. The possibility of quantifying the bilirubin value by assessing skin color is not new and was documented by Yippo in 1913, although he measured bilirubin concentration in blood, not serum.[7]

It is neither possible nor desirable to measure serum bilirubin daily in every infant for the first week after birth. Although there is a clear and semi-quantitative relationship between the

yellowness of the skin and the TSB, the variations in colour perception by the human eye, differences in neonatal skin pigmentation, and variations in both the intensity and colour of the available light affect the ability to estimate the TSB by assessing the degree of jaundice clinically.

1.2 PREVALENCE, MORBIDITY AND MORTALITY OF HYPERBILIRUBINEMIA

Hyperbilirubinemia occurs in 30-60% of term infants, and is significant (levels >12.9 mg/dl or > 221 μmol/l) in 3.5-12% of these children.[1] Davidson et al, as early as 1941, also demonstrated that about two thirds of healthy newborns appeared jaundiced during the first postnatal week.[8]

Based on a review of multiple case reports that spanned more than 30 years, the American Academy of Paediatrics subcommittee on hyperbilirubinaemea concluded that kernicterus, although infrequent, had at least a 10% mortality and at least 70% long-term morbidity. It was evident that the preponderance of kernicterus cases occurred in infants with a bilirubin level higher than 20 mg/dl (or 342 μmol/l).[9]

English et al, in a study to determine the causes and outcome of young infant admissions to a Kenyan district hospital, showed that neonatal jaundice was particularly associated with a high mortality in the first week of life, accounting for 22% of total monthly young infant admissions, with an in-patient case fatality rate of 26%. Of the 87 infants admitted with jaundice as a primary problem, 23 received an exchange transfusion, seven (30%) of whom died. The median bilirubin in the exchange transfusion group was 750 μmol/l.[10]

A study carried out to determine the neurological and developmental outcome of neonatal jaundice and sepsis in rural Kenya showed that, of the children admitted with severe neonatal jaundice who survived, 18% died after discharge. At age 18–32 months, 96% of the hospitalized neonatal jaundice survivors had motor or neurological impairment and/or developmental difficulties. These children frequently had multiple disabilities: 43% were unable to either sit and/ or stand independently, 48% had a movement disorder and 56% had an eye-movement disorder.[11] Developmental disturbance and parental concerns were more common than in other children from the community. This adverse outcome in terms of disability represented a

significant personal and socio-economic burden to the families, and was considerably higher than that reported in Western countries. [12-14]

Ahmed et al undertook a study in Nigeria which showed that jaundice and kernicterus were more severe in children born at home than in those delivered in hospital. Low birth weight and delay in reaching the hospital may have influenced the outcome. [15]

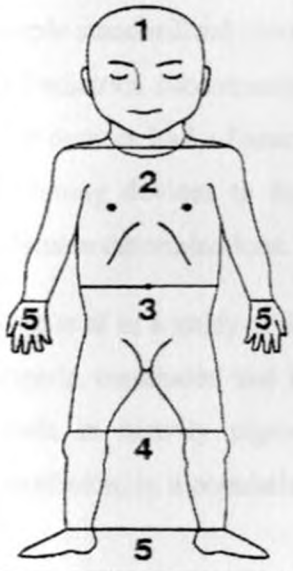
1.3 CEPHALOCAUDAL PROGRESSION OF JAUNDICE

A useful refinement in clinical assessment of jaundice is the observation that jaundice appears initially in the face of a newborn and as the TSB increases, becomes apparent on the chest and abdomen and finally, in the extremities. This observation has been confirmed by using transcutaneous biblirubin measurements. [16-18]

Knudsen postulated that the cephalocaudal progression of jaundice can be explained by conformational changes of bilirubin-albumin complexes. Although the initial binding of bilirubin to albumin is extremely rapid, final conformational changes may not occur for about eight minutes. Thus blood leaving the reticuloendothelial system and going to the proximal parts of the body contains bilirubin that is less tightly bound to albumin than that which subsequently reaches the distal parts of the body. Bilirubin that is less tightly bound is more likely to precipitate as bilirubin acid in phospholipid membranes in the skin and subcutaneous tissues, which is why the face appears jaundiced before the abdomen or the leg.[18] This concept has led to a clinical application used to grade the severity of jaundice.

1.4 ZONES FOR ESTIMATING THE CEPHALOCAUDAL PROGRESSION OF JAUNDICE

Table 1: The indirect bilirubin values corresponding to each zone are shown in the table below:



Dermal Zone	Indirect Bilirubin (mg/100 mL)		
	Mean ± SD	Range	Observations
1	5.9 ± 0.3	4.3 – 7.9	13
2	8.9 ± 1.7	5.4 – 12.2	49
3	11.8 ± 1.8	8.1 – 16.5	52
4	15.0 ± 1.7	11.1 – 18.3	45
5		> 15	29

Table 2: Correlation between icteric dermal zones of Kramer and serum bilirubin values:

Dermal zone	Mean±_SD µmol/l
1	101±5
2	152±29
3	201±31
4	257±29
5	>257

1.5 TRANSCUTANEOUS BILIRUBINOMETRY

There are at least four transcutaneous bilirubin measuring devices described in the literature. These include the Bilicheck meter, the Minolta-Air Shields meter, the Chromatics ColorMate III, and the icterometer. The first three are electronic devices while the fourth, the icterometer, is a simple standardized colour scale to aid clinical assessment. A review by the American Academy of Pediatrics subcommittee on hyperbilirubinemia showed that TcB measurement by any of the four devices had a linear correlation with TSB, and these were therefore recommended as useful screening devices to detect clinically significant jaundice and decrease the need for serum bilirubin determinations. [9]

Tina et al in a study of 127 jaundiced black infants less than two weeks old, at two hospitals in Nigeria, concluded that TcB measurements were a useful and reliable index for estimating TSB levels in heavily pigmented neonates before directing phototherapy and exchange blood transfusion, in a population in which determining reliable TSB levels was often difficult. [19]

The forehead and sternum have been the sites most frequently used for TcB measurements and have been shown to correlate well with TSB.[20-23] Five studies with the Minolta Air-shields meter found the sternum to provide the best agreement with TSB.[24-28] Six studies found no difference between measurements taken from the forehead and sternum.[21, 29-33] Two studies reported that forehead readings became less reliable in infants greater than three days of age.[34, 35] The decrease in correlation between forehead readings and TSB was presumably due to exposure of the head to sunlight.

Two studies performed using the Bilicheck meter demonstrated better performance at the forehead,[36,37] while two other studies found that TcB taken at the forehead are lower in newborns who are crying, especially at higher concentrations of serum bilirubin. [29,38]

Maisels et al suggested that measurements from the sternum were less likely to be influenced by the effects of ambient light, particularly sunlight, and may be more desirable when measurements are taken after infants have been discharged. [39]

Szabo et al studied the reliability of detection of hyperbilirubinaemia in jaundiced full term neonates either by eye or by TcB and demonstrated that assessment by the eye was less accurate.[40]

1.6 ABOUT THE ICTEROMETER

The icterometer is a plastic strip with alternating stripes of clear and painted perspex and has been in use since 1925.[41] The five stripes are of increasingly deepening yellow colour which represents increasing severity of jaundice. Measurements may be obtained from the nose, forehead, sternum or heel in daylight.[42] The yellow color of the skin is then matched with the corresponding yellow stripes on the scale. In my study, transcutaneous measurements were obtained by pressing the icterometer against the tip of the baby's nose, similar to the studies by Bilgen et al (Turkey), [2] Schumacher et al (USA), [3] Gupta et al (India) [5] and Chaibva et al (South Africa) [4].

There are at least three types of icterometers: the Perspex icterometer, the Ingram icterometer, and the Gosset icterometer.[43] However, the difference is only in the manufacturer but not in the structure or function of the instrument.

My study used the Ingram icterometer, manufactured by Thomas A. Ingram and Company, Birmingham, England (distributed in the USA by Cascade Health Care Products, Salem, Oregon).

1.7 READING THE ICTEROMETER

There are five standard colours on the scale but if the reading appears to fall between two stripes, a 0.5 score can be assigned (eg 1.5, 2.5, etc). For each score, the icterometer provides an estimate of the mean TSB and 2 standard deviations (SD) above the mean.

As a screening tool, the icterometer has performed as well as far more sophisticated instruments in term and preterm infants.[44,45] It has also been used effectively in the hospital[46] and by nurses and parents in the home. [47,48]

1.8 FACTORS AFFECTING TcB ESTIMATION

Although TcB has been shown to correlate well with TSB, there are reports suggesting that TcB measurement can be affected by a variety of factors including use of phototherapy, birth weight, gestational age, and postnatal age. [49-53]

Phototherapy results in blanching of the skin. Values obtained by TcB have been shown to decrease rapidly following the implementation of phototherapy. The average decrease in TcB measurements observed in one study of nine neonates was approximately 30% following 150 minutes of phototherapy, with much smaller decreases of approximately 4% seen in the subsequent 150 minutes.[54]

Another study reported a decrease in TcB measurement of 25% following two hours of phototherapy, and a 50% decrease after 12 hours. The decrease in TcB was much greater than that seen in TSB concentrations.[55]

Exposure to sunlight has also been found to adversely affect the correlation between TcB and TSB measurements. This finding may limit the utility of TcB in infants who are discharged and exposed to sunlight. There is however, lack of agreement on the effect of gestational age on the correlation between TcB and TSB. [29, 34]

One study evaluating the effect of newborn illness on TcB measurement found that the presence of hypoxia, hypoglycemia, infection, respiratory distress syndrome, or severity of illness did not adversely impact on TcB measurements.[37] Another study found that infants with bleeding or abdominal problems had similar agreement between TcB and TSB measures when compared to healthy newborns.[50]

1.9 RISKS AND COST IMPLICATION OF BLOOD SAMPLING

Blood sampling involves pain for the newborn infants, and this infant stress may have long term consequences.[56, 57] Other potential complications include risk of infection and osteomyelitis.[58] Therefore, as one considers the benefits of the TcB, a frequently cited and real advantage is the decreased need for invasive blood sampling which is painful, a health risk to the infant and a potential health hazard to the practitioners as well as laboratory personnel, who may be exposed at the bedside to human immunodeficiency virus (HIV) infected blood[59] and other viruses such

as hepatitis. In sub-Saharan Africa, the proper protection of the health care providers is often suboptimal or unavailable altogether. [60]

Studies suggest that a 20% -34% reduction in samples collected for bilirubin analysis could be achieved following implementation of TcB measures.[20, 22, 30, 37, 61, 62] However, Bourchier et al and Petersen et al found no difference in the number of TSB measurements. [25, 63]

Maisels et al used the Bilicheck device in a community hospital and found savings of $1600 a year when transcutaneous bilirubin was measured instead of serum bilirubin.[22] However, the cost saving might be expected to be a lot more with the icterometer given that there are hardly any operating costs beside the initial cost of purchase, unlike the Bilicheck that costs nearly $ 2 per test.

1.10 CORRELATION COEFFICIENTS, SENSITIVITY, AND SPECIFICITY OF TcB ESTIMATION vs TSB

a) The BiliCheck

Rubaltelli and colleagues, in an evaluation of 210 babies with jaundice in six European hospitals, demonstrated that the sensitivity of transcutaneous bilirubin measurement using the BiliCheck (forehead) vs. HPLC (gold standard) at higher levels (>17mg/dl) was 50%, with a specificity of 99%, giving a positive likelihood ratio (+LR) of 50 and a negative likelihood ratio (-LR) of 0.5. When comparing the lab serum bilirubin vs. HPLC, the sensitivity was 40% with a specificity of 98% which gave a +LR of 20 and an -LR of 0.6.

An analysis of covariance revealed that race, gestational age, postnatal age, and birth weight did not affect BiliCheck measurements when compared with HPLC. The researchers concluded that transcutaneous bilirubin measurement with the BiliCheck (forehead) can not only be used as a screening tool, but also as a direct substitute for serum laboratory bilirubin measurement.[36]

Although the above study population was not very heterogenous (66.7% of the patients were white while only 4.3% were black), Buthani et al also demonstrated similar findings of racial independence using the BiliCheck. [64]

b) The icterometer

A comparison of bilirubin estimated with the icterometer with bilirubin concentrations in serum show correlation coefficients ranging from 0.63 to greater than 0.97. [2-6]

Four studies reported correlation coefficient, r, of icterometer to TSB as follows:

- Turkey (n=96) r=0.78
- US Black (n=55) r=0.96
- India (n=11) r=0.97
- India (n=77) r=0.97
- US White (n=106) r=0.63
- Pooled correlation coefficient r=0.92 (95% CI 0.72-0.98)

Gupta et al showed that for Indian term infants without Phototherapy (N=77), the sensitivity, specificity, PPV, and NPV (Icterometer reading $\geq$ 3, in predicting TSB >10 mg/dl) was 97%, 71%, 78%, and 94%, respectively. [5]

For Indian preterm infants of gestational ages 35-36 weeks, without phototherapy (N=11), the sensitivity, specificity, PPV, and NPV (Icterometer reading $\geq$ 3 in predicting TSB >10 mg/dl) was 50%, 86%, 67%, and 75%, respectively. [5]

Table 3: Summary of test accuracy of Ingram icterometer at the tip of nose in healthy, term or near-term (GA≥34) infants not on phototherapy or exchange transfusion.

Study	Year	R	TP (n)	FN (n)	TN (n)	FP (n)	Sens (%)	Spec (%)	Thresholds	
									Icterometer	TSB (mg/dl)
Bilgen Turkey	1998	0.78	17	0	38	41	100	48	3	12.9
Schumacher (US,white)	1985	0.63	14	3	66	23	82	74	3	12.9
Gupta (India)	1991	0.97	Term infants (N=77)				97	71	3	10
			Preterm infants (35-36 weeks) N=11				50	86	3	10

TP = true positive; FN = false negative; TN = true negative; FP = false positive; n / N = number of subjects; Sens = sensitivity; Spec = specificity; TSB = Total Serum Bilirubin; r = regression coefficient between Icterometer and TSB.

2. PROBLEM STATEMENT

Hyperbilirubinemia is a frequent problem in term neonates. Studies have shown that up to two-thirds of healthy newborns appear jaundiced during the first postnatal week.[1,8] In Kenya NNJ accounts for about 22% monthly admissions for babies less than 60 days of age with an in-patient case fatality rate of 26%.[10] Serum bilirubin measurement remains the standard or the

mainstay of screening and diagnosing any degree of jaundice in our setting. This basically means repeated blood sampling with its attendant complications such as neonatal anemia (iatrogenic), stress, pain, infections or osteomyelitis.[58] This repeated blood sampling also has cost implications for the guardians. Infections may increase the length of hospital stay and readmission rates. It is therefore prudent to investigate whether a sensitive and specific, single screening device that is noninvasive, portable, and cost effective, can be put in place to identify low risk babies in whom testing is not indicated to reduce these complications and unnecessary blood tests.

3. STUDY JUSTIFICATION

In resource poor settings like Kenya, fairly accurate and cost-effective methods of transcutaneous bilirubin estimation should be promoted and adopted. TcB estimation in the developed countries has permeated to the household level where parents and guardians are instructed on how to monitor their baby's bilirubin levels and when to bring them back to the hospital for TSB measurements. [47, 48]

There have been few studies done to validate the use of transcutaneous bilirubin measuring instruments in the black population. Most of the studies have been done in the white population. Most of the data on black infants are from studies done with the Minolta Air –Shields and the BiliCheck instruments (electronic devices). Very few data are available from studies with the Ingram icterometer, a simple and very cheap device, hence the need to evaluate its performance in the black population.

The icterometer is convenient and cheap compared to repeated blood sampling. Since it is noninvasive, there is no pain to the neonate and there is a reduction in complications such as infections, iatrogenic anemia, and neonatal stress. The instrument is portable and therefore can be used at the physician's office and in the ward by the nurses. [46-48]

It may also offer an option for screening for purposes of referral, in the many Kenyan hospitals and health centres where often no facilities are available for serum bilirubin tests. The Ingram

icterometer costs an average of $ 20 (approximately Kshs. 1,400) with hardly any additional maintenance costs.

The most commonly used clinical method of bilirubin estimation is by pressing at the sole of the foot for the presence or absence of clinical jaundice. This has been the mainstay of screening for jaundice in the health facilities where no facilities are available for serum bilirubin tests and is currently recommended by Kenyan government guidelines. But there is no documented evidence concerning the performance of this method in our setting hence the need to evaluate it as well.

This study will be conducted primarily among term black neonates and will therefore seek to answer the question of whether TcB on these neonates using the Ingram icterometer favourably compares with TSB, and whether it therefore can be relied upon as a screening tool for significant neonatal hyperbilirubinaemia in this population.

4. STUDY OBJECTIVES

PRIMARY OBJECTIVE

To determine the sensitivity and specificity of the Ingram icterometer for predicting elevated serum bilirubin levels in term neonates at KNH.

SECONDARY OBJECTIVE

To estimate the sensitivity and specificity of clinical assessment of jaundice at the sole of the foot for predicting elevated serum bilirubin levels in term neonates at KNH.

5. MATERIALS AND METHODS

5.1 STUDY SITE

The study was conducted at the Kenyatta National Hospital-Paediatric filter clinic, Newborn Unit, and the Paediatric wards. KNH is the largest referral and teaching hospital in Kenya. It is also the primary health facility for many residents of Nairobi city and the suburban areas. It has a number of specialists in the various fields of medicine and is a centre for specialist training in the postgraduate programmes.

5.2 STUDY POPULATION

Clinically jaundiced term infants between 37 weeks gestational age and four weeks postnatal age were included in the study regardless of the place of birth and health status.

5.3 SUBJECT SELECTION

5.3.1 Inclusion criteria

1. Neonates ≥ 37 weeks gestation or ≥2500 g at birth, and ≤ 30 days postnatal age.
2. Jaundiced neonates who had not had phototherapy or exchange transfusion.
3. Neonates for whom the primary clinician had requested a TSB.

5.3.2 Babies not studied were:

1. Jaundiced infants undergoing or who had undergone phototherapy
2. Jaundiced infants who had had exchange transfusion
3. Infants born at less than 37 weeks gestation or those who were > 30 days postnatal age.

5.4 STUDY DESIGN

This was a cross-sectional study. A follow-up was done in the wards and in the newborn unit to document the frequency of phototherapy or exchange blood transfusion and the eventual outcome among those neonates who were enrolled into this study.

5.5 SAMPLING

Consecutive sampling was done among the infants presenting with clinical jaundice during the four months duration of the study. Data were collected on week-days from 9 AM to 5 PM over this period.

5.6 TcB DETERMINATION

All TcB measurements were done using the Ingram icterometer (Cascade Health Care Products, Salem, USA). The instrument was pressed on the tip of the nose with sufficient pressure to make the nose blanch (as shown in appendix 15.1). The colour of the blanched skin was then matched with the corresponding yellow hue on the icterometer. If the skin colour only matched a shade between two icterometer stripes, then a 0.5 score was assigned. For example, a skin colour

corresponding to a shade between icterometer stripes 2 and 3 would be assigned a reading of 2.5, while a skin shade between stripes 3 and 4 would be assigned a reading of 3.5. Blood sampling or TSB measurements were done within half an hour of TcB, and before phototherapy or exchange transfusion was commenced. TcB was done only on neonates on whom the primary physician had ordered for a routine TSB.

The principal investigator performed all TcB measurements throughout the study. Two measurements were done with the icterometer and the highest reading of the two was taken. This was due to the potential risks of missing out a higher reading that might have needed prompt intervention.

Clinical assessment of jaundice was performed by simply pressing on the sole of the foot until it blanched and then noting whether there was obvious yellowness or not. This was documented as significant (present) or insignificant (absent) jaundice.

5.7 TSB DETERMINATION

Blood samples were obtained via heelprick. Measurements of TSB were done in the routine biochemistry laboratory at the KNH using the Olympus AU 640 and AU 400 (the former is able to process more samples than the latter). These instruments were calibrated daily as per the manufacturer's instructions.

5.8 INTERVENTIONS OFFERED ON FOLLOW-UP

Patients were followed up to document what active interventions were instituted in the ward or NBU after a diagnosis of jaundice in them. Documentation was only made as to whether the patient had phototherapy alone, phototherapy plus exchange transfusion, exchange transfusion alone, or no active intervention. The eventual outcome at discharge was also documented from the patient's records, ie. normal, dead or severe neurological sequelae (e.g. convulsions, hypo/hypertonia, arching, feeding difficulties and any other manifestations of kernicterus).

5.9 SAMPLE SIZE ESTIMATION

To determine the optimal sample size for comparing test A with test B, we first assigned the following values:

1. An estimate of the expected value of the performance characteristic of interest for the reference test
2. The smallest proportionate difference between the reference and the new tests considered to be medically important
3. The level of significance required to accept two proportions as different, which is α (type I error).
4. The level of certainty desired to detect the medically important difference (statistical power).

The equation for sample size calculation for diagnostic test accuracy was adopted as per Flahault et al: [65]

$$N = Z_{1-\beta}\sqrt{\pi(1-\pi)} + Z_{1-\alpha}\sqrt{(\pi-\delta)(1-\pi+\delta)}/\delta^2$$

Where:

N= the minimum sample size for significant neonatal jaundice cases

α = type I error

1- β= power

$Z_{1-\alpha}$ = 1.96 at 95% confidence interval

$Z_{1-\beta}$ = 1.28 at power of 90%

π= desired sensitivity or as determined from other studies (85%)

δ= margin of precision error (±8%)

$N= 1.28\sqrt{(0.85 \times 0.15)} + 1.96\sqrt{(0.77 \times 0.07)}/0.08^2$

N= 143 neonates

6. DATA MANAGEMENT AND STATISTICAL ANALYSIS

All data emanating from this study were entered into questionnaires and then into a computer database, cleaned and verified. The data were analysed using SPSS (Statistical Package for Social Sciences) software version 13 (SPSS Inc., Chicago, USA). A two by two table was used

to estimate the sensitivity, specificity, negative and positive predictive values, and the proportion of those who would be spared blood tests if the icterometer were to be used for screening. A two by two table was also used to estimate the sensitivity, specificity, negative and positive predictive values of clinical assessment at the sole of foot. Exact binomial 95% confidence intervals around sensitivity estimates were calculated using STATA version 9.2.

The receiver-operator characteristic (ROC) curve was constructed for exploratory analyses of other possible threshold icterometer readings, i.e at 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5. This helped to determine the performance of the icterometer at different indices which has been presented as a two by two table.

Pearson's product-moment correlation coefficient, linear correlation analyses and a multiple linear regression analyses were used to detect associations between TSB and TcB and the other variables. Statistical significance was implied by a *p*-value of less than 0.05.

Data are presented as frequency tables, two by two tables, box plots, correlation plots, pie charts, and ROC curves.

7. DEFINITION OF TERMS

7.1 Sensitivity, specificity, and predictive values of the Ingram icterometer (cut-off 3) vs. TSB (cut-off 221 µmol/l)

	TSB (gold standard)	
Icterometer index (test)	**Positive** >221 µmol/l	**Negative** ≤ 221 µmol/l
Positive ≥3	**a**	**b**
Negative <3	**c**	**d**

Sensitivity: The proportion of the true positives (by TSB) that also tested positive by the icterometer (a/a+c)

Specificity: The proportion of the true negatives (by TSB) that also tested negative by the icterometer (d/b+d)

Negative predictive value: What proportion of those who tested negative on the icterometer were truly negative by the TSB (d/c+d)

Positive predictive value: What proportion of those who tested positive on the icterometer were truly positive by TSB (a/a+b)

Overall accuracy: The sum of true positives and true negatives as a percentage of the total number of observations. It is a measure of how accurately the icterometer predicts a true positive or true negative index (a+d/N).

The proportion that would be spared blood sampling if icterometer were to be used for screening is expressed as: Test negatives/ Total number tested. The target is approximately 40% sparing of blood sampling based on the study by Bilgen in 1998 in Turkey (refer to summary table 3 above).

The risk of missing an infant who may require treatment but who is screened as negative by the icterometer is expressed as: c/c+d.

7.2 Sensitivity, Specificity and Predictive Values of Clinical Assessment vs. TSB (at cut –off 257 µmol/l)

	TSB (Gold Standard)	
Clinical Jaundice	**>257 µmol/l**	**≤ 257 µmol/l**
Present	**a**	**b**
Absent	**c**	**d**

Sensitivity: The proportion of true positives by the gold standard that were picked by the clinical assessment at the sole of foot (a/a+c).

Specificity: The proportion of true negatives by the gold standard that were picked by the clinical assessment at the sole of foot (d/b+d).

Positive predictive value: The proportion of the test positives that was truly positive by the TSB (a/a+b).

Negative predictive value: The proportion of the test negatives that was truly negative by the TSB (d/c+d).

8. ETHICAL CONSIDERATIONS

Permission was sought from the research and ethics committees of KNH and the University of Nairobi, Department of Paediatrics and Child Health. Parental/ guardian's consent for enrollment was sought only after fully explaining the objectives, procedure, risk and benefits of the study. There were no added costs to the parents/guardians since icterometer tests were done only on those infants for whom routine TSB had been ordered by the primary physician. Participation was entirely voluntary. Participants were free to withdraw from the study at any time. Information obtained from the study participants was kept confidential.

Since enrolment proceeded only after the primary clinician had ordered a TSB, there were no blood tests performed on the babies for the purposes of this research alone. No infant was prejudiced on account of refusal by guardians to grant consent. Those infants who were severely jaundiced who either required phototherapy or exchange transfusion were managed appropriately in liaison with the unit doctors.

9. RESULTS

A total of 143 jaundiced term neonates were recruited into the study over a period of four months (October 2008- January 2009).

9.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Of the 143 neonates recruited, the male: female ratio was 1:1. The majority of the neonates (69.2%) came from Nairobi and its environs and the mean age at presentation was seven days.

Table 1: Baseline Characteristics of study population (n = 143)

Factor	Frequency	Percentage
Age (in days)		
• 1-7	99	69.2
• 8-14	30	21.0
• 15-21	6	4.2
• 22+	8	5.6
Mean	7.3	
Median	5.0	
Range	1-30	
Sex		
• Male	71	49.7
• Female	72	50.3
Mode of delivery		
• SVD	96	67.1
• C/S	47	32.9

Ninety nine neonates (69.2%) were from within Nairobi and its environs while 44 (30.8%) were from outside Nairobi mainly as referrals.

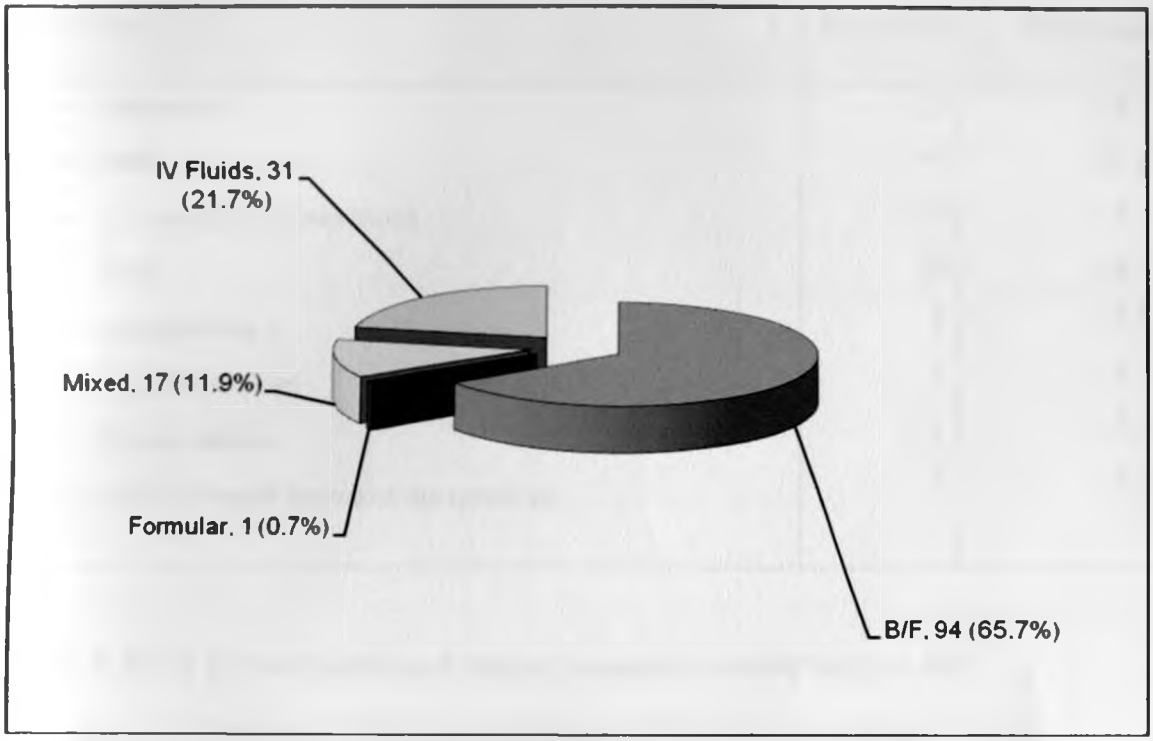
Seventy seven (53.8%) patients were referred from different health facilities within and without Nairobi while sixty six (46.2%) were either those delivered at the KNH or those seeking treatment here as their primary health facility.

Table 2: Summary Statistics for gestational age and weights (n = 143)

Factor	Gestation (in weeks)	Birth Weight (in grams)	Current Weight (in grams)
Mean	39.3	3,099.3	3,128.7
Median	39.0	3,100	3,200
Range	37-42	2,500-4,300	2,300-4,400

The mean gestational age was 39.3 weeks with a range of between 37 to 42 weeks. The mean birth weight was about 3,099.3 kg with a range of 2.5-4.3 kg which meets the criteria for term delivery. The range for current weights was 2.3 kg-4.4 kg. The lower range was possibly due to the initial weight loss in neonates in the first week of life. Generally the birth weights and current weights were similar.

Figure 1: Mode of Feeding (n=143)



Most of the neonates were breastfed (65.7%). Only the one neonate whose mother was HIV seropositive was on exclusive formular feeding. One fifth of the neonates were on intravenous fluids at the time of the study. Mixed feeding included those who were on both breast milk and formula feeding and accounted for 11.9%.

Distribution of the primary comorbidities

Total number of diagnoses made was 290. The average number of diagnoses per patient was two. The commonest comorbidity was neonatal sepsis (63.6%) followed by respiratory distress syndrome (14%), perinatal asphyxia (9.1%) and congenital malformations (9.1%). The distribution of the primary comorbidity is as shown in the table below:

Table 3: Distribution of primary comorbidity (n = 143)

Diagnosis	Frequency	Percentage
• Asphyxia	13	9.1
• NNS	91	63.6
• Congenital malformations	13	9.1
• RDS	20	14.0
• Macrosomia	2	1.4
• Hypothyroidism	2	1.4
• Severe anemia	1	0.7
• Haemorrhagic disease of the newborn	1	0.7

Table 4: Blood Culture results and clinical jaundice at sole of foot (n = 143)

Factor	Frequency	Percentage
Confirmed infection		
• Yes (+ve Culture)	20	14.0
• No (-ve Culture)	120	84.0
• Missing	3	2.0
Clinical jaundice on sole		
• Present	73	51.0
• Absent	70	49.0

As shown in the above table, a total of 140 neonates had their blood culture results. Of these, only twenty (14%) were culture positive. A majority (84%) were culture negative. This is

approximately 14% culture positivity rate in the study population. Even though this study was not designed to look at the etiological agents, some of the organisms grown in cultures included *Citrobacter sp., Klebsiella sp. Strep. Pneumonia, enterobacteriacea, Staphylococcus aureus,* etc. There was no significant association between blood culture and TSB ($p > 0.05$), but there was a significant association between positive blood culture and death ($p=0.027$)

Clinical assessment at the sole of the foot was simply documented as present or absent. Fifty one percent had clinical jaundice detectable at the soles of their feet whereas forty nine percent did not.

INTERVENTIONS OFFERED ON FOLLOW-UP

A majority of the patients (74.1%) had phototherapy alone beside the other supportive care in the units. Twenty three patients (16.1%) who had previously been on phototherapy but did not respond also underwent exchange blood transfusion. Fourteen patients did not need any active intervention for their jaundice except for the management of their comorbidities. There was no neonate who underwent exchange blood transfusion alone before undergoing phototherapy.

Table 5: Interventions (n = 143)

Interventions	Frequency	Percentage
• Phototherapy alone	106	74.1
• Phototherapy & Exchange	23	16.1
• Exchange transfusion alone	0	0
• No active intervention	14	9.8

Table 6: Outcome (n = 143)

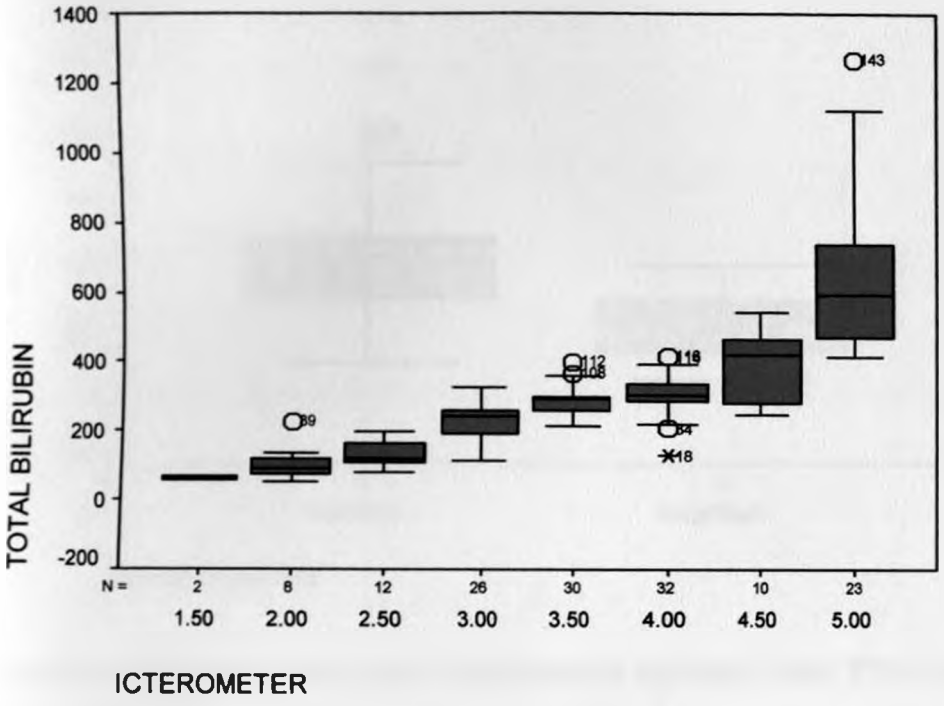
Outcome	Frequency	Percentage
• Normal	108	75.5
• Dead	20	14.0
• Major sequelae (in hospital)	15	10.5

The patients were followed up to document the outcome of the interventions at the time of discharge or death. Outcome was documented as normal for those who had no neurological sequelae; major sequelae for those who had poor feeding, hypotonia, hypertonia, lethargy, high-pitched cry, arching, persistent convulsions or stupor; dead for those who died in the hospital during follow-up. A majority of the patients (75.5%) had a normal outcome, while 25% either died or survived with major neurological sequelae.

9.2 RESULTS OF EVALUATION OF JAUNDICE

Overally, the mean, median and range of TSB was 316.3, 287.3 and 52.2-1267μmol/l, respectively.

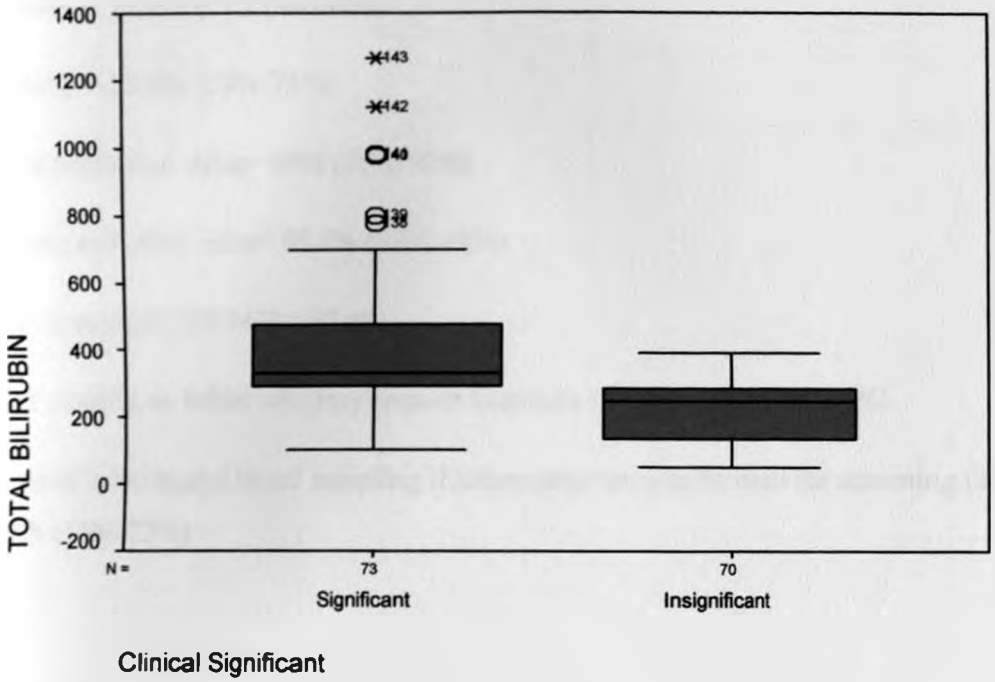
Figure 2: Association between total bilirubin and icterometer readings



The above figure is a box plot (comprising lines, boxes, whiskers and outliers) of the total bilirubin vs icterometer readings. The box represents a range of values of TSB from 25th to 75th percentile while the central line within the box represents the median TSB value for the group at the specific icterometer index. The whiskers represent a range of values between 2.5th to 97.5th percentiles.

The mean TSB levels increased with icterometer indices. One patient who came as a referral from a neighbouring district hospital had a total bilirubin level of 1267 μmol/l hence the outlier at icterometer reading of 5.00. Notably, there is some considerable overlap in the TSB readings thereby suggesting that a clinician using the icterometer does not categorise the neonates perfectly into entirely discrete groups.

Figure 3: Association between total bilirubin and clinical significance on sole



The neonates with significant (present) clinical jaundice had higher mean TSB compared to the insignificant (absent) group. When jaundice was significant (present) the median was higher and the bilirubin values were also higher. Even when the clinical assessment showed insignificant (absent) jaundice, one could still get occasional values as high as 400 μmol/l, which would require immediate intervention to avert possible neurological complications.

Table 8: Sensitivity, Specificity and predictive values of icterometer (n = 143)

Icterometer index	Total Bilirubin (μmol/l)		Total
	> 221	≤ 221	
≥ 3	104	17	121
< 3	1	21	22
Total	105	38	143

Sensitivity = 99.0% (CI 95%-100%)

Specificity = 55.3% (38%-71%)

Positive predictive value= 86% (78%-92%)

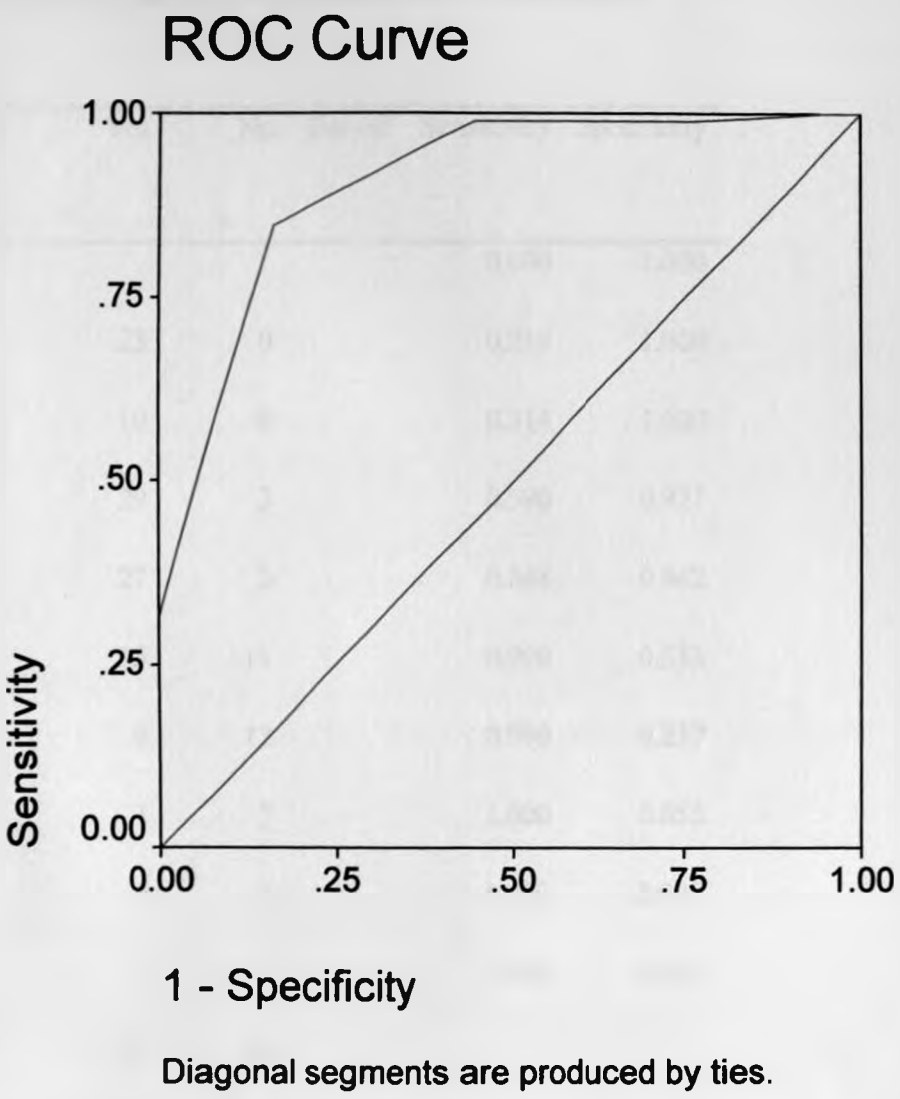
Negative predictive value= 95.5% (77%-99%)

Overall accuracy (125/143) = 87.4%

Risk of missing an infant who may require treatment (1/22) = 4.5% (1%-23%)

Proportion to be spared blood sampling if icterometer were to be used for screening (22/143) =15.4% (10%-22%)

Figure 4: ROC curve for scores of 1-5 on icterometer



Using the ROC curve, the point on the curve where it becomes almost parallel to the horizontal plane is the cut-off that was used to determine the sensitivity and specificity of the icterometer. Area under the curve is equal to 0.908, a value approaching unity, which indicates the strong correlation between the icterometer readings and the total bilirubin values.

Table 9: Sensitivity analysis of icterometer at various indices

Icterometer reading	Yes	No	Cut-off	Sensitivity	Specificity
				0.000	1.000
5	23	0		0.219	1.000
4.5	10	0		0.314	1.000
4	29	3		0.590	0.921
3.5	27	3		0.848	0.842
3	15	11		0.990	0.553
2.5	0	12		0.990	0.237
2	1	7		1.000	0.053
1.5	0	2		1.000	0.000
				1.000	0.000
Total	105	38			

From the above table, the cut-off of 3 has a sensitivity of 99% and specificity of 55.3% as reported in analyses of the primary objective. If the cut-off is adjusted to 3.5, then the sensitivity reduces to 84.8% and the specificity increases to 84%. As the index increases above 3, the sensitivity reduces while the specificity increases. As the index reduces below 3, the sensitivity increases while the specificity decreases.

Table 10: Sensitivity, specificity, and predictive values of clinical assessment on sole of foot vs total bilirubin (TSB threshold 257 µmol/l)

Clinical jaundice	Total Billirubin		OR (95% CI)	p-value
	> 257, n (%)	≤ 257, n (%)		
Yes	59 (67.0)	14 (25.5)	6.0 (2.8-12.6)	<0.001
No	29 (33.0)	41 (74.5)		

Sensitivity=67.0%

Specificity=74.5%

Positive predictive value=80.8%

Negative predictive value=58.6%

Overall accuracy (100/143) =70%

Risk of missing infant who needs treatment (29/70) =41.4%

Proportion to be spared blood sampling if clinical assessment were used for screening (70/143) =49%

Table 11: Sensitivity, specificity, and predictive values of clinical assessment on sole of foot vs total bilirubin (TSB threshold 221 µmol/l)

Clinical jaundice	Total Billirubin		OR (95% CI)	p-value
	> 221, n (%)	≤ 221, n (%)		
Yes	64 (61.0)	9 (23.7)	5.0 (2.1-11.7)	<0.001
No	41 (39.0)	29 (76.3)		

Sensitivity (64/105) = 61%

Specificity (29/38) =76.3%

Positive predictive value (64/73) = 87.7%

Negative predictive value (29/70) = 41.4%

Overall accuracy (93/143) = 65%

Risk of missing infant who needs treatment (41/70) = 58.6%

Proportion to be spared blood sampling if icterometer were to be used for screening (70/143) = 49%

9.3 ASSOCIATION OF ICTEROMETER, TSB AND OTHER VARIABLES

Table 7: Association between primary comorbidity and TSB

Primary comorbidity	Mean (SE)	95% CI (mean difference)	P-value
Asphyxias			
- Yes	285.9 (19.8)	77.2-147.3	0.538
- No	321 (17.8)		
NNS			
- Yes	354.0 (22.6)	34.4-164.5	0.003
- No	254.5 (18.2)		
Congenital malformation			
- Yes	288.5 (45.8)	80.0-144.5	0.571
- No	320.7 (17.3)		
RDS			
- Yes	251.4 (22.4)	15.1-169.5	0.100
- No	328.6 (18.4)		

There was a statistically significant association between neonatal sepsis and total bilirubin (p=0.003). It is worth noting that the commonest comorbidity was neonatal sepsis accounting for 63.6%.

Table 12: Association between clinical jaundice and TSB

Clinical jaundice	Mean (SE)	95% CI (mean difference)	P-value
Present	413.1 (25.9)	138.8-250.6	<0.001
Absent	218.8 (10.1)		

The patients with clinical jaundice at the sole of their feet had a higher mean total bilirubin compared to those without significant clinical jaundice (p<0.001).

Table 13: Icterometer threshold of 3 and outcome

Icterometer reading	Outcome			P-value
	Normal	Dead	Major sequelae	
≥ 3.0	18 (81.8)	4 (18.2)	0	0.203
< 3.0	90 (74.4)	16 (13.2)	15 (12.4)	

There was no significant association between icterometer index of 3 and the outcome.

Table 14: Association between Outcome and TSB

Outcome	Mean (SE)	95% CI (mean difference)	P-value
Normal[1]	288.7 (15.7)	Reference	Reference
Major sequelae	509.9 (72.7)	123.1-321.3	<0.001
Dead	325.6 (40.8)	42.6-118.4	<0.001

1- The reference group

The neonates with normal outcome had a lower mean total bilirubin whereas those with poor outcome (major sequelae or dead) had higher mean TSB. Overally, there was a significant association between outcome and TSB levels ($p<0.001$).

Table 15: Correlation coefficients of icterometer and serum bilirubin

Factor	Correlation Coefficient	p-value
Icterometer readings vs. Total bilirubin	0.78	<0.001
Icterometer readings vs. Indirect bilirubin	0.77	<0.001
Icterometer readings vs. Direct bilirubin	0.50	<0.001

There was a statistically significant correlation between icterometer readings and the serum bilirubin levels ($p< 0.001$).

10. DISCUSSION

About two thirds of term neonates develop jaundice in the first week of life, and this is significant (TSB > 221 μmol/l) in 3.5%-12% of these neonates. [1,8] Since serious consequences of neonatal jaundice are still common in Kenya, an accurate and noninvasive screening tool is necessary to stem progression to kernicterus, which is associated with a 10% mortality and 70% long-term morbidity.[9]

A study conducted in a rural district in Kenya showed that NNJ contributed to 22% of monthly admissions of those aged less than 60 days and was associated with a case fatality rate of 26%.[10] Another study showed that even among those who were discharged, 18% died on follow-up, while a majority survived with motor and neurological impairment. [11-14] Given this high morbidity and mortality associated with NNJ, a simple, cheap screening tool with a high sensitivity to help in early detection, referral or intervention is necessary, hence the purpose of this study.

A total of 143 neonates, clinically recognized as jaundiced, were recruited to this study over a period of four months. About two thirds of the neonates (69.2%) were in their first week of life, just like has been shown in other studies.[8] Prolonged jaundice (> 2 weeks) accounted for only 10% of the study population. However, the etiology of the prolonged jaundice was beyond the scope of this study. The male: female ratio in this study was equal.

Only term neonates meeting the eligibility criteria were recruited into the study. This resulted in the mean gestational age being 39 weeks and the mean birth weight being 3100 g, a study population similar to that of Wolf et al in Zimbabwean neonates.[06] Most of the neonates (67.1%) were delivered via spontaneous vertex delivery (SVD) while 32.9% were delivered via caesarean section (CS). CS deliveries included both elective and emergency cases.

The neonates who came as referrals accounted for 53.8% while the other 46.2% were either delivered at the KNH or were seeking treatment here as their primary health facility. Most of the referrals were from within Nairobi and were coming from health facilities that had no capacity to do serum bilirubin or phototherapy and/or exchange transfusion.

Beside the presence of neonatal jaundice, there was at least one primary comobid condition per neonate. Neonatal sepsis was the most common primary comorbidity, accounting for 63.6% of the comorbidities. Neonatal sepsis also had a significant association with total bilirubin ($p=0.003$). All the other comorbidities had no significant association with serum bilirubin levels ($p>0.005$). At least one other study has demonstrated no association between asphyxia, RDS, infections or severity of illness with TcB.[37]

Blood culture results were available for 140 patients. Of these, 14% were positive for various organisms. This percentage is lower than the 49.3%, 39.3% and 26.8% found in previous studies in the newborn unit at KNH by Hooker, Musoke and Malenga, and Kumar, respectively.[67-69] There was a significant association between blood culture positivity and death ($p=0.027$) but not with TSB ($p=0.258$).

The short-term clinical outcome of the interventions was documented as normal (75.5%), major sequelae (10.5%), or dead (14%). The finding of neurological sequelae of 10.5% in this study is lower than that by English et al and Wolf et al possibly because outcome in this study was purely in-hospital. [10, 66]

As shown on table 14, there was a significant association between poor outcome (major neurological sequelae or dead) and serum bilirubin ($P<0.001$). Patients with normal outcome (i.e. the reference group) had lower mean total bilirubin (288.7 µmol/l) whereas those who died or survived with major sequelae had higher mean total bilirubin of 325.6 µmol/l and 509.9 µmol/l, respectively. Those who died had lower mean TSB compared to those who survived with major sequelae, possibly because death was mainly due to the severity of the primary comorbidity (especially neonatal sepsis) and not just the hyperbilirubinaemia.

The Ingram icterometer is simple, practical and reliable in determining serum bilirubin levels transcutaneously. In this study a high correlation coefficient ($r= 0.78$) has been demonstrated between icterometer readings and the TSB. This is similar to the finding in the Turkey study.[2] Previous studies concluded that if the icterometric measurement was 3 or lower in a full-term infant, it was not necessary to measure serum bilirubin levels.[2, 44] Most studies have used a TSB cut-off of 221 µmol/l (at icterometer index of 3) as the threshold for significant

hyperbilirubinaemia, which level corresponds to the 40th percentile on the bilirubin normogram shown in appendix II.

In this study, the icterometer reading of ≥3 showed sensitivity, specificity, PPV and NPV of 99%, 55.3%, 86%, and 95.5% respectively, for detecting TSB of > 221 μmol/l. These findings are comparable to those of other studies as shown in the summary table 3.[2-6] For example, the study in Turkey showed sensitivity, specificity, PPV, and NPV of 100%, 48%, 29% and 100% respectively. [2] The Indian study used a cut-off TSB of 171 μmol/l (10 mg/dl), which is lower than the cut-off of 221 μmol/l used in this study.[5] It showed sensitivity, specificity, PPV and NPV of 97%, 71%, 78% and 94% respectively. The American study showed sensitivity, specificity, PPV and NPV of 82%, 74%, 38% and 95.7%, respectively.[3]

The icterometer at a cut-off of 3 was therefore quite sensitive (99%) compared to the American study at 82%. [3] This high sensitivity suggests it may be suitable for screening purposes especially in the health facilities with no capacity to do serum bilirubin tests. This will ensure that such neonates are picked up and referred early to health facilities where serum bilirubin tests and other interventions can be done.

The icterometer has a high negative predictive value (95.5%) meaning that those neonates that it classifies as having no significant jaundice are most likely to have serum bilirubin ≤ 221 μmol/l and would therefore require no blood tests or active intervention in terms of phototherapy or exchange transfusion. This NPV is within the range for the other studies.[2-6] However, in practice this means that one in 22 babies said to have 'insignificant jaundice' according to the icterometer actually has a TSB of >221 μmol/l.

It however has a low specificity (55.3%), meaning that among those who are truly negative (TSB ≤221 μmol/l), the icterometer only picks up slightly more than half. This specificity is higher than that found in the Turkey study (48%), but lower than the rest of the other studies.[3, 5, 6] This may result into subjecting a number of neonates to blood tests, referral and active interventions hence a misuse of resources.

The PPV in this study (86%) at icterometer cut-off of 3 was higher than the rest of the studies shown in the summary table 3 possibly due to differences in prevalence of jaundice at TSB > 221

μmol/l. The lowest PPV was 29% found in the Turkey study.[2] This study finding shows that when the icterometer classifies a neonate as having significant hyperbilirubinaemia, it is most likely that the neonate has TSB >221 μmol/l. This is a justification to proceed with a serum bilirubin test before initiating phototherapy and/ or exchange transfusion.

In this predominantly in-patient population comprising very sick neonates, only 15.4% would be spared blood tests if the icterometer were to be used for screening unlike in the Turkey study which showed a 40% sparing rate. [2] But the risk of missing a neonate who may have required intervention is minimal (4.5%) at this icterometer cut-off index of 3.

The ROC curve was used for exploratory analysis of the icterometer at various cut-offs (figure 4). The area under curve (AUC) was 0.908. This value is approaching unity, the perfect state, which shows the strong correlation between icterometer readings and the total bilirubin.

From the exploratory analysis (table 9), a new cut-off of 3.5 offers a better specificity of 84%, but the sensitivity reduces to 85%. This means that we are likely to miss 15% of the neonates who might have required bilirubin test and active intervention. But it also means that of all those who do not require any intervention, we will only be subjecting 16% wrongfully to such interventions. Balancing a reduction in testing and resource use against an increased risk of missing a baby with a TSB >221 μmol/l is a difficult decision, but it may be prudent to recommend this cut-off of 3.5 only for those health facilities with the capacity to do serum bilirubin and offer the necessary interventions as soon as possible.

From the box-plot of actual bilirubin values for each icterometer index reading (figure 2) it is also clear that a reading of 4.5 or 5 should immediately prompt treatment and/or referral for possible exchange transfusion as the risk of having a TSB > 400 μmol/l is high.

If we were to use a cut-off of 2.5, then the sensitivity and specificity would be 99% and 23.7% respectively. This sensitivity is equal to that at a cut-off of 3. But this will reduce the specificity by more than 30%. Since this new cut-off offers no advantage over the test cut-off of 3, it is not recommended for routine screening purposes.

Based on the dermal zones of Kramer, the sole of the foot falls under zone five and is likely to appear jaundiced at bilirubin levels of >257 μmol/l.[16] Clinical assessment at the sole of the foot was done by simply applying pressure at the sole with the thumb until it blanched and documenting whether or not jaundice was present. Seventy three patients had significant clinical jaundice whereas seventy did not. The patients with clinical jaundice at the sole of their feet had a higher mean total bilirubin (413.1 μmol/l) compared to those without significant clinical jaundice (218.8 μmol/l).

An analysis of the performance of clinical assessment (at a TSB threshold of 257 μmol/l) revealed sensitivity, specificity, PPV and NPV of 67%, 74.5%, 80.8%, and 58.6% respectively. This shows that the test is only moderately sensitive and is therefore not a good screening tool for neonatal hyperbilirubinemia since it is likely to miss out more than one third of those who need some form of intervention. The sensitivity was even lower (61%) when the TSB threshold was decreased to 221 μmol/l (threshold for icterometer index of 3). It also has a poor NPV meaning that it is likely to miss out on nearly one half of those who need intervention by wrongly classifying them as having TSB < 257 μmol/l.

Errors from sampling of blood may have occured just like in the majority of other studies that compare TcB with TSB measured in serum by laboratory instruments that utilize diazo-based chemical methods. A collection of blood from newborns is often hemolyzed and in vitro hemolysis is recognized as a source of error in bilirubin measurements due to release of hemoglobin and other intracellular compounds that can interfere with chemical-based measurements of bilirubin.[70,71] In vitro hemolysis also represents the most common reason for the rejection of specimens in the clinical laboratory.[71,72] Even though the TSB was done within half an hour after TcB, this potential confounder cannot be completely ruled out in this study and may account for some of the very high TSB readings and some of the differences in TSB and TcB measures in the same patient.

Even under ideal laboratory conditions, interlaboratory variability of bilirubin measurement has been found to be significant.[70] It has also been reported that there are significant differences in TSB levels from blood drawn by heelstick method compared with blood obtained by venipuncture.[36] This study used blood drawn by heelstick and it is possible that the values may

have been different if blood was drawn by venipuncture. However, interlaboratory variability testing was not within the scope of this study.

11. STUDY LIMITATIONS

Given that this study was done at daytime from 9.00 am to 5.00 pm, it is difficult to tell how the instrument would perform at night in the absence of natural light. A similar study may have to be undertaken to determine the performance of the instrument at night in artificial lighting.

Transcutaneous bilirubin measurements depend largely on colour perception and this may vary from one individual to the other. It is therefore possible that a similar study undertaken by a different researcher would yield slightly or completely different results. Studies have also shown that skin colour may influence the performance of transcutaneous instruments.

The use of serum bilirubin as the gold standard assumes that it is a perfect test. This may not necessarily be true since studies have demonstrated wide variations in the performance of different laboratories. Some of the studies cited have used HPLC as the gold standard and this therefore makes comparison difficult.

This study did not evaluate the entire performance of clinical assessment based on the icteric dermal zones of Kramer. Only its performance at the foot (Kramer 5) was evaluated. A study to evaluate the performance of clinical assessment based on the five dermal zones may therefore be necessary.

The study population was term neonates and therefore the results of this study may not necessarily be generalisable to the preterm population. A similar study may have to be conducted among the preterms for possible comparison with the term babies.

12. CONCLUSIONS

The Ingram icterometer predicts TSB of > 221 μmol/l at a cut-off index of 3, with a sensitivity of 99% and a specificity of 55.3%, in term babies with clinically apparent jaundice. The risk of missing a neonate who needs intervention, at this threshold, is 4.5%, and the proportion of all jaundiced neonates who might be spared blood tests if screened first with the icterometer, is 15.4%.

Generally as the icterometer index increases, the sensitivity reduces while the specificity increases. As the icterometer index reduces, the sensitivity increases while the specificity reduces.

Clinical assessment of jaundice at the sole of the foot at a TSB cut-off > 257 μmol/l, has a sensitivity of 67% and specificity of 74.5%, with the risk of missing a neonate who needs intervention at 41.4%. When the TSB threshold is reduced to > 221 μmol/l (threshold for the icterometer test), the sensitivity and specificity are 61% and 76.3% respectively, with the risk of missing a neonate who needs intervention at 58.6%.

13. RECOMMENDATIONS

1. All neonates with jaundice should be screened with the icterometer at a cut-off of 3 for maximum identification rate, especially in those health facilities where serum bilirubin tests are not done, for purposes of early referral to hospitals with the ability to do serum bilirubin.
2. Clinical assessment of jaundice at the sole of the foot is not as accurate a screening tool because of its very low sensitivity and clinical screening should perhaps be replaced by the icterometer that at a cost of less than $20 each can be used thousands of times if it is not possible to provide access to accurate blood testing.

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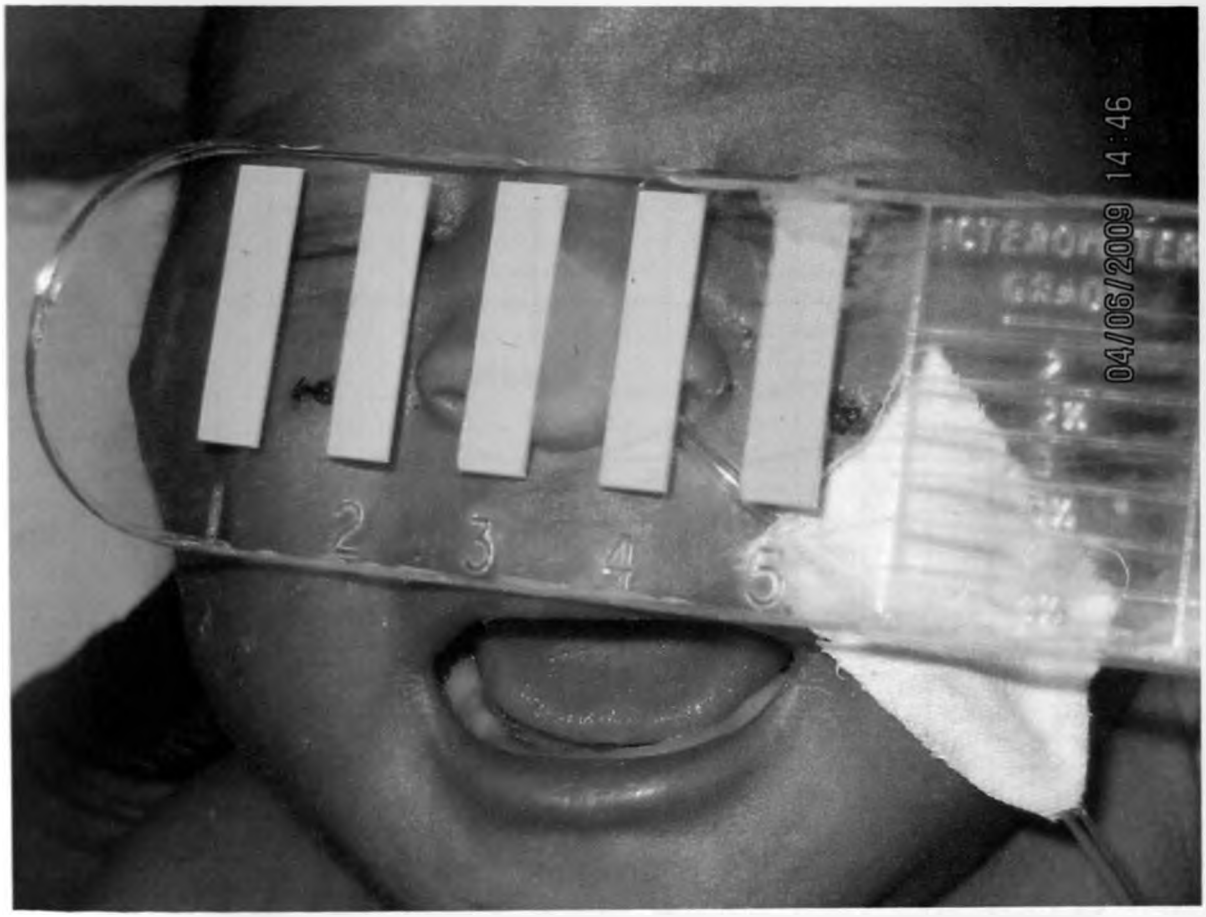
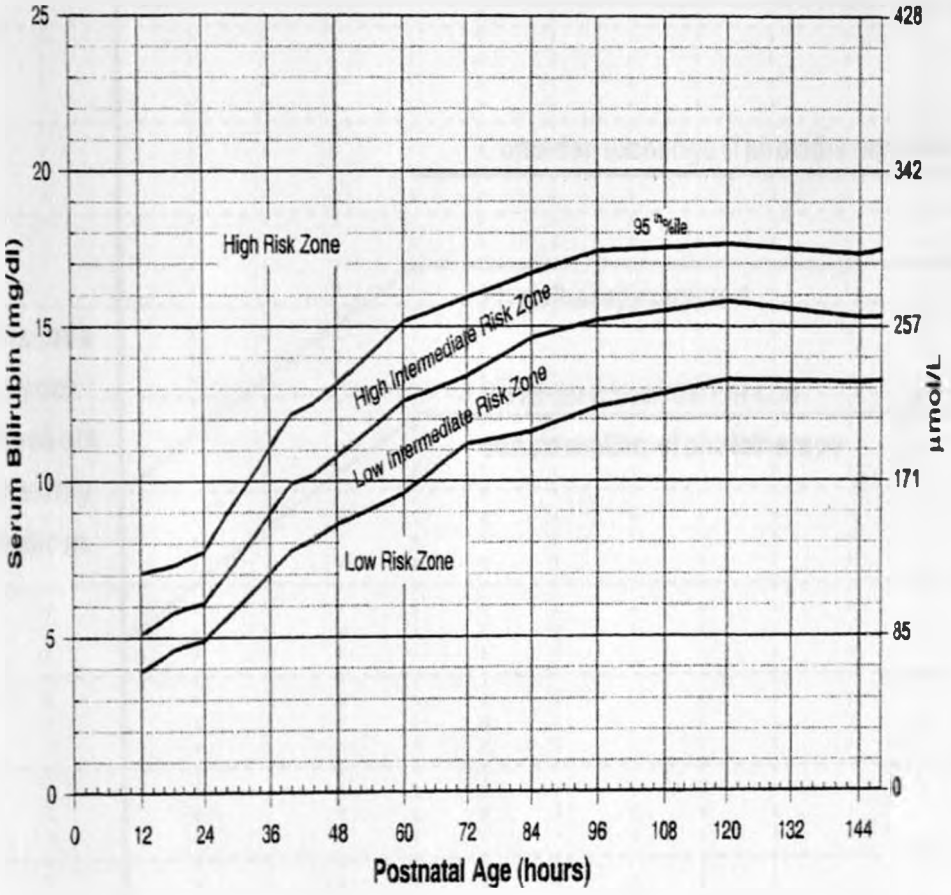
15. APPENDIX

15.1 PLACEMENT OF THE ICTEROMETER

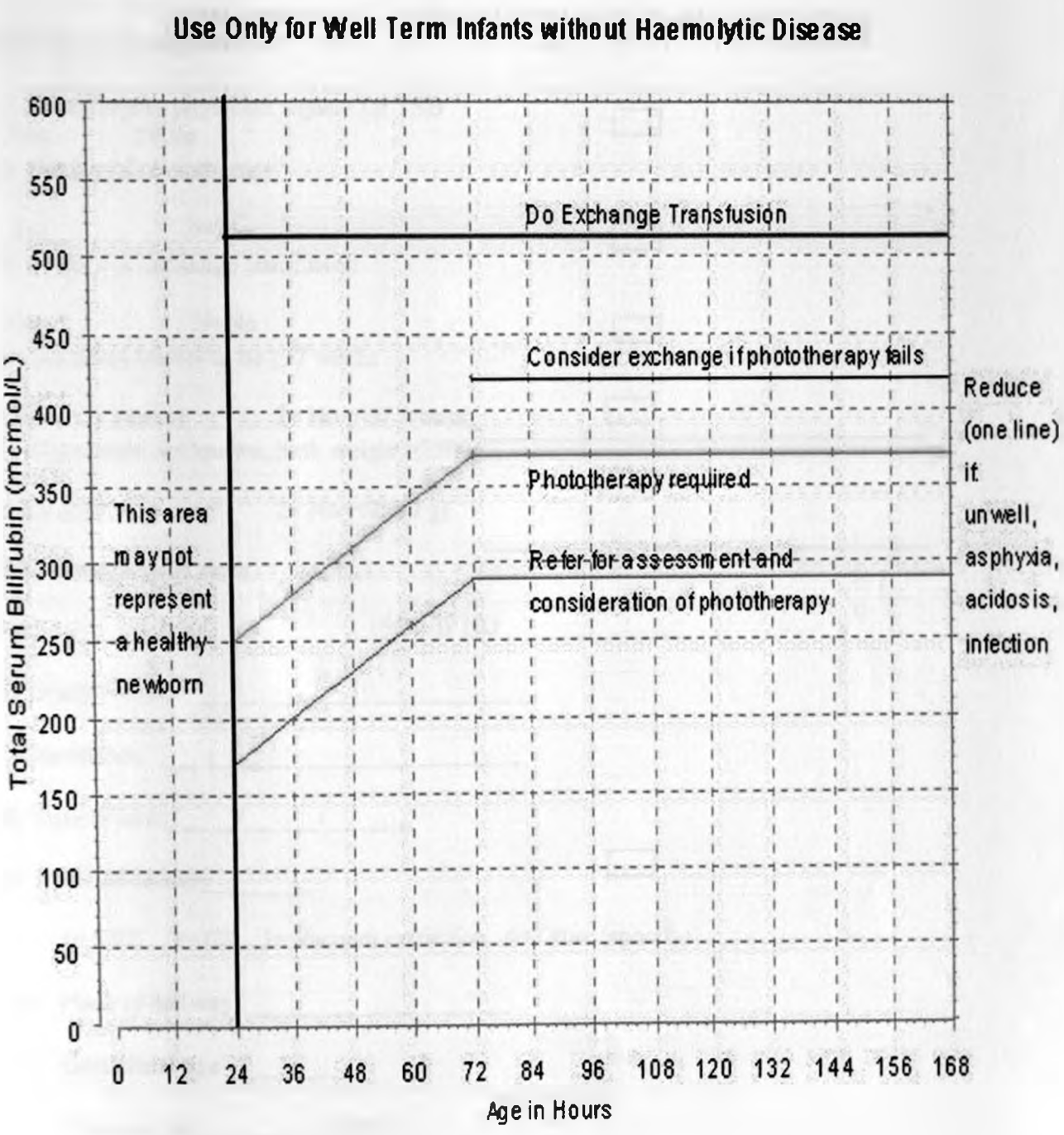


15.2 Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values



Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316

15.3 NORMOGRAM FOR WELL TERM NEONATES



15.4 STUDY PROFORMA

Eligibility screening criteria:

1) Jaundice plus physician request for TSB ☐

1= Yes 2= No

2) History of phototherapy

1= Yes 2= No ☐

3) History of exchange transfusion

1=Yes 2= No ☐

4) Gestation known to be ≥37 weeks

1= Yes (≥37 weeks) 2= No (<37 weeks) ☐

5) If gestation not known, birth weight ≥2500g ☐

1= Yes (≥2500 g) 2= No (<2500 g)

Socio-demographic data:

Date:____/_____/_____ OP/IP NO_____

6) Study Number _____

7) Residence _____

8) Date of birth _____/_____/_____

9) Mode of delivery_____ ☐

1= SVD 2= CS 3= Vacuum extraction 4= Other (specify)

10) Place of delivery_____

11) Gestational age _____

12) Postnatal age _____(days)

13) Birth weight _____ (grams)

14) Current weight_____ (grams)

15) Sex _____ ☐

1= male 2= female

16) Mode of feeding ☐

1= breastfeeding 2= formula 3= mixed 4=IV fluids

Medical history:

17) Referral from other health facility

1= Yes 2= No

18) Clinical diagnosis at admission _____

19) Confirmed infection by blood culture_____

20) Clinical assessment of jaundice on sole of feet

1= Present 2= Absent ☐

Interventions offered on follow-up:

21) Phototherapy alone

1= Yes 2= No ☐

22) Exchange transfusion alone ☐

1= Yes 2= No

23) Both phototherapy and exchange transfusion

1= Yes 2= No ☐

24) Final outcome at discharge

1= Normal
2= Dead
3= Major neurological sequelae (poor feeding, hypo/hypertonia, lethargy, arching, high-pitched cry, respiratory distress, persistent convulsions, stupor)

15.5 CLIENT CONSENT INFORMATION FORM

Study title: Evaluating the Ingram icterometer as a screening tool for significant neonatal hyperbilirubinaemia at the Kenyatta National Hospital

Investigator: Dr. Awuonda B. B. Onyango
Department of Paediatrics and Child Health, University of Nairobi

Supervisors: Dr. Florence Murilla, Lecturer University of Nairobi
Dr. Mike English, KEMRI WELLCOME TRUST Program, Nairobi
Prof. Fred Were, Asssociate professor University of Nairobi

Investigator's statement

I am Dr. Awuonda B. B. Onyango from the department of Paediatrics and Child Health of the University of Nairobi. I am carrying out a study titled, 'Evaluating the Ingram Icterometer as a screening tool for significant neonatal hyperbilirubinaemia at the KNH,' as part of my postgraduate training in the said department. The main objective is to determine the sensitivity and specificity of the icterometer compared to blood tests. I am requesting you and your baby to kindly participate in this study. Please read this consent information form carefully and ask me for any clarifications where you have any uncertainty.

Introduction

Jaundice is the yellow discoloration of the body of baby as a result of accumulation of a toxic chemical called bilirubin. This chemical may result into complications like convulsions, mental retardation and even death to the baby if it crosses over and injures some parts of the brain. Routinely infants with jaundice have a blood test done to determine the level of bilirubin, this chemical that causes yellowness of their body. This routine blood test will still be done on your baby as requested by the primary clinician. But in addition, I will also use the icterometer, which I will simply press on the baby's nose until it blanches, then match the colour of the nose with the corresponding yellow hue on the icterometer.

Benefits

This instrument has been used elsewhere for screening and was found to be a good predictor of the level and severity of jaundice. But it has not been routinely used in our country so we do not know how well it performs in our setting. My study will compare the icterometer results with those from the laboratory and if it proves accurate, then we can recommend it for the initial screening of neonatal jaundice to avoid unnecessary blood tests and pain to the babies. The results may not benefit your baby immediately but will benefit other babies in future once this study is completed. I will also make a follow-up to document what treatment was carried out on your baby and what the outcome was at the time of discharge from the hospital.

Risks

This test carries no risk to your baby. There are no invasive procedures involved here hence no harm to your baby. Refusal to participate will not jeopardize the treatment of your baby in any way. Your participation is voluntary. There will be no financial rewards to you for participating in the study.

Statement about confidentiality

The information will be obtained using coded questionnaires and will be kept in strict confidence. No specific information will be released to any person or agency without your written consent. We will discuss the findings in public and publish this study but not anything specific that could identify your baby. There will be no penalty if you so wish to withdraw from the study at any stage. You are free to ask me any questions or seek clarifications on the study procedure or on your role as the participants. I will try to answer you as best I can.

15.6 CONSENT FORM

Participant's statement

I ..... having been adequately explained to the study procedure, the risks and benefits, hereby agree to participate in the study. I understand that my participation is fully voluntary and I am free to withdraw from the study at any time. I have been given the opportunity to ask questions and seek clarifications, and these have been answered satisfactorily.

SIGNATURE ..... DATE .....

Investigator's statement

I.....declare that I have adequately explained to the above participant the study procedure, risks and benefits, and given him/her time for questions and clarifications. I have also tried to answer the questions to the best of my ability.

SIGNATURE..... DATE.....

In case you have any more issues related to this study, you can contact me on mobile phone number: 0721598901. If you have any ethical issues related to this study, you can also get in touch with the ethics and research committee chairperson at KNH, Tel: 726300-ext 44355.