# COMPARISON BETWEEN TRANSCUTANEOUS AND TOTAL SERUM BILIRUBIN MEASUREMENT IN MALAY NEONATES

**DR MAZRAH BINTI MOHAMED**

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (PAEDIATRICS)



**UNIVERSITI SAINS MALAYSIA**

**2021**

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## ACKNOWLEDGEMENT

***In the name of Allah, The Most Gracious and The Most Merciful, many thanks to Him for granted me with His grace to complete this thesis. All praise to Allah.***

My thesis would not have been possible without the kind support and help of many individuals. I would like to express my special thanks of gratitude to my supervisor, Associate Professor Dr Ariffin as well as other co- supervisor, Associate Professor Dr Noorizan and Dr Nor Rosidah who gave me the golden opportunity to do this wonderful project. Their patience, guidance and support helped me along the way in completion of this project.

Secondly, I would also like to thank my parents, my family, my colleagues and Adam Hafizuddin – my helpful research assistant who helped me a lot in preparing and finalizing this project within the limited time frame. Without their countless and endless support and encouragement, probably I would not be able to finalize this study.

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Many wonderful thanks to all the junior doctors, colleagues and nurses in the neonatal wards for helping me collecting the data and giving me chance to complete this study. I count my blessings every day to be surrounded by these thoughtful and helpful people. Their support is invaluable and is very much appreciated.

# CHAPTER 1:

# THE PRELIMINARIES

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## LIST OF ABBREVIATION

AAP : American Society of Pediatrics

SCN : Special care nursery

TcB : Transcutaneous bilirubin

TSB : Total serum bilirubin

TcB forehead : Transcutaneous bilirubin measured at forehead

TcB sternum : Transcutaneous bilirubin measured at sternum

## ABSTRACT

**Background:** Transcutaneous bilirubinometer is a portable, painless and non-invasive device to measure bilirubin. This study aims to investigate the reliability of Dräger Jaundice Meter JM-105 for the screening of neonatal jaundice in Malay neonates.

**Methods:** Prospective cross-sectional study conducted in a tertiary university hospital involving 130 jaundiced neonates who required serum bilirubin determination from day 2 to day 7 of life. Paired bilirubin samples of total serum bilirubin (TSB) and transcutaneous bilirubin (TcB) were obtained. TcB were measured at the neonates' forehead and sternum. The TcB were measured using JM-105.

**Results:** There were 130 paired samples of TSB and TcB. The mean TSB was 232 µmol/L. The mean TcB measured at forehead and sternum were 222 µmol/L and 223 µmol/L, respectively. The mean difference between TSB and TcB was 10 µmol/L at forehead and 9 µmol/L at sternum. Strong positive correlation between TSB with mean TcB forehead (r=0.82) and TcB sternum (r=0.80), and strong correlation (r=0.91) between TcB forehead and TcB sternum.

**Conclusion:** Our study demonstrated strong correlation between TcB values and TSB values. TcB measured at forehead or sternum is a good alternative as a non-invasive screening tool for non-severe hyperbilirubinemia in Malay neonates.

(207 words)



**Keywords:** *Transcutaneous bilirubin, total serum bilirubin, JM-105, jaundice, neonate*

## ABSTRAK

**Latar belakang:** Alat penyukat bilirubin kulit adalah alat yang mudah alih, tidak menyakitkan dan tidak invasif yang digunakan untuk mengesan tahap bilirubin di dalam darah. Kajian ini bertujuan untuk mengkaji kebolehpercayaan Dräger Jaundice Meter JM-105 sebagai alat pengukur tahap kuning bayi di kalangan orang Melayu.

**Kaedah:** Kajian prospektif ini yang dilakukan di hospital universiti yang melibatkan 130 bayi yang memerlukan penilaian tahap bilirubin dalam darah dari hari ke 2 sehingga hari ke 7 selepas kelahiran. Pasangan sampel yang terdiri daripada tahap kuning darah bayi (TSB) dan tahap kuning kulit bayi (TcB) diambil. TcB disukat di dahi dan dada bayi. TcB disukat menggunakan JM-105.

**Keputusan:** Sebanyak 130 pasangan sampel TSB dan TcB diambil. Purata TSB adalah 232 µmol /L. Purata TcB yang diukur di dahi dan dada masing-masing adalah 222 µmol /L dan 223 µmol /L. Perbezaan purata antara TSB dan TcB dahi adalah 10 µmol /L dan perbezaan purata antara TSB dan TcB dada adalah 9 µmol /L. Positif korelasi yang baik antara TSB dengan purata TcB dahi ($r = 0.82$) dan TcB dada ($r = 0.80$), dan korelasi antara purata TcB dahi dan purata TcB dada ($r = 0.91$) adalah baik.

**Kesimpulan:** Kajian kami menunjukkan korelasi yang baik antara nilai TcB dan nilai TSB. TcB yang disukat di dahi atau di dada adalah kaedah alternatif yang baik dan bukan invasif untuk pemeriksaan tahap penyakit kuning bayi Melayu yang tidak serius.

(231 perkataan)



**Kata kunci:** *Alat penyukat bilirubin kulit, tahap bilirubin darah, JM-105, penyakit kuning , bayi*

# CHAPTER 2:

# THE TEXT

## INTRODUCTION

Neonatal jaundice is one of the commonest conditions in neonate. This is due to hyperbilirubinemia, which commonly occurs, especially in the first week of neonatal life (1). It was reported as the most frequent cause for hospital readmission during the early neonatal period (2). Most cases are benign, but rarely severe neonatal hyperbilirubinemia can be associated with kernicterus. Other than high mortality rate, kernicterus survivors usually suffer complications such as athetoid cerebral palsy, high frequency hearing loss and intellectual disability (3). This severe neonatal hyperbilirubinemia and its sequelae can be prevented by appropriate serum bilirubin monitoring and early treatments with phototherapy and exchange blood transfusion.

Bilirubin levels can be evaluated via several methods. Total serum bilirubin (TSB) measured by biochemical laboratory is the most accurate method for bilirubin level determination. It is an invasive method and multiple needle pricks may result in infection, pain and stress to the neonates (4). The turnaround time for bilirubin test results often delay the management of neonatal hyperbilirubinemia. Serum bilirubin level also can be estimated via visual method according to Kramer's rule (5). It is roughly estimated according to cephalocaudal progression of jaundice. This method is imprecise as it requires clinical expertise and is affected by lights and clothes (6). Recently, transcutaneous bilirubinometer which uses photometry to detect bilirubin level has been used as an alternative to estimate bilirubin level.

Transcutaneous bilirubinometer is a portable, painless and non-invasive device. The bilirubin is estimated by pressing the device probe either to the neonatal forehead or sternum. It also can give an immediate result which later can reduce the burden to the health care providers.

The first transcutaneous bilirubinometer was introduced in the 1980s and the technologies related to the devices are tremendously evolving over these past few decades. Since then, numerous studies using various transcutaneous bilirubinometer devices have been done to prove its accuracy and sensitivity. The good correlation between TSB and transcutaneous bilirubin (TcB) values has made transcutaneous bilirubinometer a valuable screening tool for TSB in hyperbilirubinemia management worldwide (7,8). The American Academy of Paediatrics even recommends pre-discharge evaluation of bilirubin levels by measuring TSB or TcB in all neonates (8). Some countries as India and Mongolia also had conducted studies to implement the transcutaneous bilirubinometer as the screening tool for neonatal jaundice in their rural and limited resources population (9,10).

However, there were only limited studies done using transcutaneous bilirubinometer in our country (11). Thus, this study was aimed to investigate the reliability of transcutaneous bilirubinometer, which is Dräger Jaundice Meter JM-105 for the screening of Malay neonatal jaundice.

### 2.1.1 Study Protocol Submitted for Ethical Approval

**TITLE: COMPARISON OF TRANSCUTANEOUS AND TOTAL SERUM BILIRUBIN MEASUREMENT IN KELANTAN NEONATES**

**NAME OF STUDENT**:

DR MAZRAH BINTI MOHAMED

M. MED (PAEDIATRICS)

**NAME OF SUPERVISOR**:

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3. **DR NOR ROSIDAH IBRAHIM**
   - LECTURER, DEPARTMENT OF PAEDIATRIC, HOSPITAL USM

## 1.0 INTRODUCTION:

Neonatal jaundice is one of the commonest conditions in neonate. Most are benign but rarely severe neonatal hyperbilirubinemia can be associated with kernicterus. Other than high mortality rate, the kernicterus survivors usually suffer sequelae such as athetoid cerebral palsy, intellectual disability and high frequency hearing loss.

These sequelae are actually preventable by appropriate screening and proper monitoring of serum bilirubin in neonatal period. Frequent monitorings of serum bilirubin are needed due to rapid and early rise of serum bilirubin before the signs of bilirubin encephalopathy occurs. However, this resulted in multiple and frequent pricking to the infants during the illness.

Transcutaneous bilirubinometer devices had been invented and and the technologies related to the devices are tremendously evolving over these past few decades. Study by Bhutani *et al.* (2000) had revealed that transcutaneous bilirubin (TcB) testing by various devices has been shown to accurately estimate total serum bilirubin (TSB) level in term and near-term neonates.

Thus, the transcutanenous bilirunometer can be used as an alternative method for screening of neonatal jaundice. They are painless, non - invasive, and provide immediate result which later can reduce the burden to the health care cost and providers.

## 2.0 LITERATURE REVIEWS

Nowadays, there are various transcutaneous bilirubin devices in the market which are widely used throughout the world due to its ease of use and non-invasive in nature. Their ability to provide superior performance over visual assessment and to give immediate results made them as a choice for neonatal jaundice screening as suggested by Engle *et al. (2014*). Usage of

transcutaneous bilirubinometer will also reduce the number of inpatient total serum bilirubin determinations, hence it will reduce laboratory hospital workload and ultimately reduction in hospital expenses when comparing to serum bilirubin.

Many studies reported various performances of currently available transcutaneous bilirubinometers. Akahira-Azuma *et al.* (2013) performed a prospective study in 2011 which involved 53 term and late preterm infants. The transcutaneous bilirubin were measured at forehead and midsternum using JM-103 bilirubinometer device. The study showed strong correlation of TcB at both forehead and midsternum with TSB measured in the laboratory with R2 =0.79 at forehead and R2 =0.78 at midsternum as their result.

Mansouri *et al.* (2015) also performed a study in 2015 involving 200 term neonates. They used Bilirubinometer model BR-5000N which measures the transcutaneous bilirubin three times on the forehead. The study observed a high correlation ($r = 0.89$) between TSB and TcB. They also revealed the sensitivity and specificity of cutaneous bilirubin measurement which were 95.1% and 68%, respectively.

In one of the studies involving Asian population, Panburana *et al.* (2010) also assessed the accuracy of JM-103 meter. 224 paired of TcB-TSB specimens from 74 term and near term newborns were collected in 2008. In this study, forehead TcB were measured by the transcutaneous bilirubinometer JM-103 and the results were compared to total serum bilirubin (TSB) level. The study showed linear correlation of TcB and TSB values with significant correlation coefficient ($r = 0.81$, $p < 0.001$).

Taylor *et al.* (2015) performed a retrospective study in 2015 using Bilicheck and JM-103 bilirubinometer devices. Data were collected from 27 nursery sites in Unites States over two

week periods and out of the 8319 TcB measurements taken, over 925 TSB levels matched. This large scale study showed good correlation between paired TcB-TSB measurements (r=0.78). The investigators concluded TcB measurement provided a reasonable estimation of TSB levels especially in healthy newborns.

Only few local Malaysian studies has been performed. Boo and Ishak (2007) assessed Bilicheck transcutanoeus bilirubinometer in a tertiary centre from January 2003 to January 2005. This retrospective study involved 345 term infants. The researchers found good correlation between TSB and TcB measured at forehead ($r = 0.80$, $p < 0.0001$) and the sternum ($r = 0.86$, $p < 0.0001$). They also concluded that high TSB more than 300 μmol/L can be predicted with 100% sensitivity at certain TcB cut-off levels measured at the forehead and sternum of the infants.

## 3.0 JUSTIFICATION TO CONDUCT THE STUDY:

At present, there is no reported publication to validate Dräger Jaundice Meter JM-105 as a screening tool for neonatal jaundice in term and late preterm neonates in Malaysia.

## 4.0 STUDY OBJECTIVES:

### 4.1 GENERAL OBJECTIVE

To investigate the accuracy of Dräger Jaundice Meter JM-105 for the screening of neonatal jaundice

### 4.2 SPECIFIC OBJECTIVE

1. To determine the mean difference of total bilirubin between serum bilirubin (TSB) and transcutaneous bilirubin (TcB) level measure by Dräger Jaundice Meter JM-105

2. To determine the correlation between serum bilirubin (TSB) and transcutaneous bilirubin (TcB) measure by Dräger Jaundice Meter JM-105

3. To determine the mean difference between transcutaneous bilirubin (TcB) level measure by Dräger Jaundice Meter JM-105 at sternum and forehead.

## 5.0 METHODOLOGY

**5.1** Study design:

This is a prospective cross sectional study.

**5.2** Period of study:

The study will be conducted from 1/7/2018 until 31/8/2018.

**5.3** Reference of population:

Term and late preterm neonates with clinical jaundice in Malaysia.

**5.4** Source population:

Term and preterm neonates with clinical jaundice requiring serum bilirubin determination in Hospital USM.

## 6.0 SAMPLING METHODS:

Convenience sampling method are applied for this study.

## 7.0 SAMPLE SIZE DETERMINATION:

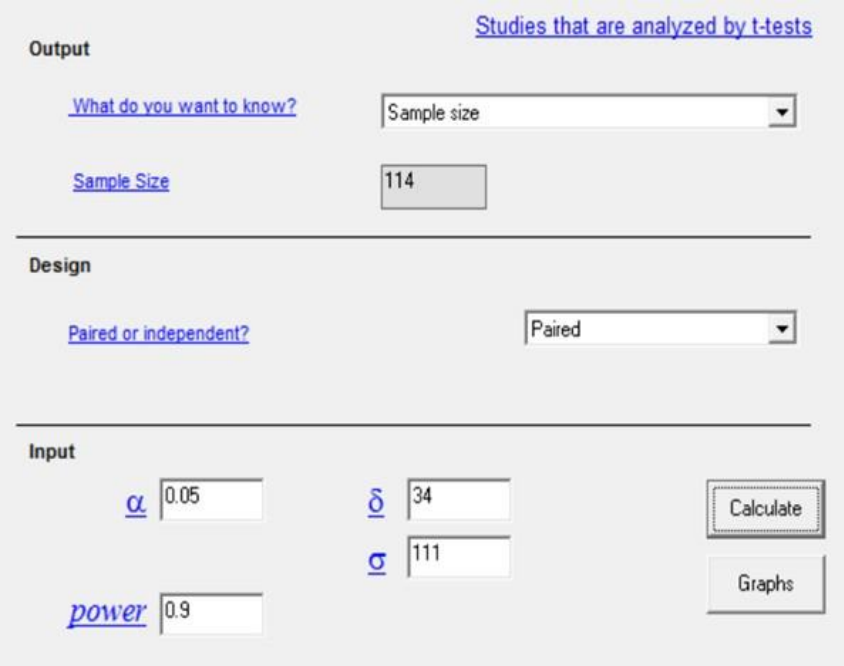
Sample size calculation were done for each specific objective.

**a) To determine the mean difference of total bilirubin between serum bilirubin (TSB) and transcutaneous bilirubin (TcB) level measure by Dräger Jaundice Meter JM-105**

Sample size is calculated using t-test calculator with paired sample size from the PS: Power and Sample Size Calculation version 3.1.2, 2014.

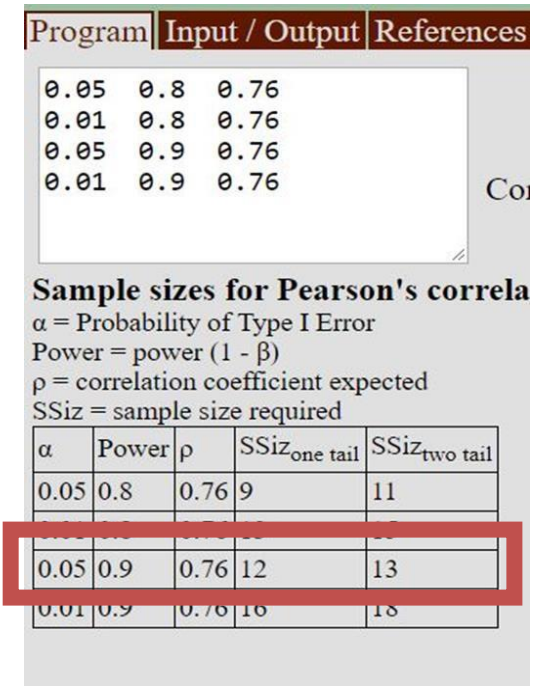
A sample size of 114 is calculated in order to detect a mean difference between TcB And TSB levels of at least 34 umol/L with a type-one error of 0.05 and statistical power of 90%. The standard deviation size calculation (111) was derived from Kitsommart *et al.* (2017).

Considering 10% of drop out, total sample size required are 126 participants.



**b) To determine the correlation between TSB and TcB measure by JM-105**

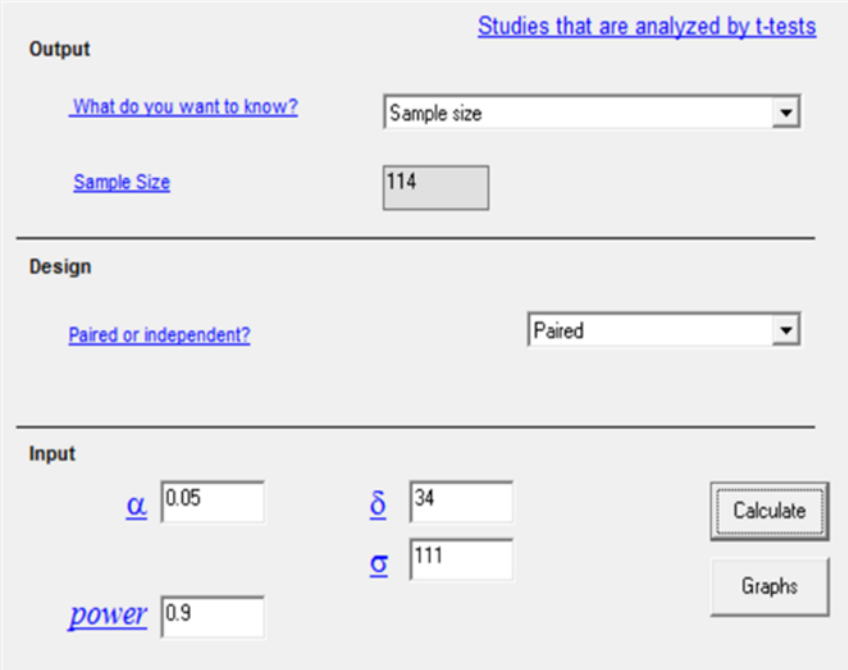
We calculate the sample size using statistic software for Pearson correlation coefficient calculator form https://www.statstodo.com/SSizCorr_Pgm.php .




A sample size of 13 infants with a type-one error of 0.05 and statistical power of 90% based on r = 0.76 according to previous study by Kitsommart *et al.* (2017).

Considering 10% of drop out, total sample size required for this objective are 15 participants.

**c) To determine the mean difference between TcB level using JM-105 measure at sternum and forehead**.




Sample size is calculated using t-test calculator with paired sample size from the PS: Power and Sample Size Calculation version 3.1.2, 2014.

A sample size of 114 is calculated in order to detect a mean difference between TcB and TSB levels of at least 34 umol/L with a type-one error of 0.05 and statistical power of 90%. The standard deviation size calculation (111) was derived from Kitsommart *et al.* (2017).

Considering 10% of drop out, total sample size required are 126 participants.

In conclusion, to determine the mean difference of total bilirubin measure by serum bilirubin (TSB) and transcutaneous bilirubin (TcB) in term and late preterm neonates; 126 paired sample of TSB-TcB are needed to detect a mean difference of 34 umol/l with SD 111 umol/l, power of 90% and alpha of 0.05 with 10% dropped out.

## 8.0 INCLUSION/ EXCLUSION CRITERIA

**8.1** Inclusion criteria:

Neonate who is clinically jaundice and:

a) More than 35 weeks of gestation

b) Birth weight more than 2 kilograms.

c) Age between 24 to 168 hours after birth (Day 2 to day 7 after birth).

**8.2** Exclusion criteria:

a) Severely ill neonates.

b) Congenital lethal malformation.

c) Neonatal jaundice who has been treated with phototherapy.

## 9.0 VULNERABILITY OF THE INFANT

As the neonates are vulnerable group, they will be investigated and treated according to the standard hospital protocol and Clinical Practice Guidelines (CPG) for neonatal jaundice from the Ministry of Health (MoH) based on the routine serum bilirubin results.

## 10.0 RECRUITMENT OF INFANT AND INFORMED CONSENT SEEKING

Parents will be explained by the researchers regarding this study for consent.

## 11.0 ASSENT FORM REQUIREMENT

Not applicable

## 12.0 RANDOMIZATION, MATCHING, BLINDING

Not applicable

## 13.0 STUDY LOCATION:

Hospital Universiti Sains Malaysia is a tertiary centre which usually manage neonatal jaundice cases.

The sites for TcB measurement are:

a) Emergency department Hospital USM

b) Postnatal wards Hospital USM

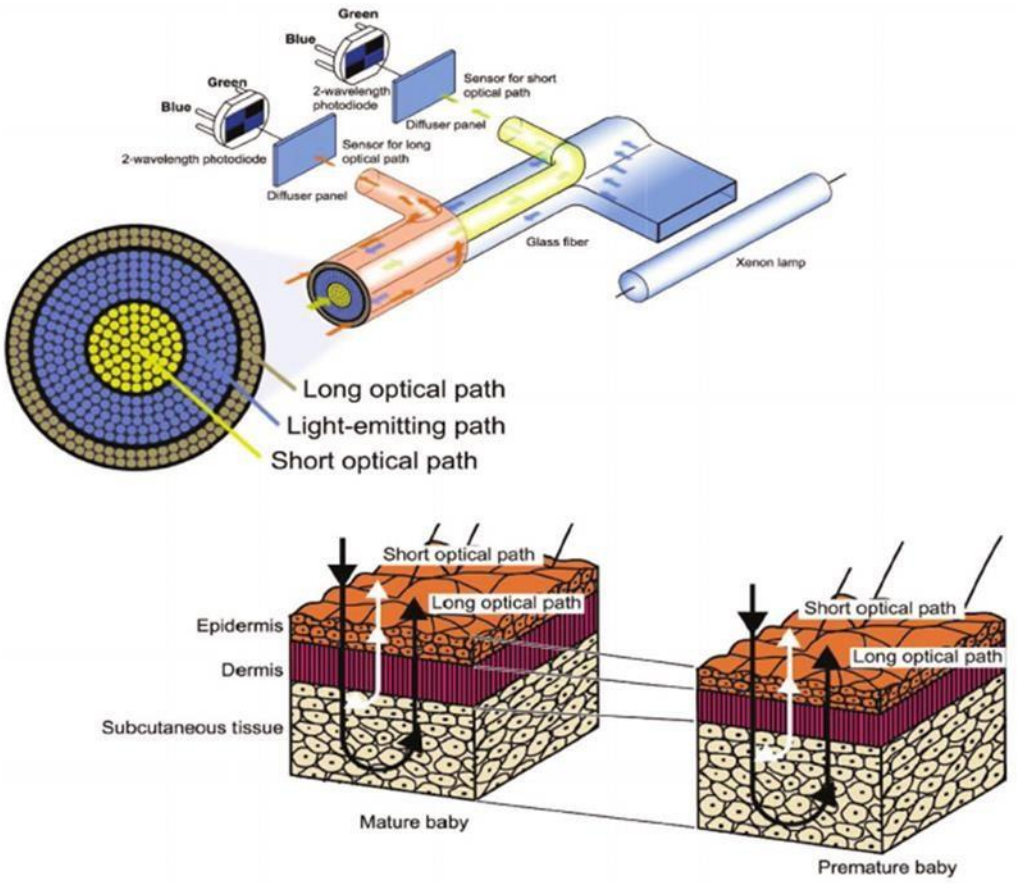
c) Neonatal wards Hospital USM

## 14.0 RESEARCH TOOL:

Dräger Jaundice Meter JM-105 is a transcutaneous bilirubinometer. It utilizes two optical pathways; a short pathway intended to reflect the composition of the skin and shallow subcutaneous tissue and a longer pathway that is more reflective of the deeper layers of the subcutaneous tissue. Both light pathways return to blue and green photocells.

Subtraction of the optical densities of the shallow pathway provides a focus on the deeper tissue. Therefore, this instrument attempts to correct for the presence of chromophores other than bilirubin by isolating them according to differences in their distribution across skin layers. It will directly provide a value representing the bilirubin concentration (mg/dL or μmol/L).

There are no disposables associated with its use. In between patients, the probe will be cleaned using alcohol swab to prevent cross infection. It is daily calibrated according to the manufacturer's instructions.




**Principal of bilirubin measurement of JM-103 and JM-105**

## 15.0 METHOD OF INTERVENTION

Any jaundiced infant who fulfills inclusion and exclusion criteria will be asked for consent from their parents or legal guardian to be enrolled in this study. Routine serum bilirubin (TSB) are taken according to standard operating procedure (SOP) and/or clinical judgement as requested by the managing team (emergency or paediatric team). The serum bilirubin will be sent immediately to chemical lab, maximum time is within 1 hour.

Two transcutaneous bilirubin (TcB) measurements will be recorded at forehead and sternum respectively using the Dräger Jaundice Meter JM-105 within 1 hour of serum bilirubin sampling. TcB will be measured by trained staff consist of an MMed Paediatric student and a research assistant. Further management of the jaundice will be decided by the doctor in charged based on the serum bilirubin level.


**Pictures showing the procedures to measure transcutaneous bilirubin at infants' forehead and sternum using Dräger Jaundice Meter JM-105.**

## 16.0 CONTROL GROUP

A paired sample consist of serum bilirubin level and transcutaneous bilirubin level measure at forehead and sternum will be taken from the same patient. The control will be the routine sample of serum bilirubin level.

## 17.0 POTENTIAL RISK TO INFANT

To date; there is no known potential harmful risk of bilirubinometer screening to human. There will be minimal risks to patient in terms of timing to get bilirubin reading by Dräger Jaundice Meter JM-105. There is no extra blood taking done for research purpose.

## 18.0 DIRECT AND INDIRECT BENEFIT TO INFANT

It is a non –invasive, painless procedure and it provides us an alternative method in measuring the bilirubin level. There will be no added cost charged to the patients. We hope that the outcome and information regarding this research will be beneficial to future patients.

## 19.0 SPECIMEN HANDLING

The transcutaneous bilirubin level will be measured using Dräger Jaundice Meter JM-105 at the forehead and sternum within 1 hour of serum bilirubin sampling. The serum bilirubin will be sent immediately to chemical lab, maximum time is within 1 hour. The serum bilirubin sample will be processed at laboratory by the colourimetric method using Architect C800 and Olympus AU400 and will get the result in same unit of Dräger Jaundice Meter JM-105 ; umol/L. After the process, the serum bilirubin sample will be kept for 2 days and then will be discarded to the yellow bin waste (as per laboratory standard protocol).

## 20.0 DURATION OF HUMAN INFANT INVOLVEMENT

During serum bilirubin sampling for determination of the jaundice level, the transcutaneous bilirubin level will be measured at the sternum and forehead from the same patient. The whole procedure including routine serum bilirubin sampling is usually about 10 to 20 minutes.

## 21.0 WITHDRAWAL CRITERIA

The parents or legal guardian have the rights to withdraw his/her baby's participation from this study at any time.

## 22.0 INCENTIVE, COMPENSATION OR REIMBURSTMENT

Involvement of the infant in this study is totally voluntary. No incentive or compensation will be given as reward.

## 23.0 DECLARATION OF CONFLICT OF INTEREST

My supervisor and I do not have any special interest in this product or the company, hence the result will be unbiased as we don't have any obligation to submit report to the Dräger Company.

## 24.0 HANDLING PRIVACY AND CONFIDENTIALITY ISSUE

Infant medical information will be kept confidential by myself and staff and will not be made publicly available unless disclosure is required by law.

Data obtained from this study does not identify infant individually but the collective result will be published for knowledge purposes.

The original medical records may be reviewed by the researcher, the Ethical Review Board for this study, and regulatory authorities for the purpose of verifying clinical trial procedures and/or data. The medical information may be held and processed on a computer.

## 25.0 COMMUNITY SENSITIVITIES & BENEFITS

It will provide the researches and staff with invaluable experiences managing the neonatal jaundice using this bilirubinometer device.

## 26.0 PROPOSED DATA ANALYSIS

The data will be processed and analysed using IBM SPSS Statistics version 22.

Numerical data are presented as mean (SD) or median (IQR) according to data distribution. The categorical data will be expressed as number and percentage.

The mean difference between total serum bilirubin (TSB) and transcutaneous bilirubin (TcB) will be evaluated by paired t- test.

The correlation between two bilirubin levels will be determined by Pearson correlation coefficient test.

The mean difference between TcB measure at the forehead and sternum will be evaluated using paired t-test.

## 27.0 EXPECTED RESULT / DUMMY TABLES

**Table 1: Clinical characteristics of infants (N = )**

| Characteristic | n (%) | Mean (SD) |
|---|---|---|
| **Gestational age** | | |
| 35-37weeks | | |
| >37weeks | | |
| **Birthweight (gram)** | | |
| 2000 – 2500 | | |
| >2501 gram | | |
| **Postnatal age during presentation (hour)** | | |
| 24 – 72 | | |
| 72.1 - 168 | | |
| **Feeding mode** | | |
| Exclusively breast feeding | | |
| Mixed feeding | | |

**Table 2: Mean difference between TSB and TcB level (forehead)**

| | Mean (SD) TSB | Mean (SD) TcB | Mean Difference 95% CI | T Stats (df) | *p- value* |
|---|---|---|---|---|---|
| **Total Bilirubin level** | | | | | |

**Table 3: Mean difference between TSB and TcB level (sternum)**

| | Mean (SD) TSB | Mean (SD) TcB | Mean Difference 95% CI | T Stats (df) | *p- value* |
|---|---|---|---|---|---|
| **Total Bilirubin level** | | | | | |

**Figure 1: Correlation between serum bilirubin levels and TcB forehead**

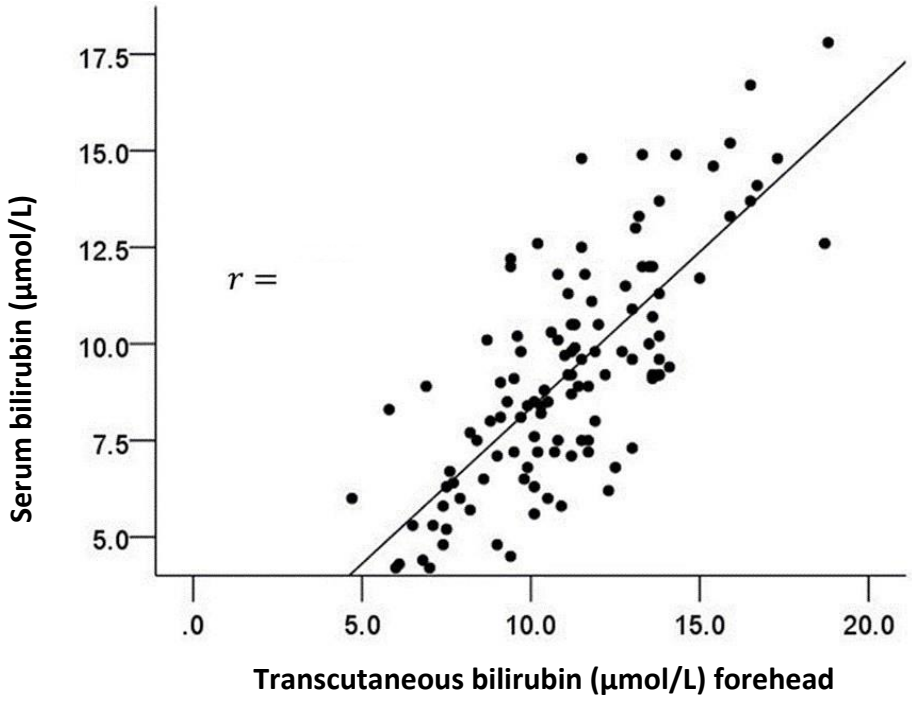


**Figure 2: Correlation between serum bilirubin levels and TcB sternum**

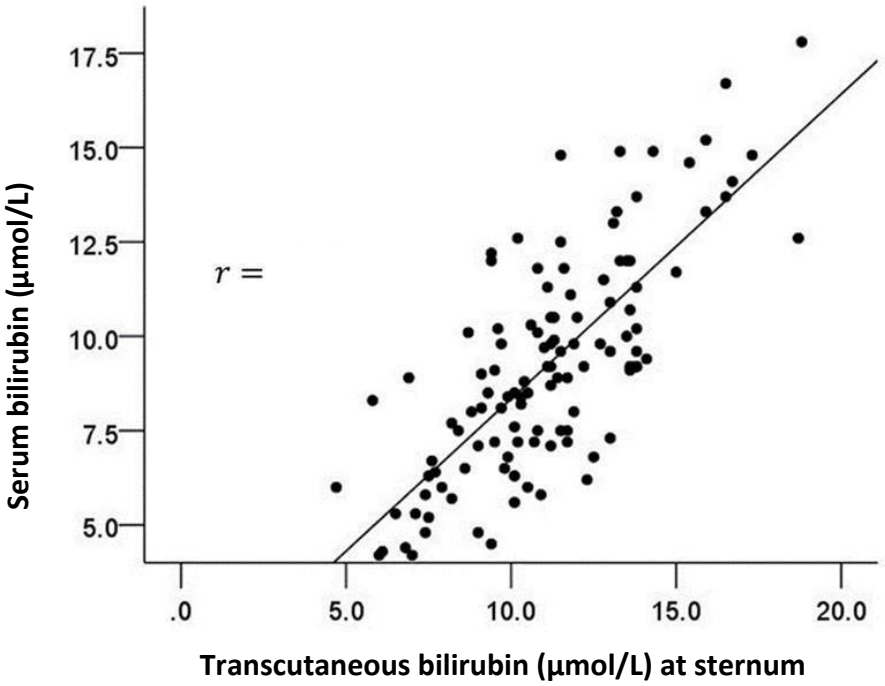



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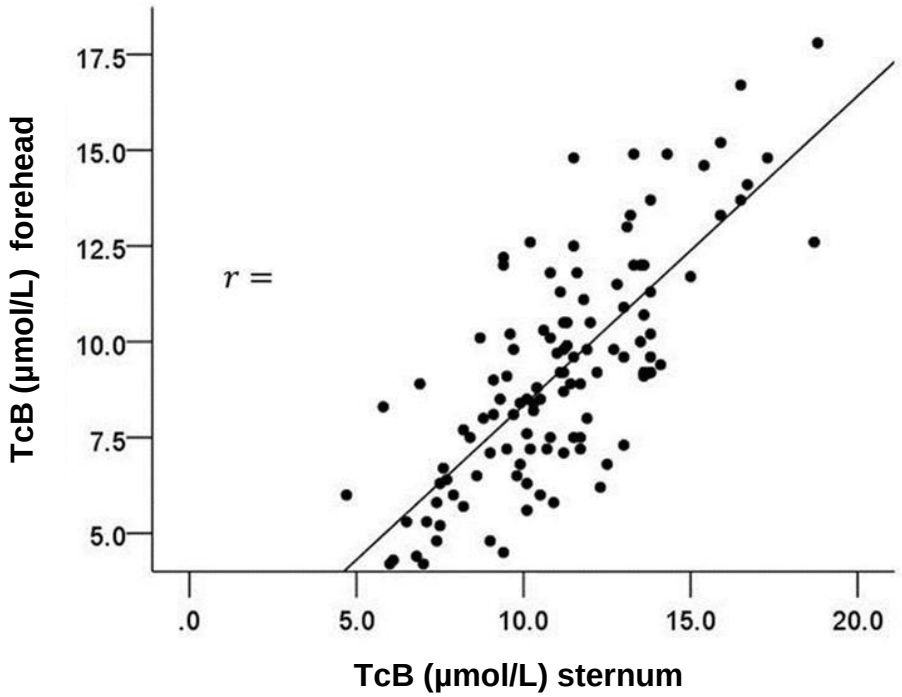
**Table 4: Mean difference between TcB level at sternum and forehead**

| | Mean (SD) TcB sternum | Mean (SD) TcB forehead | Mean Difference 95% CI | T Stats (df) | *p- value* |
|---|---|---|---|---|---|
| **Total Bilirubin level** | | | | | |

**Figure 3: Correlation between TcB at sternum and forehead**




## 28.0 PRINCIPILE INVESTIGATOR QUALIFICATION

Attached is the CVs

## 29.0 COLLABORATIVE STUDY TERMS OF REFERENCE

Not applicable

## 30.0 FLOW CHART OF THIS STUDY