Accuracy of Transcutaneous Bilirubin Measurement in Healthy Newborns

Thesis submitted for partial fulfillment of the requirement of Master Degree in Pediatrics

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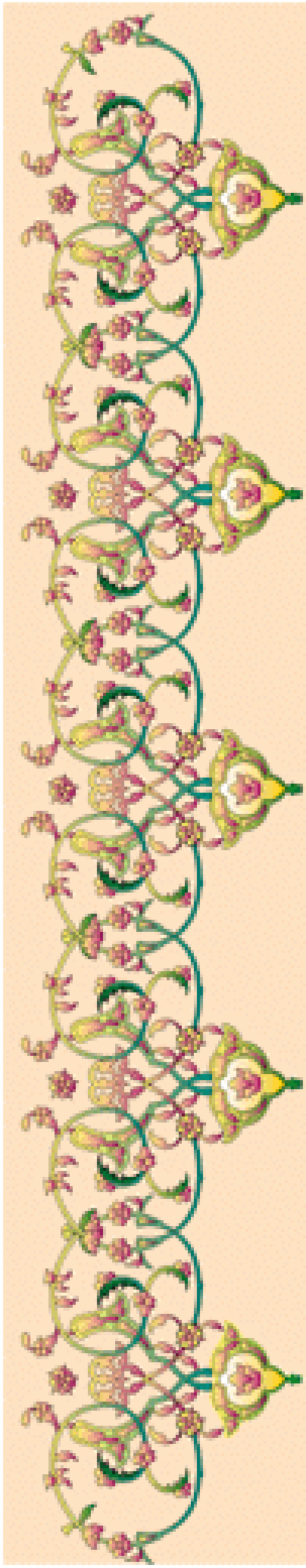

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ "

صدق الله العظيم

البقرة الآية ٣٢

Acknowledgment

At first I am sure that this work would never by crowned by success without the blessing of ***ALLAH,*** to whom my loyalty will remain forever beyond any compromise.

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Ahmed Hamed Bayoumy

List of Contents

List of Tables

List of Figures

List of Abbreviation

AAP	*American Academy of Pediatrics*
ABC	*Adenosine triphosphate binding cassette*
ATP	*Adenosine triphosphate*
C.S	*Cesarean section.*
CB	*Conjugated bilirubin*
CBC	*Complete Blood Count.*
CO	*Carbon monoxide*
COHb	*Blood carboxyhemoglobin*
CNS	*Central nervous system*
CSF	*Cerebrospinal fluid*
DAT	*Direct antiglobulin test*
DNA	*Deoxyribonucleic acid.*
ETCOc	*End-Tidal Carbon Monoxide Measurements*
G6PD	*Glucose–6–phosphate dehydrogenase.*
Hb F	*Fetal hemoglobin*
Hb S	*Sickle hemoglobin*
HO	*Heme Oxygenase*
HPLC	*High-performance liquid chromatography*
IV	*Intravenous*
IVIG	*Intravenous immunoglobulin*
JM	*Jundice meter*
LEDs	*Light–emitting diodes*
MDR	*Multidrug resistance*
Mg/dl	*Milligram / decileter022222222.*
MRPs	*Multidrug resistance-associated proteins*
NADPH	*Nicotinamide adenine dinucleotide phosphate*
NAIPs	*Neuronal apoptosis inhibitor proteins*
NICU	*Neonatal intensive care*
P.gb	*P.glycoprotein*
RBCs	*Red Blood Cells.*
Rh	*Rhesus Factor.*
SB	*Serum bilirubin*
SD	*Standard deviation*
SnMP	*Tin mesoporphyrin*
SSPP	*Statistical package for the social science*
T4	*Thyroxin 4*
TcB	*Transcutaneous bilirubin.*
TSB	*Total serum bilirubin*
U.S.A.	*United States of America.*
UCB	*Unconjugated bilirubin*
UDPGT	*Uridine diphosphoglucuronoyl transferase*
VLBW	*Very low birth weight*

INTRODUCTION

Neonatal hyperbilirubineamia is a common problem encountered in the neonates; occurring in approximately 65% of full-term neonates with peak bilirubin levels on day 5 of life ***(Maisels, 2007)***.

Early discharge of healthy term newborns after delivery has become a common practice for either medical, social or economic reasons. However, an association between the decreased length of stay and the risk of readmission to the hospital has been shown, and the most common cause for readmission during the early neonatal period is hyperbilirubinemia. It is difficult to predict which infants are at increased risk for significant and relatively late hyperbilirubinemia, and there is an obvious need to implement follow up programs or to develop predict confidential guidelines that will enable the physicians to predict or to identify which of the early discharged newborns will develop significant hyperbilirubinemia ***(Nasr El din et al., 2004)*.**

Complications of hyperbilirubinemia such as acute bilirubin encephalopathy are rare. However, the prevention of these complications has led to recommendations to screen all neonates for hyperbilirubinemia ***(Ip et al., 2004)***.

Therefore, an early identification of newborn infants at risk of developing severe hyperbilirubinemia, along with a possible bilirubin induced neurological dysfunction, and the prediction of possible need of phototherapy continue to be a problem in neonatology ***(Knupfer et al., 2005)***.

The ordering of serum bilirubin in neonates based on visual evaluation by either physicians or nursing staff is not accurate. Skin puncture for collection of blood exposes the neonate to trauma and risk of infection ***(Dai et al., 1997)***.

In July 2004, the American Academy of Pediatrics issued a clinical practice guideline, "Management of Hyperbilirubinemia in the Newborn Infant

35 or More Weeks of Gestation." This guideline recommended that all newborn nurseries must have a protocol for assessing jaundice.

However, it did not specify the method by which jaundice must be assessed. Both total serum bilirubin (TSB) and transcutaneous bilirubin (TcB) measurment are cited as acceptable ways to assess neonatal jaundice ***(Madison, 2002)***.

Transcutaneous bilirubinometer is a portable light weight instrument that uses reflectance measurements on skin to determine the amount of yellow colour present in the skin. It provides a noninvasive, cost effective screening method for significant neonatal jaundice, sparing infants and parents physical and emotional stress and medical and nursing personnel extra work and inconvenience ***(Dai et al., 1997)***.

Aim of the Work

The aim of this work was to evaluate the accuracy of transcutaneous bilirubin measurement for initial assessment of neonatal jaundice.

Review of Literature

Chapter I

Neonatal hyperbilirubinemia

Definition

Neonatal hyperbilirubinemia is defined as a total serum bilirubin level above 5 mg per dL. It is a frequently encountered problem that occurs in more than 60% of late preterm and term newborns peaking at 3–5 days of life and usually resolving by 2 weeks of age ***(Smitherman et al., 2006)***.

This common clinical finding is the result of an imbalance between production and elimination of bilirubin; a breakdown product of hemoglobin. Bilirubin formation in newborns is 2 to 3 times greater than in adults owing to the shorter life span of fetal hemoglobin compared to adult hemoglobin. The developmentally immature liver and gastrointestinal tract of the newborn are unable to excrete bilirubin as quickly as it is produced. When bilirubin accumulates in blood and body tissues, skin and eyes exhibit the yellow color characteristic of jaundice ***(Cabra and Whitfield, 2005)***.

Severe neonatal hyperbilirubinemia, defined as total serum bilirubin (TSB) concentrations >12.9 mg/dL, has been estimated to occur in up to 10% of newborns ***(Bhutani et al., 2000)***.

Chemical properties of bilirubin

Bilirubin is a nearly symmetric tetrapyrrole consisting of two rigid planar dipyrrole units joined by a methylene bridge, which is stabilized in a ridge-tile conformation by two trios of internal hydrogen bonds. Bilirubin exhibits poor aqueous solubility because it is predominantly in the un-ionized diacid form at physiologic pH. For this reason, plasma bilirubin is bound primarily to albumin and, to a much lesser degree, high-density lipoproteins, with only a trivial fraction present as the free monomer; Fig. (1) ***(Ronald et al., 2007).***

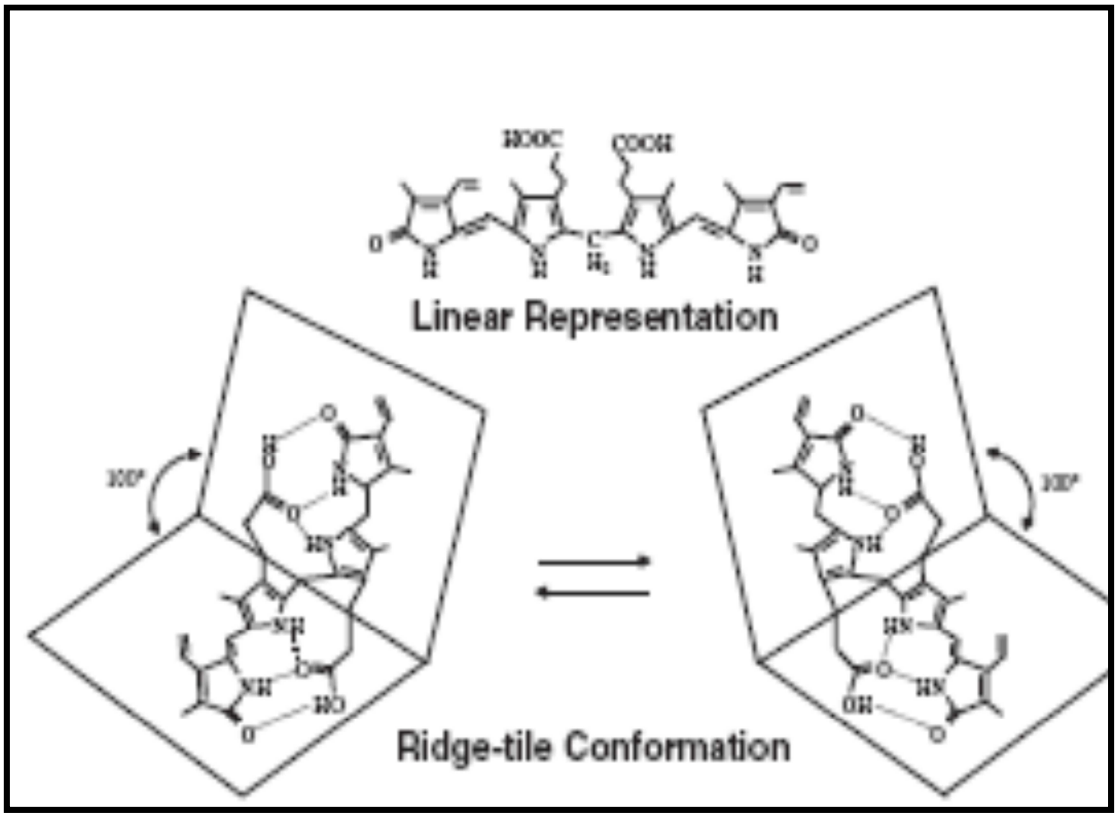

Fig. (1): The chemical structure of bilirubin (Ronald et al., 2007).

Under these circumstances, bilirubin behaves like other lipophilic substances. It is difficult to excrete but crosses easily the biologic

membranes, such as the placenta, blood-brain barrier, and hepatocyte plasma membrane.The addition of methanol or ethanol interferes with hydrogen bonding and results in an immediate diazo reaction, the basis for measurement of indirect-reacting bilirubin by Van den Bergh ***(Ives and Gardner, 1990)***.

Bilirubin Production

The normal destruction of circulating erythrocytes accounts for about 75% of the daily bilirubin production in the newborn. Senescent erythrocytes are removed and destroyed in the reticuloendothelial system, where the heme is catabolized and converted to bilirubin. The catabolism of 1 g of hemoglobin yields 35 mg of bilirubin ***(Ronald et al., 2007)***.

A significant contribution (25% or more) to the daily production of bilirubin in the neonate comes from sources other than the erythrocytes. This bilirubin consists of two major components:

- A nonerythropoietic component resulting from the turnover of nonhemoglobin heme protein and free heme, primarily in the liver.
- An erythropoietic component arising primarily from ineffective erythropoiesis and the destruction of immature erythrocyte precursors, either in the bone marrow or soon after release into the circulation ***(Maisels , 2005)***.

Cleavage of the alpha-methylene bridge of heme by membrane-bound heme oxygenase (HO) is the initiating event in heme catabolism (Fig. 2) and ultimately yields equimolar amounts of green-colored biliverdin, carbon monoxide (CO), and reduced iron. The reaction mechanism is complex and requires three molecules of oxygen and at least seven electrons donated from the nicotinamide adenine dinucleotide

phosphate (NADPH)- cytochrome-P-450 reductase system. The actual cleavage of the tetrapyrrole macro cycle containing iron is autocatalytic in the sense that the bound heme serves both as a prosthetic group and a substrate. Biliverdin is reduced rapidly in the cytoplasm, catalyzed by biliverdin reductase to bilirubin, thus linking CO production and bilirubin production ***(Vreman et al., 2001)***.

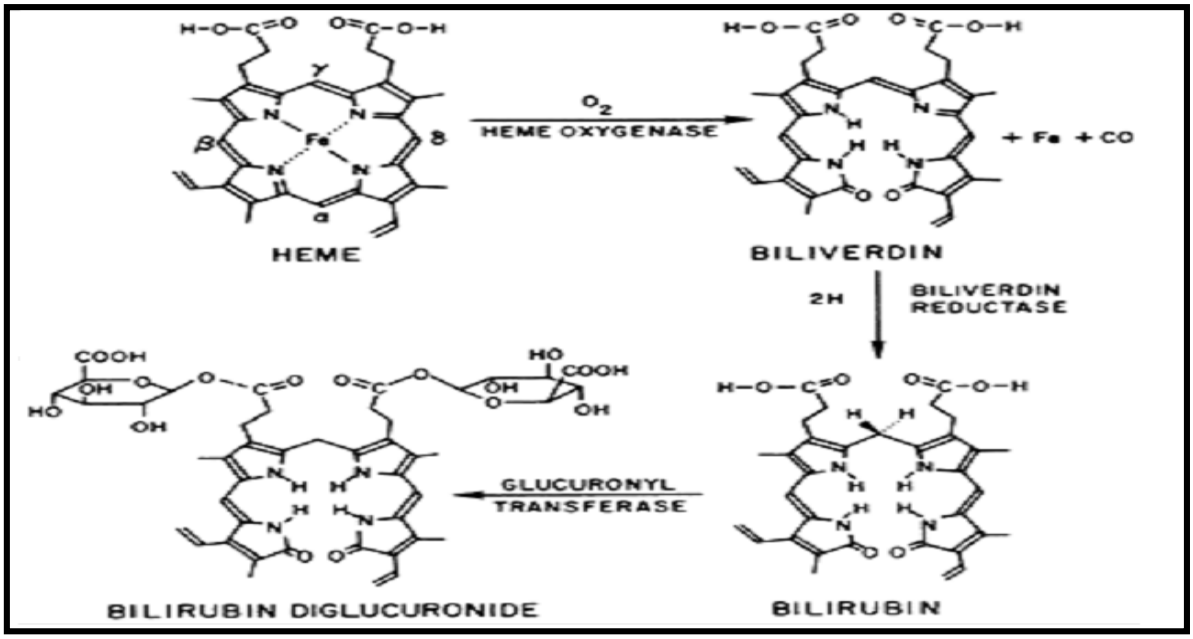

Fig. (2): Catabolism of heme (Vreman et al., 2001).

The concentration of the two well-described HO isozymes, HO-1 and HO-2, varies between tissues. For example, HO-1 predominates in spleen and HO-2 predominates in the brain. HO-2 is considered the constitutive (or "housekeeping") enzyme; it is developmentally regulated, and its expression appears to be influenced only by steroids. In contrast, HO-1 is inducible by its substrate,(heme), and various other non-heme substances and stress conditions reflecting a very complex set of biologic roles. A putative isoenzyme, HO-3, also has been reported as largely

homologous with HO-2, but with uncertain activity and unknown role **(*McCoubrey et al., 1997)***.

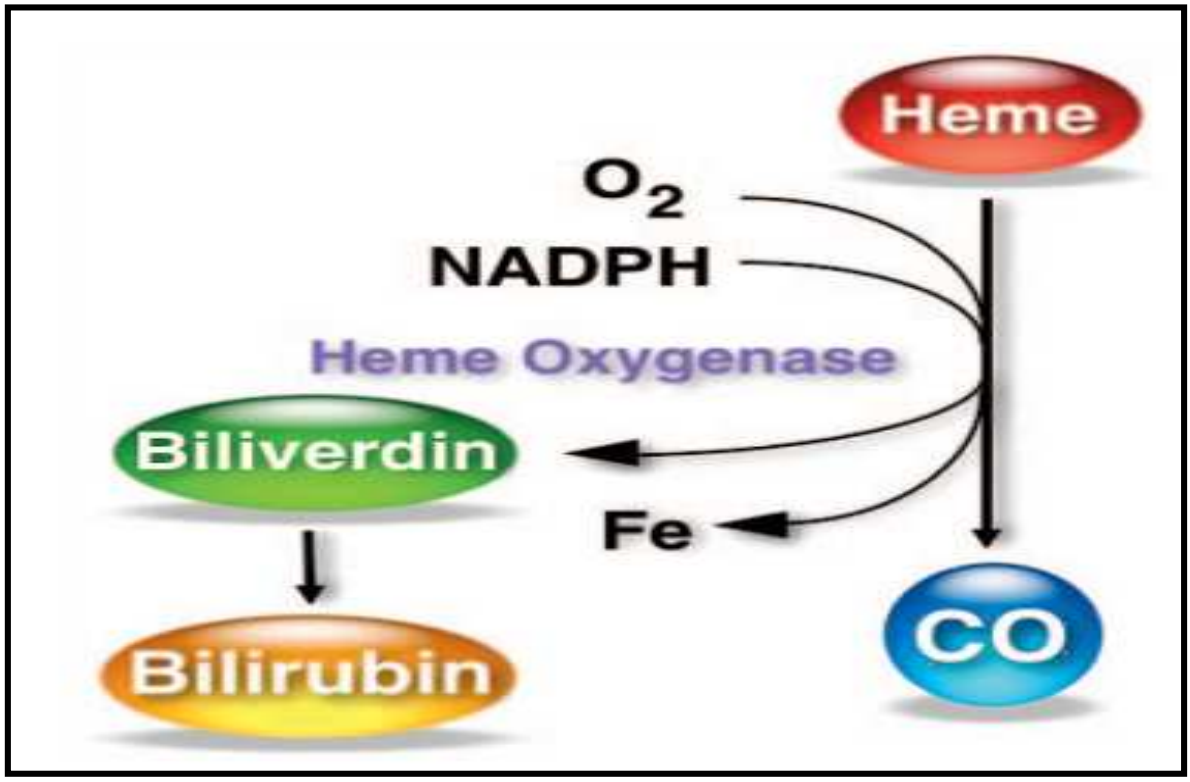

Fig. (3): ***A scheme for the origin of bilirubin (Ronald et al., 2007)***.

BILIRUBIN METABOLISM

Jaundice occurs when the liver cannot clear a sufficient amount of bilirubin from the plasma. When the problem is excessive bilirubin formation or limited uptake and conjugation, unconjugated (i.e., indirect-reacting) bilirubin appears in the blood. When bilirubin glucuronide excretion is impaired (i.e.,cholestasis), conjugated monoglucuronide diglucuronide (i.e., direct-reacting) bilirubin accumulate in plasma because of their solubility, also appear in the urine. There is also a fourth bilirubina fraction (unconjugated, monoglucuronide, and diglucuronide the first three) known as σ-bilirubin, which is formed non-enzymatically