



The Effect of Head Covering on Phototherapy-Induced Hypocalcemia in Jaundiced Full-Term Neonates

Thesis

*Submitted for Partial Fulfilment
of Master Degree in **Pediatrics***

By

Amira Said Mohamed

MBBCH. Ain Shams University-2012.

Under Supervision of

Prof. Sherein Mohamed Abd El Fattah

Professor of Pediatrics

Faculty of Medicine –Ain Shams University

Prof. Safaa Shafik Imam

Professor of Pediatrics

Faculty of Medicine –Ain Shams University

Dr. Basma Mohamed Shehata

Lecturer of Pediatrics

Faculty of Medicine –Ain Shams University

Faculty of Medicine - Ain Shams University

2019

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgments

*First and foremost, I feel always indebted to **Allah** the Most Beneficent and Merciful.*

*I wish to express my deepest thanks, gratitude and appreciation to **Prof. Sherein Mohamed Abd El Fattah**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Prof. Safaa Shafik Imam**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her sincere efforts, fruitful encouragement.*

*I am deeply thankful to **Dr. Basma Mohamed Shehata**, Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University, for her great help, outstanding support, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Amira Said Mohamed

List of Contents

Title	Page No.
List of Tables	5
List of Figures	6
List of Abbreviations.....	8
Introduction.....	- 1 -
Aim of the Work	12
Review of Literature	
▪ Neonatal Jaundice	13
▪ Phototherapy.....	50
▪ Calcium Physiology and Phototherapy Induced Hypocalcaemia	69
Patients and Methods	82
Results	89
Discussion.....	106
Summary	115
Conclusion	118
Recommendations	119
References	120
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table 1:	Classification according to mechanism of accumulation:	17
Table 2:	Causes of conjugated hyperbilirubinemia:.....	30
Table 3:	Risk Score for Neonatal Hyperbilirubinemia.....	37
Table 4:	Comparison between conventional (fluorescent) and LED Phototherapy.....	56
Table 5:	Demographic data for all study groups	90
Table 6:	Comparison between lamp and LED regarding level of total serum bilirubin	91
Table 7:	Comparison between lamp and LED regarding level of total and ionized Ca	93
Table 8:	Comparison between Lamp and LED regarding manifestations of hypocalcemia.....	96
Table 9:	Comparison between Lamp phototherapy with head cover and without head cover regarding level of total serum bilirubin	97
Table 10:	Comparison between Lamp phototherapy with head cover and without head cover regarding level of total and ionized Ca	98
Table 11:	Comparison between Lamp phototherapy with head cover and without head cover regarding manifestations of hypocalcemia.....	101
Table 12:	Comparison between LED phototherapy with head cover and without head cover regarding level of total serum bilirubin	102
Table 13:	Comparison between LED phototherapy with head cover and without head cover regarding level of total and ionized Ca	103

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Production of Bilirubin	14
Figure (2):	Billirubin metabolism	16
Figure (3):	Advancement of dermal icterus in the jaundiced newbon (kramer's rule)	36
Figure (4):	Total serum bilirubin (TSB) nomogram for designation of risk in 2,840 well newborns delivered at 36 or more weeks' gestation with birth weight of at least 2,000 g	38
Figure (5):	Minolta Air-Shields JM-103 (left) and Respironics Bilicheck (right) TcB measurement devices	40
Figure (6):	Transcutaneous bilirubin (TcB) nomogram for assessing the risk of subsequent significant hyperbilirubinemia in healthy term and near-term newborns	40
Figure (7):	Guidelines for exchange transfusion	46
Figure (8):	Mechanism of phototherapy	52
Figure (9):	Halogen Spotlight	53
Figure (10):	Two halogen lamp	54
Figure (11):	BiliBlanket Plus, courtesy of GE Healthcare	57
Figure (12):	Bilibed device home	57
Figure (13):	Guide lines for phototherapy	60
Figure (14):	The role of active vitamin D (1,25-dihydroxyvitamin D, calcitriol) and PTH	70
Figure (15):	The metabolic pathway for vitamin D	72
Figure (16):	Design of the hat	88

List of Figures *cont...*

Fig. No.	Title	Page No.
Figure (17):	Total serum bilirubin on admission, within 48hr under phototherapy and 48hr after termination of phototherapy between groups CFL & LED.	92
Figure (18):	Level of total Ca on admission and 48hr within phototherapy and after termination of phototherapy between groups CFL & LED.	95
Figure (19):	Level of ionized Ca on admission and 48hr within phototherapy and after termination of phototherapy between groups CFL & LED.	95
Figure (20):	Level of total Ca on admission and 48hr within phototherapy and after termination of phototherapy between groups Lamp with & without head cover.....	99
Figure (21):	Rate of decline of total Ca after 48hr of phototherapy between groups Lamp with & without head cover.....	100
Figure (22):	Incidence of hypocalcemia in groups Lamp with & without head cover.....	100
Figure (23):	Level of total Ca on admission and 48hr within phototherapy and after termination of phototherapy between groups LED with & without head cover.	105
Figure (24):	Rate of decline of total Ca after 48hr of phototherapy between groups LED with & without head cover.....	105

List of Abbreviations

Abb.	Full term
$\mu w / cm^2 / nm$	<i>Microwatts / centimeter square / nanometer</i>
1,25(OH) ₂ D	<i>1,25 dihydroxy vitamin D</i>
ABE.....	<i>Acute bilirubin encephalopathy</i>
Aka.....	<i>Also known as</i>
CB	<i>Conjugated bilirubin</i>
CFL	<i>Compact fluorescent lamp</i>
cm.....	<i>Centimeter</i>
CNS	<i>Crigler-Najjar syndrome</i>
d	<i>Day</i>
DJS.....	<i>Dubin-Johnson syndrome</i>
G6PD	<i>Glucose-6-phosphate dehydrogenase</i>
gm	<i>Gram</i>
GMP.....	<i>Guanosine monophosphate pathway</i>
GS	<i>Gilbert syndrome</i>
Hct.....	<i>Hematocrit</i>
HDFN	<i>Haemolytic disease of the fetus and newborn</i>
HDN.....	<i>Haemolytic disease of the newborn</i>
hr	<i>Hour</i>
IDM.....	<i>Infant of diabetic mother</i>
IV	<i>Intravenous</i>
kg	<i>Kilogram</i>
LED.....	<i>Light emitting diode</i>
mg / dl	<i>Milligram / deciliter</i>

List of Abbreviations

Abb.	Full term
<i>mg /dl /hr</i>	<i>Milligram / deciliter / hour</i>
<i>NICUs</i>	<i>Neonatal intensive care units</i>
<i>nm</i>	<i>Nanometer</i>
<i>PET</i>	<i>Partial exchange transfusion</i>
<i>PKD</i>	<i>Red cell pyruvate kinase deficiency</i>
<i>PROM</i>	<i>Premature rupture of membrane</i>
<i>PTH</i>	<i>Parathyroid hormone</i>
<i>TcB</i>	<i>Transcutaneous bilirubin</i>
<i>TORCH</i>	<i>Toxoplasma, Rubella, Cytomegalo virus, Herpes virus</i>
<i>TPN</i>	<i>Total parenteral nutrition</i>
<i>TSB</i>	<i>Total serum bilirubin</i>
<i>UCB</i>	<i>Unconjugated bilirubin</i>
<i>UDPGT</i>	<i>Uridine diphosphate glucoronyl transferase</i>
<i>UGT1A1</i>	<i>Uridine glucorinyl transeferase 1A1</i>
<i>wk</i>	<i>Weeks</i>

INTRODUCTION

Jaundice is a common cause of morbidity encountered in the first week of life. It is almost concern for the physician and a source of anxiety for the parents (*De Luca, 2010; Khosravi et al., 2001*). High bilirubin level may be toxic to the developing central nervous system and may elicit neurological impairment in newborns (*Kaplan et al., 2011*). About 60% of term newborns become visibly jaundiced in the first week of life. In most of the cases, it is benign and no intervention is required (*Dijk et al., 2009*). Approximately 5-10% of them have clinically significant jaundice that signifies the use of phototherapy (*Hansen, 2010*).

Phototherapy is the most commonly used intervention to treat severe jaundice and reduces the risk of exchange transfusion (*Ip et al., 2004*). It blunts the rise of indirect bilirubin level regardless of the etiology of jaundice (*Maisels and Kring, 2002*). Phototherapy decreases the serum bilirubin level by transforming bilirubin into water-soluble isomers that can be eliminated without conjugation in the liver (*Stokowski, 2006*).

However, this treatment modality may itself result in the development of some complications (*Ehsanipoor et al., 2008*). Though it is considered safe, a few side effects encountered in phototherapy are loose stools, hyperthermia, dehydration due to fluid loss, skin burn, retinal damage, low platelet count,

increased red cell osmotic fragility, bronze baby syndrome, riboflavin deficiency and DNA damage. A lesser known side effect, but a potential complication of phototherapy is hypocalcemia (*Cloherty et al., 2008*).

The overall prevalence of hypocalcemia in neonates receiving phototherapy was suggested to be 8.7% in full-term newborn (*Yadav et al., 2012*). The mechanism of hypocalcemic effect of phototherapy was reported by inhibition of pineal gland via transcranial illumination, resulting in decline of melatonin secretion that further decreases the release of cortisol leading to increase bone uptake of calcium and induce hypocalcemia (*Hunter, 2004; Alizadeh-Taheeri et al., 2013*).

Clinical picture of hypocalcemia in neonates includes jitteriness, irritability, excitability, lethargy and convulsions, as well as other complication like rash, loose stool, fever and dehydration (*Yadav et al., 2012*). Hypocalcemia affects many biochemical processes including cell membrane integrity, blood coagulation, function of cell membrane, neuromuscular excitability and cellular enzymatic activity (*Borkenhagen et al., 2013*).

AIM OF THE WORK

The aim of this study was to assess the effect of head covering on calcium levels in full term neonates with hyperbilirubinemia treated with different types of phototherapy.

Chapter 1

NEONATAL JAUNDICE

Neonatal Jaundice is a yellowish discoloration of skin and sclera by bilirubin which is clinically detectable in the newborn (*Wong et al., 2018*).

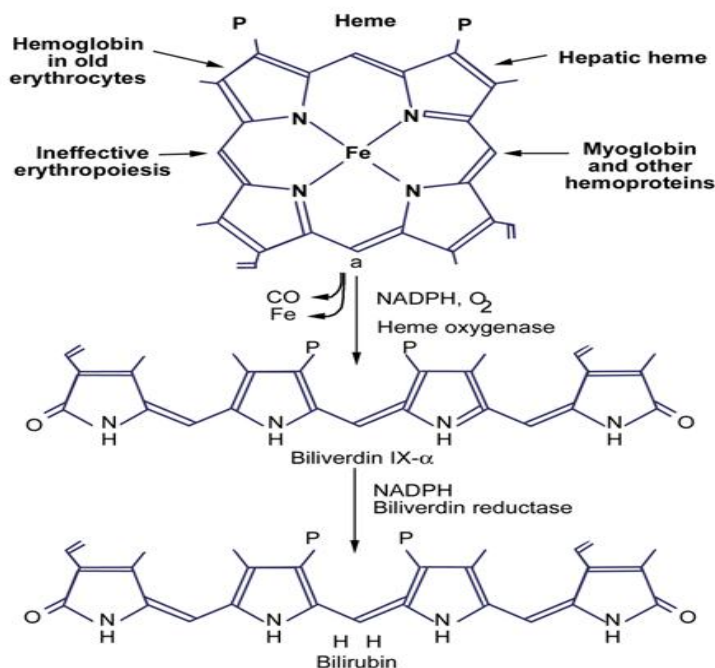
Hyperbilirubinemia is either unconjugated (which is potentially neurologically toxic and may be physiological or pathological) or conjugated (not toxic and always pathological) (*Chen et al., 2011*).

Sources of bilirubin:

Bilirubin is the end product of heme breakdown. About 80% of bilirubin originates from degradation of erythrocyte hemoglobin in the reticuloendothelial system; the remaining 20% comes from inefficient erythropoiesis in the bone marrow and degradation of other heme proteins such as cytochromes, catalase, peroxidase and tryptophan pyrrolase (*Wong et al., 2007*).

The heme ring from heme-containing proteins is oxidized in reticuloendothelial cells to biliverdin by the microsomal enzyme (Heme oxygenase) (*Erlinger et al., 2014*).

This reaction releases carbon monoxide (CO); (excreted from the lung); and iron (reutilized). Biliverdin is then reduced to bilirubin by the enzyme Biliverdin reductase (*Gregory et al., 2012*).

Bilirubin production:**Figure (1): Production of Bilirubin (Hisham *et al.*, 2014).**

The normal newborn produces 6 to 10 mg of bilirubin/Kg/day. One gram of haemoglobin results in the production of 34 mg of bilirubin (Gregory *et al.*, 2012).

Unconjugated bilirubin (UCB) exists in several forms in the blood but is predominantly bound to albumin. One gram of albumin binds 8.5 mg of bilirubin in a newborn. A minute fraction of unconjugated bilirubin in serum is not bound to albumin (Erlinger *et al.*, 2014). UCB is taken by hepatocytes at their sinusoidal surface. The impairment of uptake will result in unconjugated hyperbilirubinemia (Moerschel *et al.*, 2008).

Inside the liver cells, about 60% of bilirubin is found in the cytosol and about 25% in microsomes. Ligandin; a glutathione S-transferase; is responsible for binding bilirubin inside the cells (*Hansen, 2010*). UCB is converted to water soluble conjugated bilirubin (CB) in the smooth endoplasmic reticulum by uridine diphosphate glucoronyl transferase (UDPGT) enzyme (*Huang et al., 2004*).

Once bile reached the intestine, conjugated bilirubin is reduced to colorless tetrapyrroles by bacteria in the colon (*Cashore, 2012*). However, some deconjugation occurs in the proximal small intestine by β -glucuronidases located in the brush border (*Ann et al., 2012*). This unconjugated bilirubin can be reabsorbed into the circulation, increasing the total plasma bilirubin pool. This cycle known as '**Enterohepatic Circulation**' (*Fujiwara et al., 2015*). The process may be extensive in the neonate, partly because of limiting intake in the first days of life, prolonging the intestinal transit time by decreasing excretion of stool (*Fujiwara et al., 2015*).

The bulk of bilirubin, urobilinogen, urobilin, stercobilinogen and stercobilin are excreted in the feces. Small amounts of bilirubin and urobilinogen are reabsorbed by the intestine and return to the liver. The bilirubin is re-conjugated in the liver and re-excreted in the feces. Some of the reabsorbed urobilinogen is excreted in the urine (*Moerschel et al., 2008*).