Relationship Between Neonatal Adrenomedullin and Serum Bilirubin Levels

Thesis

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TO MY FAMILY

Abstract

In this study the correlation between serum bilirubin and AM levels was investigated in a total of 80 newborns divided into two groups according to the serum bilirubin levels. Group I (with significant hyperbilirubinemia) and Group II (without significant hyperbilirubinemia

Results: there is a high statistically significant increase in serum adrenomedullin levels in study group (group I) and control group (group II) with levels of 42.538±12.452 and 30.588±11.5902 respectively ($p<0.001$).

Conclusion: The study concluded that Adrenomedullin probably plays a significant role in adverse effects and neuronal injury steps of significant hyperbilirubinemia.

Keywords:
Hyperbilirubinemia, Adrenomedullin, Bilirubin Neurotoxicity, Neonates

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Abbreviations

7TM	Seven Trans membrane
AAP	American Academy of Pediatrics
ABE	Acute bilirubin encephalopathy
ACTH	Adrenocorticotrophic hormone
ALI	Acute lung injury
AM	Adrenomedullin
AN/AD	Auditory neuropathy/dys-synchrony
B/A ratio	The bilirubin/albumin ratio
BBB	Blood brain barrier
BIND	Bilirubin induced neurologic dysfunction
BPD	Bronchopulmonary dysplasia
cAMP	Cyclic adenosine monophosphate
CEC	Cerebral endothelial cells
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
CRLR, now known as CL	Calcitonin-receptor-like receptor
ET	Exchange transfusion
G6pD:	Glucose-6-phosphate dehydrogenase
GPCR	G-protein-coupled receptor
HDN	Hemolytic Disease of the Newborn
HIE	Hypoxic ischemic encephalopathy
IB	Indirect bilirubin
IgG	Immunoglobulin G
IVH	Intraventricular hemorrhage
IVIG	Intravenous immunoglobulin
NICU	Neonatal Intensive Care Unit

NNPT	Neonatal Phototherapy
NO	Nitric oxide
RAMP	Receptor activity modifying protein
RBC	Red Blood Cell
SnMP	Tin mesoporphyrin
TB	Total bilirubin
TcB	Transcutaneous bilirubin,
TEER	Transendothelial electrical resistance
TNF-α	Tumor necrosis factor
TSB	Total serum bilirubin,
UCB	Uncongugated bilirubin
UCB:Bf	Unbound (free) fraction
UGTs	Uridine diphosphoglucuronosyltransferase

INTRODUCTION

Bilirubin toxicity remains a significant problem despite recent advances in the care of jaundiced (hyperbilirubinemic) neonates. In Cairo University Children's Hospital, severe neonatal hyperbilirubinemia accounted for 33% of total admissions to the out born Neonatal Intensive Care Unit (NICU) in 2006 with 10 cases of kernicterus occurring each year ***(Iskander et al., 2012).***

In term infants, acute bilirubin encephalopathy with marked hyperbilirubinemia presents with a sequence of poor suckling, stupor, hypotonia progressing to hypertonia with neck or back arching & diminishing tone ***(Kamei et al., 2012)***.

Total serum bilirubin in neonatal hyperbilirubinemia (NH) can be above 20mg/dl without neonatal bilirubin encephalopathy (NBE) happening. Moreover, the symptoms of some patients with NBE can be subtle. Using only clinical presentation to differentiate patients with NBE from those with only NH is quite difficult in the neonatal period ***(Wu et al., 2013)***.

Human adrenomedullin (AM) is a small hormone of 52 amino acids. It belongs to the amylin/calcitonin gene-related peptide (CGRP) super-family, AM contains a six amino acid ring formed by an internal disulfide bond between residues 16 and 21 **(Larráyoz *et al.*, 2014**). The presence of AM production in both brain tissue and peripheral tissues implies that AM inserts its possible effects on brain tissue via complex mechanisms. Increasing synthesis of endogenous AM as a response in oxidative stress suggests that this peptide has a protective role against organ injury by inhibiting the products of oxidative stress **(Kim *et al.*, 2010).**

AM has subsequently been classified as a neuropeptide, recognizing the peptide's influence within the brain and its regulatory capacity at the blood–brain barrier **(Liverani & Paul, 2013)**. AM decreases endothelial permeability by increasing transendothelial electrical resistance (TEER), and with cAMP increase, it plays an important role in the regulation of this barrier **(Erdinc *et al.*, 2014).**

Although there are many studies performed about the probable mechanisms of bilirubin neurotoxicity on CNS, the exact mechanisms have not yet been determined. Oxidative stress occurring in newborns with hyperbilirubinemia is believed to trigger major mechanisms leading to neuronal injury on the one hand, and both neuron protective properties of AM and its nature as an intrinsic antioxidant and anti-inflammatory peptide suggest a strong relationship between bilirubin levels and AM on the other hand **(Erdinc *et al.*, 2014)**.

AIM OF THE WORK

The aim of this study is to investigate the relationship between serum bilirubin and an antioxidant, anti-inflammatory and neuroprotective peptide, adrenomedullin (AM) levels.