The Value of Umbilical Cord Blood Interleukin-6 Measurement for Prediction of Intraventricular Hemorrhage in Preterm Infants

Thesis
Submitted for Partial Fulfillment of Master Degree in pediatrics

By
Mohamed Kamal Harfoush
M. B., B. Ch. Alexandria University

Supervised by

Professor / Mohamed Ashraf Abd El - Wahed
Professor of Pediatrics
Faculty of Medicine, Ain Shams University

Doctor / Ola Galal Badr El – deen
Lecturer of pediatrics
Faculty of Medicine – Ain Shams University

Doctor / Shereen Hassan Atef
Lecturer of clinical pathology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2014

ACKNOWLEDGEMENT

First and foremost, I fell always indebted to **ALLAH**, the most kind and the most merciful.

I would like to express my thanks and gratitude to **Prof. Dr. Mohamed Ashraf Moustafa Abdel Wahed** professor of Pediatrics, Faculty of Medicine, Ain Shams University, for his kind support, guidance and valuable remarks. I am profoundly grateful for his continuous close supervision, constant help and his stimulating remarks throughout this study.

I would like to express my thanks and gratitude to **Dr. Ola Galal Badr El – deen** lecturer of Pediatrics, Faculty of Medicine, Ain Shams University, for her generous help and continuous encouragement. She provided me with valuable comments, knowledge and experience necessary for achieving this work.

I would like to express my thanks and gratitude to **Dr. Shereen Hassan Atef** Lecturer of clinical pathology Faculty of Medicine–Ain Shams University, for her generous help and continuous encouragement.

Also I would like to acknowledge my appreciation to everyone who had made this work possible.

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AD	Alzheimer disease.
AGA	Appropriate for gestational age.
BAFF	B-cell activating factors belonging to the tumor necrosis factor family.
BCMA	B cell maturation antigen.
CAC	Colitis-associated colon cancer.
CBF	Cerebral blood flow.
CISS	Constructive interference in the steady state.
CLC	Cardiotrophin-like cytokine.
CNS	Central nervous system.
CNTF	Ciliary neurotrophic factor.
CT	Computed tomography.
CT-1	Cardiotrophin-1.
CTL	Cytotoxic T Lymphocytes.
DC	Dendritic cells.
EAE	Experimental Autoimmune Encephalomyelitis
EPO	Erythropoietin
GM-CSF	Granulocyte-Monocyte Colony Stimulating Factor.
GM-IVH	Germinal Matrix-intraventeicular hemorrhage.
gp130	Glycoprotein 130.
IBD	Inflammatory bowel disease.
IFN	Interferon.
IG	Immunoglobulin.
IKKβ	Inhibitor of NF-κB kinase.
IL	Interleukin.
IL-6R	Interleukin-6 receptor.

IL-6Rα	IL-6 α-receptor.
IVH	Intraventricular hemorrhage.
JAK	Janus kinase.
LIF	Leukemia inhibitory factor**.**
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase.
MHC	Major Histocompatibility complex.
MRI	Magnetic resonance imaging. .
MS	Multiple sclerosis.
NEC	Necrotizing enterocolitis
NK	Natural killer.
NO	Nitric oxide.
OSM	Oncostatin M.
PBMCs	Peripheral blood mononuclear cells.
PC	Procalcitonin.
PDA	Patent ductus arteriosus.
PG	Prostaglandin.
PIVH	Periventricular Intraventricular hemorrhage .
PT	Preterm.
PVH/IVH	Periventricular/ Intraventricular hemorrhage.
PVL	Peri-ventricular leukomalacia.
RA	Rheumatoid arthritis.
RANKL	RANK-Ligand.
RDS	Respiratory distress syndrome.
RR-MS	Recurrent relapsing - Multiple sclerosis.
SGA	Small for gestational age.
SIRS	Systemic inflammatory response syndrome.
SLE	Systemic lupus erythrematosus

SSc	Systemic sclerosis.
STAT	Signal transducers and activators of Transcription.
T1D	Type 1 Diabetes.
TACI	Transmembrane activator, calcium modulator and cyclophilin ligand interactor.
TALL1	APOL-related leukocyte expressed ligand 1.
TGF	Tumor Growth Factor.
Th	T helper lymphocytes
THPO	Thrombopoietin
TNF	Tumor Necrosis Factors.
TNF-α	Tumor Necrosis Factors -alpha.
TRAIL	TNF-related apoptosis-inducing ligand**.**
U/S	Ultrasound.
VLBWI	Very low birth weight infants.
WMD	White matter brain damage
X-SCID	X-linked form of severe Combined Immunodeficiency.

INTRODUCTION

The etiology of preterm birth is multifactorial and involves a complex interaction between fetal, placental, uterine and maternal factors (Stoll and Kliiegman, 2004). Advanced of perinatal and natal care, including the use of antenatal steroids and exogenous surfactant, have resulted in increased survival of smaller and more immature infant (Vohr et al., 2000; Gillard et al.; 2001).

However, the improved rates of survival have been associated with increased rates of neurodevelopment morbidity in certain groups such as extremely premature infants (Volpe, 2001).

Intracranial hemorrhage is probably the most commonly encountered accident to the brain in preterm infants. Most authorities would agree that 30 – 50% of preterm infants suffer some form of intra-cranial bleeding (Burstein et al: 1989).

Early detection of abnormalities in brains of newborn infants is important as significant insults to the brain, especially in preterm babies; are most often clinically silent (Schellinger and Grant, 1986).

The introduction of high resolution real time ultrasonography has revolutionized intracranial diagnosis in the neonatal and early infancy periods. It is an easy, safe, noninvasive and relatively cheap method of diagnosis (Grant et al., 1982).

Kassal et al. (2005) hypothesized that some inflammatory markers; namely interleukins can be a useful tool to predict the later development of intraventricular hemorrhage in preterm infants especially those of very low birth weight.

AIM OF THE WORK

The aims of this study are to assess the value of measurement of umbilical cord blood interleukin-6 levels for prediction of the occurrence of intraventricular hemorrhage in preterm infants and to determine whether these levels can be correlated with cranial ultrasound results or not.

SUBJECTS AND METHODS

The study will include 90 preterm infants (gestational age<37 Weeks) born in the pediatrics Hospital of Alexandria University and in other governmental pediatrics hospitals of Alexandria.

Exclusion criteria

- Preterm babies born to mothers with preterm premature rupture of membranes or those with suspected or proved chorioamnionitis.
- Preterm babies born to mothers who received antenatal steroids.
- Full term babies (gestational age >37 weeks).

Cases will be subjected to the following

1. Adequate history taking especially regarding calculated gestational age, any maternal disease, antenatal steroids treatment and symptoms suggesting chorioamnionitis.
2. Thorough clinical examination stressing on birth weight, signs of early neonatal sepsis, and Ballard score to assess the gestational age.
3. Collection of umbilical cord blood samples for measurement of interleukin-6 levels using commercially available kits.
4. Cranial ultrasound examination during the first week of life for detection of intraventricular hemorrhage.
5. Statistical analysis of the results.

PREMATURITY

Infants born before 37 weeks gestation are considered premature. The more preterm an infant is born, the greater the risk that the infant will experience complications of prematurity. High rates of morbidity and mortality in preterm infants can be attributed to complications associated with prematurity. Approximately one third of infant deaths can be associated with prematurity. Extremely premature infants have a mortality rate around 50 percent (the highest of any gestational age group), as well as having the greatest risk of morbidity in the long-term. Prematurity accounts for 25% of children with hearing or cognitive impairments, 35 percent of those with visual impairments, and 45% of children with cerebral palsy **(Eichenwald & Stark, 2008)**.

Three standard subdivisions classify underweight infants and three are designated for the degree of immaturity (approximate gestational age at birth). Infants born weighing less than 1000 g are considered to be extremely low birth weight (ELBW). An infant born weighing between 1000 g and 1500 g is considered to be very low birth weight (VLBW). Infants born weighing between 1500 g and 2500 g are considered to be low birth weight (LBW) (WHO, 2011). An infant born before 25 weeks gestation is referred to as being extremely preterm **(Nicolas et al., 2000)**.

Infants born between 25 and 32 weeks gestation is referred to as being very preterm. An infant born from 32 to less than 37 weeks gestation is referred to as being late preterm **(Pamela et al., 2004)**.

Short term complications of prematurity

It is important to quickly stabilize infants in the delivery room to reduce their risk of developing short term complications **(Lemons et al., 2001)**.

Short term complications of prematurity are defined as those occurring during the neonatal period **(Eichenwald & Stark, 2008)**.

Premature infants are increasingly susceptible to developing short term complications with decreasing birth weight and gestational age, and are the result of anatomical or functional immaturity **(Faranoff et al., 2007)**.

Overall, the more short term complications seen in an infant, the greater the chances that the child will experience long term complications of prematurity **(Eichenwald and Stark, 2008)**.

Preterm Brain Complications

A child born very preterm uses different regions of the brain to process information than those regions a term infant uses. When an infant is born prematurely, the brain compensates for being underdeveloped to function properly in its new environment. These changes can have detrimental effects in long term **(Jobe, 2010)**.

The preterm infant born at 24 weeks gestational age has a brain weight around 100g with a smooth surface with no external architecture (gyri). While at full term, an infant's brain weighs about 350g and has a convoluted surface and great complexity **(Ment et al., 2009)**.

The brain of an ELBW neonate grows, but the surface structure is less complex than the full term brain **(Ajayi-Obe et al., 2000)**.

A preterm brain has a lower volume of deep nuclear grey matter, which can be further damaged by white matter injury **(Inder et al., 2005)**.

Preterm infants are predisposed to brain injury due to factors including hypoxia, ischemia, hyperoxia, and maternal-fetal infection. Perinatal impacts to the brain can result in inflammation, excitotoxicity, and oxidative stress. Genetic factors cause some infants to be more 12 susceptible to these complications. These factors contribute to encephalopathy of prematurity, which is white and grey matter damage of the premature brain **(Kaindl et al., 2009)**.