Impact of Neonatal Cardiovascular Compromise and its Treatment on Brain Electrical Activity and Short-term Clinical Outcome

Thesis

Submitted for Partial Fulfillment of MD Degree
in Pediatrics

By

Hoda Abd EL Rahman Mohamed Ismail
M.B, B.Ch (1989), M.Sc. (1993), Ph.D.(1997)
Ain Shams University

Under Supervision of

Prof. Nehal Mohamed El Raggal
Professor of Pediatrics-Ain Shams University

Prof. Sahar Mohamed Ahmed Hassanein
Professor of Pediatrics-Ain Shams University

Dr. Noureldin Mohamed Abdelaal
Lecturer of Pediatrics-Ain Shams University

Dr. Eman Khairy Farahat
Assistant Prof. of Medical Biochemistry and Molecular Biology
Ain Shams University

Faculty of Medicine – Ain Shams University
2019

بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

البقرة الآية ٣٢

Acknowledgement

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

I would like to express my deepest thanks and profound gratitude to ***Prof. Dr. Nehal Mohamed El Raggal*** *Professor of Pediatrics, Faculty of Medicine, Ain Shams University. It was such a great honor to work under her kind guidance. Her continuous help, combined with her sincere support obliged me to bear the responsibility toward this work.*

I am greatly indebted to ***Prof. Dr. Sahar Mohamed Ahmed Hassanein*** *Professor of Pediatrics, Faculty of Medicine, Ain Shams University. To her I owe much more than I could express and much more than I could repay for sharing her expertise and valuable time.*

It's also an honor to express my thanks to ***Dr. Noureldin Mohamed Abdelaal*** *Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University for his guidance and continuous support.*

I am sincerely thankful to ***Dr. Eman Khairy Farahat*** *Assistant Prof. of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Ain Shams University, for her continuous helpful suggestions and interest during the course of this study.*

Last but not least, I would like to thank my Family, my colleagues, my patients, and every one helped me to accomplish this work.

Hoda Abd El Rahman

List of Contents

List of Tables

Table No. Title Page No.

List of Tables (Cont...)

List of Figures

Fig. No. Title Page No.

List of Figures (Cont...)

Fig. No. Title Page No.

List of Figures (Cont...)

Fig. No. Title Page No.

List of Abbreviations

Abb. Full term

AC ..... : Adenylate cyclase
ACCM ..... : American College of Critical Care Medicine
aEEG ..... : Amplitude-integrated electroencephalography
Ao ..... : Aorta
A wave..... : Atrial contraction wave
BE ..... : Base excess
BLP ..... : Bacterial lipopeptide
BP ..... : Blood pressure
Ca..... : Calcium
cAMP ..... : Cyclic adenosine monophosphate
CBF..... : Cerebral blood flow
CDH..... : Congenital diaphragmatic hernia
CFM..... : Cerebral function monitoring
CI ..... : Confidence interval
CHD..... : Congenital heart disease
cGMP..... : Cyclic guanosine monophosphate
CPAP ..... : Continuous positive airway pressure
CRT..... : Capillary refill time
CNS ..... : Central nervous system
CO ..... : Cardiac output
COX ..... : Cyclooxygenase enzyme
CPP..... : Cerebral perfusion pressure
CSF..... : Cerebrospinal fluid
CW ..... : Continuous-wave mode of Spectral Doppler
DA ..... : Ductus arteriosus
Desc Ao..... : Descending aorta
DIC..... : Disseminated intravascular coagulation
DO2..... : Oxygen delivery
E:A ratio ..... : E and A wave velocities ratio
ECMO..... : Extracorporeal membrane oxygenation
EF ..... : Ejection fraction
EOS..... : Early onset sepsis
ET-B..... : Endothelin receptor- B

List of Abbreviations (Cont...)

Abb.	Full term
ET-A	*: Endothelin receptor-A*
ET-1	*: Endothelin-1*
E wave	*: Early wave (early diastolic blood flow)*
eNOS	*: Endothelial nitric oxide synthase*
FDA	*: United States Food and Drug Administration*
FiO2	*: Fraction of inspired oxygen*
Fn-Echo	*: Functional echocardiography*
FoCUS	*: Focused cardiac ultrasound*
FO	*: Foramen ovale*
FRC	*: Functional residual capacity*
FS	*: fractional shortening*
GA	*: Gestational age*
HFV	*: High frequency ventilation*
HRF	*: Hypoxic respiratory failure*
Hz	*: Hertz*
hrs	*: Hours*
iNO	*: Inhaled Nitric Oxide*
IVH	*: Intraventricular Hemorrhage*
IVC	*: Inferior vena cava*
IVS	*: Interventricular septum*
K	*: Potassium*
LA	*: Left atrium*
LA: Ao ratio	*: Left atrial to aortic root ratio*
LOS	*: Late onset sepsis*
LPS	*: Lipopolysaccharide*
LV	*: Left ventricle*
LVEDA	*: Left ventricular end-diastolic area*
LVEDD	*: Left ventricular end-diastolic diameter*
LVEDV	*: Left ventricular end-diastolic volume*
LVESD	*: Left ventricular end-systolic diameter*
LVESV	*: Left ventricular end-systolic volume*
LVO	*: Left ventricular output*
MAP	*: Mean airway pressure*

List of Abbreviations (Cont...)

Abb.	Full term

MAS ..... : Meconium aspiration syndrome
MPI ..... : Myocardial performance index
Mv ..... : Mitral valve
n ..... : Number
NEC ..... : Necrotizing enterocolitis
NO..... : Nitric oxide
NSE ..... : Neuron-specific enolase
NIRS..... : Near-infrared spectroscopy
NICU ..... : Neonatal intensive care unit
OER ..... : Oxygen extraction ratio
OI ..... : Oxygenation index
OSI..... : Oxygen saturation index
pre-OL..... : Progenitor cells
PaCO2..... : Arterial partial pressure of carbon dioxide
PaO2 ..... : Arterial partial pressure of oxygen
p ..... : Pressure gradient
PASP..... : Pulmonary artery systolic pressure
PDA..... : Patent ductus arteriosus
PDE3..... : Phosphodiesterase 3 enzyme
PDE5..... : Phosphodiesterase 5 enzyme
PFO..... : Patent foramen ovale
PGI2..... : Prostacyclin
PGIS ..... : Prostacyclin synthase
PG ..... : Prostaglandin
PGs..... : Prostaglandins
PEEP ..... : Positive end-expiratory pressure
P/F ratio..... : PaO2/ FiO2
PH ..... : Pulmonary hypertension
PIP ..... : Peak inspiratory pressure
PLAX..... : Parasternal long axis
PMA..... : Postmenstrual age
PNA..... : Postnatal age
PPHN..... : Persistent pulmonary hypertension of the newborn

List of Abbreviations (Cont...)

Abb.	Full term

PROM ..... : Premature rupture of membranes
PSAX..... : Parasternal short axis
PVL ..... : Periventricular leukomalacia
PVR..... : Pulmonary vascular resistance
PW..... : Pulsed-wave mode of Spectral Doppler
QS ..... : Quiet sleep
RA ..... : Right atrium
RAP..... : Right atrial pressure
RDS..... : Respiratory distress syndrome
ROC ..... : Receiver operating characteristic curve
ROS..... : Reactive oxygen species
RPA..... : Right pulmonary artery
rSO2..... : Regional tissue oxygenation
RSVP ..... : Right ventricular systolic pressure
RV ..... : Right ventricle
RVO ..... : Right ventricular output
RVSP ..... : Right ventricular systolic pressure
SaO2 ..... : Arterial oxygen saturation
SBF..... : Systemic blood flow
SD ..... : Standard deviation
sGC ..... : Soluble guanylate cyclase
SIMV..... : Synchronized intermittent mandatory ventilation
SNAP II ..... : Scoring for acute neonatal physiology
SVC..... : Superior vena cava
SVO2..... : Venous oxygen saturation
SVR..... : Systemic vascular resistance
SWC..... : Sleep-wake cycling
TI ..... : Inspiratory time
TTN..... : Transient tachypnea of newborn
TR ..... : Tricuspid regurgitation
TV ..... : Tidal volume
Tv ..... : Tricuspid valve
v ..... : Blood velocity

List of Abbreviations (Cont...)

Abb.	Full term

Vmax..... : Peak velocity
Vmax TR..... : Peak velocity of tricuspid regurgitation jet
VO2 ..... : Oxygen consumption
VO2/DO2 ... : Oxygen extraction ratio
V/Q..... : Ventilation/perfusion
VTI..... : Velocity time integral
W/AS..... : Wakefulness/active sleep
WMI..... : White Matter Injury
WBC..... : White blood cell

ABSTRACT

Background: Amplitude-integrated electroencephalography (aEEG) has been used in clinical research to study the relationship between changes in neonatal cardiovascular function and brain activity.

Aim of the Work: To evaluate the impact of cardiovascular compromise on cerebral cortical activity (aEEG measurements) in non-asphyxiated neonates with persistent pulmonary hypertension of newborn (PPHN) or those with shock and hypotension and to identify neonates at risk for neurologic compromise and the relevance of an abnormal aEEG trace to associated hemodynamic changes, therapeutic interventions and short-term clinical outcome measures in these neonates.

Study design: Fifty critically-ill neonates (30-38 weeks' gestation) with cardiovascular compromise; septic shock and hypotension (n=20), persistent pulmonary hypertension of newborn (PPHN) (n=5), or both (n=25), were enrolled into a prospective observational cohort study. All newborns were subjected to thorough history taking and clinical examination. SNAP II scoring and cardiorespiratory therapeutic interventions were recorded. Serum lactate and neuron specific enolase (NSE) levels were measured at enrollment. Functional echocardiographic evaluation and aEEG monitoring were commenced within the first 24 hours of enrollment and repeated 48-72 hours from weaned inotropic support (n=38), with follow-up of the patients to report their final outcome.

Results: Total aEEG scores were significantly lower among neonates with severe SNAP II score as compared to those with mild and moderate scores ($p = 0.021$). Initial superior vena cava (SVC) flow, right ventricular output (RVO) values and total aEEG scores were significantly lower ($p=0.000$, $p=0.000$, $p=<0.001$ respectively) in comparison to their corresponding follow-up records. Survivors (n=27) had significantly higher aEEG scores at initial and follow up assessment ($p=0.002$ & $p=0.000$) and significantly lower serum lactate and NSE levels ($p=0.000$ respectively), as compared to non-survivors. A significant positive correlation was found between total aEEG score and mean arterial blood pressure ($r=0.504$, $p=0.000$) at initial assessment, meanwhile, follow-up aEEG total scores were inversely correlated with both serum lactate and NSE levels ($r=-0.455$ & $p=0.004$) and ($r = -0.488$ & $p = 0.002$) respectively. Logistic regression analysis revealed that serum lactate level of > 34.3 mg/dl was a significantly high risk factor of mortality prediction with odds ratio (95% CI) of 44.00 (5.085 - 380.71), $p = 0.001$. ROC curve analysis showed NSE at cutoff value > 50 ng/ml has 83.3% PPV, 88.5% NPV, 86.96% sensitivity and 85.19% specificity for mortality prediction.

Conclusion: Significant derangement of brain electrical activity is encountered in critically-ill neonates with cardiovascular compromise. It could be speculated that aEEG monitoring of these neonates might help to predict their short-term clinical outcomes.

Keywords: neonatal shock; PPHN; functional echocardiography; amplitude-integrated electroencephalography (aEEG).