# NEUROPROTECTIVE ROLE OF IBUPROFEN IN HYPOXIC ISCHEMIC ENCEPHALOPATHY IN TERM INFANTS

**THESIS**

*Submitted for total Fulfillment of the M.D Degree in Pediatrics*


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**2010**

# ABSTRACT

***Introduction:*** Pro inflammatory cytokines are important mediators causing brain injury in neonates with H.I.E. ***Objective*****:** This work aims to test the hypothesis that an anti-inflammatory agent (Ibuprofen) can ameliorate the brain injury in HIE and improve neuro-developmental out come when given to term infants immediately after the insult. ***Patients and methods***: 40 asphyxiated term infants were assigned to one of two subgroups: Intervention and non-interventions; the intervention subgroup received 3 doses of oral Ibuprofen (10mg\kg at 6hrs postnatal then 5mg\kg at 24 and 48 hrs). 20 full term healthy neonates of matched age, sex and weight were served as control. Urinary PGE2 was measured at enrollment and after administration of last dose of the drug. Serial cranial sonar, clinical and neurological evaluation and developmental screening were performed. ***Results:*** Intervention and non-intervention subgroups did not differ regarding the severity of HIE at enrollment nor the incidence of neurological abnormalities at hospital discharge. The mean urinary PGE2 level was statistically significantly higher in asphyxia group compared to control group. Within the asphyxia group, there was statistically significant difference between grade II and grade III HIE regarding the mean of initial urinary PGE2 level where it was higher in grade III. Meanwhile, there was statistically significant deference between the two grades of HIE regarding the mean urinary PGE2 after the last drug dose within the intervention subgroup where it was 1.31 pg/ml ± 1.018 in grade II versus 4.37 pg/ml ± 2.07 in grade III. The results of the present study confirm the ability of neurosonography to identify wide variety of parenchymal abnormalities. As regards timing of events, earliest son graphic abnormalities to be observed were diffuse parenchymal echoes or slit like ventricles. Focal and periventricular echo dense lesion made their first appearance on day 3 of life. Interestingly, pattern and severity of son graphic findings was directly related to the severity of hypoxic injury. In striking contrast none of the patients with severe HIE (stage Ш) had normal scans. While focal parenchymal or periventricular lesions characterized severe HIE, slit like ventricles were the predominant neurosonographic abnormality in stage II HIE. ***Conclusion:*** Although level of PGE2 decreases by administration of oral Ibuprofen in grade II HIE yet early administration of the drug did not affect out comes in infants with perinatal asphyxia. This may be explained by ineffectiveness in blocking inflammatory cytokines, if dose and route of administration were inadequate, or if other mediators existed that could have a more powerful role in brain injury during hypoxia-ischemia.

**Key words:**

Asphyxia; Neonate; Neuroprotection; Urinary Prostaglandins, Ibuprofen.

# ACKNOWLEDGMENT

First, grace and foremost thanks to "God" for blessing this work until it has reached its end, as a little part of his generous help throughout our life.

I would like to express my sincere gratitude and respect to **Dr. Manal El-Sayed**, Professor of Pediatrics, Faculty of Medicine, Cairo University for her continuous guidance and supervision, her kind encouragement and support throughout the entire period of the study.

It is my pleasure to express my unlimited appreciation and deepest thanks **Dr. Marian Fathy Morgan**, Assistant Professor Chemical Pathology, Faculty of Medicine, Cairo University for her continuous supervision and great help.

I wish to thank **Dr. Khalil Abd El-Khalik**, Lecturer of Pediatrics Faculty of Medicine, Cairo University for guidance throughout this study.

Special thanks to **Dr. Yasmin Mansi**, Lecture of Pediatrics, Faculty of Medicine, Cairo University for great help.

I am deeply grateful to my family, especially to my father and mother for their generous help and encouragement.

Last but not least I would like to thank every one who helped in completing this work.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AA** | Arachidonic Acid |
| **ADR** | Adverse Drug Reactions |
| **AG** | Arachidonyol Glycerol |
| **ACOG** | American College of Obstetric and Gynecology |
| **APP** | American Academy of Pediatrics |
| **ATP** | Adenosine Triphosphate |
| **CBC** | Complete Blood Picture |
| **CBF** | Cerebral Blood Flow |
| **CDK** | Cyclin Dependent Kinase |
| **COX** | Cyclo Oxygenase Enzyme |
| **CPAP** | Continuous Positve Airway Pressure |
| **DWI** | Diffusion – Weighted Imaging |
| **EEG** | Electro Encephalo Gram |
| **ELISA** | Enzyme Linked Immune Sorbant Assay |
| **EPO** | Erythropoietin |
| **ES** | Embryonic Stem Cells |
| **GA** | Gestational Age |
| **HIE** | Hypoxic Ischemic Encephalopathy |
| **IBD** | Inflammatory Bowel Disease |
| **ICP** | Intracranial Pressure |
| **IGF1** | Insulin-like Growth Factor |
| **IVH** | Intraventricular Hemorrhage |
| **LPs** | Liposaccharride |

| | |
|---|---|
| **MRS** | Magnatic Resonance Spectroscopy |
| **N-AA** | N-Acetyl Aspartate |
| **NDO** | Neurodevelopmental Outcome |
| **NE** | New Born Encephalopathy |
| **NE** | Neonatal Encephalopathy |
| **NEP** | Neutral Endopeptidase |
| **NMDA** | N-Methyl-D Aspartate |
| **NO** | Nitric Oxide |
| **NSAID** | Non Steroidal Anti-Inflammatory Drug |
| **NSF** | Neurosonographic Finding |
| **PDA** | Patent Ductus Arteriosus |
| **PGs** | Prostaglandins |
| **PROM** | Pre-mature Rupture of Membranes |
| **PVE** | Peri ventricular Encephalomalacia |
| **PWMD** | Peri Ventricular White Matter Disease |
| **RNS** | Reactive Nitrogen Species |
| **ROS** | Reactive Oxygen Species |
| **SIADH** | Syndrome of in Appropriate Anti Diuretic Hormone Secretion |
| **SSEP** | Somatosensory Evoked Potentials |
| **TAX2** | Thromoxane Syntheses |
| **VD** | Vaginal Delivery |
| **VEP** | Visual Evoked Potentials |
| **WMD** | White Matter Disease |

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بسم الله الرحمن الرحيم

# (وقل رب زدنى علما)

(صدق الله العظيم)

(سورة طه – ١١٤)

# *Introduction & Aim of the Work*

Since the pathogenesis of neuronal death and Intraventricular hemorrhage( IVH) secondary to hypoxic-ischemic and reperfusion insults may be due to cerebrovascular dysfunction, microvascular occlusion, loss of autoregulation and vasogenic cerebral edema and all may be in part due to intra cellular calcium influx and activation of phospholipase $A_2$ with subsequent activation of cyclooxygenase enzyme and production of Prostaglandins (PG) and Thromboxanes(TxA2) ***(Evans and Levene, 1999; Sapirstein and Bonventre, 2000; Iadecola et al., 2001),*** hence indomethacin (cyclo oxygenase inhibitor) might decrease the incidence of IVH and White matter disease (WMD) in asphyxiated neonates ***(Evans and Levene, 1999).***

***Fowli and Davis (2002)*** reported that indomethacin decreases baseline cerebral blood flow (CBF) and modulates CBF changes in response to hypercarbic insults, decreases serum prostaglandin levels, and promotes germinal matrix maturation.

However, indomethacin prophylaxis for IVH has never been used widely, because of its adverse effects on renal function and gastrointestinal tract ***(Fowlie and Davis, 2002).***

In contrast, ***Shah and Ohlsson (2003)*** demonstrated that ibuprofen (another cyclooxygenase inhibitor) was effective in closing Patent ductus arteriosus (PDA) without reducing CBF or affecting cerebral vasoreactivity to arterial carbon dioxide tension or intenstinal or renal hemodynamics.

Furthermore, ibuprofen enhances CBF auto-regulation and was shown to protect neurological function after oxidative stresses ***(Lago et al., 2002).***

# *Aim of the Work*

To test the hypothesis that whether prophylactic use of oral ibuprofen after hypoxic ischemic insult in term infants would reduce the incidence of IVH and its progression into grade II-IV as well as the development of WMD among neonates with hypoxic ischemic encephalopathy in the reperfusion phase.

# Hypoxic-Ischemic Brain Injury In the Newborn

In the past, the terms hypoxic-ischemic encephalopathy (HIE) of the newborn and perinatal asphyxia have been used, rather loosely, as synonyms. Clinical signs of HIE are often wrongfully considered to result from intrapartum asphyxia. This misconception has led to HIE being considered a marker of perinatal obstetric mismanagement, one leading to many medicolegal problems ***(Feigin, 2003).***

In reality, establishing a clear relationship between perinatal brain injury and ischemia/hypoxemia is often difficult ***(Truelsen and Grenier, 2006).***

The term birth asphyxia is also imprecise, and its use is not recommended because of the implication that intrapartum anoxia has occurred ***(Paul, 2007).***

In the immediate newborn period, many factors can produce neurologic symptoms mimicking those of HIE, including prepartum and postpartum ischemia/hypoxemia, genetic factors, metabolic disease, and maternal and fetal drug use ***(Bejot, 2007).***

Because the relationship between asphyxia and HIE cannot always be established, the term newborn encephalopathy (NE) was proposed as an alternative to remove the medicolegal implications of HIE ***(Lium and Nelson, 2007).***

Newborn encephlopathy (NE) is a clinically defined syndrome of disturbed neurologic function in full-term infants that attempts to correlate symptoms in the neonatal period that have some relationship with neurologic outcomes in childhood. NE symptoms may or may not be causally linked to hypoxemia/ischemia. Far from fixing the problem, use

of the term NE just removes from obstetric practitioners the unfair blame they receive for poor neonatal outcomes ***(Lavauos, 2007).***

The National Collaborative Perinatal Project (NCPP), a prospective study of more than 50,000 pregnancies and 40,000 infants, was conducted to analyze the features of NE. Its results showed that the following were associated with increased morbidity on follow-up examination: decreased activity after the first day of life, need for incubator more than 3 days, feeding problems, poor suck, and respiratory difficulties ***(Payne, 2006).***

Other factors not mentioned in the description of NE syndrome have been associated with postneonatal morbidity. Examples are static motor deficits (cerebral palsy), mental retardation, and epilepsy. These factors include neonatal seizures, low 10-minute Apgar scores, stupor, and coma ***(Hankey, 2007).***

## PATHOPHYSIOLOGY:

In the fetus or newborn with an acute asphyxial event; initially CBF increases but after compensatory efforts fail the CBF becomes dependent on systemic blood pressure ***(Martin and Lombroso, 2006).*** As the systemic blood pressure falls, so does CBF, resulting in decreased oxygen delivery which leads to intracellular energy failure. The severity of damage is dependent not only on the initial injury but also on reperfusion injury and apoptosis ("delayed phase of neuronal injury") ***(Tonse et al. 2006).***

HIE can be divided into two broad events: **primary** and **secondary** neuronal death ***(Fanaroff and Leviton, 2006)***. **Primary** neuronal damage is due to failure of circulation, with decrease O2 delivery to the tissue and resulting failure of the Na-K ATPase pumps which results in cell edema and death ***(Walsh et al. 2006).***

**Secondary** neuronal damage occurs 8 to 72 hours after the initial insult with production of cytokines and other proinflammatory agents, excessive glutamate release and inducible nitric oxide ***(Martin and Lombroso, 2006).***

## Causes of HIE *(Martin and Lombroso, 2006).*

- ***Maternal:*** Cardiac arrest, asphyxiation, severe anaphylaxis, status epilepticus, and hypovolemic shock.
- ***Uteroplacental:*** Placental abruption, cord prolapse, uterine rupture, and hyperstimulatio**.**
- ***Fetal:*** Fetomaternal hemorrhage, severe isoimmune hemolytic disease, and cardiac arrhythmia.

## Defining Asphyxia

According to the guidelines of the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG), neonatal asphyxia requires all of the following ***(Tonse et al. 2006):***

- Profound metabolic or mixed acidemia (pH <7.00) in an umbilical artery blood sample (if obtained).
- Persistence of an Apgar score of 0-3 for longer than 5 minutes.
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia).
- Multiple organ involvement (e.g. kidney, lungs, liver, heart, intestine).