Serum Neutrophil Gelatinase Associated Lipocalin (NGAL) as a Predictor of Acute Kidney Injury in Perinatal Asphyxia

Thesis

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By

Seham Ahmed Abdel Hamed El Beltagy
(M.B; B.Ch.), Menofia University (2004)

Supervised By

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

Dr. Nermin Helmy Mahmoud
Assistant Professor of clinical pathology
Faculty of Medicine - Ain Shams University

Dr. Soha Mohamed Khafagy
Lecturer of Pediatrics
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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تقييم مستوى (ن.ج.ا.ل) بالمصل كعامل تنبوء بالاصابة الكلوية الحادة فى حالات إختناق ما حول الولادة

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مقدمة من الطبيبة
سهام احمد عبد الحميد البلتاجى
بكالوريوس الطب والجراحة جامعة المنوفية

تحت إشراف

أستاذ دكتور / نهال محمد الرجال
أستاذ طب الأطفال
كلية الطب - جامعة عين شمس

دكتور / نرمين حلمى محمود
أستاذ مساعد الباثولوجيا الاكلينيكية
كلية الطب - جامعة عين شمس

دكتور / سها محمد خفاجى
مدرس طب الأطفال
كلية الطب - جامعة عين شمس

كلية الطب
جامعة عين شمس
٢٠١١

Summary and Conclusion

Perinatal asphyxia is the medical condition resulting from deprivation of oxygen (hypoxia) to a newborn infant long enough to cause apparent harm.

The aim of this work was to evaluate the value of serum NGAL measurement as an early predictor of acute kidney injury in asphyxiated neonates.

Our study was a case - control study, carried on 20 term newborns diagnosed as HIE. Cases group had mean G.A(37.9 ±1.1)weeks and birth weight .3050±506.3 gm .while control group(20 term healthy newborns) had mean G.A(38.1± 1.07) weeks and birth weight (3317.5±409.5) gm.

Perinatal asphyxia was diagnosed based on the presence of at least two of the following:

1. Profound metabolic or mixed acidemia (pH<7.00) in an umbilical artery blood sample with base deficit >10m mol/L.
2. Persistence of Apgar score of ≤ 3 and ≤ 5 at one and five minutes respectively.
3. Neonatal neurological sequelae (seizures, coma, hypotonia).
4. Multiple organs involvement (kidney, lungs, liver, heart, intestine).

Both groups were subjected to complete history taking, thorough clinical examination, laboratory investigations including CBC, CRP, BUN, Cr.

Serum samples were collected in the first 24hrs of life from cases and controls in order to detect serum NGAL levels by ELIZA.

In the present study, the median level of serum NGAL in control group was 39.75ng/ml with IQ range of 6.0-48.0 ng/ml

Contents

List of Abbreviations

AAP	American Academy of pediatrics
ABG	Arterial Blood Gases
ACOG	American college of obstetrics and Gynecologists
ADH	anti diuretic hormone
ADPKD	autosomal-dominant polycystic kidney disease
AKI	Acute kidney injury
AMPA	amino-3-hydroxy-5-methyl-4 isoxazole propionate
APR	acute phase response
ARF	acute renal failure
ATN	acute tubular necrosis
ATP	Adenosine triphosphate
BUN	Blood urea nitrogen
CBF	cerebral blood flow
CKD	chronic kidney disease
CNS	Central nervous system
CRP	C-reactive protein
CSF	cerebrospinal fluid
D*HUS	Diarrhea-associated hemolytic-uremic syndrome
DIC	disseminated intravascular coagulation
DMSA	Dimercaptosuccinic acid
DTPA	diethylene-triamine-penta-acetic acid
EAA	Excitatory amino acid
eGFR	estimated Glomerular Filtration Rate
ER	endoplasmic reticulum
ESRD	end-stage renal disease
FENa	Fractional excretion of sodium
GABA	gamma-aminobutyric acid transaminase
GFR	glomerular filtration rate
GGT	gamma glutamyl transpeptidase
HCG	higher cystic growth
HER-2	Human epidermal growth receptor 2

List of Abbreviations (Cont.)

HIE	Hypoxic-Ischemic Encephalopathy
HMW	high molecular weight
13-cisRA	13-cis retinoic acid
HNL	Human neutrophil lipocalin
HO-1	hemeoxygenase 1
IL	interleukin
IL-18	interleukin 18
IL-1beta	interleukin-1beta
ILCOR	International Liaison Committee on Resuscitation
IVH	Intraventricular Hemorrhage
KIM-1	kidney injury molecule 1
MRI	Magnetic Resonance Imaging
NAG	N-acetyl glucosaminidase
NEC	Necrotizing Enterocolitis
NHE3	sodium hydrogen exchanger Isoform 3
NL	neutrophil lipocalin
NMDA	N-methyl-D-aspartate
NOS	nitric oxide synthase
NRP	Neonatal Resuscitation Program
OA	Osteoarthritis
SF	synovial fluid
PCI	percutaneous coronary interventions with coronary angiography
PVL	Periventricular Leukomalacia
RI	Resistive index
SCr	Serum creatinine
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	Systemic Lupus Erythrematosus
sNGAL	Serum neutrophil gelatinase-associated lipocalin
uNGAL	Urine neutrophil gelatinase-associated lipocalin
α-GST	α- glutathione S-transferase
π-GST	π-glutathione S-transferase

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Seham Ahmed Abdel Hamed El Beltagy

INTRODUCTION

Perinatal asphyxia is the medical condition resulting from deprivation of oxygen (hypoxia) to a newborn infant long enough to cause apparent harm. It results most commonly from a drop in maternal blood pressure or interference during delivery with blood flow to the infant's brain. This can occur due to inadequate circulation or perfusion, impaired respiratory effort or inadequate ventilation. Perinatal asphyxia happens in 2 to 10 per 1000 newborns that are born at term. ***(Barkovich and Truwit, 2008)***.

Hypoxic damage can occur to most of the infant's organs (heart, lung, liver, gut, and kidney). Acute kidney injury, formly known as acute renal failure, continues to represent a very common and potentially devastating problem in neonatal ICU ***(Bailey et al., 2007)***.

In current clinical practice, acute kidney injury is typically diagnosed by measuring serum creatinine .Unfortunately; creatinine is an unreliable indicator of AKI ***(Bellomo et al., 2004)*** .Serum creatinine varies with age, sex, muscle bulk, metabolism, drugs and hydration status. It will not change until >50%of kidney function has already been lost ***(Deverajan, 2007)***. Hence identification of a novel AKI biomarker has been designated as a top priority by the American Society of Nephrology ***(American Society of Nephrology, 2005)***.

Neutrophil gelatinase associated lipocalin or NGAL is a 25kDa secretory glycoprotein, belongs to the lipocalin family of proteins. Human NGAL was originally isolated from the supernatant of activated neutrophils. Renal expression of NGAL increases dramatically after renal ischemia, .This is reflected by the rapid rise in urinary NGAL reported in AKI. Serum and urine NGAL has been demonstrated to be a sensitive and specific early marker of AKI ***(Mishra et al., 2005).***

To the best of our knowledge, there is only one report studying urinary NGAL levels in preterm neonates. This report stated that serum and urine NGAL has been demonstrated to be a sensitive and specific early marker of AKI in these neonates (***Michael et al., 2008)*.**

Aim of The Work

This study was designed to evaluate the value of serum NGAL measurement as an early predictor of acute kidney injury in asphyxiated neonates.

Perinatal Asphyxia and Hypoxic Ischemic Encephalopathy

Introduction and Definition :

Hypoxic-ischemic encephalopathy (HIE) is defined as; the interruption of supply of vital nutrients to the brain, mainly oxygen and glucose, sufficiently substantial to cause irreversible damage. When the brain is depleted of oxygen, the result is hypoxic encephalopathy while impaired blood flow to the brain results in cerebral ischemia. Blood flow could be interrupted regionally, within a specific vascular distribution as with an embolic event causing a stroke, or globally as with a cardiopulmonary arrest leading to severe hypoxia and generalized ischemia ***(Korthals and Colon, 2005).*** When there is impairment in the exchange of respiratory gases, oxygen, and carbon dioxide, the result is asphyxia.

Perinatal Asphyxia is the medical condition resulting from deprivation of oxygen (hypoxia) to a newborn infant long enough to cause apparent harm. It results most commonly from a drop in maternal blood pressure or interference during delivery with blood flow to the infant's brain. This can occur due to inadequate circulation or perfusion, impaired respiratory effort or inadequate ventilation (***Barkovich and Truwit, 2008***).

There is no single tool that can yield a precise definion of Perinatal Asphyxia but the American Academy of pediatrics (AAP) and the American college of obstetrics and Gynecologists (ACOG) committees of maternal fetal medicine and fetus and newborn in 1996 defined certain criteria that must be present to confirm the occurrence of Perinatal asphyxia. In cases on which such evidence is lacking, it cannot be concluded that perinatal asphyxia exists ***(AAP and ACOG, 1996). (Table 1)***

Table (1): Essential criteria of Perinatal Asphyxia.

1) Profound metabolic or mixed acidemia (ph<7.00) in an umbilical cord arterial blood sample.
2) Persistence of an Apgar score of 0 to 3>5 minutes.
3) Clinical neurologic sequelae in the neonatal period (e.g., seizures, hypotonia, coma or HIE).
4) Evidence of multiorgan system dysfunction in the immediate neonatal period.

(AAP and ACOG, 1996)

Incidence:

Hypoxic ischemic insult is an important cause of death and disability. In Egypt and other developing countries, perinatal asphyxia is the most important cause of hypoxic ischemic brain damage in the full-term newborn infants. HIE is known to lead to a higher morbidity and mortality among these infants ***(Boo et al., 2000).*** The incidence of perinatal asphyxia is about 1.0 to 1.5% in most centers and is usually related to gestational age and birth weight. It occurs in 9% of infants less than 36 weeks gestation ***(Legido et al., 2000),*** and in 0.5% of infants more than 36 weeks gestation accounting for 20% of perinatal deaths or as high as 50% of deaths if stillborns are included ***(Levene, 1999).*** The incidence is higher in term infants of diabetic or toxemic mothers. These factors correlate less well in preterm infants; intrauterine growth retardation and breech presentation are associated with an increased incidence of asphyxia. Post mature infants are also at risk ***(Aurora and Snyder, 2004).***

Causes of Hypoxic-Ischemic Encephalopathy:

There are multiple causes of asphyxia, and they may be related to the maternal factors, placenta, umbilical cord, fetus, or infant ***(Leuthner and Das, 2004)***. Most cases of HIE result from injury in the prenatal period secondary to intrauterine asphyxia, with disturbance of gas exchange across the placenta and with respiratory failure at birth.