

Prognostic Value of Human Angiogenin For Intraventricular Hemorrhage in Preterm Neonates

Thesis

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List of Abbreviations

A	
Akt/PI3K	Akthymoma/ phosphatidylinositol 3-kinase
AGA	Appropriate for gestational age
ALS	Amyotrophic lateral sclerosis
ANG	Angiogenin
ANOVA	One way analysis of variance
ART	Assisted reproductive technology
B	
BPD	Bronchopulmonary dysplasia
C	
CBF	Cerebral blood flow
Cgmp	Cyclic guanosine monophosphate
CI	Confidence interval
CS	Cesarean section
CSF	Cerebrospinal fluid
CT	Computerized tomography
CUS	Cranial ultrasound
D	
DIC	Disseminated intravascular coagulopathy
DM	Diabetes mellitus
E	
EGF	Epidermal growth factor
ELBW	Extremely low birth weight
ELISA	Enzyme-linked immunosorbent assay
ERK1\2	extracellular-signal-regulated kinases 1\2
F	
FGF	Fibroblast growth factor
FT	Full term neonates

G	
GLN	Glutamine
GMH/IVH	Germinal Matrix Hemorrhage/Intraventricular Hemorrhage
H	
HFOV	High frequency oscillatory ventilation
HIE	Hypoxic ischemic encephalopathy
HIF1 α	Hypoxia-inducible factor 1-alpha
hPRI	Human placental ribonuclease inhibitor
Hrs	Hours
HS	Highly significant test
HTN	Hypertension
H HPW	Hypertensive pregnant women
HUVECs	Human umbilical vein endothelial cells
I	
IBD	inflammatory bowel disease
ICH	Intracranial hemorrhage
IGF-1	Insulin like growth factor-1
IQ	Intelligence quotient
IQR	Interquartile range
IM	Intra muscular
IV	Intravenous
IVH	Intraventricular hemorrhage
IU	International Unit
IUGR	Intrauterine growth retardation
L	
LBW	Low birth weight
LP	Lumbar puncture
M	
MEF2C	myocyte enhancer binding factor 2C
MMPs	Matrix metallo-proteinases
MNs	Motor neurons
mRNA	Messenger Ribonucleic acid

N	
NEC	Necrotizing enterocolitis
Ng	Nano gram
NICUs	Neonatal intensive care units
nm	Nanometer
NO	Nitric oxide
NonPCs	Non-pregnant controls
NS	Insignificant test
NTPW	Normotensive pregnant women
NVD	Normal vaginal delivery
P	
P	Probability value
PDA	Patent DuctusArteriosus
PHVD	Post-hemorrhagic ventricular dilatation
PHH	Posthemorrhagic hydrocephalus
PI3K	Phosphatidylinositol 3-kinase
PIVH	Peri-intraventricular hemorrhage
PLC	Phospholipase C
PROM	premature rupture of membranes
PVH/IVH	Periventricular/Intraventricular Hemorrhage
PVL	Periventricular leukomalacia
PT	Preterm neonates
R	
RDS	Respiratory distress syndrome
RISPASE	RNases with special biological actions
RNase	Ribonuclease
Roc	receiver operating characteristic
ROP	Retinopathy of prematurity
rRNA	Ribosomal ribonucleic acid
S	
SPSS	Statistical package for social science
T	
t-PA	Tissue plasminogen activator
tRNA	Transfer ribonuclease acid

V	
VEGF	Vascular endothelial growth factor
VLBW	Very low birth weight
VP shunt	Ventriculo-peritoneal shunt
VVO	Vesiculo-vacuolar organelles
vWF	Von Willebrand factor
W	
wks	Weeks
Y	
yrs	Years

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INTRODUCTION

Preterm birth is one of the major clinical problems in obstetrics and neonatology as it is associated with perinatal mortality, serious neonatal morbidity and in some cases childhood disability. It is reported that 60-80% of all neonatal mortality and morbidity is due to preterm birth. During the last two decades the survival for premature infants has significantly increased due to advancement in perinatal and neonatal treatment expertise and improvement in the care of high-risk mother. The survival rate of lower birth weight infant is reported to have increased from 10% to 50-60% (**Goldenberg, 2002**).



Hemorrhage into the ventricles of the brain is one of the most serious complications of premature birth despite improvements in the survival of premature infants (**Volpe, 2008**). Intraventricular hemorrhage (IVH) has been attributed to

alterations in cerebral blood flow to the immature germinal matrix microvasculature (***Perlman et al., 1985***). During the late second and early third trimesters of gestation, the microvasculature of the developing brain undergoes considerable angiogenesis to meet the metabolic needs of both the germinal matrix and the rapidly enlarging cortex (***Takashima et al., 1986***).

Large IVH has a high risk of neurological disability and over 50% of these children go on to develop progressive ventricular dilatation (***Volpe, 2008***). Post-hemorrhagic ventricular dilatation (PHVD) remains a complication of prematurity which is associated with high rate of disability, multiple impairments and adverse effect of shunt surgery for hydrocephalus (***Whitelaw et al., 2004***).

Murphy et al., (2002) have provided evidence that PHVD has a more aggressive course than previously with appreciable mortality and morbidity in extremely premature infants. Treatment is much more difficult than other types of hydrocephalus because the large amount of blood in the ventricle combined with the small size and instability of the patient make an early ventriculo-peritoneal shunt operation impossible (***Murphy et al., 2002***).

Angiogenin was originally isolated from HT-29 human colon adenocarcinoma cells and has both angiogenic and non-angiogenic properties. In non-neoplastic conditions, angiogenin is a component of the intercellular matrix encircling endothelium, fibroblasts, and smooth muscle as well as the internal elastic membrane of arterioles and capillaries (**Hu et al., 1994**). Although angiogenin would appear to act principally extravascularly or perivascularly, circulating angiogenin has been detected in serum (**Burgmann et al., 1996**).

Angiogenin expression is regulated by the Akt/phosphatidylinositol 3-kinase pathway. Classified as a member of the RISPASE (RNases with special biological actions) family of RNases, angiogenin possesses homology with other RNases, such as pancreatic RNase A. The ability of angiogenin to induce development of new blood vessels has been shown to be dependent on its ribonucleic activity (**Russo et al., 1996**). It induces angiogenesis by increasing endothelial degradation of extracellular matrix and basal lamina consequently promoting invasion and migration of individual cells. It is hypothesized that angiogenin stimulates the polymerization and release of cell surface actin, a process that may be necessary for eventual cell migration (**Folkman and Klagsbrun, 1987**). A study using cultured endothelium has shown that angiogenin binds to