قياس مستوى الأكتيفين أ في الأطفال المبتسرين حديثى الولادة واستخدامه كمؤشر للإصابة بنزيف فى المخ

رسالة للحصول على درجة الماجستير في طبِ الأطفال
مقدمة من

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كليّة الطبِّ، جامعةً عين شمس ٢٠٠٨

المقدمة:

يعد النزيف فى المخ سببا شائعا فى إصابة الأطفال المبتسرين حديثى الولادة بالإعاقة. كما يعد النزيف داخل البطين المخى هوالشكل الأكثر شيوعا فى نزيف الخ، ونظرا لأنه يؤثر على نسبة من الأطفال المبتسرين تتراوح من١٥ إلى ٢٠ % لذلك فإنه يحظى باهتمام عالى حين حدوثه.

ويعتبر نقص الأكسجين فى المخ أثناء الولادة من أخطر العوامل المؤدية لحدوث نزيف فى المخ وذلك لأنه يُعدّلُ الآلياتَ المسئولة عن تنظيمُ مجرىَ الدمّ المخّيَ مما يُسبّبُ سلسلة الأحداثِ الكيميائية الحيويةِ التى تغير الأيض (الميتابوليزم) مما يُؤدّي إلى حدوث ضررٍ بالغ بالمخ.

ويتكون الأكتيفين أ من وحدتين وهو نوع من أنواع البروتين السكرى الذى تفرزه المشيمة والأغشية الجنينية بكميات كبيرة أثناء الحمل

ويتزايد تركيز الأكتيفين بدرجة ملحوظة فى الدورة الدموية للأم مع ازدياد العمر الرحمى للجنين، بينما لا يوجد اختلاف كبير بين مستوى الأكتيفين أ فى منتصف الحمل وعند نهايته عندما يتم قياسه فى عينة من الحبل السرى للجنين. وبالرغم من ذلك فإن اضطرابات الحمل الناتجة عن نقص الأكسجين الجنينى أو المشيمى تتميز بارتفاع نسبة الأكتيفين أ فى الدورة الدموية لكل من الأم والجنين معا

وقد اتضح وجود الأكتيفين فى مناطق مختلفةمن المخ بعد التعرض لحالات متنوعة من نقص الأكسجين والإمداد الدموى للمخ. وعلاوة على ذلك فإن نقص الأكسجين بالمخ يسبب زيادة مستوى الأكتيفين أ فى الدورة الدموية للأطفال المبتسرين حديثى الولادة، ويمكن أيضا ملاحظة الزيادة فى البول والسائل النخاعى لكل الأطفال اللذين سبق تعرضهم للإختناق ويعانون من ضرر بالغ بالمخ.

هدف العملِ:

إنّ هدفَ هذه الدراسةِ أَنْ تُقيّمَ مستوى الأكتيفين فى الدم فى اليوم الأول بعد الولادة واستخدام النتائج كمؤشر لاحتمال حدوث نزيف بالمخ فى الأطفال المبتسرين حديثى الولادة

المواضيع والطرق:

سوف يتم إجراء الدراسة في الرعاية المركزة لحديثى الولادة بمستشفى النساء والولادة، والرعاية المركزة لحديثى الولادة بمستشفى الأطفال بجامعةً عين شمس وسَوف تتضمن٠ 3طفل حديث الولادة من ذوى العُمرِ الرحمى أقل من ٣٤ إسبوع تم تقسيمهم إلى مجموعتين

معايير الإستثناءِ:

الأطفال المصابين بالعيوبِ الخلقية أو الأنيميا أو من يعانون من مشاكل صحية بسبب عدم توافق فصيلة الدم مع الأم وكذلك يتم استبعاد التوائم أو إصابة الأم بمرض السكرِ .

كُلّ طفل حديث الولادة في الدراسةِ سَيخضعُ للآتى:

١ – تاريخ مرضى كافي مع التأكيدِ على مرحلة ما قبل الولادةِ ، والولادة وما بعد الولادة.

٢ – خلال الفحصِ السريريِ يتم التأكيد على تقييمِ العُمرِ الرحمى ، الوزن عند الولادة.

٣ – ترقيم عددى أبجرى عند الدقيقة الأولى والخامسة بعد الولادة.

٤ – صورة دم كاملة وسى آر بي.

٥ – إجراء اشعة موجات فوق صوتية دماغية لتَقْرير حدوث نزيف فى المخ.

٦ – قياس مستوى الأكتيفين أ فى الدم فى اليوم الأول من الولادة

INTRODUCTION

Intraventricular hemorrhage (IVH) is a major cause of neurologic disabilities in preterm newborns. Also it is the most common variety of cerebral hemorrhage, affects 15%–20% of preterm infants and therefore is a major concern in their care ***(Thorp et al., 2001).***

Perinatal hypoxia is an important risk factor in the pathogenesis of IVH because it alters mechanisms that regulate cerebral blood flow and triggers a cascade of biochemical events that begins with a shift from oxidative to anaerobic metabolism and leads to oxidative brain damage resulting from excessive production of free radicals ***(Lewen et al., 2000; Buonocore et al., 2000).***

Activin A is a glycoprotein composed of 2 βA subunits that belong to the transforming growth factor-β superfamily of differentiation factors and is expressed in the central nervous system ***(Luisi et al., 2001a)***. It is a growth factor (βA/βA dimer) mainly produced by the placenta, decidua and fetal membranes and secreted in large amounts in maternal circulation ***(Debieve et al., 2000).***

Activin A concentrations significantly increase in maternal serum with advancing gestation ***(Florio et al., 2001),*** whereas umbilical cord blood serum do not significantly differ from midpregnancy to term gestation ***(Debieve et al., 2000),***

and are significantly lower than in maternal serum. Disorders of pregnancy due to reduced placental perfusion and various degrees of feto-placental hypoxemia, such as preeclampsia and fetal growth restriction ***(Roberts and Cooper, 2001)*** are characterized by increased levels of maternal and umbilical cord activin A ***(Florio et al., 2001).***

Several models of hypoxic–ischemic brain injury have demonstrated induction of activin A in various brain regions ***(Wu et al., 1999).*** Moreover, intrauterine hypoxia increases activin A in the fetal circulation of preterm newborns ***(Florio et al., 2003),*** and high activin A concentrations have been found in cerebrospinal fluid ***(Florio et al., 2004)*** and urine of asphyxiated full-term newborns who experienced brain damage.

AIM OF THE WORK

The aim of this study is to evaluate the use of plasma activin A concentration to predict the development of intraventricular hemorrhage in preterm newborn.

PREMATURITY

Preterm deliveries are those that occur at less than 37 weeks' gestational age, Preterm births account for 75% of perinatal mortality and more than half the long-term morbidity. Although most preterm babies survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications ***(McCormick 1985).***

Classification of prematurity:

Preterm infants classification: premature infants can be classified by birth weight and appropriateness for gestational age into: premature but appropriate size for gestational age (preterm AGA), preterm but weight small for gestational age (preterm SGA), preterm but with weight large for gestational age (preterm LGA) ***(Lee and Cloherty, 2004).***

- Low birth weight (LBW): The first weight <2500 grams.
- Very low birth weight (VLBW): The first weight <1500 grams.
- Extremely low birth weight (ELBW): The first weight <1000 grams

(Stoll and Kliegman, 2004)

Epidemiology:

The obstetric precursors leading to preterm birth are:

(1) Delivery for maternal or fetal indications, in which labour is either induced or the infant is delivered by prelabour caesarean section

(2) Spontaneous preterm labour with intact membranes
(3) Preterm premature rupture of the membranes (PPROM), irrespective of whether delivery is vaginal or by caesarean section

(Tucker et al., 1991)

PPROM is defined as spontaneous rupture of the membranes at less than 37 weeks' gestation at least 1 h before the onset of contractions. The cause of membrane rupture in most cases is unknown, but asymptomatic intrauterine infection is a frequent precursor. Risk factors for PPROM are generally similar to those for preterm spontaneous labour with intact membranes, although infections and tobacco exposure play important parts ***(Mercer et al., 2000).***

Most women with PPROM begin labour spontaneously within several days; a common complication of PPROM is development of intrauterine infection and preterm labour ***(Romero et al., 1988).***

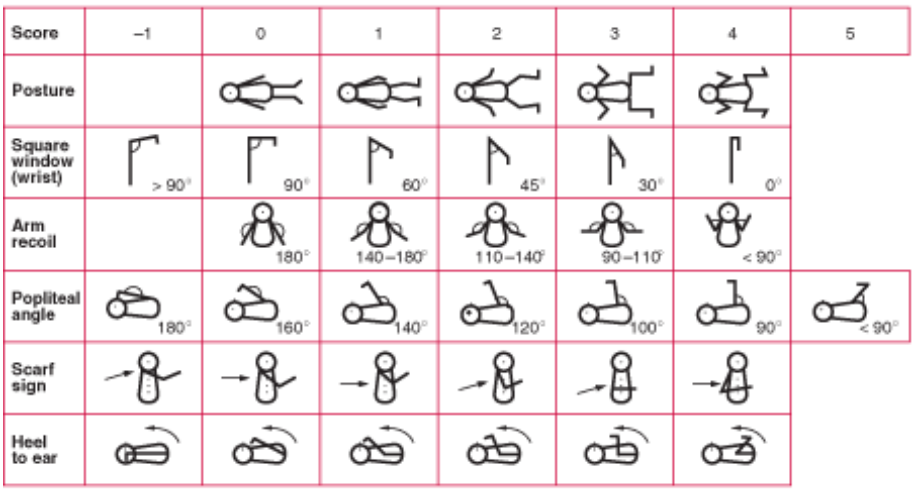
Clinical assessment of prematurity:

The newly expanded new Ballard score (NBS) provides valid and accurate assessment of gestational age for extremely premature infants that were not previously available ***(Ballard et al., 1991)***.

The system is used to evaluate the gestational age through recording physical criteria that might differentiate

extremely premature infants from more mature infants and a final score is obtained following the addition of each category score. The system is accurate ±2 weeks confirmed by last menstrual period and gestational age by prenatal ultra-sonography ***(Lee and Cloherty, 2004)***.

Neuromuscular Maturity



Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm: −1 < 40 mm: −2	> 50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: −1 tightly: −2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
−10	20
−5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Figure (1): New Ballard Score for Gestational Age Assessment ***(Ballard et al., 1991).***

Etiology:

- Women classified as black, African-American, and Afro-Caribbean are consistently reported to be at higher risk of preterm delivery ***(Goldenberg et al., 1996; Fiscella, 1996).***
- Observational studies of the type of work and physical activity related to preterm birth have produced conflicting results ***(Saurel-Cubizolles et al., 2004; Pompeii et al., 2005; Newman et al 2001)***.
- Demographic, social, or economic risks, frequent absence of health insurance, and absence of a strong supportive economic and social care ***(Newman et al., 2001).***
- An interpregnancy interval of less than 6 months confers a greater than two-fold increased risk of preterm birth ***(Smith et al., 2003).***
- Women with previous preterm deliveries had a 2.5–fold increased risk in their next pregnancy ***(Goldenberg et al., 2006; Ananth et al., 2006).***
- Persistent or recurrent intrauterine infections probably explain many repetitive spontaneous preterm births ***(Goldenberg et al., 2006).***
- Multible gestations are risk of preterm delivery, and result in 15–20% of all preterm births ***(Romero et al., 2006).***
- Vaginal bleeding caused by placental abruption or placenta preavia is associated with a very high risk of preterm delivery, but bleeding in the first and second trimesters that is not associated with either placental abruption or placenta

preavia is also associated with subsequent preterm birth ***(Krupa et al., 2006).***

- Extremes in the volume of amniotic fluid (polyhydramnios or oligohydramnios) are associated with preterm labour ***(Jakobsson et al., 2007).***
- Maternal medical disorders, such as thyroid disease, asthma, diabetes, and hypertension, are associated with increased rates of preterm delivery, many of which are indicated because of maternal complications ***(Jakobsson et al., 2007).***

Problems of prematurity:

Preterm delivery is a major cause of perinatal mortality and morbidity. Respiratory distress syndrome (RDS), persistent pulmonary hypertension, intracranial hemorrhage, as well as necrotizing enterocolitis are due to the difficulty of extra uterine adaptation due to immaturity of organ systems ***(Hohlagschwandtner et al., 2001; Watts and Saigal, 2006)***.

Table (1): Neonatal problems associated with premature infants.

Respiratory
Respiratory distress syndrome (Hyaline membrane disease)
Bronchopulmonary dysplasia
Pneumothorax, pneumomediastinum, interstitial emphysema
Congenital pneumonia
Pulmonary hypoplasia, Pulmonary haemorrhage
Apnea
Cardiovascular
Patent ductus arteriosus
Hypotension , Hypertension
Bradycardia (with apnea)
Congenital malformation
Haematologic
Anemia (early or late onset)
Hyperbilirubinemia-indirect
Subcutaneous, organ (liver, adrenal) haemorrhage.
Disseminated intravascular coagulopathy
Vitamin K deficiency.
Hydrops - immune or nonimmune
Gastrointestinal
Poor gastrointestinal function - poor motility
Necrotizing enterocolitis
Hyperbilirubinemia direct and indirect
Congenital anomalies producing polyhydraminos
Spontaneous gastrointestinal isolated perforation
Metabolic- endocrinal
Hypocalcemia
Hypoglycemia, Hyperglycemia
Late metabolic acidosis, Hypothermia
Euthyroid but low - thyroxin status
Central nervous system
Intraventricular haemorrhage
Periventricular leukomalacia
Hypoxic ischemic encephalopathy
Seizures
Retinopathy of prematurity
Deafness
Hypotonia
Congenital malformation
Kernictrus (bilirubin encephalopathy)
Drugs (narcotic withdrawal)
Renal
Hyponatremia , Hypernatremia
Hyperkalaemia
Renal tubular acidosis
Edema
Other
Infections (congenital, prenatal, nosocomial, bacterial, viral, fungal, protozoal)

(Stoll and Kliegman, 2004)

Respiratory: Premature infants may experience the following:

Apnea usually is defined as a cessation of breathing for 20 seconds or more, or of a shorter duration if associated with cyanosis or bradycardia. Different patterns have been observed in premature infants: central apnea (absent breathing movements), obstructive apnea (breathing movements, but no airflow) or mixed apnea (central and obstructive). Preterm with ELBW infants are particularly suffering from obstructive apnea, especially when in supine position with the neck in the midline, because of the weakness of the muscles of the oropharynx. The cessation of gas exchange during a significant apneic episode is manifested by hypoxemia and/or bradycardia. Recurrent episodes of apnea may affect neurodevelopmental outcome ***(Finer et al., 1992).***

Bronchopulmonary dysplasia is defined as supplemental oxygen requirement past 36 weeks' corrected age, or for more than 28 days, with radiographic changes on chest film ***(Bancalari, 2002)***.

Respiratory distress syndrome, which is the leading cause of morbidity in premature infants, is a condition of surfactant deficiency. The greatest risk factor for RDS is low gestational age, Preventing prematurity is the most important way to prevent neonatal RDS. Ideally, this effort begins with the first prenatal visit, which should be scheduled as soon as a mother discovers that she is pregnant. Good prenatal care results in

larger, healthier babies and fewer premature births ***(Rodriguez et al., 2002).***

Neurologic: Premature infants have higher risk for neurologic problems including the following:

IVH Grade I and II hemorrhages are classified as bleeding into the germinal matrix or ventricle and often are without longterm sequela. Grades III and IV hemorrhages are classified as bleeding that dilates the ventricles or has parenchymal involvement, and they are associated with significant neurodevelopmental delays. Severe hemorrhage may lead to death ***(Ritchie, 2002)***.

Cardiovascular: Patent ductus arteriosus. This vessel of fetal circulation functionally closes in the fullterm infant in the first 24 hours of life; however, it may persist in the preterm infant, leading to increased pulmonary blood flow ***(Zahka and Patel, 2002).***

Hematologic: Conditions for which premature infants are at higher risk include the following:

Anemia: Low iron stores, multiple blood tests, blood loss as a result of either organ hemorrhage or hemolysis, and rapid growth are some of the factors that make anemia a practically unavoidable hematologic complication for any premature infant ***(Berry et al., 1997).***

Jaundice: Hepatic immaturity and reduced erythrocyte lifespan, blood group incompatibilities, and increased enterohepatic circulation as a result of poor bowel motility all contribute to the fact that premature infants are very prone to develop jaundice. Because the serum bilirubin binding capacity is decreased in premature infants as a result of the lower serum albumin, the level at which toxicity for the brain and acoustic nerves may occur is much lower than that of the more mature infant ***(Odell et al., 1970).***

Vitamin K and vitamin-K-dependent coagulation factors are present at low concentrations at birth ***(Lane and Hathawy 1985)***.

Nutritional: Nutrition is an essential part of the care of the premature infant. These infants are born with very low stores of fat and carbohydrates, and they rapidly develop nutritional deficiencies in calcium, phosphorus, iron, trace minerals, and vitamins. Postnatally, they rapidly enter a catabolic state unless provided with sufficient nutrients. On the other hand, reversal of this catabolic state often is difficult because of limited feeding tolerance. The first goal of nutrition is to prevent catabolism. Usually, this will be achieved by providing a minimum of 50 kcal/kg/d. In the early days of life, satisfactory nutrition can never be achieved exclusively with milk. Parenteral nutrition provides the additional calories ***(Heird and Gomez, 1996).***