Cord blood IGF-1 and IGFBP-3 levels in asphyxiated term newborns

Ener Cagri Dinleyici, Neslihan Tekin, Omer Colak & M. Arif Aksit

Department of Pediatrics and Biochemistry, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Turkey

Correspondence to: Ener Cagri Dinleyici, MD.
Department of Pediatrics, Eskisehir Osmangazi University, Faculty of Medicine, TR – 26480, Eskisehir, Turkey
PHONE/FAX: +90 222 2290064
EMAIL: timboothtr@yahoo.com

Submitted: July 6, 2006 *Accepted: October 2, 2006*

Key words: **insulin-like growth factor; IGF; IGFBP-3; perinatal asphyxia; term; newborn; hypoxia**

Neuroendocrinol Lett 2006; **27**(6):745–747 **PMID:** 17187018 NEL270606A13

Abstract

OBJECTIVE: Determination and pathogenesis of perinatal asphyxia is still an important problem. During the asphyxial insult and recovery phase, alteration of the growth factors has been demonstrated and there is evidence that expression of insulin-like growth factors (IGF) and their insulin-like growth factor binding proteins (IGFBP) in injured sites in experimental studies. Aim of this study was to evaluate relationship between serum IGF-1, IGFBP-3 levels and perinatal asphyxia.

PATIENTS AND METHODS: 18 term-newborn who defined as perinatal asphyxia and 12 term-healthy newborn were enrolled. Umbilical cord IGF-1 and IGFBP-3 levels were detected and searched correlation with apgar scores and umbilical artery gas analysis as pH, pCO_2, pO_2, base excess, HCO_3, ctO_2, SO_2 and lactate levels.

RESULTS: Cord blood IGF-1 and IGFBP-3 levels for asphyxiated newborns were lower than normal group (27.8±2.6 ng/ml, 55.1±2.8 ng/ml respectively, $p<0.01$ for IGF-1; 1107.7±320.4, 1682.5±364.1, $p<0.001$ for IGFBP-3). Cord blood IGF-1 levels were positively correlated with birth weight; first and 5th minute Apgar score, cord blood arterial pH, ABE, HCO_3, SO_2 levels. Cord blood IGFBP-3 levels were positively correlated with first and 5th minutes Apgar scores, cord blood arterial pH, pCO_2, ABE, HCO_3, SO_2, and also negatively correlated with cord CO_2 and cord lactate levels.

CONCLUSIONS: Our study demonstrates that exposure to hypoxia and acidosis at birth strongly correlated with a fall in IGF-1 and IGFBP-3 levels in cord blood.

Introduction

Perinatal asphyxia continues to be a major cause of neonatal deaths and neurodevelopmental sequel despite marked improvement in perinatal care. Asphyxial insult, which in majority occurs in utero or intrapartum period, can trigger a cascade of pathophysiological events. While multiple biochemical cascades contribute to the pathogenesis of hypoxic-ischemic brain injury, at the same time protective mechanisms operate to prevent from ongoing injury [1–2]. During the asphyxial insult and recovery phase, alteration of the growth factors has been demonstrated and there is evidence that expression of insulin-like growth factors (IGF) and their insulin-like growth factor binding proteins (IGFBP) in injured tissues reduce cell death and improve tissue repair [3–6]. Animal studies suggest that circulating IGF-1 concentrations are influenced by hypoxia [7–8].

ORIGINAL ARTICLE

Table 1. Mother's age, birth weight, umbilical artery parameters and umbilical cord IGF-1 and IGFBP-3 levels of study group.

	Asphyxia group (n=18)	Controls (n=12)	p
Mother's age (year)	29.8 ± 1.2	28.0 ± 1.6	ns
1st minute Apgar score	3.22 ± 0.54	9.16 ± 0.16	p<0.001
5th minute Apgar score	5.83 ± 0.47	9.91 ± 0.08	p<0.001
Birth weight (g)	3 144.4 ± 81.1	3 400.0 ± 110.2	ns
Umbilical artery pH	7.06 ± 0.02	7.34 ± 0.02	p<0.0001
pO2	15.2 ± 0.9	22.0 ± 2.0	p<0.001
pCO2	66.2 ± 3.3	38.1 ± 2.7	p<0.001
ABE	−15.5 ± 0.7	−3.9 ± 1.1	p<0.0001
HCO3	12.3 ± 0.5	19.4 ± 0.5	p<0.001
SO2	18.7 ± 1.4	53.7 ± 4.2	p<0.0001
ctO2	4.32 ± 0.3	12.2 ± 1.2	p<0.001
Lactate	66.7 ± 4.6	22.0 ± 3.3	p<0.0001
IGF-1	27.8 ± 2.6	55.1 ± 2.8	p<0.01
IGFBP-3	1 107.7 ± 320.4	1 682.5 ± 364.1	p<0.001

All parameters were showed as standard ± standard error mean, except IGF-1 and IGFBP-3 as median

Since acid-base analysis of umbilical artery cord blood is a reliable indicator of fetal oxygenation in utero and at birth, we determined the relationship between umbilical cord IGF-1 and IGFBP-3 levels and umbilical cord blood gases and lactate levels. We tried to investigate the impact of asphyxia on the umbilical cord blood levels of IGF and IGFBP-3.

Materials and methods

The study group consisted of 18 newborn with perinatal asphyxia and 12 healthy gestational age and weight matched newborn. Because birth weight and gestational age could influence the serum levels of IGF-1 and IGFBP-3, all infants included to this study were term (gestational age>37 weeks) and appropriate for gestational age (birth weight is between 2 500–3 600 g). Clinical data of newborns, including gestational age, sex, birth weight, maternal age, were collected at the time of the study from each case. Gestational age was determined by New Ballard scoring system. Umbilical cord arterial blood (2 ml) was drawn at birth from each case, to assess pH, pCO_2, pO_2, HCO_3, ABE, SO_2, ctO_2, and lactate levels. Perinatal asphyxia was determined on the basis of a cord blood pH<7.1 and 5 minute Apgar score <6. First, 5th and 10th minutes Apgar scores were also recorded. After clamping the umbilical cord, umbilical artery and umbilical vein samples and 5 ml serum samples for IGF study were obtained. Cord blood sample were immediately centrifuged and serum aliquots frozen at −70 °C until subsequent analysis. Serum IGF-1 and serum IGFBP-3 levels were measured in samples of serum using a two-side immunoradiometric assay (non-extraction test, IBL-Immunobiological Laboratories, Hamburg, Germany).

Statistical analysis was studied with SPSS for Windows 10.0. Although umbilical cord IGF-1 and IGFBP-3 levels were not normally distributed, Mann-Whitney U test was used for comparison and logarithmic transformation performed for correlation analysis. Relationships between logIGF-1 and logIGFBP-3 levels with cord blood gas analysis parameters were evaluated with Pearson correlation analysis. The statistical significance was taken as p<0.05.

Results

Means of maternal age, birth weight, APGAR scores, blood gas parameters and cord blood IGF-1 and IGFBP-3 were given in Table 1 for both groups. Cord blood IGF-1 levels for asphyxiated newborns were lower than normal group (27.8±2.6 ng/ml, 55.1±2.8 ng/ml respectively, p<0.01). Cord blood IGFBP-3 levels also lower in asphyxia group (1 107.7±320.4, 1 682.5±364.1, p<0.001).

Cord blood IGF-1 levels were positively correlated with birth weight, first and 5th minute Apgar score, cord blood arterial pH, ABE, HCO_3, SO_2 levels (r=0.453, p<0.05; r=0.554, p<0.01; r=0.539, p<0.01; r=0.452, p<0.05; r=0.467, p<0.05; HCO_3 r=0.594, p<0.01, r=0.416, p<0.05). Cord blood IGFBP-3 levels were positively correlated with first and 5th minutes Apgar scores, cord blood arterial pH, pCO_2, ABE, HCO_3, SO_2, ctO_2 and lactate levels (r=0.698, p<0.001; r=0.790, p<0.001; r=0.685, p<0.001; r=0.700, p<0.001; r=0.742, p<0.001; r=0.638, p<0.01; r=0.661, p<0.001). Cord blood IGFBP-3 levels were also negatively correlated with cord CO_2 and cord lactate levels (r=−0.478, p<0.05; r=−0.533, p<0.01).

Discussion

In our study we selected only term AGA infants to exclude the physiological changes due to maturation, in IGF-1 and IGFBP-3 levels and also to exclude the effect of chronic asphyxia which cause intrauterine growth restriction. By this way we explore acute changes in the serum levels of IGF-1 and IGFBP-3 in asphyxiated newborns with hypoxia. In our study IGF-1 level in the study group was lower than the control group and decreased IGF-1 levels in cord blood was positively correlated with pH, base excess and first and 5th minute Apgar score. Cooley et al. [9] reported that those fetal cord IGF-1 levels were correlated with fetal acidosis at birth. Several experimental studies have demonstrated that during moderate acute and prolonged hypoxia, there is a small acute fall in circulating IGF-1 levels [10–11]. Bennet et al. [8] determined IGFs and IGFBPs in premature fetal sheep before and after asphyxia by cord occlusion. During the acute phase of recovery from asphyxia there was a profound fall (80%) in circulating levels of IGF-1. Kornhauser et al. [12] concluded that serum IGF-1 is lower in asphyxiated newborns, perhaps a result of hypoxia. The significance of the post-asphyxial fall in IGF-1 is unknown. It has been speculated that the low plasma levels of IGF-1 following trauma or hypoxic-ischemic injury could reflect redistribution or targeting of IGF-1 from the peripheral blood plasma pool to injured tissue [13–15]. Gluckman et al. [5] showed that IGF system activated by hypoxic-ischemic injury with IGF-1, IGFBP-2 and IGFBP-3 being induced in glial cells in the region of injury, in initial few days.

In our asphyxiated cases, cord blood IGFBP-3 levels were also lower than the control group and were positively correlated with first and 5th minutes Apgar scores, cord blood arterial pH, ABE, HCO_3, SO_2, ctO_2 and negatively correlated with pCO_2 and lactate levels. Since IGFBP-3 is the main carrier protein for IGF-1, we can speculate that reduced levels of IGFBP-3 in cord blood is due to the migration of IGFBP-3 bounded with IGF-1 to injury site.

Accordingly, it is not surprising that such growth factors would be altered by cerebral hypoxia-ischemia, and that their administration might be neuroprotective. Since central administration of IGF-1 after cerebral ischemia in fetal sheep or hypoxia-ischemia in adult rats can reduce both infarction and selective neuronal loss in a dose-dependent manner [4]. Gluckman et al. [5] have found a concomitant reduction in the incidence of post-asphyxial seizures and secondary cytotoxic edema. Perhaps administration of IGFBP-3 together with IGF-1 will be helpful for the action of IGF-1 in the injured site.

Early detection of the degree of cerebral damage in newborns who suffered birth asphyxia is relevant to prognosis and treatment strategies. Defining the alteration of these growth factors in response to asphyxia may contribute to explain the pathogenesis and neuroprotective mechanisms in the evidence of perinatal asphyxia. This study shows that IGF-1 and IGFBP-3 are well correlated with umbilical cord blood gases and lactate levels. Since the degree of asphyxia affects the degree of neuronal damage, treatment strategies with growth factors to prevent further neuronal damage, can be planned on the basis of cord blood IGF-1 and IGFBP-3 levels.

REFERENCES

1 Perrone S, Bracci R, Buonocore G. New biomarkers of fetal-neonatal hypoxic stress. Acta Paediatr Suppl. 2002; **91**:135–8.
2 Shankaran S. The postnatal management of the asphyxiated term infant. Clin Perinatol. 2002; **29**:675–692.
3 Guan J, Skinner SJ, Beilharz EJ, Hua KM, Hodgkinson S, Gluckman PD, Williams CE. The movement of IGF-I into the brain parenchyma after hypoxic-ischaemic injury. Neuroreport. 1996; **7**: 632–636.
4 Guan J, Bennet L, George S, Waldvogel HJ, Faull RL, Gluckman PD, Keunen H, Gunn AJ. Selective neuroprotective effects with insulin-like growth factor-1 in phenotypic striatal neurons following ischemic brain injury in fetal sheep. Neuroscience. 2000; **95**:831–9.
5 Gluckman PD, Guan J, Williams C, Scheepens A, Zhang R, Bennet L, Gunn A. Asphyxial brain injury- the role of IGF system. Mol Cell Endocrinol. 1998; **140**:95–9.
6 Robertson JG, Belford DA, Ballard FJ. Clearance of IGFs and insulin from wounds: effect of IGF-binding protein interactions. Am J Physiol. 1999; **276**:E663–71.
7 Guan J, Williams CE, Skinner SJ, Mallard EC, Gluckman PD. The effects of insulin-like growth factor (IGF)-1, IGF-2, and des-IGF-1 on neuronal loss after hypoxic-ischemic brain injury in adult rats: evidence for a role for IGF binding proteins. Endocrinology. 1996; **137**:893–8.
8 Bennet L, Oliver MH, Gunn AJ, Henies M, Breier BH. Differential changes in insulin-like growth factors and their binding proteins following asphyxia in the preterm fetal sheep. J Physiol. 2001; **531**:835–41.
9 Cooley SM, Donnelly JC, Geary MP, Rodeck CH, Hindmarsh PC. Maternal and fetal insulin-like growth factors 1 and 2 (IGF-1, IGF-2) and IGF BP-3, and their relationship to acidosis at delivery. J Perinat Med. 2004; **32**:418–21.
10 McLellan KC, Hooper SR, Rocking AD, Delhanty PJD, Philips ID, Hill DJ, Han VKM. Prolonged hypoxia induced by reduction of materanl uterine blood flow alters insulin-like growth factor-binding protein –1 (IGFBP-1) and IGFBP-2 gene expression in the ovine fetus. Endocrinology. 1992; **131**:1619–28.
11 Iwamoto HS, Murray MA, Chernausek SD. Effects of acute hypoxemia on insulin-like growth factors and their binding proteins in fetal sheep. Am J Physiol. 1992; **263**:E1151–6.
12 Kornhauser C, Dubey LA, Garay ME, Perez-Luque EL, Malacara JM, Vargas-Origel A. Serum and urinary insulin-like growth factor-1 and tumor necrosis factor in neonates with and without acute renal failure. Pediatr Nephrol. 2002; **17**:332–6.
13 Reinhardt RR, Bondy CA. Insulin-like growth factors cross the blood-brain barrier. Endocrinology. 1994; **135**:1753–61.
14 Schwab S, Spranger M, Krempien S, Hacke W, Bettendorf M. Plasma insulin-like growth factor I and IGF binding protein 3 levels in patients with acute cerebral ischemic injury. Stroke. 1997; **28**:1744–8.
15 Thissen JP, Underwood LE, Kietelslegers JM. Regulation of insulin-like growth factor-I in starvation and injury. Nutr Rev. 1999; **57**:167–76.