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Ischemia-modified albumin levels in cord blood: A case-control study in uncomplicated and complicated deliveries

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Abstract

Background: In the past few years ischemia modified albumin (IMA) has emerged as a new biomarker of ischemia in the area of monitoring acute coronary syndromes. We hypothesized that reduced blood flow, such as that resulting from vascular compression in complicated labors or placental ischemia, may increase IMA. IMA level in cord blood could then serve as an indicator of fetal hypoxia and fetal tissue ischemia and serve as a biomarker of the severity of these conditions. *Methods:* We performed a case-control study with 26 newborns (12 normal term deliveries, Apgar 8–9; and 14 complicated labors or pre-term deliveries, Apgar 5–8). Complications were: prematurity (3), fetal distress (6), premature rupture of membranes (6), intrauterine growth retardation (3), pre-eclampsia (1). We also studied 30 healthy adults. IMA was measured in serum from cord blood (or venous blood for adults) by the decrease in cobalt 2+ binding.
Results: IMA levels in neonates from non-complicated deliveries are significantly higher (45%, $p<0.005$) than those of an adult control population, suggesting that IMA may increase as a consequence of labor. This increased IMA in neonates could not be accounted for by the changes in albumin concentration. It is conceivable that a transient increase in IMA reflects, in part, transient localized tissue ischemia due to the external forces exerted on the fetus during the mechanism of labor. IMA levels in cord blood from neonates from complicated deliveries are 50% higher than in neonates from uneventful deliveries ($p<0.05$) while their albumin values are not significantly different (32 ± 3 vs. 33 ± 2 g/l). Moreover, IMA seems to be responsive to hypoxic fetal distress, showing values more than 300% higher in cases of severe fetal hypoxia (Apgar 5 $n=2$: 2.19 ± 0.01 AU vs. 0.64 ± 0.24 for controls). IMA values did not correlate significantly with either lipoperoxides or CRP levels.

Abbreviations: IMA, ischemia modified albumin; CRIB, clinical risk index for babies; CRP, C-reactive protein; DTT, dithiothreithol; SNAP, score for neonatal acute physiology.

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Conclusions: This is the initial reporting of IMA levels in cord blood from normal deliveries compared to healthy adult ranges and neonates from complicated deliveries. Cord blood IMA levels may be an indicator of fetal ischemia and/or hypoxia. This test could become an additional biomarker to be used in conjunction with other markers and/or clinical scores aimed at determining risk of neurological complications of fetal distress.

Keywords: Fetal distress; Oxidative stress; Hypoxia

1. Introduction

The role of the clinical laboratory with regard to biomarkers with a predictive value for neurological sequelae of fetal hypoxia or distress remains limited [1–5]. In the past few years a new biomarker of ischemia has emerged in the area of monitoring acute coronary syndromes. It has been proposed that albumin modification by reactive oxygen species produced during ischemia, leads to modifications in the DAHK amino terminus resulting in loss of copper or cobalt binding of the albumin molecule [6]. Ischemia modified albumin (IMA) results from oxidative damage that is still not clear at the molecular level, but reperfusion after an ischemic event may damage serum albumin as much as, if not more than, ischemia itself [6–10]. IMA has been studied primarily in selected adult populations thought to display myocardial involvement, and in the absence of confounding clinical conditions. Other organs seem to be also responsible for the increase in IMA [6,11–13].

In view of these considerations, we hypothesized that reduced blood flow, such as that resulting from vascular compression in complicated labors or placental ischemia, causes insufficient oxygenation, anaerobic metabolism, localized acidosis and may increase IMA. Levels in cord blood may also serve as an indicator of fetal hypoxia and fetal tissue ischemia and serve as a biomarker of the severity of these conditions.

2. Material and methods

2.1. Patients

We performed a case-control study with 26 newborns (12 normal term deliveries, Apgar 8–9; and 14 complicated labors or pre-term deliveries, Apgar 5–8). We also studied 30 healthy adults. Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment using the New Ballard Score. Complications were: prematurity (3), fetal distress (6), premature rupture of membranes (6), intrauterine growth retardation (3), pre-eclampsia (1). To classify infants as appropriate or small for gestation, reference of weight was made to Lubchenko's charts of intrauterine growth. The cord blood samples were obtained from the Obstetrics Unit Dokkyo University School of Medicine. The control adult subjects in the study (15 male and 15 female, aged 25–45 y) were selected from a healthy population of hospital workers at the Northern Yokohama Hospital, Showa University Tsuzuki-ku, Yokohama City. Informed consent was obtained from all subjects. The protocol was approved by the institutional review board of Showa University, and investigations were performed in accordance with the principles of the Helsinki declaration.

Four milliliters of venous blood sample from the umbilical cord was collected in evacuated dry tubes with separating gel just after delivery of the neonate. Blood was centrifuged at 800 $\times g$, at 4 °C for 15 min and separated serum was immediately analyzed or frozen at − 80 °C until use.

Chemicals: All chemicals are analytical grade and purchased from Sigma (St. Louis, MO).

2.2. Apparatus

Spectrophotometric measurements were made in a Beckman DU 640 spectrophotometer (Beckman Coulter Inc, Fullerton CA). IMA was measured by the decrease in cobalt 2+ binding as previously described [10]. We introduced minor modifications in the method to adapt it to a 96-well plate reader. Briefly, we add 100 μl of patient serum to 25 μl of a solution of 1 g/