Journal of Critical Care (2012) **27**, 469–473

ELSEVIER

Journal of Critical Care

Hypothermia attenuates the severity of oxidative stress development in asphyxiated newborns☆

Hiroki Kakita MD, PhD[a], Mohamed Hamed Hussein MD, PhD[a,b,c,*], Shin Kato MD, PhD[a], Yasumasa Yamada MD, PhD[d], Yoshiaki Nagaya MD[a], Hayato Asai MD[a], Tatenobu Goto MD, PhD[a], Koichi Ito MD, PhD[a], Tokio Sugiura MD, PhD[a], Ghada Abdel-Hamid Daoud MD, PhD[e], Tetsuya Ito MD, PhD[a], Ineko Kato MD, PhD[a], Hajime Togari MD, PhD[a]

[a]*Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*
[b]*Neonatal Intensive Care Unit, Pediatric Hospital, Cairo University, Cairo, Egypt*
[c]*Medical Research Department, EgyBlood, VACSERA, Giza, Egypt*
[d]*Department of Neonatology, Aichi Human Service Center Central Hospital, Japan*
[e]*Obstetrics and Gynecology Department, EgyBlood, VACSERA, Giza, Egypt*

Keywords:
Oxidative stress;
Total hydroperoxide;
Biological antioxidant potential;
Asphyxia;
Brain hypothermia

Abstract

Purpose: This retrospective case-control study aimed to examine the development of oxidative stress in asphyxiated infants delivered at more than 37 weeks of gestation.

Material and Methods: Thirty-seven neonates were stratified into 3 groups: the first group experienced hypothermia (n = 6); the second received hypothermia cooling cup treatment for 3 days, normothermia (n = 16); and the third was the control group (n = 15).

Serum total hydroperoxide (TH), biological antioxidant potential, and oxidative stress index (OSI) (calculated as TH/biological antioxidant potential) were measured within 3 hours after birth.

Results: Serum TH and OSI levels gradually increased after birth in hypothermia and normothermia cases. At all time points, serum TH and OSI levels were higher in hypothermia and normothermia cases than in control cases. Serum TH and OSI levels were higher in normothermia cases than in hypothermia cases at days 3, 5, and 7.

Conclusion: This study demonstrated that hypothermia attenuated the development of systemic oxidative stress in asphyxiated newborns.

1. Introduction

Perinatal asphyxia encephalopathy is associated with high morbidity and mortality rates worldwide and is a major burden for patients, their families, and society. There is an urgent need to improve outcomes in affected infants. Perinatal asphyxia is

☆ This study had no financial support from extramural sources.

* Corresponding author. Department of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Tel.: +81 52 853 8246; fax: +81 52 842 3449.

E-mail addresses: hamed@nagoya-cu.ac.jp, drmhamed@yahoo.com (M. Hamed Hussein).

0883-9441/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcrc.2011.12.013

an insult caused by a lack of oxygen or lack of perfusion in various organs. Almost every organ of the body is affected by asphyxia, which leads to multiorgan failure, but the predominant insult occurs in the central nervous system [1]. The mechanism of cellular injury after hypoxia or ischemia is poorly understood, but it is probably mediated by an excess concentration of neurotransmitters, oxygen free radicals, and lipid peroxidation, which, in turn, leads to a cascade of damaging events [2]. We have previously reported that cerebrospinal fluid total hydroperoxide (TH) and oxidative stress index (OSI) are higher in severely asphyxiated newborns than in others [3]. Oxidative injury has been implicated as a causal factor in several complications of newborns, including bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, and perinatal asphyxia encephalopathy [4,5]. Neonates are at high risk of oxidative stress and are extremely susceptible to oxidative damage from reactive oxygen species (ROS) [5].

There is now increasing evidence that brain hypothermia reduces the brain injury caused by asphyxia [6,7]. Hypothermia attenuates blood-brain barrier damage, the release of excitatory neurotransmitters is reduced, free radical production is lessened, and anti-inflammatory cytokine levels are increased [2,8]. The mechanism of protection remains unclear.

The present study was undertaken to evaluate the level of systemic TH and OSI in neonates with asphyxia and to ascertain whether or not hypothermia treatment has an effect on oxidative stress.

2. Materials and methods

This retrospective case-control study examined asphyxiated infants delivered at more than 37 weeks of gestation who had been admitted to the neonatal intensive care unit at Aichi Human Service Center Central Hospital between January 2008 and September 2009. The inclusion criterion was a diagnosis of asphyxia. *Perinatal asphyxia* was defined as the need for positive pressure ventilation for more than 1 minutes during postnatal resuscitation and an Apgar score of 6 or less at 5 minutes. During this period, infants without perinatal asphyxia who cried immediately after birth and did not require positive pressure ventilation for resuscitation served as the control subjects. The control group included 15 cases, of which, 4 had initial vomiting and/or poor feeding, 2 had hypoglycemia, and 9 had mild transient tachypnea, and for which a brain magnetic resonance imaging (MRI) was obtained around the age of 12 months after informed parental consent to estimate the brain development and to be enrolled in the study as part of a control group.

Clinical inclusion criteria of hypothermia were an Apgar score of 5 or less at 10 minutes after birth; a continued need for resuscitation, including endotracheal or mask ventilation at 10 minutes after birth; or severe acidosis and/or severe lactic acidosis, defined as pH less than 7.0 within 60 minutes of birth, and lactic acid more than 8 mmol/L after 60 minutes of birth, in an arterial or venous blood sample. Exclusion criteria were infants older than 6 hours after birth at the time of hypothermia commencement, major congenital abnormalities, refractory hypotension, persistent pulmonary hypertension, and disseminated intravascular coagulation.

2.1. Hypothermia treatment

We fitted a cooling cap (Medi Cool MC-2100; Mac8, Tokyo, Japan) around the head for 72 hours in eligible infants. The system consisted of a small thermostatically controlled cooling unit and pump that circulated water through the cap. All infants were nursed under a radiant overhead heater, which was servocontrolled to the infant's abdominal skin temperature and adjusted to the nasopharynx temperature at 34°C. At the start of hypothermia, the overhead heater was turned off for a few hours to accelerate cooling; it was subsequently turned back on once the nasopharynx temperature had fallen to around 34°C. At the end of the 72-hour cooling period, the infants were slowly rewarmed at no more than 0.5°C/h until their temperature was within the normal temperature range.

Arterial blood samples were obtained from the radial artery or umbilical cord blood sample (≤6 hours after birth). Arterial blood gases were analyzed using a Rapid Lab 348 analyzer (Chiron, Emeryville, Canada). Serial arterial or venous blood samples were obtained until 7 days after birth.

Total hydroperoxide and biological antioxidant potential (BAP) were measured, without knowing the diagnosis, using a d-ROMs kit and a commercial assay kit, respectively (Diacron SRL, Parma, Italy), as previously described [9,10]. Oxidative stress index was determined as the ratio of TH to BAP because the shift in the oxidative/antioxidative balance toward the oxidative side is considered to be indicative of oxidative stress [9].

Magnetic resonance imaging was performed for all patients with perinatal asphyxia when they were around a month of age. Infants were assessed during their neonatal intensive care unit stay by a pediatric neurologist until they were discharged. *Abnormal findings* were defined as a loss of the posterior limb of the internal capsule, abnormal signal intensity in the basal ganglia and thalami, brain stem lesions, loss of gray/white matter differentiation, and cortical highlighting at T1 or T2 weighting. Infants were assessed again at approximately 12 months of age. Abnormal outcomes included death, severe disability, hearing loss, and cerebral palsy.

Written informed consent was obtained for each infant from their parents. All study protocols were approved by the ethics committee of Aichi Human Service Center Central Hospital.

2.2. Statistical analysis

Statistical analyses were performed using SPSS for Windows version 13.0 software (SPSS, Chicago, Ill).