



## Serum cortisol levels in asphyxiated infants with hypotension

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### ABSTRACT

**Background:** Hemodynamic instability due to cardiovascular insufficiency is a common complication in asphyxiated, cooled neonates. Hypotension is often resistant to volume and catecholamine administration, which could be related to low serum cortisol values. Relative adrenal insufficiency (RAI) has not been studied in detail in critically ill, hypotensive neonates with perinatal asphyxia between the 0 and 168th postnatal hours (during and immediately after hypothermia treatment).

**Aims:** To assess serum cortisol values in asphyxiated, hypotensive infants treated with hypothermia and examine the relationship between serum cortisol values and severity of illness.

**Methods:** We conducted a retrospective cohort study between 2007 and 2016, including term neonates with moderate-to-severe hypoxic-ischemic encephalopathy who underwent standard hypothermia treatment. Cortisol values were measured in 79 infants whenever hypotension occurred in the first week of life.

**Results:** Serum cortisol values displayed an exponential decay characteristic after birth with 89% of the measurements being  $< 15 \mu\text{g/dL}$ , the threshold of RAI. Infants with more severe condition measured on the SNAP-II scale had significantly higher cortisol values during hypothermia (moderate-severe  $5.0 [3.9; 10.9] \mu\text{g/dL}$  vs mild condition  $2.8 [2.0; 4.6] \mu\text{g/dL}$ ;  $p = 0.002$ ). Eventually 57% of patients received low-dose hydrocortisone supplementation (HCS) at a median dose of  $0.6 [0.5; 1.0] \text{mg/kg}$  due to hemodynamic instability and suspected RAI. Among those who were available for follow-up, patients with or without HCS scored similarly on the Bayley-II.

**Conclusions:** Our results suggest that asphyxiated, cooled infants presenting with hypotension were likely to have low serum cortisol values. Further studies are needed to test the efficacy and long-term safety of hydrocortisone administration in the treatment of hypotension in asphyxiated, cooled neonates.

### 1. Introduction

Relative adrenal insufficiency (RAI) is a condition characterized by inappropriately low cortisol secretion despite the extent of stress or severity of illness present [1]. Based on laboratory measurements, relative adrenal insufficiency is defined as a random serum cortisol value that is  $< 15 \mu\text{g/dL}$  or a  $< 9 \mu\text{g/dL}$  rise in serum cortisol in response to ACTH stimulation [2–4], although ACTH test is seldom performed due to critical condition of patients. Recently, RAI has been suggested to play a role in hemodynamic instability and hypotension of critically ill neonates, but compared to the adults, there are still very few studies conducted in this population.

Birth asphyxia is one of the leading cause of neonatal mortality and adverse neurological sequelae [5], and hypothermia treatment has emerged as standard of care in patients with moderate-to-severe

hypoxic-ischemic encephalopathy (HIE) [6]. Hemodynamic instability is a frequent complication in asphyxiated neonates, and it occurs in similar rates in infants at normothermia or hypothermia [7,8]. Hypotension is often resistant to volume and catecholamine administration, which could perhaps be related to RAI. The incidence and clinical characteristics of RAI among asphyxiated cooled neonates at risk of circulatory failure has not been described before. In addition, patient outcomes after low-dose hydrocortisone supplementation in asphyxiated neonates have not been studied either.

Therefore, the aim of our study was to investigate serum cortisol values during the first week of life in critically ill asphyxiated neonates with hypotension. We also studied the incidence of hydrocortisone supplementation and the patient outcomes at 2 years of age in this patient population.

**Abbreviations:** BSID-II, Bayley Scales of Infant Development, Second Edition; HCS, hydrocortisone supplementation; HIE, hypoxic-ischemic encephalopathy; MDI, mental developmental index; PDI, psychomotor developmental index; RAI, relative adrenal insufficiency; SNAP-II, Score for Neonatal Acute Physiology; VIS, Vasoactive-Inotropic Score

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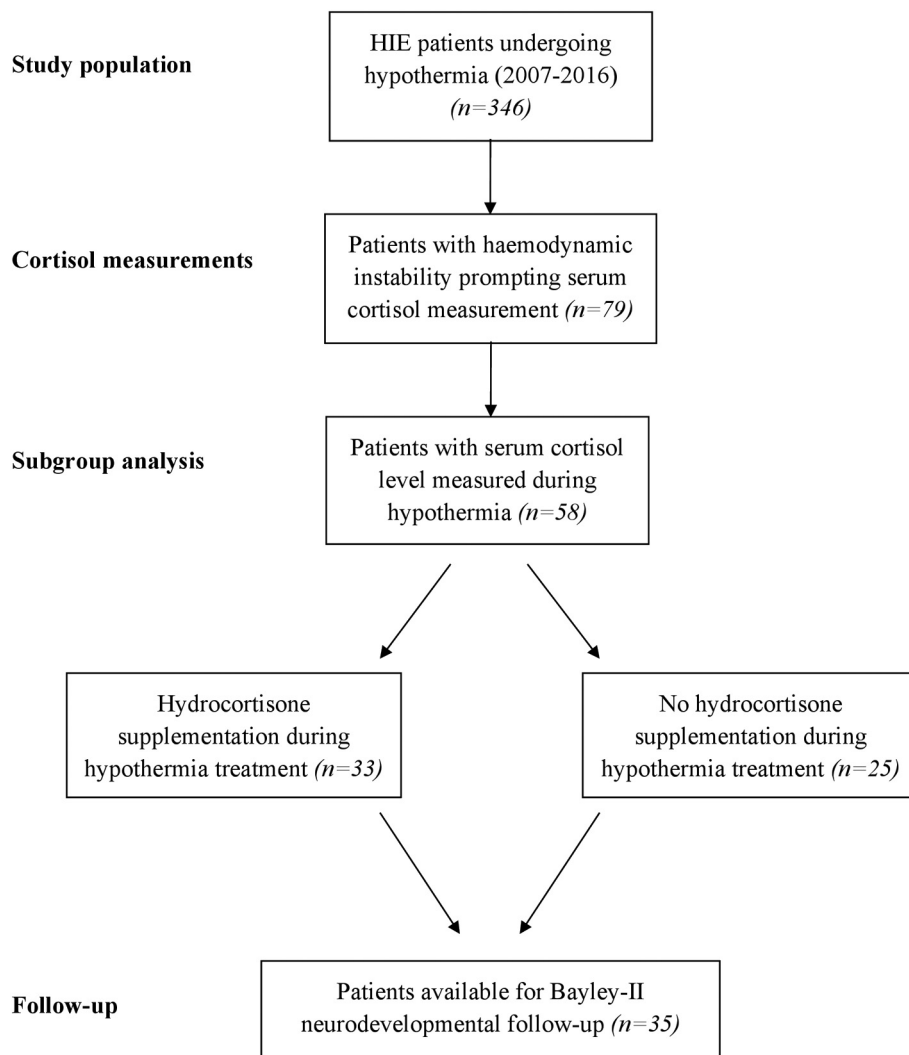


Fig. 1. Flowchart of the study subjects.

## 2. Patients and methods

### 2.1. Patient population

This is a retrospective cohort study, conducted between 2007 and 2016 in the Neonatal Intensive Care Unit of the 1st Department of Pediatrics, Semmelweis University, with ethical permission (11790-2/2016/EKU). Medical records of 346 term neonates with moderate-to-severe HIE were reviewed, who received standard 72-hour hypothermia treatment, as described in the TOBY trial [7]. For the present analysis, we evaluated 79 patients who had hypotension that prompted serum cortisol measurements during 0–168th postnatal hours. Each patient had a single randomly taken venous blood sample for cortisol measurement. Patient selection is demonstrated in Fig. 1.

For studying adrenal function during hypothermia treatment, we performed a subgroup analysis including patients whose cortisol values were measured between the 12 and 85th hours of postnatal life ( $n = 58$  patients). In this subgroup, we excluded measurements that were made during the first 12 postnatal hours, based on prior knowledge that cortisol values are considerably higher due to the stress experienced during labor and delivery [9,10]. Hypothermia treatment was started within the first 6 postnatal hours, lasted 72 h, followed by 7 h of re-warming phase, adding up to a maximum of 85 h of postnatal life. Infants with congenital malformation, metabolic disorder and bilateral adrenal hemorrhage were excluded from analysis.

### 2.2. Study procedures

Serum cortisol concentrations were measured by electrochemoluminescent immunoassays (Elecsys, Cobas E411, Roche, Basel, Switzerland).

Hypotension was defined clinically, if mean arterial blood pressure was less than gestational age in weeks. Our protocol recommends single or repeated dose of isotonic saline, followed by infusion of inotropes (dopamine/dobutamine/norepinephrine/epinephrine/milrinone as appropriate). As a center practice, in cases of severe hemodynamic instability and suspected relative adrenal insufficiency hydrocortisone was administered (0.5–1 mg/kg/6 h) as rescue therapy.

For the subgroup analysis, clinical severity of illness measures included the Score for Neonatal Acute Physiology (SNAP-II) [11] recorded within 12 h of the cortisol measurement and the Vasoactive-Inotropic Score (VIS) [12].

Brain imaging was carried out on a 3 Tesla Philips Achieva MR scanner (Philips Medical Systems, Best, The Netherlands), at the MR Research Center of Semmelweis University. Short term outcome was evaluated at the end of the intensive care. Long term outcome was registered in a subgroup of patients who were available to follow-up ( $n = 35$ ) using the Bayley Scales of Infant Development, Second Edition (BSID-II) mental and psychomotor developmental indices (termed MDI and PDI, respectively) [13].

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