Early Human Development 113 (2017) 49–54

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

A comparative analysis of ante- and postnatal clinical characteristics of extremely premature neonates suffering from refractory and non-refractory hypotension: Is early clinical differentiation possible?☆,☆☆,☆☆☆,☆☆☆☆

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ABSTRACT

Background: About 25% of hypotensive ELBW infants are refractory to intravascular volume expansion and inotropic drugs (VI) and require hydrocortisone (HC). Such neonates suffer from complications of prolonged hypotension and extended therapy with VI. ELBW infants with refractory hypotension (RH) are clinically and biochemically indistinguishable from those who respond to VI.

Objective: Early identification and differentiation of ELBW infants susceptible to steroid dependent hypotension from those who respond to inotropic medications.

Methods: In a retrospective study the ante- and postnatal clinical characteristics of ELBW infants who received hydrocortisone (HC) for refractory hypotension (RH) were compared to those who responded to volume-inotropes (VI).

Results: Infants in HC group had lower birth weight (BW, 675 ± 121 g) and gestational age (GA, 25.1 ± 1.3 weeks) and higher mean airway pressure and oxygen requirements, all independent of antenatal steroid (ANS) exposure. The receipt of ANS (p 0.01) and occurrences of maternal diabetes mellitus (GDM, p 0.01) were lower in HC group. ANS (OR 0.5, 95% CI 0.2–0.9, p 0.01) and GDM (OR 0.3, 95% CI 0.09–0.9, p 0.04) reduced the risk for RH. HC group had higher risk for IVH (OR 2.1, 95% CI 1.02–4.2 p = 0.04) which declined in the multivariate analysis. A trend towards lower risk of ventriculomegaly (VM) was noted in HC group (OR 0.3, 95% CI 0.1–1.1), which became significant after controlling for BW (OR 0.2 95% CI 0.07–0.9, p 0.04). Similar trend was noted for maternal hypertension.

Conclusion: Hypotension in ELBW infants who are ≤ 25 wks of GA and unexposed to ANS and GDM is refractory to VI therapy. Such neonates may benefit from an initial therapy with, or earlier institution of hydrocortisone. The trend towards a higher risk for VM with VI therapy needs validation in future studies.

Abbreviations: ANS, antenatal steroid; BW, birth weight; DOL, day of life; ELBW, extremely low birth weight infants; GA, gestational age; GDM, gestation associated diabetes mellitus; HC, hydrocortisone; IVH, intraventricular – periventricular hemorrhage; MAP, mean airway pressure; MBP, mean arterial blood pressure; PHTN, pregnancy associated hypertension; RH, refractory hypotension; SIP, spontaneous intestinal perforation; VI, volume- inotropes; VM, ventriculomegaly

☆ Financial disclosure: Authors have no financial relationship relevant to this article to disclose.
☆☆ Funding source: The project was done with no funding support.
☆☆☆ Conflict of interest: The authors have no conflict of interest relevant to this article to disclose.
☆☆☆☆ Contributors' statement
Dr. Verma conceptualized and designed the study, supervised the data collection, wrote and edited the manuscript and approved the final manuscript as submitted.
Dr. Dasnadi collected and entered data for analysis, reviewed and approved the final manuscript as submitted.
Dr. Zhao and Dr. Chen performed the statistical calculations, reviewed and approved the final manuscript as submitted.

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http://dx.doi.org/10.1016/j.earlhumdev.2017.07.010
Received 26 April 2017; Received in revised form 19 June 2017; Accepted 2 July 2017

What is already known on this subject

- About 25% of the hypotensive ELBW infants are refractory to the routine primary therapy with intravascular volume expansion and inotropic drugs (VI) and require hydrocortisone (HC).
- Neonates susceptible to refractory hypotension (RH) suffer from the potential complications of prolonged hypotension and unsuccessful extended therapy with VI.
- ELBW with RH are clinically or biochemically indistinguishable from those who respond to VI.

What this study adds

- Infants of < 25 weeks of gestational age, and those who are unexposed to antenatal steroid and maternal diabetes mellitus are susceptible to refractory hypotension.
- ELBW infants with RH suffer from more severe hypotension and pulmonary disease compared to those who respond to VI therapy.
- ANS and GDM decrease the risk of refractory hypotension in ELBW infants.

1. Introduction

Early postnatal hypotension has been associated with intraventricular-periventricular hemorrhage (IVH), adverse neurodevelopmental outcomes and death in the very low birth weight infants [1,2]. Its incidence is estimated to be between 20 and 45% [3,4] and its prevalence inversely related to gestational age [5].

Neonatal hypotension is treated with intravenous infusion of volume expanding fluids and inotropic drugs, such as dopamine, dobutamine and epinephrine. These interventions could further compromise the tissue perfusion by inducing a pathological ductus arteriosus consequent to volume overload and via the dose dependent cardio-vasoactive properties of inotropic drugs [6,7]. About 25% of the hypotensive extremely low birth weight infants (ELBW, birth weight < 1000 g) fail to respond to the volume-inotropes (VI) treatment and require hydrocortisone (HC), independent of their serum cortisol concentrations, to normalize their blood pressure [6–8]. Early identification of such infants and timely institution of hydrocortisone might shorten the duration of their exposure to sustained hypotension, aggressive volume expansion and inotropic drugs, as well as their consequent complications. With our current knowledge, ELBW infants susceptible to hypotension refractory to the conventional therapy of VI cannot be clinically or biochemically distinguished from those who are steroid dependent during the initial presentation of the morbidity. These infants therefore, undergo an extended and eventually unsuccessful treatment with VI before the definitive therapy is instituted.

The objective of this study was to identify the specific subgroup population of ELBW infants who suffer from hypotension refractory to inotropes, so that hydrocortisone can be introduced in them as the primary therapeutic agent or early in the course following deficient response to VI. For this purpose we compared the antenatal and postnatal clinical characteristics of ELBW infants who present with hypotension refractory to volume and inotrope infusions with those who respond to such interventions. We hypothesized that the clinical profile of infants with refractory and non refractory hypotension do not differ and such ELBW infants cannot be distinguished at the onset or early in the course of the disease.

2. Methods

2.1. Population

In a retrospective study, all inborn and out born non anomalous ELBW infants admitted to the neonatal intensive care unit of the University of Maryland Hospital, Baltimore between January 2003 and December 2009 were identified from the institutional database for possible inclusion in the study. Those infants who expired within the first 24 h of life or were transferred out of the institution during the study period were excluded. The study was approved by the institutional review board (Fig. 1).

The definition of hypotension uniformly utilized for treatment was a decrease in the mean arterial blood pressure (MBP) below the numerical value of the gestational age, associated with oxygen desaturations, bradycardia or decreased perfusion [8]. The latter was suggested by a decrease in urine output to < 1 ml/kg/h for 2 h or a capillary refill time > 3 s [8]. Arterial blood pressure was continually measured from an indwelling peripheral or umbilical arterial catheter connected to a transducer monitoring system zeroed at the midaxillary line (Abbott Critical Care Systems Transpac IV, Abbott Australasia, Kurnell, New South Wales, Australia). The wave form and numerical values of MBP were recorded (Agilent CMS 2000, Component Monitoring System, Agilent Technologies Inc., Andover, MA) and continually displayed on a bedside monitor (Viridia CMS 2000 series, Hewlett-Packard, Waltham, MA). The same bedside monitor was also used to measure and display cardio respiratory data including arterial oxygen saturation, which was continuously monitored via a neonatal sensor (Nellcore, Covidien, MA). The peripheral blood pressures were obtained by the oscillometric technique (Dinamap, Criticon, Tampa, FL) in infants without an indwelling catheter. In such infants an arterial catheter was obtained after enrollment. Refractory hypotension was defined as the inability to maintain acceptable MBP despite treatment with maximum doses of dopamine, dobutamine and/or epinephrine, in addition to volume expansion with intravenous normal saline or 5% albumin. The maximum doses of dopamine and dobutamine used were 20 mcg/kg/min. Epinephrine was used in the doses of 0.05–1 mcg/kg/min. Intravenous volume expanders were given as aliquots of 10–20 ml/kg/bolus as per the clinical teams' decision based on our definition of hypotension as specified above. There was no predefined number of boluses to be used before vasopressors were started and all decision was based on the clinical care taking team's judgment. Those who responded to volume and did not require inotropes were not included in the study as per the study protocol. Hydrocortisone was given intravenously in the doses of 2 to 4 mg/kg/day to treat refractory hypotension [8].

2.2. Variables

The following maternal variables were studied: clinical or histological chorioamnionitis, pre-existing or pregnancy associated diabetes mellitus (GDM) and hypertension (PHTN), receipt of antenatal steroids (ANS), any tocolysis, duration of rupture of membrane for > 18 h (PROM) and a history of substance abuse, including nicotine, cocaine, narcotics, cannabis and other illegal substances.

As for the neonatal variables for acute clinical course and complications, data were collected for the first 14 days of life and included the following: gestational age (GA); birth weight (BW); sex; race; mode of delivery - vaginal versus C-Section; apgar scores at 1 and 5 min of life; highest mean airway pressure (MAP) and fractional inspired oxygen (FiO_2) on postnatal days of life (DOL) 1, 3, 7 and 14; receipt of surfactant in doses > 1; total number of days on antibiotics; Patent ductus