Extended Abstract

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Current Treatment of Hypotension in ELBW Infants: Complications and Controversies

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Abstract

Introduction: Early postnatal hypotension (EPH) in premature infants is treated with vasopressor-inotropes (VI) in escalating doses, followed by hydrocortisone (HC) if VI therapy fails. There is no report on the adverse effects of this standard clinical practice.

Objective: To investigate the complications associated with the escalating treatments of hypotension with sequential inotropes and hydrocortisone in ELBW neonates.

Methodology: In a retrospective case-control study the complications and adverse outcomes associated with VI (VI) and HC (HCVI) treatments were compared with contemporaneous normotensive medication naïve controls (C) via standard univariate and multivariate analyses.

Anti-hypotensive treatments are often started in response to a low blood pressure (BP) or signs of low cardiac output (CO) in critically ill neonates. The challenge for clinicians in the neonatal intensive care unit (NICU) is to dissect out the etiology of the hemodynamic changes, decide if the changes are pathologic or transitionally appropriate, and then tailor the treatment regimen for the patient, the condition, and gestation. This process all occurs while being cognizant that a hemodynamic state evolves throughout the chronological age of the neonate and the course of illness and is affected by concurrent treatments, such as ventilation. Studies in Europe, North America, and Australia all highlight that practices are variable across countries and continents with respect to which patient, when and how to treat with cardiotonic drugs (1–6).

A national Canadian database reported that 10% of neonates of <29 weeks had been treated with inotropes on days 1–3 (0–36% within the 27 NICUs). The treated neonates were less likely to have received antenatal corticosteroids, more likely have a smaller birthweight, a higher SNAPS II, TRIPS score, and need for ventilation, and had a higher mortality and incidence of intraventricular hemorrhage. Recently, a Norwegian population database study indicated that 2.7% of all NICU patients received inotropes at any point of their NICU stay; 28 and 4.1% of <28 and <36 weeks of gestation, respectively, and 13% of <1,500 g infants. These numbers are similar to those reported by Lasky et al. in American NICU . Multiple inotropes were associated with an increased mortality. Indeed, the use of inotropes was associated with an increased mortality, after adjusting for gender, gestation, and 5-min Apgar.

Given variations in gestation, birthweight, and perinatal states along with the cardiopulmonary transition, it is challenging to provide a robust definition of hypotension. Many practitioners still define hypotension as a mean BP lower than the gestational age of the baby, most likely deferring to its ease of use. However, BP increases over time after birth, and it is cautious to use this definition past the first days of life. Although it has not been validated in larger studies, BP monogram's may be a promising alternative to help define hypotension, especially for those patients with extremely low BP.

Transitional and neonatal physiology including foetal shunts as well as disease pathology and iatrogenic effects of concurrent treatments can all contribute to the disruption of hemodynamic homeostasis. During the postnatal transition after birth, there are significant changes in the output of both ventricles as well as systemic and pulmonary vascular resistance which contribute to the initial "physiological" decrease in BP. However, little information is available regarding the minimal effective BP and or blood flow for tissue perfusion in this postnatal hemodynamic state. Permissive hypotension becomes a managerial approach when "hypotension" or low BP is noted in neonates, especially the preterm neonates. It is contemporary to adopt a functional definition of hypotension in the context of clinical effects of hypotension using clinical-biochemical markers of tissue hypo-perfusion. In pathological conditions such as hypoxia and sepsis, poor myocardial contractility and pulmonary hypertension, which can further be aggravated by acidosis, cause hypotension and tissue hypo-perfusion. Systemic vasodilation or vasoplegia is often found in sepsis, profound hypoxia, or postoperatively. Sick neonates often have impaired auto regulation or a redistribution of organ blood flow that alters the relationship between BP, CO, and organ perfusion. A systematic review comparing permissive and BP value-based hypotension therapeutic strategies in the very preterm infant highlighted the paucity of quality data for either therapeutic approach or little published evidence to link hypotension or treatment to short- and long-term outcomes. Given the paucity of randomized trials of anti-hypotensive therapeutics and contradictory data from large cohort studies, there is wide variation in therapies using protocolzed or clinical, laboratory and/or technology-based approach. While it still remains common to treat hypotension with a fluid boluses followed by an infusion of anti-hypotensive medication, fluid bolus administration may not be beneficial and indeed be harmful. Conversely, in neonates with compromised intravascular volume due to blood or fluid loss, or capillary leak, fluid administration is essential for proper hemodynamic responses and augments effects of inotropes or pressors. Therefore, fluid therapy should be given with meticulous attention to the intravascular fluid balance or measures, especially for those extremely preterm neonates. Burns ET al. reported that dopamine was the most commonly used vasoactive agent with a median duration of administration of 46h is mostly advised.

Results: VI (n=74) Vs. C (n=124): Birth weight (BW), gestational age (GA) and receipt of antenatal steroid (ANS) did not differ. The occurrence of gestation associated diabetes mellitus (GDM) and risks for patent ductus arteriosus (PDA), intraventricular-periventricular hemorrhage (IVH), spontaneous intestinal perforation (SIP), ventriculomegaly (VM) and oxygen dependence at 36 postmenstrual week of life (BPD) were higher in VI group. HCVI (n=69) Vs. C: HCVI recipients had lower BW, GA and receipt of ANS. The risks for IVH, BPD, air leaks and PDA were higher in the treated infants. The

occurrences of SIP, VM and GDM did not differ while that of maternal hypertension trended to be less in HCIV recipients (p = 0.06).

Conclusions: Hypotensive ELBW infants treated with vasopressor-inotropes or with hydrocortisone-vasopressor-inotropes are susceptible to IVH, BPD and PDA. Those who receive inotropes are at additional risks for SIP and VM. GDM increases the occurrence of hypotension which responds to VI and does not need HC. Maternal hypertension does not contribute to VI responsive and trends to decreases VI refractory hypotension.