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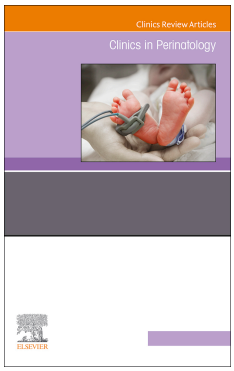

Corticosteroids for Neonatal Hypotension

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PII: S0095-5108(20)30067-1

DOI: https://doi.org/10.1016/j.clp.2020.05.015

Reference: CLP 1183

To appear in: *CLINICS IN PERINATOLOGY*

Please cite this article as: Kumbhat N, Noori S, Corticosteroids for Neonatal Hypotension, *CLINICS IN PERINATOLOGY* (2020), doi: https://doi.org/10.1016/j.clp.2020.05.015.

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Disclosure: No disclosures

Abstract:

Several limitations and controversies surround the definition of hypotension; however, it remains one of the most common problems faced by the neonate. Approximately,15-30% of neonates with hypotension fail to respond to volume and/or vasopressor or inotropes. They are considered to have 'refractory hypotension'. While it is thought to have multiple etiologies, absolute and relative adrenal insufficiency is considered as the main reason for refractory hypotension. This review focuses on the role of adrenal insufficiency in causing refractory hypotension in preterm and term infants, the different options of corticosteroids available and their risk benefit profiles.

Key Points:

- Among preterm and term infants with hypotension, approximately 15-30% have vasopressor-resistant hypotension, with a higher incidence among the most immature patients.
- Relative adrenal insufficiency is considered the main cause of vasopressor-resistant hypotension
- There is no consensus on diagnosis and treatment of vasopressor-resistant hypotension.
- Although corticosteroids are effective in improving blood pressure in hypotensive infants, they are not recommended as a first line of treatment.
- Hydrocortisone as a rescue treatment improves blood pressure primarily by improving vascular tone and maintaining cardiac output despite weaning vasopressors/inotropes.

Key Words:
Adrenal insufficiency, dexamethasone, hydrocortisone

INTRODUCTION

In the absence of accurate and practical tools to assess blood flow and vascular resistance, clinicians have relied on blood pressure (BP) values as a marker of adequate cardiovascular function for decades[1]. Both invasive and non-invasive BP measurements can be easily accomplished in infants with acceptable precision and population-based normal values are available [2] [3] [4] [5]. Little is known about the lower thresholds of BP below which organ blood flow or function is impaired or organ damage occurs in preterm infants, especially during early postnatal transition. Indeed, there is no universally agreed upon criteria for the diagnosis of hypotension in this population[6] [7]. Some controversies stem from the fact that the lower BP thresholds are variable and different not only for populations with different background but also variable at different time points within an individual patient. The complexities and difficulties associated with designing and executing randomized controlled trials involving hypotension that target relevant outcomes are among other reasons for the ongoing controversies and lack of consensus on the definition. As BP is the product of interaction between systemic vascular resistance (SVR) and cardiac output (CO), without knowledge of SVR or CO, the BP values, although important, only give an incomplete picture of macro circulation. Despite these limitations and the controversy surrounding its definition, hypotension is commonly treated in the neonatal intensive care units (NICU) albeit at different thresholds.

REFRACTORY HYPOTENSION

The rate of hypotension ranges from 20-50% in the NICU populations[8] [9] [10]. Most cases of hypotension respond to volume and/or medications such as vasopressors or inotropes. Approximately, 15-30% of patients with hypotension remain hypotensive despite multiple or high doses of vasopressor or inotropes; with a higher incidence among lower gestational ages[11] [12] [13]. This group of patients has what is commonly referred to as “refractory hypotension” or “vasopressor- or inotrope-resistant hypotension”. Although, corticosteroid can be effective in treating hypotension, given the side effects and concern for poor long-

term outcome, they are not recommended as the first line therapy for hypotension[14 15]. Therefore, in this review we will focus on steroid as rescue treatment for hypotension unresponsive to volume and vasopressors or inotropes.

Although refractory hypotension can be secondary to poor cardiac function, vasodilation with and without cardiac dysfunction is the primary underlying pathophysiology[16]. Pathogenesis of the vasodilatory shock unresponsive to volume and vasopressors or inotropes include down-regulation of cardiovascular adrenergic receptors, activation of ATP-dependent potassium channels, upregulation of inducible nitric oxide synthase and down-regulation of renin-angiotensin system[17]. Recently, a polymorphism in the glucocorticoid receptor gene was shown to be associated with refractory hypotension in premature infants [18] . Prolonged exposure to catecholamines results into desensitization of the adrenergic receptor, resulting into continued hypotension in critically ill patients despite treatment [19]. In clinical scenarios such as septic shock and necrotizing enterocolitis, the inflammatory cytokines and increased nitric oxide can lead to severe vasodilation and refractory hypotension and an adequately functioning adrenal gland is necessary to maintain cardiovascular integrity. Absolute and relative adrenal insufficiency is therefore considered the main reason for refractory hypotension and corticosteroid is used as the treatment of choice. As such, we will focus on adrenal function and corticosteroid replacement in this review.

ADRENAL INSUFFICIENCY IN PRETERM INFANTS

Cortisol levels remain low until 32 weeks of gestation as early exposure to glucocorticoids could potentially disrupt cellular growth and proliferation[20]. This is achieved as a result of a complex interaction between three units: fetus, mother and placenta. The fetal adrenal gland contains the following steroidogenic enzymes: 17-hydoxylase, 20-desmolase (CYP17 or P450C17), 21-hydroxylase (CYP21A2 or P450c21), cholesterol side-chain cleavage (CYP11A1 or P450scc), aldosterone synthase (CYP11B2 or P45 0c11), and 3 ß -hydroxysteroid dehydrogenase (3 ß HSD)[21]. The latter enzyme required for

conversion of fetal cholesterol into cortisol, is only seen in mid-gestation[22]. Prior to this, placental progesterone serves as the necessary precursor for cortisol production.

Maternal cortisol passively transfers into the fetus and suppresses the fetal hypothalamic-pituitary-adrenal (HPA) axis. Dehydroepiandrosterone (DHEA) is secreted by the fetus and transfers to the placenta where it is converted into placental estrone and estradiol which in turn increases the production of placental 11 ß -hydroxysteroid dehydrogenase type 2 (11 ß HSD Type 2). This oxidizes the maternal cortisol into a biologically inactive cortisone; however, this occurs in later portions of gestation. This regulates fetal exposure to maternal cortisol and thereby mitigates the negative feedback on the fetal HPA axis[23]. The placenta also releases corticotropin releasing hormone (CRH), which unlike the hypothalamic CRH, does not have a negative feedback response to cortisol. Closer to term, the production of placental CRH increases exponentially which stimulates the fetal adrenal gland which in turn increases fetal cortisol production [24]. This complex interplay (Figure 1) is interrupted when an infant is born prior to 30 weeks of gestation uniquely placing the preterm infant at risk for adrenal insufficiency.

ADRENAL INSUFFICIENCY IN LATE PRETERM AND TERM INFANTS

Multiple studies have suggested that critically ill term and late preterm infants also have issues with cortisol synthesis. Term infants undergoing surgery such as cardiac repair for complex congenital defects as well as those with congenital diaphragmatic hernia have been shown to have cortisol levels that do not correlate with their degree of stress which is an indicator of impaired cortisol production in these infants[25] [26] [27] Khashana et al found evidence for relative deficiency in cortisol synthesis in term ill infants as suggested by presence of high steroid precursor levels and a beneficial response to hydrocortisone [28]. In a retrospective chart review, Fernandez et al reported that 56% of the 32 hypotensive, mechanically ventilated infants studied had cortisol levels < 15 mcg/dl (a cutoff used to define adrenal insufficiency, see below).[29] Administration of hydrocortisone led to a reversal of the hemodynamic instability . Subsequently, the same authors designed a prospective study to determine cortisol and adrenocorticotropin (ACTH) responses with critical illness, in term and late preterm infants. In critically

ill infants, the median baseline cortisol level was 4.6 mcg/dl, and 74% of the values were < 15 mcg/dl. Baseline cortisol, stimulated cortisol as well as ACTH levels did not increase linearly with the severity of illness and the ACTH stimulated cortisol values were similar in the healthy and ill infants. This study concluded that dysfunction within other portions of the HPA axis causes cortisol deficiency in term and late preterm infants implying presence of a secondary adrenal insufficiency as a cause for cardiovascular instability[30]. This is different from the cause of cortisol deficiency in preterm infants, which is mainly due to primary adrenal insufficiency.

RELATIVE ADRENAL INSUFFICIENCY

Relative adrenal insufficiency (RAI) has been extensively described in adult and pediatric literature[31]. Multiple studies have demonstrated similar findings in preterm and term population [32] [33] [34] [35]. In RAI, acutely ill patients have blunted response to ACTH stimulation and cortisol level that is insufficient for the degree of stress. Typical presentation is one of cardiovascular compromise with, hypotension and shock [36]. In the neonates, it often manifests in the first 2 weeks after birth, although corticosteroid responsive refractory hypotension can also occur at later times[37]. Some of the mechanisms for RAI include: 1) inadequate perfusion of the adrenal gland due to hypotension leading to decreased cortisol production; 2) decreased cortisol production with decreased adrenal ACTH receptor binding in the presence of inflammatory cytokines (endotoxin and tumor necrosis factor alpha); and/or 3) lack of the adrenal gland's reserve to adapt to increased metabolic requirements[38] [39].

CHALLENGES IN DIAGNOSING RAI

There is strong literature supporting the presence of RAI, however, there is no consensus on its definition or criteria for its diagnosis [40] [41]. In critically ill adults, a random cortisol level less than 15 mcg/dL has been used for diagnosis of RAI which might benefit from steroid replacement. It is recommended that a patient with random cortisol level between 15-34 mcg/dL should undergo an ACTH stimulation test. After stimulation, an increase in cortisol level less than 9 mcg/dL represents RAI. Some have proposed

similar cutoffs for diagnosis of RAI in sick term and late-preterm infants [30]. A more recent recommendation for adults with shock uses a random cortisol level of <18 mcg/dL for diagnosis of RAI and corticosteroid replacement[42]. This cutoff for random cortisol did not identify a subset of neonates with acute respiratory distress syndrome and vasopressor dependent shock that would benefit from hydrocortisone [43]. Among very low birth preterm infants, serum cortisol values on the seventh postnatal day has high specificity and positive predictive value however, it has low sensitivity and negative predictive value for diagnosing early neonatal hypotension[44]. In another study, low cortisol level at 12 to 48 hours was associated with lower vasopressor use but was not predictive of hydrocortisone use [45]. In the absence of clear threshold diagnosis of RAI remains challenging.

STEROID AND CARDIOVASCULAR FUNCTION

Corticosteroids are important in preserving cardiovascular integrity and function. Corticosteroids maintain and /or improve blood pressure by; 1) increasing vascular tone and integrity, 2) increasing myocardial contractility and function, 3) increasing vascular responsiveness to catecholamines and angiotensin II and 4) decreasing capillary leak and maintaining intravascular volume. Corticosteroids bring vascular stability through genomic and non-genomic mechanisms. There is a significant delay in achieving genomic actions since they require corticosteroid transfer into the cell nucleus, transcription and then translation to new protein. Nongenomic effects on the other hand occur as soon as the molecule binds to the cell surface leading to a cascade of events including calcium and sodium transmembrane cycling [46]. During severe illness, stimulation of the beta- and alpha-adrenergic receptors results into desensitization and endocytosis of the intact phosphorylated receptors [47]. Both these processes are reversible, however, continued exposure to its ligand leads to downregulation of the adrenergic receptors. Recovery from this requires biosynthesis of new receptors which is enhanced by corticosteroid replacement[48]. Through non-genomic mechanisms via interaction with putative cell membrane bound steroid receptor, steroids bring about an improvement in hemodynamics[49].

Cohort studies, randomized controlled trials and a meta-analysis of these trials have consistently shown that hydrocortisone improves BP in hypotensive preterm infants [50 51 52 14]. In neonates with vasopressors-inotropes resistant hypotension, both dexamethasone and hydrocortisone increase BP by about 2 hours and decrease vasopressor/inotropes by 6-12 hours after initiation of the steroid [48 53 54 55]. The improvement in cardiovascular function appears to be primarily related to improvement in vascular tone[56] (Figure 2).

TREATMENT OF ADRENAL INSUFFICIENCY

The debate that surround the definition of hypotension and when and if to treat it extends into the choice of treatment and the risks involved. Recent surveys designed to assess management practices for hypotension concluded that neonatologists have varying opinions regarding hypotension management and most treatment strategy was driven by institutional protocol rather than pathophysiology[8 12]. Although steroids can be effective in increasing BP, given their potential for side effects, they are best used as a rescue rather than first line treatment of hypotension. Dexamethasone and hydrocortisone are the two steroids that are typically used in the NICU, however, dexamethasone for treatment of refractory hypotension has fallen out of favor due to concerns over long term neurodevelopmental outcomes. Dexamethasone improves cardiovascular function and increase BP via its glucocorticoid effects [55 57 58 54]. As mentioned earlier, the main concern with dexamethasone exposure is the risk of poor neurodevelopmental outcomes among preterm infants. Hippocampus, an area within the brain important for learning and memory, has both mineralocorticoid as well as glucocorticoid receptors. When exogenous cortisol is given at physiologic concentrations it only binds to the mineralocorticoid receptors, however, at high stress doses it binds to the glucocorticoid receptors. Dexamethasone suppresses the endogenous cortisol secretion leading 'chemical adrenalectomy' which ultimately leaves the mineralocorticoid receptors unoccupied[24 59]. These unoccupied mineralocorticoid receptors undergo neuronal apoptosis which could be prevented by simultaneous administration of steroid with mineralocorticoid activity[60 61]. Multiple studies, especially in the context of bronchopulmonary dysplasia

(BPD) prevention, have demonstrated that infants exposed to dexamethasone have smaller brain or hippocampal volumes with associated adverse neurodevelopmental outcomes namely impaired learning and memory [62 63 64 65 66].

Hydrocortisone

Due to potential adverse neurodevelopmental outcomes, most clinicians have turned to hydrocortisone to treat refractory hypotension. Table 1 summarizes some of the studies that used hydrocortisone to treat refractory hypotension[67 52 14 53 68 69 70 71]. Although these studies had relatively small sample sizes, the effect of hydrocortisone on improving cardiovascular function was so consistent and robust that it would take 74 and 188 future studies demonstrating no effect of hydrocortisone on BP increase and vasopressor/inotrope wean, respectively, to eliminate the statistical power of the present findings[52]. Various dosing regimens exist in the literature; doses range from 20 to 100 mg/m^2/day [72]. As shown in Table 1, the dosage used in refractory hypotension varies significantly. Several factors complicate the determination of an ideal dose; 1) infants native cortisol is identical to exogeneous hydrocortisone making it difficult to differentiate between the two; 2) while total cortisol is measured, only free cortisol is active; and 3) high concentrations of cortisol in critically ill patients might be due to decreased metabolism and/or decrease excretion. Given the potential for side effects, the lowest effective dose should be used [73]. Compared to adults and older children, infants have a longer serum half-life for hydrocortisone. In a population based pharmacokinetic study of unbound hydrocortisone in critically ill infants with vasopressor resistant hypotension, among 62 infants with median gestational age of 28 weeks, the typical half-life for unbound hydrocortisone was 2.9 hours [74]. As the hydrocortisone clearance increases at 35 weeks of gestation, the more immature preterm infants should receive hydrocortisone at longer intervals [74]. Based on the published data in patients with refractory hypotension, a 1-2 mg/kg initial dose followed by 0.5-1 mg/kg every 8-12 hours in preterm infants <35 weeks and every 6-8 hours in late preterm and term infants is recommended (Table 1). The duration of treatment is guided by the cardiovascular response. Some patients have significant response after the first one or two doses and

vasopressors/inotropes are weaned off [53] [75]. These patients can be at risk for hypertension if hydrocortisone is continued. Therefore, timely discontinuation of hydrocortisone is imperative to avoid high normal or hypertension especially in preterm infants at risk of intraventricular hemorrhage.

Short-term Side Effects

Simultaneous exposure to cyclooxygenase inhibitors and hydrocortisone (and other steroids) during the first postnatal week increases the risk of spontaneous intestinal perforations [76] [77]. To avoid risk of spontaneous intestinal perforation in preterm infants who had received steroids for refractory hypotension, some have used acetaminophen to treat patent ductus arteriosus (PDA). However, it is unclear if acetaminophen poses lower risk than indomethacin or ibuprofen. Nguyen et al reported two cases of intestinal perforation in preterm infants treated with acetaminophen for PDA closure following hydrocortisone administration[78]. Other short-term side effects include transient hyperglycemia and hypertension and rarely myocardial hypertrophy.

Long-term Side Effects

While there is little information on long term outcomes of preterm and term infants following hydrocortisone use for refractory hypotension, studies assessing neurodevelopmental outcome after hydrocortisone treatment for prevention of BPD are, in general, reassuring. A placebo-controlled trial showed that early (first 10 days), hydrocortisone (cumulative dose 11.5 mg/kg) treatment for the prevention of BPD was not associated with an increased incidence of cerebral palsy [77]. In fact, hydrocortisone group had better outcome in certain aspects of neurodevelopmental exam at 18 to 22 months[79]. In follow up study of a large and more recent double-blinded RCT for prevention of BPD, hydrocortisone treatment for the first 10 day (cumulative dose 8.5 mg/kg) was not associated with adverse neurodevelopmental outcome [80] [81]. On the other hand, a small RCT found a trend for a higher rate of neurodevelopmental impairment in the hydrocortisone group (cumulative dose 11.5 mg/kg, first 10 days)

compared to placebo at school age [82]. Table 2 summarizes the studies that assessed long-term neurodevelopmental outcomes after hydrocortisone exposure primarily for BPD.

As for brain structural changes on MRI, a pilot RCT assessing effect of hydrocortisone (cumulative dose of 17 mg/kg starting at 10 days) showed no difference in regional brain volume at term equivalent compared to the controls[83]. While a retrospective study showed smaller cerebellar volume, most case control studies have shown no difference in cerebral and cerebellar tissue volumes on MRI at term equivalent in preterm infants treated with hydrocortisone for BPD compared to the controls [84 85 86 87 88]

SUMMARY

Hypotension is a common problem in the NICU. A significant subset of hypotensive infants fails to respond to volume and vasopressors/inotropes treatment. These patients may have RAI and respond to corticosteroids. Due to more favorable safety profile, hydrocortisone has emerged as the preferred steroid for refractory hypotension. Within 2-4 hours of initiating hydrocortisone the BP improves and within 6-12 hours vasopressors/inotropes can be weaned. Despite this robust response to hydrocortisone treatment, many questions remain unanswered to date. For example, who is the ideal candidate for treatment and how do we identify them; what is the ideal dose and length of treatment; what are the long-term effects when used for refractory hypotension. In the absence of answers to above questions, it is prudent to utilize steroids judiciously and minimize exposure as much as possible.

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Tables and Figures:

Figure 1: The feto-maternal-placental role in fetal adrenal development.

Maternal, placental and fetal factors play a role in fetal adrenal development. They are as follows; 1. Maternal cortisol is passively transferred to the fetus and suppresses the fetal hypothalamic-pituitary-adrenal (HPA) axis, 2. Placental 11 beta hydroxysteroid dehydrogenase (11B HSD) oxidizes the maternal cortisol to biologically inactive cortisone, this releases the fetal HPA axis from the negative feedback of maternal cortisol in the later part of gestation, 3. Placental corticotropin releasing hormone (CRH) stimulates the fetal HPA which increases exponentially prior to delivery.

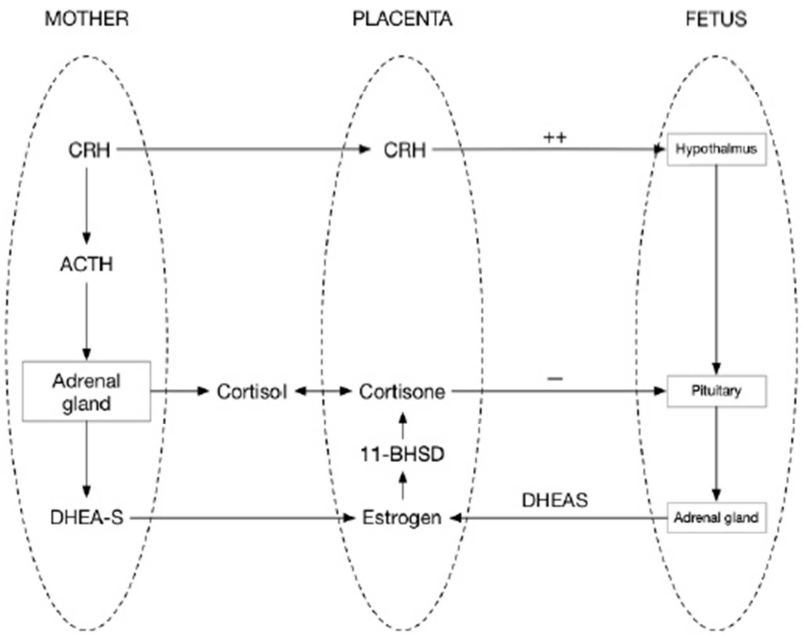

Figure 2: Changes in cardiovascular function in response to hydrocortisone in pressor resistant hypotension (A) and (B) depict changes in mean BP and dopamine dosage (DA), respectively. (C) through (F) demonstrate the percentage changes relative to baseline (0 hour) in SVR (C), stroke volume (SV) (D), heart rate (HR) (E), and LVO (F). BP, Blood pressure; SVR, systemic vascular resistance.
Modified with permission from Noori S, Friedlich P, Wong P, Ebrahimi M, Siassi B, Seri I: Hemodynamic changes after low-dosage hydrocortisone administration in vasopressor-treated preterm and term neonates. Pediatrics 118:1456–1466, 2006.)

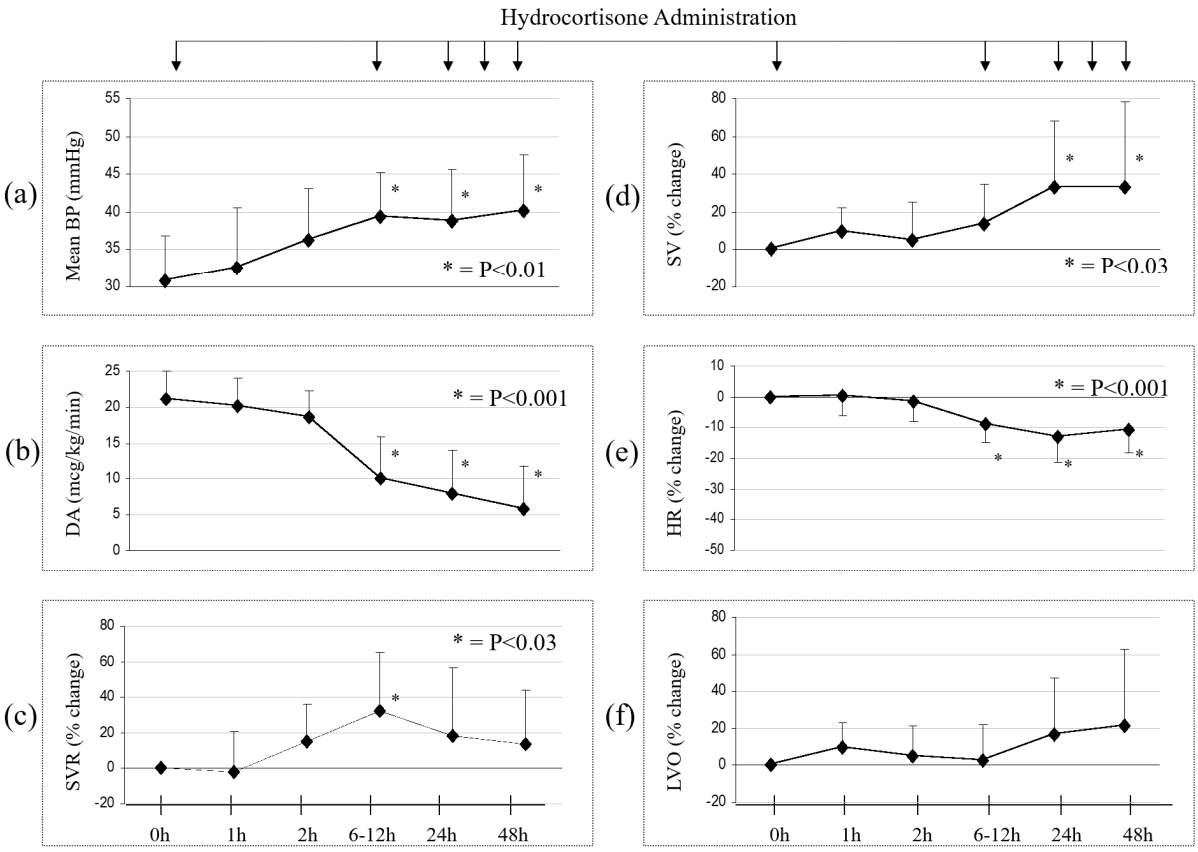

Table 1: Table summarizing studies assessing effect of hydrocortisone on blood pressure in refractory hypotension.

Authors	Year	N	Dose	Findings/Conclusions
Helbock et al[67]	1993	6	Initial: 0.1-2 mg/kg Mt: 1.5-6 mg/kg per day	• All six newborns showed rise in BP • Time to increase BP was shortest when initial dose was higher
Ng et al[89]	2001	5	1mg/kg q 4h X 5 days HCN (for 3 patients) Or 0.5 mg/kg dexamethasone (for 2 patients)	• Inotropes were decreased within 50 minutes to 3.5 hours after adequate corticosteroids were administered
Seri et al[90]	2001	21	2-6 mg/kg/day for 1-3 days	• BP improved by 2 hours and vasopressor/inotrope dose weaned by 6 hours
Ng et al[91]	2006	48	1mg/kg q 8h X 5 days	• vasopressor support weaned off 72 hours after starting treatment
Noori et al[53]	2006	20	Initial: 2mg/kg, Mt 1mg/kg q 12h X 2 days	• BP improved without compromising cardiac function, systemic perfusion, or cerebral and renal blood flow

Table 2: Studies evaluating long-term neurodevelopmental outcomes after hydrocortisone exposure.

Author	Year	N	Findings/Conclusions
Watterberg et al [77]	2004	360	• HCN exposed infants receiving indomethacin had higher rates of gastrointestinal perforations compared to placebo exposed infants.
Watterberg et al[79]	2007	252	• Early low dose HCN exposure did not increase risk of cerebral palsy in survivors • HCN exposed infants had improved developmental outcomes
Patra et al[92]	2015	175	• HCN exposure for > 7 days associated with poor fine motor skills at 12 months • Increased cumulative HCN exposure negatively impacted receptive and expressive language skills in the 1st year and motor skills in the

			2nd year
Rademaker et al[86]	2007	226	• Motor function and cerebral palsy risk were similar in both groups, after risk adjustment
Peltoniemi et al [82]	2016	37	• HCN exposed infants had higher rates of neurological impairment at 2 years of age compared to placebo exposed infants
Baud et al[81]	2017	379	• Exploratory analysis of the PREMILOC trial[80] • Early low dose HCN was not associated with a statistically different neurodevelopmental outcomes at 2 years of age

HCN = Hydrocortisone