Hydrocortisone for Treatment of Hypotension in the Newborn

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The purpose of this article is to review the risks and benefits of hydrocortisone in the treatment of hypotension in the newborn.

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Abstract

Newborns, and especially premature newborns, are at significant risk for developing hypotension in the first week or two after birth. The etiology of hypotension in the newborn may vary, but the very low birth weight and extremely low birth weight preterm infants are less likely to respond to conventional cardiovascular support when they develop hypotension. This article reviews the least conventional treatment using hydrocortisone for hypotension that is refractory to conventional volume replacement and/or vasopressor medications with the underlying assumption that sick and premature newborns have a relative or measured adrenal insufficiency. The addition of hydrocortisone in the treatment of hypotension in the newborn is becoming more common but is not universally advocated. However, the supportive evidence is growing, and, as reviewed, use of hydrocortisone requires judicious and cautious regard.

Keywords: hydrocortisone; hypotension; shock; vasopressor resistant; very low birth weight infants; relative adrenal insufficiency

Newborns are at risk for systemic hypotension during the immediate postnatal period. They generally respond to volume for hypovolemia or vasopressor inotropes for most other causes. However, when the newborn with hypotension becomes refractory to the more common therapies, hydrocortisone may be considered as an adjunct treatment. A recent review found a trend toward increased use of hydrocortisone for treatment of neonatal hypotension in the past decade.[1] The assumption underlying the use of hydrocortisone is presumptive adrenal insufficiency, and, although serum cortisol levels may be useful, cortisol levels may not be diagnostic despite effective clinical response to hydrocortisone.

INCIDENCE

Hypotension is common in the sick premature newborn, and incidence increases with decreasing gestation. The incidence of hypotension in very low birth weight (VLBW) newborns (<1,500 g at birth) is 20 percent.[2] In extremely low birth weight (ELBW) newborns (<1,000 g at birth), the highest-risk group, the incidence of hypotension ranges from 20 to 45 percent.[3–5] The incidence of hypotension in newborns of any gestation with sepsis occurs at a reported incidence of 38–69 percent.[6] The incidence of hypotension in term newborns following cardiac surgery for congenital heart defect repair is 25 percent.[7]

ETIOLOGY

Hypotension in the premature infant may be due to hypovolemia, alterations in systemic vascular resistance with abnormal distribution of fluid into the extravascular space, or myocardial dysfunction associated with hypoxia. Hypotension associated with sepsis is largely caused by alterations in circulatory volume, and hypotension in postoperative congenital heart disease is likely caused by myocardial dysfunction. The etiology of hypotension is reviewed in Table 1.[8]

PATHOPHYSIOLOGY

After delivery, the newborn heart must transition from pumping to a low-resistance vascular bed (placenta) to a higher-resistance

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TABLE 1 ■ Etiology of Hypotension

Pathophysiologic Mechanism	Pathogenesis	Underlying Pathophysiology	Etiology
Hypovolemic	Insufficient circulating blood volume; reduced preload	Impaired cardiac output and reduced oxygen-carrying capacity from anemia	• Maternal hemorrhage • Twin-to-twin transfusion • Newborn hemorrhage
Distributive	Decreased systemic vascular resistance leading to distribution of vascular volume into extravascular space; altered afterload	Reduced systemic vascular resistance leading to venous or third spacing of fluid from intravascular to extravascular space	• Sepsis release of vasoactive mediators, altering vascular tone and endothelial permeability • Streptococcal or staphylococcal toxic shock • Hydrops fetalis • Adrenal insufficiency
Cardiogenic	Cardiac dysfunction with a decrease in cardiac output; reduction in myocardial function	Myocardial dysfunction	• Myocarditis • Hypoxic ischemic conditions • Congenital heart block • Congenital heart defects with impaired flow and obstructive lesions

From Adcock LM. Etiology, clinical manifestations, and evaluation of neonatal shock. UpToDate Web site. http://www.uptodate.com/contents/etiology-clinical-manifestations-and-evaluation-of-neonatal-shock. Updated July 18, 2014. Accessed May 30, 2014.

vascular bed (systemic circulation). If the required adaptive changes for effective cardiac output or peripheral vasoconstriction are delayed or impaired, hypotension will result.[9] Systemic hypotension is associated with increased morbidity and mortality in the newborn, and especially in the VLBW newborn.[10,11] Hypotension leads to loss of autoregulated vital organ blood flow with altered organ function from ischemic damage.[12,13] The primary concern is the likely impairment of central nervous system perfusion with hypotension that may result in ischemic damage to the brain, thereby increasing risk of intraventricular hemorrhage and periventricular leukomalacia.[14]

DIAGNOSIS

Recognition of hypotension is traditionally dependent on blood pressure (BP) measurements. Although near-infrared spectroscopy (NIRS) has been able to demonstrate impaired cerebral blood flow autoregulation, this technology is not commonly used in the clinical NICU setting for diagnosis. Therefore, BP measurement remains the available measure of tissue perfusion.[14] Diagnosing low systemic blood flow by BP alone is problematic because the normal gestational and postnatal age–dependent BP range is not known, and the BP indicating loss of autoregulation or tissue damage in the immediate postnatal period is unknown for the VLBW newborn.[11,15,16]

Despite the lack of clear BP norms in premature newborns, researchers commonly define hypotension as a mean BP that is below the fifth or tenth percentile of the normative data for the infant's gestational and postnatal age.[11,17] Clinicians, however, may define hypotension as a mean BP less than the gestational age in weeks or <30 mmHg. Evidence for use of either of these BP values as the threshold for treatment is lacking. Clinical signs of poor perfusion including delayed capillary refill times, impaired renal function, and acidosis coupled with a preferred mean BP threshold may be a more accurate reflection of the need for treatment.[11,13,18,19] Weindling and Subhedar suggested hypotension could be defined clinically as a BP level that improved with vasopressor agents.[9] There remains no consensus of normal BP values in the VLBW newborn to use for intervention threshold or for evaluating effectiveness of hypotension therapy.[20]

TREATMENT

The standard first-line treatment for hypotension because of hypovolemia is volume replacement. Neonatal hypotension, not specifically because of hypovolemia, is usually treated with cautiously titrated vasopressor inotropes including dopamine and epinephrine to promote vasoconstriction or increase afterload resulting in increased BP, achieving normal tissue perfusion. Often, the use of or addition of dobutamine, a synthetic sympathomimetic amine that provides direct positive inotropic effect, will increase BP by improving cardiac contractility and cardiac output. Dobutamine commonly either results in a variable decrease or has no effect on peripheral vascular resistance.[21] When the effectiveness of carefully titrated inotropes is inadequate or limited, hydrocortisone is often the next level of treatment.

HYDROCORTISONE

Cortisol levels increase with increasing gestation, and lower cortisol levels are commonly reported in VLBW premature infants, which may predispose this population to reduced cardiovascular responsiveness to catecholamines.[22,23] Some authors have suggested a subset of VLBW premature newborns may be less responsive if not refractory to standard vasopressor management. This apparent unresponsiveness to vasopressor therapy may be because of primary adrenal insufficiency manifesting as neonatal hypotension.[24–26] One would

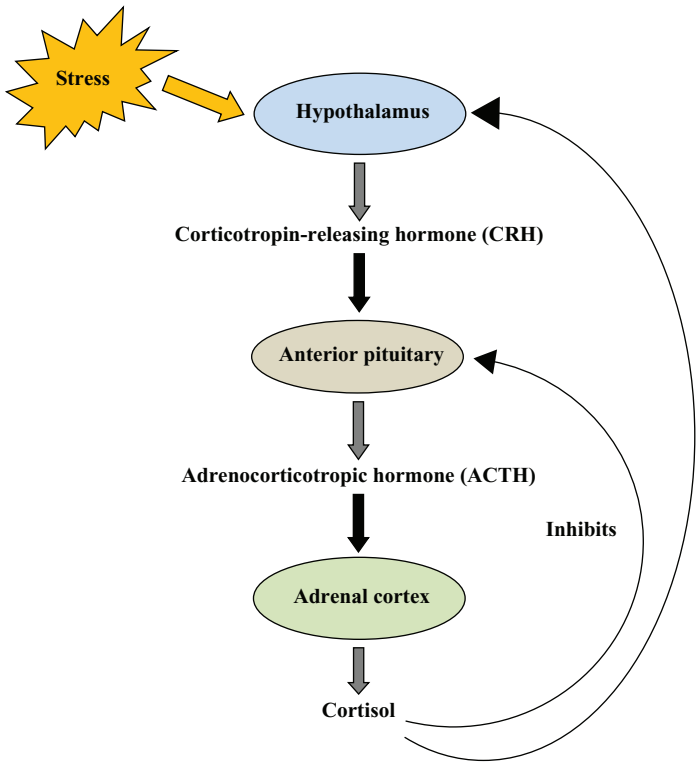
assume this postulated etiology of adrenal insufficiency could be diagnosed by a low cortisol level or baseline serum cortisol concentration <138 nanomole per liter (nmol/liter) or <5 micrograms per deciliter (mcg/dL).[26,27] However, symptoms of adrenal insufficiency do not always correlate with the serum cortisol levels, and the normal cortisol level associated with hypotension may be secondary to a relative adrenal insufficiency (RAI). In RAI, the cortisol level is adequate for most functions but insufficient for acute illness or prematurity.[4,28] This may be similar to the critical illness–related corticosteroid insufficiency (CIRCI) described in critically ill adults with a form of adrenal insufficiency who have cortisol levels inadequate for the severity of underlying stress level of the patient, suggesting an alteration in cortisol level or an altered response to cortisol level.[29]

Pharmacology of Hydrocortisone

Hydrocortisone is the identical molecule to cortisol, a glucocorticoid hormone produced by the zona fasciculata of the adrenal cortex. As a review, cortisol is synthesized from cholesterol in the adrenal cortex. It is the primary hormone produced by the adrenal cortex, which also produces aldosterone and some sex hormones. The adrenal medulla produces all of the epinephrine and some of the body's norepinephrine (Table 2).[30] The adrenal cortex releases cortisol in response to adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary gland. The ACTH production is stimulated by the corticotrophin-releasing hormone secreted by the neuroendocrine cells of the hypothalamus stimulated by stress. As with other endocrine hormones, cortisol release is controlled by a feedback system (Figure 1).[30] Cortisol increases glucose formation from amino acids and glycerol; stimulates the conversion of glucose to glycogen, thus increasing glucose use and protein and fat breakdown which leads to impaired growth or weight gain, increased blood glucose, and often to hyperglycemic levels; promotes salt retention; increases water retention; and increases calcium excretion. It increases the expression of adrenergic receptors in the vascular wall, thus enhancing reactivity to norepinephrine from the adrenal medulla and angiotensin II from the kidney.[30,31]

Like cortisol, hydrocortisone increases BP by increasing the sensitivity of the vasculature to the vasoconstricting effects of epinephrine and norepinephrine. In the absence of cortisol, widespread vasodilatation occurs, resulting in hypotension. Hydrocortisone is the weakest of the pharmaceutical forms of cortisol, with prednisolone being approximately four times more potent than hydrocortisone and dexamethasone approximately 25 times more potent in

FIGURE 1 ■ Cortisol feedback system.



Modified from Barrett EJ. The adrenal gland. In: Boron WF, Boulpaep EL, eds. *Medical Physiology.* 2nd ed. Philadelphia, PA: Saunders; 2012:1057-1073.

TABLE 2 ■ Adrenal Gland Hormones[29]

Structure	Hormone Released	Function
Adrenal Cortex		
Zona glomerulosa	Mineralocorticoids (mainly aldosterone)	Increase • Urine excretion of K^+ • Reabsorption of Na^+ • Retention of water
Zona fasciculata	Glucocorticoids (mainly cortisol)	Increase • Gluconeogenesis • Blood glucose • Retention of water Anti-inflammatory effects
Zona reticularis	Androgens (mainly DHEA)	Sex hormone precursor
Adrenal Medulla		
Chromaffin cells (functional postganglionic equivalent cells)	Epinephrine (synthesized solely in adrenal medulla) Dopa Dopamine Norepinephrine	Catecholamine fight or flight responses to stress Increase heart rate and contractility, vasoconstriction, mobilization of fuel stores, pupillary dilation

Abbreviation: DHEA 5 dehydroepiandrosterone.

Modified from Barrett EJ. The adrenal gland. In: Boron WF, Boulpaep EL, eds. *Medical Physiology.* 2nd ed. Philadelphia, PA: Saunders; 2012:1057-1073.

the glucocorticoid effect.[30–32] The presumed mechanism of action for hydrocortisone is twofold. Initially, it inhibits catecholamine metabolism and catecholamine reuptake, leading to an increase in BP within hours of administration. Hydrocortisone increases vascular and smooth muscle cell cytosolic calcium availability and inhibits prostacyclin and nitric oxide production, reducing inflammation. Second, glucocorticoids induce gene expression, resulting in upregulation of cardiovascular adrenergic receptors.[15]

Indications and Dosing

Hydrocortisone is effective after appropriate volume replacement with isotonic saline or blood products, if BP is not improved on dopamine at 10 mcg/kg/minute. The goal when used to treat hypotension is to improve BP to thereby prevent severe and prolonged impairment in cerebral blood flow with associated long-term morbidity and mortality. Use of hydrocortisone may help prevent complications associated with excessively high doses of inotropes such as compromise in cardiac function, systemic perfusion, cerebral blood flow, and autoregulation and renal blood flow.[33] Before starting a course of hydrocortisone for RAI, it is recommended to obtain a baseline cortisol level prior to treatment. Although not all newborns with hypotension have diagnostic low cortisol levels, a cortisol level of ≤5 mcg/100 mL is diagnostic of adrenal insufficiency.[26] A cortisol level <15 mcg/100 mL has been found to respond to hydrocortisone treatment, whereas a level ≥15 mcg/100 mL does not respond to hydrocortisone therapy.[34]

Dosing recommendations for hydrocortisone treatment of hypotension secondary to RAI refractory to dopamine at >10 mcg/kg/minute vary in the literature. Common recommendations are to dose at 15 mg/m^2, or 1–2 mg/kg every 6–12 hours, by intravenous infusion.[11,34,35] Dosing interval for term newborns or infants 35 weeks gestation or more is every 6–8 hours, and dosing interval for infants <35 weeks is every 8–12 hours.

The water-soluble form of hydrocortisone, hydrocortisone sodium succinate, is available as a powder for injection and can be reconstituted in preservative-free sterile water for injection as 50 mg/mL and further diluted to 1 mg/mL in normal saline, or D_5W, stable for three days if refrigerated.[36]

Hydrocortisone is presumed to have a half-life of eight hours. Many report a therapeutic response with an increase in blood pressure using a dose of 1 mg/kg/dose every 8–12 hours for RAI. In addition, by 24–48 hours after starting hydrocortisone, there is not only an expected improvement in BP but also an improvement in urine output and ability to reduce vasopressor support. Within 24 hours after a positive response to hydrocortisone therapy with improved BP and urine output and tolerance of reduced vasopressor support, it is recommended that hydrocortisone dose be reduced to 0.5 mg/kg/dose. If the infant has not been treated with hydrocortisone for longer than three days, the drug does not need to be tapered but can be discontinued.[11,34–36]

Side Effects and Contraindications of Hydrocortisone

Some of the side effects of short-term hydrocortisone administration (two to three days) include hypokalemia, abdominal distension, esophagitis, impaired wound healing, petechiae, convulsions, growth suppression, hypertension, and hyperglycemia. Gastric bleeding and gut perforation are side effects especially if administered in combination with nonsteroidal anti-inflammatory drugs including indomethacin and ibuprofen for patent ductus arteriosus closure.[37]

Hydrocortisone is specifically contraindicated if the infant has a systemic fungal infection because steroid therapy can cause hyperglycemia, providing a glucose-enriched environment for *Candida albicans*.[38] Steroid therapy also can affect immune competence by altering phagocytosis, reducing the circulating lymphocyte subpopulations, inhibiting the cytokine responses, and impairing cell-mediated immunity in premature infants.[39] Long-term use may result in multisystem complications, adrenal insufficiency, and risk of neurodevelopmental impairment.[36,40] Unlike early long-term studies in infants who received high-dose dexamethasone, one long-term prospective study examined the use of low-dose hydrocortisone for the treatment of adrenal insufficiency in 252 ELBW infants and found no associated increased incidence of cerebral palsy with some indication of improved developmental outcome at 18–22 months.[41] Nevertheless, further prospective studies are essential, and careful consideration is warranted before instituting steroid therapy for hypotension in this vulnerable population of ELBW and VLBW newborns.

Treatment of hypotension because of RAI in the newborn and especially the VLBW infant with hydrocortisone remains under investigation but is becoming more common in clinical practice although its mechanism of action is not clearly understood.[1] BP levels that clearly define intervention threshold are lacking.[20] Low cortisol levels may not be diagnostic of RAI nor predictive of VLBW infants likely to respond to corticosteroid treatment for refractory hypotension, but they provide an important baseline.[42] Dosing regimens are many, and despite some evidence that hydrocortisone improves BP, minimal effective dose and long-term neurodevelopment outcomes have yet to be determined.[20] To date, there is no conclusive evidence "that treating hypotension in VLBW infants decreases mortality and neurologic morbidity."[13(p9)] Ongoing research is clearly needed, and the past issues with steroids should guide a cautious level of practice and judicious use of hydrocortisone in treating this vulnerable patient population.

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