

Hypovolemia and the Newborn: Is there a Role for Arginine Vasopressin?

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Hypovolemia and hypovolemic shock are both chief causes as well as complications of critical illness. In the neonatal period, this is a very important and sizable problem that contributes to morbidity and mortality preterm as well as term infants.

According to the 2011 Neonatal Network Report [1] 4000 infants were born at less than 32 weeks in Canada over a 12-month period. Of these, 15% had Intraventricular Haemorrhage (IVH) and half of those had a brain parenchymal component of haemorrhage. The relation between IVH and hypovolemia is dual: not only does IVH elicit shock in many cases, but antecedent low systemic blood flow has been implicated as a cause of IVH. Of the same 2011 preterm cohort [1], 5% had necrotizing enterocolitis whereas 10% had a serious pulmonary hemorrhage. More than 10% had surgery during their neonatal intensive care unit (NICU) stay. All of these conditions are almost always associated with hypovolemia requiring treatment. Another line of evidence emphasizing the importance of adequate circulating volume in the neonatal period comes from data on delayed cord clamping [2]. This procedure clearly improves hemodynamics in small preterm infants and possibly reduces the incidence of IVH, but it is not done in the sickest infants who may need it the most, since a contraindication for delayed cord clamping is "immediate need of resuscitation". Thus the infants who are expected to have the worst circulatory parameters also start with lower blood volumes.

When looking at treatments for hypovolemia in the preterm, the numbers are impressive: up to 52% of neonates less than 1500 g receive volume loading during the first 24 hours of their hospital stay and up to 50% are transfused during the first week [3]. For the term infant, data are less detailed, but the incidence of large fetomaternal hemorrhage is up to 5 to 6% at term [4]. According to the American College of Surgeons guidelines for Advanced Trauma Life Support (ACS ATLS[®]) [5], haemorrhage in adult patients is divided into four classes of increasing severity and therapeutic requirements. In the neonate, however, haemorrhage and hypovolemia are not specifically classified. This may be related to the significant differences between the adult and neonatal circulatory physiology. The neonate has higher O₂ delivery requirements, a lower cardiac output reserve, and immature regulation of the macro- and microcirculations. The impact of hypoxia-ischemia on the developing brain and other organs is also very different. Thus, resuscitation strategies following hypovolemia in the neonate and child are based upon extremely limited direct data. Treatments and physiological targets remain controversial and are not standardized [6-8]. For this reason, significant variation exists in the amount and type of fluids administered for restoring blood pressure and circulating volume as well as any pharmacological support of the circulation. A major knowledge gap concerns the regulatory mechanisms elicited in response to hypovolemia shock in the neonate, aimed at restoration of blood pressure, circulating volume and O₂ delivery to tissues and organs notably the brain, kidney and gut.

Controlled hemorrhage has been the mainstay of modeling hypovolemic shock. In response to compensated haemorrhage, various endocrine changes assist in restoring blood pressure and blood volume such as an increase in plasma and central levels of arginine vasopressin (AVP). Decompensated haemorrhage is, however, associated with a precipitous decline in AVP levels. It appears from studies in

adult animals that the deleterious consequences of decompensated haemorrhage can be overcome, at least in part, by treatment with AVP or its analogue terlipressin.

An endogenous hormone with osmoregulatory, vasopressor, thermoregulatory, and central nervous system (CNS) effects, AVP is a neurohypophysial peptide hormone, synthesized in the hypothalamus. AVP exerts its physiological effects through activation of three receptor subtypes designated as V1Rs, V2Rs, and V3Rs, all members of the G-protein receptor coupled superfamily. V1Rs are located in vascular smooth muscle cells and elicit smooth muscle contraction, mediating the vasopressor activity of AVP. As a vasoconstrictor, AVP is several-fold more potent than norepinephrine and angiotensin II. V2Rs are located in the kidney on principal cells of the cortical collecting duct. They mediate antidiuretic effects upon stimulation, through integration of aquaporins into the luminal cell membrane, leading to increased reabsorption of water. V3Rs are present in the central vasopressinergic system and their activation modulates learning, memory, social behavior, thermoregulation, the baroreflex action as well as the release of adrenocorticotrophic hormone [9-12]. The numerous physiological effects of AVP could make it an excellent choice for use in the treatment of decompensated haemorrhage [13-17]. It has very little pressor effect in normal healthy subjects in whom AVP levels are normal; vasodilated septic shock patients and animals in haemorrhagic shock are deficient in AVP; administration of AVP in the setting of hypovolemia appropriately raises serum AVP levels and increases blood pressure; activation of V1Rs by AVP increases peripheral vascular resistance; activation of V2Rs by AVP increases water reabsorption by the kidney; within the CNS, AVP potentiates the baroreflex through activation of V3Rs.

As stated above, there is a decrease in both circulating and cerebrospinal fluid levels of AVP [18,19] that coincides with the onset of haemorrhagic shock. Considerable evidence has emerged over the last decade that this marked decrease in AVP is an important factor in the syndrome of hypovolemic shock in adults. For example, replacing AVP reduces blood loss and stabilizes blood pressure in trauma patients with haemorrhagic shock refractory to catecholamines [13,18-25]. In patients with hepatorenal syndrome and gastrointestinal haemorrhage, the analogue of AVP - terlipressin, inhibits splanchnic blood flow which reduces portal pressure and variceal bleeding, leading to an increase in blood volume and improved kidney function [26]. Early AVP combined with standard crystalloid resuscitation in patients with

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traumatic brain injury and haemorrhagic hypotension reduces the total fluid required for resuscitation, and improves intracranial pressure as well as cerebrovascular compliance, thereby preventing acute circulatory collapse during fluid resuscitation. For its promising role as an adjunct to fluid resuscitation in haemorrhagic shock, [13,17,27] a multicenter, randomized, controlled, international clinical trial is currently underway to assess the effects of AVP versus saline placebo in adult trauma patients with refractory haemorrhagic shock, known as the VITRIS study (Vasopressin in refractory traumatic hemorrhagic shock, haemorrhagic) [15,16].

Recently, Carroll et al. published a prospective pilot trial that supports the feasibility of a future randomized controlled trial for the use of AVP in pediatric patients with hypovolemic shock who are refractory to epinephrine, similar to the aforementioned VITRIS study [28]. Vasopressin and terlipressin have both been used in neonates as a last resort in cases of refractory hypotension, generally with good symptomatic effect. Little is known, however, regarding their physiological effects in hypovolemia during the neonatal period.

In previous experiments in conscious lambs and young adult sheep, we showed that in response to compensated haemorrhage, there is an increase in plasma levels of AVP in lambs, which is similar to that seen in adults [29,30]. To date, however, no role for AVP in reversing the deleterious effects of decompensated hypovolemia has been investigated in the newborn period nor is it known whether AVP should even be considered as part of resuscitation strategies in the neonate.

The following issues remain to be addressed in future studies in newborn models:

(1) What are plasma AVP levels in decompensated hypovolemia / haemorrhage? Do they follow the same profile as that seen in the adult?

(2) What are the effects of haemorrhagic hypovolemia and fluid resuscitation strategies in the presence of the V1R agonists? Are they similar to or different from the effects of AVP in the adult?

(3) Does the distribution of V1Rs, V2Rs and V3Rs change after haemorrhagic shock in key tissues in the newborn (aorta, brain, heart, gut, kidney)?

The future of resuscitation strategies in the neonate requires important advances in physiological knowledge, and studies centered on the above questions are needed to clarify if AVP or specific agonists might play an important clinical role.

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