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Vasopressin and Terlipressin for Pediatric Refractory Shock

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ABSTRACT
Objective: *To review the physiology and the published literature on the role of vasopressin in shock in children.*
Results: *Beneficial effects have been reported in vasodilatory shock and asystolic cardiac arrest in adults. Solid evidence for vasopressin use in children is scanty. Observational studies have reported an improvement in blood pressure and rapid weaning off of catecholamines during administration of low-dose vasopressin. Dosing in children is extrapolated from adult studies.*
Conclusions: *Vasopressin offers promise in shock and cardiac arrest in children. However, in view of the limited experience with vasopressin, it should be used with caution. Results of a double blind, randomized controlled trial in children with vasodilatory shock will be available soon.*
Keywords: *Children; cardiac arrest; inotrope; vasopressin; shock; septic shock.*

Introduction

Shock and hemodynamic compromise are among the most dramatic, dynamic, and life threatening problems faced in pediatric critical care, with an unacceptably high mortality rate of up to 53% [1]. Aggressive volume resuscitation is the mainstay of the initial management of hemodynamic instability in children. Catecholamines are the most common vasoactive agents used to maintain blood pressure and vital organ perfusion. However, decreased vascular and myocardial sensitivity to catecholamines has been demonstrated in shock, and as a result, unacceptable adverse effects may precede the desired clinical effects [2].

A few small comparative clinical trials and a systematic review reported no single catecholamine agent as superior in improving outcomes in shock[3]. The effects of catecholamine agents on the cardiovascular system in children and infants are not without controversy. They may increase the heart rate (via -receptors), hence increasing myocardial oxygen consumption. In addition, if increased blood pressure occurs by increasing systemic vascular resistance, some end-organ perfusion may be compromised with high-dose catecholamine vasopressors [4].

It has also been suggested that prolonged infusions of catecholamines in infants may impair myocardial performance, leading to a survival disadvantage[5]. Hence, the evaluation of alternative and adjunctive therapies targeted at specific pathophysiologic pathways to reverse shock is important. Vasopressin has been used since the 1950s primarily to treat patients with diabetes insipidus and to control gastrointestinal bleeding. However, only in the past decade has there been renewed interest in the use of low-dose vasopressin as a potent vasopressor as per its original description 100 yrs ago[6]. Encouraged by reports in adult patients with cardiac arrest and vasodilatory shock, some authors have proposed that arginine vasopressin and its analogs are potentially beneficial agents for the treatment of shock and cardiopulmonary arrest in children [7].

Physiology of Vasopressin

Vasopressin is synthesized in the hypothalamus as the prohormone preprovasopressin. Prepro-vasopressin is degraded to pro-vasopressin, which migrates along neuronal axons to the posterior pituitary, where it is subsequently released in three fragments: vasopressin, neurophysin II, and copeptin. Most newly synthesized vasopressin is stored intracellularly, and only 10% to 20% of the total hormonal pool within the posterior pituitary can be readily released under appropriate stimuli [8].

Once secreted into the circulation, vasopressin is accompanied by its carrier protein, neurophysin II, which does not appear to have any independent biological activity. The function of copeptin is unclear. Vasopressin is cleaved by vasopressinase and has a half-life of approximately 5–15 mins, which is why vasopressin is administered by continuous infusion during the management of vasodilatory shock [9].

Vasopressin is responsible for multiple physiologic functions, the most well known being vasoconstriction of vascular smooth muscle and osmoregulation. The vasopressor effect of this pituitary extract was first observed by Drs. Oliver and Schäfer (6) in 1895; however, it was 20 yrs before its strong antidiuretic effects were recognized, at which point this hormone was renamed antidiuretic hormone[10]. After its isolation and synthetic preparation were accomplished by Du Vigneaud et al. [11] in 1954 (Du Vigneaud subsequently was awarded the Nobel Prize), it was recognized that the same hormone in the posterior pituitary possessed both antidiuretic and vasopressor effects. However, it is now recognized that vasopressin has many other physiologic functions, including effects on memory, sleep cycles, temperature regulation, hemostasis, insulin, and corticotropin release [12].

The effects of vasopressin on various vascular beds and tissues are complex and at times appear to be paradoxical. The diversity of its actions are related to the location and density of tissue-specific G-protein-coupled vasopressin receptor subtypes, which are currently classified into V1 vascular, V2 renal, V3 pituitary, oxytocin, and P2 purinergic receptors (Table 1) [13].

V1 vascular receptors are located on vascular smooth muscle and mediate vasoconstriction. However, in the pulmonary circulation, vasopressin activation of V1 receptors mediates the release of nitric oxide (NO) and causes pulmonary vasodilation, in contrast to its vasoconstrictive action in the systemic circulation. Oxytocin receptors are a subset of vasopressin receptors found in the uterus, in the mammary gland, and, more recently, in endothelial cells of human umbilical vein, aorta, and pulmonary artery.

Vasopressin's binding to oxytocin receptors increases intracellular calcium, stimulating the release of NO and thus mediating vasodilation. Purinergic P2 receptors are located in cardiac endothelium and may play a role in cardiac contractility and selective coronary vasodilation. Vasopressin therefore not only is important in the control of water balance and cardiovascular regulation but also is actively involved in coordinating the autonomic and endocrine responses to homeostatic disturbances.

Regulation of Vasopressin Secretion

The normal plasma vasopressin concentration in hemodynamically stable patients ranges between 1 and 7 pg/mL, depending on the level of hydration and osmolality. The most important stimuli for vasopressin release are increased plasma osmolality, hypotension, and hypovolemia. Under normal conditions, vasopressin plays a minimal role in the vascular regulation of blood pressure, and its main role is in the regulation of water balance [14].

During this time, secretion is regulated primarily by changes in plasma osmolality via input from osmoreceptors, and vasopressin levels may rise as high as 20 pg/mL during maximal urine osmolality [15]. Vasopressin secretion is also under the control of the sympathetic nervous system. Under resting conditions or when stretched, baroreceptors inhibit vasopressin secretion. Decreased activity due to low blood pressure decreases baroreceptor neuronal output and results in the release of vasopressin from the hypothalamus. N

onosmotic stimuli, such as hypovolemia and hypotension, shift the osmotic threshold for vasopressin release to the left, without altering the slope or sensitivity of the relationship of vasopressin and plasma osmolality [16]. Therefore, regardless of plasma osmolality, during the initial phase of shock extremely high levels of vasopressin, in the range of 300 –1800 pg/mL, can be observed [17].

At these plasma concentrations, vasopressin is a critical mechanism for maintaining systemic vascular resistance and arterial blood pressure, and baroregulation overrides osmoregulation. There is an exponential inverse relationship between plasma vasopressin levels and the degree of hypotension. Small reductions in blood pressure to the order of 5% to 10% from baseline usually have little or no effect on plasma vasopressin, whereas a 20% to 30% decrease results in a 20- to 30-fold increase in serum vasopressin levels[18]. Other important secretagogues of vasopressin include endotoxin

and proinflammatory cytokines (i.e., interleukin-1, interleukin-6, tumor necrosis factor-) [19, 20]. Other nonosmotic stimuli, such as pain, nausea, hypoxia, anesthetic agents, and various endogenous and exogenous chemicals, such as norepinephrine and acetylcholine, may also trigger vasopressin release.

Vasopressin Levels in Shock

A biphasic vasopressin response has been described, particularly in vasodilatory shock states where high levels are observed in the initial phase of profound hypotension, followed by inappropriately low levels to the order of 3–10 pg/mL as shock progresses. It seems unlikely that increased vasopressin clearance from the plasma accounts for vasopressin depletion, given observations that vasopressinase levels remain undetectable in this scenario. Several mechanisms responsible for vasopressin deficiency have been proposed, including the depletion of neurohypophyseal stores, impaired baroreflex-mediated release of vasopressin attributable to autonomic dysfunction, and down-regulation of vasopressin production by increased central NO production [15].

The NO-mediated inhibition of vasopressin release may also have important implications in the pathogenesis of adrenal insufficiency, which is commonly observed in critically ill patients, as vasopressin modulates adrenocorticotropic hormone production [12].

Recent studies suggest that cytokines, such as interleukin-1, tumor necrosis factor, and interferon-alfa may also contribute to vasopressin receptor down-regulation and reduced efficacy of exogenous hormone [28]. These observations of endogenous absolute or relative vasopressin deficiency in critically ill adults have been used to justify a role for exogenous vasopressin infusions in patients in refractory shock. Supporting data for absolute or relative vasopressin deficiency from pediatric studies, however, are limited and inconsistent.

The observations in adults clearly identify endogenous vasopressin deficiency, especially in vasodilatory shock, while the pediatric studies are inconsistent in that both cold and warm shock patients were not distinguished. These clinical differences between children and adults with shock reflect the age-related complexity of pathophysiologic mechanisms, which extends beyond vasopressin dysregulation. Therefore, the reliability of endogenous vasopressin level as a marker for use and indeed response to exogenous vasopressin infusions has not been adequately explored in children.

Measurement of Vasopressin Levels

A limitation of measuring circulating vasopressin levels is that the mature hormone is unstable, has a short half-life, and is largely attached to platelets, which are not measured in plasma. Accordingly, vasopressin concentration in platelet-rich plasma is approximately five to six fold higher than that in platelet-depleted plasma.

Hence, interpretation of static measurements of vasopressin may be misleading. Copeptin, a stable peptide of the vasopressin precursor, is secreted in an equimolar ratio and thus mirrors the production of vasopressin. Plasma copeptin measurements recently were shown to be much more stable and easy to determine, and therefore copeptin has been proposed as a more sensitive and a potential prognostic marker in patients with sepsis [35, 36].

A Role for Vasopressin in Shock

It is now well recognized that vasopressin has multiple physiologic functions beyond the control of water balance and cardiovascular regulation. Hence the name antidiuretic hormone is outdated, although the term vasopressin is still not indicative of its function beyond the vascular and renal systems. Vasopressin also plays an important role in homeostasis during shock states, like septicemia, and cardiopulmonary arrest. There is evidence that the human body discharges vasopressin as an adjunct stress hormone to catecholamines in life-threatening situations, such as shock and cardiac arrest [12].

Vasopressin has been recognized as an important stress hormone after thermal injury in children and during congestive heart failure in neonates. Vasopressin levels have been noted to be higher in patients with cardiac arrest who were successfully resuscitated compared with those in whom spontaneous circulation was not restored [12].

The most promising therapeutic role for vasopressin is in the management of vasodilatory shock states and cardiopulmonary resuscitation.

Vasopressin in Vasodilatory Shock

The efficacy of vasopressin has been demonstrated in various groups of patients with vasodilatory shock, including sepsis, post perfusion syndrome following cardiopulmonary bypass, and prolonged hemorrhage, and in hemodynamically unstable organ donors.

Vasodilatory shock may result from many causes, and they share common pathogenic mechanisms that are responsible for vascular smooth muscle dysfunction and vascular hyporesponsiveness to catecholamines [2].

Vasopressin is an attractive agent in this setting as it reverses the mechanisms responsible for vasoplegia and catecholamine resistance.

Vasoconstrictor Effects of Vasopressin- Vasopressin directly inactivates adenosine triphosphate sensitive potassium channels in vascular smooth muscle, a critical mechanism responsible for the pathologic vasodilation and resistance to catecholamine pressors that characterize vasodilatory shock.

In addition, vasopressin blunts the increase in cyclic guanosine monophosphate induced by NO and atrionatriuretic peptide and inhibits the production of interleukin-1, mechanisms strongly implicated in the pathogenesis of vasodilation. While inappropriately low plasma vasopressin levels have been described in adults and pediatric patients with vasodilatory shock, such patients appear to demonstrate a hypersensitivity to the pressor effects of exogenous vasopressin [15].

The overall effect of vasopressin on systemic blood pressure is minimal at normal plasma concentrations and in healthy individuals. Although vasopressin infusions of 0.2–2 units/min rarely affect blood pressure in euvolemic or normotensive subjects, low-dose infusions of 0.04 units/min substantially increase systemic pressure in patients with catecholamine-refractory hypotension. It is likely that because plasma vasopressin is low in this condition, its vascular receptors are available for occupancy by exogenous hormone. In contrast, exogenous nor-epinephrine may not increase receptor occupancy to the same extent, as endogenous concentrations of nor-epinephrine are high, which in turn may cause desensitization of receptors.

Furthermore, there is evidence for adrenergic receptor down regulation in addition to hyper-polarization from the activation of potassium-adenosine triphosphate channels, which results in decreased vascular sensitivity to catecholamines despite high endogenous concentrations and exogenous infusions. The administration of low-dose vasopressin, however, has been shown to not only initiate vasoconstriction but also potentiate the vasoconstrictor effects of catecholamine pressors.

Vasodilator Effects of Vasopressin

Although vasopressin is a potent systemic vasoconstrictor, the same low-dose infusion of vasopressin concurrently causes vasodilation in pulmonary, cerebral, and coronary circulations via oxytocin receptor stimulation and endothelial NO release [13]. Low-dose vasopressin may thus be more beneficial in preserving vital organ perfusion when compared with catecholamine pressors. Investigators have demonstrated in patients with septic shock that low-dose vasopressin not only improved mean arterial blood pressure and cerebral perfusion pressure but also spared the microcirculation to the mesenteric and renal beds when compared with nor-epinephrine or phenylephrine.

Renovascular Effects

Paradoxically, vasopressin (or antidiuretic hormone) increases urine output and creatinine clearance in patients with septic shock when compared with nor-epinephrine. This effect has been attributed to V1-receptormediated, selective renal efferent arteriolar constriction. In contrast, increasing doses of catecholamine vasopressor agents increase the resistance in both afferent and efferent glomerular arterioles, which can contribute to decreased glomerular filtration rate and creatinine clearance and thus decreased urine output.

Endocrine Effects

Vasopressin is a potent stimulator of adrenocorticotropic hormone and, consequently, cortisol release which are important considerations given the prevalence of adrenocortical dysfunction in the critically ill population. The interaction of corticotropin and vasopressin release in shock is complex and incompletely understood, and the influence of exogenous administrations of vasopressin and steroids on the respective axes is being explored.

Since corticosteroids have been shown to reverse tachyphylaxis against exogenous catecholamines, it has been suggested through an ovine model of endotoxemia that methylprednisolone may reverse vasopressin hyporesponsiveness.

Vasopressin has also been reported to mediate atrial natriuretic factor and angiotensin II secretion as well as stimulate prolactin and endothelin I release. This latter effect on prolactin secretion plays a significant role in the cellular immune response, which in turn has important implications in the critically ill population with septic shock. In summary, vasopressin is an attractive adjunctive or alternative to catecholamine vasoactive agents in vasodilatory shock for the following reasons:

Vasopressin reverses the principle pathologic mechanisms responsible for vasoplegia, patients with vasodilatory shock exhibit an increased sensitivity to the pressor effects of vasopressin,

low-dose vasopressin restores responsiveness to catecholamine resistance, and vasopressin has concurrent organ-specific vasodilator effects that may hence preserve vital organ flow. In this era of "endocrine support" in the critically ill, the final rationale for the use of vasopressin is to restore a physiologic hormone deficiency state.

Clinical Application of Vasopressin in Pediatric Shock: The Evidence.

The evidence for the use of low-dose vasopressin in catecholamine-resistant vasodilatory shock states in adults is increasing, and the current literature demonstrates its efficacy on short-term clinical end points, such as mean arterial blood pressure, systemic vascular resistance, and decreased catecholamine requirements. However, the beneficial effects on important patient outcomes, such as mortality, are yet to be determined.

Solid evidence in children remains scant, as these studies are primarily observational in nature. However, each of these studies observed an improvement in blood pressure during the administration of low-dose vasopressin, enabling a rapid wean off catecholamine agents, and none reported adverse effects related to vasopressin. Improvement in systemic blood pressure was not necessarily associated with improved survival. Admittedly, in many of the earlier studies vasopressin was used as rescue therapy where shock was deemed refractory.

Vasopressin during Cardiopulmonary Resuscitation

Experimental protocols for cardiopulmonary resuscitation (CPR) in adults and animals have suggested that vasopressin is superior to epinephrine in increasing vital organ blood flow, in particular coronary arterial and cerebral blood flow, when administered intravenously as well as endo bronchially or via intra-osseous route. In a prospective study of 40 patients with out-of hospital ventricular fibrillation resistant to electrical defibrillation, a significantly larger number of patients who received 40 units of vasopressin intravenously compared with 1 mg of epinephrine were successfully resuscitated and survived for 24 hrs.

However, an in-hospital cardiac arrest, triple-blind, randomized controlled trial failed to demonstrate a survival advantage for vasopressin over epinephrine. Subsequently, a comparison of vasopressin and epinephrine for out-of-hospital cardiac arrest, which included 1,186 adult patients, demonstrated a significantly better outcome among patients with asystole who received vasopressin, although no significant difference in outcome was demonstrated in patients with ventricular tachycardia or pulseless electrical activity.

In pediatric asphyxia animal models, vasopressin alone during CPR was less effective than epinephrine alone, whereas vasopressin plus epinephrine was as effective as epinephrine alone. However, when cardiac arrest was evoked by ventricular fibrillation, the combination of vasopressin and epinephrine was superior to either drug alone for resuscitation. A retrospective case series of children with cardiac arrest suggested that vasopressin (0.4 units/kg per dose) is beneficial during prolonged pediatric cardiac arrest, following failure of conventional CPR.

A second retrospective case series of pediatric cardiac arrests unresponsive to epinephrine found that return of spontaneous circulation was achieved in six of eight episodes that were treated with 15–20 g/kg of terlipressin, and four of those patients survived without neurologic sequelae.

Reported adverse effects related to exogenous vasopressin include coronary ischemia, increased myocardial afterload, ischemic skin lesions and wound complications, new-onset tachyarrhyth-mias, and splanchnic hypoperfusion. The adverse effects of vasopressin are dose related, and experience suggests that these observed side effects may be limited at doses up to 0.04 units/min. Complications appear to be more commonly reported when there is co-

administration of vasopressin and prolonged use of moderate- to high-dose nor-epinephrine.

The actions of vasopressin on the heart are complex, and the studies are seemingly contradictory. Depending on the species studied, the dose used, and the experimental model, vasopressin can cause coronary vasoconstriction or vasodilation and exert positive or negative inotropic effects. V1-receptor-mediated coronary vasoconstriction is a dose dependent phenomenon that may be attenuated by the endothelial vasodilating actions mediated via the oxytocin receptor or P2 receptor.

Conclusion

Vasopressin is a promising agent in shock and during cardiopulmonary resuscitation; however, the recommendations for its use in the pediatric literature are based on limited clinical data. It is clear that vasopressin may have an emerging role in pediatrics, but it should be embraced with caution. Despite numerous reports and small observational studies describing the successful and potentially life-saving effects of vasopressin in children, its benefits have only been reported in patients with vasodilatory shock and adults with asystolic cardiac arrest.

Results of adult experience cannot be generalized to the pediatric population, as adults and children differ in physiology, predisposing diseases, and even shock management strategies. Adults and children have different adaptive responses that must be considered when assessing their hemodynamic status and selecting vasoactive agents. A further challenge to our ability to select the most appropriate patients who may benefit from vasopressin therapy is the inaccuracy with which we can predict their hemodynamic status by physical exam.

Awareness of evolving hemodynamic status during shock in children dictates that the fluid and vasoactive regimens be constantly reevaluated when there is a poor response. Generalized conclusions about the action of vasopressin on microcirculatory perfusion should be made with caution. The dosage, the vasopressin-analog used, the child's hemodynamic physiology, and severity of illness are all important factors to consider in assessing the efficacy of vasopressin in pediatrics. While we acknowledge that vasopressin is a valuable adjunct in catecholamine-resistant shock states, the results of major clinical outcome studies must be awaited before vasopressin is introduced into standard treatment protocols. Its administration is not without risks, particularly when combined with prolonged use of moderate- or high-dose pressor agents. The use of vasopressin, like any empirical therapy, requires assessment of therapeutic end points and surveillance for potential adverse effects, using clinical and biochemical markers of end-organ perfusion, measurements of cardiac index, oxygen utilization indexes, and monitoring of the microcirculatory homeostasis, which are all important tools during the titration of vasoactive therapy in critically ill patients.

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