Hemodynamic and metabolic effects of vasopressin infusion in children with shock

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Abstract

Objective: Vasopressin is a neuropeptide hormone which has been used clinically for more than 50 years and plays a major role in circulatory homeostasis and in the regulation of serum osmolality. Recent work has emphasized its role in the treatment of septic shock. This paper reviews the physiology of this neurohormone and the available evidence in favor of its use as a vasodilator for children in shock.

Sources: MEDLINE, using the terms vasopressin, vasodilation, shock and septic shock, plus synonyms and related terms. Classic publications on the topic were also reviewed and selected depending on their relevance to the study objectives.

Summary of the findings: Vasopressin is synthesized in the neurohypophysis and released in response to a decrease in plasma volume or an increase in serum osmolality. The action of vasopressin is mediated by the activation of oxytocin receptors and of several G protein-coupled receptors, which are classified according to their location and intracellular transmission routes as V1 receptors (or V1b), V2 and V3 receptors (or V1b). The main role of vasopressin is to induce vasoconstriction. However, in certain organs, it can also induce selective vasodilation. Several clinical studies in adults and children have reported that the effects of vasopressin for the treatment of vasodilatory septic shock, due to a variety of causes, are both beneficial and safe.

Conclusions: The evidence is restricted. Most studies are retrospective and include a small number of patients. Nevertheless, there is significant experience concerning the use of vasopressin in Pediatrics. Vasopressin has a beneficial clinical effect in children and can be indicated in the treatment of refractory vasodilatory shock, after adequate volume resuscitation and when high doses of other vasopressors are not effective.

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Introduction

Homeostasis of the human body depends on highly complex systems involved in hydroelectrolytic regulation and, in this context, vasopressin plays a central role. Its effects have been studied for more than a century, since Oliver & Schafer[1] observed the vasoconstrictor effect of a hypophysis extract. Years later, two researchers, Farini[2] and von del Venden,[3] independently described therapeutic effects of a hypophysis extract in the treatment of insipidus diabetes, thus reporting its antidiuretic effect. After it was synthesized in a laboratory, in 1954, described by du Vigneaud,[4] it was proved that both effects were from the same hormone. Since then, vasopressin has been studied and used in several different clinical situations.

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Much work has been done, demonstrating a complex system of synthesis, storage, secretion and regulation of vasopressin, in addition to its many different functions on specific receptors distributed throughout the body in such a manner as to perform its main effects, the regulation of plasma osmolality and arterial blood pressure, in harmony with several other hormones.

The present study describes the complex physiology of vasopressin, including its clinical effects and interactions with other hormones, and reviews several clinical studies in adults and children, in which vasopressin was used for the treatment of vasodilatory septic shock, offering new prospects for the treatment of this clinical condition.

Vasopressin synthesis

Vasopressin is a nonapeptide with a disulphide bridge between two cysteines.[5] It is synthesized in the magnocellular neurons located in the supraoptic and paraventricular nuclei of the hypothalamus as part of a large prohormone, named pre-pro-neurophysin II, which contains vasopressin (with 9 amino acids), neurophysin II (with 95 amino acids) and a glycoprotein (with 39 amino acids). After cleavage of this prohormone, vasopressin migrates along the supraoptic-hypophyseal tract and is packaged into granules in the axon terminals of the magnocellular neurons located in the neurohypophysis (posterior pituitary).[6,7] Approximately 10 to 20% of the body's stores of the hormone can be promptly secreted into the blood flow in response to depolarization in these neurons. When stimulus is sustained, vasopressin secretion continues, although at much lower rates. The complete cycle of vasopressin synthesis, transport, and storage takes approximately 1 to 2 hours.[7,8] This biphasic response of vasopressin explains phenomena observed in early phases of septic shock.[6]

Vasopressin release

The regulation of plasma vasopressin levels is an extremely complex subject. As a general rule, we can state that there are two main stimuli capable of inducing the release of vasopressin into the blood: increase in plasma osmolality and hypovolemia.[6]

Plasma osmolality depends on the interaction between behavioral responses, such as regulation of thirst, and physiologic responses, through the balance between vasopressin and atrial natriuretic peptide. There are osmoreceptors located peripherally in the portal system, connecting through the vagus nerve directly to the nucleus of this nerve, which connects to the magnocellular neurons. This is a strategic location, as fluid intake can be detected early, transmitting the information to the central nervous system (CNS) and rapidly suppressing the release of vasopressin into the blood. Central osmoreceptors are located in the anteroventral portion of the third ventricle, irrigated by veins that are not protected by the blood brain barrier and which, for this reason,

are susceptible to plasma osmolality variations. Furthermore, plasma hypertonicity directly results in depolarization of magnocellular neurons and, inversely, hypotonic conditions result in hyperpolarization.[6,9] This is an extremely sensitive system, so osmolality variations of just 2% are enough to evoke the secretion of vasopressin.[10]

Hypotension and hypovolemia are extremely potent vasopressin secretion stimuli. Afferent impulses originate at baroreceptors located in the left atrium, aortic arch and carotid sinus and also make use of the vagus nerve to ascend to the CNS. Cardiac receptors sense decreases in plasma volume, while aortic and carotid sinus receptors sense decreases in arterial blood pressure. Stimulation of these receptors tonically inhibits vasopressin secretion. When the stimulation subsides, vasopressin is released once more. In cases of hemorrhagic shock, however, there is a systemic response to the fall in blood volume detected by the cardiac baroreceptors, with secretion of atrial natriuretic peptide, norepinephrine and renin, occurring before vasopressin is released, which itself only takes place once the arterial baroreceptors finally register a fall in arterial blood pressure.[10] Therefore, vasopressin plays a crucial role only when a decrease in arterial blood pressure of more than 10% is detected. On the other hand, blood volume resuscitation will inhibit vasopressin secretion by stimulating cardiac receptors.

Interestingly, osmoregulation is mantained even though circulating vasopressin levels are elevated. There is a change in the sensitivity of osmoreceptors, demanding even more elevated vasopressin levels to mantain osmolality when there is concomitant hypovolemia.[10,11]

Several other stimuli are described in the regulation of vasopressin. Catecholamines tend to produce a stimulating effect through central alpha 1-adrenergic receptors. In high doses, however, secretion may be reduced due to catecholamines acting on alpha 2- and beta-adrenergic receptors.[12,13] Vasopressin stimulates the release of adrenocorticotrophic hormone, while glucocorticoids produce negative feedback on the neurohypophysis.[10,13] Other mediators also participate in the secretion of vasopressin, such as acetylcholine, through nicotinic receptors, histamine, nicotine, dopamine, cytokines, endotoxins, and angiotensin II. Increase in $PaCO_2$ or decrease in PaO_2, detected by carotid chemoreceptors elevate vasopressin levels. Pain, nausea and pharyngeal stimuli are also capable of releasing vasopressin along central afferent pathways.[7] Atrial natriuretic peptide and opioids inhibit vasopressin by the mediation of nitric oxide.[10,13]

Plasma levels

Under normal conditions, mean serum vasopressin levels are at 2 pg/mL, and usually remain below 4 pg/mL.[6,11,13] As plasma osmolality increases, these levels can rise to 10 pg/mL, or up to a maximum of 20 pg/mL to produce diuresis at maximum concentration. When its vasoconstrictor effect

is needed, vasopressin can reach levels of 10 to 200 pg/mL.[14] Vasopressin undergoes hepatic and renal metabolism and has a short half-life, approximately 10 to 35 minutes.[6,11]

Systemic effects of vasopressin

Vasopressin has a series of specific receptors located in a variety of cells and tissues. Its main actions are vasoconstriction of the systemic vascular bed, and can cause vasodilation of certain organs, and regulation of plasma osmolality, acting on the renal collector ducts. Vasopressin may also act as a neurotransmitter.

Vasopressin action is mediated by the activation of oxytocin receptors (OTRs) and by several G protein-coupled receptors, which are classified as V1 receptors (or V1b), V2 and V3 receptors (or V1b) (5), according to their location in the body's tissues and to their intracellular transmission routes by second messengers.[13,14]

V1 receptors are located in the vascular smooth muscle cells in the systemic, splanchnic, renal and coronary circulation. Activation of V1 receptors results in elevated intracellular calcium concentrations, smooth muscle contraction and vasoconstriction.[13] V2 receptors mediate vasopressin antidiuretic actions in the nephron, and V3 receptors play a role as second messengers in the anterior pituitary gland. OTRs are located in the myometrium and the mammary myoepithelial cells, where they mediate smooth muscle contraction, and are also present at the surface of the endothelial cells, where their activation causes elevated calcium concentrations, activation of the inducible nitric oxide synthase enzyme and production of nitric oxide, resulting in vasodilation.[14]

Receptors selectively found in the afferent arterioles cause selective vasoconstriction and may increase glomerular filtration rate. This phenomenon may explain the improvement in diuresis observed with the use of vasopressin in shock states, which is an effect that cannot be reproduced by the use of catecholamines.[15] Studies using animal models as well as with isolated human coronary arteries have already demonstrated the occurrence of vasoconstriction on the coronary vascular bed. However, recent studies using *in vivo* models have shown that vasodilation may also occur. Under hypoxic conditions, at low coronary artery cell oxygen tensions, vasodilation would then be the expected effect.[14] It has been observed that there may be a direct positive inotropic effect of vasopressin, depending on its concentrations and on the balance of its effect on the coronary circulation.[16] It has also been observed, in one clinical study, that vasopressin possibly exerts a positive inotropic effect on patients with vasodilatory shock, since an increase in afterload with no proportional decrease in cardiac output was recorded.[14] Similarly, a study of patients with refractory septic shock after cardiac surgery has shown increased contraction force in the left ventricle and decrease in both cardiac output and the need for other vasopressors.[17] Regardless of the mechanism, low-dose vasopressin can improve cardiac performance.[18-22]

There is still a fifth receptor on which vasopressin acts, the P2-purinergic receptor. This receptor is normally stimulated by the adenosine triphosphate (ATP) released by platelets and other injured tissues and, through activation of the cascade via phospholipase C, mobilizes intracellular calcium and stimulates both phospholipase A and nitric oxide synthase to produce prostacyclin and nitric oxide, respectively, both causing vasodilation of the vascular smooth muscle wall. We can also find these receptors in the heart, and their activation by the ATP released by platelets, endothelial cells and impaired myocardium provokes increase in intracellular calcium and increase in force of cardiac contraction, with no increase in chronotropism.[14,21,22]

Vasodilatory septic shock

Vasodilatory septic shock may occur due to various reasons, including sepsis, prolonged hypotension, certain drugs, inadequate oxygenation, as in carbon monoxide intoxication, anaphylaxis, glucocorticoid deficiency and others. Several studies have suggested that there may be common mechanisms involved in all these types of shock. These mechanisms would be: activation of potassium channels sensitive to ATP (K_{ATP} channels), activation of nitric oxide synthase and vasopressin deficiency.[15]

Adequate vasoconstriction requires activation of receptors for hormones and neurotransmitters at the surface membrane of blood vessel muscle cells, activating cascades of intracellular reactions that culminate in an increase in intracellular calcium, which forms compounds with calmodulin, which, together, phosphorylate myosin, producing contraction. When the K_{ATP} channel is activated, it allows potassium to be released from the cell, causing membrane hyperpolarization and blocking the entry of calcium. Activation of this channel may be mediated by atrial natriuretic peptide, adenosine, and nitric oxide, substances that are normally at increased levels during shock.[15,23]

Nitric oxide is produced in the smooth muscle and vascular endothelial cells by nitric oxide synthase, which can be induced by various cytokines, such as interleukin-1, interleukin-6, tumor necrosis factor-alpha, interferon gamma and adenosine. Nitric oxide acts on the dephosphorylation of myosin and on the relaxation of smooth muscle of the vascular wall, but also acts on the activation of the intracellular calcium-sensitive K channel. This channel regulates, or limits, cell contraction, allowing K to be released, hyperpolarizing the membrane and further blocking calcium entry. This mechanism may explain the resistance to catecholamines observed in many patients.[15,24]

Vasopressin plays a crucial role in maintaining arterial blood pressure by baroreflex-mediated high- dose vasopressin secretion into the blood flow during hypotension, as previously described. In the early phases, blood pressure is maintained, however, in prolonged hypotension, levels are

insufficient and absolute or relative deficiency occurs, probably because of depletion of pituitary vasopressin stores.[15,25] Exogenous vasopressin administration can reestablish normal arterial blood pressure, even in patients resistant to other vasoconstrictors, such as noradrenaline and angiotensin II.[15]

Plasma vasopressin levels in vasodilatory shock

Morales et al. carried out a study of dogs with hemorrhagic shock, in which vasopressin levels were measured during the acute stage of shock, and recorded levels greater than 300 pg/mL. After 90 minutes of hypotension, levels fell to less than 30 pg/mL.[25]

Sharshar et al. described an increase in vasopressin levels measured during the first 8 hours of shock, with values between 4.1 and 16 pg/mL in 16 of 18 patients tested (88%). They performed sequential assays for up to 96 hours of the clinical course, demonstrating a progressive decrease in serum levels. In another group of patients, assays were taken at random and an inverse correlation was observed between circulating vasopressin levels and duration of shock ($r^2 = 0.12$, $p = 0.021$). Assays performed after 36 hours showed inappropriately low levels with relation to the systolic blood pressure at that moment. The authors suggest that the increased levels between 3.6 and 30 pg/mL observed in the early phase of shock should still be considered as low and should be defined as a relative deficiency, since about 29% of patients with these levels were still hypotensive.[26]

Another paper by the same lead author reports observations of three adult male patients, with septic shock, who underwent CNS magnetic resonance imaging due to various neurological symptoms. In all three patients, no signal was detected from the posterior pituitary, and the ratio between the signal intensity of the posterior and anterior pituitary was significantly reduced when compared to examinations performed on healthy or critically-ill, but non-septic patients. Plasma vasopressin levels in these patients were 1.6, 1.8, and 16 pg/mL. One of the patients repeated the magnetic resonance imaging 5 months after his recovery, resulting in normalization of the findings. The patient's vasopressin level had also normalized.[27]

Landry et al. have also measured plasma vasopressin levels in 19 patients with septic shock and 12 patients with cardiogenic shock, recording mean values of 3.1±1.0 and 22.7±2.2 pg/mL, respectively. The differences were attributed to autonomic failure and to the impaired sympathetic nervous system function observed in septic patients.[14]

Vasopressin hypersensitivity in septic shock

Exogenous vasopressin administration in healthy subjects does not produce an increase in arterial blood pressure. On the other hand, hypersensitivity to vasopressin infusion can be observed in subjects with vasodilatory shock, with significant increases in arterial blood pressure when low dosages of vasopressin are given. This effect can be explained by several observations: by the availability of receptors for vasopressin, since the levels of this hormone in plasma are decreased; by poor baroreflex mechanism function, since patients may be at autonomic failure, as most of them are sedated or comatose; by the direct action of vasopressin on vascular smooth muscle; and by a boost in the effect of noradrenaline, through blockage of K_{ATP} channels and intracellular calcium-sensitive K, allowing calcium to enter the cell.[15]

In contrast with noradrenaline and its alpha 1-receptor, low vasopressin levels allow V1 receptors to remain available and block mechanisms which would induce their downregulation. There has been speculation that sepsis could induce changes to the proportions and affinity of receptors, but experimental studies are discordant. With relation to V2 and oxytocin receptors, there is no evidence in the current literature describing relevant alterations.[13,15]

The autonomic nervous system, through the regulatory mechanisms of baroreceptors and chemoreceptors, regulates vasopressin release and also suffers modulation of vasopressin effects.[13] It is common knowledge that patients with autonomic nervous system failure are hypersensitive to vasopressin[28] and that administration of this hormone to septic patients does not cause the bradycardia reflex observed in healthy subjects.[14]

Vasopressin acts directly on vascular smooth muscle (via its V1 receptor) allowing calcium to enter the cell. This action blocks K_{ATP} channels, responsible for membrane hyperpolarization (and which remain open during vasodilation). Therefore, vasopressin can restore sensitivity to catecholamines and act synergically on vasoconstriction. This synergy is also mediated by vasopressin action, inhibiting dephosphorylation of myosin chains.[13]

Finally, vasopressin also acts stimulating adrenocorticotrophic hormone and releasing cortisol. It is now known that a state of absolute or relative deficiency of this hormone occurs, and that its replacement is of fundamental importance in refractory shock,[29] as it can restore sensitivity to catecholamines.[13,30]

Clinical studies with vasopressin in adults

There are several reports available in the medical literature on the use of vasopressin in the treatment of vasodilatory shock in adult patients with promising results. Some studies are discussed below.

In 1998 and 1999, Argenziano et al. published two retrospective studies in which vasopressin was used in the treatment of refractory shock in cardiac surgery postoperative care with extracorporeal circulation (40 patients) and cardiac posttransplant care (20 patients) at a dosage of 0.1 U/min. In both

studies, a dramatic improvement in mean arterial blood pressure was described, making the reduction or weaning of noradrenaline possible without relevant side effects.[31,32]

Tsuneyoshi et al. administered vasopressin at a dosage of 0.04 U/min to 16 patients with refractory septic shock, over 16 hours, followed by gradual weaning. A significant increase in arterial blood pressure was observed, with no alteration in cardiac index, cardiac output, central venous pressure or pulmonary artery pressure. Diuresis improved significantly. No myocardial ischemia or tachyarrhythmias occurred and there was no evidence of mesenteric ischemia.[33]

Patel et al. performed a clinical trial using vasopressin and comparing it to noradrenaline in a group of 24 adult patients with septic shock and on high doses of noradrenaline. Patients were randomized to be treated, for 4 hours, with a solution of vasopressin or noradrenaline, while maintaining systemic arterial blood pressure stable. A significant reduction in the dosage of noradrenaline required (from 25 to 5.3 μg/min, p < 0.001) was observed in the vasopressin group, when compared to the noradrenaline group (from 20 to 17 μg/min). There was significant improvement in diuresis in the vasopressin group. There was no difference in relation to the fraction of sodium excretion and neither were there any differences in gastric perfusion (measured by gastric mucosal-arterial pCO_2 gradient), in the S-T segment, or the occurrence of arrhythmias or signs of myocardial ischemia.[34]

Dünser et al. carried out a randomized controlled study of patients with vasodilatory shock, caused by systemic inflammatory response syndrome (SIRS) or postoperative cardiac complications, refractory to fluid resuscitation and to noradrenaline at a dose of 0.5 μg/kg/min. These patients were randomized to be treated with vasopressin at a dose of 4 U/hour or to be kept on noradrenaline in escalating doses. In patients who received vasopressin, decreases were observed in cardiac output (p = 0.003) as well as increases in mean arterial blood pressure (p < 0.001) and cardiac index (p = 0.001). The required dosage of noradrenaline also decreased significantly. Tachyarrhythmias occurred more in the noradrenaline group (54.3 versus 8.3%, p < 0.001). There was improvement in splanchnic perfusion measured by gastric tonometry, with the combined use of both drugs. There was no difference in terms of arterial pH, lactate, hepatic enzymes or platelets, or in the occurrence of ischemic cutaneous lesions. A significant increase in bilirubin was observed with vasopressin administration.[35]

In 2004, the same lead author published a study reporting assay results of the serum levels of several hormones in 38 patients with vasodilatory shock. It demonstrated basal vasopressin levels of 8.6±4.6 pg/mL, increasing to 179.2±90.1 pg/mL after 24 hours of vasopressin administration (4 U/hour). There were no alterations in serum levels of ACTH, cortisol, renin, angiotensin II, aldosterone or atrial natriuretic peptide, while prolactin levels increased. It was

also reported that vasopressin response to the increase in blood pressure after vasopressin infusion was started was independent of the basal level.[36]

Klinzing et al. carried out a study with 12 patients for whom noradrenaline was swapped for enough vasopressin to maintain the same arterial blood pressure, using doses between 0.06 and 1.8 U/min. They detected decreased cardiac output and cardiac index, in addition to decreased peripheral oxygen delivery and consumption, increased gastric pCO_2 (related to the reduction in local perfusion) and a tendency towards plasma lactate increase. The authors suggest that high doses of vasopressin may have deleterious effects, and that vasopressin administration alone has clinical effects inferior to noradrenaline.[37]

In 2005, Luckner et al. published, a large scale review of 316 cases treated at 23 Austrian intensive care centers and described effects on hemodynamics, clinical presentation and laboratory results. The mean age of patients was 66.8±14 years, there was a diagnosis of septic shock in 32.6%, postoperative care for cardiac surgery in 42.7% and SIRS due to a variety of causes in 24.7%. Patients underwent blood volume resuscitation, with support from milrinone, adrenaline, and noradrenaline and corticosteroids replacement according to their usual protocol. When there was a need for noradrenaline at doses higher than 0.2 μg/kg/min, vasopressin administration was then started at a dose of 0.4 U/hour. Increases were observed in mean arterial blood pressure and peripheral vascular resistance, as well as decrease in cardiac output, central venous pressure and the mean pulmonary artery pressure, all considered statistically significant (p < 0.001). It was also possible to discontinue a proportion of the hemodynamic support provided by other drugs. Cardiac index decreased in hyperdynamic patients, with no significant alteration in the normal or hypodynamic ones, suggesting improvement in cardiac performance. It was not possible to detect vasopressin-related adverse effects, although increase in bilirubins was reported in several patients.[38]

The early use of vasopressin in shock states was analyzed by Lauzier et al. and published in 2006. They recruited 23 patients in the 12 first hours of shock, before any other vaso-active drug was started and patients were randomized to receive either vasopressin (0.04 to 0.2 U/min) or noradrenaline (0.1 to 2.8 μg/kg/min), allowing the use of the other drug if arterial blood pressure stabilization was not achieved. Clinical and laboratory parameters were evaluated within 48 hours. There was no difference between the groups in terms of arterial blood pressure, central venous pressure, pulmonary artery occlusion pressure and mean pulmonary artery pressure. There was a decrease in the cardiac index of the vasopressin group. In 85% of the patients treated with vasopressin, association with noradrenaline became necessary, but with significantly lower doses compared to the group treated with this drug alone. None of the noradrenaline group

patients needed with the addition of vasopressin. There were no differences in gastric tonometry between the two groups. In the vasopressin group, creatinine improved, and an increase in bilirubins was detected, with no increase in hepatic enzymes. There was one coronary vasospasm event in the vasopressin group, with improvement in condition after reduction of the dose infused.[39]

Currently, vasopressin is known to play a role in refractory shock, with several studies reporting improvements in hemodynamic parameters, as described above. It has been suggested that doses considered low, between 2 and 4 U/hour, and used as hormone replacement, are more appropriate, since there is a relative hypersensitivity in patients in shock states, and deleterious effects have not been demonstrated, allowing a reduction in the doses of other catecholamines, thus lowering the risks of their undesirable effects.[40,41]

Clinical studies with vasopressin in children

The studies on vasopressin for vasodilatory shock in the pediatric population that are now available are very recent. They are retrospective and report on small numbers of patients, with a wide variation in age and primary diagnosis. The main studies are commented on below.

In 1999, Rosenzweig et al. published one of the first reports on the use of vasopressin in children. The cases of 11 patients aged between 3 days and 15 years were retrospectively reviewed. They were in postoperative care for cardiac surgery, in a state of shock refractory to the use of multiple vasopressor drugs and in a state considered critical with vasopressin being administered as a last resort. Two of these patients exhibited severely compromised myocardial function. Vasopressin was started in the operating room (five patients), in the intensive care unit within 12 hours of postoperative period (five patients), or 2 days after surgery (one patient, due to septic shock). Doses were between 0.0003 and 0.002 U/kg/min, adjusted according to clinical response. An increase in mean arterial blood pressure of 31% (45±11 for 59±11, p < 0.0005) was verified. There was no difference in right atrial pressure or cardiac output. It was possible to reduce vasopressor support (p < 0.005). There was no difference in diuresis, serum bicarbonate or plasma sodium measured at baseline and 24 hours after vasopressin was started. Nine of these 11 patients survived the initial hours of the study; the two patients with myocardial failure died 6 hours and 6 days after intervention. Eight patients survived to hospital discharge.[42]

In 2000, Katz et al. published a study carried out with 35 brain dead patients on support for organ donation, who needed vasopressin for the treatment of insipidus diabetes, compared with 19 patients in similar clinical conditions although without diabetes. Vasopressin doses varied considerably, with a mean of 0.041±0.069 U/kg/h. The outcome under analysis was the need for inotropic and vasopressor

support, by group. A significant difference was observed in relation to the need for support with alpha 1-agonists. It proved possible to reduce this support in seven of nine patients in the vasopressin group versus none of nine patients in the control group (OR 7.3, p < 0.01). There were no reports of arrhythmias, reduced diuresis or any other toxic effects. No difference was observed in the results of the transplantation either, and the authors inferred from this that vasopressin did not reduce perfusion of organs to be transplanted.[43]

In 2002, Liedel et al. published a report on five cases of pediatric patients in extremely severe clinical situations, who received vasopressin for refractory shock, two of them were newborn infants and three were oncology patients between 7 and 13 years old. The doses used were between 0.0006 and 0.008 U/kg/min, or 0.04 and 0.06 U/min in the case of the 13-year-old patient. All of them exhibited increased mean arterial blood pressure, it was possible to reduce other vasopressor drugs, and diuresis improved. No occurrences of hydroelectrolytic disturbances were reported. Two patients survived.[44]

A study carried out in Japan by Masutani et al. and published in 2005, retrospectively reviewed 12 patients, aged between 1 day and 21 years, in 15 situations, between 1999 and 2003, in which vasopressin was used for refractory shock caused by neurological lesions (five cases), drugs (prostaglandin E1, one case, and intoxication with angiotensin-converting enzyme inhibitor, four cases) and septic shock (five cases).Vasopressin was started after dopamine administration produced no adequate response. Doses ranged between 0.0002 and 0.004 U/kg/min. Increase in arterial blood pressure was observed in 12 patients, while increase in diuresis was observed in nine patients. Three patients exhibited no response to vasopressin. There was no difference in response between cases of shock from different causes. Patients survived in 11 reported clinical situations.[45]

There is a report of three cases of extremely premature newborns, published in 2006, in which vasopressin was administered for refractory septic shock in one case and for cardiogenic shock in two twins. The patient with septic shock received vasopressin at a dose of 0.035 U/kg/min, with a good response, with increased arterial blood pressure and improvement in diuresis, subsequent improvement from shock and survival. The twins were receiving extremely high doses of adrenaline and noradrenaline, when they were started on vasopressin at doses between 0.01 and 0.1 U/kg/min. They showed transitory improvement in arterial blood pressure, but cardiac function decreased and they died.[46]

A note on terlipressin

Terlipressin is a synthetic analog of vasopressin with a great affinity for the V1 receptor and a longer duration of action. It is a prodrug which needs to be converted into its active form, named lysine vasopressin. This metabolism takes

place over a period of 4 to 6 hours, which explains the longer duration of its action and the intermittent bolus form of administration. Peak plasma levels occurs after 1 to 2 hours, and the half-life in healthy adults is between 50 and 70 minutes. It was initially studied for treatment of digestive bleeding in adults due to esophageal and gastric varices, and has recently been used for refractory shock in adults and in children. There is no established dose for children, and the case reports published used a dosage of 0.02 mg/kg every 4 hours, for a maximum of 72 hours. This scheme was deduced from doses used in adults, which were between 1 and 2 mg every 4 hours. Similar to vasopressin, the initial studies report significant improvement in arterial blood pressure and the possibility of reducing other vasoactive drugs, but there are reports of ischemia of the intestines or extremities, oliguria, rhabdomyolysis and hyperkalemia, so clinical studies are needed to define its role in refractory shock.[47-50]

Current role of vasopressin in vasodilatory shock

Sepsis and septic outcomes depend on early diagnosis and implementation of time-sensitive treatments guided by objectives.[51] These treatments include aggressive fluid resuscitation followed by well-planned treatment with medication, which aims to restore perfusion and microcirculation. Often, the vasoactive agents have to be adjusted in order to reach the preestablished objective. We start volumetric resuscitation with isotonic solutions (> 60 mL/kg), usually normal saline, but colloids can also be used. If, despite adequate fluid resuscitation, patients exhibit hot shock with signs of high cardiac output and low systemic vascular resistance, the use of a vasopressor such as noradrenaline should be considered. If patients show signs of cold shock with prolonged capillary refill, weak and filiform pulse, normal arterial blood pressure (low cardiac output, high systemic vascular resistance), the use of dopamine, adrenaline or dobutamine should be considered. Concomitant treatment with stress dose of corticosteroids is indicated at the moment.[51,52]

It has already been observed that, in conditions associated with severe sepsis, adults and children are very sensitive to exogenous vasopressin administration. However, after a more prolonged shock, vasopressin levels decrease, resulting in a relative deficiency. This phenomenon occurs due to osmoregulation or impaired baroregulation, or due to the inhibiting effects of increased nitric oxide on vasopressin release.[13]

The use of vasopressin as a vasopressor in the treatment of septic shock and vasodilation resistant to noradrenaline is mentioned as a viable option by the American College of Critical Care Medicine Task Force of 2001,[53] and its indication was broadened in 2007 when these recommendations were reviewed (Joseph A. Carcillo, personal communication).

In this new version, vasopressin would be indicated for children in states of shock and with high cardiac index and low systemic vascular resistance when infusion of noradrenaline and fluids does not resolve hypotension. They call attention to the fact that potent vasoconstriction caused by the drug may reduce cardiac output and they recommend vasopressin be used with monitoring of cardiac output and/or central venous saturation. They also recommend, in this situation, additional inotropic therapy with low-dose adrenaline or dobutamine. (Joseph A. Carcillo; 2007, personal communication)

We tend to start treatment with vasopressin in patients that have been correctly resuscitated with fluids, that do not exhibit hypocalcemia or hypoglycemia, that have previously received corticosteroids and that have not responded to initial pharmacological support with catecholamines. These patients already need high doses of vasopressors, such as noradrenaline infusion (higher than 1 µg/kg/min). We start using a vasopressin dose of 0.0005 U/kg/min (dilution of 200 U/mL), gradually adjusting the dose up to an ideal dose of 0.002 U/kg/min, with the possibility of reaching a maximum dose of 0.008 U/kg/min. The expected response is a significant increase in arterial blood pressure and cardiac output, allowing a reduction in noradrenaline infusion.[54,55]

Special attention should be paid to prevention of hyponatremia in these patients, who should go through strict laboratory monitoring. In a double-blind, randomized and controlled study on the use of vasopressin in children with severe respiratory disease,[56] we observed that, even in low doses (0.0005 U/kg/min), vasopressin significantly increased the mean arterial blood pressure of patients, but that, over a 12-hour period, a marked reduction was noticed in urine output and sodium concentration, increasing the occurrence of hyponatremia.

Conclusion

Studies with adults and children have demonstrated an important beneficial effect of vasopressin in refractory shock, especially as a rescue treatment, when other vasoactive drugs are no longer being used and are escalating to risky levels with regard to the occurrence of adverse effects. In this context, studies demonstrate the benefits of vasopressin regarding safety, but monitoring of cardiac output, superior vena cava saturation and natremia is advised at the start of treatment and during adjustments. Adjuvant inotropic support is usually necessary.

The evidence is limited, studies are mostly retrospective and with small numbers of patients, further controlled studies are still needed to establish doses and the safety profile of administering arginine-vasopressin and terlipressin for septic shock. However, there has been quite significant experience in Pediatrics regarding the use of vasopressin as a rescue agent for the treatment of septic shock with low systemic vascular resistance.

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