Emerging Role of Vasopressin

MK Daga*, KJ Singh**, N Kumar***

Abstract

Ionotropic agents are frequently used in vasodilatory shock like conditions of septic or nonseptic origin. Conventional catecholamines such as norepinephrine are used at a very high dose with possibility of adverse effects in many patients. One often encounters refractoriness to these drugs. Infusion of vasopressin (VP) which is detectable at inappropriately low level in advanced phase of septic shock might allow withdrawal of catecholamines, as it maintains adequate mean arterial pressure (MAP), improves urine output and leaves perfusion of vital organs unhindered. Vasopressin has been found to be superior to epinephrine in animal models and some human trials, especially in patients with resistant ventricular fibrillation (VF) while doing cardiopulmonary resuscitation (CPR). Analogues of VP have also been used for diuresis in patients of hepatorenal syndrome.

INTRODUCTION

Vasopressin (VP) better known as antidiuretic hormone is a nonapeptide synthesized in hypothalamus and released from posterior pituitary gland.1 It is an important hormone from the point of view of maintaining cardiovascular homeostasis in the body. It has been used for long time in patients of central diabetes insipidus and also in patients with variceal bleed but its vasopressor properties are now under review to be exploited in certain critical illness.

Septic shock is one such condition characterized by diminished arteriolar tone in the body. VP which has unique action of constricting peripheral arterioles while leaving blood flow to vital organs unhindered, may be better than other vasopressor agents or at least can augment their action in a favorable way.2-4 Studies have shown the effectiveness of VP in decreasing catecholamine requirement in septic shock.2,5,6 Other condition with nonseptic vasodilatory shock such as those occurring post cardiopulmonary bypass (CPB) or after placement of left ventricular assist devices (LVAD) may similarly benefit from this drug.7,8

This molecule has also been studied by many authors for possible use during cardiopulmonary resuscitation (CPR) either alone or in combination with epinephrine and results have been encouraging.9 Analogues of this drug have also been found to be useful in eliciting a paradoxical diuretic effect in patients with hepatorenal syndrome and refractory ascitis.10

PHYSIOLOGY OF VASOPRESSIN ACTION

Supraoptic and paraventricular nuclei of hypothalamus synthesize VP, which then migrates to axonal terminals of these neurons at posterior pituitary gland and is stored here in granular from1. Its release is regulated by osmotic and nonosmotic stimuli. Apart from hyperosmolality, profound hypovolemia and shock are one of the most potent non osmotic stimuli for release of VP1,11. This effect is mediated via afferent impulses from stretch receptors in aortic arch and carotid sinus and to a lesser degree from left arterial stretch receptors.1 Discharges from these afferent inputs inhibit VP release and vice versa. Despite its potent vasoconstrictor action, this hormone dose not have any significant effect on blood pressure in normal individuals,2,5 this is probably the result of baroreceptor mediated decrease in heart rate.2 But its role in maintaining cardiovascular homeostasis is significant in conditions of shock and animals with diabetes insipidus tolerate shock poorly.12 The normal fasting blood level of VP is 4 pg/ml, a concentration enough for its action on renal collecting ducts.1,12 But its vasopressor effects require a much higher serum concentration (about 10-200 pg/ml).12 In early phase of shock its plasma level may reach > 100 pg/ml but levels come down later and may be inappropriately low in prolonged septic shock.1,13,14

Actions of VP are mediated via its three receptor subtypes designated as V1 (V1R/V1a), V2 (V2R) and V3 (V1b).1,11 V1 vascular receptors mediate vasoconstrictor effect of VP through activation of phospholipase C and increasing cytosolic Ca++, V2 renal receptors mediate its antidiuretic effect and V3 pituitary receptors are central receptors that cause adrenocorticotropin hormone (ACTH) release. VP also acts on oxytocin receptor

*Professor; **Ex Senior Resident; ***Senior Resident, Department of Medicine, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi.
Received : 18.10.2004; Revised : 29.9.2005; Accepted : 3.4.2006
(OTR) which is important from the point of view of its vasodilator action on certain vital organs through nitric oxide (NO) mediated pathway. Fig. 1 summarizes the physiological effects of VP.

**EMERGING CLINICAL USES OF VP**

1. **Septic shock**: This is a type of vasodilatory shock, found in patients having serious infections. Shock like state is the result of profound vasodilation in most of the peripheral arteriolar bed in various tissues, resulting in reduced perfusion of vital organs. It has 50% mortality despite treatment with fluids, antibiotic and vasopressor agents. Probable mechanisms responsible for this vasodilatory state are enumerated in Table 1. Many patients of septic shock show poor response to conventional catecholamine, probably related to receptor downregulation, increased NO level and activation of K+ ATP channels in blood vessel smooth muscle cells. Most form of shock like states cause high levels of VP levels in the body. But haemorrhage and septic shock cause biphasic changes in vasopressin concentrations, high concentrations in early shock which decreases as the shock state progresses. It has been observed by Landry et al and also corroborated in other studies as well. Probable reason for this VP deficiency is depletion of neurohypophyseal stores after prolonged stimulation. Apart from this, autonomic insufficiency which leads to impaired release of VP and elevated endogenous norepinephrine levels that have a central inhibitory effect on vasopressin release have also been implicated for its low level in this condition. Autonomic dysfunction was observed by some workers, when they found that reflex bradycardia was not seen in these patients when they were given pharmacological doses of VP.

In addition to adequate volume replacement, catecholamine vasopressors (especially norepinephrine) are the mainstay of treatment in these patients, to maintain adequate mean arterial pressure. The response to catecholamine is poor and high doses are associated with potentially fatal adverse effects. These include decreased renal and mesenteric blood flow, increased pulmonary vascular resistance and arrhythmias resulting from β adrenergic effect. Poor response to catecholamine is in part due to receptor downregulation. In contrast to catecholamine treatment, patients of septic shock have increased responsiveness to VP even in low doses. In many studies VP infusion in the dose of 0.01-0.04 U/min resulted in improved mean arterial pressure and permitted withdrawal of catecholamines. Apart from this it has also been found to improve urine output. This reversal of oliguria is not only related to improvement of mean arterial pressure, because norepinephrine dosage to maintain similar arterial pressure does not result in same urine output. In a prospective randomised controlled study of 48 patients with catecholamine resistant shock it was shown that a combined infusion of vasopressin and norepinephrine was superior to norepinephrine alone. Vasodilatory effect of VP in cerebral, coronary and pulmonary vasculature is likely to make it more beneficial in this condition. VP also inactivates K⁺-ATP channel and also blunts c-GMP response of nitric oxide (NO), the two important mechanisms of vasodilation in septic shock. Early data from different studies point to a favorable outcome in patients managed with low dose vasopressin infusion in septic shock, but whether it translates into mortality benefit remains to be seen. Large scale studies are needed to collect significant clinical data before recommendation can be made.

2. **Nonseptic vasodilatory shock**: Nonseptic causes of vasodilatory shock are prolonged cardiopulmonary bypass(CPB), after placement of mechanical assist devices, cyanide poisoning, carbon monoxide intoxication, and late irreversible phase of haemorrhagic shock. Generalization regarding these nonseptic causes of vasodilatory shock cannot be made because different pathogenic mechanisms may be in the core of initiation of the event, though final common pathway of vasodilatory process may be the same. Hence even though VP is effective in septic shock, clinical studies

---

**Table 1 : Actions of exogenous vasopressin infusion**

- ↑ C-GMP
- Inhibition K⁺-ATP channels
- Counters vasopressin deficiency
- Improves catecholamine responsiveness

---

© JAPI • VOL. 54 • MAY 2006 www.japi.org 377
are required before this treatment strategy could be employed in these settings. Studies so far have been done in post CPB patients and after left ventricular assist device (LVAD) placements and results have favored its use in these situations presenting as vasodilatory shock.

In a study by Argenziano et al, 10 patients with vasodilatory shock after placement of LVAD on weaning from CPB, were given at 0.10/min or placebo. Baseline plasma VP was inappropriately low in 7 of the 10 patients. Infusion of VP significantly improved mean arterial pressure and norepinephrine requirement was decreased. In another study by Argenziano et al, 145 patients undergoing CPB for elective surgery were enrolled for a prospective study. Vasodilatory shock was found to be associated with VP deficiency especially in patients with low ejection fraction and those receiving ACE inhibitors. VP significantly improved mean arterial pressure reducing the requirement for catecholamines. Similar studies conducted by Rosenzwig et al and Morales et al have shown significant benefit from using VP as a pressor agent in this situation.

3. Cardiopulmonary resuscitation (CPR): Epinephrine which has been used for many decades during CPR has recently come under criticism. Use of this drug is associated with many β receptor mediated adverse effects. It increases myocardial oxygen consumption, predisposes to ventricular arrhythmia, causes ventilation perfusion defect due to pulmonary vasoconstriction and may lead to post resuscitation myocardial dysfunction. There is lack of clinical data about its efficacy in CPR. Moreover epinephrine reduces myocardial action potential, increasing the possibility of reentry action potentials hitting excitable tissue which in turn may provoke or stabilize VF. In a recent study its effect was found to be no better than a saline placebo. Certain other studies point out that its use has not enhanced hospital discharge rate. Despite lack of clinical data supporting its use, it is still being recommended by European and American guidelines for adult advanced life support, because of lack of an alternative vasopressor agent which can be employed in this setting.

One of the important determinant for responsiveness of ventricular fibrillation (VF) to defibrillation is maintenance of coronary perfusion pressure (CPP) above 20-30 mmHg. So an alternative drug should have sufficient vasoconstrictor activity to improve CPP during CPR and should also leave the cerebral perfusion intact for better neurological outcome. Recent research works have focused on VP to be employed either as an alternative to epinephrine or to be used in conjunction with it during CPR, however current international guidelines for CPR considers vasopressin only as a secondary alternative to epinephrine because of limited clinical data on efficacy of vasopressin.

Lindner and colleagues measured levels of endothelin, catecholamines, VP and ACTH in CPR in 60 patients. Results showed that patients who could be resuscitated had significant higher plasma VP concentration and ACTH concentration than those who could not be revived. In contrast, catecholamine concentration was more in failed resuscitation group. In many porcine models of CPR, VP treated group was found to have better outcome when chances of resuscitation and neurological recovery was assessed. It has also been found to increase adrenal medullary blood flow during CPR.

In the first prospective trial in humans Lindner and colleagues compared 40 U iv VP to 1 mg iv epinephrine in patients with resistant VF (those not reverting after 3 DC shock) in an out-of-hospital setting. Out of 40 patients enrolled in the study significantly higher number could be resuscitated with VP and 24 hr survival was better in VP treated group. However when this protocol was conducted for in-hospital patient population in another study no significant survival advantage was observed, probably because of other comorbid conditions in this patient population. Synergistic effect of VP and epinephrine was studied by Mulligan et al on CPP during CPR in animal model. Increase in CPP was more rapid in the group receiving both drugs than with VP alone, whereas CPP was maintained for significantly longer duration either with VP or VP + epinephrine than epinephrine alone. This animal study showed us that due to rapid response of epinephrine and longer duration of action of VP it may be advantageous to use both the drugs together. It has been suggested to first administer 1mg of epinephrine, followed alternately by 40 IU of vasopressin and 1mg epinephrine every 5 mins in adult cardiac arrest victims regardless of initial electrocardiographic rhythm.

Other factors which can be advantageous when iv access is not easy is, rapid absorption of VP though endotracheal and intravenous route. Epinephrine requires considerably higher doses for endotracheal absorption.

Present guidelines by American Heart Association and European Resuscitation Council for adult advanced cardiac life support recommend use of 40 U VP as an alternative to 1 mg epinephrine in adult patients with resistant VF (level II b evidence). But as of now it has not been recommended for want of adequate clinical data in patients having pulseless electrical activity, asystole and in pediatric population. Further trials on a larger scale may confirm our faith in this drug while performing CPR.

4. Hepatorenal syndrome (HRS): Despite being an antidiuretic hormone, it has diuretic effect in certain clinical situation. VP analogues have been utilized in patients of hepatorenal syndrome, in whom even diuretics and dopamine (low dosage) are not effective.
Terlipressin and ornithine vasopressin have been used in cirrhotic patients with renal dysfunction and reversal of oliguria along with improvement in renal parameters have been observed. In patients of refractory ascites, terlipressin restored sensitivity to exogenous arterial natriuretic peptide. It has been postulated that VP analogues, by reverting peripheral vasodilation in HRS restore blood flow to renal cortical tissue, improving oliguria. Vasopressin analogues used in conjunction with albumin improve renal function in hepatorenal syndrome.

In the study by Eisenman and co workers low dose VP was found to cause diuresis not only in patients of HRS but also is patients of end-stage heart failure. First of these two conditions is characterized by peripheral vasodilatation, the other one by peripheral vasoconstriction. So they proposed that the diuretic action of VP analogues is not due to its action on peripheral vasculature, but probably its effect on V1 receptors in kidney, or because of synergistic effect with ANP and oxytocin, in volume overloaded patients.

**Note of Caution**

Use of VP may be associated with some adverse effects. Although most of the reports have not cited any adverse consequences of low dose VP, some of the reports have found rise in liver enzymes, bilirubin and decrease in platelet counts after VP use. This is particularly true if doses of more than 0.04 U/min are used. These effects are probably due to gastrointestinal ischemia and coagulation system derangement. Some of the other reports have associated the drug with arrhythmia, myocardial infarction, hyponatraemia, anaphylaxis, bronchospasm and urticaria besides severe skin necrosis after its extravasation.

Cost is the other factor which dampens the enthusiasm of using it on a wider scale. It is very costly in comparison to epinephrine.

**Conclusion**

VP can be used in catecholamine resistant vasodilatory shock of either septic or non septic origin decreasing the requirement of catecholamine to maintain adequate mean arterial pressure. But whether it changes the mortality statistics remains to be seen. Currently VP is recommended for use in adult patients with resistant VF as an alternative to epinephrine but not recommended for asystole, pulseless electrical activity and in pediatric population. Good diuretic response of VP analogues when used in low doses in volume loaded patient of HRS and refractory ascites has been seen. Long term outcome of the use of vasopressin for these newer uses is still unknown. Scope of use may widen after further controlled clinical studies.

**References**

21. Krisme De, Wengel V, Voelckel WG, Stadlbauer KH, Berger


---

**Announcement**

**Rabindranath Tagore Oration - 2007**

Suggestions are invited from Fellows of ICP for the following assignments so as to reach Dr. Sandhya Kamath, Hon. General Secretary not later than 31st July, 2006.

**Rabindranath Tagore Oration (2007)**

The prescribed nomination/application is available from the API Office. Persons are selected from the suggestion received from Fellows of Indian College of Physicians. The recommendations for the above assignment must be accompanied with reasons for recommending a particular person showing the value of his/her research and eight copies each of three of his/her best publications. All relevant papers in connection with the suggestions, such as the bio-data, list of publications etc., should be submitted in 8 sets by the proposer. The recipient of the above oration should deliver a lecture pertaining to his/her work at the CME APICON 2007 in February. The orator should preferably be a fellow of ICP. The oration should be of any subject in the discipline of Medicine.

A person who has received an API/ICP oration in the past is not eligible for any oration. The member of the Governing Body of API and the Members of the Faculty Council of ICP are not eligible to received any oration.

The complete application form for the above oration should reach Dr. Sandhya A Kamath, Hon. General Secretary of API/ICP, at Unit No. 6 and 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E Moses Road, Near Mahalaxmi Station West, Mumbai 400 011, not later than 31st July, 2006.

Dr. Sandhya Kamath
Hon. General Secretary

---

**Announcement**

**ICCD-WCCN - 2006**

International College of Cardiology and World College of Nutrition are organizing their 4th International Congress on Cardiovascular Disease (ICCD 2006) and XI World Congress on Clinical Nutrition (WCCN 2006) - an Unique Joint Congress - ICCD - WCCN - 2006 at Hotel Renaissance, Mumbai from 17th to 19th November 2006.

For further details, please contact: Dr. SB Gupta, Organizing Secretary, 18, Greylands, Railway Officers’ Flats New Marine Lines, Mumbai 400 020.

Ph : 022-23717246 (Hosp) 022-22624556 ® 022-22651044 (Telefax)

Cell : 09821364565/09821638617 E-mail : sbgupta@vsnl.net

Dr. Shashank Joshi, Organizing Secretary, B/23, Kamal Pushpa, 6, Bandra Reclamation, Mumbai 400 050.

Ph : 022-26402769 © 022-26420107 ® Cell : 09820186302 E-mail : srjoshi@bom5.vsnl.net.in