

A Role for Vasopressin during Resuscitation of Traumatic Shock

Masamitsu Sanui, MD*, **Stephen M Cohn, MD, FACS**, **David R King, MD**,
Ara J Feinstein, MD, **Albert J Varon, MD, FCCM***, **Kenneth G Proctor, PhD**
Ryder Trauma Center, Departments of Surgery and Anesthesiology*
University of Miami School of Medicine, Miami, FL
1800 NW 10th Ave. Suite 215, Miami, FL 33136

E-mail: kproctor@miami.edu

SUMMARY

In the past few years, arginine vasopressin (AVP) has emerged as a rational alternative to catecholamines for the hemodynamic support of refractory vasodilatory shock and cardiopulmonary arrest. The therapeutic potential of AVP in traumatic shock is now being evaluated. Our laboratory investigations have revealed an apparent benefit of AVP when compared to standard fluid resuscitation in clinically relevant models of brain injury and chest injury. Further experimental work and subsequent clinical trials appear justified to validate the efficacy of AVP for resuscitation of trauma patients.

1.0 INTRODUCTION

AVP has been used to treat patients for almost 100 years, but some exciting new indications have been suggested in a recent comprehensive review [1]. The basic physiology is well defined. It is a nonapeptide antidiuretic hormone that is formed primarily in the supraoptic nuclei of the hypothalamus and is stored in large secretory granules in nerve terminals in the posterior pituitary gland. Several stimuli release AVP, including increases in plasma osmolarity, volume contraction, trauma, pain, anxiety, and certain drugs (morphine, nicotine, tranquilizers, and some anesthetics). Perhaps the most potent stimuli for AVP release is hemorrhage; a loss of 25% of the blood volume can cause as much as a 50 fold increase in the rate of AVP secretion. The biological actions are mediated by V1 (vascular), V2 (renal) and V3 (anterior pituitary) receptors. The half-life of exogenous AVP is 10-35 minutes. The secondary messenger system at the V1 receptor involves a G-protein coupled phosphoinositide pathway leading to increased cytosolic calcium levels and vascular smooth muscle contraction.

The routine use of vasoconstrictors has historically been discouraged in hypovolemic patients, since organ blood flow and oxygen delivery can be compromised [2]. Unfortunately, early aggressive fluid replacement can also have undesired effects [3-6]. Furthermore, prolonged hemorrhage, cardiogenic shock, and sepsis may evolve into a refractory phase characterized by unresponsiveness to either fluid replacement or catecholamines [7, 8]. Recently, AVP was found to effectively restore systemic circulation in some of these conditions [8-14]. This counterintuitive finding has prompted a resurgence of interest in this hormone. The purpose of this report is to review some recent clinical and laboratory data on the therapeutic use of AVP in these critical conditions and to explore its potential in traumatic shock.

Paper presented at the RTO HFM Symposium on "Combat Casualty Care in Ground Based Tactical Situations: Trauma Technology and Emergency Medical Procedures", held in St. Pete Beach, USA, 16-18 August 2004, and published in RTO-MP-HFM-109.

Report Documentation Page

*Form Approved
OMB No. 0704-0188*

Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.

1. REPORT DATE 01 SEP 2004	2. REPORT TYPE N/A	3. DATES COVERED -	
4. TITLE AND SUBTITLE A Role for Vasopressin during Resuscitation of Traumatic Shock		5a. CONTRACT NUMBER	
		5b. GRANT NUMBER	
		5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)		5d. PROJECT NUMBER	
		5e. TASK NUMBER	
		5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Ryder Trauma Center, Departments of Surgery and Anesthesiology* University of Miami School of Medicine, Miami, FL 1800 NW 10th Ave. Suite 215, Miami, FL 33136		8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)		10. SPONSOR/MONITOR'S ACRONYM(S)	
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited			
13. SUPPLEMENTARY NOTES See also ADM001795, Combat Casualty Care in Ground-Based Tactical Situations: Trauma Technology and Emergency Medical Procedures (Soins aux blessés au combat dans des situations tactiques : technologies des traumatismes et procédures médicales d'urgence)., The original document contains color images.			
14. ABSTRACT			
15. SUBJECT TERMS			
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified	
			18. NUMBER OF PAGES 6
			19a. NAME OF RESPONSIBLE PERSON

2.0 AVP FOR VASODILATORY SHOCK

AVP has little effect on blood pressure under normal conditions, but the hemodynamic response to exogenous AVP may be augmented in shock states [7]. Malay et al performed a randomized controlled trial with septic shock patients (n=10) in the trauma ICU [9]. Low-dose AVP (0.04 U/min) increased systolic pressure from 98 to 125 mmHg and permitted successful withdrawal of all other catecholamine vasoactive drugs. All patients survived in the AVP group while two died within 24 hours in the control group. Another randomized controlled study in patients (n=10) with vasodilatory shock after cardiopulmonary bypass [10] showed that AVP (0.1 U/min) increased mean arterial pressure (MAP) from 57 to 84 mmHg, and reduced norepinephrine requirement.

3.0 AVP FOR SHOCK STATES: THE RATIONALE

Prolonged shock is characterized by a biphasic AVP response. A large initial peak of plasma AVP (100-1000 pg/mL) is followed by inappropriately low levels (e.g. <50 pg/mL) for the degree of hypotension [1, 8]. Similarly, in critically ill patients during late septic shock, AVP levels (3.1 pg/mL) [11] are within the normal range for well-hydrated humans (< 4 pg/mL) [1]. Postulated mechanisms of the endogenous AVP deficiency in shock states include: depletion of neurohypophyseal stores of AVP; inhibition of AVP release due to impaired autonomic reflex; and the inhibitory effect of high levels of circulating norepinephrine [1]. The endogenous AVP deficiency and the purported hypersensitivity to exogenous AVP provide the justification for low-dose AVP therapy in shock states.

4.0 AVP FOR CARDIOPULMONARY ARREST

Cardiopulmonary arrest may be another indication. Endogenous AVP levels are higher in resuscitated patients than in non-resuscitated patients after cardiopulmonary arrest [15]. Laboratory data and clinical trials support the benefits of AVP on coronary perfusion pressure [12], myocardial blood flow [16], restoration of spontaneous circulation [13, 17], and neurological recovery [17]. In a multicenter randomized controlled trial, AVP was equivalent to epinephrine in the management of ventricular fibrillation, but superior to epinephrine in patients with asystole [14].

5.0 AVP FOR TRAUMA WITH HEMORRHAGE

Investigators have questioned the use of aggressive fluid resuscitation for the treatment of uncontrolled hemorrhage prior to surgical intervention [3, 4]. In this context, a porcine model of uncontrolled hemorrhage was adopted to evaluate the effects of AVP on survival after liver injury [18]. A bolus dose (0.4 U/kg, n=9) was administered followed by 0.08 U/kg/min continuous infusion until the bleeding was controlled, when standard fluid resuscitation was initiated. Eight of nine AVP animals survived more than 7 days, while all fluid resuscitation animals (n=7) and all placebo animals (n=7) died in the hemorrhage period. A similar study was conducted to compare the effect of AVP to epinephrine on short-term survival [19]. AVP (n=7), but not epinephrine (n=7) or placebo (n=7), improved survival in uncontrolled hemorrhage after liver injury. These findings suggest that delayed fluid resuscitation combined with AVP infusion may be beneficial. However, a concern remains about possible visceral ischemia by large dose AVP [7].

6.0 AVP FOR TRAUMATIC BRAIN INJURY (TBI)

Hypotension, hypoxemia and increased intracranial pressure (ICP) after TBI are strongly associated with poor outcome [20, 21]. Although hypertonic/colloid solutions [5] or vasoactive agents [22] have been advocated to maintain cerebral perfusion pressure (CPP), reduce the fluid requirement and minimize ICP changes, the validity of vasoactive agents in this setting is undetermined. In a porcine model, phenylephrine improved CPP but did not increase cerebral blood flow in uncontrolled hemorrhage after TBI [23]. Clinical trials have suggested that norepinephrine is superior to dopamine in optimizing both ICP [24] and cerebral blood flow [22]. There is one case report, in which early use of AVP appeared efficacious for a patient with severe TBI (GCS 4) complicated with hypotension refractory to fluid and sympathomimetics [25].

We have performed two series of studies to evaluate the therapeutic potential of AVP during resuscitation from hemorrhagic shock after TBI. In the first series, anesthetized swine (n=19) received standardized fluid percussion TBI and severe hemorrhagic hypotension with MAP < 20 mmHg and isoelectric EEG for 12 minutes. Three animals died before randomization. The survivors were resuscitated with a clinically relevant protocol [26, 27] including administration of normal saline, blood and mannitol (1 g/kg) to maintain CPP > 60 mmHg. Either continuous AVP (0.1 U/kg/hr) or placebo infusion was administered in blinded fashion. Our data showed that the total fluid required to maintain CPP was reduced by half in the animals receiving AVP, the transfusion requirement was reduced by 40%, cerebrovascular reactivity to carbon dioxide was improved, and ICP were reduced (11±1 vs 23±2 mmHg).

In a second series (n=14), the duration of hypotension and isoelectric EEG after TBI was extended to 20 min, which caused a greater number of primary deaths (n=4). Then the identical resuscitation protocol was initiated with AVP bolus (0.2 U/kg) followed by continuous infusion (0.1 U/kg/hr). All AVP animals (n=5) survived 5 hours after TBI, while 3 animals died within 67min in the placebo group (n=5). Altogether, these data suggest a therapeutic potential for AVP during fluid resuscitation from severe TBI.

7.0 AVP FOR PULMONARY CONTUSION

The deleterious effects of large amount of fluid administration on pulmonary contusion have been suggested in animal models, but the efficacy of limiting fluid, either with hypertonic solutions or with vasoactive agents has not been supported by clinical evidence [6]. In our laboratory, the potential benefits of AVP were examined in a porcine lung contusion model combined with hemorrhagic hypotension [28]. After a blast to the chest with a captive bolt gun and hemorrhage to MAP < 30 mmHg for 20 minutes (n=20), there were 3 deaths. The survivors were resuscitated with crystalloid and randomized to either AVP (0.1 U/kg followed by 0.4 U/kg/hr) or placebo. All AVP animals (n=8) survived 5 hours, while 4 of 9 placebo animals died within 120 min after the injury. With AVP vs placebo, the total fluid required to maintain MAP was reduced by two-thirds, ventilatory mechanics (compliance, airway resistance, and airway pressures) were improved, and ventilation/perfusion was improved.

The major limitation of our animal studies is related to safety and specificity. We observed AVP reduced cardiac index in accordance with decrease in heart rate, and thus O₂ extraction was increased and lactate clearance was delayed. These parameters eventually returned to normal within 5 hours, but ischemia of visceral organs and distal extremities cannot be ruled out. Finally, despite previous studies which suggest unique benefits of AVP vs catecholamines [12, 14, 19], it is possible that the benefits we observed are related to reduced fluid requirements and are not AVP-specific. Further experimental work and subsequent clinical trials appear justified to validate the safety and efficacy of AVP for resuscitation in trauma patients.

8.0 ACKNOWLEDGEMENTS

The authors' research was supported by: Grants # N000140210339, #N000140210035 from the Office of Naval Research. In addition, we would like to thank George Beck of Impact Instrumentation (West Caldwell, NJ) for providing the ventilators; Concetta Gorski, RN, BS, CCRA, Integra LifeSciences Corporation, (Plainsboro, NJ) for providing the camino monitors and LiCOX probes; Cindy Elidrissi, RN of Aspect Medical Systems (Natick, MA) for providing the bispectral EEG monitor; and Terry Shirey, PhD of Nova Biomedical (Waltham, MA) for providing the Stat Ultra Blood Gas and Electrolyte Analyzer.

9.0 REFERENCES

- [1] Holmes CL, Patel BM, Russell JA, et al. Physiology of vasopressin relevant to management of septic shock. *Chest*. 2001; 120: 989-1002
- [2] Weil MH, Shubin H, Carlson R. Treatment of circulatory shock. Use of sympathomimetic and related vasoactive agents. *JAMA*. 1975; 231: 1280-1286
- [3] Stem SA. Low-volume fluid resuscitation for presumed hemorrhagic shock: helpful or harmful? *Curr Opin Crit Care*. 2001; 7: 422-430
- [4] Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994; 331: 1105-1109
- [5] Wade CE, Grady JJ, Kramer GC, et al. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma*. 1997; 42: S61-65
- [6] Cohn SM. Pulmonary contusion: review of the clinical entity. *J Trauma*. 1997; 42: 973-979
- [7] Robin JK, Oliver JA, Landry DW. Vasopressin deficiency in the syndrome of irreversible shock. *J Trauma*. 2003; 54: 149-154
- [8] Morales D, Madigan J, Cullinane S, et al. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. *Circulation*. 1999; 100: 226-229
- [9] Malay MB, Ashton RC Jr, Landry DW, et al. Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma*. 1999; 47: 699-703
- [10] Argenziano M, Choudhri AF, Oz MC, et al. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. *Circulation*. 1997; 96: II-286-290
- [11] Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation*. 1997; 95: 1122-1125
- [12] Morris DC, Dereczyk BE, Grzybowski M, et al. Vasopressin can increase coronary perfusion pressure during human cardiopulmonary resuscitation. *Acad Emerg Med*. 1997; 4: 878-883

- [13] Lindner KH, Prengel AW, Brinkmann A, et al. Vasopressin administration in refractory cardiac arrest. *Ann Intern med.* 1996; 124: 1061-1064
- [14] Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med.* 2004; 350: 105-113
- [15] Lindner KH, Strohmenger HU, Ensinger H, et al. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology.* 1992; 77: 662-668
- [16] Voelckel WG, Lurie KG, McKnite S, et al. Effects of epinephrine and vasopressin in a piglet model of prolonged ventricular fibrillation and cardiopulmonary resuscitation. *Crit Care Med.* 2002; 30: 957-962
- [17] Stadlbauer KH, Wagner-Berger HG, Wenzel V, et al. Survival with full neurologic recovery after prolonged cardiopulmonary resuscitation with a combination of vasopressin and epinephrine in pigs. *Anesth Analg.* 2003; 96: 1743-1749
- [18] Stadlbauer KH, Wagner-Berger HG, Raedler C, et al. Vasopressin, but not fluid resuscitation, enhances survival in a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. *Anesthesiology.* 2003; 98: 699-704
- [19] Voelckel WG, Raedler C, Wenzel V, et al. Arginine vasopressin, but not epinephrine, improves survival in uncontrolled hemorrhagic shock after liver trauma in pigs. *Crit Care Med.* 2003; 31: 1286-1287
- [20] The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Resuscitation of blood pressure and oxygenation. *J Neurotrauma.* 2000; 17: 471-478
- [21] The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Intracranial pressure treatment threshold. *J Neurotrauma.* 2000; 17: 493-495
- [22] Steiner LA, Johnson AJ, Czosnyka M, et al. Direct comparison of cerebrovascular effects of norepinephrine and dopamine in head-injured patients. *Crit Care Med.* 2004; 32: 1049-1054
- [23] Alspaugh DM, Sartorelli K, Shackford SR, et al. Prehospital resuscitation with phenylephrine in uncontrolled hemorrhagic shock and brain injury. *J Trauma.* 2000; 48: 851-863
- [24] Ract C, Vigue B. Comparison of the cerebral effects of dopamine and norepinephrine in severely head-injured patients. *Intensive Care Med.* 2001; 27: 101-106.
- [25] Yeh CC, Wu CT, Lu CH, et al. Early use of small-dose vasopressin for unstable hemodynamics in an acute brain injury patient refractory to catecholamine treatment: a case report. *Anesth Analg.* 2003; 97: 577-579
- [26] The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Congress of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Update notice: cerebral perfusion pressure. Guidelines for the management of severe traumatic brain injury. Approved by the ANNS on March 14, 2003

A Role for Vasopressin during Resuscitation of Traumatic Shock

[27] King DR, Cohn SM, Proctor KG. Intracranial pressure, coagulation changes, and neurologic outcome after resuscitation from experimental traumatic brain injury with Hetastarch. *Surgery* (in press)

[28] Kelly ME, Miller PR, Greenhaw JJ, et al. Novel resuscitation strategy for pulmonary contusion after severe chest trauma. *J Trauma*. 2003; 55: 94-105